

An Introduction to Continuum Electrostatics

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The Solvation free energy (ΔG_{Sol}) is the free energy change, that occurs, when you transfer a molecule from vacuum to a solvent of high dielectric ϵ . This Solvation free energy (ΔG_{Sol}) has three components

$$\Delta G_{sol} = \Delta G_{elec} + \Delta G_{vdw} + \Delta G_{cav} \quad (1)$$

The electrostatic component ΔG_{elec} is particularly important for polar and charged solutes due to the polarization of the solvent which is modeled as a uniform medium of constant dielectric ϵ . The Van der Waals interaction term ΔG_{vdw} can further be split into attractive term, ΔG_{att} and a repulsive term, ΔG_{rep} . The ΔG_{cav} is the free energy required to form the solute cavity within the solvent. ΔG_{cav} is positive and describes the entropic penalty associated with the reorganization of the solvent molecules around the solute together with the work done against the solvent pressure in creating the cavity.

To get the accurate evaluation of ΔG_{elec} (The electrostatic component of Solvation free energy) for example the molecule in figure 1, one can follow one of the following methods:

1. Using simple Coulomb electrostatics
2. Solution to the Poisson-Boltzmann Equation.
3. Generalized Born Methods.

1. Simple Coulomb Electrostatics:

Coulomb's law describes the interaction force between two static point charges. Suppose we have two charges q_1 and q_2 , then these two charges interact with each other with a force given by the Coulomb equation:

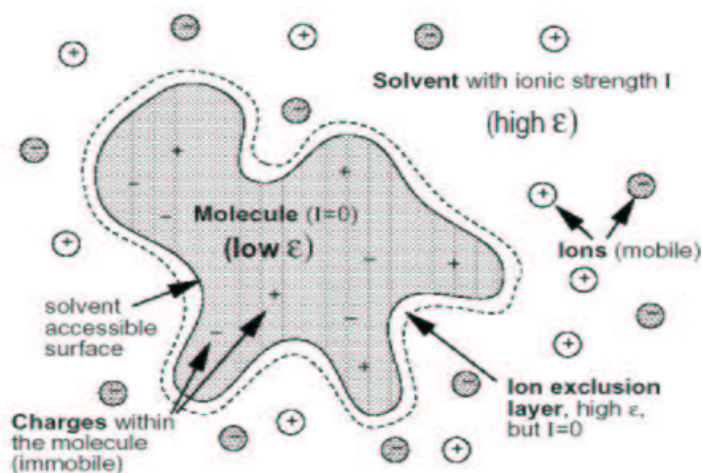


Figure 1: A molecule in a heterogeneous dielectric medium.

$$F = C \frac{q_1 q_2}{r^2} \quad (2)$$

Where F is the force of interaction between the charges q_1 and q_2 , C is a constant which is given by $\frac{1}{4\pi\epsilon_0\epsilon}$ and r is the magnitude of the distance between the two charges. The permittivity of vacuum, $\epsilon = 1$, i.e., when the charges are placed in vacuum.

For Evaluating ΔG_{elec} , using the Coulomb model, we do not account for the change in dielectric when one moves from the solute environment to that of the solvent. Usually the charges are screened by solvent and this effect is not considered in this simple treatment. This model also ignores the reaction field of the solvent.

2. The Poisson-Boltzmann Equation:

A Brief Derivation:

To describe the electrostatic component of Solvation energy ΔG_{elec} in molecules, like the one depicted in figure 1, the Poisson Equation can be used. The Poisson equation relates the variation of the potential ϕ within a medium of uniform dielectric constant ϵ to the charge density ρ .

$$\nabla^2 \phi(\vec{r}) = -\frac{4\pi\rho(\vec{r})}{\epsilon} \quad (3)$$

The Poisson Equation is thus a second-order differential equation. For a set of point charges in constant dielectric medium, the Poisson equation reduces to the simple Coulombs law equation.

If the dielectric ϵ is not constant, but changes with position \vec{r} then the Poisson equation adopts the following form:

$$\nabla \cdot [\epsilon(\vec{r})\nabla\phi(\vec{r})] = -4\pi\rho(\vec{r}) \quad (4)$$

If mobile ions are present in the medium, their distribution in response to the electric potential can be accounted by the Poisson Equation. The ions are prevented from congregating at the locations of extreme potential due to the repulsive interactions with the each other and natural thermal motion in the solvent. The ion distribution in the solvent is described by the Boltzmann distribution of the following form:

$$n(\vec{r}) = \mathcal{N}\exp(-\mathcal{V}(\vec{r})/k_B T) \quad (5)$$

Where $n(\vec{r})$ is the number density of ions at a particular point \vec{r} , \mathcal{N} is the bulk number density and $\mathcal{V}(\vec{r}) = \phi(\vec{r})$ in the mean-field approximation; ($\phi(\vec{r})$: the field produced by the charge distribution) is the energy change to bring the ion from infinity to the position \vec{r} , k_B is the Boltzmann Constant and T is the temperature.

