Importance of Atomic Charge Concepts in Empirical Force Fields: The SCALCHA Approach to Obtaining Atomic Charges

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A general, exactly defined and simple method to obtain the parameters for empirical force fields, as applied in molecular dynamics simulations, is of great interest today. Electrostatic interactions play a very important role in molecular structures. Therefore, there is a need for a method to determine atomic charges for all molecules of biological relevance that can be used in the current monopole approach. We introduce a general, determined and simple method to project atomic charges, for example from quantum mechanical calculations, onto the existing empirical force fields.

INTRODUCTION

Electrostatic interactions have long been recognized to play a very important role in biomolecular structures, their dynamics and function. Examples where electrostatics have been recognized as being particularly important are in protein-ligand interaction and interactions within a protein involving helices.[1,2] Therefore, a proper treatment of electrostatics is needed in force field calculations.[3,4] A molecular dynamics simulation on cytochrome c under different dielectrical conditions illustrates the importance of the dielectric medium.[5] These examples show how much the evaluation of the structure and dynamics of biological molecules depend on a proper description of all the electrostatic effects. New approaches to model solute/solvent interactions (dielectric media effects) in *ab initio* quantum chemical calculations have been proposed.[6-9]

Typical examples of molecular dynamics algorithms and force fields are the program packages AMBER, CHARMM, DISCOVER, GROMOS and X-PLOR. Their para-

meters have been developed for amino acids, nucleotides and only a few special residues like the heme-group, some ions and several solvent molecules, but not for all possible biological molecules. Therefore, the question addressed by our current research and described in this chapter is the following:

How can one derive atomic charges for molecules that match the requirements of empirical force fields?

There is clearly a need for an exactly defined method that is simple and generally applicable for as many different molecules as a biological chemist desires, especially various enzyme substrate molecules and their derivatives. Charge concepts based on orbital electronegativities appear to be promising.[10,11]

There are some general rules on how to go about it once an empirical force field is defined. These include the following: The magnitude of the charges should correspond to the charges used in the force field. The concept of charge groups should be maintained (see below), and the method should be simple and as free of arbitrary choices as possible. These rules are a consequence of the fact that, on the one hand, it is rather time consuming to do a proper complete parametrization for each particular compound exactly in the same way the whole force field has been derived and, on the other hand, it becomes rather arbitrary if it is not done in any rigorous way. This general philosophy has recently been applied by Stewart in a rigorous parametrization of the PM3 method[12] and should be used in empirical force field methods in comparable ways. Especially in the case of a series of derivatives, the small differences between similar groups may be hard to judge. The idea of just carrying out a quantum mechanical calculation to obtain atomic charges and to use them directly in empirical force fields is problematic as well: even the absolute values for atomic charges from quantum mechanics and the charges from empirical for fields can be rather different. One reason might be that the former are calculated *in vacuo*, whereas the latter implicitly contain all kinds of (experimentally measurable) ensemble properties such as density, heat of formation, diffusion constants *etc.*[13] for the liquid and solid state.

Another reason is the difficulty of deciding which conformation to take: the conformations of molecules may be different *in vacuo*, in solution and in crystals, and both proteins and ligands are of course flexible. The concept of taking *in vacuo* structure minima (as from quantum mechanics; including neighboring excited structures[14]) would leave out, to a great extent, the ensemble properties from condensed phases. Taking only crystal structures from data-basis for parametrization on the other hand, always gives molecular structures that are modulated by ensemble properties and do not represent the intrinsic molecular structures. Possibly, the new concept of PROBE (force fields of the second class: DISCOVER, 1991[14]) or a combined quantum mechanical and molecular mechanical approach[15] might give good results. Thus, parametrization clearly *is* a difficult subject.

Here, we try to explain how quantum mechanical methods like *ab initio* or semiempirical self-consistent field calculations (for example AM1[16,17] and PM3[12]) and the population analysis of their wavefunctions by the method of Mulliken (MPA[18]), the natural hybrid orbital method (NPA[19]), the distributed multipole method (DMA[20]) or electrostatic fit (CHELP[21]) might be used as a basis for our scaling-projection concept. The SCALCHA approach (SCAled CHArges[22]) performs a fit of atomic charges for an arbitrary chosen molecule onto an existing empirical force field.

