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DelPhi Web Server: A comprehensive online suite for electrostatic calculations of biological macromolecules and their complexes

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Abstract

Here we report a web server, the DelPhi web server, which utilizes DelPhi program to calculate electrostatic energies and the corresponding electrostatic potential and ionic distributions, and dielectric map. The server provides extra services to fix structural defects, as missing atoms in the structural file and allows for generation of missing hydrogen atoms. The hydrogen placement and the corresponding DelPhi calculations can be done with user selected force field parameters being either Charmm22, Amber98 or OPLS. Upon completion of the calculations, the user is given option to download fixed and protonated structural file, together with the parameter and Delphi output files for further analysis. Utilizing Jmol viewer, the user can see the corresponding structural file, to manipulate it and to change the presentation. In addition, if the potential map is requested to be calculated, the potential can be mapped onto the molecule surface. The DelPhi web server is available from http://compbio.clemson.edu/delphi_webserver.

Keywords

DelPhi; electrostatics; proteins; continuum models; electrostatic potential; Finite-Difference Poisson-Boltzmann solver

1. Introduction

Electrostatic force has profound role in molecular biology [1–4]. However, computing electrostatic properties of biological objects has always posed challenging and significant problems to the biomedical computational community [5, 6]. The main reason for this difficulty is that biological macromolecules are made of thousands/millions of atoms, with different size and partial charge. More importantly, these molecules perform their function in a water phase. Since the individual positions and orientations of the water molecules are not know *a priori*, modeling the water phase is not trivial.

The importance of electrostatic interactions and energies is illustrated by the fact that proteins, DNAs, and RNAs are made of charged atoms and frequently the entire molecule(s) carry significant net charge as well. Since all atoms have charge, along with the small

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(angstrom scale) distances that are prevalent in biological systems, the magnitude of electrostatic interactions is typically very large and frequently overpasses other energy components [7–9]. Also, many biological phenomena are predominantly electrostatic in origin as is salt-dependence of binding [10–13] and folding [14], pH-dependence[15, 16], and pKa shifts in proteins [17, 18] and RNAs [19]. Moreover, electrostatics is the only long range force that is present within biological systems. All of these factors illuminate the importance of electrostatics in biology, which ultimately leads to the necessity of determining accurate electrostatic energy of biological systems and objects within these systems.

A major difficulty that is posed within the area of electrostatic calculations is modeling the solvent surrounding the biological macromolecules. Two general approaches [20, 21] are currently being used, explicit [22, 23] and implicit models [24–27], although hybrid approaches were introduced as well [28–31]. Without focusing on the differences (both advantages and disadvantages) of these methods (interested readers are referred to excellent papers [20, 24, 32–35]), we briefly outline a particular resource, DelPhi [36, 37], version 5, which is based on the continuum approach and solves the Poisson-Boltzmann equation via the Finite-Difference algorithm [38]. The biological entities (proteins, DNAs, RNAs, lipid membranes and other small molecules), are treated at an atomistic level of detail and considered a low dielectric cavity region surrounded by a water phase modeled as a continuum media with a high dielectric constant. The mobile ions in the water phase are treated as non-interacting particles and their effect is calculated through the Boltzmann law. The corresponding equations are solved on a grid and the electrostatic components of a variety of energies are calculated [37, 39]. While being user-friendly, the usage of DelPhi (as a stand-alone software package) still requires the user to have a local computer, to be able to protonate the 3D structure of interest, and perhaps fix structural defects if they are present. Selection of the input parameters and output quantities can also be problematic for some inexperienced users. All of these factors motivated us to create a Delphi web server which is aimed to provide easy access to performing electrostatic calculations in biological systems without prior knowledge and without having a computational infrastructure in place.

