Hybrid Particle-Field Model for Conformational Dynamics of Peptide Chains

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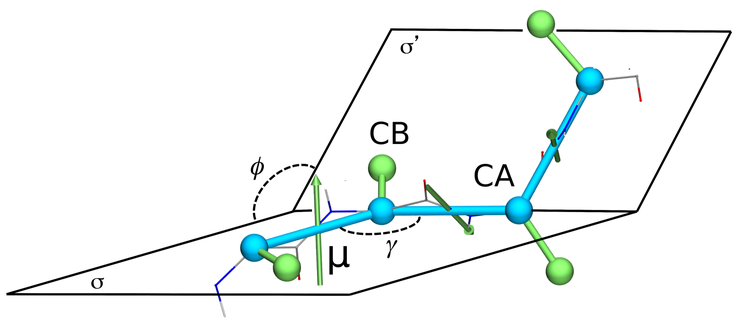
Abstract

We propose the first model of a polypeptide chain based on a hybrid-particle field approach. The intramolecular potential is built on a two-bead coarse grain mapping for each amino acid. We employ a combined potential for the bending and the torsional degrees of freedom that ensures the stabilization of secondary structure elements in the conformational space of the polypeptide. The intermolecular interactions comprising both the solute and the explicit solvent are treated by a density functional based mean-field potential. Through a series of molecular dynamics simulations, we demonstrate that the model is able to capture all the main features of polypeptides.

The model



The backbone of the polypeptide is represented by CA beads. The side chain beads and dipoles, CB and μ are reconstructed using a virtual site approach from the positions of three consecutive CA. The potential energy is given by:

$$V_{\text{model}} = V_{\text{bond}} + V_{\gamma,\phi} + V_{\text{LJ}} + V_{\mu,\mu} + W[\{\rho\}].$$

Here the first four terms models intramolecular interactions of a single polypeptide, and W models intermolecular interactions between the polypeptides and with the solvent.

Conclusions and outlook

Formation of a hydrophobic core drives the assembly of simple tertiary and quaternary structures.[1] Sequences with mixed hydrophobic/hydrophilic patterns localize and fold differently at water/lipid interfaces than in the bulk solvent.

The model can be extended by tailoring force fields for each of the 20 amino acids, focusing on the χ-interaction matrix and propensity potential. Furthermore, the electrostatic force calculation can be improved by using the recently developed hybrid particle-field method with electrostatics.[2,3]

References

[1] Bore et al. *J. Chem. Theory Comput.* **2018**, 14, 1120-1130.
[2] Kolli et al. *J. Chem. Theory Comput.*, **2018** 14, in press.
[3] Zhu et al. *Phys. Chem. Chem. Phys.* **2016**, 18, 9799

Acknowledgements

The authors acknowledge the support of the Norwegian Research Council through the CoE Hylleraas Centre for Quantum Molecular Sciences (Grant n. 262695) and by the Norwegian Supercomputing Program (NOTUR) (Grant No. NN4654K).

Hybrid particle field

Interaction energy:

$$W = \int \mathrm{d}\mathbf{r} \left(\frac{\mathrm{k_B T}}{2} \sum_{\mathrm{ij}} \chi_{\mathrm{ij}} \rho_{\mathrm{i}}(\mathbf{r}) \rho_{\mathrm{j}}(\mathbf{r}) + \frac{1}{2\kappa} \left(\sum_{\mathrm{j}} \rho_{\mathrm{j}} - 1 \right)^2 \right).$$

Potential felt by particles of type i:

$$V_i^{\text{ext}}(\mathbf{r}) = \frac{\delta W}{\delta \rho_i(\mathbf{r})} = k_{\mathrm{B}} T \sum_j \chi_{ij} \rho_j(\mathbf{r}) + \frac{1}{\kappa} \left(\sum_j \rho_j(\mathbf{r}) - 1 \right).$$

The corresponding force is given by $\mathbf{F}(\mathbf{r}) = -\boldsymbol{\nabla} V_i^{\text{ext}}(\mathbf{r})$.

Modeling of amino acid hydrophobicity:

χ_{ij}	CA	$\mathrm{CB_P}$	$\mathrm{CB_H}$	$\mathrm{H_2O}$
CA	0	0	0	0
$\mathrm{CB_P}$	0	0	α	0
$\mathrm{CB_H}$	0	α	0	α
$\mathrm{H_2O}$	0	0	α	0

Subscripts H and P corresponds to hydrophobic and polar side chains. α controls hydrophobicity ($\alpha > 0$ is hydrophobic, and $\alpha \leq 0$ is hydrophilic).

