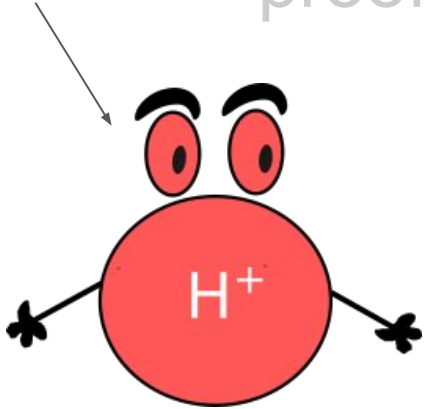
university of groningen

(A) Titratable Martini model

proof of concept and future directions



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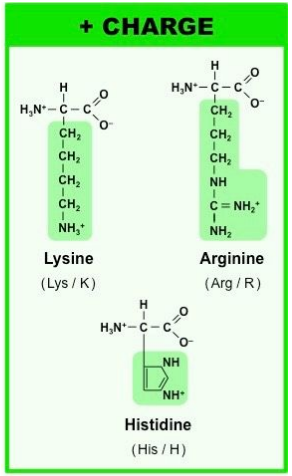
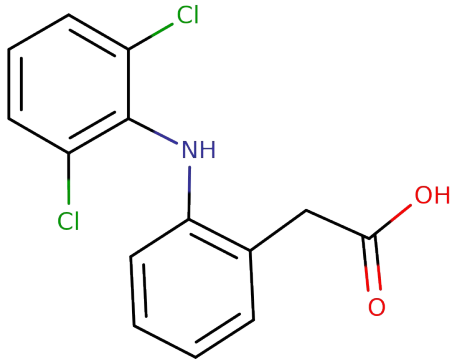
Many thanks to: Siewert-Jan, Paulo, Jonathan, Alex, Peter, Haleh

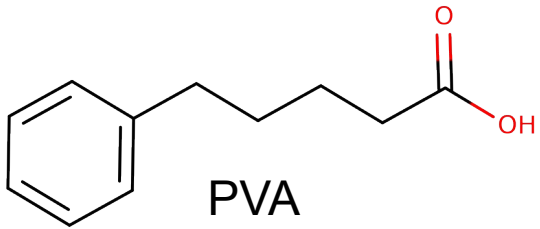
Why should we care about pH effects?