A SHORT DISCUSSION OF THE ELECTROSTATICAL INTERACTIONS IN MD

The non-bonded interactions V_{nb} between all atoms in molecular dynamics usually consists of three terms. Two terms are for the van der Waals interactions, one for the attractive forces with a $1/r^6$ dependency and one for the repulsive forces with a $1/r^{12}$ dependency. The third term describes the electrostatical interactions in the monopole approach, which we are discussing here.

$$V_{nb}(\bar{r}_1, \ldots \bar{r}_N) = \sum_{i<j}^{N} \left(\frac{C_{12}(ij)}{r_{ij}}\right)^{12} - \left(\frac{C_6(ij)}{r_{ij}}\right)^6 + \frac{q_i q_j}{4\pi\varepsilon_0\varepsilon_r r_{ij}} \qquad (1)$$

Charge distributions, e.g. atomic charges q_j, may be obtained from experimental data[23,24] or from quantum mechanical[25,26] or semiempirical calculations.[27,15]

Three different methods for obtaining atomic charges (the method according to Mulliken[18]), generalized atomic polar tensors, topological ones) have been discussed for a Ti- and a Fe-molecular complex,[28] and it was found that Mulliken charges vary widely with the applied basis set, whereas the other two methods seem to be rather insensitive to them. Hartree-Fock calculations (using a Mehler-Paul basis set) have been performed[29] to determine atomic charges for amino acids. The routines QUEST (especially for the AMBER force field[30]) and CHELP[21] calculate atomic charges from the potential at many given points (from quantum mechanical wave functions). These charges have then been used for molecular dynamics simulations. This can be done since the current force fields contain electrostatic monopoles only. It should be mentioned once again that these charges must fit into the concept of the force field to give proper results in the simulations.

It seems reasonable to neglect higher order multipole terms[20,31-33] in a first approximation since an effective force field should be computationally efficient. Simple point charge water models are capable of reproducing the radial distribution functions of water and other molecular ensemble properties very well.[34-37] The resulting trajectories of solute and water molecules[38] displayed molecular structures that are in good agreement with X-ray structures as mentioned above.

We introduce a practical approach to making an easy fit of atomic monopole charges that have been calculated, for example with quantum mechanical methods, to be used in molecular dynamics force fields:

THE SCALCHA PROJECTION

First Approach

This approach should be used to determine charges in a series of similar molecules. First, the atomic charges for all atoms i of two molecules, A and B, have to be calculated using quantum mechanical methods (denoted $qA_{qm}(i)$ and $qB_{qm}(i)$). Next, the atomic charges for molecule A need to be determined using the rules of the empirical force field ($qA_{emp}(i)$). Now, the differences between the smallest and largest charges are set into correlation:

$$dq = \frac{qA_{emp}(i_{max}) - qA_{emp}(i_{min})}{qA_{qm}(i_{max}) - qA_{qm}(i_{min})} \qquad (2)$$

In the following step, the quantum mechanical charge of each atom is scaled and added to the empirical charge of the same atom.

$$qB_{emp}(i) = qA_{emp}(i) + dq \times \left(qB_{qm}(i) - qA_{qm}(i)\right) \qquad (3)$$

In the case of molecule A containing more atoms than molecule B, the missing atoms in B are treated as if their charge was zero. The newly determined charges $qB_{emp}(i)$ are similar to those determined for the empirical force field, but they additionally contain the quantum mechanical features.

The net charge of the newly designed molecule deviates from the desired total net charge for molecules B. Therefore, it is necessary to fit the charges to the desired total net charge for the whole molecules or for each molecular charge group. A charge group is a chemically reasonable group of atoms used during molecular dynamics simulations with a cutoff radius for calculating the nonboned interactions. The value (neutral, $+1$, -2, *etc.*) of each charge group (or the complete molecule) is reached *via* the following recursive algorithm.

The fitted charge $qB'_{emp}(i)$ on atom i of molecule B is calculated (Eq. 4) from $qB_{emp}(i)$ by adding the charge difference $dg, n_g(i)$.

$$qB'_{emp}(i) = qB_{emp}(i) + dg, n_g(i) \qquad (4)$$

where g is the charge group to which atom i belongs. Each atom is in exactly one charge group. Inside each charge group g the atoms are ordered according to

$$qB_{emp}(a) < qB_{emp}(b), \ where \ n_g(a) > n_g(b) \qquad (5)$$

n_g is a list of unique (Eq. 7) indices running from 1 to the size of g, such that

$$a \in g \qquad if \quad n_g(a) \in [1, |g|] \qquad (6)$$

and

$$n_g(a) \neq n_g(b) \qquad for \quad a \neq b, \ a, b \in g. \qquad (7)$$

A list d_g of charge differences $d_{g,k}$ for each charge group is calculated *via* the recursive function f.

$$d_g = (d_{g'1}, d_{g'2}, \ldots d_{g'|g|}) \qquad (8)$$
$$= f(1, \Delta q_g, 0, 0, \ldots, 0)$$

The value Δq_g represents the charge difference between the desired value Q_g for the charge group g and the total sum of charges belonging to the group after projection.

$$\Delta q_g = Q_g - \sum qB_{emp}(j), \quad for \ j \in g \qquad (9)$$

Function f is defined as:

$$f(s, v_1) = v_1 \tag{10}$$

$$f(s, v_1, v_2, \ldots v_l) = f(s, V_1, V_2, \ldots V_m) \therefore f(s+m, V_{m+1}, V_{m+2}, \ldots v_l) \tag{11}$$

where:

$\quad \therefore$ denotes the concatenation of two lists

$$m \quad = \text{trunc}(I/2) \tag{12}$$

$$V_1 \quad = v_1{}^* r / (1 + r) \tag{13}$$

$$V_{m+1} = v_1 / (1 + r) \tag{14}$$

$$r \quad \doteq S_l / S_h \tag{15}$$

$$S_l \quad = \sum q B_{emp}(j) - m_g, \quad \text{for } n_g(j) = s \ldots s + m - 1 \tag{16}$$

$$S_h \quad = \sum q B_{emp}(j) - m_g, \quad \text{for } n_g(j) = s + m \ldots s + 1 - 1 \tag{17}$$

$$m_g \quad = \begin{cases} |\max q B_{emp}(j)|, & \text{for } j \in g \quad \text{if } \Delta q_g > 0 \\ -|\min q B_{emp}(j)|, & \text{for } j \in g \quad \text{if } \Delta q_g < 0 \end{cases} \tag{18}$$

Function f distributes the charge difference Δq_g over all atoms in charge group g. Initially, the function starts with the total charge difference assigned to the first atom in the group (Eq. 8). Step by step, this charge is distributed over all atoms of the charge group. In each cycle, a portion of the charge difference on the first atom is given to the charge difference with index m + 1 (Eq. 13, 14). This procedure is again applied on the left and right half of the charge list (Eq. 11) until the list contains only one atom (Eq. 10).

The charge difference is split according to relation r. This relation r depends on the total charge $q B_{emp}(i)$ of the corresponding atoms for the left and right half of the list (Eq. 15). Parameter s of function f gives the reference to the total charges (Eq. 16, 17). The sum of the charges on the atoms of left and right of the list is modified by m_g (Eq. 18). Due to the definition of m_g (Eq. 18), the sign of all elements in both sums (Eq. 16, 17) is the same and, therefore, relation r is positive. The atoms in the charge groups are ordered descending by their total charge $q B_{emp}(i)$ (Eq. 5). Therefore, S_l is smaller than or equal to S_h if $\Delta q_g > 0$ or larger if $\Delta q_g < 0$. By this means, highly charged atoms gain more charge difference than weakly charged ones. A change of the overall character of the molecules, *i.e.* changing the sign of the atom charges, should be avoided.

The recursive algorithm (Eq. 3 to 18) is generally applicable to obtaining charge groups in empirical force field structures. Two examples for this SCALCHA approach are given in Tables I and II.

Second Approach

In the approach mentioned above it is necessary to have three complete reference charge sets, namely the two quantum mechanical (or semiempirical) ones and one

TABLE I

Atom names	PCNH MPA	PCN MPA	PCNH GROMOS reference	PCN SCALCHA	PCN SCALCHA final
N	−0.784	−0.776	0.129	0.133	0.143
C1	0.310	0.251	0.127	0.093	0.100
C2	0.373	0.392	0.150	0.161	0.134
O1	−0.735	−0.748	−0.360	−0.367	−0.428
P	1.438	1.315	0.630	0.559	0.559
O2	−0.756	−0.874	−0.635	−0.703	−0.786
O3	−0.817	−0.899	−0.635	−0.683	−0.764
O4	−0.742	−0.895	−0.548	−0.636	−0.715
H/−	0.417	0.000	0.398	0.000	0.000
C3	0.438	0.427	0.248	0.242	0.259
C4	0.413	0.379	0.248	0.228	0.244
C5	0.445	0.428	0.248	0.238	0.255
Total	0.000	−1.000	0.000	−0.734	−1.000

The first and second columns contain the calculated absolute MPA charges of mono-protonated phosphorylcholine and deprotonated phosphorylcholine. The third column represents the charges for mono-protonated phosphorylcholine as guessed from the empirical force field. The result for deprotonated phosphorylcholine after application of the first part (projection) of SCALCHA is given in the fourth column. The last column contains the final SCALCHA charges after the recursive function has been applied.

TABLE II

Atom names	PCNH MPA	CCN MPA	PCNH GROMOS reference	CCN SCALCHA	CCN SCALCHA final
N	−0.784	−0.788	0.129	0.127	0.105
C1	0.310	0.353	0.127	0.152	0.134
C2	0.373	0.439	0.150	0.188	0.351
O1	−0.735	−0.708	−0.360	−0.344	−0.316
P/C	1.438	0.835	0.630	0.283	0.470
02/C7	−0.756	0.119	−0.635	−0.130	−0.048
03/−	−0.817	0.000	−0.635	0.000	0.000
04	−0.742	−0.584	−0.548	−0.457	−0.457
H/−	0.417	0.000	0.398	0.000	0.000
C3	0.438	0.444	0.248	0.251	0.250
C4	0.413	0.438	0.248	0.262	0.262
C5	0.445	0.451	0.248	0.252	0.250
Total	0.000	1.000	0.000	0.583	1.000

