J. of the Chosun Natural Science
Vol. 4, No. 2 (2011) pp. 99 – 102

A Review about the Importance of Protonation of Ionizable Molecules on the Predictability of CoMFA

Gugan Kothandan†

Abstract

Effect of protonation and deprotonation of ionization compounds is an important application in Comparative molecular field analysis (CoMFA). There are enough information's were reported about different CoMFA applications such as Series design and selection of training set, Geometries and optimizations of molecules, Effect of partial atomic charges, bioactive conformations and alignment, Interaction energy fields, Effects of different grid spacing etc. However limited information's are available about the ionization of compounds. This study aimed at the critical review of about the effects of protonation of ionizable molecules and its impact on the predictability of CoMFA models. We also discussed about previous implications and the things needed to be considered to come for a final conclusion about its impact on CoMFA predictability.

Key words : 3D QSAR, CoMFA, Protonation

1. Introduction

Predicting the biological activity of a candidate drug, as well as its pharmacokinetic properties and toxicity, early in the drug discovery process has the ability to significantly reduce the cost of developing drugs[1]. An important computational approach in predicting properties in drug discovery is the quantitative structure-activity relationship (QSAR) method, which correlates biological activity to chemical properties/descriptors in a series of structures[2]. Lead optimization, in which a chemical showing promise is modified to improve its usefulness as a drug, is a vital component of the drug discovery process. Quantitative structure-activity relationship (QSAR) methods can facilitate this process by elucidating the chemical characteristics that are favorable and unfavorable through statistical analysis of a series of chemical analogues.

Three-dimensional (3D)-QSAR techniques such as comparative molecular field analysis (CoMFA)[3] and comparative molecular similarity index analysis (CoMSIA)[4] are popular[5] due to their ability to generate both highly predictive and easily interpretable models. The process of undertaking a 3D-QSAR can generally be broken down into three parts:

1. Molecular alignment: The alignment or superimposition of the molecules involves deciding on a common pattern of receptor binding so that all of the molecules can be placed in this pattern [3].

2. Calculation and sampling of molecular fields: Force fields are used in CoMFA to describe the interactions that typically occur between a ligand and the target macromolecule. The forces primarily responsible for ligand-protein interactions include the steric (also known as dispersion or van der Waals), electrostatic, hydrogen-bonding and hydrophobic molecular fields. The aligned molecules are placed within a 3D grid or lattice of points. This grid is used as a means of sampling the interaction between the individual molecules (of the aligned set) and various probes placed at each of the lattice points of the grid[3,6].

3. Analysis of molecular fields: Typically, partial least squares regression (PLSR) is used to determine the linear function that maps molecular field values into the binding affinity of the ligand [3].

There are also many choices to be considered in a CoMFA analysis[7]: biological data, selection of com-

Centre for Bioinformatics, Department of Biochemistry, School of Life sciences, University of Madras, Guindy Campus, Chennai - 600025, INDIA

†Corresponding author : guganmsc@gmail.com
(Received : May 24, 2011, Revised : June 17, 2011, Accepted : June 20, 2011)

pounds and series design, generation of three-dimensional structure and charges of the ligand molecules, conformational analysis and establishment of bioactive conformations, alignment of molecules, position of lattice points and choice of force fields and calculation of interaction energies, statistical analysis of data and the selection of final model, display of results, and design of forecasting the activity of unknown compounds. At each stage there are a multitude of technical options, the choice of which can significantly influence the utility of the models generated. Furthermore, there is little good evidence to suggest which options are best, thereby leaving these complicated choices to the end user.

Among the different choices mentioned above molecular conformation and alignment is really an important issue and CoMFA results are sensitive to alignment. After the selection of particular conformation for alignment, partial atomic charges are required for calculation of the electrostatic interaction energies. As partial charges are used to calculate the electrostatic fields in CoMFA studies, the quality of the partial charges calculated should influence the quality of the electrostatic field and hence the ability of CoMFA models to predict the activity of new chemicals. There have been a number of studies that directly or indirectly have assessed the influence of different partial charge calculation methods on CoMFA prediction accuracy[8-11]. Although many groups investigated this issue from early days of CoMFA and there seems to be no consensus answer.

Similarly, protonation of ionizable molecules should also be an issue in the predictability of CoMFA. However, not many reports were reported regarding this issue. This prompted us to initiate a review paper concerning the protonation and deprotonation state of ligand molecules. This study aimed at producing a review on the effects of protonation on the predictability of CoMFA. We reported some of the previous results and we also urged the importance of further implication.