With the development of modern internet connection technology, a large amount of web server based methods within computational biology have been on the rise [40–46]. These listed servers provide the biomedical community with tools for sequence alignment [47–51], structure alignment and prediction [52–55], estimation of the folding energy change upon mutations [56, 57], and many others [44, 53, 58, 59]. However, with the pronounced exception of the APBS server [43], the community was not offered a web-based tool for calculating electrostatic potential and energy of biological macromolecules. Here, we report such a web-based resource, which is built around the DelPhi program [25, 36]. The Delphi web server is intended to provide an easily accessible, user friendly method for calculating electrostatic parameters and energies of systems made of biological macromolecules and objects. It allows the usage of four different force field parameters, offers fixing structural errors, and builds up hydrogen atoms with the corresponding 3D structure of the molecule(s). Our newly developed DelPhi web server gives any user the capability of performing extensive electrostatic calculations with automated, fast runs, coupled with support and data analysis. The user receives a package of their results along with the needed parameter and PDB files in both human-readable and technical formats. By providing this free and easily accessible service, the field of biological electrostatic calculations can be performed with ease and minimal, if any, complications. The 3D structure of the biological macromolecule selected by the user is visualized and the user is given options to choose different presentations and to map the calculated potential map onto molecular surface.

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2. DelPhi web server algorithm and architecture

2.1 Overview of the methodology of computing electrostatic energies and potential with DelPhi

In order for a successful completion of a DelPhi run, at minimum four files are needed. The input files that are needed for the web server are as follows: the users PDB file, a DelPhi format specific parameter file, and the charge and size files with force field parameters. The PDB file must be in the conventional PDB format, however, it must contain all hydrogen atoms, along with any missing atoms to assure correct partial charges assignment. The online web server that is presented in this paper provides the user with the option to utilize additional software for these extra functions. The software that is provided in conjunction with the DelPhi web server are packages called “profix” [60] (a software module within the JACKAL package, http://wiki.c2b2.columbia.edu/honiglab_public/index.php/Software:Jackal_General_Description), which predicts and places any missing atoms/residues, and the TINKER Molecular Dynamics Software [61, 62] for inserting all missing hydrogen atoms.

It is necessary for DelPhi to have a force field’s charge and size parameters for each atom. These parameter files are provided within the web server application, but the user also has the ability to upload his or her own. The provided files that are available for use within the web server are Amber98 [63], Charmm22 [64], OPLS [65–67], and PARSE [68, 69] force field parameters. The user should use caution with using their own charge/size files, however, since these files must match with what was used for the predicting methods and/or the molecular dynamics software that was used.

The core of the DelPhi application’s parameter files is the DelPhi format file. This parameter file specifies all of the needed values/parameters that are used within the DelPhi algorithm. These minimum specifiers are as follows: grid scale, percentage fill of grid by molecule, interior and exterior dielectric constants, probe radius, salt concentration, boundary conditions, and a convergence criterion. These values can be chosen from a default list (provided if the user is unsure or new to choosing these values) or can be manually entered for his or her specific run. DelPhi also has various energies that can be outputted which are also specified within this file. The available energies that can be calculated are: coulombic, solvation, and grid energies. DelPhi builds molecular surface according to the Lee and Richard’s model. Detailed description of all parameters and functions available in DelPhi can be found in DelPhi manual (http://compbio.clemson.edu/delphi.html).

2.2 Architecture of DelPhi web server

The web server follows a client-server architecture built on PHP[70] and HTML[71]. Various Perl[72] scripts are present to maximize utilization of the web server’s resources by the client. The main work-flow of the server can be broadly classified into two parts based on its visibility to the end users, namely (a) the client facing server, and (b) the high performance computational server. The overall web server work-flow is shown in Figure 1. On the end-user facing server side, users fill up details as text input and file uploads. The input text and files get stored on *Compbio* server, subsequent processing is done on it and the files along with relevant data are then passed to the *Palmetto Cluster* (http://citi.clemson.edu/training_palm) for the energy calculation. Meanwhile, a confirmation email is sent to the user informing him/her on successful submission of their job. Once the files are on the *Palmetto cluster*, scripts will pass the jobs on queue for processing on the cluster on a periodic basis. When a job is processed, another script, also running at a certain time-interval, will take those files along with the output, and pass it back to *Compbio* server. Processed jobs, upon reaching *Compbio* server, will be processed by another script (again,

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running at a specific time-interval), moved to a different directory wherefrom users will be able to access and download them. Simultaneously, users will be notified via email of a successful completion of their jobs and relevant output download link will be provided to them. Below we describe these components separately.