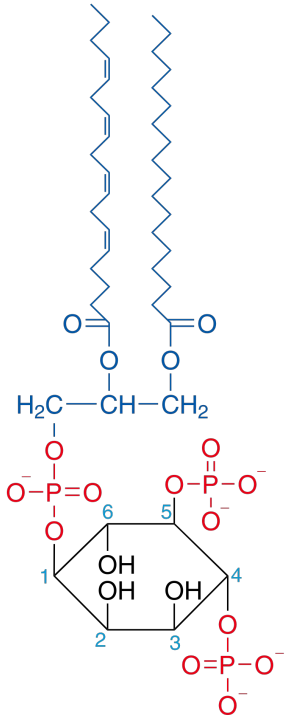
Amino-Acids



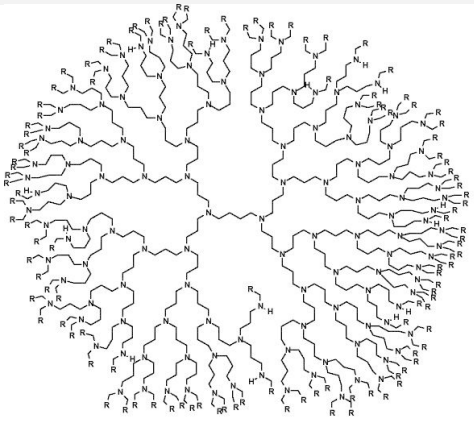
Diclofenac



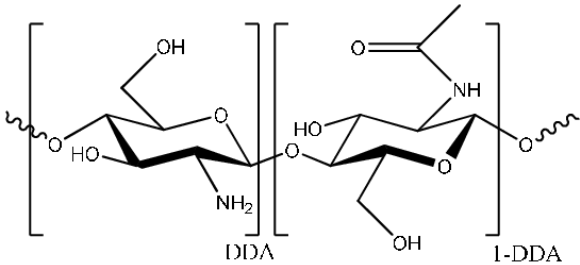
PVA



PIP2-lipid



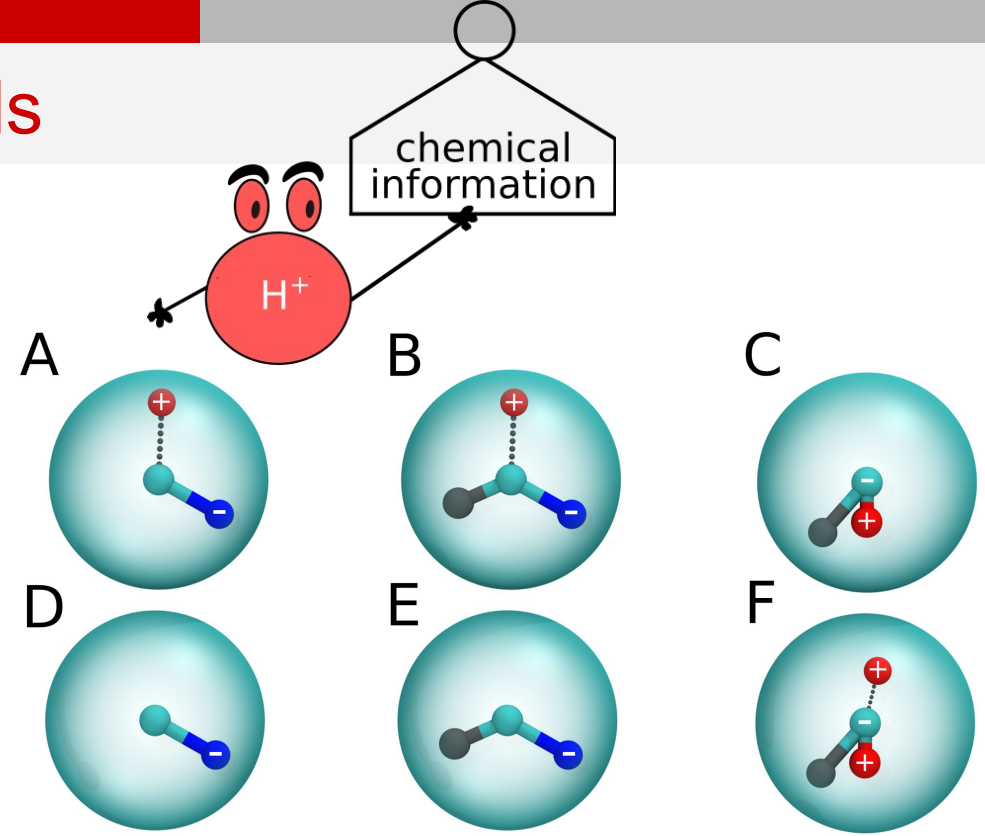
Poly(propylene imine)



Chitosane

Titratable Martini Beads

- proton bead as carrier of chemical information
- reversibly bind proton bead
- dummy beads assist in proton binding
- acids become charged upon deprotonation
- bases become neutral upon protonation

