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Original article

A comparison of different electrostatic potentials on prediction accuracy in CoMFA and CoMSIA studies

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ABSTRACT

Computational chemistry is playing an increasingly important role in drug design and discovery, structural biology, and quantitative structure–activity relationship (QSAR) studies. For QSAR work, selecting an appropriate and accurate method to assign the electrostatic potentials of each atom in a molecule is a critical first step. So far several commonly used methods are available to assign charges. However, no systematic comparison of the effects of electrostatic potentials on QSAR quality has been made. In this study, twelve semi-empirical and empirical charge-assigning methods, AM1, AM1-BCC, CFF, Del-Re, Formal, Gasteiger, Gasteiger–Hückel, Hückel, MMFF, PRODRG, Pullman, and VC2003 charges, have been compared for their performances in CoMFA and CoMSIA modeling using several standard datasets. Some charge assignment models, such as Del-Re, PRODRG, and Pullman, are limited to specific atom and bond types, and, therefore, were excluded from this study. Among the remaining nine methods, the Gasteiger–Hückel charge, though commonly used, performed poorly in prediction accuracy. The AM1-BCC method was better than most charge-assigning methods based on prediction accuracy, though it was not successful in yielding overall higher cross-validation correlation coefficient (q^2) values than others. The CFF charge model worked the best in prediction accuracy when q^2 was used as the evaluation criterion. The results presented should help the selection of electrostatic potential models in CoMFA and CoMSIA studies.

1. Introduction

Quantitative structure–activity relationship (QSAR) studies play an important role in ligand-based drug discovery and design [1]. Such ligand-based approaches are especially critical when the NMR or crystal structure of the target protein is unavailable. As two of the most popular QSAR methods, Comparative Molecular Field Analysis (CoMFA) [2] and Comparative Molecular Similarity Indices Analysis (CoMSIA) [3] employ interactive graphics and statistical techniques for correlating several molecular features, such as steric and electrostatic properties with their biological activities. In CoMFA, the biological properties of molecules are correlated with steric and electrostatic potential energies in terms of Lennard–Jones and Coulombic potentials, respectively. The steric and electrostatic potential energies are calculated by a probe atom, located at each vertex of a spaced lattice, in which a series of molecules are embedded. The performance of the standard CoMFA procedure requires the specification of both conformations and alignments of

Abbreviations: 3D-QSAR, Three-dimensional quantitative structure–activity relationship; CoMFA, Comparative molecular field analysis; CoMSIA, Comparative molecular similarity indices analysis; THR, Thrombin; ACE, Angiotensin converting enzyme; THER, Thermolysin; GPB, Glycogen phosphorylase b; AchE, Acetylcholinesterase; COX-2, Cyclooxygenase-2; DHFR, Dihydrofolate reductase; BZR, Benzodiazepine receptor; HIVPR, Human immunodeficiency virus protease; COMT, Catechol-O-methyltransferase; EGF-R, Quinazoline type epidermal growth factor receptor; PLS, Partial least square; LOO, Leave-one-out; CV, Cross-validation; NCV, Non-cross-validation; q^2, Cross-validated correlation coefficients; r^2, Conventional correlation coefficients; BCC, Bond-charge corrections; RESP, Restrained electrostatic potential.

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molecules. As a complementary technique, CoMSIA introduces hydrophobic and hydrogen bond donor and receptor indices to supplement the steric and electrostatic indices. Therefore CoMSIA has the advantage of reducing computational sensitivity to small changes in molecular alignments or the grid orientations [4]. The evaluation of CoMSIA fields (steric, electrostatic, hydrophobic, and hydrogen bond donor and receptor) is performed by using a probe atom within the lattice box, in which aligned molecules are embedded. Despite their popularity, CoMFA and CoMSIA analyses can be highly sensitive to the parameters used in QSAR modeling, including the setting of steric fields, molecular alignments and grid spacing and dimensions [5,6]. Because of these variances, there have been interests in finding ways to enhance QSAR quality and in building robust CoMFA and CoMSIA models [7–9].

Molecular mechanics (MM) are most commonly used in calculating the interaction energies in CoMFA and CoMSIA studies because a high level simulation, such as quantum mechanics (QM), is very time- and resource-consuming. In such MM calculations, assigning the proper electrostatic charges to the ligands is very important to the eventual success and may affect the QSAR quality as suggested by Sorich and coworkers' recent publication [10]. Till now many efforts have been made to develop accurate charge assignment methods. Some *ab initio* methods, such as the restrained electrostatic potential (RESP) method [11]. are regarded as the most accurate way in assigning the electrostatic charges based on QM simulation. However, the time-consuming nature of *ab initio* calculations is a major barrier to high-throughput charge assignments. Other semi-empirical and empirical methods, including AM1 [12,13], AM1-BCC [14,15], CFF [16], Del-Re [17,18], Formal, Gasteiger [19,20], Gasteiger–Hückel, Hückel, MMFF [21–25], PRODRG [26], Pullman [27], and VC2003 [28] charges, are also widely used for their convenience and speed. So far there are no clear guidelines for the selection of charge models even though Kroemer and coworkers reported one simple comparison of various *ab initio* and semi-empirical charge models in CoMFA [29]. Therefore, we were interested in a comparative study of the above-mention twelve types of charge models for their prediction accuracy of biological activities in CoMFA and CoMSIA studies. This study should provide very useful information for the rational selection of charge models in constructing reliable and robust CoMFA and CoMSIA models.

