KU LEUVEN

Small molecule parametrization

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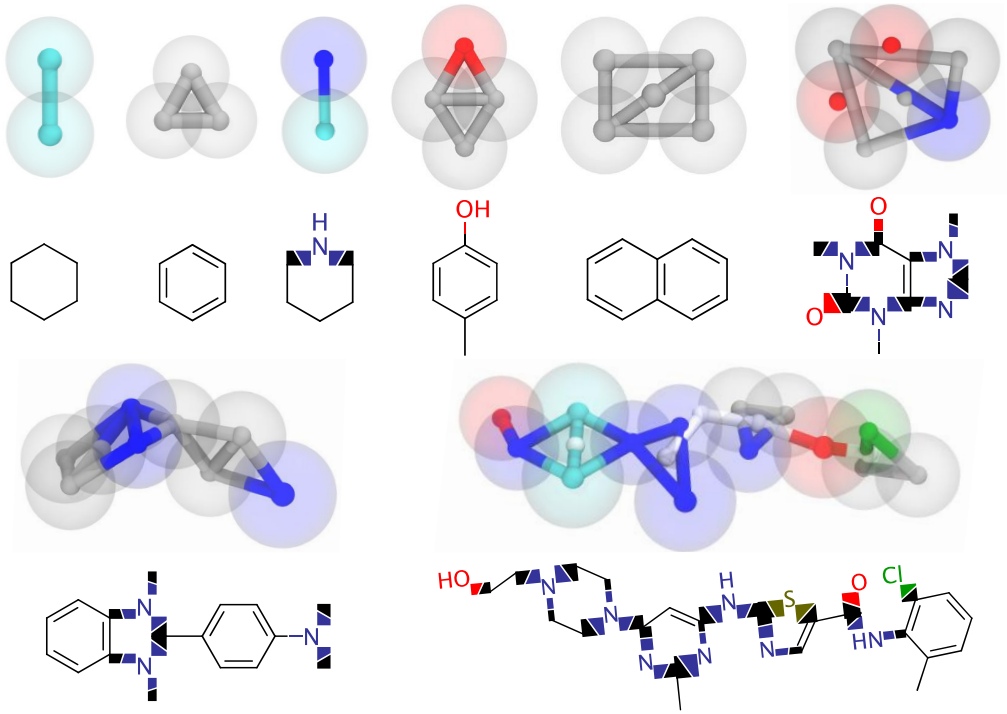
Outline

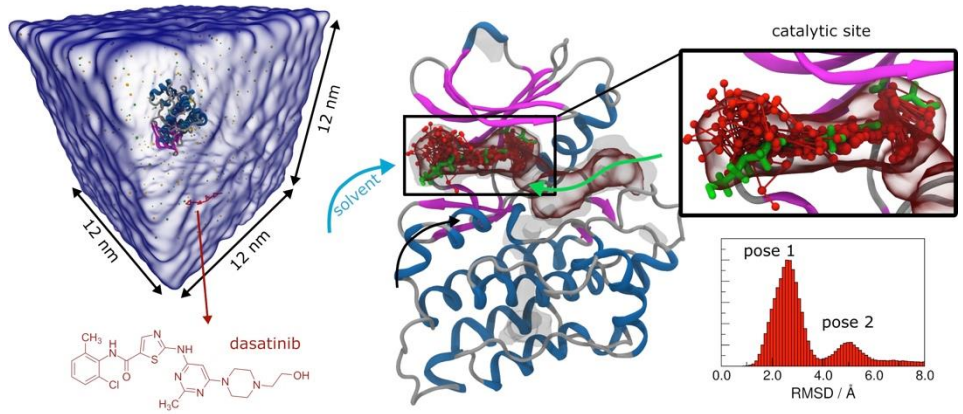
- Small molecules – why?
- One-slide recap of Martini 3 key features
- Coarse-graining small molecules with Martini 3
  - Basics of linear, branched, and ring-like fragments
  - Step 1: Atoms-to-bead **mapping**
  - Step 2: Bead type assignment (→ **nonbonded**)
  - Step 3: **Bonded** interactions: basics and advanced
  - Model validation and refinement
- Small molecule database
- Emerging tools for automated parametrization
- Take-home messages

Small molecules – why?

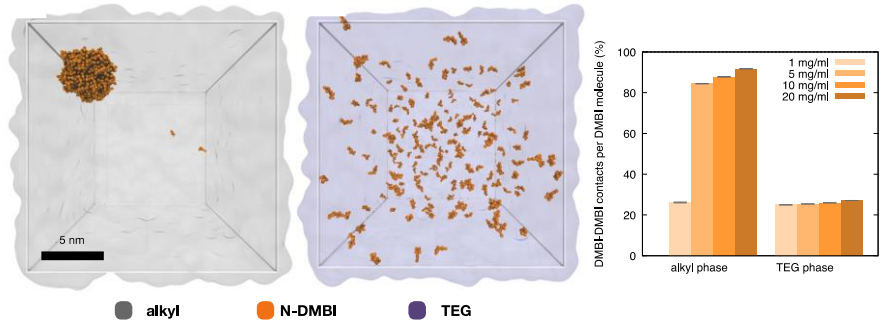


Alessandri, Barnoud, Gertsen, *et al.*,
Adv. Theory Simul. **2022**

- Building blocks for (bio-) macromolecules
- Protein-ligand binding simulations
- Self-assembly of small molecules (on surfaces)
- Molecular dopants in organic electronics
- …



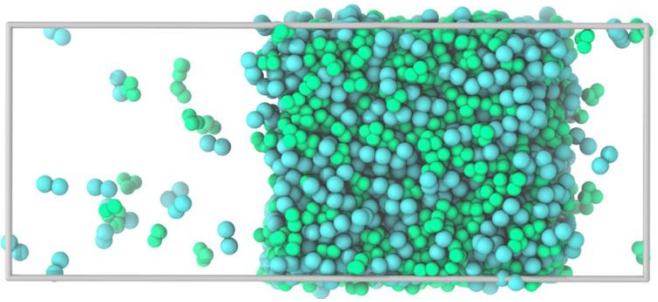
Souza, Thallmair, *et al.*,
Nat. Commun. **2020**



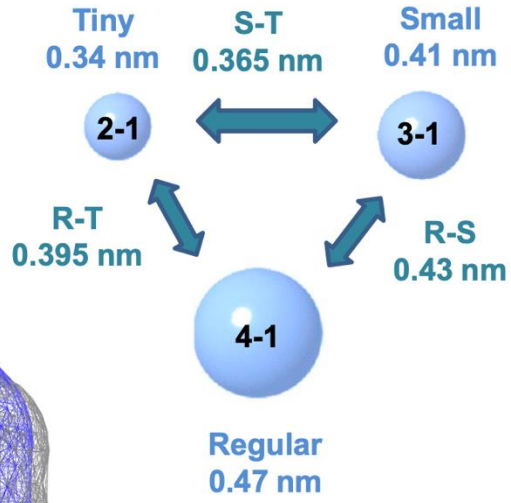
Liu, Qiu, Alessandri, *et al.*,
Adv. Mater. **2018**

Martini 3 key features

- main parametrization target remains the **free energy of transfer** (octanol/water, hexadecane/water, etc.)
- **now also miscibility** data (mixing behavior, free energy of mixing)

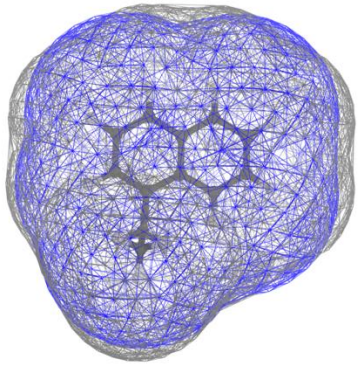


- **three bead sizes** – regular, small, and tiny – now** **fully balanced**
- **more beads**, more interaction levels



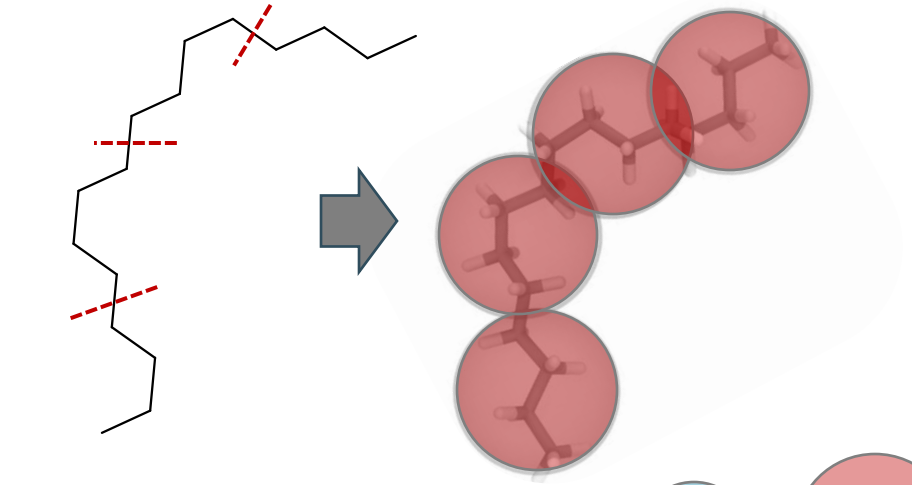
- **size/shape** importance

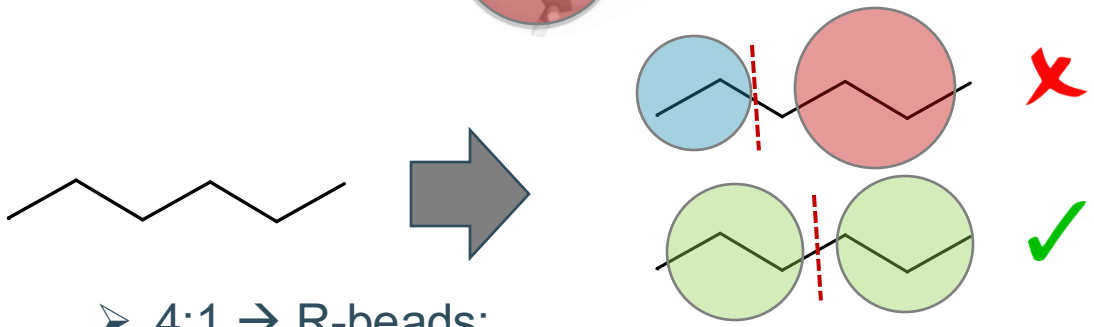
→ **center-of-geometry** based mapping (including *hydrogens*)



Coarse-graining small molecules: basics

Linear molecules/fragments:

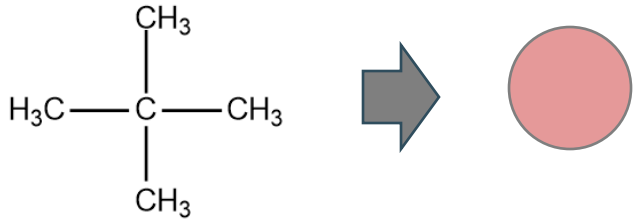




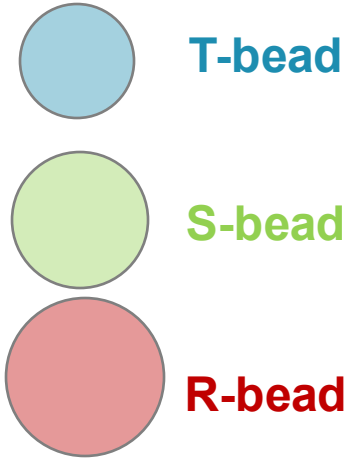
- 4:1 → R-beads;
  3:1 → S-beads;
  2:1 → T-beads

- preserve symmetry

Fully branched molecules/fragments:



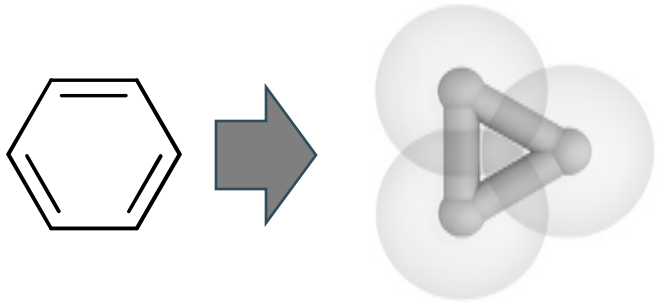
- Use **one size less**, e.g.,
  5:1 → R-bead,
  4:1 → S-beads, etc.



