Design and applications of reduced point charge models of proteins
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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 destructured protein conformations. In particular, destructured protein-ligand conformations appear to be stable under all-atom MD simulation conditions.

1. Method

1.1. Smoothing of the Coulomb potential

\[ V_{\text{sm}}(r) = \sum_{i} \frac{q_i}{\epsilon \sqrt{r_i^2 + r^2}} \]

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

\[ V_{\text{sm}}(r) = \sum_{i} \frac{q_i}{\epsilon \sqrt{r_i^2 + r^2}} \]

The Poisson equation is applied to generate the corresponding smoothed atomic charge density (CD) distribution function, \( \rho_{\text{sm}}(r) \):

\[ \nabla^2 \rho_{\text{sm}}(r) = -\frac{\rho_{\text{sm}}(r)}{\epsilon} \]

1.2. Location of critical points (CP) in \( \rho_{\text{sm}}(r) \)

A hierarchical merging algorithm, based on the idea of Leung et al. [4], is used to locate local extrema in \( \rho_{\text{sm}}(r) \). At scale \( \Delta \), each atom of a molecular structure is considered as a starting point of the merging procedure. As \( \Delta \) increases, each point moves along a gradient path to reach a location in the 3D space where \( \rho_{\text{sm}}(r) \) is zero.

1.3. Charge fitting

Charges are fitted to unsmoothed Amber99 molecular electrostatic potential (MEP) or force (MEF) grids [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.

2. Molecular dynamics applications to Ubiquitin

Program: Gromacs 4.5.5 [9].

2.1. Simulation conditions

<table>
<thead>
<tr>
<th>Force fields</th>
<th>Force field terms preserved for the number of protein charges</th>
<th>SR energy values and forces are strongly modified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amber99SB and TIP3P-Ew, PME</td>
<td>All</td>
<td>Non-atomic point charges + virtual sites defined vs selected atoms</td>
</tr>
</tbody>
</table>

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

2.2. RMSD and final snapshots at 300 K

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

3. Intra-molecular H bonds

Distributions are strongly affected when using a RPCM.

4. Protein-water interface

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

5. Stability of destructured conformations

RPCMs allow to generate deformed but stable conformations.

- Ubiquitin-Vps27 complex (1Q0W.pdb)
- Ubiquitin-intoUB1M1 complex (2MBB.pdb)

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