2. Materials and methods

2.1. Datasets

Ten datasets, including ligands for thrombin [30] (THR), angiotensin converting enzyme (ACE), [31] thermolysin (THER), [3] glycogen phosphorylase b (GPB), [32] acetylcholinesterase [33] (AchE), cyclooxygenase-2 (COX-2), [34] dihydrofolate reductase (DHFR), [35,36] benzodiazepine receptor (BZR), [37] human immunodeficiency virus protease (HIVPR), [7] and catechol-O-methyltransferase (COMT), [38] were used for comparing the effects of different charge models on CoMFA and CoMSIA modeling. The structures of representative compounds from each dataset are shown in Fig. 1. CoMFA and CoMSIA studies of these data sets were conducted by following the same method—the molecular alignment and the division of training and test sets—as depicted in the Weaver's [39] and Tervo's studies [7,38]. The work of Weaver and coworkers disclosed that the preparation of training and test sets was performed by "cherry picking" with a maximum dissimilarity algorithm [40,41] and further optimization was conducted by using the Monte Carlo procedure [41]. The aim of this approach is to ensure maximal diversity of the test set and similar distributions of biological activities for both training and test sets.

2.2. Electrostatic potential assignments

Semi-empirical charges, including AM1, AM1-BCC, and VC2003, were assigned by the QuACPAC 1.1 program [28]. Calculations of empirical Del-Re, Formal, Gasteiger, Gasteiger–Hückel, Hückel, MMFF, and Pullman charges were performed by the SYBYL 7.3 package [42]; CFF charges were assigned by the Discovery Studio 2.0 program [43] and PRODRG charges by the Dundee PRODRG2 online server [26].

2.3. CoMFA and CoMSIA modeling

In the case of CoMFA, the steric and electrostatic potential energies were calculated by using the Tripos force field with the probe atom having the *van der waals* radius of a sp^3-hybridized carbon and a + 1 charge. A lattice with 2 Å grid spacing and extending at least 4 Å in each direction beyond the aligned molecules was used. The truncation for both steric and electrostatic energies was set to ±30 kcal/mol and the electrostatic contributions were ignored at lattice intersection with maximum steric interactions. The CoMSIA similarity index descriptors were calculated by using a dummy sp^3-hybridized carbon with +1 charge. The same lattice box used in the CoMFA calculations was also applied to the CoMSIA calculations. Similarity indices were calculated between the probe and each atom of the molecules based on a Gaussian distance function. The attenuation factor's default value (0.30) was used. Two different CoMSIA models were used as was in the Weaver study [39]: CoMSIA basic model contains steric and electrostatic indices, and CoMSIA extra model consists of hydrophobic indices, hydrogen bond indices, or both hydrophobic and hydrogen bond indices in addition to steric and electrostatic indices. The selection of hydrophobic indices, hydrogen bond indices, and both hydrophobic and hydrogen bond indices used in CoMSIA extra model was the same as depicted in the Weaver study.

2.4. Partial least square analyses

Several validation methods were applied in Partial Least Square (PLS) analyses for evaluating models' quality: leave-one-out (LOO) cross-validation, cross-validation (CV), and non-cross-validation (NCV). For CV, the molecules in the training set were divided into 10 groups. CoMFA and CoMSIA descriptors were employed as independent variables and biological activities were treated as dependent variables. The minimum-sigma (column filtering) value was used to remove descriptors with low variance by omitting the grid point of energy variation less than a threshold of 2.0 kcal/mol for CoMFA and 1.0 kcal/mol for CoMSIA, respectively. The optimal number of components was determined by the LOO cross-validation to give the highest cross-validated correlation coefficients (q^2) and the lowest standard error (*SE*). The optimal number of components used in the CV analyses was employed to derive the non-cross-validated model, which was assessed by conventional correlation coefficients (r^2), *SE*, and *F*-values. The reliability on test sets was estimated using correlation coefficient r^2 provided by the NCV model.

2.5. Comparison of cross-validated and non-cross-validated correlation coefficients

A q^2 value of at least 0.5 is used as the criterion for QSAR robustness [44]. In addition, prediction accuracy on test sets is also required for the external validation of 3D-QSAR models. Herein, we compared the charge-assigning methods in terms of the number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ for training and test sets, respectively.