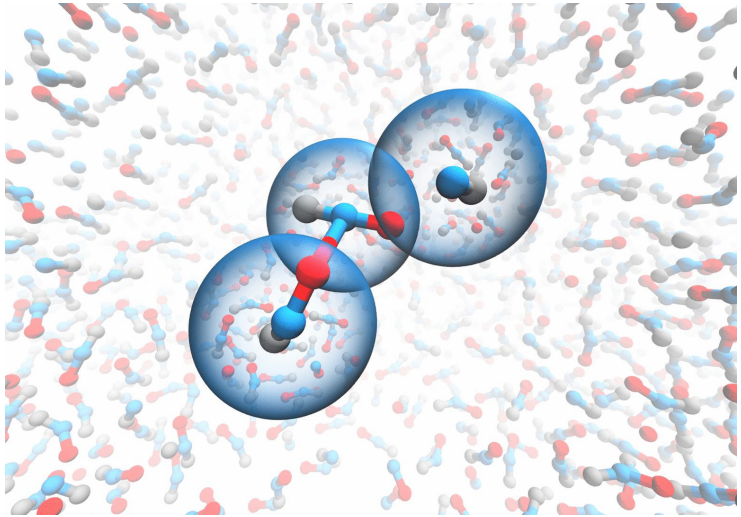


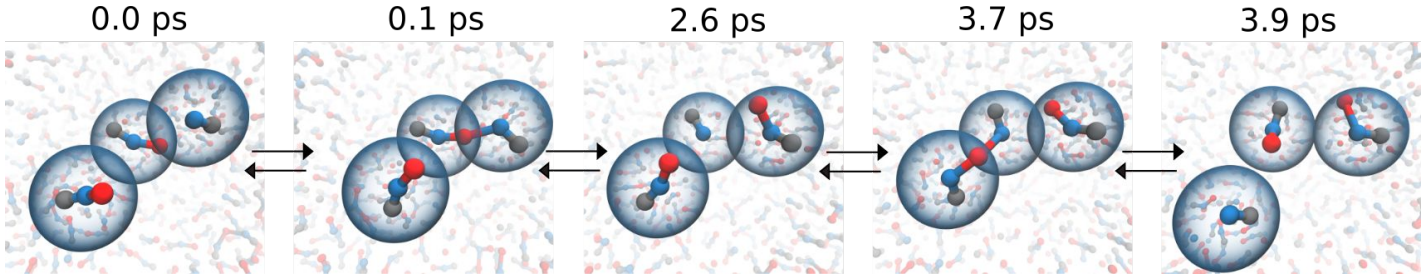
A: neutral water B: neutral acid C: neutral base

D: charged water E: charged acid F: charged base

Proton hopping in Martini water

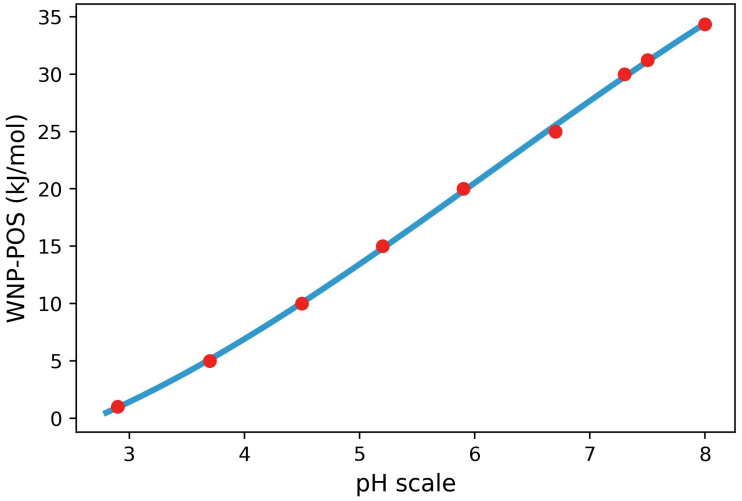
- Dynamic exchange of protons in Grauthauss like fashion
- Fast proton transport allows for fast equilibration





Titratable Martini pH: Inversion of reasoning

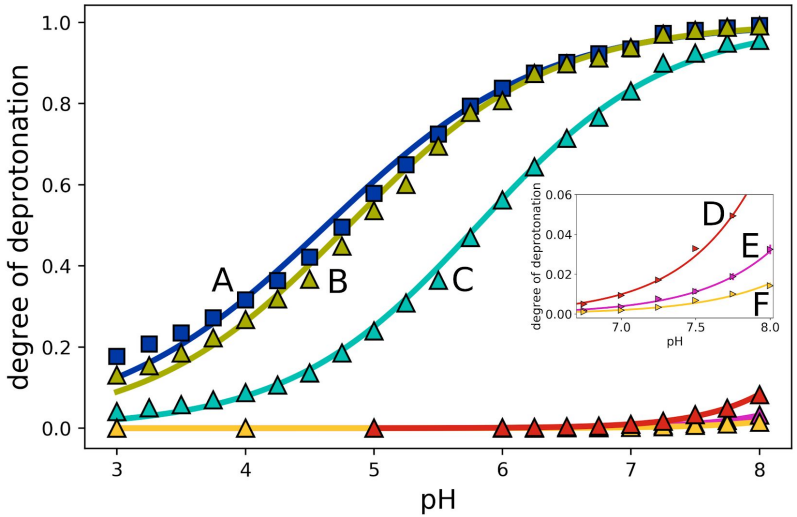
- increase pH -> increase of concentration of H3O+
- pH is defined by change in proton-water interaction (i.e. change availability)
- Properties of pure water retained:
  - Solvation free energies of neutral beads
  - Density within 10%
  - Surface tensions slightly improved
  - PC bilayer properties essentially same after Q-bead readjustment