2. Protonation and deprotonation on CoMFA

Protonation is the process of addition of a proton (H+) to an atom or a molecule. The reverse process of protonation is deprotonation. Under physiological conditions, the organic ligand molecules (acid/base) needs to be protonated and deprotonated. Virtually all drug-like molecules are weak acids or bases. This means that they contain at least one site that can reversibly disassociate or associate a proton (a hydrogen ion) to form a negatively charged anion or a positively charged cation. Molecules that disassociate protons are acids, and those that associate protons are bases. The reversibility means that a sample is always in equilibrium with some fraction protonated and the rest deprotonated. Among the drug like molecules, the site would be subjected to protonation/deprotonation is mostly of piperazine, acetic acid, amine, pyridine, guanidine, tetrazole etc. These derivatives should be considered for protonation/deprotonation to consider the CoMFA analysis close to reality. Whether, protonation and deprotonation of ligand molecules affects the predictability of CoMFA should be addressed. This is an important issue and considered to be one of the limitations of CoMFA.

3. Results reported in the literature

When ionizable molecules are involved, one must decide which protonation state of the molecule to be considered in CoMFA calculations. Many researchers are working on this issue and reports are available in the literature. Li et al[12]. Studied the inhibition of spermidine transport into L120 cells by 46 polyamine analogs. The compounds contained from one to four cationic groups and were primary, secondary and tertiary alkyl amines. All are positively charged at physiological pH. Different protonation states of ionization were used in the analysis in order to get the best CoMFA model. Positively charged group was used for those compounds with amino group having pKa values above 8. When the compounds having pKa value less than 5, the neutral species were used. In the case of compounds having pKa fell between 5 and 7, both charged and uncharged structures were included separately in the calculations. For the azridine analogs, the protonated form was used if the pKa values were above 6 and both if the pKa values was below 6. Similarly, Tong and his group[13] also studied the effect of ionization in their study with two classes of acetylcholinesterase inhibitors, N-benzylpiperidine benzisoxazoles and 1-benzyl-4-[2-(N-benzoylamino) ethyl]-piperidines. They investigated the influence of charged species on CoMFA using both neutral and protonated species, although the compounds involved were

thought to be protonated. A better CoMFA model was obtained with protonated species and two different alignments. Marshall and his group also examined on a series of 93 diverse inhibitors of HIV-1 protease inhibitors[14,15]. From five different alignments of 59 molecules in a test set, two best results were obtained from alignment I and alignment V. In the alignment I molecules in the neutral form were aligned, whereas in alignment V molecules in the protonated form were aligned. However, it was also observed that the molecules in the neutral form gave better results (q2 = 0.78, r2 = 0.98) than the one in the protonated form (q2 = 0.64, r2 = 0.99). Interestingly, the electrsostatic contribution in both the models was found to be similar. The model was also predicted externally and it was concluded that based on the statistical results, which of the two models were better.

4. Further implications

The results obtained from the above analysis didn't give clear cut information. Some suggested that considering protonation would be desirable and some quoted in the other way. Similarly, Gohlke and his group performed 3D-QSAR analysis with molecules either protonated or neutral form for a series of Nictonic acetylcholine receptor antagonists[16]. They proclaimed that only a small influence on the statistical results is expected because of the fact that CoMFA and CoMSIA only relate differences in molecular structure to differences in binding affinities, and the change in protonation state affects all molecules in equal measure. The reason for inconclusive results is that, all the reported results were based on only a single dataset. Mittal et al. tested the effects of steric field settings and also the effect of partial charges on a number of QSAR datasets[17,18]. Similarly, to gain further insights and to find whether protonation affects the predictability of CoMFA results, analysis should be done on number of QSAR datasets. This may provide some conclusive answer whether protonation really affects or improves the predictability of CoMFA.

5. Conclusion

3D-QSAR techniques will continue to make a valuable contribution to the computer assisted analysis of structure activity relationships. Significant advances have been made in CoMFA, however many limitations and problems still remain and it has been unsolved. Considering the protonation state of ionizable compounds is also one of the limitations and it still unsolved. The current study deal about need of giving insights about the importance of the protonation of ionizable molecules was discussed. Due to the paucity of the data, a critical review about the effect of protonation of ionizable molecules on the predictability of CoMFA was explained. Previous results were well discussed and need for further implications are pointed out. This review could be useful for the research community working on the limitations of CoMFA.

References

[1] S. A Roberts, "High-throughput screening approaches for investigating drug metabolism and pharmacokinetics", Xenobiotica., Vol. 31, pp. 557-589, 2001.