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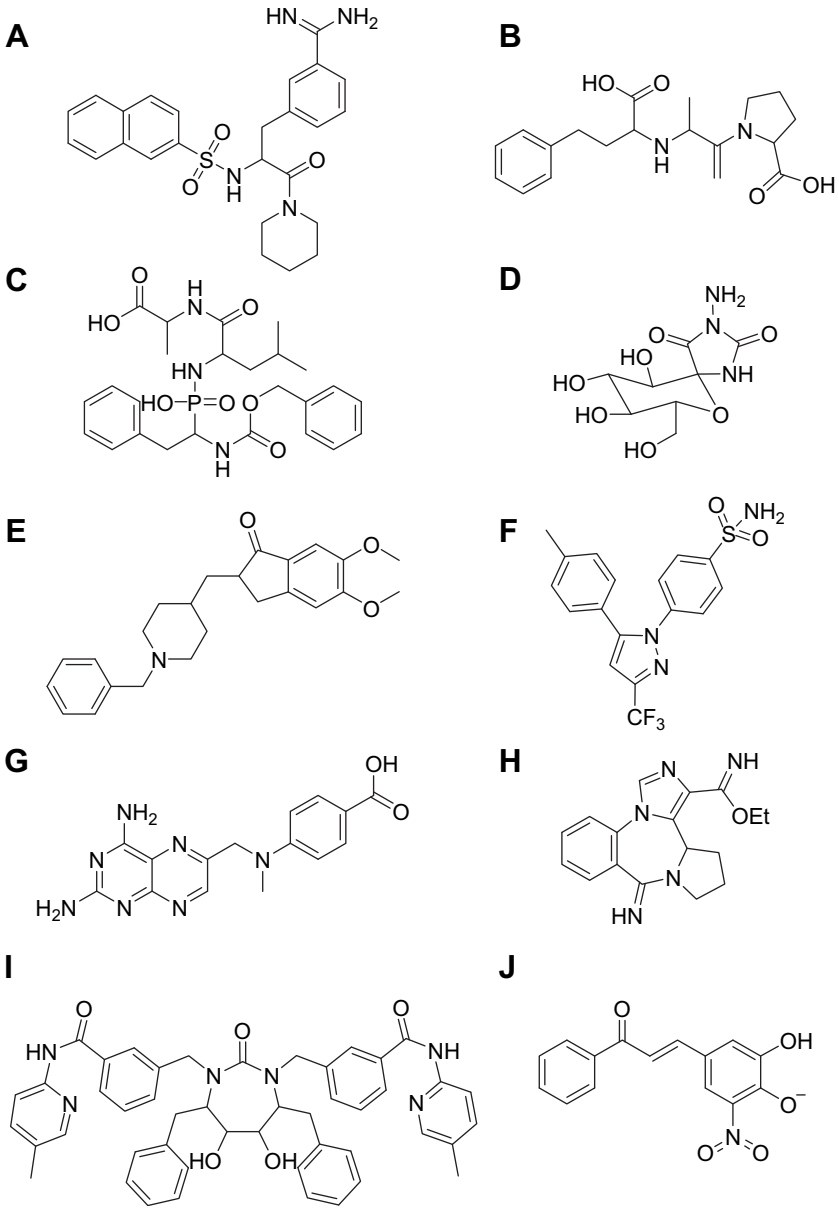

Fig. 1. Representative molecules from each data set: (A) THR; (B) ACE; (C) THER; (D) GPB; (E) AchE; (F) COX-2; (G) DHFR; (H) BZR; (I) HIVPR; (J) COMT.

2.6. Ranking and scoring

The quality of each charge model was determined by the correlation coefficient for the same dataset. Because of the difficulty in comparing the correlation coefficients among different datasets, two specific procedures, ranking and scoring, were applied to overcome this dilemma. First, the charge models were ranked by the correlation coefficients in 3D-QSAR studies within the same data set. In such statistical analyses and comparisons, the Del-Re, PRODRG, and Pullman charge models were excluded because of their limitations on the specific atom and bond types allowed. Second, in the scoring phase, the model with the lowest correlation coefficient was granted a score of 1, the second lowest was granted a score of 2, and so on. The quality of charge models was evaluated by using q^2 for training sets and r^2 for test sets. Finally, scores for each charge method in the same 3D-QSAR method were summed up to evaluate charge's performance for training and test sets.

3. Results and discussion

3.1. Effects of parameter settings

It should be noted that there are many factors affecting the outcome of a QSAR study. Thus, it is possible to present the better results depended on the specific parameter setting. A previous study by Peterson et al. using 9 datasets to generate 6120 models by various combinations of parameters for each datasets had concluded that optimizing various parameters can improve the prediction accuracy of CoMFA models [8]. However, the optimal parameter values are not generally provided in the study. Therefore, we believe that using the default parameter setting can generate the most generally applicable results. On the other hand, the molecular alignment is also a critical step in CoMFA and CoMSIA studies. The molecular alignments of ten datasets are shown in Fig. 2 and Fig. 3. However, it is not easily standardized and the effect of alignment on charge assignments is uncertain. Such factor may

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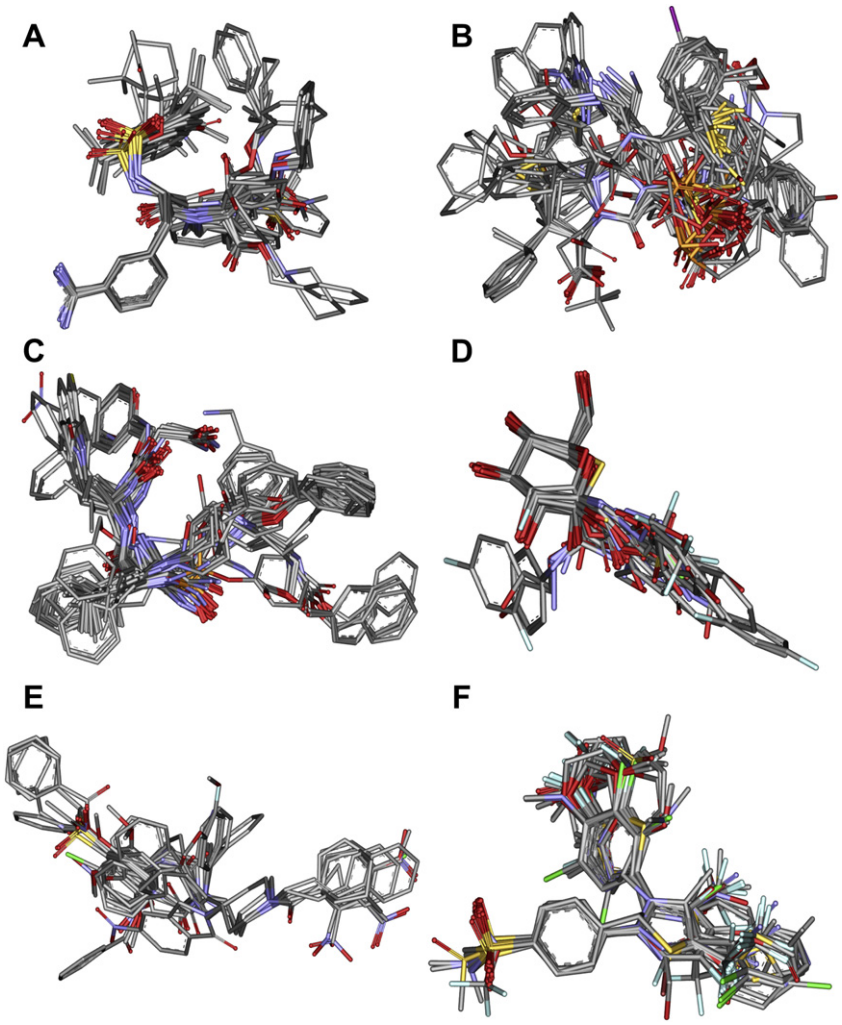