The first and second columns contain the calculated absolute MPA charges of mono-protonated phosphorylcholine and acetylcholine. The third column represents the charges for, mono-protonated phosphorylcholine as guessed from the empirical force field. The result for acetylcholine after application of the first part (projection) of SCALCHA is given in the fourth column. The last column contains the final SCALCHA charges after the recursive function has been applied.

from the empirical force field. In the second approach, we use only the complete quantum mechanical charges of one molecule ($qA_{qm}(i)$ and the information about empirical charges of all or only some n characteristic atoms. In this case, we apply a linear regression:

$$qA_{emp}(i) = a + b \times qA_{qm}(i) \qquad (19)$$

$$a = \frac{1}{n} \sum \left(qA_{emp}(i) \right) - \frac{b}{n} \sum \left(qA_{qm}(i) \right)$$

$$b = \frac{\sum \left(qA_{emp}(i) \times qA_{qm}(i) \right) - \frac{1}{n} \sum \left(qA_{emp}(i) \right) \times \sum \left(qA_{qm}(i) \right)}{\sum \left(qA_{qm}(i)^2 \right) - \frac{1}{n} \sum \left(qA_{qm}(i) \right) \times \sum \left(qA_{qm}(i) \right)}$$

The error is expressed as the correlation coefficient, which is a measure for the quality of the obtained charges. After using this procedure, the recursive algorithm can be applied to obtain charge group neutrality, as explained above.

Third Approach

There is sometimes no information at all about the quantum mechanical atomic charges and only the topology of the new molecule is known. In this case, one at least needs to know as many empirical atomic charges as possible from the most similar atoms already existing in the force field.

Again, a linear regression for the remaining atoms is performed to calculate the missing charges of the whole molecule and afterwards, if desired, the recursive algorithm can produce the charge group neutralities.

SCALCHA RESULTS

For three molecules in the crystalline state, (i) phosphorylcholine[39], (ii) cholinesulfate[40] and (iii) acetylcholine[41], (Figure 1a,b,c), we have calculated the atomic charges from wavefunctions on HF/3-21G* and AM1 level of approximation using the GAUSSIAN 86 program package.[42] There are some other reports on charges for acetylcholine and related molecules.[43,44] We have taken the atomic positions as described in the X-ray diffraction studies and we have added the missing hydrogen positions by placing them in standard geometry with the INSIGHT display program. The hydrogen positions were geometry- optimized in the SCF procedures. Optimization of only their bond lengths gave large energetic and geometrical changes since the hydrogen positions from X-ray structures are not well defined. For example, in the phosphorylcholine structure, the crystal water molecules were reported with bond lengths between 0.68 and 1.08 Å. When the complete hydrogen positions were optimized, *i.e.* their bond lengths, angles and torsional angles, only minor additional change occurred in comparison to bond length optimization (for example: STO-3G total energy of deprotonated phosphorylcholine after hydrogen bond lengths optimization was –432.26 kJ/mole, after bond lengths and -angle optimization –442.75 kJ/mole and after bond lengths, -angle and torsional angle optimization –532.48 kJ/mole[45]). For the HF/3-21G* cal-

(a)   PHOSPHORYLCHOLINE CRYST
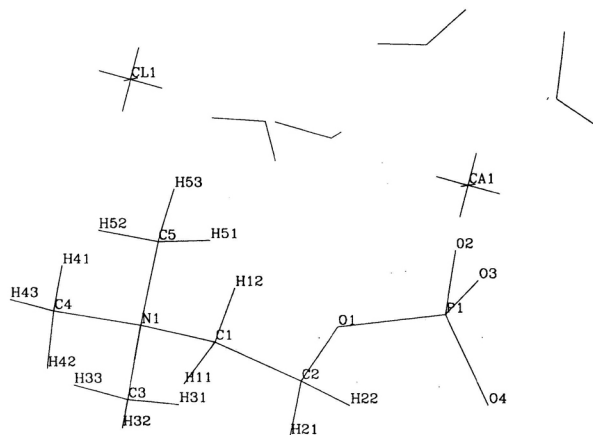
(b)   CHOLINESULFATE CRYST

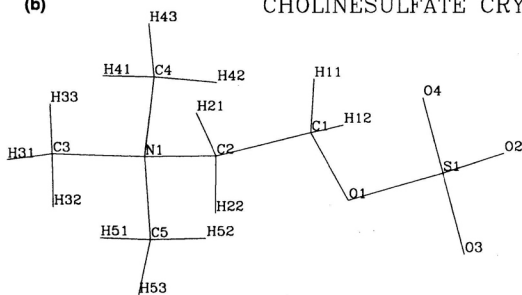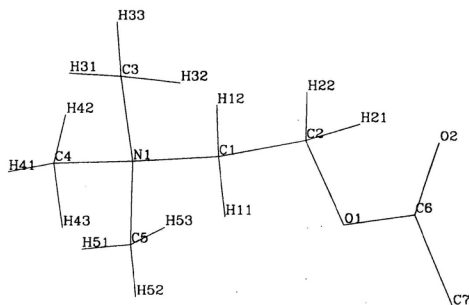**(c)**   ACETYLCHOLINE CRYST

Figure 1a,b,c. Crystal structures of (a) phosphorylcholine, (b) cholinesulfate. and (c) acetylcholine. The geometries are from the X-ray structures[39-41] with hydrogen positions as described in the text.

culations, we only optimized the bond lengths. However, for the AM1 calculations, we optimized either the bond lengths or the complete hydrogen positions.

