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Partial charges

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Abstract: Partial charge in theoretical chemistry usually refers to atomic charge, which reflects net charge carried by an atom in a chemical system, and closely related to many properties of atoms. Partial charge has important theoretical significance and has very wide applications in the field of computational chemistry. In this chapter, basic concept about partial charge will be described, well-known partial charge calculation methods will be overviewed. This chapter also compares partial charges calculated by different methods for typical molecules, so that readers can quickly understand their similarities and differences. Computer codes for evaluating popular partial charges will also be mentioned. Finally, we give suggestions on the selection of partial charges in practical research.

Keywords: Partial charge; Atomic charge; Wavefunction analysis; Population analysis; Quantum Chemistry

6.1 Concept of partial charge

6.1.1 What is partial charge?

In a chemical system, due to formation of ionic bonds or polar covalent bonds, action of an external electric field, electron ionization and attachment and so on, atoms can have a non-integer net charge, which is known as partial atomic charge, and can also simply be referred to as partial charge or atomic charge. Partial charge is generally represented by a point charge located at nuclear position, which is one of the simplest and most intuitive ways to describe charge distribution in chemical systems.

Partial charge is never a physically observable quantity, and it is therefore impossible to have a unique definition. Partial charges may be determined indirectly through some experimental data[1], such as molecular multipole moment, infrared spectrum intensity and frequency, ligand field splitting energy, NMR shift, and so on. However, the data acquisition in this way is relatively inconvenient, the correspondence between the data and partial charges is often highly empirical, and unstable systems or transient electronic states cannot be studied. The development of computational chemistry has made it possible to obtain partial charges conveniently, quickly and reasonably[2-7]. Since the very famous Mulliken charge[8-10] was proposed in 1955, at least fifty methods of evaluating partial charges have been proposed so far, many researchers are still trying to improve the calculation methods in recent years. These methods have different characteristics and emphases, and researchers need to choose the most appropriate one according to their actual needs.

Partial charge uses *e* as the unit, which is the abbreviation of elementary charge and corresponds to the amount of charge carried by a single proton. Elementary charge is the charge unit in the atomic unit (a.u.) system, therefore unit of partial charge can also be written as a.u. In the literatures, unit of partial charge is often omitted since this will not cause any ambiguity.

Notice that partial charge is quite different to oxidation state (OS), the latter is always integer and corresponds to the hypothetical charged state if all heteronuclear bonds formed by the atom are assumed to be fully ionic. Usually, magnitude of OS is by far larger than partial charge. For example, partial charge of oxygen in water molecule calculated by most methods is in the range of -0.3 to -1.0, while its OS is -2. Partial charge is also in sharp contrast to formal charge, which is defined based on Lewis structure and calculated as N(valence electrons in free atom) − N(nonbonding electrons) − N(electrons in related bonds)/2, where N indicates number of electrons of corresponding kind. Like OS, formal charge is also integer, but their values are often different. In the case of water molecule, both hydrogen and oxygen have formal charge of zero. It is obvious that the partial charges calculated in a meaningful way could reflect actual charge distribution in chemical systems significantly better than OSs and formal charges. The main practical uses of OSs and formal charges are just bookkeeping and classification.

6.1.2 Theoretical significances and practical applications of partial charge

Theoretical significance of calculating and investigating partial charges is quite evident. First, partial charges can help chemists easily understand charged state of atoms, and can be conveniently and quantitatively compared between different geometries, electronic states, and external environments. Moreover, there are wavefunction analysis methods utilizing partial charges. For example, the condensed Fukui function[11] and condensed dual descriptor[12], which are quite popular in predicting preferential reactive sites, can be evaluated based on partial charges corresponding to different charged states of a molecule. Note that the partial charge itself is also important in identifying reaction sites, namely the more negative (positive) the partial charge is, the more likely the atom is a favorable electrophilic (nucleophilic) reaction site[13-15]. In addition, partial charges of the atoms in a fragment can be summed up to fragment charge, which is also quite valuable. For instances, fragment charge of a functional group can be used to compare and discuss its electron-withdrawing or electron-donating capabilities, and fragment charge can be used to evaluate percentage of charge transfer character (CT%) of electron excitations.

Partial charge also has numerous practical applications in the field of computational chemistry, some of which are mentioned below:

1. Partial charge is an important atomic descriptor, which can be used to predict or explain many properties related to atoms. For example, partial charge of the site containing dissociable proton is closely related to the corresponding pK_a[16,17]. Partial charges show strong correlation with NMR chemical shifts and core electron binding energies[18-20]. C–O bond dissociation energy (BDE) of alkoxy roaming reactions is found to be correlated with partial charge of carbon of the reactant molecules[21].

2. Partial charge at the site where a chemical reaction occurs is closely related to the reaction barrier. It is frequently found that reaction barriers of analogous systems can be successfully explained and accurately predicted based on the partial charges. For example, Liu et al. studied reactions of monosubstituted-benzene molecules reacting with hydrogen fluoride, they found that there is a nice linear correlation between Hirshfeld charge on the regioselective carbon atoms and reaction barriers. Furthermore, they found Hirshfeld charge of the reacting atom in more than twenty organic molecules has excellent linear relationship with experimental nucleophilicity and electrophilicity scales of Mayr[22]. In addition, prominent correlation between barrier heights of keto−enol tautomer reactions and Mulliken charges of the keto/aldehyde carbons is detected by Heufer and coworkers[21].
3. Partial charge plays a crucial role in the molecular force field. Most molecular force fields have a fairly simple potential function, which are generally based on partial charges to rapidly calculate electrostatic interactions between atoms. Therefore, molecular dynamics (MD) and Monte Carlo simulations based on molecular force fields are inseparable from partial charges, and the choice of calculation method of partial charges directly affects the quality of the simulation result. In the field of molecular docking, partial charges are also extensively adopted in the design of forcefield-based scoring functions[23].
4. Partial charge is employed in wide variety of computational chemistry methods. For example, In GFN-xTB[24] and SCC-DFTB[25] theories, partial charges are used to very quickly estimate electronic energy; partial charge is involved in DFT-

D4 dispersion correction to estimate atomic polarizabilities and C_6 coefficients[26]; many implicit solvation models such as SM12[27], uESE[28], generalized Born[29] and Poisson-Boltzmann[30] calculate electrostatic part of solvation energy by means of partial charges; electrostatic potential (ESP) of huge systems such as protein can be generated by partial charges with minimal cost; comparative molecular field analysis (CoMFA) often employs partial charges to rapidly yield ESP on evenly distributed grids for large amount of ligands[31]; molecular surface can be divided into polar and nonpolar parts according to magnitude of partial charge of exposed atoms; energy decomposition analysis based on forcefield (EDA-FF) employs partial charges to estimate electrostatic interaction contribution to overall interaction energy[32].