Fig. 2. The molecular alignments of (A) THR; (B) ACE; (C) THER; (D) GPB; (E) AchE; (F) COX-2.

potentially affect the comparison. Thus, we applied the alignment methods from the original studies to partially overcome this influence.

3.2. Constrained atom types for Pullman, Del-Re, and PRODRG charge assignments

The qualities of the charge models were assessed in terms of their correlation coefficients derived from PLS analyses for all datasets. The use of ten independent datasets provides diverse ligand characteristics and ensures the reliability of the statistical work. It needs to be emphasized that some methods may result in failure of charge assignments. For example, Del-Re and Pullman charges could lead to assignment mistakes for those molecules containing S–O, S–N, C–Se, and C–P bonds as well as fluorine atoms. The work of van Aalten et al. [26] indicated that the PRODRG charge model is limited to certain atom types such as H, C, N, O, P, S, F, Cl, Br and I. In addition, the PRODRG charge model does not support those molecules including atoms with more than four bonds and bonds between non-carbon atom and halogens. Such structural features also exist in datasets used in this study, including the phosphonyl derivatives in the THER data set and those with N–Cl bonds in the BZR data set, which results in failure of charge calculation. For all the above-mention reasons, the Del-Re, PRODRG, and Pullman charges were excluded from our discussions.

3.3. Comparison of cross-validated and non- cross-validated correlation coefficients

For these nine charges studied, the CV and NCV results of QSAR studies are listed in the Tables 1 and 2 for training and test sets, respectively. Details of the QSAR results are given in the Supplementary Data section. It is believed that an accurate charge should perform well in not only prediction accuracy but also in avoiding failure for both training and test sets. The number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ for training and test sets, respectively, is listed in Fig. 4. The nine charges are arranged in order of decreasing value (from left to right) based on the sum of the number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$. The Formal charge model yielded the lowest number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ models in all cases as well as the Hückel charge. The Gasteiger–Hückel and Gasteiger charge gave the better performance than the Formal and Hückel charge; however, these four charges were among the lowest number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ models when compared to the others.

The AM1-BCC, AM1, and VC2003 charge-assigning results yielded the same number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ models that were superior to the Gasteiger–Hückel, Gasteiger, Hückel, and Formal charge models. In contrast, the CFF and MMFF charge made the best performance on generating the number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ models. In such analysis, it appears that the different charge-assigning methods yielding the same number of models have

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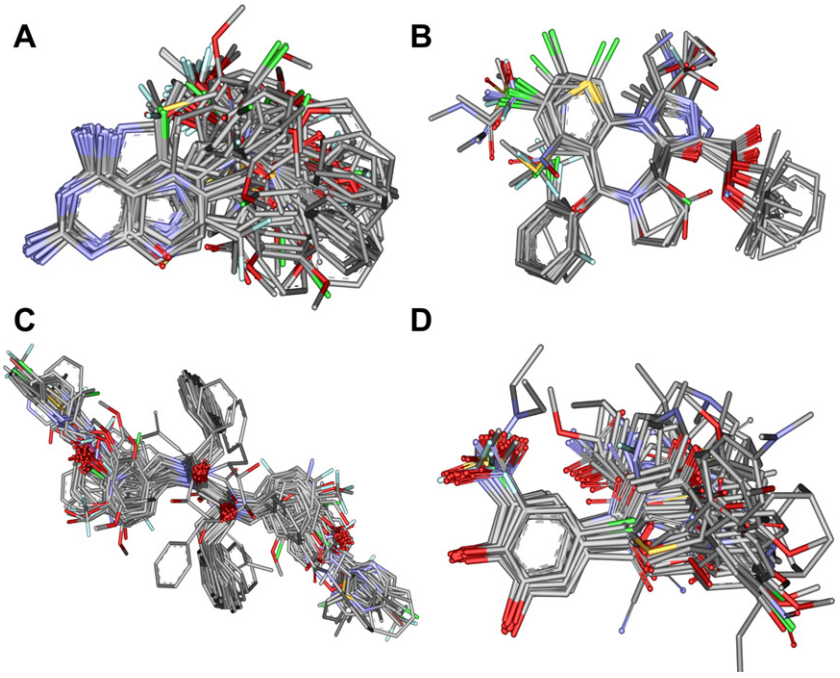

Fig. 3. The molecular alignments of (A) DHFR; (B) BZR; (C) HIVPR; (D) COMT.

similar power on electrostatic potential calculation. It should be noted that the values of q^2 and r^2 generated from the QSAR studies are the parameters used to compare with each other in the literature. However, the difference in prediction accuracy could not be easily compared between the AM1 and AM1-BCC charges in such analysis. Such result does not coincided with a previous study by Jakalian et al. supporting the idea that the additional BCC addition to the AM1 charge model can improve the charge-assigning

Table 1
The q^2 values of all charge-assigning methods in terms of CoMFA, CoMSIA Basic, and CoMSIA Extra study for all datasets, and the number of component is shown in parenthesis.

