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 (UBQ, IQQW).

1. Method

1.1. Smoothing of the Coulomb potential

\[ V_r(x) = \sum \frac{q_i}{r} \]

Unsmoothed molecular electrostatic potential (MEP) for each atom using FES-QPQ (1).

\[ V_s(x) = \sum \frac{q_i}{r} \cdot \exp \left( \frac{-r}{\sigma_s} \right) \]

Smoothed MEP (3).

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

\[ -\nabla^2 \rho_s(x) = \sum \frac{q_i}{r} \cdot \exp \left( \frac{-r}{\sigma_s} \right) \]

Smoothed charge density.

1.2. Example

Fig. 1. Smoothed CD of a peptide-like molecule.

3. 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 \( \rho_s \).

- At scale \( \sigma_0 \), 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:

\[ V_s(x) = 0 \]

These trajectories are defined by:

\[ r_{s,j}(x) = r_{s,j}(0) + \Delta = \exp \left( \frac{-r_{s,j}}{\sigma_0} \right) \]

\[ \Delta = \text{displacement step} \]

Fig. 2. Illustration of the CD of a peptide-like molecule smoothed by the FES-QPQ method.

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.

Side chain charges are first assigned (7,8), then backbone charges are fitted using the side chain charge values as constraints.

Fig. 3. Reduced point charge model based on local extrema of CD peaks (40% of the total charge density).

5. Effect of fitting conditions on charges and forces

Charges fitted to forces allows to better approximate short-range forces (5).

6. Molecular electrostatic potential

Ubiquitin (UBQ pdb): 76 amino acids - 1231 atoms

Fig. 5. MEP isocontours of Ubiquitin: CP, AT - CP_V, AT_V.

2. Molecular dynamics applications

1. Simulation conditions

Gromacs 4.5.5 (9)

Amber99SB and TIP4P-Ew force fields, PME

All force field terms are preserved except the number of protein charges \( \rightarrow \) Ca+ values and forces are strongly modified.

N-amino acid point charges \( \rightarrow \) virtual site defined as selected atoms.

Equilibration: 40 ns

Production: 20 ns

NPT (1 bar, 300 K)

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

Fig. 6. Reduced point charge models of three amino acid residues.

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

3. Stability of deconstructed conformations

Ubiquitin-Vps27 complex (IQQW pdb).

RPCMs allow to generate deformed but stable protein conformations.

4. Intra-molecular H bonds

Distributions are strongly affected by a RPM.

5. Protein-water interface

Distance and distance presentations trends similar to the all-atom case.

Table 1. Mean numbers of H bonds, Ca+ from the Ubiquitin surface and their self-diffusion coefficient G

<table>
<thead>
<tr>
<th>Time (ns)</th>
<th>H bonds</th>
<th>Ca+</th>
<th>D (nm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>360</td>
<td>576</td>
<td>1.05</td>
</tr>
<tr>
<td>500</td>
<td>283</td>
<td>435</td>
<td>2.05</td>
</tr>
<tr>
<td>1000</td>
<td>254</td>
<td>455</td>
<td>2.22</td>
</tr>
</tbody>
</table>

The first shell of H2O molecules is unstructured and appears to be more compact. The dynamics is slower.

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 Ca+ 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.

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