5. In the quantum mechanics / molecular mechanics (QM/MM)[33] and embedded cluster[34] calculations, it is the standard way of employing partial charges to represent the electrostatic field due to MM atoms or environmental atoms on the subsystem explicitly described by quantum chemistry method.
6. Partial charges are very valuable in studying weak interactions. According to the signs of partial charges, it can be easily judged that which atoms have electrostatic attraction and electrostatic mutual repulsion effects. Furthermore, according to the magnitude of partial charges, strength of electrostatic-dominated interactions, such as hydrogen bonding[35], can be estimated.

6.1.3 Limitations of partial charge

It is important to emphasize that there are evident limitations in describing charge distribution of chemical systems in terms of partial charges. As the point charge at position of nucleus, partial charge essentially represents atoms having a spherically symmetrical charge distribution. Therefore, anisotropy character of charge distribution within atomic space cannot be captured by partial charge at all. Consideration of the anisotropy sometimes can never be ignored in the investigation of non-covalent interactions. For example, halogen bond is formed by a covalently bonded halogen atom via its σ-hole region as Lewis acid and an electronegative atom mainly through electrostatic interaction, if the charge distribution of the halogen atom is simply represented as a partial charge, then the σ-hole will not exist and the halogen bond cannot be discussed at all[36]. Another example is that Lu et al. pointed out that the electrostatic interaction between two N_2 or two H_2[35], and between two cyclo[18]carbon molecules[37], has a significant control effect on the dimer configuration. If only partial charges are employed to describe the molecular charge distributions, it is obviously impossible to reveal the role of electrostatic interaction on the configuration and binding strength of the dimer, because all atoms in these molecules have exactly zero partial charge due to molecular symmetry.

It is noteworthy that if charge distribution of an atom is represented in terms of electric multipole expansion, then partial charge corresponds to monopole moment, and the description of charge distribution anisotropy needs to simultaneously consider atomic dipole, quadrupole or even higher order of moments[38,39]. Alternatively, additional point charges away from atom center may be introduced to describe the anisotropy effect. For example, it was found that simply adding a point charge in the direction towards σ-hole from nucleus for halogen atom is adequate to describe its halogen bond[40]. The various limitations of partial charges in describing charge distribution were extensively discussed by Kramer et al.[41]

6.1.4 What is a good method of calculating partial charges?

Due to the experimental unobservability of partial charge, there is no absolute right or wrong way for calculating it. But there are three requirements that must be met, at least the deviation should be very small, otherwise the method will be physically meaningless. The requirements are: (1) Partial charges should have good rotation invariance. In the absence of an external field, if the calculated partial charges differ evidently before and after rotating the system, then the method must be unreliable because the orientation of the system is essentially arbitrary. (2) Sum of partial charges should be equal to the overall net charge of the system. (3) Distribution of partial charges should be consistent with the symmetry of the studied structure.

In addition, an ideal partial charge calculation method should also meet the following requirements:

1. For calculation methods based on the quantities derived by quantum chemistry, the partial charges should converge to constant values smoothly when the basis set is gradually approaching completeness limit. A method well satisfying this condition is known to have a good basis set stability or low basis set sensitivity.
2. Calculation method should have concise and clear physical meaning, and introducing excessive empirical parameters should not be avoided.
3. Partial charges calculated for typical chemical systems should conform to

conventional chemical concepts, such as the rule of electronegativity. However, notice that the electronegativity rule is not valid for some special systems. As an example, dipole moment of carbon monoxide is almost zero, implying the two atoms should have comparable net charge, though electronegativity of oxygen is by far larger than that of carbon.

4. Calculated partial charges should be able to well reproduce the observable properties that related to charge distribution, such as electric dipole and multipole moments, electrostatic potential.
5. Applicability of calculation method should be as broad as possible. Ideally, the method should be applicable to atoms involving any form of chemical bonds, any element, any molecular shape (linear, planar, cluster, etc.), equilibrium and largely distorted structures, both isolated and periodic systems, both ground and excited state, wavefunctions represented by both all-electron and pseudopotential basis sets, with and without external field perturbation.
6. Partial charges in functional groups should have transferability to some extent due to the independence nature of functional groups, and partial charges should not vary greatly because of a minor change in chemical environment, such as a slight change in molecular conformation during MD simulation.
7. Algorithm should be easy to implement, less computationally intensive, as well as have low-memory requirement and good numerical stability.

6.1.5 Classification of partial charge calculation methods

The partial charge calculation methods that have been proposed so far can be divided into the following categories according to their main ideas:

1. Partial charges based on wavefunction: In this category, the number of electrons carried by each atom (atomic population) is calculated directly based on electronic wavefunction or density matrix derived from quantum chemistry calculations. Then, the partial charge of an atom is simply the difference between its nuclear charge and atomic population. Representative methods in this category include Mulliken[8-10], MMPA[42-44], Löwdin[45], and NPA[46].
2. Partial charges based on real space partition of electron density: The commonality of this kind of methods is that the entire three-dimensional space is divided into subspaces corresponding to different atoms, and electron density is integrated in each subspace to obtain atomic population. Different ways of partitioning atomic spaces correspond to different methods of calculating partial charges. Representative methods in this category include atom-in-molecules (AIM)[47,48], Hirshfeld[49], Hirshfeld-I[50], VDD[51], MBIS[52], DDEC[53], and so on.
3. Partial charges based on fitting electrostatic potential (ESP): These methods determine partial charges by making them maximally reproduce the ESP calculated by quantum chemistry methods in the region close to molecular van der Waals (vdW) surface. Representative realizations of this idea include: MK[54], CHELPG[55], RESP[56], RESP2[57], REPEAT[58], AM1-BCC[59,60].
4. Partial charges based on equalization of electronegativity: The methods in this category generate partial charges mainly based on the principle of Sanderson's equalization of electronegativity. Representative methods: EEM[61,62], QEq[63],

PEOE (Gasteiger)[18,64], PEPE[65], MPEOE[66].

5. Partial charges based on other ideas: There are many other ways to determine partial charges using different ideas from the above, well-known ones include ADCH[38], CM5[67], MMFF94[68], GAPT[69].

In the next section, we will review known partial charge calculation methods listed above. Then in Section 6.3, some molecules will be taken to compare the results of some popular calculation methods. Section 6.4 will briefly mention computer programs that can calculate partial charges. The final section will conclude this chapter and provide our suggestions for the choice of partial charges.