Dataset	AM1	AM1-BCC	CFF	Formal	G-H	Gasteiger	Hückel	MMFF	VC2003
CoMFA									
ACE	0.648 (3)	0.646 (3)	0.636 (3)	0.634 (3)	0.643 (3)	0.636 (3)	0.644 (3)	0.642 (3)	0.649 (3)
AchE	0.601 (6)	0.566 (6)	0.614 (6)	0.493 (6)	0.516 (6)	0.497 (6)	0.503 (6)	0.591 (5)	0.587 (6)
BZR	0.397 (2)	0.431 (4)	0.412 (4)	0.322 (5)	0.346 (5)	0.389 (5)	0.238 (3)	0.421 (4)	0.363 (3)
COX2	0.460 (5)	0.451 (5)	0.445 (4)	0.348 (5)	0.432 (5)	0.405 (5)	0.352 (6)	0.441 (5)	0.445 (4)
DHFR	0.619 (4)	0.640 (4)	0.642 (4)	0.604 (6)	0.623 (4)	0.621 (5)	0.640 (4)	0.650 (4)	0.644 (4)
GPB	0.305 (4)	0.387 (4)	0.427 (3)	0.126 (3)	0.217 (3)	0.153 (2)	0.184 (3)	0.337 (4)	0.245 (4)
THER	0.447 (4)	0.461 (4)	0.494 (6)	0.436 (4)	0.467 (6)	0.473 (6)	0.423 (4)	0.456 (4)	0.459 (4)
THR	0.544 (4)	0.546 (4)	0.532 (4)	0.518 (4)	0.541 (4)	0.538 (3)	0.519 (4)	0.540 (4)	0.570 (3)
COMT	0.476 (6)	0.365 (6)	0.585 (5)	0.274 (4)	0.446 (5)	0.352 (5)	0.416 (4)	0.535 (6)	0.597 (6)
HIVPR	0.541 (3)	0.517 (3)	0.534 (3)	0.450 (3)	0.434 (3)	0.525 (3)	0.429 (3)	0.543 (3)	0.486 (3)
CoMSIA Basic									
ACE	0.652 (2)	0.650 (3)	0.649 (3)	0.636 (3)	0.645 (3)	0.644 (3)	0.651 (3)	0.647 (3)	0.651 (3)
AchE	0.525 (6)	0.411 (4)	0.493 (5)	0.452 (4)	0.476 (5)	0.483 (5)	0.436 (3)	0.404 (3)	0.474 (4)
BZR	0.394 (3)	0.421 (3)	0.413 (3)	0.192 (2)	0.349 (3)	0.378 (3)	0.222 (4)	0.411 (3)	0.363 (3)
COX2	0.423 (4)	0.468 (5)	0.464 (5)	0.185 (6)	0.391 (4)	0.359 (4)	0.289 (6)	0.424 (3)	0.447 (5)
DHFR	0.626 (6)	0.630 (4)	0.638 (6)	0.595 (6)	0.623 (4)	0.624 (5)	0.570 (5)	0.605 (5)	0.625 (6)
GPB	0.267 (5)	0.340 (6)	0.599 (6)	0.069 (3)	0.224 (5)	0.163 (5)	0.116 (2)	0.365 (6)	0.160 (6)
THER	0.467 (3)	0.484 (3)	0.534 (3)	0.472 (3)	0.509 (3)	0.504 (3)	0.479 (3)	0.500 (3)	0.474 (3)
THR	0.590 (4)	0.585 (5)	0.680 (6)	0.608 (6)	0.607 (5)	0.606 (5)	0.646 (5)	0.615 (5)	0.630 (4)
COMT	0.578 (2)	0.522 (3)	0.642 (6)	0.235 (4)	0.476 (5)	0.319 (5)	0.395 (1)	0.631 (5)	0.675 (3)
HIVPR	0.570 (3)	0.619 (4)	0.633 (3)	0.381 (3)	0.524 (3)	0.408 (3)	0.470 (3)	0.614 (3)	0.581 (4)
CoMSIA Extra									
ACE	0.673 (3)	0.675 (2)	0.665 (2)	0.672 (3)	0.671 (2)	0.672 (2)	0.681 (2)	0.673 (2)	0.675 (2)
AchE	0.575 (6)	0.556 (5)	0.515 (6)	0.505 (6)	0.527 (6)	0.530 (6)	0.521 (6)	0.503 (6)	0.501 (6)
BZR	0.462 (4)	0.408 (4)	0.438 (4)	0.384 (5)	0.424 (3)	0.424 (3)	0.372 (5)	0.426 (3)	0.430 (4)
COX2	0.592 (5)	0.602 (5)	0.540 (5)	0.546 (6)	0.575 (6)	0.579 (5)	0.571 (5)	0.582 (4)	0.577 (4)
DHFR	0.644 (4)	0.649 (4)	0.660 (5)	0.640 (4)	0.672 (4)	0.667 (4)	0.646 (3)	0.654 (4)	0.648 (4)
GPB	0.593 (3)	0.582 (2)	0.655 (3)	0.613 (3)	0.602 (3)	0.612 (3)	0.480 (3)	0.611 (2)	0.591 (2)
THER	0.451 (3)	0.479 (3)	0.536 (3)	0.470 (3)	0.512 (3)	0.513 (3)	0.470 (3)	0.505 (3)	0.461 (3)
THR	0.706 (4)	0.711 (4)	0.731 (5)	0.749 (5)	0.729 (5)	0.735 (4)	0.751 (4)	0.727 (4)	0.732 (4)
COMT	0.697 (2)	0.711 (4)	0.746 (6)	0.692 (5)	0.742 (6)	0.728 (6)	0.684 (6)	0.753 (6)	0.592 (6)
HIVPR	0.681 (4)	0.729 (6)	0.711 (5)	0.583 (4)	0.659 (4)	0.663 (4)	0.589 (4)	0.706 (4)	0.717 (6)