Coarse-graining small molecules: basics

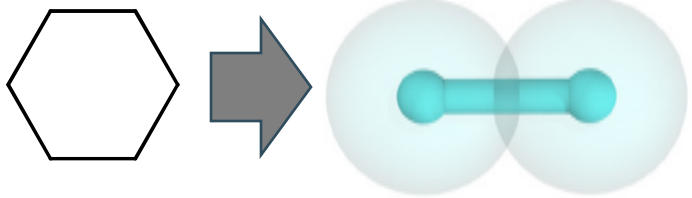
Modeling **aromatic** and **aliphatic** ring-like fragments:

- Benzene



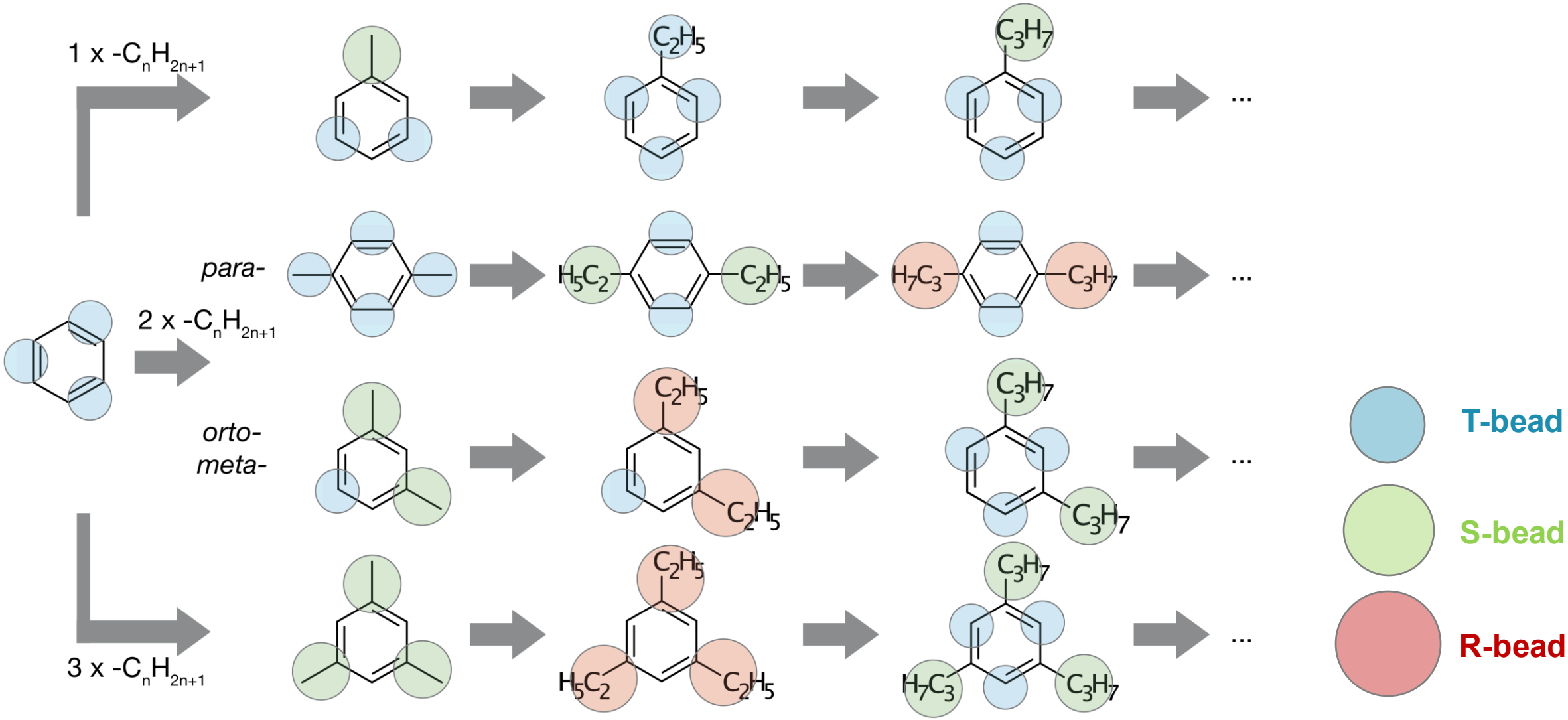
- Aromatic rings, i.e., atom-thick structures → **T-beads**
- **TC5** is the bead type of choice for –CH=CH– groups in aromatics
- **constraints**

- Cyclohexane



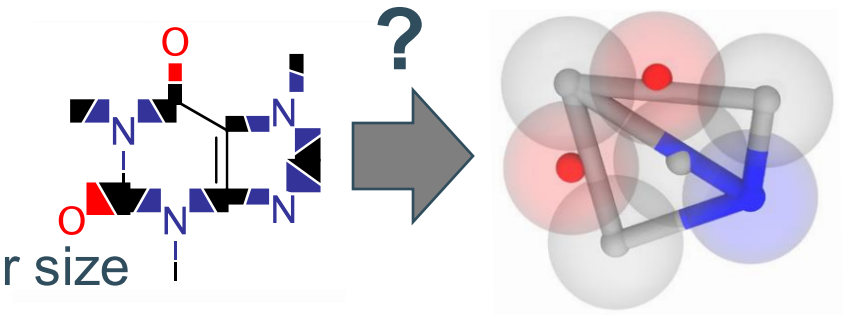
- aliphatic rings, i.e., bulkier, saturated structures → **S-beads**
- **SC3** is the bead type of choice for $–CH_2–CH_2–CH_2–$ groups in rings
- **harmonic bonds**

Mapping substituted ring-like fragments



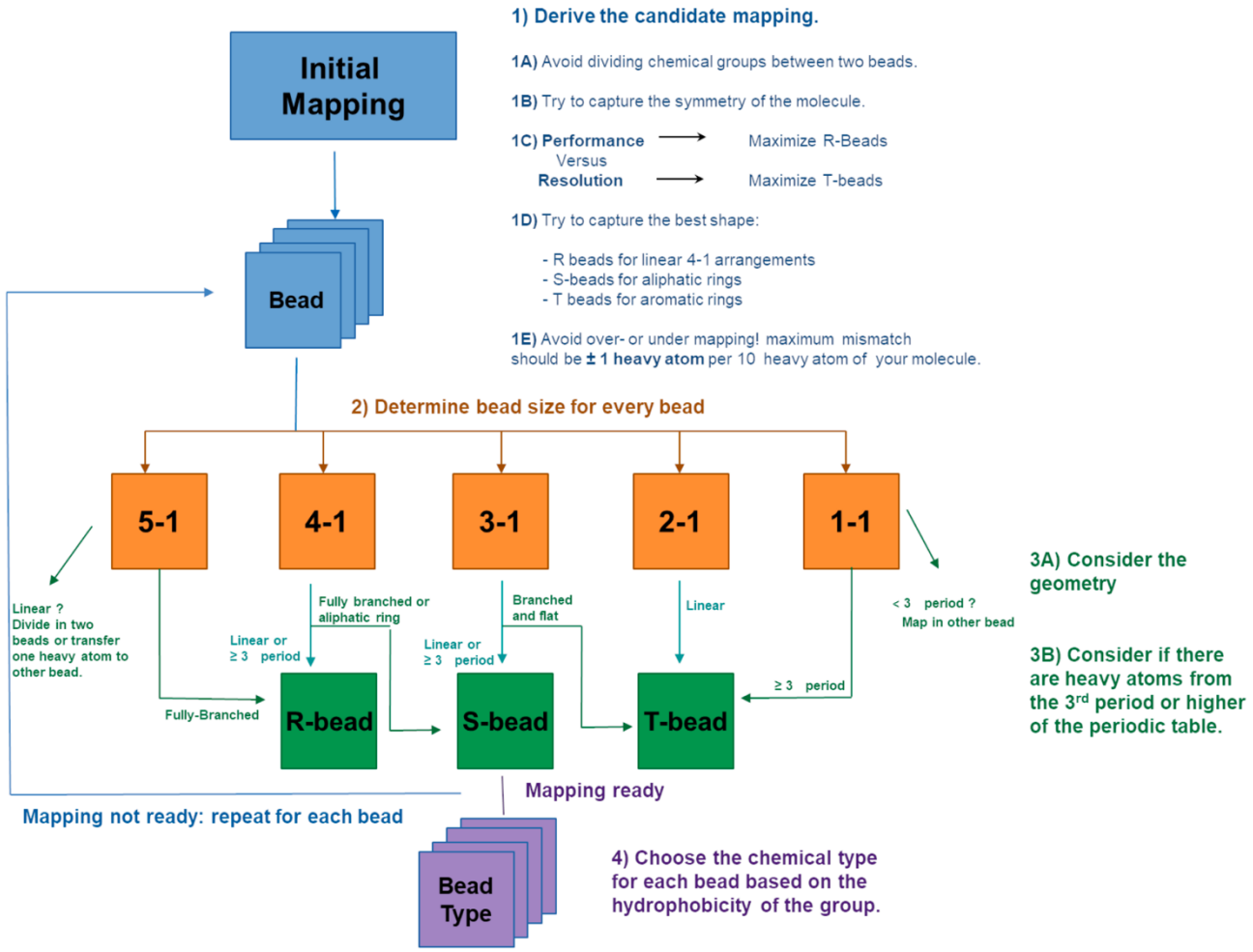
Atoms-to-bead **mapping** principles

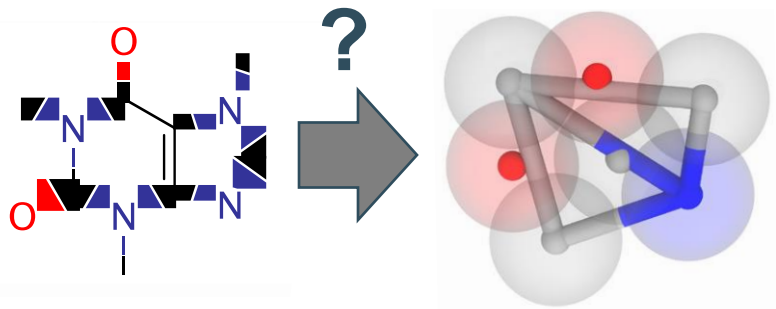
1. Map all the non-hydrogen atoms with the minimum possible number of beads (→ **maximize R-beads**).
2. Preserve the **symmetry, volume, and shape** of the molecule as much as possible, with aromatic rings being best described by T-beads and aliphatic rings by S-beads.
3. 4-to-1, 3-to-1 and 2-to-1 mappings of ***linear* fragments** → regular, small, and tiny beads, respectively.
4. fully **branched** fragments should usually use beads of smaller size
5. avoid dividing **functional groups** (e.g., amide or carboxylate) between two beads;
6. do **not "overmap"/"undermap"** → *rule of thumb*: optimize number of beads such that the maximum mismatch in mapping is ±1 non-hydrogen atom every 10 non-hydrogen atoms;