2.3 The client facing server

It is responsible for handling user data storage, user uploaded file storage, notification of successful completion of submission of request, notification upon completion of job and finally displaying the result. User input related data was stored using MySQL[73] for fast and efficient retrieval as well as reliable storage. The overall architecture of the application is general (with regards to application modification), robust, and allows users to have a high level of flexibility in regard of input and output options.

When the end user is interacting with the server, the user fills up pertinent details as text input as well as uploading various files. As for text input, the user needs to provide the following details (a) which portion of the PDB file the user wishes to have Delphi running the calculations for (ATOM and/or HETATM), (b) whether to run profix and TINKER, and (c) choice of Delphi parameters (which can be from a default set, provided by us, or manually given).

Also, the user needs to upload his/her PDB file and choose from a list of default charge and size force field parameters (Amber98, Charmm22, OPLS, and Parse) or, for added flexibility, the user has the option to upload their own charge and size files. The user is given an option to request linear or non-linear PB equation to be solved.

Finally, the user is given the option for choosing output based on the different types of energies to be calculated (for the time being, this feature is limited to Coulombic, Solvation and Grid Energies). Also, for the visualization purpose of output, the user can choose from a potential or dielectric constant map.

Once all the inputs are fed into the system correctly, an email is dynamically sent to the user confirming the order and providing him/her with the request reference number which is used for identifying each request uniquely.

2.4 High-performance computing (HPC) server

This server gets all inputs necessary for a successful Delphi run. Cron jobs take the inputs per request, adds it to the queue of the jobs to be processed on the *Palmetto* high-performance computing facility (http://citi.clemson.edu/training_palm). Each node has 4GB RAM capable of handling Delphi runs up to approximately grid size of 500. Once the jobs are processed, another cron job runs to collect the results of Delphi run along with other necessary files. There is no limitation of the length of the execution time.

2.5 Downloadable files, results and visualization

Upon completion of the calculations, the user receives email notification that the job is finished along with ID number and a link. Clicking on the link, the user is directed to the DelPhi web server download and visualization page. On this page, the user are given options to download the results, protonated and fixed PDB files and parameter files used in this particular job. In addition, the page utilized Jmol which is a 3D Java viewer for chemical structure and users can render and manipulate the structure of molecules with great flexibility (Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org/). If the user had requested potential map to be calculated, then the potential map in “cube” format is also available for download and for visualization. By clicking on

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the potential map file, the user initiates procedure which results in mapping the potential onto molecular surface of the corresponding biological macromolecule.

3. Tests of DelPhi accuracy

The core of the DelPhi web server is the DelPhi program, which provides numerical solution of PB equation and delivers the corresponding electrostatic energies. In this section we benchmark DelPhi calculated energies against analytical solutions and test DelPhi energies for convergence, if analytical solution is not available. Following the work of Guowei Wei and co-workers [74, 75], the results will be discussed in terms of accuracy order as well.

3.1 Testing the accuracy of the calculated energies against analytical solution

In this section we will consider simple systems for which analytical solution for the electrostatic component of the energy is available. Although such systems are typically made of objects with regular shapes, from point of view of the grid algorithm, they are equally difficult to model as irregularly shaped biomolecules.