The atomic charges were derived according to Mulliken (MPA, GAUSSIAN 86[42]), from a distributed multipole analysis (DMA) approach[20,46], from the natural hybrid orbital analysis (NPA)[19] and from the electrostatic potential fit routine CHELP.[21] The absolute atomic charge values as obtained from these methods are displayed in Figures 2a,b,c,d and the corresponding ones after application of the SCALCHA, routine (first approach) in Figures 3a,b,c.

As a reference molecule (for the first approach), we used phosphorylcholine with one hydrogen attached to the phosphate group. INSIGHT suggested three possible hydrogen positions. Therefore, we performed a complete AM1 optimization. We selected the INSIGHT position closest to the AM1 minimum to be consistent, as far as possible, with the crystal structures, including as few as possible data from calculations. This structure will be called the 'crystal structure' in our HF/3-21G* calculations.

The reference charges (called GROMOS charges in this article) for phosphorylcholine have been selected from the standard force field (GROMOS 87[47]) using the residues lysine and FMN (flavinmononucleotide[22]). Mono-protonated phosphorylcholine has been chosen to be the standard reference molecule.

It should be stressed that we have selected these charges and applied some general rules of the force field to carry out standard simulations. In no way have we performed any calculations or optimizations to really fit these molecules in the GROMOS force field, in the way the original parameters were optimized.

ABSOLUTE CHARGES FROM MPA, NPA, CHELP OR DMA ANALYSIS AND GROMOS 87

Mono-protonated phosphorylcholine has a net charge of zero, it is a zwitterion with two charge groups. Deprotonated phosphorylcholine is doubly negatively charged on the phosphate group; thus, it has a net charge of minus one.

We have performed HF/3-21G* and AM1 calculations (GAUSSIAN 86). Phosphorylcholine (mono-protonated, Figure 2a; deprotonated Figure 2b) shows atomic charges ranging from about −1.3 to +2.5 e. The highest charge values are from the NPA method, whereas GROMOS charges are less pronounced. The phosphate atom has the largest charges. There is an overall agreement about the sign (plus or minus) of the atomic charges between all methods for all but two atoms: the nitrogen and the C1 atom. The nitrogen atom carries negative charge in MPA, NPA and AM1, whereas GROMOS, CHELP, and DMA suggest a positive value. The neighboring C1 atom is negative in CHELP and DMA (deprotonated form only), but is positive in all other methods. These are the largest disagreements between the methods, besides the magnitudes in general.

Cholinesulfate charges range from about −1.2 to +2.75 e (Figure 2c). The general result is comparable to that of phosphorylcholine. The sulfur atom contains the largest positive charges. All methods agree for all atoms, with the exception of the value for the nitrogen atom.

Acetylcholine has less pronounced atomic charges, ranging from about −0.8 to +1.2 e (Figure 2d). There is a disagreement between the methods on the nitrogen charge again, and on the C7 atom (the new CH_3 group) between CHELP and the other methods. The center atom C6 has high positive charge, as do the sulfur and phosphate atoms.

PHOSPHORYLCHOLINE, PROTONATED CALCULATED-CHARGES

(a)

PHOSPHORYLCHOLINE CALCULATED CHARGES

(b)

CHOLINESULFATE CALCULATED CHARGES

(c)

ACETYLCHOLINE CALCULATED CHARGES

(d)