6.2 Methods of calculating partial charges

6.2.1 Partial charges based on wavefunction

6.2.1.1 Mulliken method

The Mulliken method[8-10] is the oldest method of population analysis and deriving partial charges. Its algorithm is quite simple and calculation cost is negligible compared to single point energy calculation, therefore almost all quantum chemistry programs support calculating Mulliken charges, and even print them by default.

The idea of Mulliken method is fairly easy to understand. First, consider the normalization condition of molecular orbitals or natural orbitals as follows (orbitals are assumed to be real for simplicity, similarly hereinafter).

$$\int [\varphi_i(\mathbf{r})]^2 \, \mathrm{d}\mathbf{r} = 1 \tag{1}$$

where φ_i denotes wavefunction of orbital i, $\mathbf{r}$ is coordinate vector in three-dimensional space. Orbital can be expressed as linear combination of basis functions, χ

$$\varphi_i = \sum_{\mu} C_{\mu,i} \chi_m \tag{2}$$

where $C_{\mu,i}$ is coefficient of basis function μ in orbital i. By substituting Eq. 2 into Eq. 1, we have

$$\sum_{\mu} C_{\mu,i}^2 + \sum_{\mu} \sum_{\nu \neq \mu} C_{\mu,i} C_{\nu,i} S_{\mu,\nu} = 1 \tag{3}$$

in which the first and second terms in the left-hand side are known as local term and cross term, respectively. $S_{\mu,\nu} = \int \chi_\mu(\mathbf{r}) \chi_\nu(\mathbf{r}) \mathrm{d}\mathbf{r}$ is element of overlap matrix. Mulliken method defines composition of basis function μ in orbital i as

$$\Theta_{\mu,i} = C_{\mu,i}^2 + \sum_{\nu \neq \mu} C_{\mu,i} C_{\nu,i} S_{\mu,\nu} \tag{4}$$

That is, the local term is fully assigned to the corresponding basis function, while each cross term is divided equally between the corresponding two basis functions. Then, population of an atom can be straightforwardly obtained as

$$p_A = \sum_{i} \eta_i \sum_{\mu \in A} \Theta_{\mu,i} \tag{5}$$

where η stands for orbital occupation number. Finally, Mulliken charge of an atom is simply obtained as $q_A = Z_A - p_A$, with Z_A being nuclear charge. It is noteworthy that the atomic Mulliken population can also be equivalently evaluated based on single-particle reduced density matrix **P**:

$$p_A = \sum_{\mu \in A} (\mathbf{PS})_{\mu,\mu} \tag{6}$$

There are some known serious problems of Mulliken population and partial charge: (1) The bisection of the cross terms is somewhat arbitrary, the difference between atoms is not taken into account, which is the main reason why Mulliken charges sometimes underestimate ionicity of bonds. (2) Composition of a basis function in an orbital, that is the Θ term defined by Eq. 4, may be negative or larger than 1, which obviously lacks physical meaning and shows inherent shortcoming of the theory of Mulliken population analysis. (3) Basis set sensitivity is extremely large. Mulliken charge does not smoothly converge with increase size of basis set, and the result is often quite unreasonable when diffuse functions are employed. For example, with B3LYP[70]/aug-cc-pVTZ[71] wavefunction of ethanol, the Mulliken charge of the carbon in methyl group (−0.67) is even much more negative than the oxygen (−0.46), which obviously violates the fact that oxygen has much larger electronegativity than carbon. The charges of the carbon and oxygen at B3LYP/cc-pVTZ level, namely −0.28 and −0.34 respectively, look much more reasonable. Due to the above defects, using Mulliken charge is generally deprecated.

The reason why the Mulliken charge is incompatible with diffuse functions is easy to understand. Assuming that two atoms A and B are bonded and a basis set containing diffuse functions is adopted, since the diffuse functions of atom A conspicuously cover the atomic space of atom B, it will cause a certain number of electrons that should belong to atom B to be wrongly assigned to atom A, this clearly undermines the reasonableness of Mulliken charges. At the same time, it should also be noted that when calculating Mulliken charges, using a larger basis set never necessarily leads to a better result. For example, Mulliken charges calculated with a high-quality 4-zeta basis set such as def2-QZVP[72] may even be worse than those with a 2-zeta basis set such as 6-31G*[73], because some basis functions of def2-QZVP exhibit semidiffuse feature[74].

6.2.1.2 MMPA methods

In view of the unreasonableness of Mulliken population in dividing cross terms, some researchers proposed different ways to improve it, they are collective known as modified Mulliken population analysis (MMPA). For example, Ros and Schuit defined composition of an basis function in an orbital as

$$\Theta_{\mu,i} = C_{\mu,i}^2 / \sum_{\nu} C_{\nu,i}^2 \tag{7}$$

This method is commonly referred to as C-squared Population Analysis (SCPA). Ostensibly, SCPA avoids explicit partition of the cross terms, however, we have proved that it is equivalent to dividing each cross term according to the ratio of square of basis function coefficient to the sum of squares of all coefficients[75]. An advantage of SCPA compared to Mulliken method is that Θ is always in the range of [0,1], and meantime overlap matrix is not explicitly needed. Stout and Politzer proposed to divide each cross term according to the ratio of the squares of coefficients of the corresponding two basis functions[44], but the partial charge calculated by this method does not have unitary transformation invariance of basis functions and degenerate MOs[76]. Bickelhaupt et al. proposed to divide each cross term according to the ratio of the sums of the local terms of the corresponding two basis functions in all occupied MOs[43].

Although the MMPA methods yield more reasonable results than the Mulliken method sometimes, the serious basis set sensitivity problem was not resolved, which keeps them from becoming popular.

6.2.1.3 Löwdin method

If Löwdin orthogonalization for basis functions is performed prior to Mulliken population analysis, the resulting partial charges are known as Löwdin charges[45]. Löwdin charges also suffer from excessive basis set dependency problem like Mulliken charges, and the Löwdin orthogonalization does not have a clear physical meaning. There is no obvious advantage of Löwdin charges over Mulliken charges.

Redistributed Löwdin population analysis (RLPA) aims to alleviate sensitivity of Löwdin charges to inclusion of diffuse basis functions. It redistributes the population on the diffuse functions to different atoms, so that the result is approximately consistent with that obtained when the diffuse functions are not added. RLPA never became popular.

6.2.1.4 NPA method

The natural population analysis (NPA) proposed by Weinhold and coworkers[46] is a key ingredient of the famous natural bond orbital (NBO) theory framework[77]. The partial charge derived by NPA is known as NPA charge or natural charge, and sometimes incorrectly referred to as NBO charge in literatures. The key idea of NPA is to elegantly transform the wavefunction described by the original basis set, which only has mathematical meaning, to that mainly described by a set of orthogonal minimal bases, which has strong physical meaning. This treatment greatly suppressed the aforementioned basis set sensitivity issue of Mulliken method, diffuse functions can be safely used, and meantime the difficulty of dividing cross terms is implicitly bypassed. The practical result of NPA is usually more reasonable than the Mulliken method, especially for systems containing ionic bonds. Due to these advantages, nowadays NPA has become one of the most popular methods of deriving partial charges. Note that NPA charges need to be used with cautious for systems containing transition metal, lanthanide and actinide atoms[78-80].