3.1.1. Electrostatic component of the solvation (Born) energy of a sphere— Consider an atom (sphere) in a solvent, then using the Born formula, the electrostatic component of solvation energy is given by [76]:

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

where Q and r is charge and radius of the atom, ε_{int} - is interior dielectric constant. The solvent dielectric constant is ε_{ext}. The numerical calculations from Delphi are shown on Fig. 2. Three different cases were calculated, corresponding to three different radii (Fig. 2). In all cases, the increase of the scale (grid resolution) makes DelPhi energies closer to the corresponding analytical solutions. After scale larger than 3 grids/A, in all cases, the energies calculated with DelPhi match exactly the analytical solutions. As to be expected, the solvation energy of larger spheres (larger radius) is easier to calculate.

3.1.2. Spherical cavity immersed in high dielectric medium—Following previously published work of Honig and co-workers [1], let's consider a spherical protein within a high dielectric medium (Fig. 3) without ions. Within the sphere there are two charges, shown as Q_i and Q_j in Fig. 3. The total electrostatics energy of the molecule is [1]:

where ΔG^{c}_{ij} is the pairwise coulomb interaction energy, ΔG^{pol}_{ij} is the pairwise polarization interaction energy and $\Delta G_{self}=\Delta G^{self}_{ii}+\Delta G^{self}_{jj}$ is the total self-energy. The formulas for the corresponding energy terms are taken from Ref. [1] and are provided below:

$$\Delta G^{c}_{ij}=\frac{1}{4\cdot\pi\cdot\varepsilon_0}\cdot\frac{Q_i\cdot Q_j}{\varepsilon_{\text{int}}\cdot R_{ij}}, \quad (3)$$

$$\Delta G^{pol}_{ij}=\frac{1}{4\cdot\pi\cdot\varepsilon_0}\cdot\frac{Q_i\cdot Q_j}{\varepsilon_{\text{int}}}\cdot\sum_{n=0}^{\infty}B_{n,ij}\cdot P_n\left(\cos\left(\theta_i-\theta_j\right)\right), \quad (4)$$

$$\Delta G^{self}_{ii}=\frac{1}{4\cdot\pi\cdot\varepsilon_0}\cdot\frac{Q_i^2}{2\cdot\varepsilon_{\text{int}}}\cdot\sum_{n=0}^{\infty}B_{n,ii}, \quad (5)$$

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Where

$$B_{n,ij}=\frac{(R_i \cdot R_j)^n}{b^{2\cdot n+1}} \cdot \frac{(n+1)\cdot(\varepsilon_{\text{int}}-\varepsilon_{ext})}{(n+1)\cdot\varepsilon_{ext}+n\cdot\varepsilon_{\text{int}}}, \quad (6)$$

and P_n (cos ($\theta_i - \theta_j$)) are Legendre polynomials.

The results calculated with DelPhi for two charges in the spherical region are shown in Fig. 4 and compared with the corresponding analytical solution. Similar observation as above can be made: as the scale increases (the grid resolution) the numerical solutions quickly approaches the analytical one. The results are practically independent on grid size and at scale about 4 grids/A, the relative error is less than 0.5%. The accuracy orders are 0.44 and 1.36, respectively, for mesh size h=0.25 and h=0.125, respectively. For accuracy order details for other PB solvers, see Refs. [74, 75].

3.1.3. Electrostatic component of solvation energy of a sphere approaching semi-infinite dielectric region—Consider 3D case such that the space d < 0 is occupied by homogeneous dielectric medium with low dielectric constant, ε_1, while the region d > 0 is taken by high dielectric homogeneous medium of ε_2 (Fig. 5). A sphere with a low dielectric constant ε_1 is initially positioned in region with high dielectric constant and stepwise moves into the region of low dielectric constant (Fig. 5).