Souza, Alessandri, Barnoud, Thallmair, Faustino, Grünewald, Patmanidis, *et al.*, *Nat. Methods* **2021**
Alessandri, Barnoud, Gertsen, Patmanidis, de Vries, Souza, Marrink, *Adv. Theory Simul.* **2022**

Atoms-to-bead **mapping** principles: flowchart



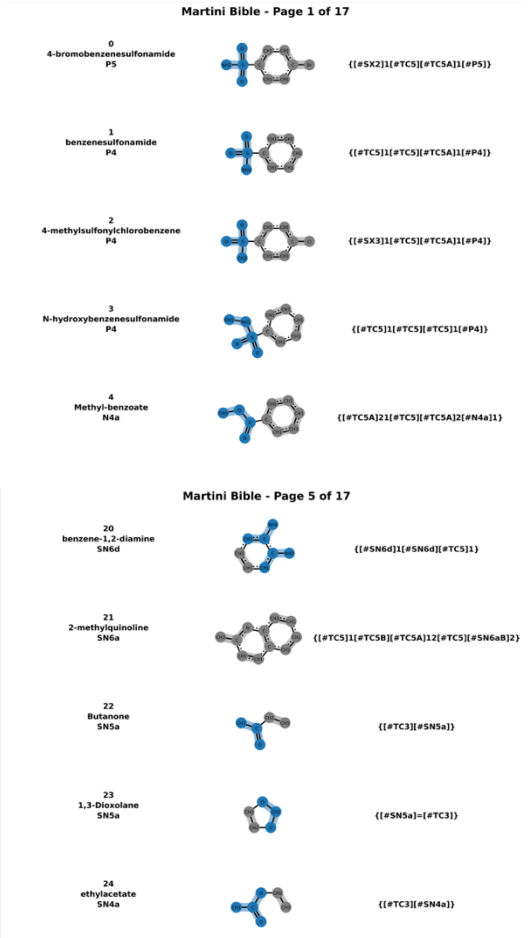


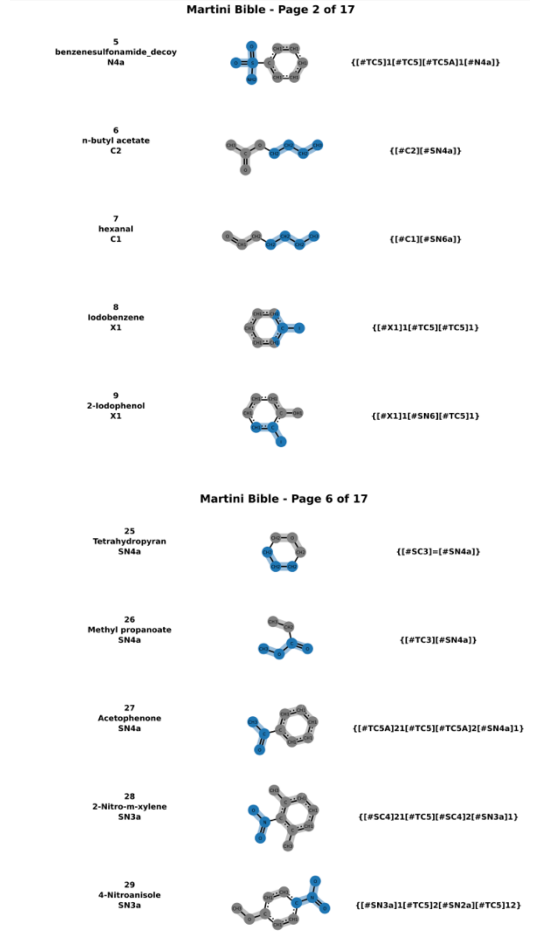
Supplementary Figure 6: General rules for mapping and choice of bead sizes.

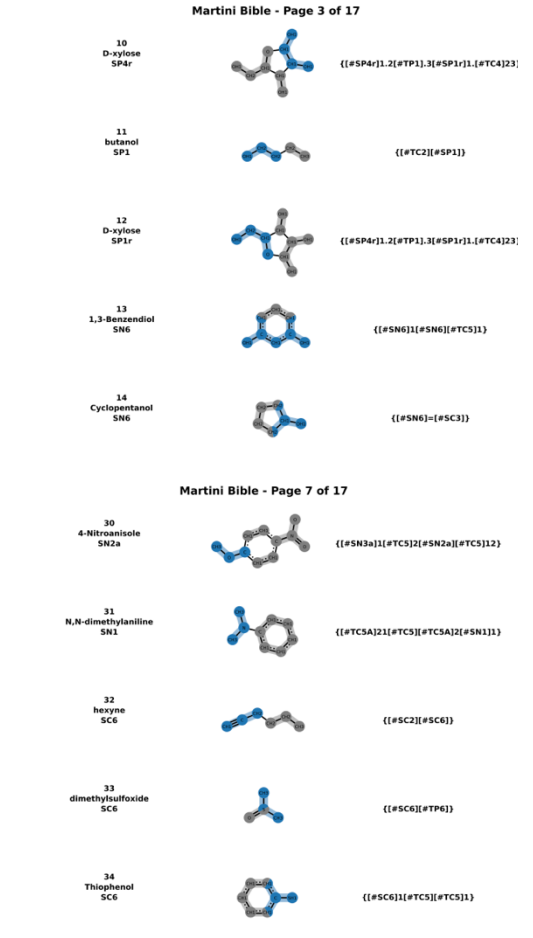
Bead type choice (→**nonbonded**)

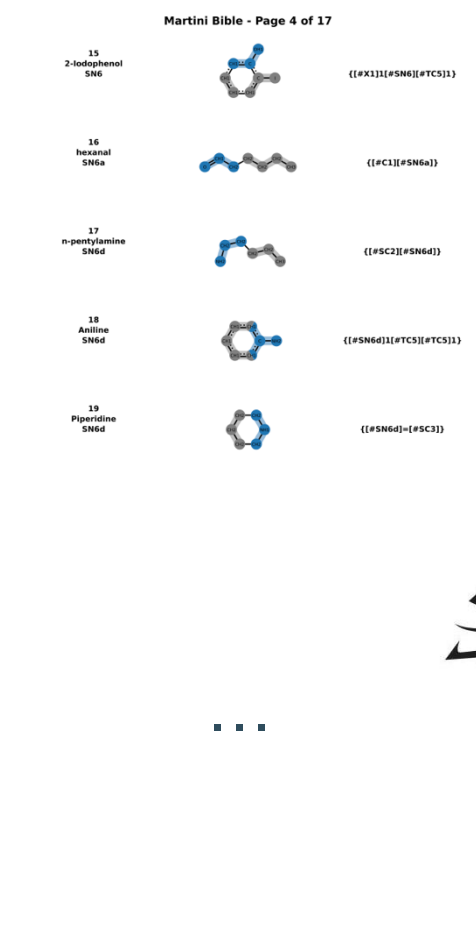
1. Initial bead type assignments → use the “Martini 3 Bible”

Bead type choice (→**nonbonded**): “Martini bible”



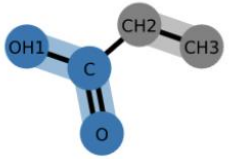
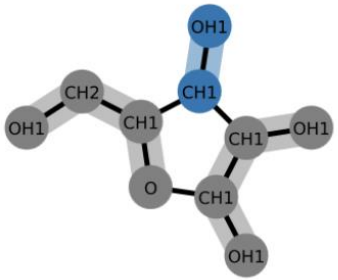
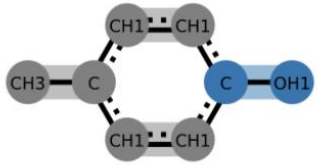






github.com/Martini-Force-Field-Initiative/M3-Bible

Bead type choice (→**nonbonded**): “Martini bible”

...	...	...	
56 **propionic acid** **TP2a**	example mapping		**{[#TC3][#TP2a]}**
57 **D-xylose** **TP1**			**{[#SP4r]1.2[#TP1].3[#SP1r]1.[#TC4]23}**
59 **p-Cresol** **TN6**			**{[#TN6]1[#TC5]2[#TC5A][#TC5]12}**
...	...	...	

github.com/Martini-Force-Field-Initiative/M3-Bible

Bead type choice (→**nonbonded**): Validation & refinement

1. Initial bead type assignments → use the “Martini 3 Bible”

2. Compute the free energy of transfer for the model and compare to the experimental free energy of transfer of the molecule (*ideal case*)

2B. Compute the free energy of transfer for fragments of the model and compare to the experimental free energy of transfer of such fragments

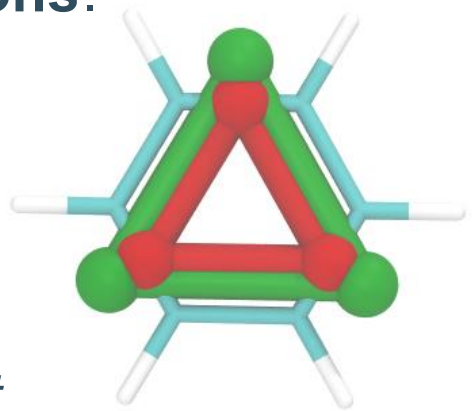
2C. Compute the free energy of transfer for the model and compare to the predicted (atomistic force field; or alternatively XLogP3, COSMO-RS, …) free energy of transfer of the molecule

