The Generalized Born Model

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As indicated by its name, GB is an extension of the famous but old Born solvation model. Born model can only deal with spherical solute, but GB model was designed to be applied to solute molecules of any shape, such as biomolecules. Let's begin with the Poisson equation in an equivalent form for the Green function

$$\boldsymbol{\nabla}\left[\epsilon(\mathbf{r})\boldsymbol{\nabla}G(\mathbf{r}_i, \mathbf{r}_j)\right] = -4\pi\delta(\mathbf{r}_i, \mathbf{r}_j) \tag{1}$$

with the two-dielectric model, the solution inside the dielectric boundary is

$$G(\mathbf{r}_i, \mathbf{r}_j) = \frac{1}{\epsilon_{in}(\mathbf{r})|\mathbf{r}_i, -r_j|} + F(\mathbf{r}_i, \mathbf{r}_j) \tag{2}$$

The first term in the Green function has the familiar form of the Coulomb potential due to a single charge source, while the second term is introduced so the Green function can satisfy certain boundary conditions. And we have the Laplace equation

$$\boldsymbol{\nabla}^2 F(\mathbf{r}_i, \mathbf{r}_j) = 0. \tag{3}$$

The electrostatic part of the solvation free energy is

$$\Delta G = \frac{1}{2}\sum_i q_i\left[\phi(\mathbf{r}_i) - \phi(\mathbf{r}_i)|_{vac}\right] \tag{4}$$

in a classical form, where $\phi(\mathbf{r}_i)$ and $\phi(\mathbf{r}_i)|_{vac}$ are the electrostatic potential computed in solution and gas phase, respectively, with the same charge distribution. Note that this simple formula is only valid for the linearized PB equation. Comparing Eq. 3 and 4, we will find

$$\Delta G_{el} = \frac{1}{2}\sum_{i,j} F(\mathbf{r}_i, \mathbf{r}_j)q_i q_j \tag{5}$$

Computing $F(\mathbf{r}_i, \mathbf{r}_j)$ for an arbitrary charge distribution inside an arbitrary molecular boundary can only be done numerically as the original PB equation. In order to find a simple, closed form formula for ΔG_{el}, further approximations must be made.

According to Kirkwood, the solution of the Poisson equation for a spherical molecule in terms of its Green function is

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$$F(\mathbf{r}_i, \mathbf{r}_i)^{sphere} = -\frac{1-\beta}{A\epsilon_{in}} \sum_{l=0}^{\infty} \frac{t_{ii}^l}{1 + \frac{l}{l+1}\beta} \tag{6}$$

$$F(\mathbf{r}_i, \mathbf{r}_j)^{sphere} = -\frac{1-\beta}{A\epsilon_{in}} \sum_{l=0}^{\infty} \frac{t_{ii}^l P_l(cos\theta)}{1 + \frac{l}{l+1}\beta} \tag{7}$$

where $t_{ij} = r_i r_j / A^2$, $r_i = |\mathbf{r}_i|$, A is molecular radius, θ is the angle between $\mathbf{r}_i$ and $\mathbf{r}_j$, $\beta = \epsilon_{in}/\epsilon_{out}$. Here, the self-contribution term $F(\mathbf{r}_i, \mathbf{r}_i)$ has been separated from the interaction part $F(\mathbf{r}_i, \mathbf{r}_j)$.
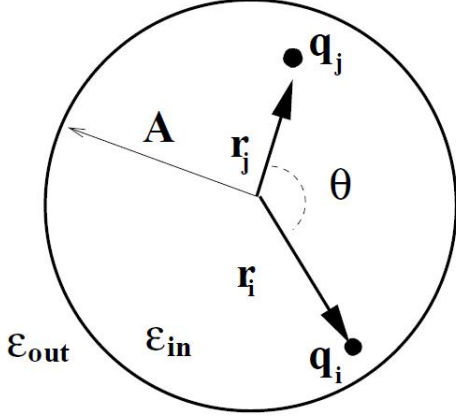
Although Eq. 7 is exact, it is not useful in practice, because the correcponding infinite series converge slowly when t_{ij} approaches one. This is the typical case for biomolecules where largest charges tend to be placed nearly the molecular surface. Consider the typical case of aqueous solution, $\epsilon_{out} \gg \epsilon_{in} \geq 1$. After making the approximation $\epsilon_{out} \to \infty$, which in this case is equivalent to $\beta = 0$, the dependence on l in the denominators disappears, and we can use the well-known identity for the sum of Legendre polynomials along with the geometrical identity $cos\theta = \left(r_i^2 + r_j^2 - r_{ij}^2\right)/2r_i r_j$ to obtain for $F(\mathbf{r}_i, \mathbf{r}_j)^{sphere}$

$$F(\mathbf{r}_i, \mathbf{r}_i)^{sphere} = -\frac{1}{\epsilon_{in}} \frac{1}{A - r_i^2/A} \tag{8}$$

$$F(\mathbf{r}_i, \mathbf{r}_j)^{sphere} = -\frac{1}{\epsilon_{in}} \frac{1}{\sqrt{r_{ij}^2 + \left(A - \frac{r_i^2}{A}\right)\left(A - \frac{r_j^2}{A}\right)}} \tag{9}$$

