MARTINI WORKSHOP 2017

SELF-ASSEMBLY OF PEPTIDES AND PEPTIDE DERIVATIVES USING MARTINI SIMULATIONS

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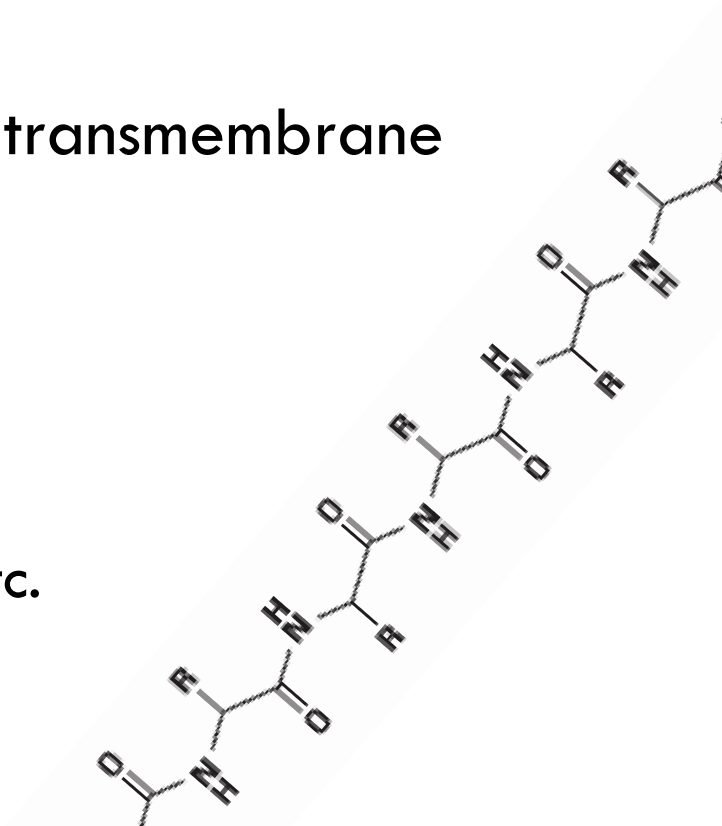
Proteins vs peptides

- Peptides are not (always) the same as small proteins
  - No tertiary structure on their own
  - Typically <10 amino acids
- On their own: biological functions (transmembrane helices, ligands etc.)
- In abundance: materials
  - Undesired: amyloid plaques
  - Desired: hydrogels, vesicles, tubes etc.



Peptides as materials

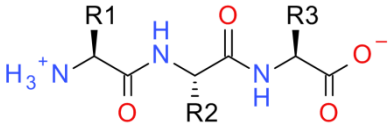
a new way to look at biomolecules

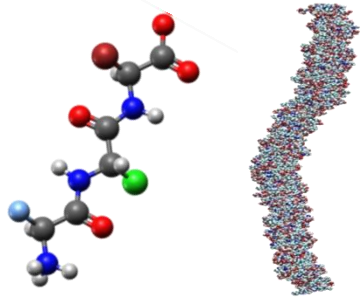
Short peptides:

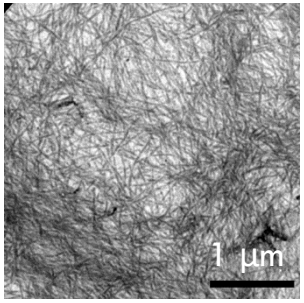
- Assemble at low concentrations
- Are biocompatible and biodegradable
- Are cheap to produce
- Are hard to see → simulations

e.g. hydrogels

$A_1A_2A_3$



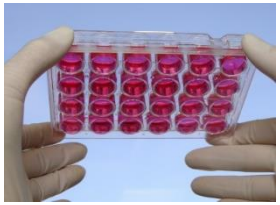




Applications

- Vegetarian replacement of gelatin
- Creams and cosmetics

- Capsules for drug delivery
- Wound dressing



- Encapsulation of catalysts
- 3D Cell culture

biogelx

Nano-FM BV

Understanding vs. predicting peptides

1. You see
2. You simulate
3. You understand

OR

1. You understand
2. You simulate
3. You see

Simulating short peptides: **why use Martini?**

Simulations, because:

- The assembly path is informative
- Too many possibilities to try in the lab

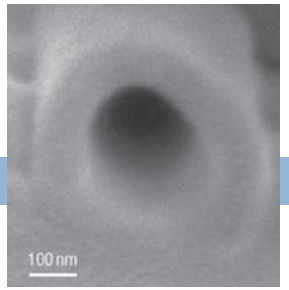
Coarse-graining, because

- Self-assembled structures contain MANY molecules
- Self-assembly takes time

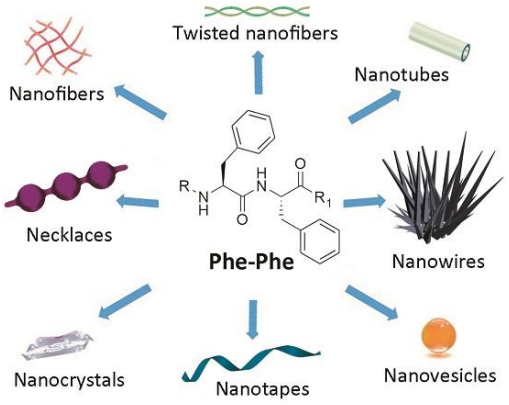
Martini, because

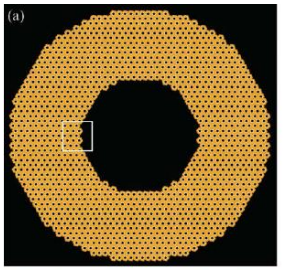
- Martini was "born this way"
  - Whimley-White peptides
  - Nanostructures through amphiphilicity = oil-water partitioning

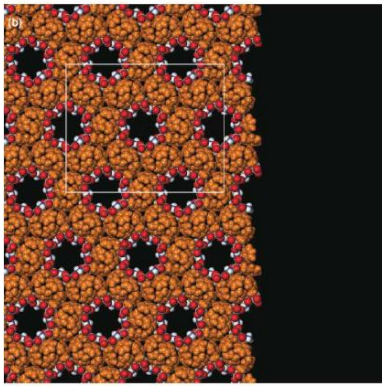
Diphenylalanine

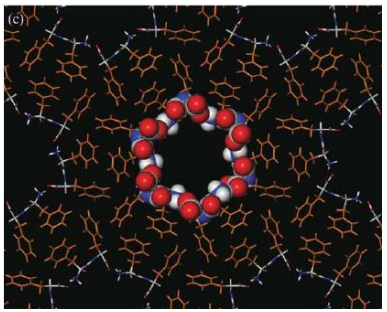


- Forms nanotubes in water (Gazit, Science 2003)
- Crystal structure known (Görbitz, 2006)
  - From chemical vapour deposition
- Can we simulate it?
  - Structure in water
  - Dynamics

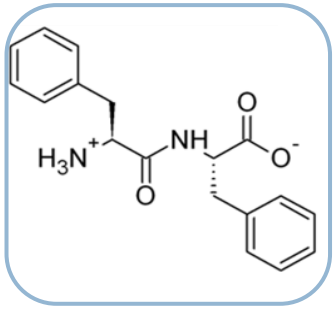






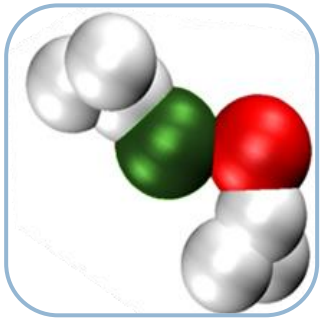


General workflow



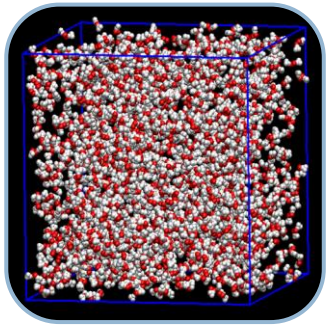
- Atomistic coordinates

Martinize.py



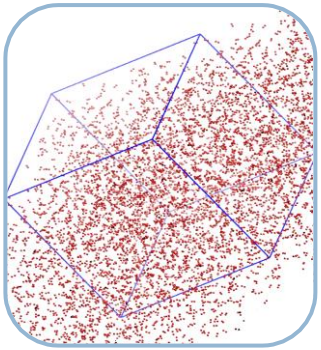
- Coarse-grained coordinates and mapping

solvate



- Initial solvated coordinates

mdrun



- Final coordinates and trajectory

Examples of simulated peptides

- Ultrashort peptides
  - FF, and other dipeptides [1,2]
  - All tripeptides [3,4]
- Peptide derivatives (increasing the amphiphilic nature)
  - 3-armed BTA [5,6]
  - Fmoc-peptides [6]
  - Peptide nanocarriers [7]
- Amyloid peptides
  - Alzheimer's [8]
  - hIAPP [9]