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Table 2
The r^2 values of all charge-assigning methods in terms of CoMFA, CoMSIA Basic, and CoMSIA Extra study for all datasets.

Dataset	AM1	AM1-BCC	CFF	Formal	G-H	Gasteiger	Hückel	MMFF	VC2003
CoMFA									
ACE	0.488	0.487	0.492	0.474	0.481	0.479	0.475	0.491	0.488
AchE	0.521	0.545	0.586	0.534	0.508	0.515	0.542	0.505	0.545
BZR	0.091	0.210	0.241	0.317	0.333	0.217	0.131	0.259	0.217
COX2	0.239	0.295	0.331	0.223	0.213	0.256	0.245	0.292	0.319
DHFR	0.511	0.530	0.550	0.509	0.489	0.537	0.462	0.535	0.537
GPB	0.357	0.433	0.419	0.181	0.313	0.152	0.243	0.418	0.424
THER	0.427	0.452	0.350	0.449	0.427	0.393	0.480	0.428	0.424
THR	0.685	0.683	0.696	0.674	0.692	0.658	0.695	0.696	0.643
COMT	0.547	0.227	0.470	0.036	0.084	0.057	0.091	0.365	0.535
HIVPR	0.601	0.571	0.564	0.516	0.476	0.587	0.466	0.565	0.571
CoMSIA Basic									
ACE	0.490	0.527	0.514	0.465	0.478	0.474	0.470	0.518	0.512
AchE	0.671	0.783	0.703	0.364	0.596	0.603	0.431	0.645	0.680
BZR	0.101	0.116	0.134	0.007	0.142	0.069	0.110	0.154	0.137
COX2	0.148	0.243	0.313	0.137	0.255	0.287	0.241	0.260	0.259
DHFR	0.565	0.553	0.577	0.494	0.476	0.506	0.448	0.488	0.561
GPB	0.626	0.511	0.504	0.130	0.488	0.431	0.169	0.547	0.414
THER	0.496	0.533	0.573	0.483	0.542	0.504	0.544	0.517	0.515
THR	0.661	0.531	0.619	0.593	0.650	0.566	0.650	0.582	0.618
COMT	0.628	0.373	0.685	0.007	0.168	0.114	0.227	0.555	0.584
HIVPR	0.554	0.644	0.571	0.444	0.643	0.504	0.455	0.559	0.584
CoMSIA Extra									
ACE	0.497	0.507	0.503	0.478	0.510	0.499	0.489	0.501	0.500
AchE	0.624	0.627	0.619	0.529	0.551	0.546	0.537	0.579	0.607
BZR	0.164	0.158	0.158	0.103	0.119	0.112	0.127	0.133	0.155
COX2	0.529	0.511	0.389	0.570	0.558	0.541	0.579	0.505	0.503
DHFR	0.585	0.577	0.578	0.563	0.556	0.562	0.559	0.549	0.561
GPB	0.548	0.556	0.494	0.569	0.571	0.560	0.602	0.555	0.564
THER	0.506	0.554	0.603	0.496	0.559	0.520	0.562	0.546	0.536
THR	0.675	0.645	0.678	0.652	0.677	0.622	0.662	0.679	0.681
COMT	0.602	0.589	0.610	0.543	0.610	0.549	0.614	0.585	0.464
HIVPR	0.713	0.716	0.718	0.687	0.727	0.685	0.685	0.667	0.689

accuracy. Therefore, the approach of ranking and scoring analyses was performed to precisely compare the prediction accuracy between twelve charge-assigning methods in the following section.

3.4. Ranking and scoring analyses

The statistic scores for the remaining nine charges, including AM1, AM1-BCC, CFF, Formal, Gasteiger, Gasteiger–Hückel, Hückel, MMFF, and VC2003, in 3D-QSAR studies are shown in Fig. 5a for training sets and Fig. 5b for test sets. Among these charge models, the Formal charge gave the lowest score of 67 for training sets and 82 for test sets. In another word, the performance of the Formal charge is significantly poorer than the others. This poor situation may be caused by the inaccurate charge assignments since no partial charges are assigned to atoms using this charge model.