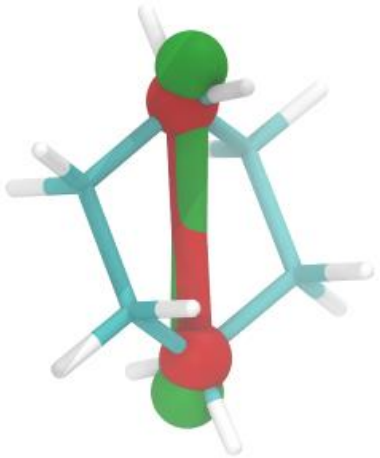
3. If good → yay! If not good → refine bead type choice

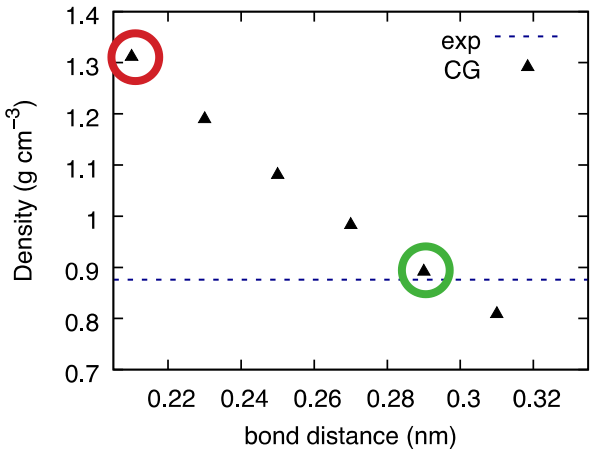
Bonded parameters: reference & center-of-geometry (COG)

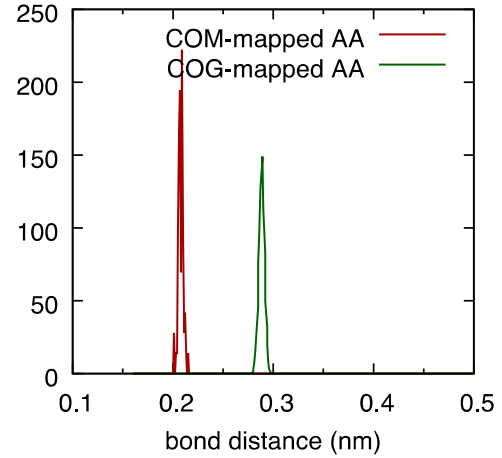
For small molecules, bonded parameters are usually** derived from **atomistic simulations**.

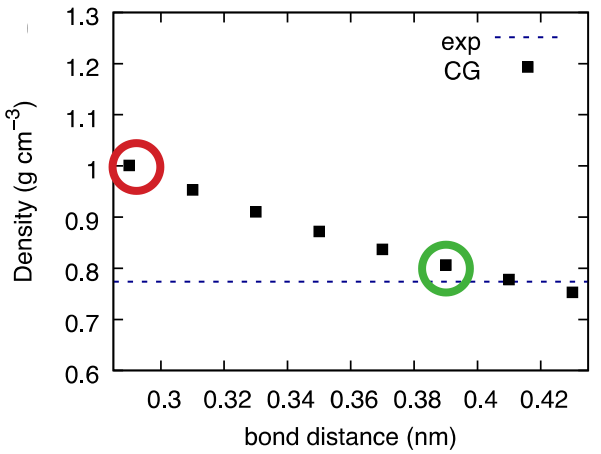
COG-based mapping of atomistic structures (*done taking into account the hydrogen atoms*) constitutes the default procedure for obtaining bonded parameters in Martini 3 – **why?**

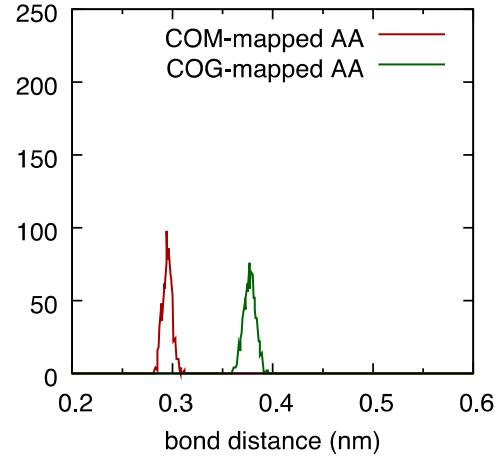








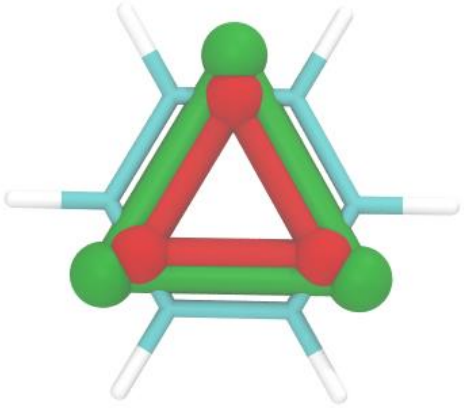


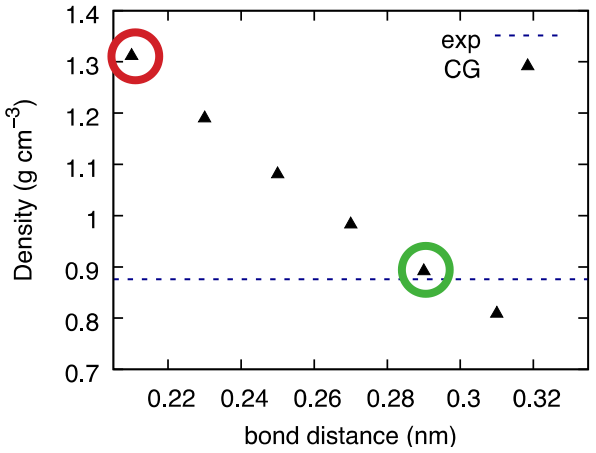


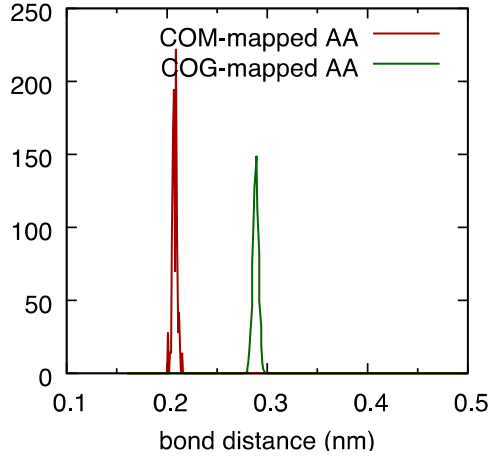
** For examples of alternative approaches, see e.g., (1) next talk by MN Melo or (2) Bartender (later in this presentation).
Alessandri, Barnoud, Gertsen, Patmanidis, de Vries, Souza, Marrink, *Adv. Theory Simul.* **2022**

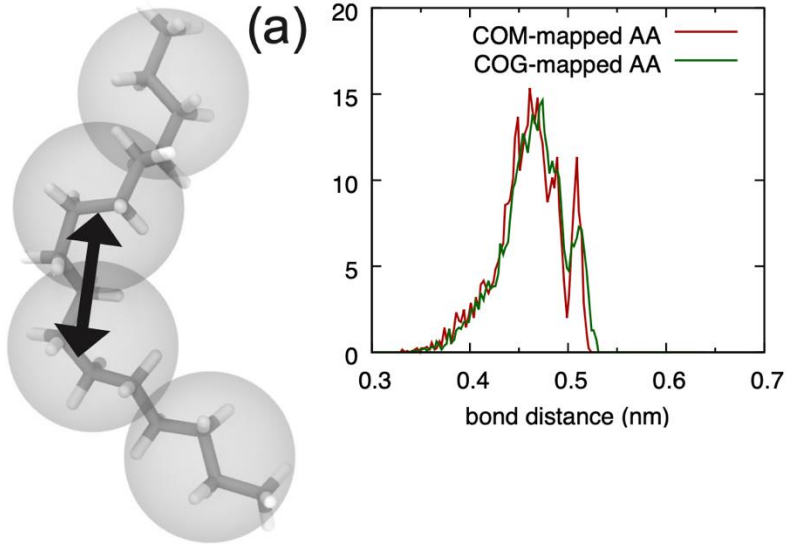
center-of-geometry = COG
center-of-mass = COM

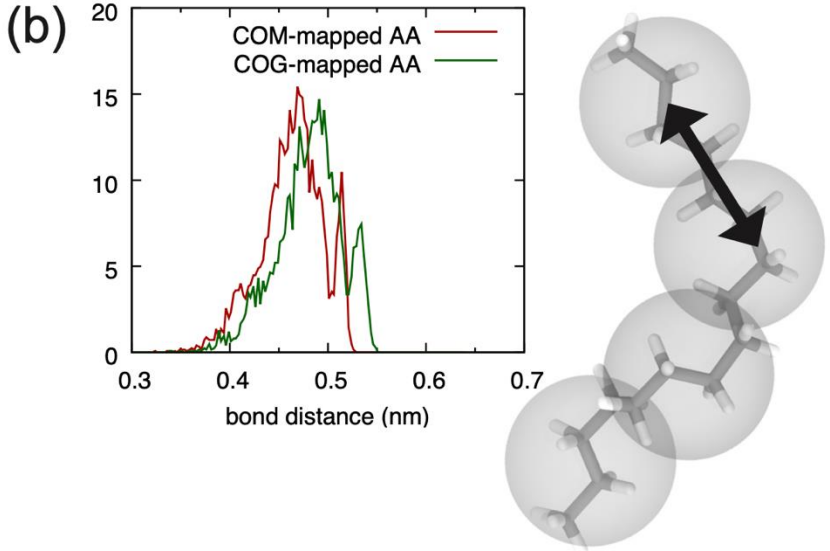
Bonded parameters: COG *vs* COM











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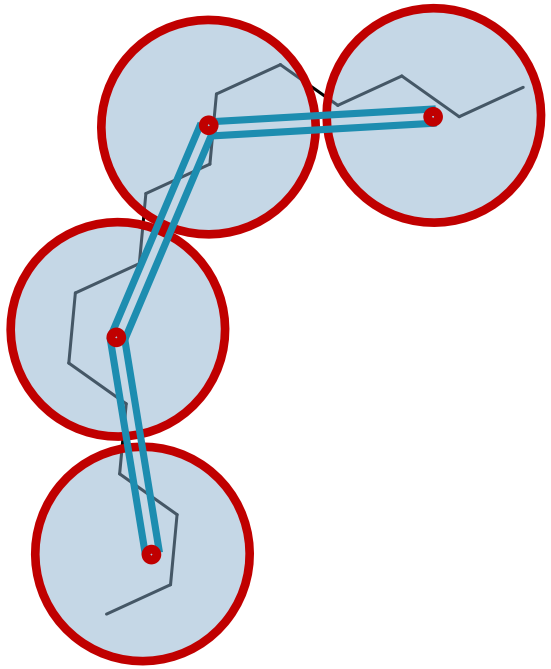
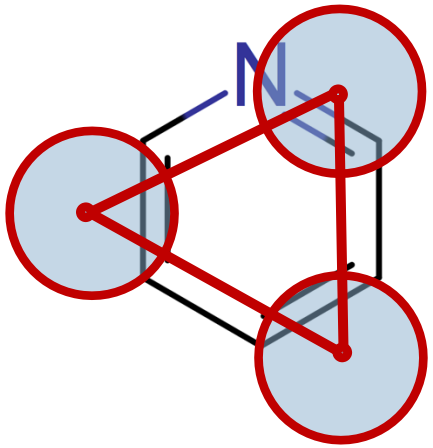
Alessandri, Barnoud, Gertsen, Patmanidis, de Vries, Souza, Marrink, *Adv. Theory Simul.* **2022**

