Determination of protein reduced electrostatic models from smoothed molecular electrostatic potentials

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Publication date:
2009

Document Version
Peer reviewed version

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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 poster, 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 *V*, as a function of the degree of smoothing *t*:

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.
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: $\vec{\nabla}V(t) = 0$

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:

$$\vec{r}_{V(t)} = \vec{r}_{V(t-\Delta t)} + \frac{\Delta}{V(t)}\vec{\nabla}V(t)$$

2. Molecular electrostatic potential

$$V_A(\vec{r}) = \sum_{a\in A}\frac{Z_a}{\left|\vec{r}-\vec{R}_a\right|} \quad \text{Unsmoothed}$$

$$V_{A,t}(\vec{r}) = \sum_{a\in A}\frac{Z_a}{\left|\vec{r}-\vec{R}_a\right|}\,erf\left(\frac{\left|\vec{r}-\vec{R}_a\right|}{2\sqrt{t}}\right) \quad \text{Smoothed [11]}$$

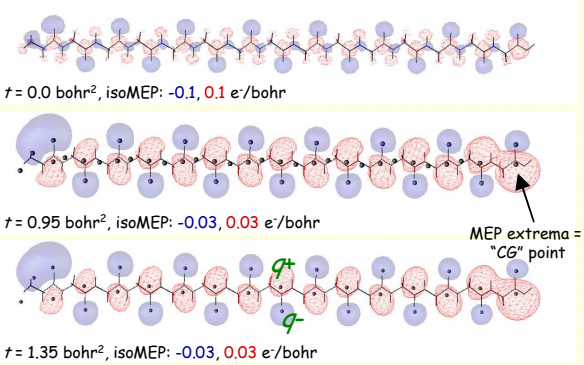
3. Determination of *CG* charges

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.

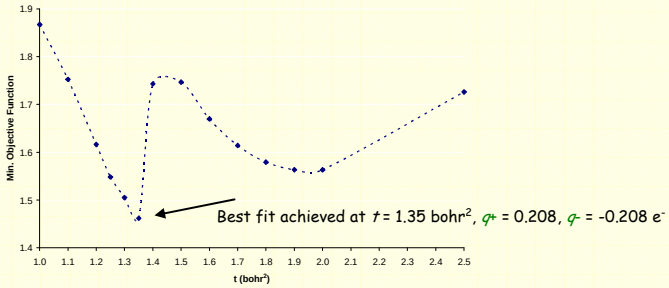
4. Determination of backbone "*CG*" charges

a) Construction of Gly_{15} in an extended conformation (Ω = 180°, Φ = -139°, Ψ = 135°) using SMMP05 [13], a Monte Carlo/Simulated Annealing program.

b) Application of the hierarchical merging/clustering algorithm



c) Charge fitting *vs.* unsmoothed MEP as a function of *t*:



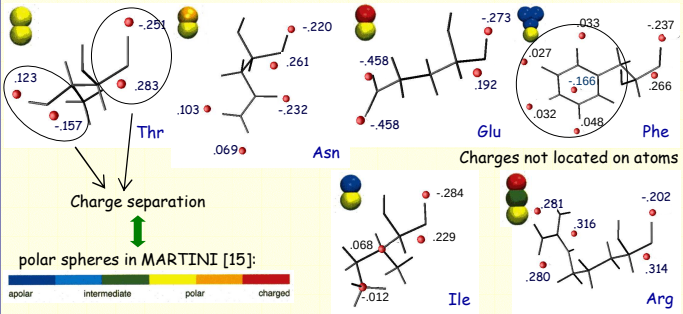
5. Determination of "*CG*" charges of amino acid side chains

a) Construction of Gly7-AA-Gly7 in an extended conformation (Ω = 180°, Φ = -139°, Ψ = 135°) with various AA rotamers [14] using SMMP05 [13]. Examples:

	Conformation	χ1 (°)	χ2 (°)	χ3 (°)	χ4 (°)	Occurrence (%)
Arg	*g-, t, g-, g-*	300	180	300	300	9.5
	g-, t, g-, t	300	180	300	180	11.9
	g-, t, g+, t	300	180	60	180	12.2
	g-, t, t, t	300	180	180	180	12.2
Asn	*t, Nt*	180	0			11.1
	t, Og-	180	300			21.3
	t, Og+	180	60			23.6

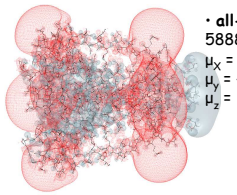
b) Use of "*CG*" points obtained at $t = 1.35$ bohr² (see sections 1 and 2)

c) "*CG*" charge fitting with additional constraints: Gly_{15} charges (see section 3) except for the points located on the central AA. Examples:



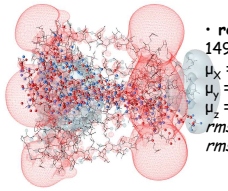
6. Application to potassium ion channel KcsA (1bl8.pdb)

- 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⁻)



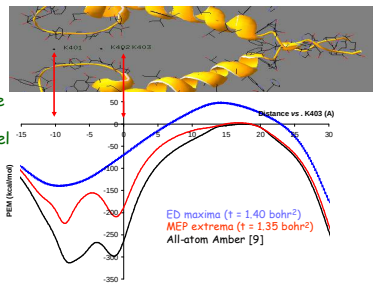
- **all-atom model**
  5888 atoms
  μ_x = 1237.7
  μ_y = 496.1
  μ_z = 141.5 D

IsoMEP: -0.1, 0.1 e⁻/bohr



- **reduced model**
  1492 point charges
  μ_x = 1255.2
  μ_y = 496.1
  μ_z = 183.6 D
  rmsdV = 7.6 kcal/mol
  rmsdμ = 45.5 D

MEP profile along channel axis



- When the model is based on only one "*CG*" for each AA backbone, the two-minima region does not show up, and the zero-potential is displaced (blue curve).
- Reduced point charge-based profile looks similar to the all-atom one, except for a « damping » effect (red *vs.* black curve).

7. Conclusions, on-going work

- A "*CG*" model built from a smoothed MEP
  - seems to be a more significant electrostatic model 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)

References

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