Modeling electrostatic potential and energies in Molecular Biophysics

DelPhi program – maintenance and development

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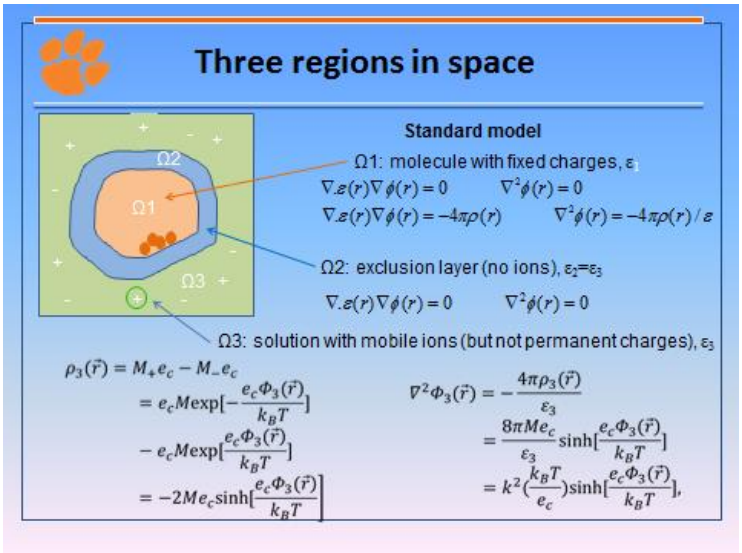
Benchmarking: Mr. Brandon Campbell

Overview

One of the main problems in modeling the electrostatic potential of biological macromolecules is that they exist in water at a given ionic strength and that they have an irregular shape. Analytical solutions of the corresponding Poisson-Boltzmann Equation (PBE) are not available for such cases and the distribution of the potential can be found only numerically. Schematically the problem of solving PBE is shown on the figure on the left. DelPhi, developed in Professor Barry Honig's lab in 1986, was the first PBE solver used by many researchers. The widespread popularity of DelPhi is due to its speed, accuracy (calculation of the electrostatic free energy is only slightly dependent on the resolution of the grid) and the ability to handle extremely high grid dimensions. Additional features such as assigning different dielectric constants to different regions of space, modeling geometric objects and charge distributions, and treating systems containing mixed salt solutions also attracted many researchers. In addition to the typical potential map, DelPhi can generate and output the calculated distribution of either the dielectric constant or ion concentration, providing the biomedical community with extra tools for their research. DelPhi is maintained and developed by the "DelPhi Development Team".



Current efforts are focused on rewriting DelPhi algorithms from Fortran 95 to C++ code, while modernizing them and adding new features. This development will make the C++ DelPhi object-oriented code with easily portable modules such so new algorithms and programs can quickly

be included in the distribution. The new features, some of the already included, some of them in process to be included in DelPhi are: various definitions of molecular surface; Gaussian-based smooth dielectric constant, parallel code, etc.

Implementation and benchmarking results (Brandon Campbell)

Implementation

The PBE model treats solvent as continuum medium with high dielectric constant. Biomolecules are considered as low dielectric cavities made of charged atoms. Ions in the water phase are modeled as non-interacting point charges and their distribution obeys the Boltzmann law. Utilizing the Gauss-Seidel method, DelPhi solves both linear and nonlinear PBE in a cube of N×N×N grid points.

In order to calculate the electrostatic energies of biomolecules, a series of subroutines are implemented (Figure 1). First of all, user-desired parameters are specified in a parameter file.