Although the partial charge defined based on quantum chemistry introduced in the next sections must also have certain degree of basis set dependence, after all basis set quality directly determines quality of electronic structure, their basis set sensitivity is much smaller than that of Mulliken method, generally similar to or lower than NPA[7].

This comes from the fact that these partial charges are calculated based on physically observable properties such as electron density and ESP, which converge smoothly as the basis set gradually approaches the complete limit.

6.2.2 Partial charges based on real space partition of electron density

6.2.2.1 AIM method

The atom-in-molecules (AIM) theory framework proposed by Bader defines a way of calculating partial charge, which is known as AIM charge and occasionally referred to as Bader charge. The AIM theory defines the zero-flux surface of electron density as the interface between atoms, namely every point $\mathbf{r}'$ in the surface satisfies the condition $\nabla\rho(\mathbf{r}')\cdot\mathbf{n}(\mathbf{r}') = 0$, where ρ is electron density and $\mathbf{n}$ is unit normal vector of the surface. The independent space of each atom divided by the interfaces is called atomic basin, which corresponds to the atomic space defined by AIM theory. The AIM charge is calculated as the difference between nuclear charge and integral of ρ in the AIM atomic basin (Ω):

$$q_A = Z_A - \int_{\Omega_A} \rho(\mathbf{r})\,\mathrm{d}\mathbf{r} \tag{8}$$

The definition of AIM atomic basins has a clear mathematical meaning, and also has a certain physical meaning, that is, each atomic basin satisfies the Virial theorem. However, there is no evident chemical meaning of the basins, and in rare cases the basins cannot be obtained. For example, there are so-called pseudoatoms between lithium atoms in the lithium crystal[81]. Due to the existence of basins corresponding to the pseudoatoms, the atomic basins of lithium atoms no longer fill the whole space, certainly AIM charge of the atoms cannot be meaningfully evaluated. In addition, an atom does not necessarily have a corresponding basin. In the KrH^+ system, since the widely distributed electrons of the krypton heavily submerged the hydrogen, there is no basin individually corresponding to each atom, and thus AIM charges cannot be calculated. Furthermore, as will be illustrated in Section 6.3, AIM charge often has poor chemical meaning, and its magnitude is usually significantly larger than any other partial charges, and sometimes it violates the concept of electronegativity. Because the interatomic boundaries defined by the AIM method are irregular, the algorithm for integrating atomic basins is complicated, this is another disadvantage of the AIM method.

Due to the aforementioned shortcomings of the AIM charge, it has very limited practical significance and is rarely used in molecular systems. However, for periodic systems, AIM charge is widely used in literatures. We believe the main reason is that most first-principle programs are based on plane-waves, and many methods such as Mulliken cannot be used directly in this case. On the other hand, very few partial charge calculation methods are supported in mainstream first-principles programs, while these programs usually can generate grid data files of electron density, by which AIM charges can be quickly and easily obtained using additional codes like Bader and Multiwfn via grid-based algorithm.

6.2.2.2 Voronoi and VDD methods

The Voronoi method sets up a vertical plane at midpoint between each pair of adjacent atoms. These vertical planes divide the entire space into Voronoi polyhedra, and each one corresponds to an atom. Voronoi polyhedra also correspond to Wigner-

Seitz unit cells in periodic systems. Rousseau et al. integrate ρ in the Voronoi polyhedra to obtain atomic populations and corresponding partial charges[82]. Note that they adjusted the position of the intersection point between the vertical plane and the line linking adjacent atoms, so that the distances between the intersection point and the two atoms are proportional to the vdW radii of the two atoms. Another closely related method is Voronoi deformation density (VDD)[51], which directly integrates deformation density in Voronoi polyhedra to obtain partial charges. These partial charge calculation methods did not receive much attention because of their ambiguous physical meaning and no better performance than the popular Hirshfeld method described in the next section.

6.2.2.3 Hirshfeld method

The AIM and Voronoi methods described above partition the space discretely, there is another class of partition methods, which is known as fuzzy partition. Their commonality is that an atomic weighting function is defined to describe the space belonging to each atom, the function varies smoothly everywhere with value range of [0,1], and the sum of values of all atomic weighting functions at any position is exactly 1.0. Obviously, the atomic space defined in this way does not have a sharp boundary.

The Hirshfeld method is the most representative and oldest fuzzy partition method, its atomic weighting function is defined as

$$w_A^{\mathrm{Hirsh}}(\mathbf{r}) = \frac{\rho_A^{\mathrm{free}}(\mathbf{r})}{\sum_B \rho_B^{\mathrm{free}}(\mathbf{r})} \tag{9}$$

where ρ_A^{free} denotes spherically averaged electron density of atom A in its free state. The denominator in Eq. 9 corresponds to promolecular density, which corresponds to the ρ of the system prior to presence of electron polarization and transfer due to formation of interatomic interactions. The Hirshfeld partition has a clear idea, and its meaning was also interpreted from perspective of information theory[83]. Hirshfeld charge is defined as

$$q_A^{\text{Hirsh}} = Z_A - \int w_A^{\text{Hirsh}}(\mathbf{r})\rho(\mathbf{r})\,\mathrm{d}\mathbf{r} \tag{10}$$

The presence of atomic weighting function in the integrand constrained the integration performed in the corresponding atomic space.

Hirshfeld charge is easy to implement and robust, the result is generally meaningful and fairly insensitive to the choice of basis set, so it is widely used in literatures. In particular, it is worth mentioning that Hirshfeld charge is more suitable for predicting reaction sites than any other atomic charges[13-15]. The main disadvantage of Hirshfeld charge is that its overall magnitude is evidently too small, and ESP and dipole moment are poorly reproduced[7].

It is worth mentioning that the Hirshfeld charges given by different programs are different to a certain extent, mainly because the free state atomic densities employed by them to calculate the Hirshfeld weighting functions are somewhat different.