Amino acid propensity

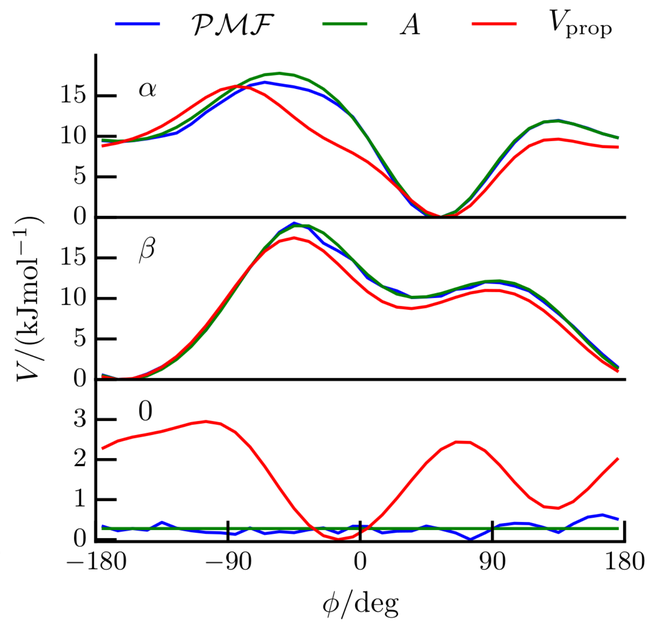
Combined bending and torsional potential:

$$V_{\gamma,\phi} = V_{\text{prop}}(\phi) + \frac{1}{2} k \left(\gamma - \gamma_0(\phi) \right)^2,$$

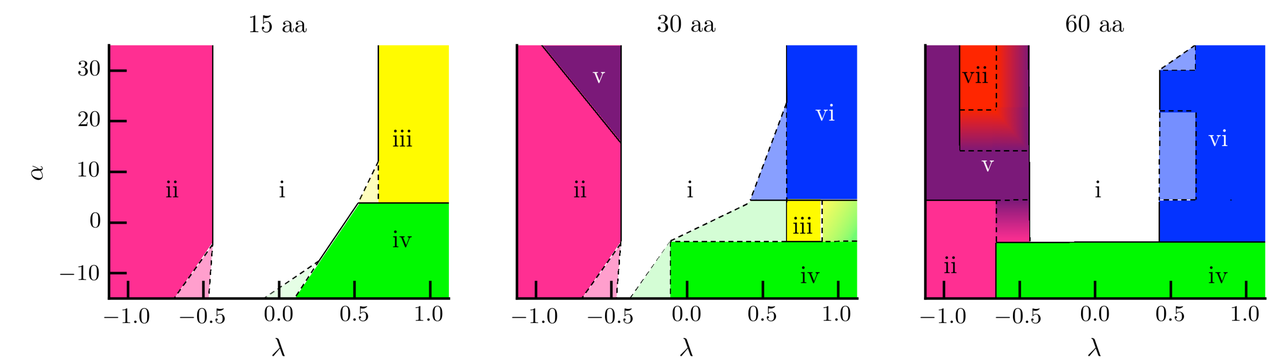
where $\gamma_0(\phi)$ is the Park-Levitt line.
Propensity is parametrized by λ:

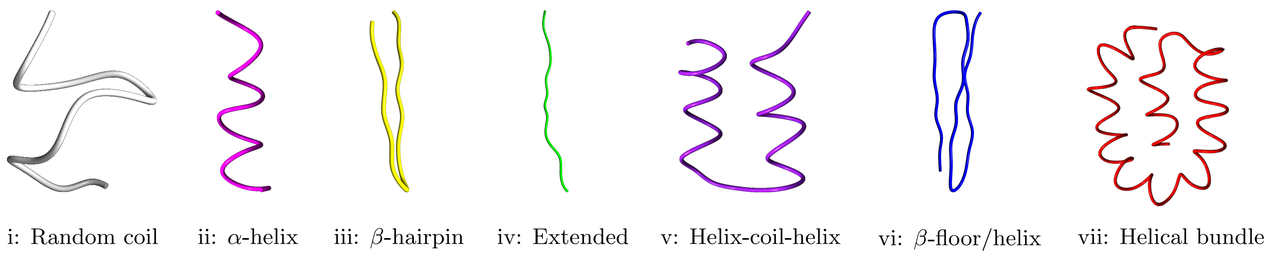
$$V_{\text{prop}}(\lambda, \phi) = \frac{1}{2} \left(|\lambda| - \lambda \right) V_\alpha(\phi) + \frac{1}{2} \left(|\lambda| + \lambda \right) V_\beta(\phi) + \left(1 - |\lambda| \right) V_0(\phi),$$

where $\lambda = \{-1, 0, 1\}$ corresponds to a peptide with propensity towards α-helix, random coil and β-structures.



Phase diagram - hydrophobicity and propensity





i: Random coil ii: α-helix iii: β-hairpin iv: Extended v: Helix-coil-helix vi: β-floor/helix vii: Helical bundle

Amphiphilic protein-membrane interaction