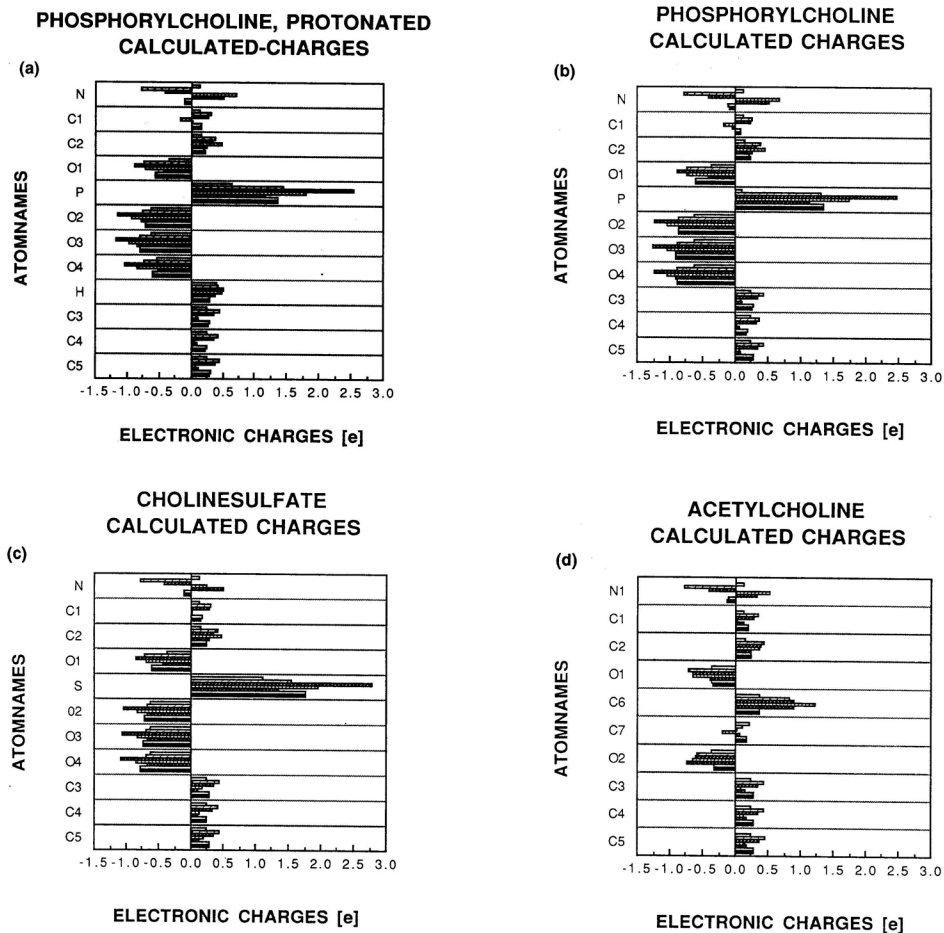
Figure 2a,b,c,d. Absolute charges from quantum mechanical (HF/3- 21G*) or AM1 calculations and application of the MPA, NPA, CHELP, DMA methods. The GROMOS charges are the selected reference charges as explained in the text. (a) Phosphorylcholine, mono- protonated, reference molecule for SCALCHA projection. (b) Phosphorylcholine, deprotonated. (c) Cholinesulfate. (d) Acetylcholine. Geometries and atom labels are shown in Figure 1.

- ▨ GROMOS87
- ◪ AB INITIO, MPA
- ◩ AB INITIO, NPA
- ⠿ AB INITIO, CHELP
- ▨ AB INITIO, DMA
- ☐ AM1, H-bonds opt.
- ■ AM1, all H-param. opt.

SCALED CHARGES WITH THE SCALCHA (FIRST APPROACH) METHOD

The SCALCHA method gives charges that are much more comparable to the absolute magnitude of the GROMOS87 charges for almost all atoms.

In the case of phosphorylcholine (Figure 3a), all methods agree qualitatively for all atoms including the nitrogen. The largest deviation is on the phosphorus atom, where GROMOS suggests a small and all other methods a large value.

In cholinesulfate (Figure 3b), the general behavior remains: again the sulfur atom has the highest charge, but here GROMOS favors a larger value than all the other methods do. The only qualitative difference occurs for the nitrogen atom, where CHELP suggests a negative charge and all other methods a positive one.