(1) Frederix, P. W. J. M.; Ulijn, R. V.; Hunt, N. T.; Tuttle, T. *J. Phys. Chem. Lett.* **2011**, *2* (19), 2380.
(2) Guo, C.; Luo, Y.; Zhou, R.; Wei, G. *ACS Nano* **2012**, *6* (5), 3907.
(3) Frederix, P. W. J. M.; Ulijn, R. V.; Tuttle, T. et al., *Nat. Chem.* **2015**, *7* (1), 30.
(4) Abul-Haija, Y. M.; Scott, G.; Sahoo, J. K.; Tuttle, T.; Ulijn, R. *Chem. Commun.* **2017**.
(5) Bochicchio, D.; Pavan, G. M. *ACS Nano* **2017**, *11* (1), 1000.
(6) Piskorz, T. K.; van Esch, J. H. unpublished.
(7) Rad-Malekshahi, Bonvin, Weingarth et al., JACS **2015**, 137 (24), 7775.
(8) Seo, M.; Rauscher, S.; Pomès, R.; Tieleman, D. P. *J. Chem. Theory Comput.* **2012**, *8* (5), 1774.
(9) Pannuzzo, M.; Raudino, A.; Milardi, D.; Rosa, C. L.; Karttunen, M. *Sci. Rep.* **2013**, *3*, srep02781.