6.2.2.4 Hirshfeld-I method

The choice of the free state of the atoms used in calculating Hirshfeld weighting functions notably influences the resulting Hirshfeld charges, however the choice is somewhat arbitrary. For example, in calculation of Hirshfeld charges for NaCl, the free states can be chosen as the neutral Na and Cl, or the ionic Na^+ and Cl^-, the corresponding results are significantly different. The Hirshfeld-I method (HI) introduces an iterative process to the Hirshfeld method to eliminate the dependency of initial choice of the free states[50]. In HI method, the weighting function of atom A at iteration n is defined as

$$w_A^{(n)}(\mathbf{r}) = \frac{\rho_A^{\text{free},(n-1)}(\mathbf{r})}{\sum_B \rho_B^{\text{free},(n-1)}(\mathbf{r})} \tag{11}$$

The free-state atomic density of the current iteration is obtained by linear interpolation between adjacent charged states according to the partial charge at last iteration:

$$\rho_A^{\text{free},(n)}(\mathbf{r}) = (q_{\text{up}} - q_A^{(n-1)})\rho_{A,\text{low}}^{\text{free}}(\mathbf{r}) + (q_A^{(n-1)} - q_{\text{low}})\rho_{A,\text{up}}^{\text{free}}(\mathbf{r}) \tag{12}$$

where q_{up} and q_{low} are upper and lower integers of partial charge of atom A at iteration n-1, while $\rho_{A,\text{up}}^{\text{free}}$ and $\rho_{A,\text{low}}^{\text{free}}$ are spherically averaged free-state density of atom A at the corresponding two charged states, respectively. The iteration is performed until convergence of partial charges is sufficiently reached.

HI is more physically sound than Hirshfeld method, as it considered response of atomic spaces to actual chemical environment. The value of the HI charges is significantly larger than that of Hirshfeld charge and more in line with common chemical intuition. HI charges have conspicuously better capability in reproducing ESP than Hirshfeld charges[84]. A key disadvantage of HI is that it generally takes 20-30 iterations to obtain converged result, hence the calculation is significantly more time-consuming than Hirshfeld for large systems. Another critical problem of HI is that nonexistent anion, such as O^{2-}, may be involved during calculation. Although the density of the anion state can be produced normally by a calculation using a finite atomic center basis set, it is essentially unphysical and shows very strong diffuse character. As a result, atomic weighting function of the corresponding atom will excessively extend to other atomic spaces, possibly leading to unreasonable partial charge.

There are some variants of HI, such as Hirshfeld-E[85], Hirshfeld-Iλ[86] and the fractional occupation Hirshfeld-I (FOHI)[87]. Besides, there are also other partial charge calculation methods related to the idea of iterative refinement of atomic spaces, such as iterated stockholder atoms (ISA)[88], minimal basis iterative stockholder (MBIS)[52], density derived electrostatic and chemical (DDEC)[53]. The DDEC method is constantly evolving and the latest version is DDEC6[89]. Among them, MBIS and DDEC have received increasingly attentions in recent years, they exhibit satisfactory performance in reproducing ESP. Limited to the length of this chapter, these methods will not be introduced in detail. Interested readers are referred to the dedicated review of these methods by Ayer et al.[90] A known problem of MBIS is that it does not perform well for molecular anions[90].

6.2.3 Partial charges based on fitting electrostatic potential

6.2.3.1 Common ESP fitting methods

In chemical systems, ESP is defined as follows, which measures interaction energy of present system and a unit point charge placed at point **r** without consideration of charge polarization effect

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \mathrm{d}\mathbf{r}' \qquad (13)$$

where **R** is nuclear position. It can be seen that ESP comes from both nuclear and electronic contributions. In the region close to nuclei, ESP is always positive because nuclear charges play a dominant role. However, the ESP in the region outside vdW surface can be either positive or negative depending on electronic structure of nearby regions, and thus has unique chemical significance[91].

The ESP produced by partial charges is simply expressed as

$$V^q(\mathbf{r}) = \sum_A \frac{q_A}{|\mathbf{r} - \mathbf{R}_A|} \tag{14}$$

It is the consensus that the ESP derived from partial charges should be able to well reproduce the exact ESP (usually derived quantum chemically according to Eq. 13) outside vdW surface. This condition is particularly important if the partial charges will be used for molecular force field to represent electrostatic interaction.

ESP fitting refers to a class of methods of deriving partial charges by minimizing the difference between V^q and V in the regions of chemical interest. Most ESP fitting methods realize this purpose by least square fitting to minimize the following error function with a constraint to keep the sum of all partial charges equal to the net charge of the system

$$F(q_1, q_2 ... q_N) = \sum_i [V^q(\mathbf{r}_i) - V(\mathbf{r}_i)]^2 \tag{15}$$

where the summation loops over all fitting points, N is number of atoms. A unique advantage of deriving partial charges by ESP fitting is that additional constraints may be imposed to make net charge of a fragment correspond to an expected value, and make equivalent atoms share exactly identical charges. These constraints can be employed for special purposes, for example, making the net charge of a repeating unit in a polymer an integer so that the partial charges of the unit have transferability. However, these constraints must reduce reproducibility of ESP to some extent.

Cox-Williams[92], Merz-Kollman (MK)[54], charges from electrostatic potentials (CHELP)[93] and CHELP using a grid based method (CHELPG)[55] are four practical realization of the philosophy of ESP fitting. They only differ by the distribution of fitting points and their results are generally comparable. CHELPG is the most popular one among them. In this method, the fitting points are uniformly distributed in a rectangular box surrounding the whole molecule. The nearest distance between the box and any atom is 2.8 Å. The fitting points within vdW surface and those farther than 2.8 Å away from vdW surface are removed. The smaller the spacing between the fitting points, the more accurate the result and better rotational invariance, but the more expensive the calculation. Usually spacing of 0.3 Å is adequate to produce satisfactory result.

The partial charges obtained in this way certainly have better ESP reproducibility than any other kinds of methods. Since ESP and electric multipole moments are both reflections of charge distribution, the ESP fitting charges can usually reproduce molecular dipole moment and quadrupole moment very well. Some fitting methods deliberately take accurate reproduction of dipole moment as an additional constraint in the fitting[94], in practice it is never necessary. Note that as mentioned in Section 6.1.3, partial charge is just a very simple model of representing charge distribution, one should not expect that ESP fitting charges can reproduce ESP nicely anywhere outside vdW surface. For example, the featured ESP distribution due to presence of lone pair, σ-hole and π electrons cannot be well represented by V^q[41].

For periodic systems, Eq. 15 cannot be used for ESP fitting because only relative ESP value between different positions is meaningful, while absolute ESP value is ill-defined due to the arbitrariness of the reference. Repeating Electrostatic Potential Extracted ATomic (REPEAT) focuses on deriving partial charges from ESP for surface and porous systems[58]. Its key difference to other ESP fitting methods is that it essentially fits variation rather than value of ESP, and meantime periodicity is also properly taken into account. The fitting points of REPEAT are distributed on vacuum region over surface systems or within cavities of bulk systems.