When these effects are incorporated into the Poisson equation, we obtain the Poisson-Boltzmann Equation

$$\nabla \cdot \epsilon(\vec{r})\nabla\phi(\vec{r}) - \kappa' \sinh[\phi(\vec{r})] = -4\pi\rho(\vec{r}) \quad (6)$$

Where κ' is related to the Debye-Hückel inverse length κ , by:

$$\kappa' = \frac{\kappa^2}{\epsilon} = \frac{8\pi N_A e^2 I}{1000\epsilon k_B T} \quad (7)$$

Where I is the ionic strength of the solution and N_A is the Avogadro's Number.

Equation(6) is a non-linear differential equation and can be written in an alternative form by expanding the hyperbolic sine function as a Taylor series

$$\nabla \cdot \epsilon(\vec{r})\nabla\phi(\vec{r}) - \kappa'\phi(\vec{r}) \left[1 + \frac{\phi(\vec{r})^2}{6} + \frac{\phi(\vec{r})^4}{120} + \dots \right] = -4\pi\rho(\vec{r}) \quad (8)$$

The linearized Poisson-Boltzmann Equation can written by taking only the first term in the Taylor expansion, as

$$\nabla \cdot \epsilon(\vec{r})\nabla\phi(\vec{r}) - \kappa'\phi(\vec{r}) = -4\pi\rho(\vec{r}) \quad (9)$$

Equation (9) cannot be solved analytically for complex geometries. So the Poisson-Boltzmann Equation is solved by the numerical method, Finite Difference Method, in which the protein (solute) is put in a cubic grid along with the solvent. Values of the the electrostatic potential, charge density, dielectric constant and ionic strength are assigned to each grid point. The atomic charges usually don't coincide with the grid points. The charge allocation to each of the eight grid points is done in such a way that the closer

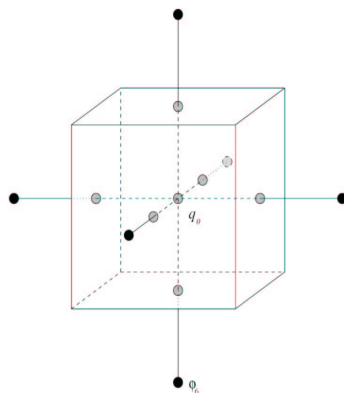


Figure 2: Part of the grid used to solve the PBEQ

the charge to the grid point the greater proportion of its total charge that is allocated. The derivatives in the Poisson-Boltzmann equation are then determined by the finite difference formula.

The potential at a grid point shown in figure 2 having a charge q_0 associated with the grid point is given by

$$\phi_0 = \frac{(\sum_{i=1}^6 \epsilon_i \phi_i) + 4\pi \frac{q_0}{h}}{(\sum_{i=1}^6 \epsilon_i) + \kappa_0^2 f(\phi_0)} \quad (10)$$

Where h is the grid spacing and the function $f(\phi_0)$ in the denominator has the value 1 for the linearized Poisson-Boltzmann Equation and is equivalent to the series expansion $(1 + \phi_0^2/6 + \phi_0^4/120 + \dots)$ for the non-linear case.

Focusing:

There is a problem at the borders of the grid, since the grid points at the border have less than six neighboring points. So if the grid is much larger than the molecule the border grid points are far away from the molecule, that ϕ outside of the grid can be set to zero. If one has a huge grid the computational cost gets very expensive because more the number of grid points, more is the computation. So one could use a low resolution, huge grid and interpolate the electrostatic potential from this calculation to a high resolution, small grid. Such focusing steps can be repeated, if necessary.

3. Generalized Born Methods:

Born-Onsager Models:

Important contributions to the electrostatic contribution to the free energy of Solvation were made by Born (1920) and Onsager (1936). Born derived the electrostatic compo-

ment of free energy of Solvation by placing a charge within a spherical solvent cavity. In Born's model, $\Delta G_{(elec)}$ of the ion (a charge in the a spherical solvent cavity) is equal to the work done in transferring the charge from vacuum to medium of high dielectric, ϵ . In other words, this ($\Delta G_{(elec)}$) is equal to charge the ion in these two different environments. Onsager extended this model to a dipole in a spherical cavity.