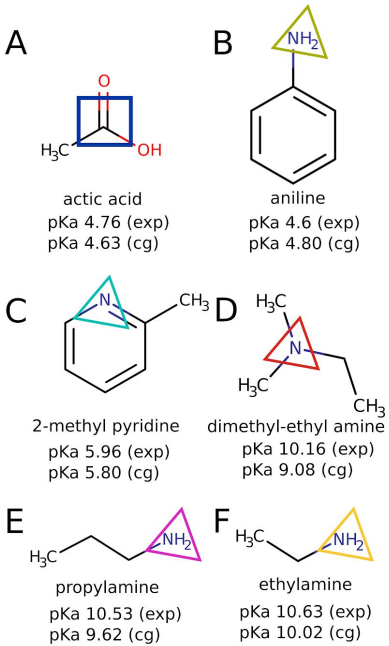


Titratable Beads: Acids and Bases

- 5 building blocks beads represent different tiratable fragments
- Match pKa by finding the best proton titratable bead interaction
- Interaction with dummy beads generic of acids/bases

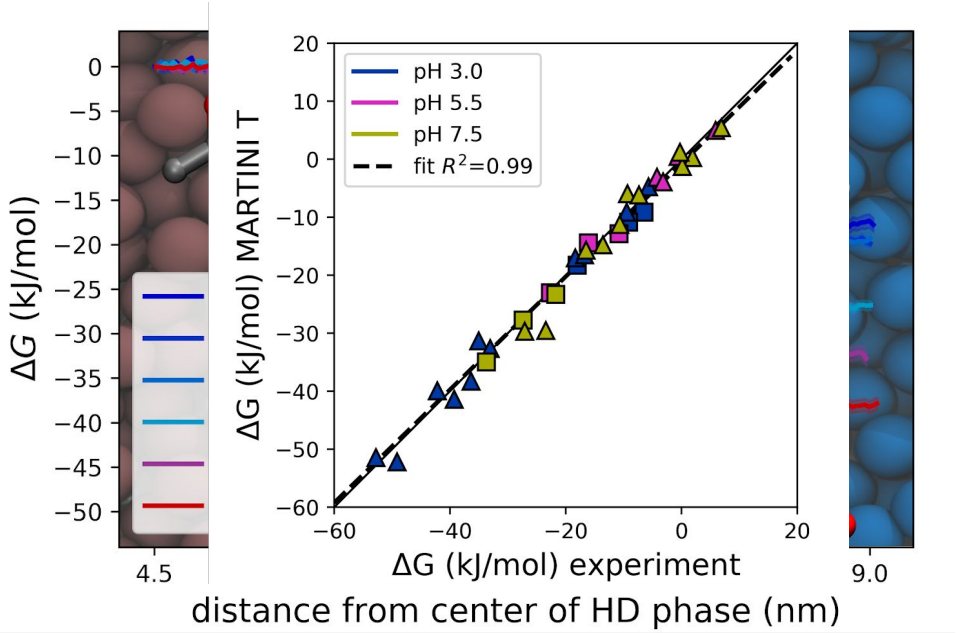
- Qualitative trends in pKa curves well reproduced
- Curves are somewhat stretched
- Different interaction with proton bead -> adjust water interaction





