Design of reduced point charge models for proteins
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Introduction

Reduced point charge models (RPCMs) for proteins are obtained from topological analyses of smoothed charge density (CD) distribution functions. For each amino acid, the RPCMs involve two backbone charges and up to six charges on the side chain. RPCM-based molecular dynamics (MD) trajectories are compared to all-atom ones for Ubiquitin based-systems (1UBQ, 1Q0W).

1. Method

1.1. Smoothing of the Coulomb potential

$$V_r(x) = \sum_i q_i r_{i}^{-\alpha}$$

Unsmoothed molecular electrostatic potential (MEP) Amber99 atomic charges [1] are assigned to atoms using FDSQPM (2).

The Poisson equation is applied to generate the corresponding smoothed atomic charge density function, $$\rho_{\text{smooth}}(x)$$:

$$\nabla^2 \rho_{\text{smooth}}(x) = -\varepsilon \rho_{\text{smooth}}(x)$$

2. Example

CD of GlyHHis

3. Location of critical points (CP) in $$\rho_{\text{smooth}}$$.

A hierarchical merging algorithm, based on the idea of Leung et al. [4], is used to locate local extrema in $$\rho_{\text{smooth}}$$.

- At scale $$\sigma$$, each atom of a molecular structure is considered as a starting point of the merging procedure.
- As $$\sigma$$ increases, each point moves along a gradient path to reach a location in the 3D space where:

$$\nabla^2 \rho_{\text{smooth}}(x) = 0$$

These trajectories are defined by:

$$\rho_{\text{smooth}}(x) = \rho_{\text{smooth}}(x_{i}) + \Delta \rho_{\text{smooth}}(x_{i})$$

$$\Delta =$$ displacement step

4. Charge fitting

Charges are fitted either to unsmoothed Amber99 MEPs or MEPs [5].

- Considering various amino acid rotamers [6], with constraints: total electric charge & total dipole moment.
- Side chain charges are first assigned [7,8], then backbone charges are fitted using the side chain charge values as constraints.

5. Effect of fitting conditions on charges and forces

Changes fitted to forces allow to better approximate short-range forces [5].

6. Molecular electrostatic potential

Ubiquitin (1UBQ.pdb) - 76 amino acids - 1231 atoms

2. Molecular dynamics applications

1. Simulation conditions

Gromacs 4.5.5 [9]

Amber95SB and TIP4P-Ew force fields, PME

All force field terms are preserved except the # of protein charges = CB+ν energy values and forces are strongly modified.

- Atomic point charges = virtual sites defined vs. selected atoms

Equilibration: 40 ns

Production: 20 ns

NPT (1 bar, 300 K)

2. RMSD and final snapshots at 300 K (Ubiquitin)

3. Stability of deconstructed conformations

Ubiquitin-Yap27 complex (1Q0W.pdb)

RPCMs allow to generate deformed but stable protein conformations.

4. Intra-molecular H bonds

Distributions are strongly affected with a RPCM.

5. Protein-water interface

Distance and angle distributions present trends similar to the all-atom case.

Conclusions

- RPCMs allow the approximation of the MEP of rigid proteins.
- They also allow simulations of flexible structures by MD provided they involve a good description of the short range Coulomb energy terms.
- Charges fitted to electrostatic forces allow a better approximation of the short-range forces.
- Charges located on atoms allow a better approximation of the CB+ν energy terms.
- Secondary structure elements can be destructed due, notably, to a loss in the number of H-bonds. It allows the sampling of new conformations that can be stable under all-atom MD conditions.
- RPCMs involve modifications of the interfacial water structure and dynamics.