Born showed that the work to charge the ion in a medium of dielectric constant ϵ is equal to $q^2/2\epsilon a$, where q is the charge on the ion, a is the radius of the ion (the radius of the cavity in the medium) and ϵ is the permittivity of the medium. The electrostatic component of free energy of Solvation is the difference in the work done in charging the ion in medium of high dielectric ϵ and in vacuum.

$$\Delta G_{elec} = \frac{q^2}{2a\epsilon} - \frac{q^2}{2a} \quad (\epsilon = 1, vacuum)$$

$$\Delta G_{elec} = -\frac{q^2}{2a} \left(1 - \frac{1}{\epsilon}\right) \quad (11)$$

Generalized Born Equation (GB):

Consider a system of particles, each with a radii a_i and charge q_i . The total electrostatic free energy of such a system is given by the sum of coulomb energy and the Born energy of Solvation in the medium of relative permittivity ϵ . (This is just the correction to the coulomb energy in which the charges are screened according to the Born equation. If $\epsilon = 1$ as in vacuum, we end with normal Coulomb electrostatics in vacuum)

$$G_{elec} = \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{\epsilon r_{ij}} - \frac{1}{2} \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^N \frac{q_i^2}{a_i} \quad (12)$$

The first term of the above equation can be written as

$$\sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{\epsilon r_{ij}} = \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{\epsilon r_{ij}} + \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{r_{ij}} - \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{r_{ij}}$$

On rearranging this equation we get,

$$\sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{\epsilon r_{ij}} = \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{r_{ij}} - \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{r_{ij}} \quad (13)$$

Substituting Equation (13) back into Equation (12), we obtain the GB Equation as a sum of three terms,

$$G_{elec} = \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{r_{ij}} - \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{r_{ij}} - \frac{1}{2} \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^N \frac{q_i^2}{a_i} \quad (14)$$

Now we take the difference of the above equation in a solvent with permittivity of ϵ and in vacuum ($\epsilon = 1$). For the situation in vacuum the second and the third term in Equation 14 go to Zero because $\epsilon = 1$ in vacuum and we will have only the first term of Equation 14 left behind for the situation in vacuum.

So we can write,

$$\Delta G_{elec} = \left[\sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{r_{ij}} - \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{r_{ij}} - \frac{1}{2} \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^N \frac{q_i^2}{a_i} \right] - \left[\sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{r_{ij}} \right] \quad (15)$$

Which results in,

$$-\left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{r_{ij}} - \frac{1}{2} \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^N \frac{q_i^2}{a_i} \quad (16)$$

If we notice carefully that for just one charge (ion), $r_{ij} = 0$ and the above equation reduces to the familiar Born equation (Equation 11). So the Born equation for single ion is generalized to a system having N charges. So the name ‘‘Generalized Born Equation’’

Still and co-workers (*JACS*, 1990), combined the two terms in equation 16 into one term and re-wrote Equation 16 as follows

$$\Delta G_{elec} = -\frac{1}{2} \left(1 - \frac{1}{\epsilon}\right) \sum_{i=1}^N \sum_{j=1}^N \frac{q_i q_j}{f(r_{ij}, a_{ij})} \quad (17)$$

The function $f(r_{ij}, a_{ij})$ depends on the inter-charge distance, r_{ij} and the Born radii, a_{ij} of each ion. One can seek this function to be used in the Equation 17, such that in the self ($i = j$) terms, it acts as the ‘‘Effective Born Radii’’ and in the pair-wise terms ($i \neq j$), it acts as an ‘‘Effective Interaction distance’’. The most common form chosen is

$$f(r_{ij}, a_{ij}) = [r_{ij}^2 + R_i R_j \exp(-r_{ij}^2/4R_i R_j)]^{\frac{1}{2}} \quad (18)$$

Where, R_i and R_j is the ‘‘Effective Born Radii’’ of atom i and j respectively, which not only depends on a_i and a_j but also on the relative positions of all other atoms. If we have $r_{ij} = 0$, i.e., we are looking at the case where $i = j$, then the function interpolates to radius of that particular ion. ($(R_i^2)^{\frac{1}{2}} = R_i$) and when we have two ions far apart then $\exp(-r_{ij}^2/4R_i R_j)$ tends to 0 when r_{ij} becomes large, so the function interpolates in this case to $(r_{ij}^2)^{\frac{1}{2}} = r_{ij}$