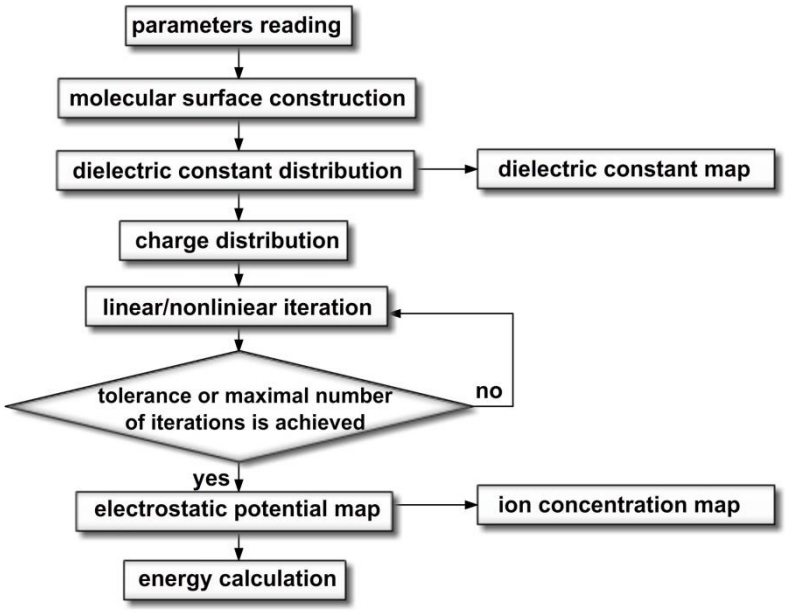


Figure 1

This parameter file controls the initial set up of the run and provides the file names of the coordinate, charge and size files. One can specify the scale and the filling and DelPhi automatically will calculate what the corresponding grid size should be. According to the coordinate and size file, DelPhi generates the molecule surface by utilizing a rapid constructing method. Different grids are set dielectric constant values which construct a three dimensional dielectric constant map. Next, the charges are assigned to atoms and then distributed to the grids. Using distributed charges and dielectric constant map, DelPhi initiates iterations to solve linear or nonlinear PBE. Iterations stop when user specified tolerance or maximal number of iterations is achieved. Then DelPhi derives the three dimensional electrostatic potential map. Using this potential map, DelPhi can also generate the ion concentration map. If requested, dielectric constant, electrostatic potential, and ion

concentration maps can be saved in files and visualized by visualization software. Using charges distribution and potential maps, the Coulombic, grid and solvation energies are calculated.

1.1 A sphere in water

The first example we present is a charged atom with low dielectric constant ε_{int} immersed in a continuum media with high dielectric constant ε_{ext}. In this example, electrostatic component of solvation energy ΔG^{sol} can be obtained by Born formula and is explicitly given by

$$\Delta G^{sol} = -\frac{Q^2}{2 \cdot 4 \cdot \pi \cdot \varepsilon_0} \cdot \frac{1}{r}\left(\frac{1}{\varepsilon_{\text{int}}} - \frac{1}{\varepsilon_{ext}}\right), \qquad (1)$$

where Q and r are charge and radius of the charged atom, as shown in Figure 2A.

Setting $\varepsilon_{\text{int}} = 4.0$, $\varepsilon_{ext} = 80.0$ and $Q = 10 \cdot e$, values of ΔG^{sol} obtained by eqn. (1) are -6673.71kT, -3336.86kT and -2224.57kT (rounded to two decimals) for radius $r = 1$Å, 2Å and 3Å, respectively. These values are compared to those obtained by DelPhi at various scales (points/ Å) and the results are shown in Figure 2B. It is clear that no visual differences can be observed when scale is greater than 0.5 points/Å.