Apparent free energy of Transfer

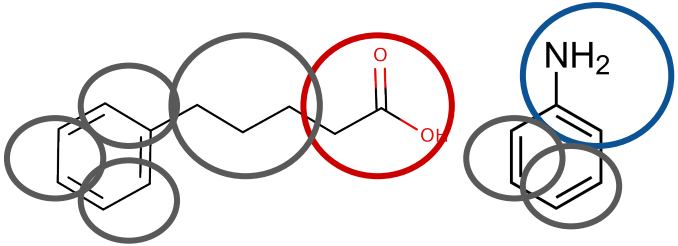
- 5 building block beads adjusted to match pH-dependent free energy of transfer (i.e. distribution coefficient instead of partition)
- pH-dependent interactions with water
- 12 additional compounds tested
- Characteristics:
  - Mean absolute error: 1.75 kJ/mol
  - R^2 0.98

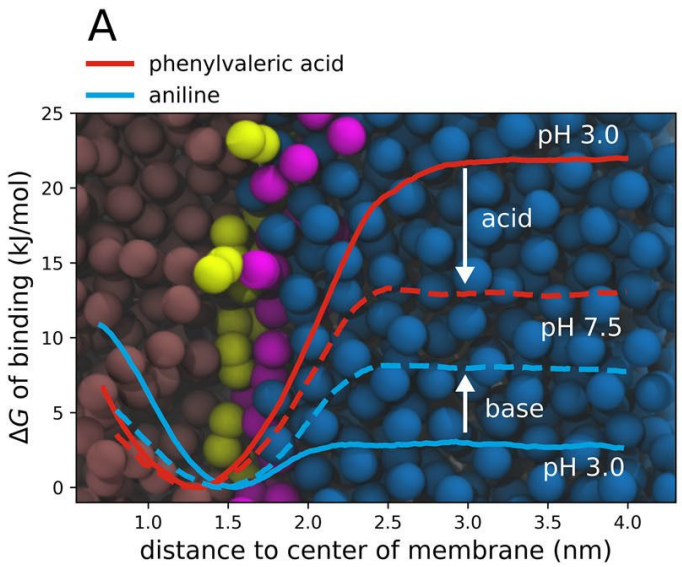


Membrane Affinities

- good qualitative description
  - Acetic-Acid at pH7.5 from unbound to mostly bound
  - Aniline opposite trend
  - Trends preserved for acids and bases

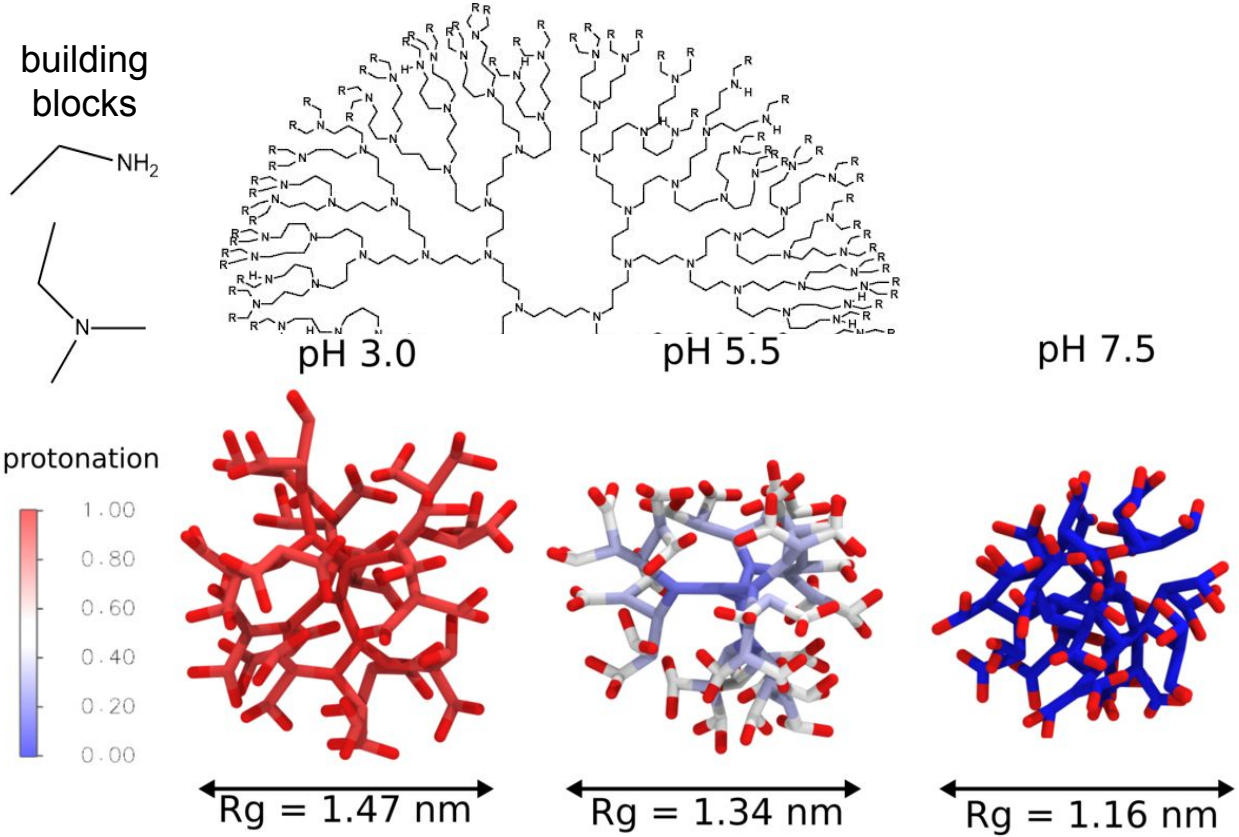
- Membrane affinity for 11 compounds:
  - Correlation (R^2=0.91)
  - MAE 3.48 kJ/mol
  - Predicting affinities for ionic compounds is hard even for established methods