Ideally, R_i (effective Born radii) should be so chosen that if one were to solve the Poisson Equation for a single charge q_i placed at position of atom i , and the dielectric boundary determined by all the molecule's atoms and their respective radii with no charge on them, then the self energy of the charge i in this reaction field, $q_i\phi_{\text{reac}}(r_i)/2$ would be equal to $-(q_i^2/2R_i)(1 - 1/\epsilon)$. i.e.,

$$\Delta G_{\text{elec}} = q_i \frac{\phi_{\text{reac}}(\vec{r}_i)}{2} = -\frac{q_i^2}{2R_i} \left(1 - \frac{1}{\epsilon}\right) \quad (19)$$

Obviously, this procedure per se would not have a practical advantage over the GB methods if one were to solve the Poisson-Boltzmann Equation to get the effective Born radii. To find a more rapid way to calculate the effective born radii, we can turn to the formulation of electrostatics in terms of energy density $u(\vec{r})$.

Analytical Continuum Electrostatics (ACE):

ACE approach to the description of electrostatic component of Solvation free energy ΔG_{elec} is defining Electrostatic free energy in a particular medium, G_{elec} , in terms of energy density $u(\vec{r})$. The energy density $u(\vec{r})$ of an electrostatic field generated by a charge distribution $\rho(\vec{r})$ can be expressed in terms of the electric displacement vector $D(\vec{r})$, where $D(\vec{r})$ is defined as

$$D(\vec{r}) = \epsilon(\vec{r})\vec{E}(\vec{r}) \quad (20)$$

Writing $u(\vec{r})$ in terms of the electric displacement vector $D(\vec{r})$, we have,

$$u(\vec{r}) = \frac{1}{8\pi\epsilon(\vec{r})}\vec{D}^2(\vec{r}) \quad (21)$$

By integrating the energy density over full space, the electrostatic energy G_{elec} can be written as

$$G_{\text{elec}} = \int_V u(\vec{r})\vec{d}r = \frac{1}{8\pi} \int_V \frac{1}{\epsilon(\vec{r})}\vec{D}^2(\vec{r})\vec{d}r \quad (22)$$

Now we can split this integral expression into two parts, one over the volume of the solute (for eg. protein) V_p with a low dielectric ϵ_p and the other is the integral over the remaining volume of the solvent V_s with a high dielectric ϵ_s .

$$G_{\text{elec}} = \frac{1}{8\pi\epsilon_s} \int_{V_s} \vec{D}^2(\vec{r})\vec{d}r + \frac{1}{8\pi\epsilon_p} \int_{V_p} \vec{D}^2(\vec{r})\vec{d}r \quad (23)$$

We can introduce, what is called the ‘‘Reduced Dielectric’’, $\Delta\epsilon$ and define it as,

$$\frac{1}{\Delta\epsilon} = \frac{1}{\epsilon_p} - \frac{1}{\epsilon_s} \quad (24)$$

Since $\epsilon_p < \epsilon_s$, the reduced dielectric constant $\Delta\epsilon$ is always positive. Using this ‘‘Reduced Dielectric constant’’ in Equation 23, we can rewrite it extending the first integral over the full space V by adding and subtracting $\frac{1}{8\pi\epsilon_s} \int_{V_p} \vec{D}^2(\vec{r}) \vec{d}r$ to Equation 23, we have,

$$G_{elec} = \frac{1}{8\pi\epsilon_s} \int_{V_s} \vec{D}^2(\vec{r}) \vec{d}r + \frac{1}{8\pi\epsilon_p} \int_{V_p} \vec{D}^2(\vec{r}) \vec{d}r + \frac{1}{8\pi\epsilon_s} \int_{V_p} \vec{D}^2(\vec{r}) \vec{d}r - \frac{1}{8\pi\epsilon_s} \int_{V_p} \vec{D}^2(\vec{r}) \vec{d}r$$

We could combine the first and the third term and write the integral over the whole volume, V . The second and the fourth term can be combined to give the expression with the ‘‘Reduced Dielectric Constant’’, $\Delta\epsilon$ over the solute volume V_p . Then we have,

$$G_{elec} = \frac{1}{8\pi\epsilon_s} \int_V \vec{D}^2(\vec{r}) \vec{d}r + \frac{1}{8\pi\Delta\epsilon} \int_{V_p} \vec{D}^2(\vec{r}) \vec{d}r \quad (25)$$

This expression is still exact. No approximations are done so far. An approximation can be introduced by assuming that the first term corresponds to the situation in a homogeneous dielectric medium and describe the dielectric displacement $\vec{D}(\vec{r})$ by simple Coulomb field. This is what is called ‘‘*Coulomb Field Approximation*’’. This assumption is not exact since the dielectric displacement \vec{D} in both the integrals of equation 25 should satisfy the boundary conditions on the electric field at the interface between the solute and the solvent, i.e., the tangential component of the electric field $\vec{E} = \vec{D}/\epsilon$ and the normal component of the dielectric displacement \vec{D} do not change when passing through the solute-solvent boundary.