Bonded parameters: basic constructions

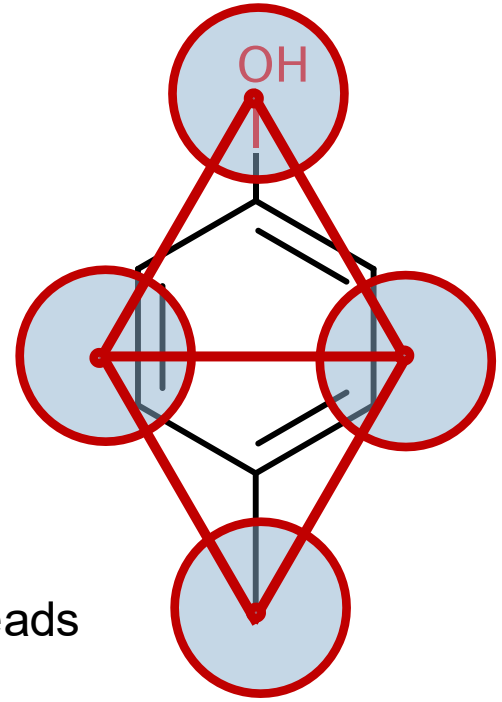
Which bonded parameters do we need?



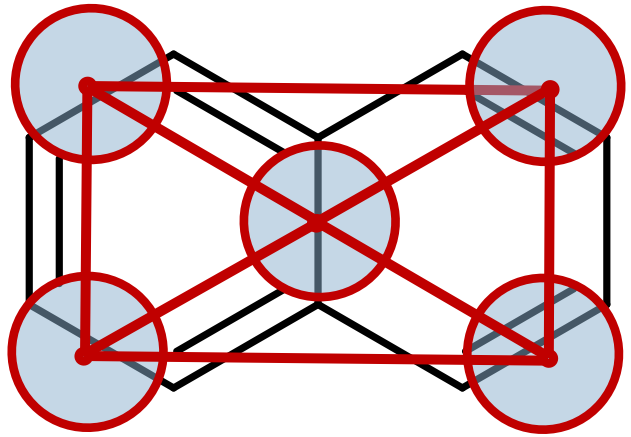
16 atoms → 4 R-beads
3 bonds, 2 angles



6 (aromatic) atoms → 3 T-beads
3 constraints



8 atoms → 4 T-beads
5 constraints, 1 improper dihedral, exclusions



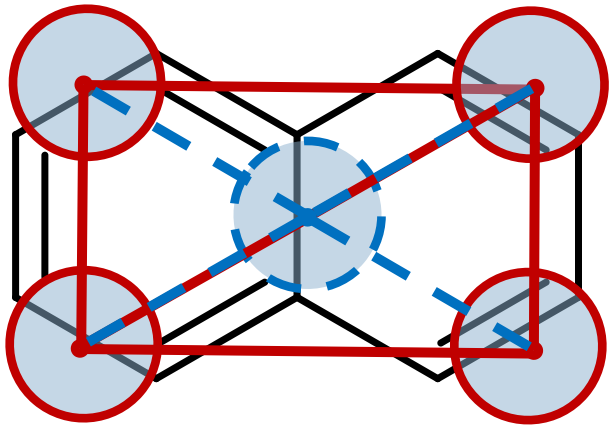
10 (aromatic) atoms → 5 T-beads
8 *interconnected* constraints…!

…

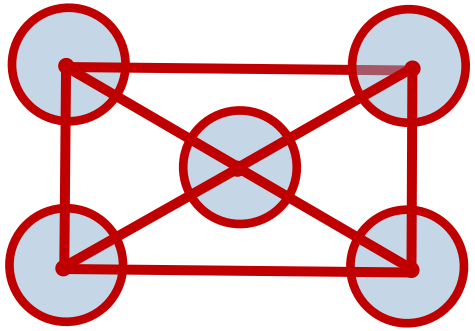
Bonded parameters: from basics to advanced constructions

Which bonded parameters do we need?

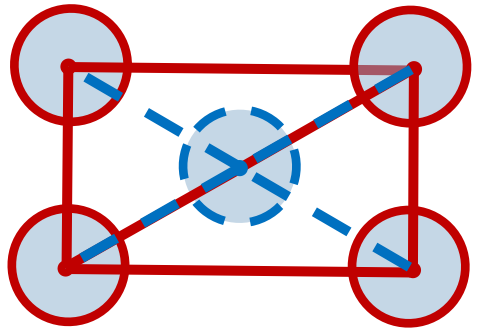
[A]
"Hinge"



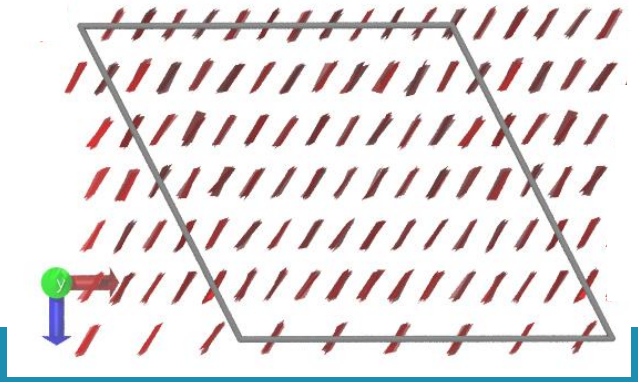
10 (aromatic) atoms → 5 T-beads
1 virtual interaction site, 5 constraints ("hinge")**,
1 improper dihedral, exclusions



Vs



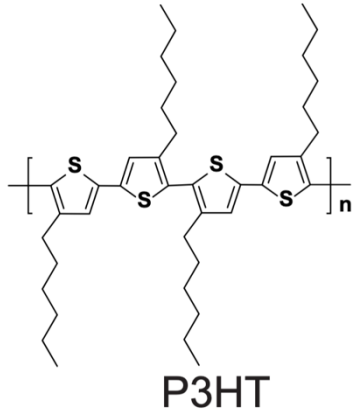
NAPH crystal (432 molecules)		
Nope	Runs with dt = 20 fs?	Yes
X	Performance (ns/day)	X+45%



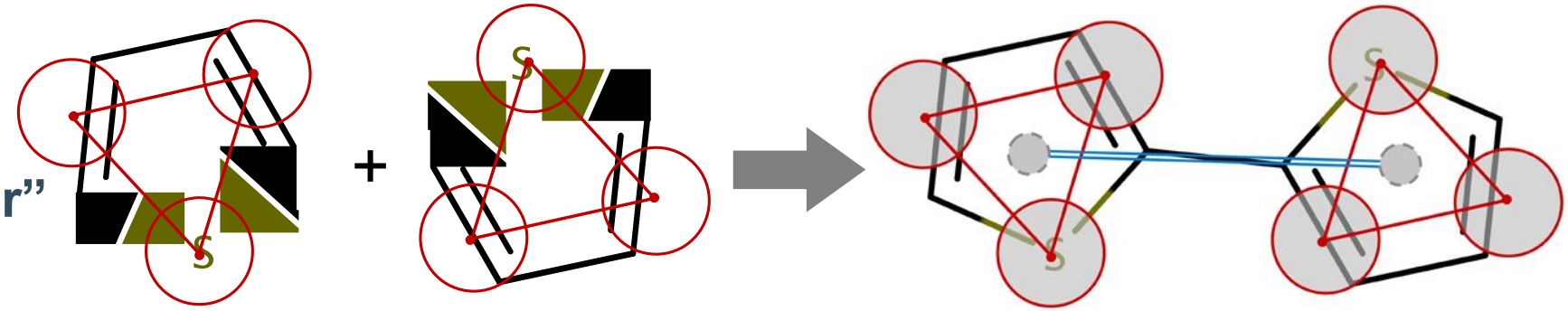
** Inspired by Melo, Ingólfsson, & Marrink, *JCP* **2015**
Alessandri, Barnoud, Gertsen, Patmanidis, de Vries, Souza, Marrink, *Adv. Theory Simul.* **2022**

Bonded parameters: advanced constructions

Which bonded parameters do we need?

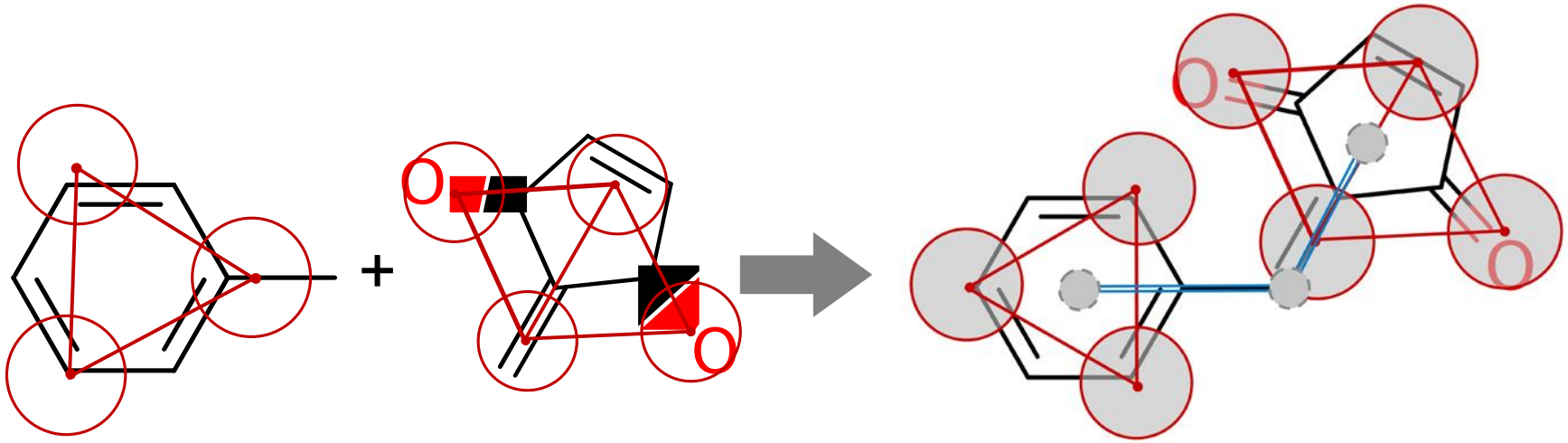


[B] "Divide and Conquer"