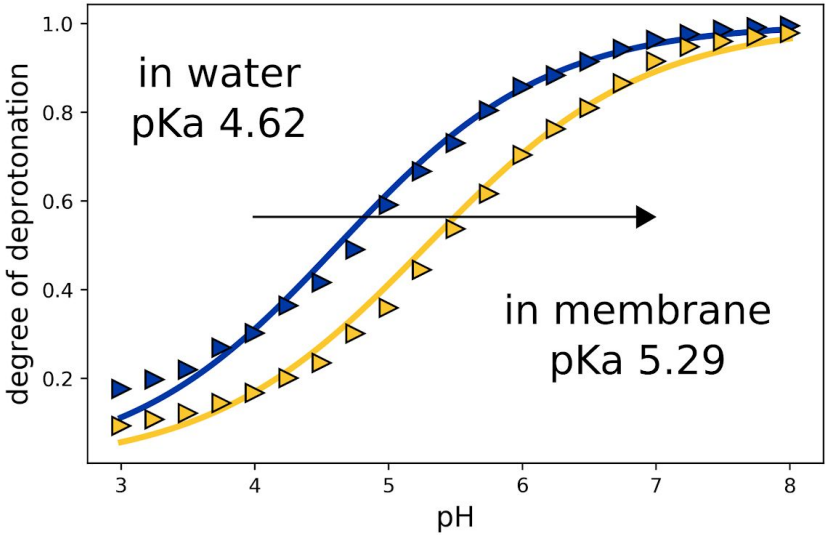
Titration of a dendrimer with Martini

- 126 titratable beads
- Change in protonation from 100% to ~50% from pH 3 to pH 7.5
- Experimental change is also ~50%[1]
- 26% reduction in radius of gyration
- Predict total charge within 12% of exp.



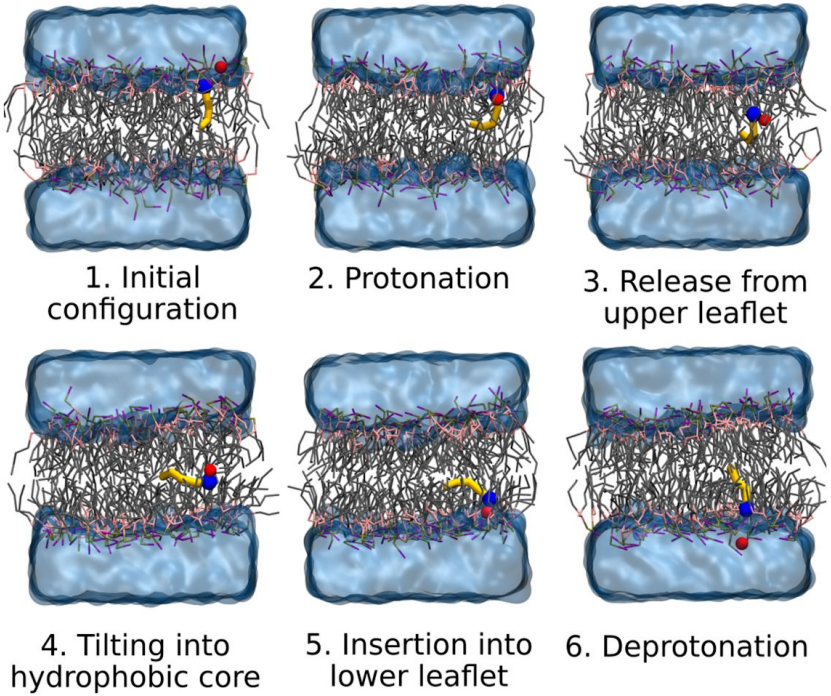
[1] Duijvenbode et al. (1998)