This assumption is shown to introduce a small percentage of error of at most a few percent in the Electrostatic free energy (Schaefer & Froemmel, 1990). Qualitatively, we can justify this assumption. If the solute is small, all the charges are highly exposed to the solvent. So there is a very small change from the Coulomb field. If, on the other hand, the solute is large, say a protein, most of the contribution to the Electrostatic free energy comes from the second integral and the error introduced is small in the calculation of Electrostatic free energy G_{elec} . Such a kind of approximation is not possible for the second integral in Equation 25, which is more difficult to evaluate.

One can now write Equation 25 using the Coulomb Field Approximation. We could now split the Electrostatic free energy G_{elec} into Self Energy term, G_i^{Self} , the interaction of atoms with themselves and Interaction Energy term, G_{ij}^{Int} , the interaction of atom i with atom j

$$G_{elec} = G_E = \sum_i \left(G_i^{self} + \sum_{j>i} G_{ij}^{Int} \right) \quad (26)$$

Where both the terms run up to the total number of atoms, N . Now rewriting Equation 25 using the coulomb field approximation for the first integral,

$$G_i^{self} = \frac{q_i^2}{2\epsilon_s R_i} + \frac{1}{8\pi\Delta\epsilon} \int_{V_p} \vec{D}_i^2(\vec{r}) d\vec{r} \quad (27)$$

$$G_{ij}^{int} = \frac{q_i q_j}{\epsilon_s |\vec{r}_{ij}|} + \frac{1}{8\pi\Delta\epsilon} \int_{V_p} \vec{D}_i(\vec{r}) \vec{D}_j(\vec{r}) d\vec{r} \quad (28)$$

The self energy G_i^{self} for a point charge yields a diverging energy contribution. So the atom is no longer considered a point charge, but a sphere with radius R_i . This point charge is evenly distributed over the surface of this sphere and the Electrostatic free energy is given by the Born energy term as in equation 11.

Solvation Free Energy:

We know that Solvation free energy, ΔG_{elec} is formally written as the difference between the electrostatic free energy in the heterogeneous dielectric medium G_{elec} (both the solute and the solvent), according to equation 26 and the electrostatic free energy in homogeneous dielectric medium, G_{hom} . Formally one can write it as:

$$\Delta G_{elec} = G_{elec} - G_{hom} \quad (29)$$

The partitioning of the electrostatic free energy into vacuum and solvated case is simple if one assumes that the solute interior has a dielectric constant of 1 such that the solute in vacuum constitutes a system with homogeneous dielectric where the Born's Self energy and Coulomb's law are valid. So we can write

$$G_{hom} = \sum_i \left(\frac{q_i^2}{2\epsilon_p R_i} + \sum_{j>i} \frac{q_i q_j}{\epsilon_p |\vec{r}_{ij}|} \right) \quad (30)$$

Again we can split the electrostatic free energy into a self energy term and a interaction energy term:

$$\Delta G_{elec} = \Delta G^{self} + \Delta G^{int} = \sum_i \left(\Delta G_i^{self} + \sum_{j>i} \Delta G_{ij}^{int} \right) \quad (31)$$

Using Equations 27, 28 & 30 in the equation 29 we have,

$$\Delta G_i^{self} = \frac{q_i^2}{2\epsilon_s R_i} + \frac{1}{8\pi\Delta\epsilon} \int_{V_p} \vec{D}_i^2(\vec{r}) d\vec{r} - \frac{q_i^2}{2\epsilon_p R_i} \quad (32)$$

and

$$\Delta G_{ij}^{int} = \frac{q_i q_j}{\epsilon_s |\vec{r}_{ij}|} + \frac{1}{8\pi\Delta\epsilon} \int_{V_p} \vec{D}_i(\vec{r}) \vec{D}_j(\vec{r}) d\vec{r} - \frac{q_i q_j}{\epsilon_p |\vec{r}_{ij}|} \quad (33)$$

Using the expressing for reduced dielectric $\Delta\epsilon$ as in Equation 24, we can write the above equation as

$$\Delta G_i^{self} = -\frac{q_i^2}{2\Delta\epsilon R_i} + \frac{1}{8\pi\Delta\epsilon} \int_{V_p} \vec{D}_i^2(\vec{r}) \vec{d}r \quad (34)$$

$$\Delta G_{ij}^{int} = \frac{q_i q_j}{\Delta\epsilon |\vec{r}_{ij}|} + \frac{1}{8\pi\Delta\epsilon} \int_{V_p} \vec{D}_i(\vec{r}) \vec{D}_j(\vec{r}) \vec{d}r \quad (35)$$

We will use the Generalized Born equation for calculating the interaction energies of the charges. We now need an integral approach to calculate the Self energies in Equation 34.