In the space $d > 0$ (right side in Fig. 5) the total energy ΔG is the sum a solvation energy (1), (the first term in (7)) and polarization interaction with boundary (the second term in (7)) (see [1]).

$$\Delta G(d>0)=\frac{1}{4\cdot\pi\cdot\varepsilon_0}\cdot\frac{Q^3}{2\cdot r}\cdot\left(\frac{1}{\varepsilon_2}-\frac{1}{\varepsilon_1}\right)+\frac{1}{4\cdot\pi\cdot\varepsilon_0}\cdot\frac{\varepsilon_2-\varepsilon_1}{\varepsilon_2+\varepsilon_1}\cdot\frac{Q^2}{4\cdot\varepsilon_2\cdot d}. \quad (7)$$

When $d < 0$ (left side in Fig. 5) the total energy ΔG is only a polarization energy.

$$\Delta G(d<0)\frac{1}{4\cdot\pi\cdot\varepsilon_0}\cdot\frac{\varepsilon_1-\varepsilon_2}{\varepsilon_1+\varepsilon_2}\cdot\frac{Q^2}{4\cdot\varepsilon_1\cdot d}. \quad (8)$$

The results from DelPhi calculations are shown with filled dots in Fig. 5, while the analytical solution (if available) is given by a solid line. It can be seen that numerical solutions exactly match expected values.

3.2 Testing DelPhi energies for convergence

In this section we will calculate the total electrostatic energy of real biological macromolecules. Obviously in such cases, the analytical solution is not available. However, we will investigate the sensitivity of the calculated energies with respect to scale (the grid resolution).

3.2.1. Protein of typical size (barstar)—Barstar is a protein made of 90 amino acids and represent a typical case of a medium protein. The 3D structure is experimentally available, PDB ID 1A19 [77]. The structure was submitted to DelPhi web server and the protons were added with TINKER.

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Figure 6 shows the results from numerical calculations carried out with DelPhi web server at different scales and two grid sizes. One can see that the grid size, being large in this case, does not affect the results. Increasing of the scale makes the output energies almost independent of the scale and at scale > 3.5 grids/A the calculated energies are practically constant. The convergence order is 0.94 at mesh size 0.5, taking as a reference the energy obtained at h=0.25.

3.2.2. The largest protein in PDB database—By performing a search on Protein Data Base (PDB) [78], we identified the largest protein in terms of longest polypeptide chain. It is a crystal structure of mammalian fatty acid synthase (ID 2VZ8) with contains 29969 atoms (1962 amino acids). Fatty acids are aliphatic acids fundamental to energy production and storage, cellular structure and as intermediates in the biosynthesis of hormones and other biologically important molecules.

Figure 7 shows the calculated total electrostatic energy of fatty acid synthase. At low grid resolution (small scale) the results fluctuate with the change of the scale, but after reaching scale of about 1.7 grids/A, the curve flattens out and the calculated energy is almost scale independent.

4. Availability

The web server is available from URL (http://compbio.clemson.edu/delphi_webserver). It was tested on various web browsers as Opera 11.50, Chrome 12.0, Firefox 3.6+, Safari 5.0, Internet Explorer 8.0+ and the following operating systems: Windows XP, Windows Vista, Windows 7, CentOS 5, Ubuntu 10.10.

