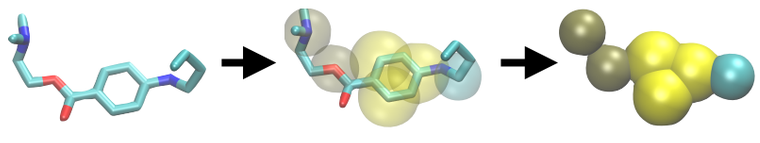
High-throughput screening of drug-membrane thermodynamics

We introduce an importance sampling of chemical space via high-throughput MD simulations of the coarse-grained (CG) Martini model [1], in order to investigate the physical and chemical properties of small molecules inserted in a phospholipid bilayer. This approach allows us to identify linear relationships between key features of the potential of mean force and the water/oil partitioning of a compound [3]. We show that the results are representative of the transmembrane behavior of ~500,000 small molecules due the many-to-one mapping introduced by coarse-graining. We compare the coarse-grained predictions with atomistic simulations results by introducing a multiscale sampling technique which leverages CG configurations in order to enhance the sampling of the atomistic system [4].

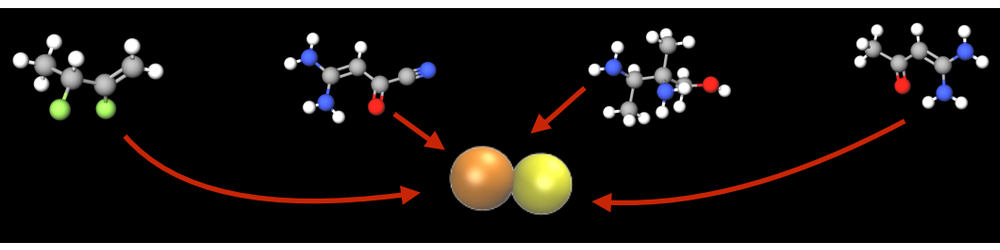
R. Menichetti*,[a], K. H. Kanekal*, K. Kremer* and T. Bereau*

MAX-PLANCK-GESELLSCHAFT

WHY MARTINI?