Sub-division of Solute volume:

To evaluate the integral in Equation 34, we introduce a molecular density function $P_S(\vec{r})$ describing the solute volume according to

$$P_S(\vec{r}) = \begin{cases} 1 & \text{if } \vec{r} \text{ is inside the solute volume} \\ 0 & \text{Otherwise} \end{cases} \quad (36)$$

and rewrite Equation 34, with this Molecular density function $P_S(\vec{r})$.

$$G_i^{self} = -\frac{q_i^2}{2\epsilon_s R_i} + \frac{1}{8\pi\Delta\epsilon} \int_{V_p} \vec{D}_i^2(\vec{r}) P_S(\vec{r}) \vec{d}r \quad (37)$$

Now we introduce an atomic density function $P_k(\vec{r})$ by splitting the Molecular density function $P_S(\vec{r})$ into a sum of atomic density functions. For each k , there is one density function $P_k(\vec{r})$ describing the volume distribution of the atom k . We write,

$$P_S(\vec{r}) = \sum_k P_k(\vec{r}) \quad (38)$$

The contribution of each atom k to the self energy of atom i , G_{ik}^{self} is given by:

$$G_{ik}^{self} = \frac{1}{8\pi\Delta\epsilon} \int_{V_p} \vec{D}_i^2(\vec{r}) P_k(\vec{r}) \vec{d}r \quad (39)$$

In Equation 39, the self energy of atom i is given by its Born self energy in the solvent dielectric ϵ_s plus a sum of $N - 1$ integral terms G_{ik}^{self} involving all other solute atoms $k \neq i$. This integral is inversely proportional to the factor $\Delta\epsilon$, which is characteristic of a transfer from the dielectric ϵ_s to ϵ_i . In other words, G_{ik}^{self} is the energy required to replace the solvent dielectric by the solute dielectric within the volume of atom k , provided that there is only the charge of atom i available to generate the electric field.

In the normal case of a solvent with a high dielectric constant than the solute, both $\frac{1}{\Delta\epsilon}$ and G_{ik}^{self} are positive. Since the dielectric displacement $\vec{D}(\vec{r}) = \epsilon \vec{E}$ decreases with increasing distance from the charge i , G_{ik}^{self} represents an effective, repulsive interaction between the charge i and atom k of the solute because the atom k prevents the charge i from an

energetically favorable interaction with the solvent dielectric within the volume of atom k .

There are two limiting cases to the self energy, G_i^{self} : the first corresponds to a single ion in solution and the second to a charged atom embedded in an infinite solute with uniform dielectric ϵ_p . For an ion in solution, only the first term remains in equation 37. In the second case, if the charge on the atom i is uniformly distributed on the surface of the sphere with the Van der Waals radius R_i and the sum of the integration volumes $\sum_{k \neq i} P_k$ represents all the space except the Van der Waals sphere of atom i , the integral $\frac{1}{8\pi\Delta\epsilon} \int_{V_p} \vec{D}_i^2(\vec{r}) P_k(\vec{r}) d\vec{r} = \sum_{k \neq i} G_{ik}^{self}$ in equation 37 & 39, must yield the Born transfer energy, $q_i^2/(2\Delta\epsilon R_i)$. When this is added to the first term, $q_i^2/(2\epsilon_s R_i)$ results in the correct Born self energy term $q_i^2/(2\epsilon_p R_i)$ in the solute dielectric..

In practice, its not easy to find a suitable way to find the atomic density functions $P_k(\vec{r})$. By representing the atomic volumes by sphere, leads to overlap of bonded pairs and there are cavities between neighbored non-bonded atoms. Instead of having a very discontinuous solute dielectric medium, both the charge distribution of atom i , $\rho_i(\vec{r})$ and the atomic density function of atom k , $P_k(\vec{r})$, are represented by 3-Dimensional Gaussian.