6.2.3.2 RESP and relevant methods

In principle, ESP fitting charges are most suitable for MD simulation based on molecular force field because of their superior reproducibility of ESP. However, there are three obvious problems in common ESP fitting charges such as CHELPG, which hinder their application in force field, especially for the flexible molecules whose conformation frequently change during MD process: (1) ESP fitting charges have large dependence on molecular conformation (2) The charges fitted for a single geometry are often not in line with the equivalence of chemically equivalent atoms (such as the three hydrogens of methyl group) (3) Charges of heavily buried atoms show evident numerical instability in the ESP fitting procedure since they are far from the fitting points. See Ref. [95] for detailed discussion about these aspects.

Restrained ElectroStatic Potential (RESP) proposed by Kollman and coworkers aims to circumvent the above three problems[56]. A hyperbolic penalty function is introduced with adjustable parameters to each non-hydrogen atom to suppress magnitude of its fitted charges. In addition, equivalent constraints are imposed to guarantee that chemically equivalent hydrogens have identical fitted charge. With appropriate selected parameters and an elaborately designed two-stage fitting process of RESP, the aforementioned three problems are largely resolved. Here we do not introduce the implementation details of the RESP method, we refer interested readers to the original paper and the detailed introduction in Section 3.9.16 of Multiwfn program manual. RESP has become one of the most popular ways of evaluating partial charges in the field of forcefield-based MD simulation, and the very famous AMBER[96] and GAFF[97] forcefields employ RESP as the standard way of deriving partial charges.

Evaluation of RESP charges for macromolecules or huge number of small molecules is computationally demanding. AM1-BCC is a method to approximately produce RESP charges of HF/6-31G* level with significantly lower cost. In this method, Mulliken charges are firstly obtained based on the very cheap AM1 semi-empirical method, and then empirical correction is applied according to bonding relationship between atoms[59]. TPACM4 is another inexpensive approximation to RESP[98].

RESP2 charge[57] is expressed as $q_A^{\mathrm{RESP2}} = (1-\delta)q_A^{\mathrm{gas}} + \delta q_A^{\mathrm{water}}$, where q^{gas} and q^{water} are RESP charges evaluated under vacuum and the water environment represented by implicit solvation model, respectively. It is found that the RESP2 charge with δ of 0.5 to 0.6 based on DFT density is ideal for MD simulation in water and more recommended than RESP.

6.2.4 Partial charges based on equalization of electronegativity

The methods in this section are all based on the electronegativity equilibrium principle proposed by Sanderson[99], which argues that the greater the electronegativity of an atom, the stronger its ability to receive electrons; when atoms form bonds, the electrons of the atoms with lower electronegativity will flow to the atoms with greater electronegativity, and in this process, electronegativity of the former and the latter will increase and decrease, respectively. When electronegativities of all atoms become equal, the charge distribution corresponds to actual equilibrium state.

Electronegativity equalization method (EEM) is a very rapid way of determining partial charges based on the above idea, which is independent of wavefunction while only requires geometry information and empirical parameters to generate the charges. In this method, electronegativity of an atom is defined as

$$\chi_A = (\chi_A^0 + \Delta\chi_A) + 2(\eta_A^0 + \Delta\eta_A)q_A + \sum_{B \neq A} \frac{q_B}{|\mathbf{R}_B - \mathbf{R}_A|} \tag{15}$$

where χ^0 and η^0 are Sanderson electronegativity and Parr-Pearson hardness of corresponding element, respectively, while $\Delta\chi$ and $\Delta\eta$ are fitted parameters. EEM charges are easily determined by simultaneously solving linear equations corresponding to the following conditions

$$\begin{aligned} &\chi_1 = \chi_2 = \dots = \chi_N \\ &\sum_A q_A = Q \end{aligned} \tag{16}$$

where Q is the net charge of the whole system, N is number of atoms. The result of EEM is largely determined by the parameters used. Different researchers have fitted different EEM parameters[100,101]. For example, if the parameters proposed for reproducing MK charges of B3LYP/6-31G* level are used[102], then the resulting EEM charges will also be close to those charges. Although EEM provides a very fast, cheap and convenient method to calculate partial charges, its scope of application is heavily limited, namely the applicable systems must be highly analogous to the training set of the parameters, and it can hardly be used for ionized states, excited states, transition states, and so on.

The popular charge equilibration method (QEq)[63] can be viewed as a variant of EEM, they only differ by the definition of atomic electronegativity. There is no very evident advantage of QEq over EEM. QTPIE modified the form of QEq, so that the partial charges can exhibit correct asymptotic behavior during dissociation process of chemical bond[103]. E-QEq[104] and I-QEq[105] extended QEq specifically to derive partial charges of metal-organic frameworks, and perform significantly better than QEq for this type of system.

PEOE (Partial equalization of orbital electronegativity) charge is also known as Gasteiger and Gasteiger-Marsili charges[18,64]. PEOE defines atomic electronegativity in a different way to EEM, and interatomic connectivity rather than 3D structure is needed to derive PEOE charges. PEOE charges are calculated via an iterative process. In every iteration, certain amount of electron is transferred between each pair of bonded atoms. In contrast to the EEM, PEOE iteration does not finally meet but partially meet the electronegativity equalization condition due to the damping factor in the equation for evaluating interatomic electron transfer. Because the computational cost of PEOE is negligible even for fairly large systems and meantime merely 2D structure information is needed as input, PEOE has been supported by many molecular design, molecular docking and cheminformatics softwares. Originally PEOE can only be used to organic molecules without π conjugation, the partial equalization of π-electronegativity (PEPE) method eliminates this limitation[65]. PEOE has very poor capability in reproducing molecular dipole moment and ESP[7]. To improve PEOE in this aspect, PEOE was modified by various researchers, which can be collectively referred to as modified PEOE (MPEOE)[66,106,107].

In general, EEM, PEOE and similar methods are highly empirical, with limited applicability and reliability. They are only suitable for use when partial charges based on quantum chemistry cannot be readily calculated due to excessive computational cost and complexity.

6.2.5 Partial charges based on other ideas

It was found that the main reason why Hirshfeld charges have a too small magnitude and have poor reproducibility of ESP is that atomic dipole moments are completely neglected. In the atomic dipole moment corrected Hirshfeld charges (ADCH)[38], atomic dipole moment of each atom is expanded to correction charges placed at neighboring atoms, then ADCH charge is just the sum of Hirshfeld charge and the correction charge. ADCH charge is found to be reasonable in chemical sense, its magnitude is notably larger than Hirshfeld charge and in better agreement with chemical intuition. Molecular dipole moment produced by ADCH charges is proved to be exactly identical to that calculated quantum chemically, and the ESP reproducibility of ADCH charges is significantly improved over that of Hirshfeld charges[7]. ADCH does not bring detectable computational overhead over Hirshfeld method, and its basis set stability is as good as Hirshfeld. These advantages have led to the increasing use of ADCH charges in the literatures.