[2] M. Dias, R. Mittal, R. McKinnon and M. Sorich, "Systematic statistical comparison of comparative molecular similarity indices analysis molecular fields for computer-aided lead optimization", J. Chem Inf. Model., Vol. 46, pp. 2015-2021, 2006.

[3] R. D. Cramer, D. E. Patterson and J. D. Bunce, "Comparative molecular field analysis (CoMFA) I. Effect of shape on binding of steroids to carrier proteins", J. Am. Chem. Soc., Vol. 110, pp. 5959-5967, 1988.

[4] G. Klebe, U. Abraham and T. Mietzner, "Molecular Similarity Indices in a Comparative Analysis (CoMSIA) of Drug Molecules to Correlate and Predict Their Biological Activity", J. Med. Chem., Vol. 37, pp. 4130-4146, 1994.

[5] L. L. Zhu, T. J. Hou, L. R. Chen and X. J. Xu, "3D QSAR Analyses of Novel Tyrosine Kinase Inhibitors Based on Pharmacophore Alignment", J. Chem. Inf. Comput. Sci., Vol. 41, pp. 1032-1040, 2001.

[6] G. Klebe, "Comparative Molecular Similarity Indices Analysis: CoMSIA", Perspect. Drug Discovery Des., Vol. 12, pp. 87-104, 1998.

[7] K. H. Kim, "Comparative Molecular Similarity Field Analysis (CoMFA), In dean, P. M. (Ed.) Molecular similarity in drug design", Blackie Academic & Professional, London., pp. 291-331, 1995.

[8] L. Belvisi, G. Bravi, G. Catalano, M. Mabilia, A. Salimbeni and C. Scolastico, "A 3D QSAR CoMFA study of non-peptide angiotensin II receptor antag-

onists", J. Comput.-Aided Mol. Des., Vol. 10, pp. 567-582, 1996.

[9] K. H. Kim, G. Greco and E. Novellino, "A critical review of recent CoMFA applications", Perspect. Drug Discovery Des., Vol. 12, pp. 257-315, 1998.

[10] R. T. Kroemer, P. Hecht and K. R. Liedl, "Different electrostatic descriptors in comparative molecular field analysis: A comparison of molecular electrostatic and Coulomb potentials", J. Comput. Chem., Vol. 17, pp. 1296-1308, 1996.

[11] A. Shagufta, G. Kumar, M. Panda, I. Siddiqi, "CoMFA and CoMSIA 3D-QSAR analysis of diaryloxy-methano-phenanthrene derivatives as antitubercular agents", J. Mol. Model., Vol. 13, pp. 99-109, 2007.

[12] Y. L. Li, A. D. Mackerell, M. J. Egorin, M. F. Ballesteros, D. M. Rosen, Y. Y. Wu, D. A. Blamble and P. S. Callery, "Comparative molecular field analysis-based predictive model of structure function relationships of polyamine transport inhibitors in L1210", Cancer. Res., Vol. 57, pp. 234-239, 1997.

[13] W. Tong, E. R. Collantes, Y. Chen and W. J. Welsh, "A comparative molecular field analysis study of N-benzylpiperidines as acetylcholinesterase inhibitors", J. Med. Chem., Vol. 39, pp. 380-387, 1996.

[14] T. I. Opera, C. L. Waller and G. R. Marshall, "3D-QSAR of human immunodeficiency virus (I) protease inhibitors: 3. Interpretation of CoMFA results", Drug Des. Discovery., Vol. 12, pp. 29-51, 1994.

[15] C. L. Waller, T. I. Opera, A. Giolitti and G. R. Marshall, "Three-dimensional QSAR of human immunodeficiency virus-I protease inhibitors: 1. A CoMFA study employing experimentally determined alignment rules", J. Med. Chem., Vol. 36, pp. 4152-4160, 1993.

[16] H. Gohlke, S. Schwarz, D. Gundisch, M. C. Tilotta, A. Weber, T. Wegge, and G. Seitz, "3D QSAR Analyses-Guided Rational Design of Novel Ligands for the (α4)2(β2)3 Nicotinic Acetylcholine Receptor", J. Med. Chem., Vol. 46, pp. 2031-2048, 2003.

[17] R. R. Mittal. R. A. McKinnon and M. J. Sorich, "Effect of steric molecular field settings on CoMFA predictivity", J. Mol. Model., Vol. 14, pp. 59-67, 2008.

[18] R. R. Mittal, L. Harris, R. A. McKinnon and M. J. Sorich, "Partial Charge Calculation Method Affects CoMFA QSAR Prediction Accuracy", J. Chem. Inf. Model., Vol. 49, pp. 704-709, 2009.