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Determination of protein reduced electrostatic models from smoothed molecular electrostatic potentials
Laurence Leherte, Daniel P. Vercauteren
Laboratoire de Physico-Chimie Informatique, Groupe de Chimie Physique Théorique et Structurale, University of Namur - Belgium (FUNDP)

Introduction
The design of coarse grain (CG) models [1] and their corresponding potential functions [2] for protein computational studies is currently an active field of research, especially in solving long-scale dynamics problems such as protein folding, protein-protein docking. For example, to eliminate fast degrees of freedom, it has been shown that one can rely on CG representations only, or on mixtures of CG and more detailed descriptions (3,4) in order to significantly increase the time step in molecular dynamics (MD) simulations. Among the parameters involved in CG potentials, the electrostatic interactions are of major importance (5) since they govern local and global properties such as their stability (6), their flexibility (7).

In this paper, we present an approach to design and evaluate reduced point charge models obtained from smoothed molecular electrostatic potentials (MEP). In a previous approach [8], electron density (ED)-based “CG” were determined through a merging/clustering procedure of atom trajectories generated in progressively smoothed ED distribution functions. In the present work, atoms are clustered according to their trajectories defined in a smoothed MEP function, more particularly the Amber potential reported in [9]. A fitting algorithm is applied to evaluate “CG” charges.

1. Location of “CG” points
A hierarchical merging algorithm, based on the idea of Leung et al [10], is used to locate local maxima and minima in a MEP function, as a function of the degree of smoothing t:
1.1 At scale t = 0, each atom of a molecular structure is considered as a local maximum or minimum of V. All atoms are thus considered as the starting points of the merging procedure.
1.2 As t increases from 0.0 to a given maximal value, each point moves continuously along a gradient path to reach a location in the 3D space where \( V(t) = 0 \).

On a practical point of view, this consists in following the trajectory of the points within the MEP function calculated at \( t \) according to Equation:
\[
\nabla V(t) = \hat{r}(t) \Delta V(t) + \frac{\Delta V(t)}{\sqrt{t}} V(t)
\]

2. Molecular electrostatic potential
\[
V_A(\hat{r}) = \sum_{\text{all } i = 1} Z_{i} \frac{1}{r_i - \hat{r}_i} \quad \text{Unsmoothed}
\]
\[
V_A(\hat{r}) = \sum_{\text{all } i = 1} Z_{i} \frac{1}{r_i - \hat{r}_i} \left( \frac{1}{2} \right) \quad \text{Smoothed [11]}
\]

3. Determination of CG charges
This is achieved through the program QFIT [12] to get “CG” point charges fitted from an unsmoothed MEP grid, considering the following constraints: the total molecular charge and dipole.

4. Determination of backbone “CG” charges
a) Construction of Gly7-Asp7-Gly7 in an extended conformation (\( \Omega = 180^\circ, \Phi = 139^\circ, \Psi = 135^\circ \)) using SMMP05 [13], a Monte Carlo/Simulated Annealing program.
b) Application of the hierarchical merging/clustering algorithm.
\[
\hat{r} = 0.0 \text{ bohr}, isomEP: -0.01 \text{ e/bohr}
\]
\[
\hat{r} = 0.95 \text{ bohr}, isomEP: -0.03 \text{ e/bohr}
\]
\[
\hat{r} = 1.35 \text{ bohr}, isomEP: -0.03 \text{ e/bohr}
\]

5. Determination of “CG” charges of amino acid side chains
a) Construction of Gly7-Asp7-Gly7 in an extended conformation (\( \Omega = 180^\circ, \Phi = 139^\circ, \Psi = 135^\circ \)) with various AA rotamers [14] using SIMMPOS [13]. Examples:

6. Application to potassium ion channel KcsA (1bl8.pdb)
- Positioning of “CG” points through QUATFIT, a superposition algorithm [16], using the above templates and the PDB structure of KcsA.
- Extra (+) and (-) charges on terminal N and O → 1492-point model (total charge = +4 e)

7. Conclusions, on-going work
- A “CG” model built from a smoothed MEP seems to be more significant than a description based on AA centers-of-mass, for simulating electrostatic effects close to the protein → a more complete CG model would involve distinct steric and electrostatic centers
- can be derived for any set of point charges (Amber99, Gromos43A1 also set)
- Transferability has to be confirmed (in progress)
- Easy interfacing with APBS [17], a Poisson-Boltzmann equation solver (tests in progress)