To assemble or not to assemble

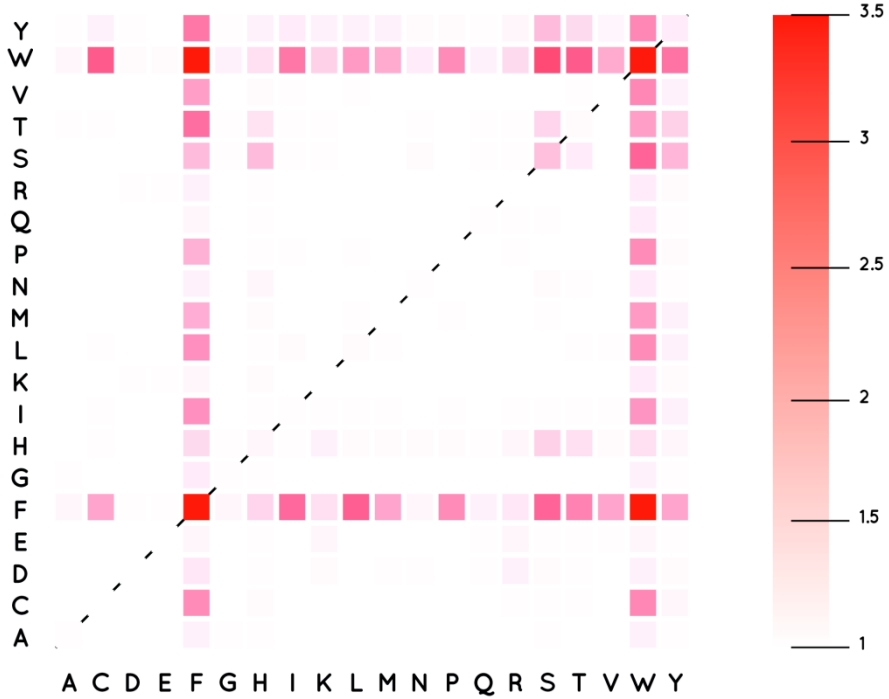
A peptide is useful when it

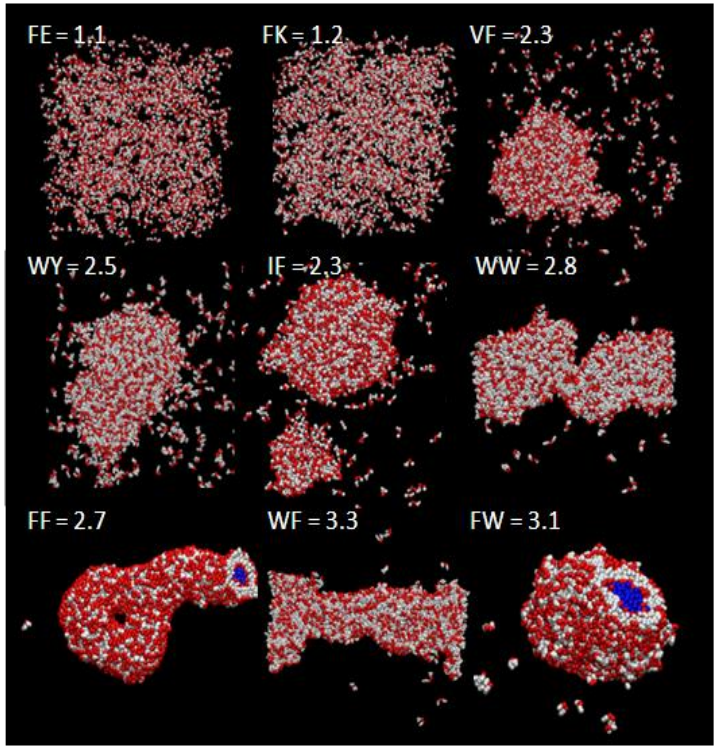
1. … is first of all soluble in water
2. … after some time/change, assembles in water
3. … forms fibrous networks, tubes or vesicles

4. … is biocompatible
5. … gives a transparent material

Results – does it assemble?