Since both the diagonal and off-digonal terms depend only on $A - \frac{r_i^2}{A}$, which we call the effective Born radius R_i of atom i. (Compare Eq. 8 with the Born equation of a spherical

charged solute in solution) The effective Born radius represents how much the atom is buried within the low dielectric solute. We rewrite Eq. 8 and 9

$$F(\mathbf{r}_i, \mathbf{r}_i) = -\frac{1}{\epsilon_{in}} \frac{1}{R_i} \tag{10}$$

$$F(\mathbf{r}_i, \mathbf{r}_j) = -\frac{1}{\epsilon_{in}} \frac{1}{\sqrt{r_{ij}^2 + R_i R_j}} \tag{11}$$

If we can by any means calculate ΔG_{el} or equivalently $F(\mathbf{r}_i, \mathbf{r}_i)$ for each atom in the molecule, we can compute R_i via

$$R_i = -\frac{1}{2} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) \frac{q_i^2}{\Delta G_{ii}} \tag{12}$$

for finite ϵ_{out}. Taking Eq. 12 into Eq. 11, we obtain the cross term $F(\mathbf{r}_i, \mathbf{r}_j)$ as a function of R_i, R_j, and r_{ij}. For realistic biomolecular shapes, the specific form of $F(\mathbf{r}_i, \mathbf{r}_j)$ currently used by the generalized Born is slightly more complicated

$$\begin{aligned} \Delta G_{el} &= \frac{1}{2} \sum_{i,j} F(\mathbf{r}_i, \mathbf{r}_j) q_i q_j \\ &\approx -\frac{1}{2} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) \sum_{i,j} \frac{q_i q_j}{\sqrt{r_{ij}^2 + R_i R_j \exp\left(-\gamma \frac{r_{ij}^2}{R_i R_j}\right)}}. \end{aligned} \tag{13}$$

Still et al chose $\gamma = 1/4$, and is often referred to as the GB model or "canonical" GB. It differs from the exact sphere-based Eq. 8 and 9 in two respects. (1) the use of $\gamma \neq 0$ and (2) slightly different dependence on the dielectrics via the prefactor $\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}}$. The use of $\gamma \neq 0$ leads to more accurate estimates of ΔG_{el} for non-spherical geometries of realistic molecules. This is likely due to charges exist for which more of the electric field lines between the charges go through the high dielectric region, effectively reducing the pairwise interaction. Still took this effect into account by allowing for steeper decay of the charge-charge interaction with the distance in $F(\mathbf{r}_i, \mathbf{r}_j)$. In order to carry out a practical GB calculation, one needs the effective Born radii for all the atoms. Although we can calculate R_i using Eq. 12, by solving, for instance, the Poisson equation to obtain ΔG_{ii} first, obviously it is not practical, because solving PE is very expensive. Now, the question becomes how to compute the effective Born radius for all the atoms in a molecule efficiently and *accurately*. Since different GB

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implementations use the same basis function, they differ only in the method for calculating R_i.
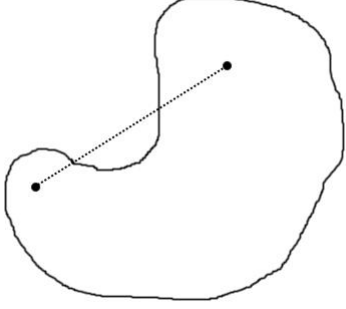
The screening effects of monovalent salt are currently introduced into the GB model via an approximate, yet very simple and computationally inexpensive empirical correction to the main formula, Eq. 13

$$\Delta G_{el} = -\frac{1}{2}\left(\frac{1}{\epsilon_{in}} - \frac{\exp(-0.73\kappa f^{GB})}{\epsilon_{out}}\right)\sum_{i,j}\frac{q_i q_j}{f^{GB}}. \tag{14}$$

where $f^{GB} = \sqrt{r_{ij}^2 + R_i R_j \exp\left(-\gamma\frac{r_{ij}^2}{R_i R_j}\right)}$, and κ is the Debye-Huckel screening parameter.