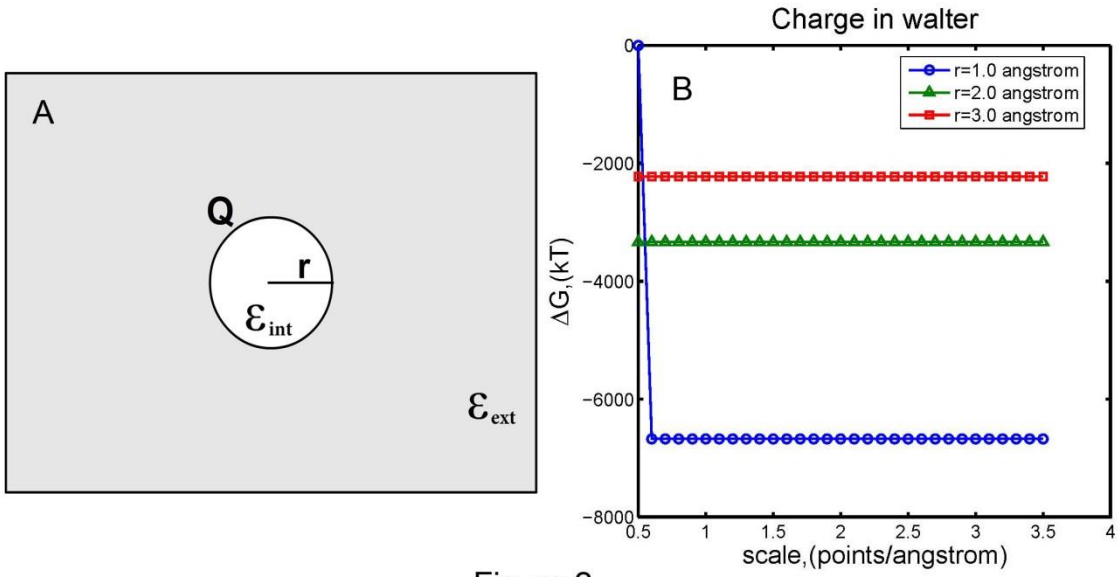


Figure 2

1.2 Two charges in a protein

The next example, shown in Figure 3A, presents a spherical protein with radius b located inside a media without any ions. Dielectric constants interior and exterior of the protein are denoted by

ε_{int} and ε_{ext} again. Two atoms with radii r_i and r_j are centered at points with polar coordinates (R_i, θ_i) and (R_j, θ_j). Both atoms are placed inside the protein and are assigned charges Q_i and Q_j. This example has been studied by B. Honig and his co-workers and the analytical solution of the electrostatic component of solvation energy is given in [1]. The electrostatic energy ΔG is composed of four parts:

$$\Delta G = \Delta G_{ij}^{c} + \Delta G_{ij}^{pol} + \Delta G_{ii}^{self} + \Delta G_{jj}^{self}, \tag{2}$$

where ΔG_{ij}^{c} is the Coulombic energy of atom i, j, ΔG_{ij}^{pol} is the pairwise polarization interaction energy, ΔG_{ii}^{self} is the total self-energies of atom i and ΔG_{jj}^{self} is the total self-energies of atom j. The individual energy can be calculated by

$$\begin{aligned}
\Delta G_{ij}^{c} &= \frac{1}{4 \cdot \pi \cdot \varepsilon_0} \cdot \frac{Q_i \cdot Q_j}{\varepsilon_{\text{int}} \cdot R_{ij}}, \\
\Delta G_{ij}^{pol} &= \frac{1}{4 \cdot \pi \cdot \varepsilon_0} \cdot \frac{Q_i \cdot Q_j}{\varepsilon_{\text{int}}} \cdot \sum_{n=0}^{\infty} B_{n,ij} \cdot P_n\left(\cos\left(\theta_i - \theta_j\right)\right), \\
\Delta G_{ii}^{self} &= \frac{1}{4 \cdot \pi \cdot \varepsilon_0} \cdot \frac{Q_i^{\,2}}{2 \cdot \varepsilon_{\text{int}}} \cdot \sum_{n=0}^{\infty} B_{n,ii},
\end{aligned} \tag{3}$$

where $B_{n,ij} = \dfrac{\left(R_i \cdot R_j\right)^n}{b^{2 \cdot n+1}} \cdot \dfrac{(n+1) \cdot \left(\varepsilon_{\text{int}} - \varepsilon_{ext}\right)}{(n+1) \cdot \varepsilon_{ext} + n \cdot \varepsilon_{\text{int}}}$ and $P_n\left(\cos\left(\theta_i - \theta_j\right)\right)$ is the n$^{\text{th}}$ order Legendre polynomial.