Acetylcholine (Figure 3c) displays disagreement on the nitrogen and the C7 atomic charges, all other charges are qualitatively equivalent in all methods.
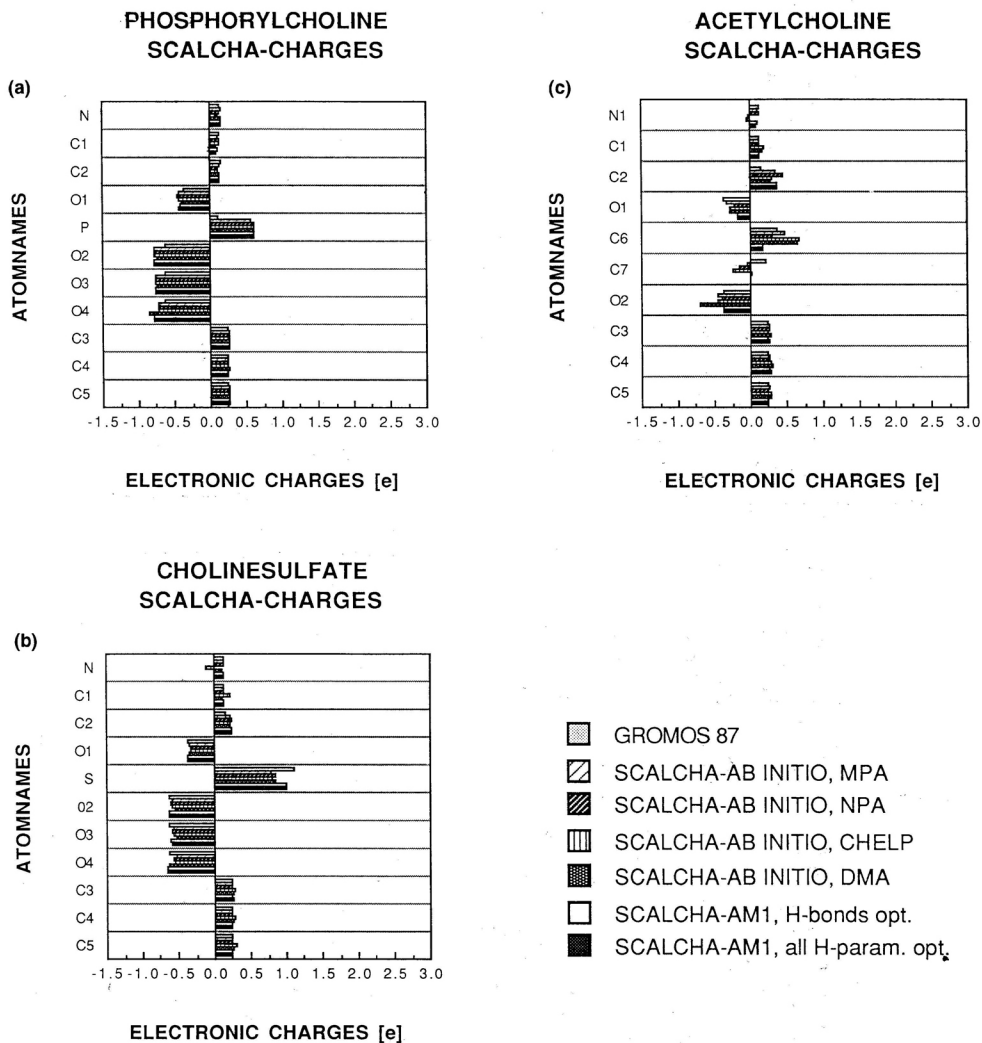
PHOSPHORYLCHOLINE SCALCHA-CHARGES

(a)

ACETYLCHOLINE SCALCHA-CHARGES

(c)

CHOLINESULFATE SCALCHA-CHARGES

(b)

GROMOS 87
SCALCHA-AB INITIO, MPA
SCALCHA-AB INITIO, NPA
SCALCHA-AB INITIO, CHELP
SCALCHA-AB INITIO, DMA
SCALCHA-AM1, H-bonds opt.
SCALCHA-AM1, all H-param. opt.

Figure 3a, b, c. Charges of (a) phosphorylcholine, deprotonated; (b) cholinesulfate and (c) acetylcholine after SCALCHA-projection (first approach) to phosphorylcholine, mono-protonated (GROMOS reference).
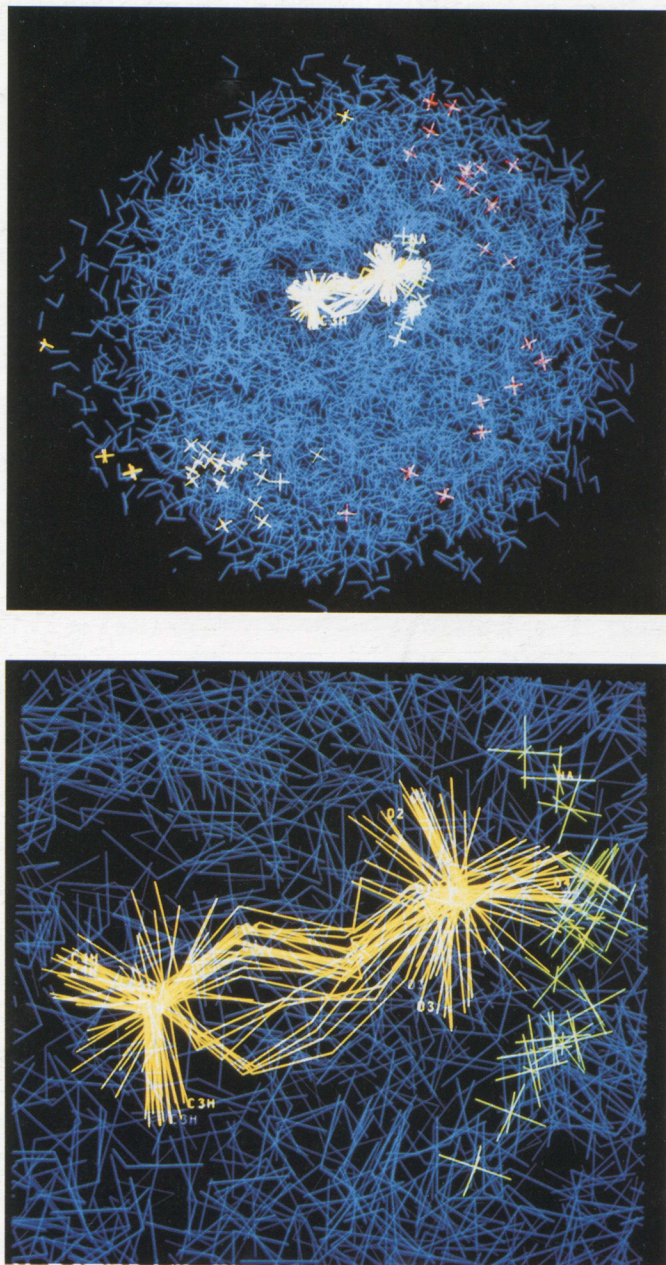
Figure 4a, b. A trajectory of phosphorylcholine, deprotonated, from a molecular dynamics simulation over 25 pico seconds in water at 300 K, (a) whole system, (b) part of Figure 4a.