CM5 charge[67] is somewhat akin to the ADCH charge, both of them were defined as a post correction to the Hirshfeld charge. Unlike ADCH, which is free of empirically fitted parameters, calculation of correction charge of CM5 involves global parameters as well as parameters for individual elements, and it is dependent of interatomic distances. The parameters were optimized for best reproduction of highly accurate experimental or theoretical molecular dipole moment. It is noteworthy that the CM5 charge calculated under vacuum enhanced by a factor or 1.2, namely 1.20*CM5 charge, is well-suited to be used with OPLS-AA forcefield to perform MD simulation in water phase[108]. In our own viewpoint, the correction charge of ADCH is somewhat more elegant than that of CM5, as no element-dependent fitted parameters are involved, and it is yielded fully based on real electronic structure.

MMFF94 is a popular molecular forcefield for organic system, it also defines an easy way of generating partial charges[68]. The initial charge is determined directly by atom type, then post-corrected to yield final charge to take into account polarity of bonds formed by the atom. The involved empirical parameters were derived from fitting molecular dipole moments and interaction energies of HF/6-31G* level. Like PEOE, MMFF94 charges only depend on 2D structure, and the time consumption is extremely low. Although its reproducibility of ESP is obviously not as good as that of ESP fitting charges, at least it is much better than PEOE[7].

Generalized atomic polar tensor (GAPT) is defined as the average of the diagonal elements of the atomic polarization tensor[69]. GAPT is computational demanding, its cost is equivalent to performing a harmonic frequency analysis, while it does not show obvious advantage in terms of reasonableness and reproducibility of ESP, so few literatures employ GAPT charges nowadays.

In addition to the methods described above, there are also many other partial charge calculation methods. But since they have never been popular, and some methods are only suitable for certain special types of systems and applications, they are not covered in this chapter.

6.3 Partial charges of typical molecules

In this section, some typical molecules are taken to illustrate the results of some partial charge calculation methods introduced earlier, so that readers will have an intuitive understanding about the basic characters of different methods. The data are collectively given in Table 1. All partial charges except for NPA were calculated by the Multiwfn 3.8 program[109] developed by us based on the high quality B3LYP/def2-TZVP wavefunction generated by Gaussian 16[110], the geometries were optimized at the same level and there is no imaginary frequency. NPA was calculated using the same condition via NBO 7.0.7 code[111]. Note that a comprehensive comparison between various methods in different aspects, including reproducibility of dipole moment and ESP, basis set dependency, relationship with electronegativity and so on, has been made by us[7]. There are also comparison and correlation analysis articles about partial charges by other researchers[52,112-114].

Table 1 Partial charges of typical molecules calculated by some popular methods. Notably unreasonable values are highlighted.

molecule	atom	Mulliken	Hirshfeld	ADCH	HI	MBIS	CM5	CHELPG	NPA	AIM
H_2O	H	0.316	**0.153**	0.368	0.457	0.442	0.319	0.376	0.460	0.562
	O	-0.632	**-0.307**	-0.735	-0.915	-0.885	-0.639	-0.751	-0.919	-1.125
HCCH	C	-0.190	-0.093	-0.247	-0.210	-0.260	-0.146	-0.230	-0.232	-0.168
	H	0.190	0.092	0.247	0.210	0.260	0.146	0.230	0.232	0.168
HCN	H	0.189	0.127	0.283	0.207	0.227	0.187	0.183	0.227	0.215
	C	-0.180	0.055	0.003	0.083	0.091	0.127	0.185	0.074	0.947
	N	**-0.009**	-0.182	-0.287	-0.290	-0.318	-0.314	-0.367	-0.301	**-1.161**
CH_3NO_2	C	-0.244	-0.020	-0.219	-0.516	-0.431	-0.108	-0.322	-0.478	**0.233**
	H	0.152	0.059	0.136	0.175	0.181	0.125	0.133	0.227	0.080
	H	0.150	0.065	0.137	0.178	0.181	0.129	0.140	0.232	0.077

	N	0.379	0.252	0.401	0.831	0.709	**0.067**	0.792	0.512	0.483
	O	-0.295	-0.208	-0.295	-0.421	-0.411	-0.169	-0.438	-0.360	-0.476
CO	C	-0.010	0.084	-0.020	0.165	0.135	0.130	0.008	**0.487**	**1.201**
SO_2	S	0.656	0.454	0.500	1.071	0.893	0.542	0.561	**1.586**	2.417
	O	-0.328	-0.227	-0.250	-0.535	-0.446	-0.271	-0.281	-0.793	-1.208
ClF_3	Cl	0.720	0.482	0.551	0.915	0.691	0.528	0.604	**1.250**	1.301
	F(axial)[b]	-0.304	-0.214	-0.240	-0.375	-0.291	-0.228	-0.270	-0.470	-0.474
	F(equat.)[b]	-0.111	-0.054	-0.070	-0.165	-0.110	-0.072	-0.065	-0.311	-0.354
$FeCl_3$	Fe	0.871	0.496	0.363	1.549	/[a]	0.667	0.933	1.357	1.500
	Cl	-0.290	-0.165	-0.121	-0.516	/[a]	-0.222	-0.311	-0.452	-0.500
$Ni(CO)_4$	Ni	0.248	-0.122	-0.244	-0.166	/[a]	0.114	0.047	0.279	0.546
	C	-0.054	0.125	0.124	0.245	/[a]	0.116	0.121	0.384	1.036
	O	-0.008	-0.094	-0.063	-0.203	/[a]	-0.144	-0.135	-0.454	-1.173
CLi_4	C	-1.853	**-0.806**	-1.765	-3.219	**-4.275**	**-1.095**	-1.848	-3.317	-3.275
	Li	0.463	**0.202**	0.441	0.805	**1.069**	**0.274**	0.458	0.829	0.819
NaCl	Na	0.648	**0.579**	0.757	0.898	**0.946**	0.694	0.753	0.910	0.883
MgO	Mg	**0.697**	**0.573**	0.879	1.029	0.933	0.744	0.885	1.067	1.242
SO_4^{2-}	S	0.875	**0.268**	0.691	2.565	1.824	0.417	1.604	2.551	**3.862**
	O	-0.719	**-0.567**	-0.673	-1.141	-0.956	-0.604	-0.901	-1.138	-1.466
NO_3^-	N	0.425	0.220	0.492	1.109	1.038	**0.088**	1.049	0.679	0.899
	O	-0.475	-0.407	-0.497	-0.703	-0.679	**-0.363**	-0.683	-0.560	-0.629
Sum of |value|[c]		11.2	6.8	11.2	19.2	18.7	8.5	14.1	20.2	25.7

[a] Cannot be calculated because current implementation of MBIS in Multiwfn does not support elements heavier than Ar.