Substituting $Q_i = Q_j = 10 \cdot e$, $R_i = R_j = 5\sqrt{2}\text{A}$, $\theta_i = \pi/4$, $\theta_j = 3\pi/4$, $b = 10\,\text{Å}$, $r = 1\text{Å}$, $\varepsilon_{\text{int}} = 2.0$ and $\varepsilon_{ext} = 80.0$ into eqn. (2) – (3) yields $\Delta G = -5083.19$ kT after rounding to two decimals. Numerical calculations were performed on DelPhi by varying grid size = 85, 125, and 165 at many scales. The numerical results, together with the value of ΔG, are compared and shown in Figure 3B. One can see that the numerical solutions converge to the real solution quickly as scale increases for all three tested grid sizes.

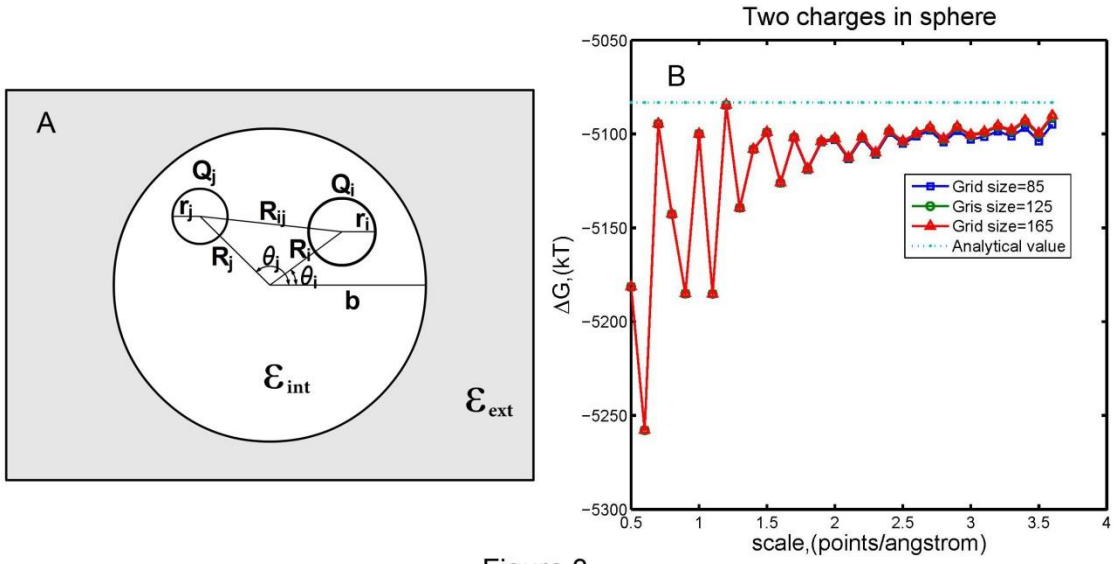


Figure 3

1.3 A sphere in semi-infinite dielectric region

The third example is more complicated and differs from the other two that the space is split into two regions of media with different dielectric constants, as shown in Figure 4A. Dielectric constant in the left region is ε_1 and that in the right region is $\varepsilon_2 (\varepsilon_2 > \varepsilon_1)$. A sphere with radius r and dielectric constant ε_1 is initially positioned in the right region. The distance between the center of the sphere and the boundary of two regions is denoted by d. Let the sphere move towards the boundary and eventually get into the right region, we say $d > 0$ when the center of the sphere is still in the right region and $d < 0$ when it is in the left region. The sign of d only indicates the position of the sphere. During the moving process of the sphere, except the moment when the sphere intersects both regions (i.e., $|d| \le r$), the electrostatic component of the solvation energy ΔG can be analytically expressed as a function of distance d