$$\rho_i(\vec{r}) = q_i \pi^{-3/2} \hat{R}_i^{-3} \exp\left(-\frac{(\vec{r} - \vec{r}_i)^2}{\hat{R}_i^2}\right) : \hat{R}_i = \frac{R_i}{\sqrt{\pi/2}} \quad (40)$$

$$P_k(\vec{r}) = \frac{4}{3\sqrt{\pi}\alpha^3} \exp - \frac{(\vec{r} - \vec{r}_i)^2}{(\alpha\tilde{R}_k)^2} \quad (41)$$

Where R_i is the Van der Waals radius of atom i , the width parameter \hat{R}_i of the charge distribution is chosen such that the Born self energy of the Gaussian-distributed charge is the same as if the charge was evenly distributed on the sphere of radius R_i . The width parameter \tilde{R}_k of the volume distribution is the effective atom radius derived from the average solvent-inaccessible volume contribution \tilde{V}_k of different atom types in the solute.

The Gaussian are normalized such that

$$q_i = \int_V \rho_i(\vec{r}) d\vec{r} \quad (42)$$

and

$$\tilde{V}_k = \frac{4\pi\tilde{R}_k^3}{3} = \int_V P_k(\vec{r}) d\vec{r} \quad (43)$$

The volume parameter \tilde{V}_k does not depend on the smoothing factor α , which is introduced to control the width of the individual atomic functions $P_k(\vec{r})$.)

Coulomb Field Approximation to the the Self Energy:

To evaluate the volume integral in Equation 39, the dielectric displacement $\vec{D}(\vec{r})$ at a given point \vec{r} due to a charge i at \vec{r}_i can be approximated by the Coulomb field $\vec{D}_i(\vec{r}) = q_i/|\vec{r} - \vec{r}_i|$ for a point charge. The advantage of this approximation is that we can integrate the energy density of the electric field without prior knowledge of the electrostatic potential and introduce the electrostatic potential by a iterative procedure (Sklenar & Lavery, Theoretical Biochemistry and Molecular Biophysics, 1990).

Since the reaction field is defined as the non-Coulombic contribution in an inhomogeneous dielectric, the Coulomb field approximation assumes that the reaction field contribution to the energy density of the electric field can be neglected. In the usual case the polarizability of the solvent is higher than the solute polarizability ($\because \epsilon_s > \epsilon_p$), the reaction field leads to the focusing of the field lines towards the solvent and decrease in magnitude of the dielectric displacement in the solute interior. Therefore, omission of the reaction field when integrating \vec{D}_i over the volume of each atom k in the interior of a large solute can be expected to an over-estimation of the energy G_{ik}^{self} .

In applications to biological molecules, in particular small solutes and solutes with high degree of solvent exposure, the over estimation error is expected to be small.

Self Energy Approximation:

In a homogeneous dielectric, ϵ , the potential ϕ_i of the Gaussian charge distribution ρ_i , using Equation 40, is

$$\phi_i(\vec{r}) = q_i \frac{erf(|\vec{r} - \vec{r}_i|/\tilde{R}_i)}{\epsilon|\vec{r} - \vec{r}_i|} \quad (44)$$

where "*erf*" denotes the error function. Based on the Coulomb field approximation, the dielectric displacement of the Gaussian charge distribution is

$$\vec{D}_i(\vec{r}) = -q_i \vec{\nabla} \frac{erf(|\vec{r} - \vec{r}_i|/\tilde{R}_i)}{|\vec{r} - \vec{r}_i|} \quad (45)$$

Using Equation 45 and Equation 40 into Equation 39, we have,

$$G_{ik}^{self} = \frac{q_i^2}{6\pi^{3/2}\Delta\epsilon\alpha^3} \int_V \left(\vec{\nabla} \frac{erf(|\vec{r} - \vec{r}_i|/\tilde{R}_i)}{|\vec{r} - \vec{r}_i|} \right)^2 \exp\left(-\frac{(\vec{r} - \vec{r}_k)^2}{(\alpha\tilde{R}_k)^2}\right) \vec{d}r \quad (46)$$

Again, this integral is not analytically solvable. However, a suitable approximation can be used if G_{ik}^{self} is finite and monotonically decreasing with the distance $|\vec{r}_{ik}|$. This assumption fails in the limit $R_i \rightarrow 0$ and if the ratio $R_i/(\alpha\tilde{R}_k)$ is larger than a critical value that is close to unity. By numerically integrating the above equation, it turns out

that at short range ($|\vec{r}_{ik}| < \alpha\tilde{R}_k$), G_{ik}^{self} decreases like a Gaussian while it approaches $q_i^2\tilde{V}_k/(8\pi\Delta\varepsilon|\vec{r}_{ik}|^4)$ at long range. This behavior leads to the following *Ansatz*.