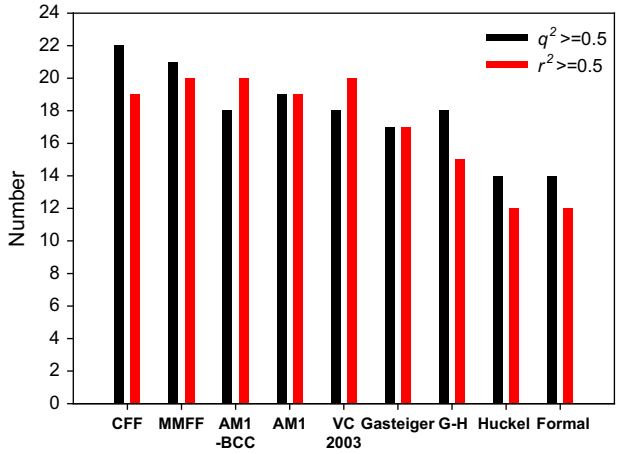

Fig. 4. Comparison of nine different types of charge models in terms of the number of $q^2 \geqq 0.5$ for training sets and $r^2 \geqq 0.5$ for test sets.

Comparing the Gasteiger method with the MMFF partial charge calculation, the scores given by the MMFF charge are higher by 39 for training sets and 49 for test sets than the Gasteiger method. The MMFF partial charge calculation gave the score of 172 for training sets and 156 for test sets, which are higher by 39 for training sets and 49 for test sets than Gasteiger method. In addition to the analysis in the number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ models, this study has demonstrated that the MMFF charge has the better CoMFA and CoMSIA prediction performance than the Gasteiger method. A previous study on one set of quinazoline type epidermal growth factor receptor (EGF-R) inhibitors using CoMFA and CoMSIA indicated that the Gasteiger charge gave slightly better performance than the MMFF method [45]. Another study by Shagufta et al. using 44 compounds of diaryloxymethano-phenanthrene derivatives found that the Gasteiger and MMFF charges had similar prediction accuracy for CoMFA study [46]. Sorich and coworkers' very recent studies, in which the MMFF charges showed statistically significant better prediction accuracy than Gasteiger method, was consistent with our results [10]. The discrepancy between ours with Mittal's results and two previous studies most likely resulted from previous comparisons being limited to a single data set and, thus, assessing the probability of the result occurring by chance.

Using the AM1-BCC charge resulted in a score of 174 for training sets and 177 for test sets, which are higher by 12 for training sets and 19 for test sets than calculations using the AM1 charge. Such difference is in agreement with the findings by Jakalian et al. [15], which suggest that the additional bond-charge corrections (BCC) to the AM1 method can improve the electrostatic assignments. Our

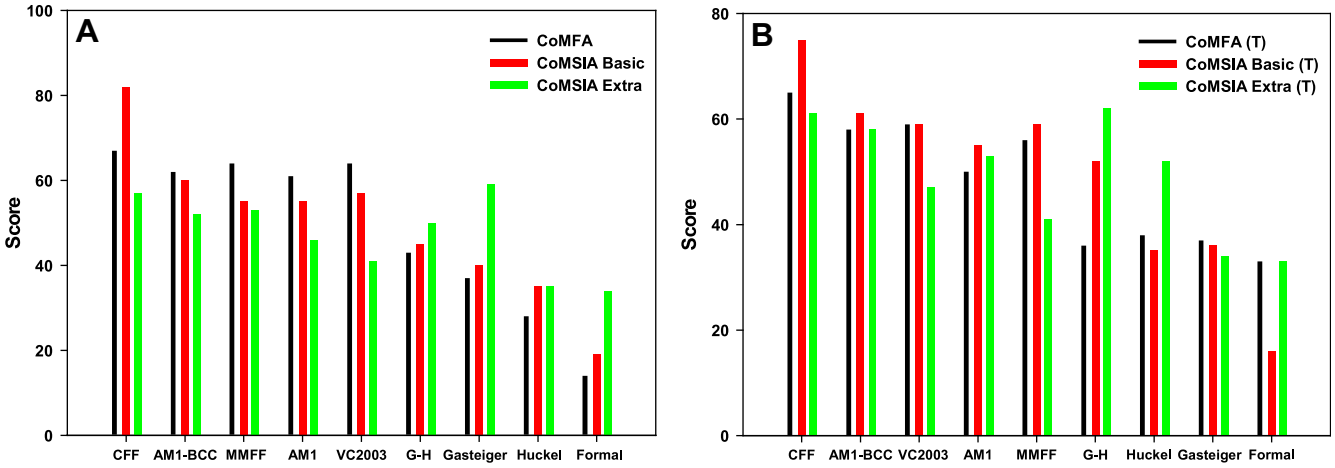

Fig. 5. Comparison of nine different charge models in terms of scores given by three 3D-QSAR models: nine charges were arranged in order of decreasing value (from left to right) based on the sum of the scores given by each charge model for (a) training sets (b) test sets. CoMSIA_Basic: CoMSIA with steric and electrostatic indices. CoMSIA_Extra: CoMSIA with use of hydrophobic, hydrogen bond, and both hydrophobic and hydrogen bond indices in addition to steric and electrostatic indices. T: The analyses for the test sets. G–H: Gasteiger–Hückel.

previous studies using 114 datasets also suggested that the application of the AM1-BCC charge in DOCK5.4 can improve docking performance compared to the AM1 model [47]. Moreover, the work of Dill and coworkers suggested that the AM1-BCC method in electrostatic charge assignments worked as well as computationally expensive *ab initio* methods [48]. Although the semi-empirical calculations perform the charge assignment by a more detailed description of the atom and hence are considered more accurate, the cost of greater computational time is an important factor to consider.