$$\Delta G = \begin{cases} \dfrac{1}{4\cdot\pi\cdot\varepsilon_0}\cdot\dfrac{Q^2}{2\cdot r}\cdot\left(\dfrac{1}{\varepsilon_2}-\dfrac{1}{\varepsilon_1}\right)+\dfrac{1}{4\cdot\pi\cdot\varepsilon_0}\cdot\dfrac{\varepsilon_2-\varepsilon_1}{\varepsilon_2+\varepsilon_1}\cdot\dfrac{Q^2}{4\cdot\varepsilon_2\cdot d}, & \text{when } d > r, \\ \dfrac{1}{4\cdot\pi\cdot\varepsilon_0}\cdot\dfrac{\varepsilon_2-\varepsilon_1}{\varepsilon_1+\varepsilon_2}\cdot\dfrac{Q^2}{4\cdot\varepsilon_1\cdot d}, & \text{when } d < -r. \end{cases} \quad (4)$$

We plot eqn. (4) by a smooth solid blue curve in Figure 4B, here we set $\varepsilon_2 = 80.0$, $\varepsilon_1 = 2.0$, $r = 2$ Å, $Q = 1\cdot e$. Numerical results obtained by running DelPhi at a series of discrete d values are shown by red circles in the same figure 4B and they fit the curve very well. Once again, our test in this example indicates that DelPhi delivers accurate numerical approximations to the real solution.

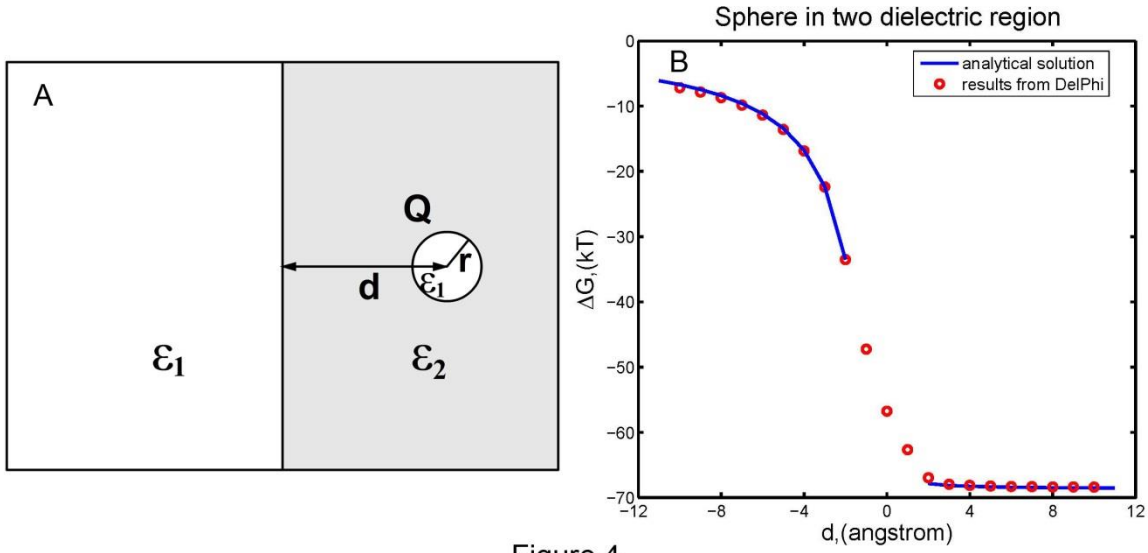

A
Q
r
d
ε_1
ε_2
ε_1
Sphere in two dielectric region
B
analytical solution
results from DelPhi
ΔG,(kT)
d,(angstrom)
0
−10
−20
−30
−40
−50
−60
−70
−12
−8
−4
0
4
8
12

Figure 4