→ polymers! **

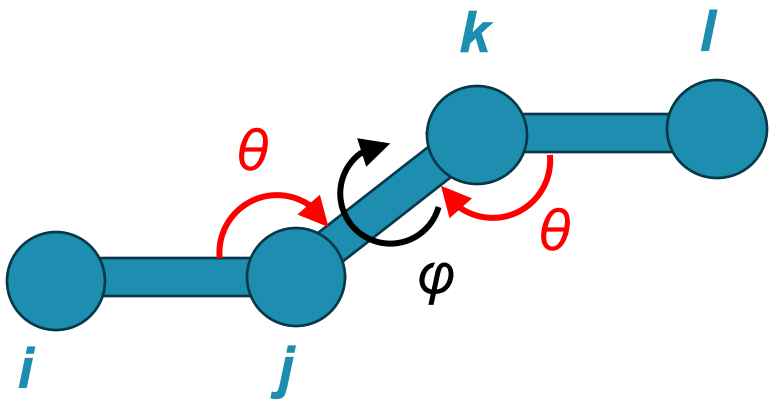
[C] "Molecular Turn"



…

Alessandri, Barnoud, Gertsen, Patmanidis, de Vries, Souza, Marrink, *Adv. Theory Simul.* **2022**
** Janeliunas, TU Delft PhD thesis **2014**; Alessandri, *et al.*, *J. Am. Chem. Soc.* 2017

Bonded parameters: careful with dihedrals

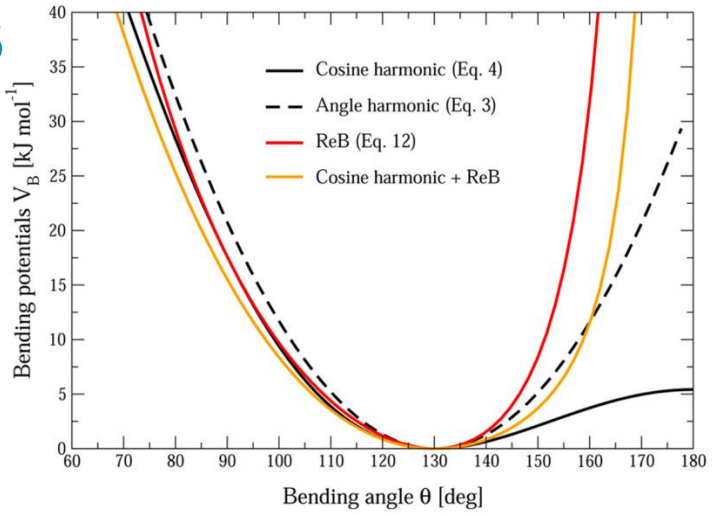


Problem:

If the *i-j-k-l* particles become collinear**
→ division by 0 when computing the torsion potential
→ numerical instability

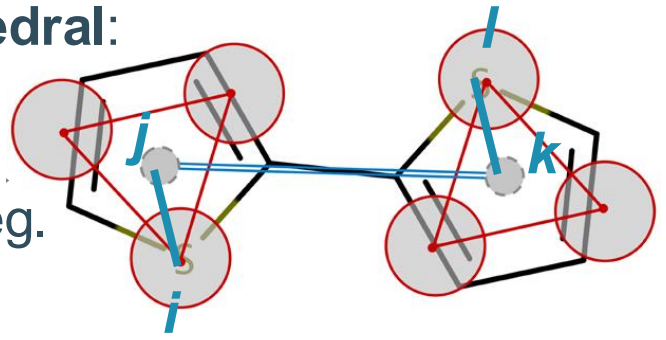
Strategies to avoid this:

1) **Restricted Bending potential** for i-j-k and/or j-k-l



2) **Combined bending-torsion potential**: expression that avoids the division by 0

3) **Dummy-assisted dihedral**: define the dihedral so that i-j-k and j-k-l are far from 0 & 180 deg.



Bulacu, Goga, Zhao, Rossi, Monticelli, Periole, Tieleman, Marrink, *J. Chem. Theory Comput.* **2013**

** This situation will basically never happen in atomistic simulations, but it can occur (frequently) in coarse-grained simulations

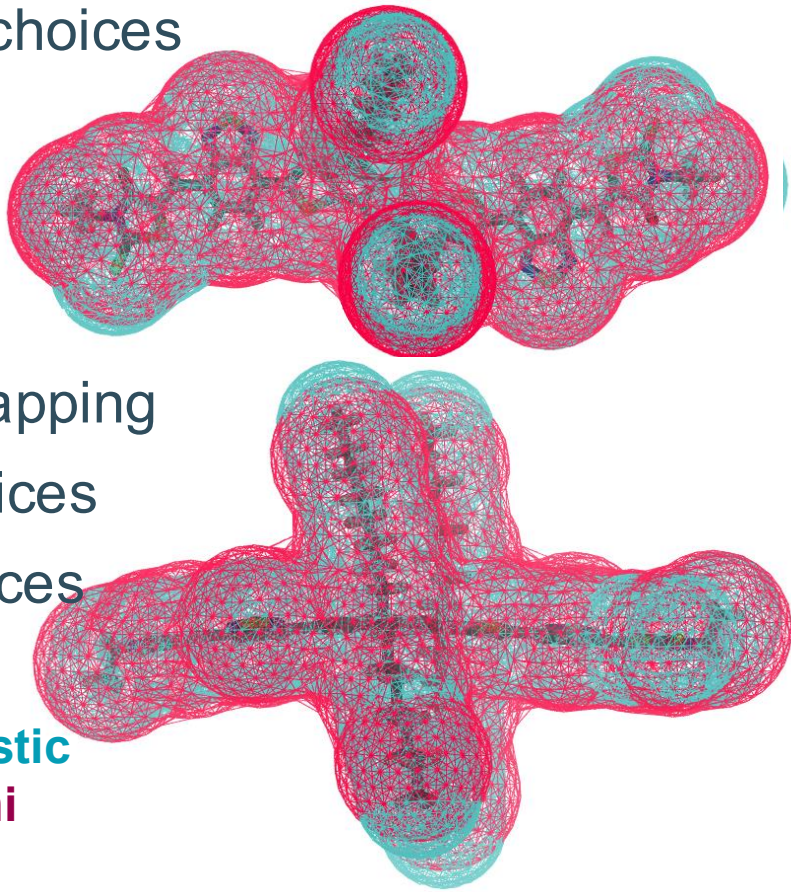
Model validation and refinement

Basic validation:

- **Free energy of transfer/partitioning** → refine bead type choices

Intermediate validation:

- **SASA/molecular volume** → refine bonded parameters/mapping
- **Mass density** → refine bonded parameters/bead type choices
- $\Delta H_{vaporization}$** → refine bonded parameters/bead type choices
- **Miscibility (qualitatively, ΔG_{excess})** → refine bonded parameters/bead type choices



** only the **Martini general trend** should be followed, as quantitative agreement with exp. cannot be achieved;
for an in-depth discussion, see: Alessandri, Souza, *et al.*, *J. Chem. Theory Comput.* **2019**

Model validation: application-specific

Application-specific validation targets:

- Often molecule class-dependent: Lipid? Ligand? Solvent? Ionic liquid? Nanoparticle? Polymer? ... see also other Workshop lectures!

Few examples about small molecules:

- PMFs of dimerization → Alessandri, *et al.*, *Adv. Theory Simul.* **2022**
- phase transition temperatures → Vazquez-Salazar, *et al.*, Green. Chem. **2020**

For more inspiration, see also what people have been doing in the literature:

- (**general**) Marrink, Monticelli, Melo, Alessandri, Tieleman, Souza, *WIRES Comput. Mol. Sci.* **2023**
- (**material-oriented**) Alessandri, Grünewald, & Marrink, *Adv. Mater.* **2021**

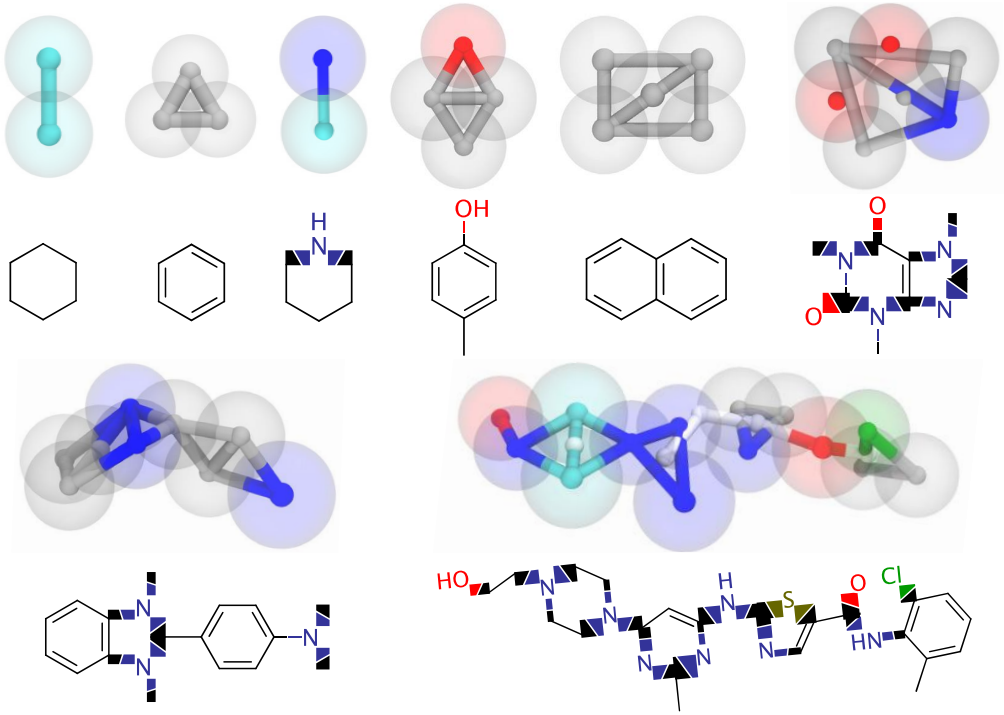
Martini 3 small molecule database

MARTINI 3
SMALL·MOLECULES

- Well-validated Martini 3 models for **90** small molecules
- Find it at: github.com/Martini-Force-Field-Initiative/M3-Small-Molecules

- Not only GROMACS topology files but also "supporting files" (AA-to-CG and CG-to-AA mapping files, reference AA files, etc.)