Generally, Gasteiger–Hückel charges are widely used in both drug design and discovery, and structural biology and bioinformatics. However, it needs to be noted that in our studies the Gasteiger–Hückel charge, with a score of 138 for training sets and 150 for test sets, did not yield the best results. Comparing the Gasteiger–Hückel charge with the AM1 charge, the scores given by the AM1 charge are higher by 24 for training sets and 8 for test sets than the Gasteiger–Hückel charge. Besides, the AM1-BCC charge gave the higher score by 36 for training sets and 27 for test sets than the Gasteiger–Hückel charge. In addition to the analysis in the number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ models, our result indicates that semi-empirical methods such as the AM1 and AM1-BCC charges provides the more accurate results than the Gasteiger–Hückel charge. Such results presented here is also consistent with the work of Mittal et al. [10]. However, Kim et al. [49]reviewing from 8 studies [29,50–56]. each involving a single dataset, commented that there was no significant difference in prediction accuracy between the Gasteiger methods and semi-empirical methods. In contrast, a previous study by Choo et al. [57] using 32 aryl-sulfonyl-imidazolidinone derivatives indicated that the AM1 yielded a much higher q^2 value than the Gasteiger–Hückel charge. Another study on human COMT enzyme kinetics presented that the AM1 charge gave better performance in CoMFA and CoMSIA studies than the Gasteiger–Hückel charge [58]. According to these previous studies using a single dataset, there is no clear guideline indicating whether the semi-empirical charges provide a higher prediction accuracy. However, our results confirm that instead of the Gasteiger–Hückel charge the semi-empirical methods, AM1 and AM1-BCC, indeed give reasonable prediction potential through charge calculation.

The use of CFF charges gave the highest scores for all datasets: 206 for training sets and 201 for test sets, which are higher by 34 for training sets and 45 for test sets than calculations using the MMFF charge model. Both CFF and MMFF charge-assigning methods are derived from *ab initio* calculation and experimental data. The MMFF charge is designated to be a transferable force field that accurately treats conformational energetics and non-bonded interactions. In contrast, the CFF charge as a class II force field has been extensively used to study the energetics and dynamics of many biomolecules [59,60]. Although the same number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ models was generated between the CFF charge calculation results and MMFF charges, the significant difference in the score had demonstrated that the CFF charge indeed performed more accurately in CoMFA and CoMSIA studies than the MMFF charge. Comparing the CFF charge with the AM1-BCC charge model, which gave the second best performance in CoMFA and CoMSIA studies, the CFF charge yielded a higher score by 32 for training sets and 24 for test sets than the AM1-BCC charge model. In addition to the analysis in the number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ models, it is our opinion that the CFF charge works the better performance in CoMFA and CoMSIA studies than the AM1-BCC charge. According to the aforementioned result and our previous study [47], the AM1-BCC gave the better CoMFA and CoMSIA prediction performance than AM1 and therefore, the CFF charge made the much higher accuracy in CoMFA and CoMSIA prediction than the AM1 charge: higher score by 44 for training sets and 43 for test sets. The result of the analysis in the number of $q^2 \geqq 0.5$ and $r^2 \geqq 0.5$ models for the AM1 charge also corresponds to this trend. The failure of charge assignment by using AM1 may result from the lack of the BCC application. Therefore, we suggest that the CFF charge, an empirical method, overall outperforms the AM1-BCC and AM1 charge that are semi-empirical methods in CoMFA and CoMSIA prediction.

In general, the prior studies comparing the effect of the partial charge calculation methods are very difficult to interpret because the results are conflicting. Our study, however, showed significant differences in the prediction accuracy based on nine charge-assigning methods. As a class II force field, the CFF charge has additional cross terms in potential energy calculations. However, most of previous studies used the CFF charge for molecular dynamics, modeling, and docking studies instead of QSAR studies [59–61]. On the basis of our results, we believe that the use of CFF charges could provide more accurate CoMFA and CoMSIA models for drug design and discovery. On the other hand, as an empirical method the CFF charge derived from high level quantum mechanical calculations provides the advantages of not only shorter computation time but also more accurate CoMFA and

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CoMSIA prediction than the conventional approaches,. In summary, we suggest that the CFF charge model work the best among these nine types of charges in assigning the proper electrostatic potentials to various atoms in CoMFA and CoMSIA studies.

4. Conclusions

This study performed a comparison of nine partial charge calculations on prediction accuracy in CoMFA and CoMSIA studies, because there were no clear guidelines on the selection of electrostatic potential methods. The semi-empirical charges (AM1 and AM1-BCC) yielded superior predictive CoMFA and CoMSIA models than using the Gasteiger and Gasteiger–Hückel charges which are commonly used in QSAR studies. The AM1-BCC charge using the additional BCC terms added to the AM1 charge indeed improve the CoMFA and CoMSIA prediction accuracy than the AM1 charge and gave the superior QSAR models than the MMFF charge.

The CFF partial charge calculation method was found to result in the most predictive CoMFA and CoMSIA models. As an empirical charge-assigning method with a short computing time, the CFF charge offer advantages over the other eleven semi-empirical and empirical charges in performing the most accurate electrostatic potential calculations for CoMFA and CoMSIA studies.

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Supplementary Data

The tabulation of LOO-CV correlation coefficients (q^2), CV correlation coefficients (q^2), and NCV correlation coefficients (r^2) values given by nine different charges using three 3D-QSAR methods and ten datasets. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2009.12.063.

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