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# Design of a reduced point charge model for proteins: Molecular Dynamics Applications

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## Framework

This work is part of a more general project on multiresolution analysis of three-dimensional (3D) molecular fields. More specifically, it is related to the topological analysis of smoothed charge density (CD) distribution functions. From such functions, we show how to obtain a reduced point charge model (also named here coarse grain (CG) model) for proteins and we assess the applicability to molecular dynamics (MD) simulations of protein structures.

## Reduced Point Charge Model

### 1. Smoothed Charge Density

$$V_A(\vec{r}) = \sum_{a \in A} \frac{q_a}{|\vec{r} - \vec{R}_a|}$$

Unsmoothed electrostatic Coulomb potential generated by molecule A. Amber99 atomic charges [1] are assigned to atoms using PDB2PQR [2].

$$V_{A,t}(\vec{r}) = \sum_{a \in A} \frac{q_a}{|\vec{r} - \vec{R}_a|} \exp\left(-\frac{|\vec{r} - \vec{R}_a|}{2\tau}\right)$$

Smoothed electrostatic potential [3]

$$-\nabla^2 V_{A,t} = \frac{\rho_{A,t}}{\epsilon_0}$$

Poisson Equation  $\rightarrow$  Smoothed CD  $\rho_{A,t}$  ( $\tau$  = smoothing degree)

$$\rho_{A,t} = \frac{q_a}{(4\pi)^{3/2}} e^{-\tau^2/4r^2}$$

Analytical expression of  $\rho_{A,t}$

### 2. Location of CGs in $\rho_{A,t}$

A hierarchical merging algorithm, based on the idea of Leung *et al.* [5], is used to locate local extrema in  $\rho_{A,t}$ .

- At scale  $\tau = 0$ , each atom of a molecular structure is considered as a starting point of the merging procedure.
- As  $\tau$  increases, each point moves along a gradient path to reach a location in the 3D space where  $\nabla \rho_{A,t} = 0$

These trajectories are defined by:

$$\vec{r}_{\rho_{A,t}} = \vec{r}_{\rho_{A,t-\Delta}} + \frac{\Delta}{\rho_{A,t}} \nabla \rho_{A,t} \quad \Delta = \text{displacement step}$$

### 3. Backbone CGs

- An extended strand  $\beta$ -Gly<sub>15</sub> is built considering ( $\Omega = 180^\circ$ ,  $\Phi = -139^\circ$ ,  $\Psi = 135^\circ$ ) using the program SMMP05 [5].
- Atomic charges are assigned using PDB2PQR [2].
- The merging/clustering program is then applied separately to negative and positive charges of  $\beta$ -Gly<sub>15</sub>. The central motif is isolated and further used as template for the backbone of any amino acid residue (see Figure below).

### 4. Side Chain CGs

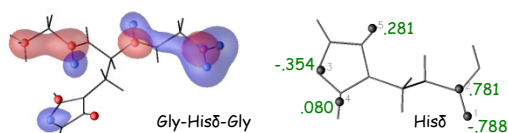
- Each isolated amino acid is considered with various conformations [6] built using SMMP05 [5].
- Atomic charges are then assigned using PDB2PQR [2].
- CGs are finally obtained using the merging/clustering program.

### 5. Charge Fitting

It is achieved with the program QFIT [7] to get CG point charges fitted from an unsmoothed electrostatic potential grid, considering the various rotamers with two constraints: molecular charge and dipole.

Charges are assigned in two steps. First, side chain CGs are treated. Second, backbone charges are adjusted while keeping the side chain charges to their pre-determined values.