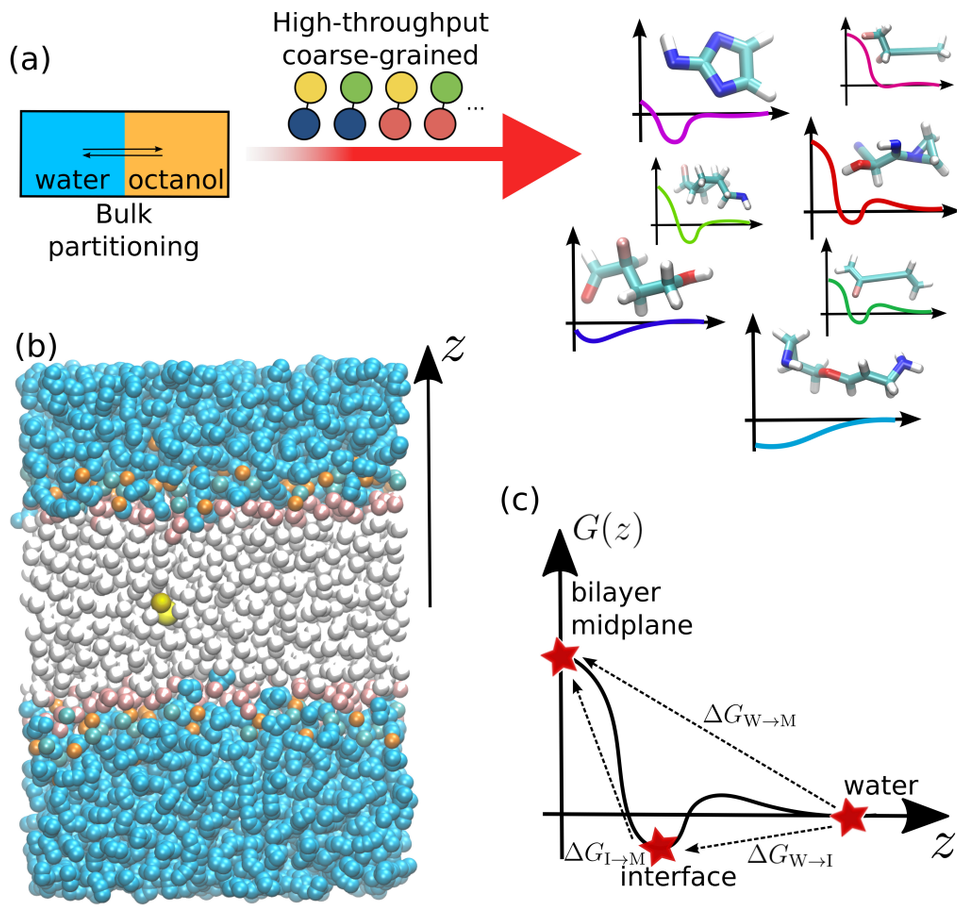


1) Smoother (free) energy landscape

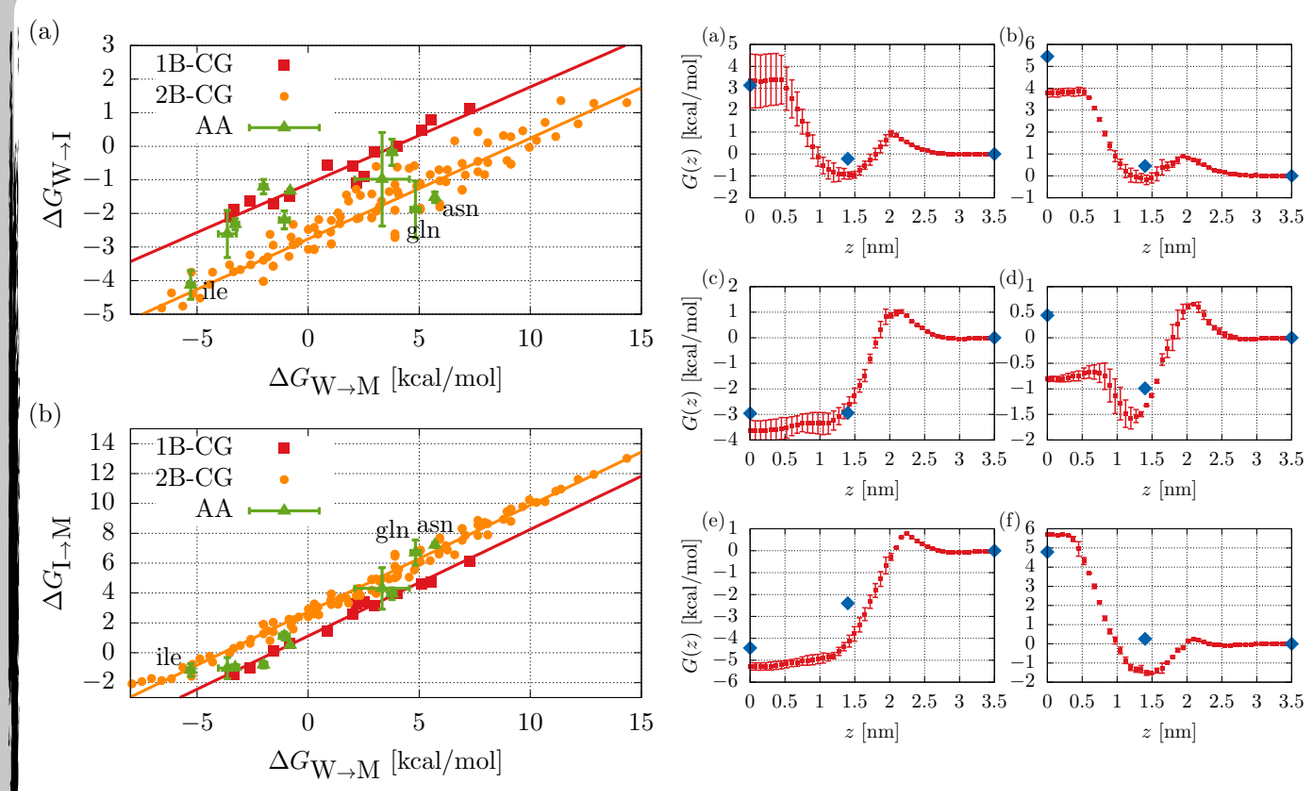


2) Reduced chemical space

SYSTEM



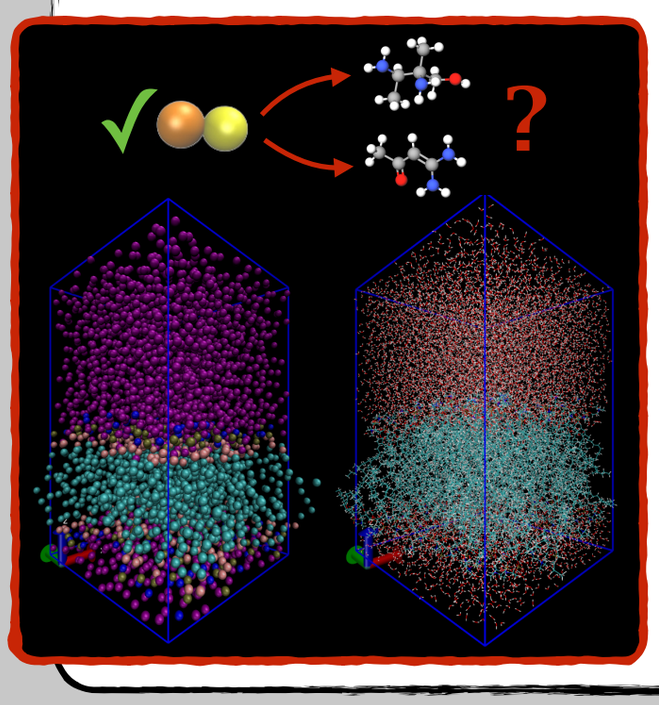
LINEAR RELATIONS [3]



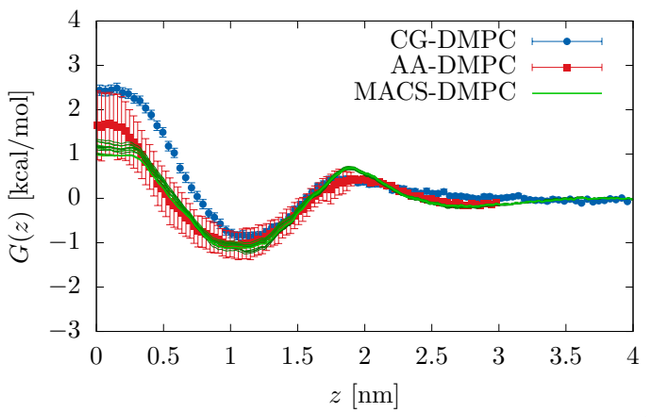
Linear relations between interfacial free-energy barriers along the potential of mean force and water/oil partitioning.
Inexpensive prediction for more than 500,000 compounds.

BACK TO ATOMISTIC

Efficient phase-space sampling by leveraging coarse-grained simulations [4]

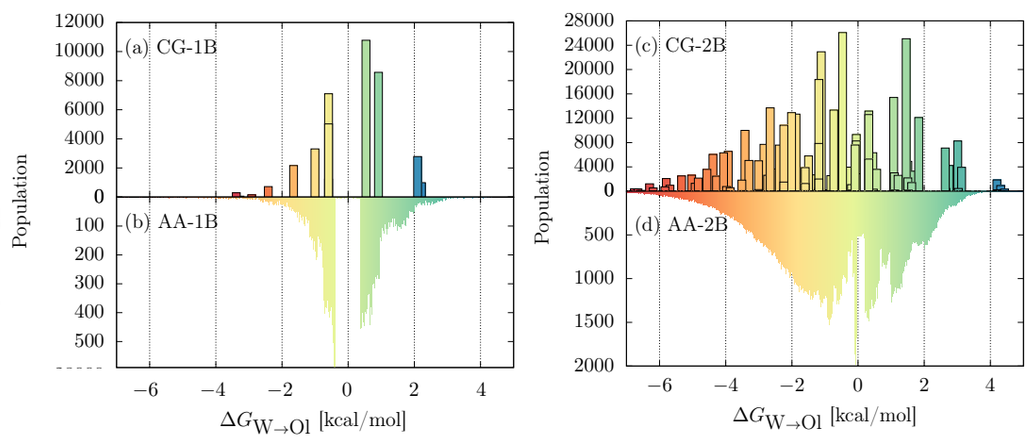


1) Select a set of **uncorrelated** snapshot from the CG trajectory.
2) Backmap each CG configuration onto atomistic.
3) Run a set of **short** atomistic simulations.
4) Average over the set.



COARSE-GRAINING CHEMICAL SPACE

Automated parametrization of the Martini force-field [1][2] for coarse-graining ~500,000 small molecules.



- Many compounds map onto one CG representation.
- Discrete number of Martini [1] bead types coarsens variety of chemical groups.

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REFERENCES:
[1] S. J. Marrink et al., J. Phys. Chem. B **111**, 7812 (2007).
[2] T. Bereau and K. Kremer, J. Chem. Theory Comput. **11**, 2783 (2015).
[3] R. Menichetti, T. Bereau et al., J. Chem. Phys. **147**, 125101 (2017).
[4] R. Menichetti, K. Kremer and T. Bereau, Biochem. Biophys. Res. Commun. (in press) doi: https://doi.org/10.1016/j.bbrc.2017.08.095 (2017).

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