- Study of all 20 x 20 dipeptides
- AP score = $SASA_{begin}$ / $SASA_{end}$

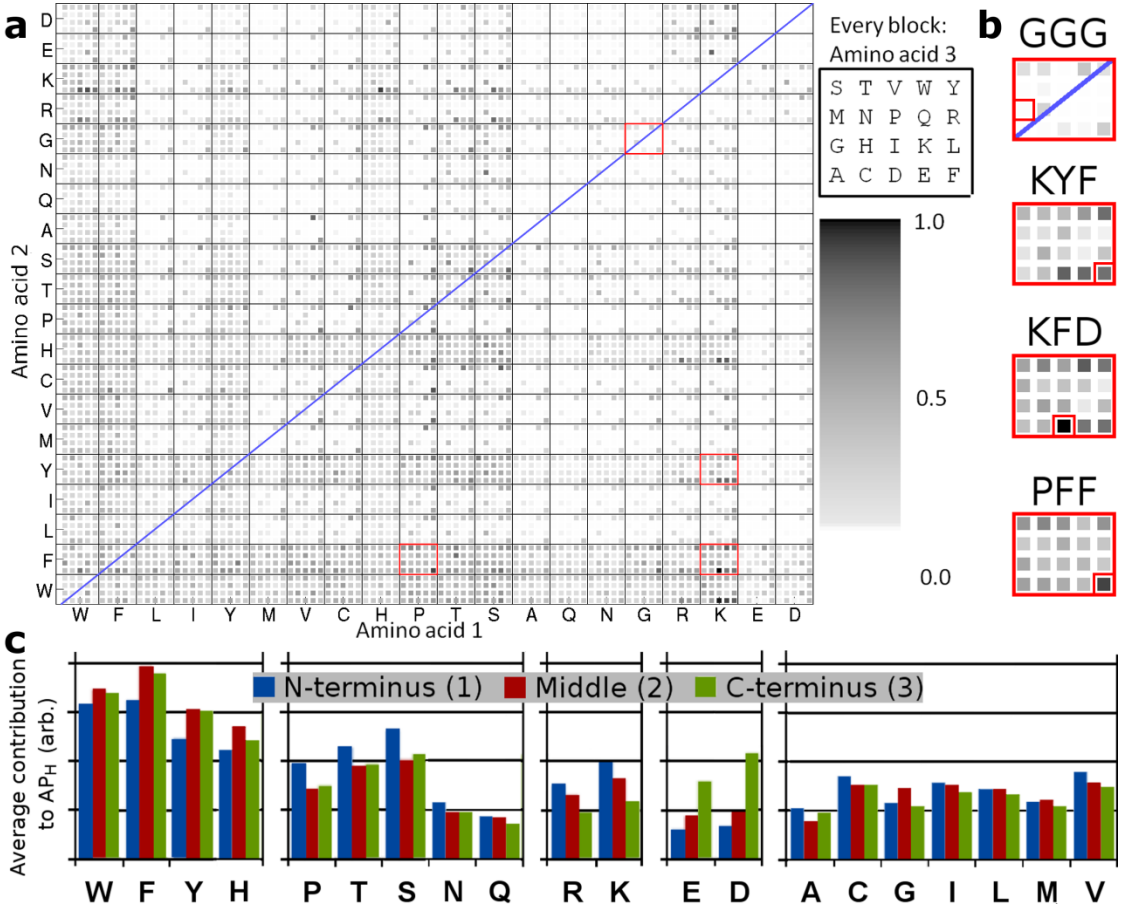




(1) Frederix, P. W. J. M.; Ulijn, R. V.; Hunt, N. T.; Tuttle, T. *J. Phys. Chem. Lett.* **2011**, *2* (19), 2380.

Tripeptides

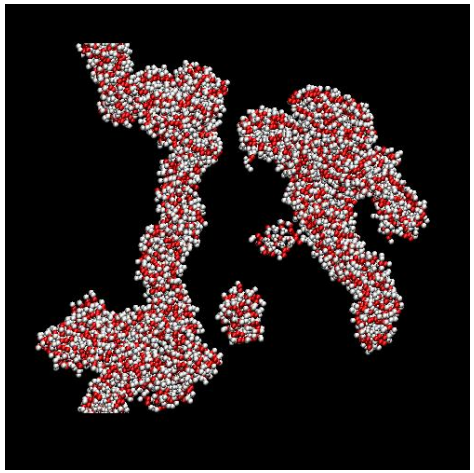
8,000 tripeptides, ~100,000 CPU hours

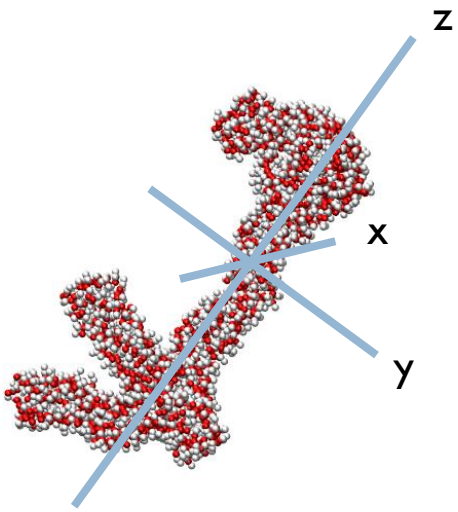


(3) Frederix, P. W. J. M.; Scott, G. G.; Abul-Haija, Y. M.; Kalafatovic, D.; Pappas, C. G.; Javid, N.; Hunt, N. T.; Ulijn, R. V.; Tuttle, T. *Nat. Chem.* **2015**, *7* (1), 30..

Results – is it fibrous?

- Extraction of largest cluster of molecules
- Calculation of the *moments of inertia*