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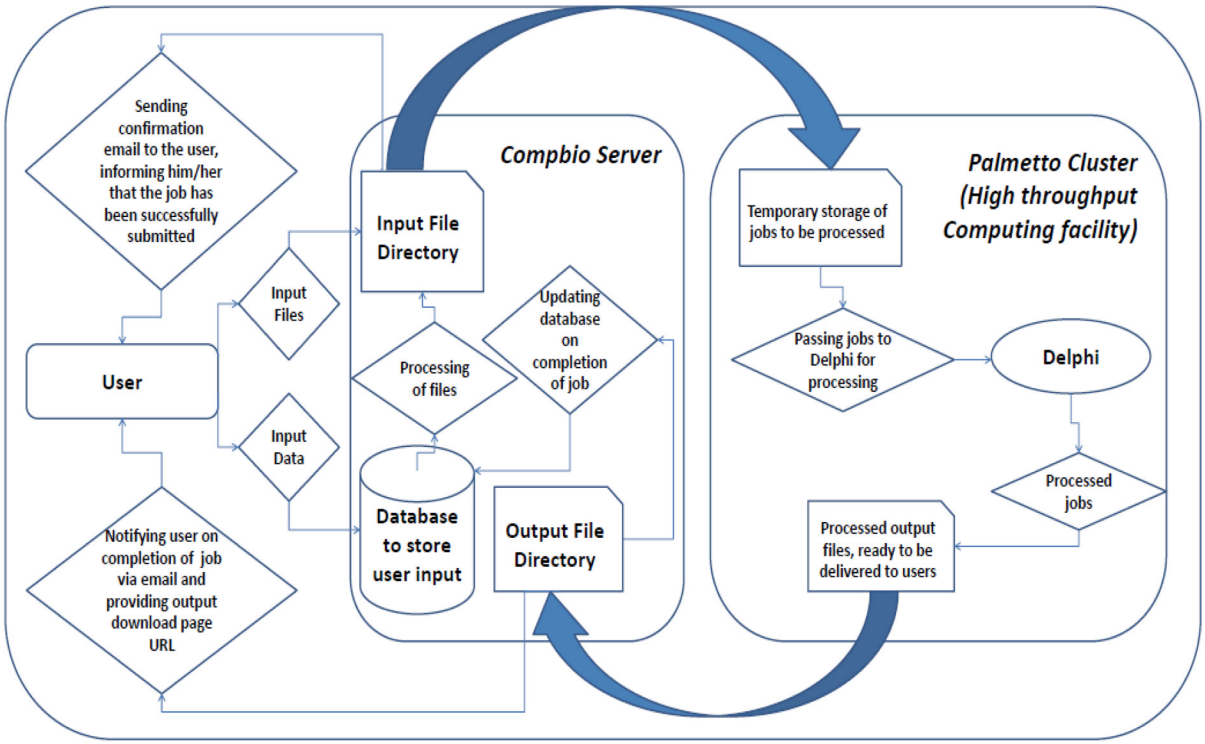


Figure 1.
Architecture of Delphi web-server (http://compbio.clemson.edu/delphi_webserver/).