$$G_{ik}^{self} = \frac{q_i}{\Delta\varepsilon\omega_{ik}} \exp\left(-\frac{|\vec{r}_{ik}|^2}{\sigma_{ik}^2}\right) + \frac{q_i^2\tilde{V}_k}{8\pi\Delta\varepsilon} \left(\frac{|\vec{r}_{ik}|^3}{|\vec{r}_{ik}|^4 + \mu_{ik}^4}\right)^4 \quad (47)$$

The parameters ω_{ik} and σ_{ik} determine the height and width of the Gaussian that approximates G_{ik}^{self} in the short-range domain. The first term of Equation 47 becomes negligible for large $|\vec{r}_{ik}|$ and the second term vanishes at $|\vec{r}_{ik}| = 0$ due to the parameter μ_{ik} . The parameters in Equation 47 are determined by calculating analytically the exact value for G_{ik}^{self} and the second derivative $\partial^2 G_{ik}^{self}/\partial|\vec{r}_{ik}|^2$ at $|\vec{r}_{ik}| = 0$ using Equation 46. This is possible since $|\vec{r}_{ik}| = 0$ means that $\vec{r}_i = \vec{r}_k$. At $|\vec{r}_{ik}| = 0$, the second term in Equation 47 as well as its second derivative vanish, so that the parameters ω_{ik} and σ_{ik} can be determined using the following relations:

$$\omega_{ik} = \frac{3\pi\alpha_{ik}^4\tilde{R}_k}{4(Q_{ik} - \arctan Q_{ik})} \quad (48)$$

$$\sigma_{ik} = \sqrt{\frac{3\alpha_{ik}^2\tilde{R}_k^2(Q_{ik} - \arctan Q_{ik})}{(3 + f_{ik})Q_{ik} - 4\arctan Q_{ik}}} \quad (49)$$

with

$$Q_{ik} = \frac{q_{ik}^2}{\sqrt{2q_{ik}^2 + 1}} : f_{ik} = \frac{2}{q_{ik}^2 + 1} - \frac{1}{2q_{ik}^2 + 1} : q_{ik}^2 = \frac{\pi}{2} \left(\frac{\alpha_{ik}\tilde{R}_k}{R_i}\right)^2 : \alpha_{ik} = \max\left(\alpha, \frac{R_i}{\tilde{R}_k}\right) \quad (50)$$

The long range parameter μ_{ik} is determined by making sure that the value of the Born energy term of a charge q_i in a homogeneous dielectric medium with the dielectric constant ε_p is maintained. this yields

$$\mu_{ik} = \frac{77\pi\sqrt{2}R_I}{512\left(1 - \frac{2\pi^{3/2}\sigma_{ik}^3 R_i}{\omega_{ik}\tilde{V}_k}\right)} \quad (51)$$

Interaction Energy Approximation:

For calculating the interaction energy between two solute charge i and j , the Generalized Born equation is used. This method takes into account of the effect of both charge-charge distance, r_{ij} and the degree of solvent exposure of the interacting charges. One could define a parameter b_i which reflects the degree of charge burial of solute charge i . This value is chosen such that the atomic Solvation energy ΔG_i^{self} of the charge is equal to the Born Solvation energy of a sphere with identical charge, q_i , and radius b_i called the "Born Radii". Since ΔG_i^{self} is already calculated, the effective born radii b_i can be written

as:

We know that

$$\Delta G_i^{self} = -\frac{q_i^2}{2\Delta\epsilon b_i} \quad (52)$$

rearranging, we have

$$b_i = -\frac{q_i^2}{2\Delta\epsilon\Delta G_i^{self}} \quad (53)$$

In the same way as above, we could write ΔG_{ij}^{self} can be written in terms of an effective interaction distance R_{ij}^{solv} taking into account the solute volume as:

$$\Delta G_{ij}^{int} = -\frac{q_i q_j}{\Delta\epsilon R_{ij}^{int}} \quad (54)$$

putting together Equations 53 & 54 we get to our familiar Generalized Born Equation along with the self energy of the solute charge i :

$$\Delta G_{elec} = -\sum_i \left(\frac{q_i^2}{2\Delta\epsilon b_i} + \sum_{j>i} \frac{q_i q_j}{\Delta\epsilon R_{ij}^{solv}} \right) \quad (55)$$

As before, the effective interaction distance R_{ij}^{solv} is given by the function (refer to the Generalized Born Methods) $R_{ij}^{solv} = \sqrt{|\vec{r}_{ij}|^2 + b_i b_j \exp(-|\vec{r}_{ij}|^2/4b_i b_j)}$.

References:

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