Design and applications of reduced point charge models of proteins
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Publication date:
2015

Document Version
Peer reviewed version

Link to publication
Citation for published version (HARVARD):

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Introduction

Reduced point charge models (RPCMs) of 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. Using MD simulations, RPCM-based representations of ubiquitin systems (1UBQ, 1Q0W, 2MBB) allow to generate deconstructed protein conformations. In particular, deconstructed protein-ligand conformations appear to be stable under all-atom MD simulation conditions.

1. Method

1. Smoothing of the Coulomb potential

\[ V_s(r) = \sum \frac{q_a}{\epsilon} \left( 1 - \frac{R_s}{R_s + r}^2 \right) \]

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

\[ V_{MEP}(r) = \sum \frac{q_a}{\epsilon} \left( 1 - \frac{R_s}{R_s + r}^2 \right) \]

Smoothed MEP [3]

The Poisson equation is applied to generate the corresponding smoothed atomic charge density (CD) distribution function, \( \rho_s(r) \):

\[ \nabla \cdot \frac{\nabla \rho_s}{\epsilon} = q_a \]

2. Location of critical points (CP) in \( \rho_s \)

A hierarchical merging algorithm, based on the idea of Leung et al. [4], is used to locate local extrema in \( \rho_s \).

- Charges located on atoms allow a better approximation of the short-range forces.
- Charges fitted to electrostatic forces allow a better approximation of the short-range forces.
- Charges located on atoms allow a better approximation of the Coulomb energy terms.
- RPCMs involve modifications of the interfacial water structure and dynamics.
- Secondary structure elements can be deconstructed due, notably, to a loss in the number of H-bonds. It allows the sampling of new conformations that are stable under all-atom MD conditions. It can be due to stabilized protein-solvent and/or protein-ligand interactions. No unique trend is observed as for.

2. Molecular dynamics applications to Ubiquitin

Program: Gromacs 4.5.5 [9]
Force fields: Amber99SB and TIP4P-Ew, PME
All force field terms are preserved except for the number of protein charges \( \rightarrow \) CD, and Cb short range (SR) energy values and forces are strongly modified. Non-atomic point charges \( \rightarrow \) virtual sites defined as selected atoms.

Equilibration: 40 ns
Production: 20 ns
NPT (1 bar, 300 K)

3. Intra-molecular H bonds

Distributions are strongly affected when using a RPCM.

The increased RMSD values reflect a deformation of the protein structure, especially of the CP_MEP and AT_MEP sets of charges.

3.1. Native Deconstructed

3.2. Native Deconstructed

3.3. Native Deconstructed

3.4. Native Deconstructed

4. Protein-water interface

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

5. Stability of deconstructed conformations

RPCMs allow the generation of deformed but stable conformations.

- Ubiquitin-Vps27 complex (1Q0W.pdb)

- Ubiquitin-iota UBM1 complex (2MBB.pdb)

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 Coulomb energy terms.

- RPCMs involve modifications of the interfacial water structure and dynamics.

- Secondary structure elements can be deconstructed due, notably, to a loss in the number of H-bonds. It allows the sampling of new conformations that are stable under all-atom MD conditions. It can be due to stabilized protein-solvent and/or protein-ligand interactions. No unique trend is observed as for.

References