Templates are thus obtained for each amino acid residue [8]. For instance:



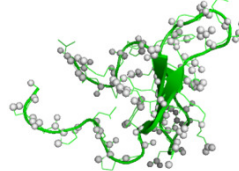
## Références

- Wang *et al.*, J Comput Chem 21 (2000) 1049 (2) pdb2pqr.sourceforge.net (3) Amara & Straub, Phys Rev B 53 (1996) 13857 (4) Leung *et al.* IEEE T Pattern Anal 22 (2000) 1396 (5) Eisenmenger *et al.* Comp Phys Comm 174 (2006) 422, www.smmp05.net (6) Simms *et al.*, Prot Eng Des Select 21 (2008) 369, www.dynamomics.org (7) Borodin *et al.* Force Field Fitting Toolkit, www.eng.utah.edu/~gdsimth/fff.html (8) Leherte & Vercauteren, J Comput Aided Mol Des 25 (2011) 913 (9) Heisterberg, Ohio Supercomputer Center, translation from FORTRAN to C and Input/Output by Labanowski, 1990 (10) Leherte & Vercauteren, J Phys Chem A 115 (2011) 12531 (11) TINKER - Software Tools for Molecular Design, http://dasher.wustl.edu/tinker/

## Molecular Dynamics Applications

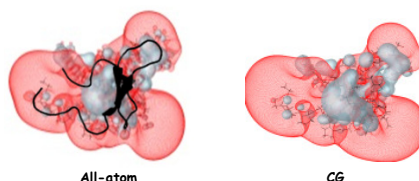
### 1. Ubiquitin protein-ligase Nedd4-2 (PDB access code 1WR3)

- The positioning of CGs is achieved with QUATFIT [9], a superposition algorithm, using the amino acid templates and the PDB structures of the proteins.
- End positive and negative charges ( $\pm 0.929 \text{ e}$ ) are added on terminal N and OXT atoms.

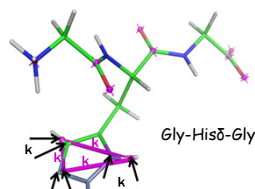


36 aa / 577 atoms / 158 point charges or CGs (white spheres) [10]

### 2. Isocontours of the electrostatic potential ( $-0.05, 0.05 \text{ e}/\text{bohr}$ )



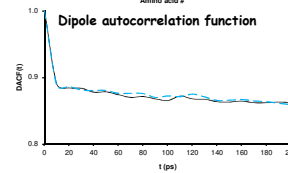
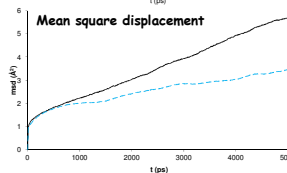
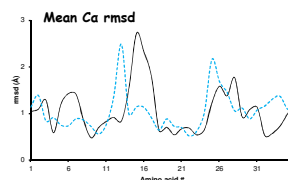
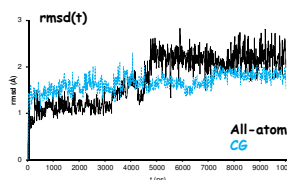
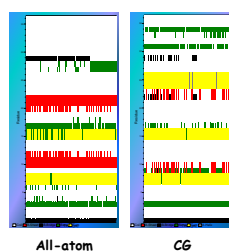
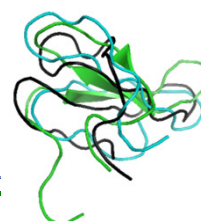
### 3. Implementation



The new set of charges was implemented in the program TINKER [11]. The fact that the point charges are not necessarily located on atoms makes the implementation challenging and, as a first trial, the original code was not modified. Thus, the charges are treated as additional particles ( $m = 2$ ) held together and to heavy atoms of the molecular structure by harmonic bonds [10].

### 4. Results

10 ns ( $10^7 \times 1 \text{ fs}$ )  
T = 298 K  
Vacuum  
CPU time AA/CG = 2



## Conclusions

CG locations and number are determined only from the topography of the CD distribution functions. Charge centers differ from atom centers  $\rightarrow$  challenge for MD applications. Some secondary structure elements are preserved vs. the all-atom model as well as the global fold of the peptide. Dynamical results are in agreement with the all-atom ones, but the mean square displacement is reduced. One also observes an increased conformational stability of the CG model. As a perspective, we are considering the instantaneous update of the CG model during the MD simulation (to avoid to assign a mass to the CGs).