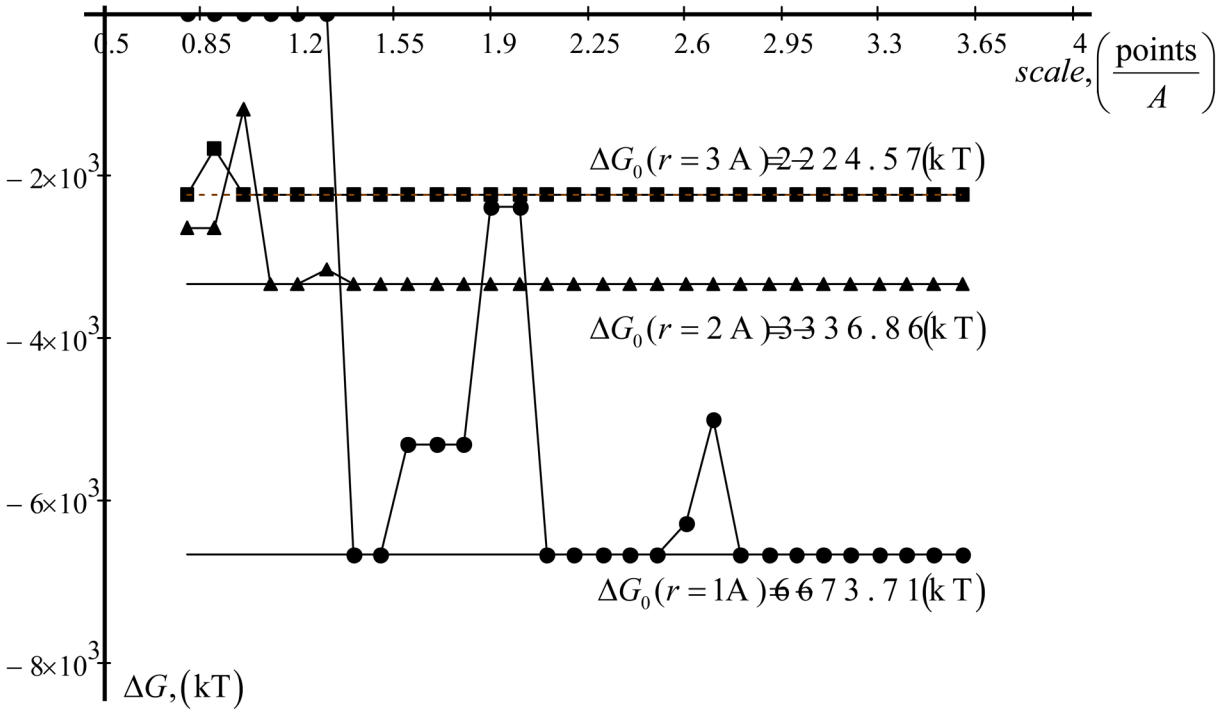


Figure 2.

Solvation energy. $Q = 10 \cdot e$, where e is elementary charge. $\varepsilon_{\text{int}} = 4$, $\varepsilon_{ext} = 80$. Analytical value ΔG_0 is calculated with eq. (1).

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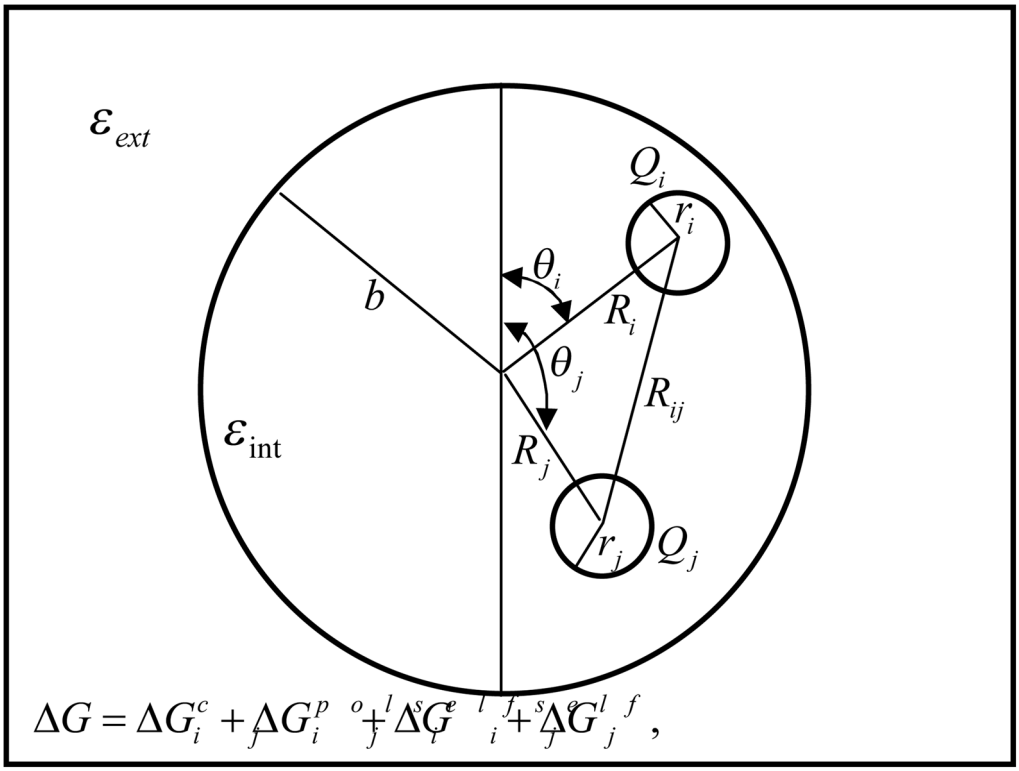


Figure 3.
A spherical protein with interior dielectric constant ε_{int} within a high dielectric medium with ε_{ext}. Charge Q_i has a radius r_i and located at the point [12] (R_i, θ_i). Distance between charges is R_{ij}. b is the radius of spherical region.