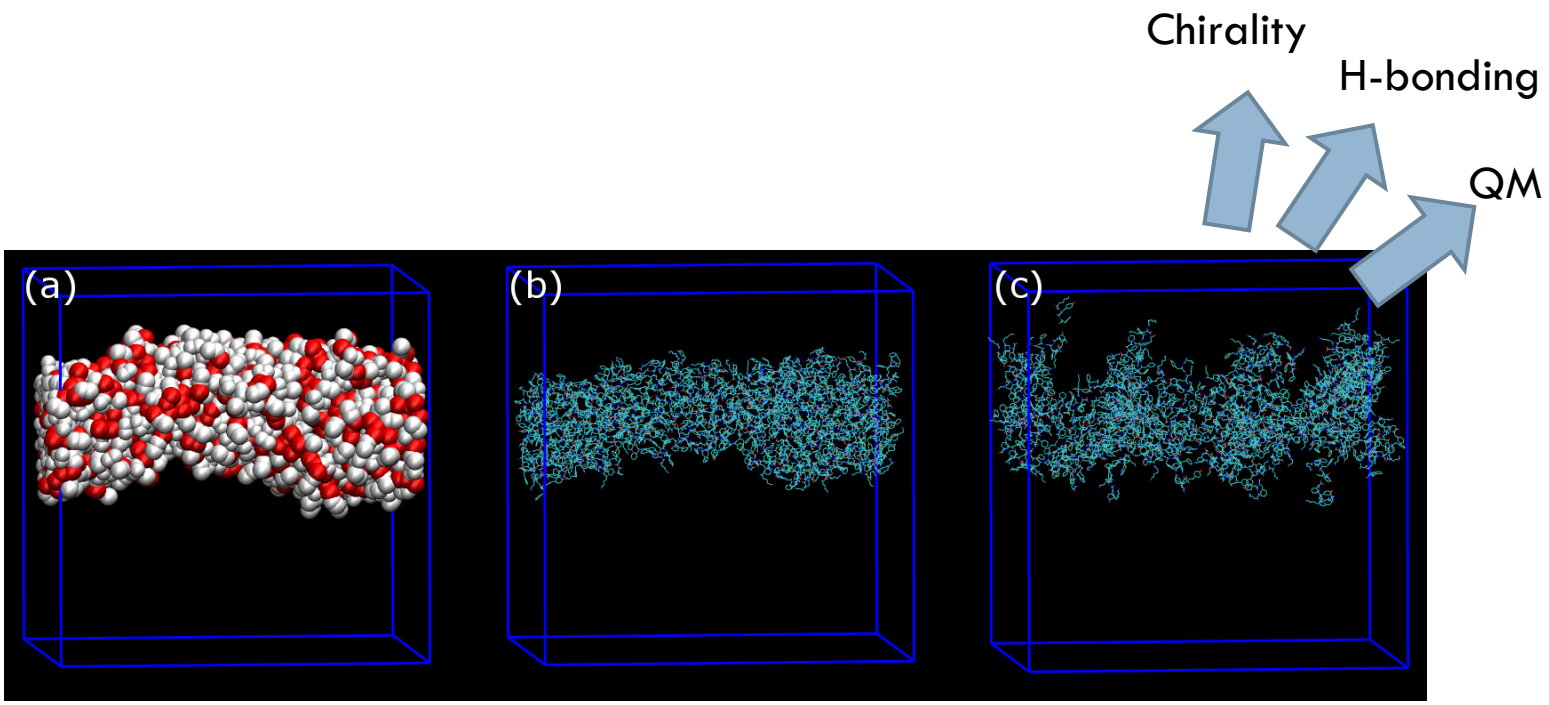


$I_z >> I_y \approx I_x$

↓

Fibrous

Backmapping



CG result | Backmapped AA | after equilibration

Frederix, Beljonne, Otto, Marrink et al., ACS Nano ASAP **DOI:** 10.1021/acsnano.7b02211

Useful tools and tutorials

Scripts

- Martinize
- Backward

Tutorials

- High-throughput peptide self-assembly
  - Learn automation creation of peptide coordinates, setup and running of simulations, and analysis.
  - See peptide behaviour under self-assembling conditions

Self-assembly: order without solids

Is it self-assembly or...

- Random aggregation
- Precipitation
- Crystallization

Hydrophobic things aggregate, but often we need partially hydrophilic (amphiphilic) molecules, H-bonds and / or charge-charge interactions to make well-defined nanostructures!

But wait, …

- What about my protecting groups?
  - No parameters available for amino acid modifications on termini or side chains. Yet. Look in the Martini tables!

- What about my ions and (co-)solvent?
  - Ions are rudimentary in Martini 2.2 and 2.2P, all ions are the same, except from the charge.
  - Water-oil partitioning is right, other solvents should be parametrized with care!

But wait, …

- What about my critical aggregation concentration?
  - Assembly simulations often run > 10 times concentrated
- What about my long peptide?
  - Secondary structure becomes more and more important
    - Atomistic simulations to sample conformational space helpful
  - Some peptides may even have tertiary structure
  - Martinize.py secretly adds elastic bonds to extended structures of peptides ≥ 4 amino acids

Summary

- Peptide self-assembly, especially at the CG level, is dominated by amphiphilicity, or thermodynamics, which Martini is good at.

- For simple peptides, the analysis and understanding of the simulations is the hardest part!