    As a general result, we can see that SCALCHA provides atomic charges that are
in the order of magnitude of the empirical force field and fulfill the charge group con-
cept, if desired, so that the intermolecular interactions could most probably be ade-
quately described in the molecular dynamics simulations. On the other hand, this con-
cept makes it possible to have exactly defined charges for a group of very similar
molecules. Their small intramolecular differences, which can be expressed by the quan-
tum mechanical calculations, are projected onto the empirical force field. The method
is clearly an approximation. It saves the complicated derivation of force field charges
for molecules that have not been defined yet in the rigorous way as it was done during
the construction of the force field.

    We would like to mention the results from a simulation[22] where the influence of
atomic charges on phosphorylcholine in water at 300 K was demonstrated (Figure
4a,b). The simulations were performed under the same conditions, the only difference
being the atomic charges on the phosphorylcholine molecule. It appeared that the tor-
sional flexibility of the backbone atoms in phosphorylcholine is higher using GROMOS
charges than pure unscaled quantum mechanical charges (HF/3-21G*, MPA) that make
the molecule look 'stiff'. The scaled charges from SCALCHA lie in between (Figure 5).
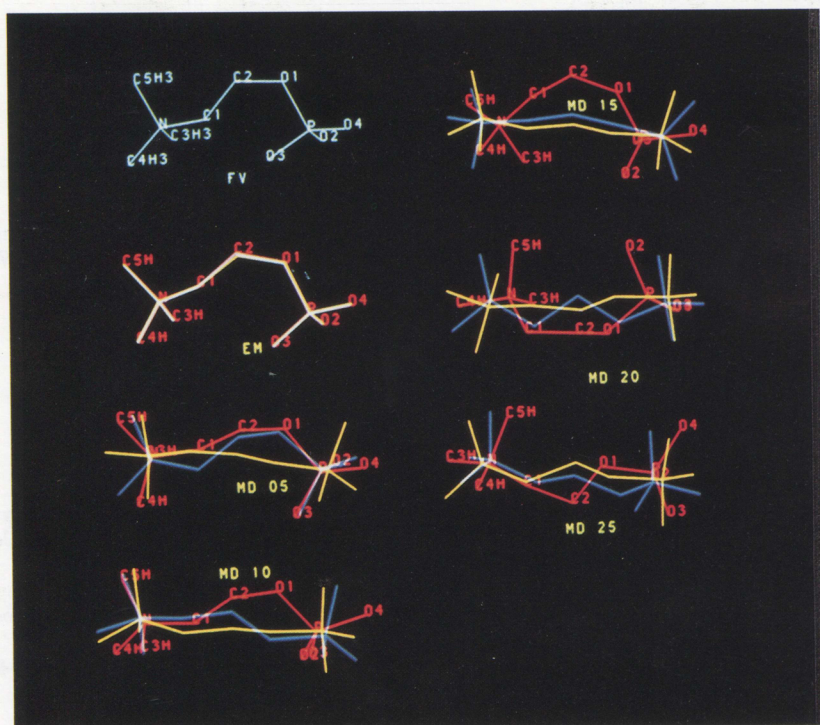

Figure 5. Phosphorylcholine as in Figure 4, but from three trajectories (water and ions removed)
with different sets of charges. Yellow: charges from HF/3-21G*/MPA; red: GROMOS reference;
blue: SCALCHA projection (first approach).

Since we are preparing simulations for the calculation of differences in the free energies between different antibody/antigen complexes, where the electrostatic contributions should be of great importance, the SCALCHA concept could be necessary in order to reproduce the experimentally determined binding constants.

CONCLUSION

We have introduced the SCALCHA concept to perform a projection of atomic charges as derived from quantum mechanical or semiempirical wavefunctions (which describe the intramolecular properties *in vacuo*) onto the current molecular dynamics for fields. The concept is independent of both of these standard methods, its only meaning is a proportional reorganization of molecular atomic charges. We thought that this was necessary, at least, in order to reach the same order of magnitude of charge values that are used in the empirical force fields which describe the molecules in their ensembles in solution or crystalline state.

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SAŽETAK

Uloga atomskih naboja u metodi potencijalnog polja: važnost za proučavanje međudjelovanja proteina i liganada

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Predložena je nova metoda određivanja naboja atoma u okviru metode potencijalnog polja i ilustrirana njihova uloga u proračunu interackija između nekih proteina i liganada.