Oleic Acid Flip-Flop using Martini

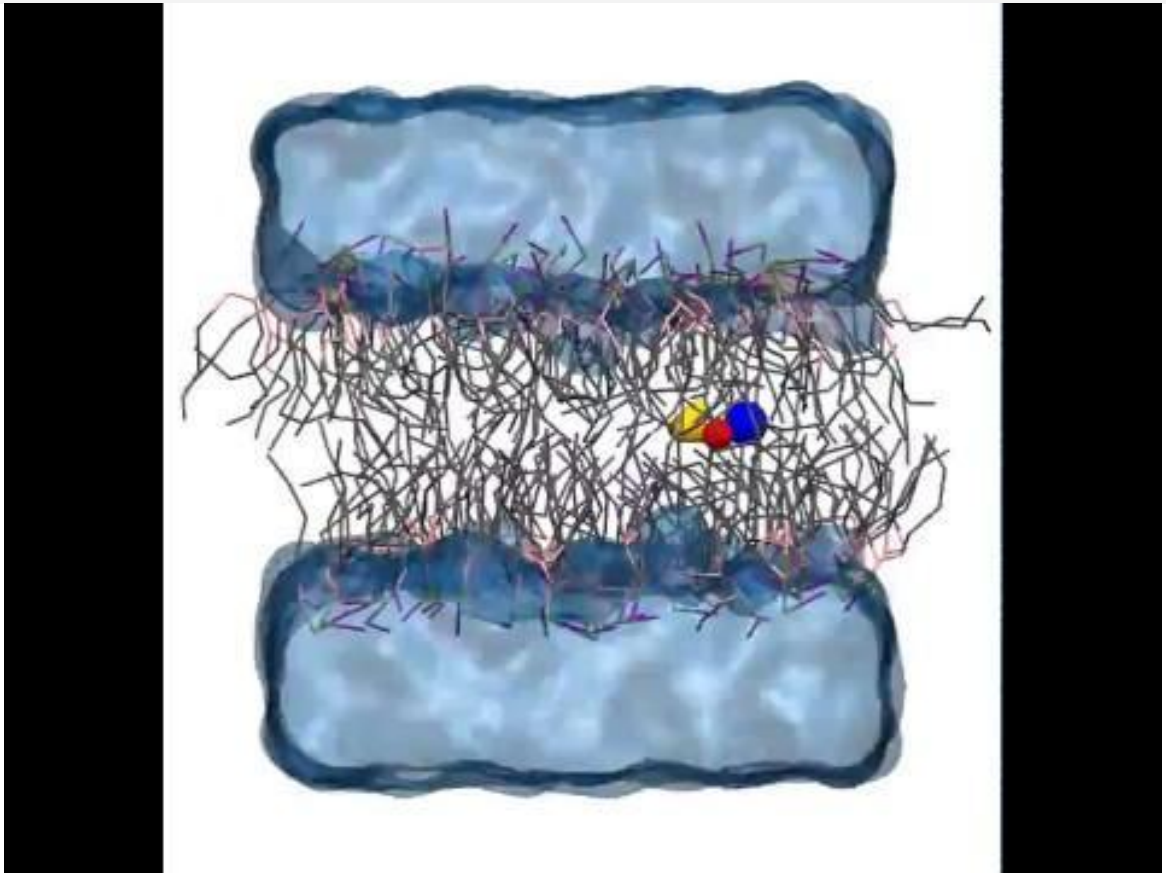


Experimentally ~1-2 pKa units

About 70% oleate ions

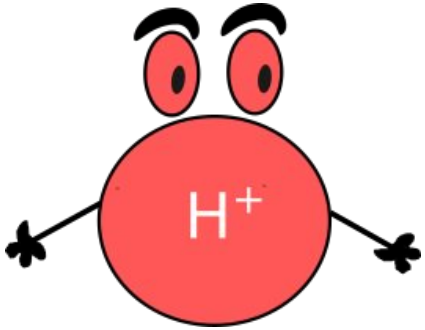


Oleic Acid Flip-Flop with Martini



Conclusion

- Incorporate effects of titration in simple and intuitive manner
- Keep simplicity of Martini model
- Comparatively cheap and transferable simulation protocol
- Limited by accessible pH range, some problems with primary amine
- Complex molecule properties emerge by stitching together building-blocks
- Not a simple interpolation of FF parameters, space for controlled fine-tuning



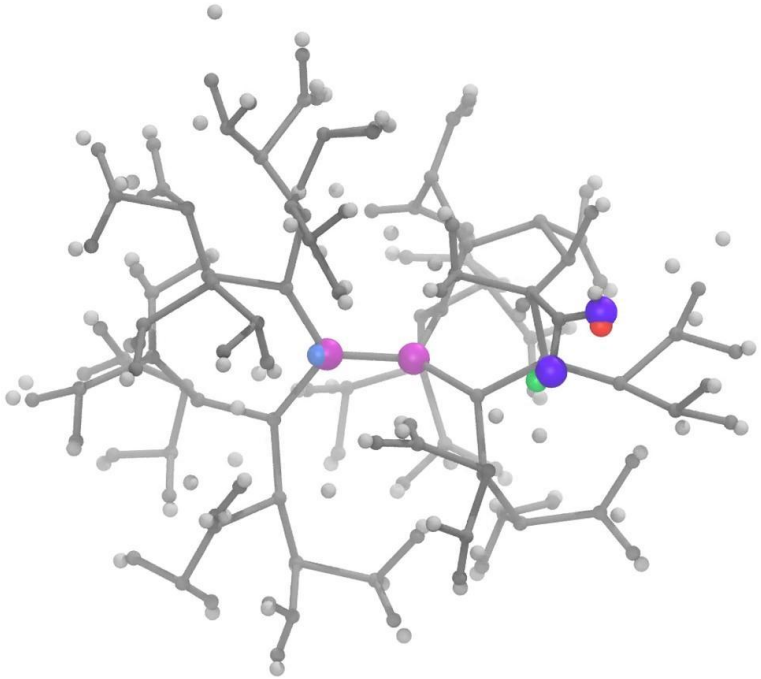
Future directions for titratable Martini

1. Improve titration curves
2. Systematic rules how to build larger molecules
3. Titratable polymers
4. Titratable proteins
5. Titratable Martini as medium for other reactions

Many Thanks to:

- Siewert
- Paulo
- Jonathan
- Peter
- Haleh
- And everyone else

Example 1: Titration of a dendrimer with MARTINI



Explicit Protons in coarse-grained models

"When a distinguished but elderly scientist states that something is possible, he is almost certainly right. When he states that something is impossible, he is very probably wrong." (Arthur C. Clarke)

“Sure it will work”, Siewert-Jan Marrink

Apparent Free Energy of Transfer CG-case

Acid

$$\Delta G_{transf.}(pH) \approx \begin{cases} dG^{neutral}_{transf.} - RT \times Log(10) \times n \times (pKa - pH) & pH > pKa \\ dG^{neutral}_{transf.} & pH \leq pKa \end{cases}$$

- Above pKa Acids are too hydrophobic if n < 1

Base

$$\Delta G_{transf.}(pH) \approx \begin{cases} dG^{neutral}_{transf.} + RT \times Log(10) \times n \times (pKa - pH) & pH < pKa \\ dG^{neutral}_{transf.} & pH \geq pKa \end{cases}$$

- Below pKa Bases are too hydrophobic if n < 1