[b] ClF_3 has two axial and an equatorial fluorine atoms.

[c] Sum of absolute values of all listed partial charges except for $FeCl_3$ and $Ni(CO)_4$.

First, from the statistical data in the last row of Table 1, it can be seen that there is a general relationship between the magnitude of partial charges: AIM > NPA ≥ HI ≥ MBIS > CHELPG > Mulliken ≈ ADCH > CM5 > Hirshfeld. For most cases, AIM and Hirshfeld methods severely overestimate and underestimate partial charges, respectively.

Although there is no strict reference to measure the reasonability of partial charges, it can still be seen from the data in Table 1 that some partial charges are clearly unreasonable for specific molecules. The charge of N atom in HCN calculated by Mulliken method is nearly zero, which is unlikely reasonable compared to the charges calculated by other methods. The Mulliken charge of Mg atom in MgO is only about 0.7, which largely underestimates the ionicity of the Mg-O bond. The Hirshfeld charge is not only small as a whole, but also ridiculously small for certain systems. For example, the Hirshfeld charge of O atom in water is merely –0.3, that of S atom in SO_4^{2-} is only 0.27, and that of C atom in CLi_4 is only –0.81, whose magnitudes are even lower than half of the corresponding charges calculated by other methods. The post-correction on Hirshfeld charges introduced by ADCH method significantly improves the representation of charge distribution for these systems. ADCH shows chemically meaningful result for all atoms in Table 1, and at the same time, the values of ADCH charges are within a reasonable range, neither generally high nor generally low. Hirshfeld-I also greatly improves Hirshfeld method, however, from Table 1 it can be found that the overall magnitude of Hirshfeld-I charges is somewhat too large, and ionicity is overestimated to a certain extent. The partial charges of MBIS are close to those of Hirshfeld-I, but ionicity of individual systems is exaggerated even more, and even contrary to common sense. For example, the MBIS charge of Li atom in CLi_4 even reaches 1.07, which is obviously false as each Li atom cannot transfer more than one electron to the C atom. CM5 charges in Table 1 show some obvious problems. For example, the partial charge of N atom in CH_3NO_2 calculated by CM5 is only 0.07, and that of N atom in NO^{3-} is merely 0.09. For these atoms, not only the post-correction introduced by CM5 does not improve the issue that the Hirshfeld charges are generally too small, but further worsen the problem. In contrast, the ADCH method performs well for these cases, implying that the post-correction scheme of ADCH is often more reliable. Compared with other partial charges, it can be found that NPA charge is somewhat too large for atoms in many systems, such as SO_2 and ClF_3. The dipole moment of carbon monoxide is almost zero. From the results of ADCH method, which can fully accurately reproduce molecular dipole moment, it can be recognized that the partial charges of C and O atoms in this system should also be very close to 0. However, the partial charge of C atom calculated by NPA method is as high as 0.49, which clearly cannot be considered as an acceptable result. AIM charge has overall largest magnitude, and charges of many atoms are severely overestimated, as highlighted by the bolded values in Table 1. Furthermore, sometimes AIM charge fully lacks chemical meaning. For example, in CH_3NO_2 molecule, the AIM charge of the C atom is larger than that of H by 0.15, which is fully contrary to the principle of electronegativity. Such a misleading result may lead researchers to qualitatively misjudge actual charge distribution of a chemical system.

6.4 Computer codes for evaluating partial charges

In this section we provide an incomplete list of computer codes for evaluating some popular partial charges to facilitate readers to utilize them in practical studies.

- Mulliken and Löwdin: Multiwfn[109], almost all mainstream quantum chemistry programs including Gaussian[110] and ORCA[115], CP2K[116]
- MMPA: Multiwfn

- NPA: NBO 3.1 module in Gaussian, NBO[111], JANPA[117]
- AIM: Multiwfn, AIMALL[118], AIM2000[119], Bader[120]
- Hirshfeld: Multiwfn, Gaussian, ORCA, CP2K, VASP[121], Horton[122]
- Hirshfeld-I: Multiwfn, CP2K, VASP, Horton
- ADCH: Multiwfn
- CM5: Multiwfn, Gaussian
- MBIS: Multiwfn, Horton
- CHELPG: Multiwfn, Gaussian, ORCA
- RESP: Multiwfn, AmberTools[123], CP2K (note that atomic equivalences, charge constraints and restraints can be set in CP2K, but standard two-stage fitting of RESP is not supported)
- REPEAT: CP2K
- MMFF94: OpenBabel, Avogadro
- EEM: Multiwfn, EEM SOLVER[124], VCharge[125], NEEMP[101]
- Gasteiger: Multiwfn, AmberTools, OpenBabel[126]
- QEq: Gaussian, OpenBabel
- AM1-BCC: AmberTools
- GAPT: Gaussian

In the above list, Gaussian and ORCA are two of the most popular quantum chemistry programs, which mainly calculate isolated systems. CP2K and VASP are two of the most popular first-principle programs, which mostly aim at calculation of periodic systems. Other softwares in the list are designed for different purposes.

Multiwfn is a versatile wavefunction analysis code, evaluation of partial charges is one of the functions it is very good at. From the list it can be seen that Multiwfn supports very rich methods, and most of which not only support molecules and clusters, but are also applicable to periodic systems. Multiwfn is freely accessible at http://sobereva.com/multiwfn.

6.5 Concluding remarks

In this chapter, we introduced concept, significance, calculation methods and related computer programs of partial charge. We hope this chapter can help readers better understand and apply partial charge in studying practical problems. In the end, we provide some suggestions for the selection of partial charge calculation methods:

1. For studying charge distribution characteristics of molecular systems, ADCH is a good choice, HI, MBIS and NPA can also be considered simultaneously. Although there are some known issues in Mulliken method, it is still useful for rough discussions and comparisons as it is the cheapest and the most widely supported method by calculation programs; however, the use of diffuse functions must be avoided in this case.
2. In the case of employing partial charges in MD simulations based on classical force fields, for rigid molecules, CHELPG is generally satisfactory; for flexible molecules, RESP and RESP2 methods are more suitable; for solid surfaces and porous systems, REPEAT is our most recommended method; for dense solids, MBIS and DDEC6 may be preferential choices. To quickly generate partial charges

of a very large organic system, EEM based on suitable parameters and MMFF94 are very useful.

3. For predicting reaction sites and discussing reactivity, Hirshfeld charge is robust and highly recommended[13-15].

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