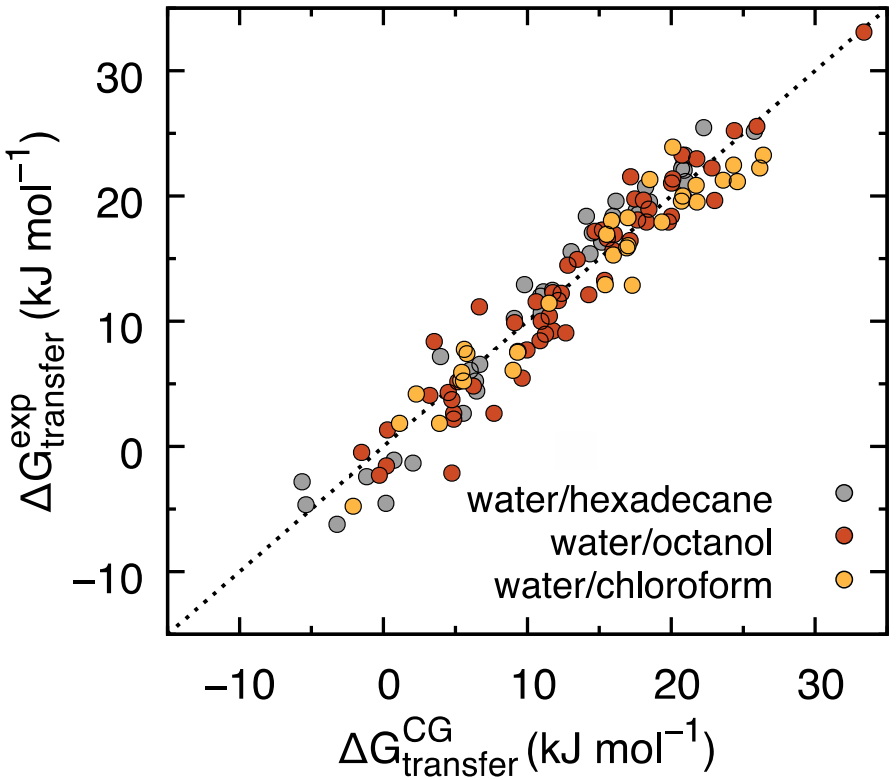
- What do do with the models?
  - Just download and use the models
  - Use as reference points to build other models
  - Benchmark for automated topology building
  - Building blocks for more complex (macro)molecules

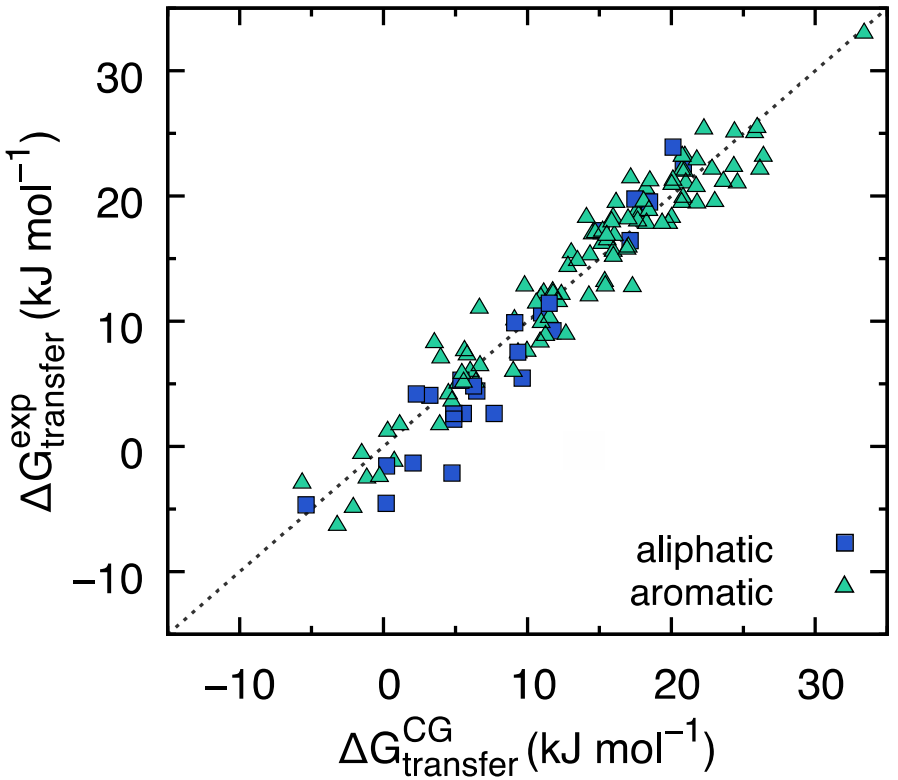


Small molecule database: validation

MARTINI 3
SMALL·MOLECULES

- Free energy of transfer (aka partitioning free energy):





	MAE (kJ/mol)
$\Delta G_{HD \rightarrow W}$	1.8
$\Delta G_{OCO \rightarrow W}$	1.8
$\Delta G_{CLF \rightarrow W}$	2.2

mean absolute error = MAE

Small molecule database: validation

MARTINI 3
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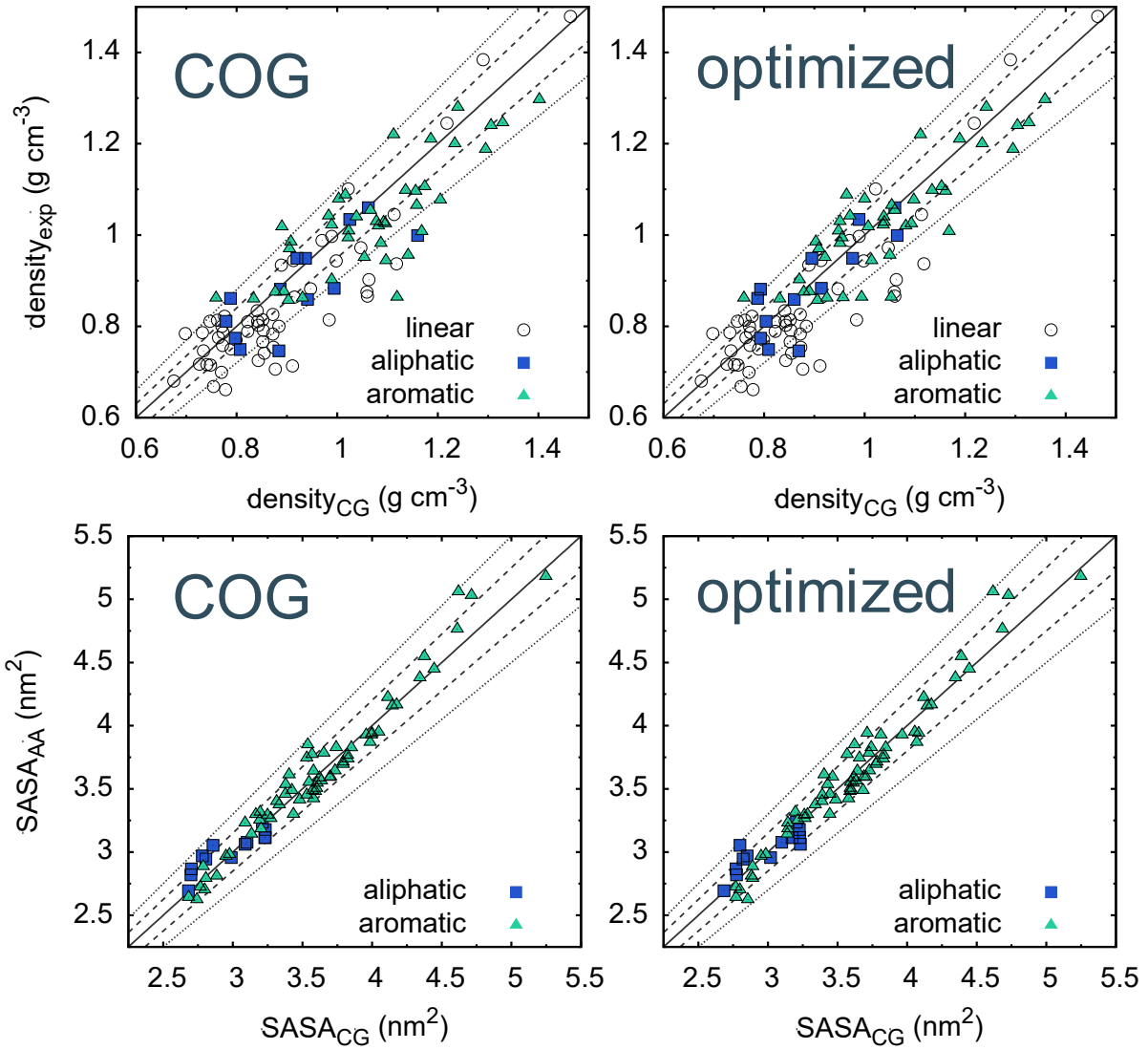
- Mass density:
- SASA:



	density MAPE (%)
COG	7.2
optimized	5.8

mean absolute percentage error = MAPE

Emerging tools for automated parametrization

Class I: CG bonded interaction fitting given a mapping file and initial CG topology

- `PyCGTool`: github.com/jag1g13/pycgtool (**2017**)
- `Bartender` (see tutorial): github.com/Martini-Force-Field-Initiative/Bartender (**2024**)
- `Fast_forward` (lecture after coffee + tutorial): github.com/fgrunewald/fast_forward (**2025**)

Class II: Class I + run (iteratively) CG simulations (possibly more targets & bead type optimization)

- `SwarmCG`: github.com/GMPavanLab/Swarm-CG (**2020**, **2023**)
- `CGcompiler`: github.com/kaistroh/CGCompiler-lipids (**2023**)

Class III: Full automated topology builders: from SMILES/PDB to CG topology

- `cg_params`: github.com/cgkmw-durham/cg_param_m3 (**2021**, **2025**)
- `Automartini`: github.com/Martini-Force-Field-Initiative/Automartini_M3 (**2015**, **2025**)

Emerging tools for automated parametrization: Bartender

The idea behind Bartender:

~~atomistic classical force field~~ 

GFN-xTB semiempirical quantum chemical method 

What Bartender needs:

1. PDB file of the molecule
2. Mapping file and bonded definitions

What Bartender does:

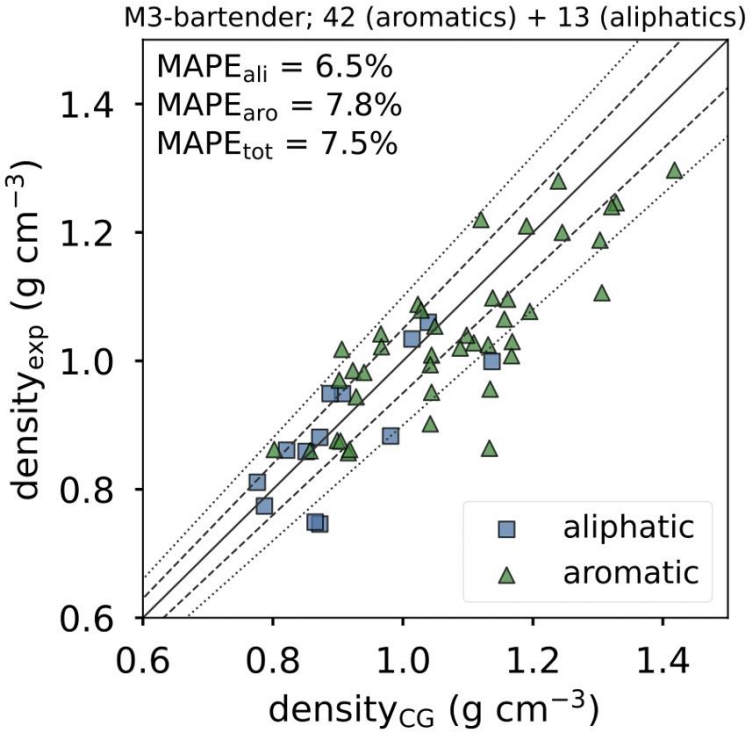
1. Runs GFN-xTB
2. Maps the trajectory, fits the bonded, gives you the CG topology file

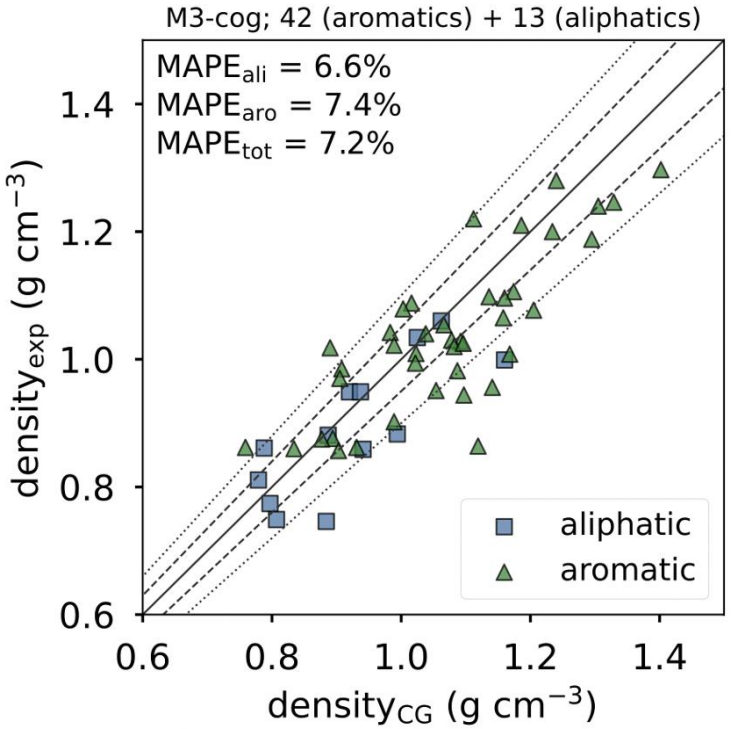
github.com/Martini-Force-Field-Initiative/Bartender

Pereira, Alessandri, Domínguez, Araya-Osorio, Grünewald, Borges-Araújo, *et al.*, *J. Chem. Theory. Comput.* **2024**
GNF-xTB: Bannwarth, et al. *WIRES Comput. Mol. Sci.* **2021**

Emerging tools for automated parametrization: Bartender

MARTINI 3
SMALL·MOLECULES





- For small, ring-like molecules:
  Bartender = human.

- For more complex, drug-like ligands: good starting point but may need refinement and sampling may be an issue.

github.com/Martini-Force-Field-Initiative/Bartender

Take-home messages (I)

- Take inspiration from already-developed small molecule models:
  - MArtini Database (https://mad.ens-lyon.fr/explore)
  - cgmartini.nl/docs/downloads/
  - github.com/Martini-Force-Field-Initiative/M3-Small-Molecules

- Here's the building block table *aka* "Martini 3 Bible":
  github.com/Martini-Force-Field-Initiative/M3-Bible

- The following manuscripts (incl. Supporting Information!) explain things in great detail:
  - Souza, Alessandri, Barnoud, Thallmair, Faustino, Grünewald, Patmanidis, *et al.*, *Nat. Methods* **2021**
  - Alessandri, Barnoud, Gertsen, Patmanidis, de Vries, Souza, Marrink, *Adv. Theory Simul.* **2022**

Take-home messages (II)

- Validation targets → use to refine the model if necessary

- Additional validation targets are application/molecule class-dependent.
  For some more inspiration see these reviews:
  - (**general**) Marrink, Monticelli, Melo, Alessandri, Tieleman, Souza, *WIRES Comput. Mol. Sci.* **2023**
  - (**material-oriented**) Alessandri, Grünewald, & Marrink, *Adv. Mater.* **2021**
  - (**general**) Marrink & Tieleman, *Chem. Soc. Rev.* **2013**

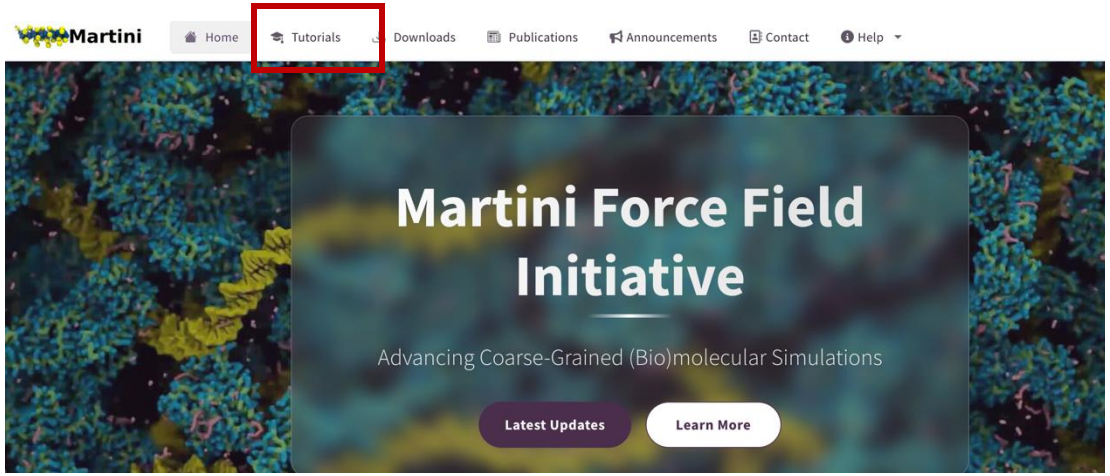
- More complex small molecules → more complex model constructions. It can be time-consuming. Try to use as much as possible constructions available in the already-developed models (see previous slide). If you develop new constructions, let us know!

- Explore use of emerging parametrization tools.

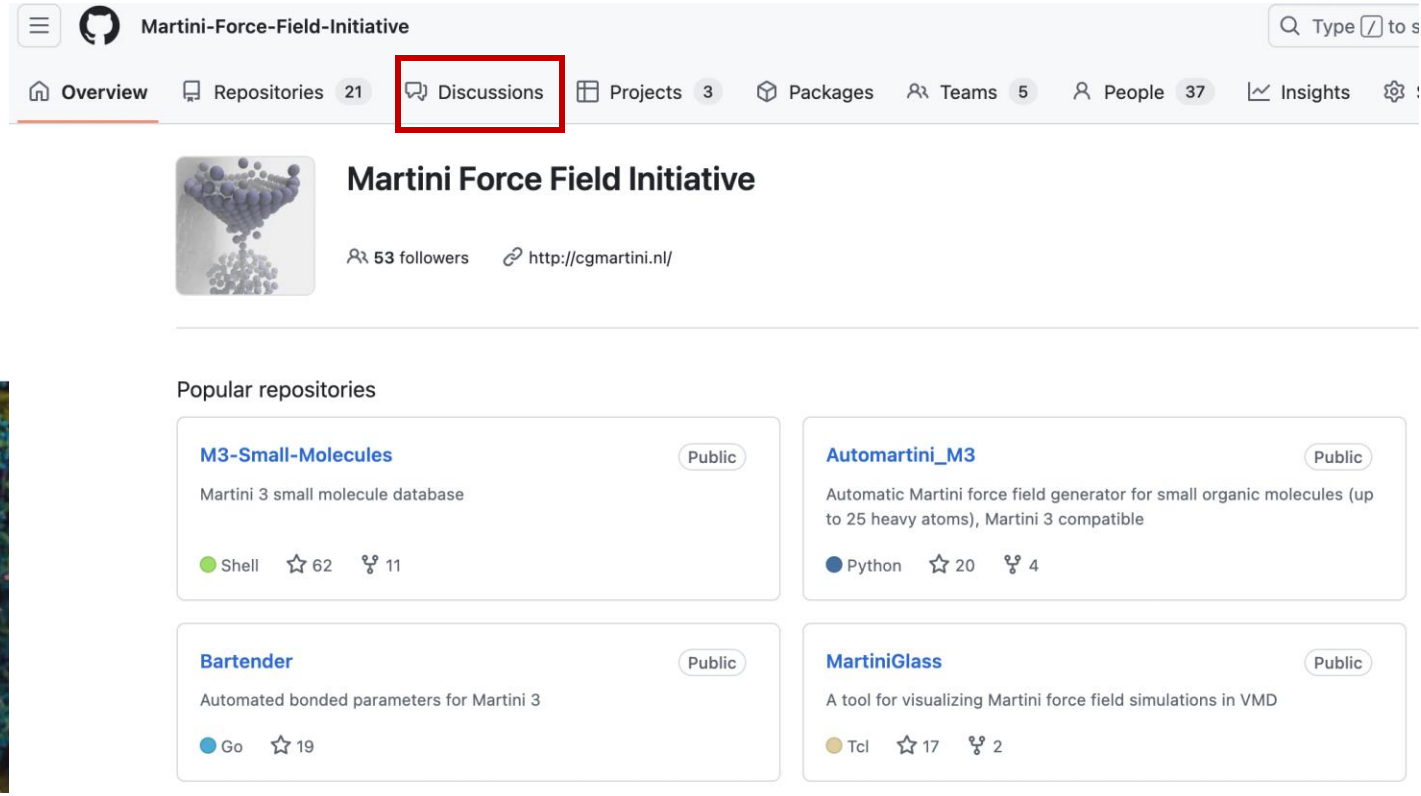
Take-home messages (III)

- More resources:

Martini cgmartini.nl



github.com/Martini-Force-Field-Initiative/



Tutorials this afternoon – 3 “flavors”

• **Parametrization of a new small molecule - (a) Classic Method**	**Description:** Learn how to parametrize new molecules for Martini
• **Parametrization of a new small molecule - (b) Semi-automated using Fast_Forward**	**Description:** Learn how to parametrize new molecules for Martini in a semi-automated way using Fast_Forward
• **Parametrization of a new small molecule - (c) Bartender for semi-empirical QM reference data**	**Description:** Learn how to parametrize new molecules for Martini using semi-empirical QM

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Gilberto Pereira
…

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