Updates on the charge flux parameters for oganic molecules

Here we report the recent update on the charge flux (CF) parameters for organic molecules. The functional forms of CF remain the same as our previous publication.1 This set of parameters are derived from a bigger amount of organic molecules (484 neutral molecules). In addition, the atomic multipoles have been re-derived with the AMOEBA+ protocol. That being said, this set of parameters are mainly designed for the use with the AMOEBA+ force field.

The atomic types used for CF have already been made consistent with the atomic classes for valence parametrization, so it is more convenient for Tinker to recognize those parameters. Readers can refer to amoebaplusCFluxType.dat and amoebaplusBondedType.dat in amoebaplus\_parameter/dat. The old version ([amoebaplus\_parameter](https://github.com/prenlab/amoebaplus_parameter)/prm/cflux2021.prm) will be deprecated.

The standard set of CF parameters has been recorded in [amoebaplus\_parameter](https://github.com/prenlab/amoebaplus_parameter)/prm/cflux2022.prm. They are derived from the dipole moment fitting on a group of ~46500 configurations generated by 482 neutral molecules, which involves various functional groups and chemical structures far more than that used previously1. From **Table 1**, the RMSD of components of absolute dipole moments (Equation 1) is 0.1224 Debye, and the RMSD of relative values (Equation 2, is the difference between any configuration and the equilibrium structure) is 0.0786 Debye. Compared with the data from our previous work1, in which we reported the RMSD of absolute values 0.1369 Debye from ~10000 configurations generated by 216 molecules, this new set of parameters has better performance and covers more distinct situations. Also, the distribution of the CF parameters (both bond , angle and coupled bond ) was observed to concentrate in the range of -0.33~0.3, which is much smaller than that of the old version when considering the different units of the angle CF used in the new (rad-1) and the old version (deg-1). It indicates the new CF parameters avoid overfitting and possess higher transferability. Moreover, some of the CF parameters from different bonds or angles are very similar, which makes it possible to combine them into a single parameter shared by several structures. Also, the parameters for certain structures are extremely small and can be set to 0. Hence, the number of parameters has been reduced to ~450. Those zero-valued parameters have been still kept in our new set to guarantee all known structures from our database can be found by the assignment program.

Besides this standard parameter set, we produced another more general CF parameter set based on only element and hybridization, and the specific typing can be found in amoebaplus\_parameter/dat. It is designed for more general situations, in which the new molecules have bonds or angles beyond the span of our database. The absolute RMSD of components is 0.1238 Debye and the relative RMSD is 0.0843 Debye by using the general CF parameters on our database. These values are slightly larger than what we obtained based on the atomic classes for valence terms, meaning that CF effects are not so sensitive to the number of types. The CF can only be regarded as a correction to dipole moment in structural deformation, so using more types to classify CF effects from more detailed structures is not necessary sometimes. To guarantee both the accuracy and adequate description of different structures, we embedded both the basic and general CF parameter set in our program, which will automatically switch to general CF assignment if there exists a bond or angle out of reach of the database.

In summary, comparing to the previous set of CF parameters, this set is improved in these aspects: (1) increased coverage of molecules and number of deformed conformations have been used in parametrization; (2) consistent atom typing with the bond/angle terms in the previous publication; and (3) consistent dipole extrapolation scheme with AMOEBA+ force field; (4) resulted CF parameters are in appropriate range.

**Table 1.** Statistical comparison of QM molecular dipole moments and molecular mechanics (MM) values calculated by AMOEBA+ model with CF implementation of standard types and general types.

|  |  |  |  |
| --- | --- | --- | --- |
| **Statistics** | **Standard types** | **General types** | **No CF** |
| **RMSD**  **Componentsa)**  **(debye)** | Abs: 0.1224  Rel: 0.0786 | Abs: 0.1238  Rel: 0.0843 | Abs: 0.1809  Rel: 0.1511 |
| **RMSD**  **Totalb)**  **(debye)** | Abs: 0.1315  Rel: 0.0855 |  | Abs: 0.2008  Rel: 0.1666 |
| **R2 c)** | 0.993 |  | 0.983 |

a). RMSD over all x, y, z components of dipole moments from the molecules. b). RMSD over the total dipole moments of the molecules. c). the correlation coefficient.

**Reference**

1. Yang, X.; Liu, C.; Walker, B. D.; Ren, P., Accurate description of molecular dipole surface with charge flux implemented for molecular mechanics. *The Journal of Chemical Physics* **2020,** *153* (6), 064103.