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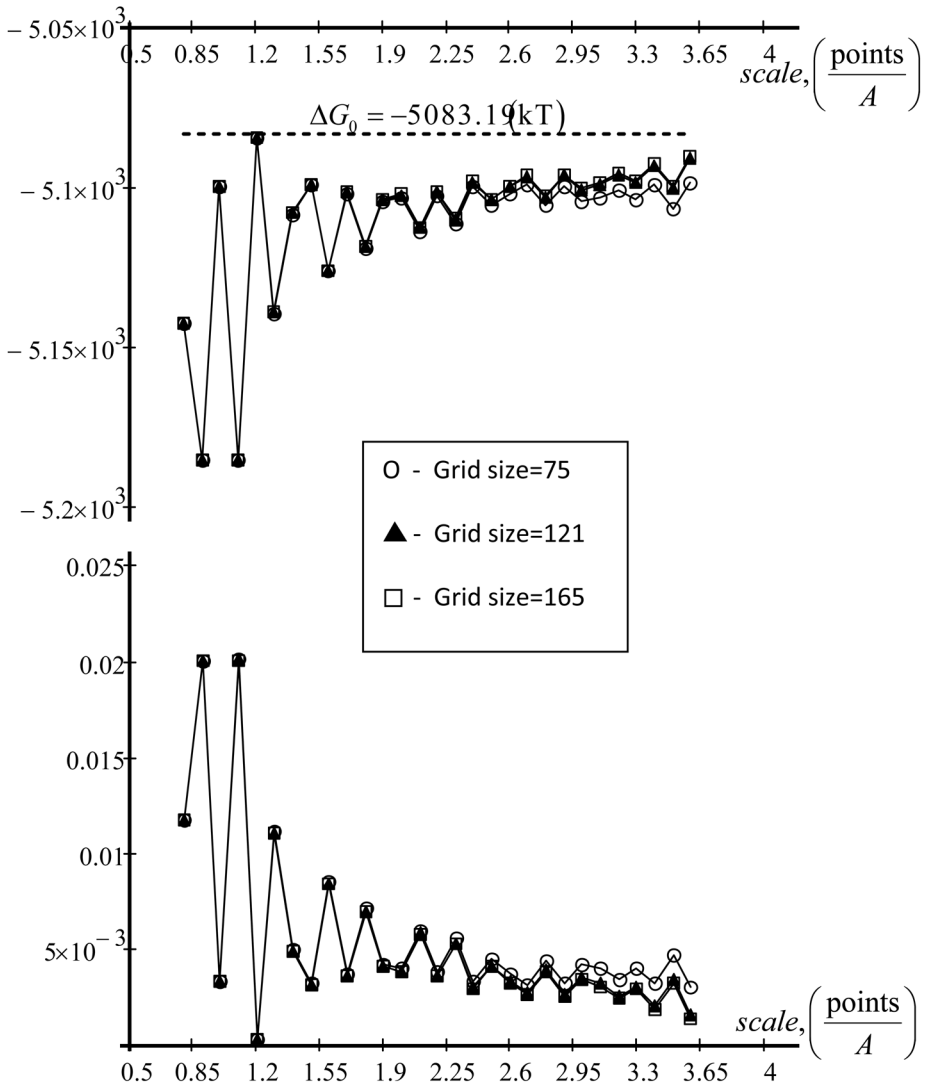


Figure 4.

Top - dependence of total energy of two charges ΔG in a spherical protein in water from scale (grid size fixed) is shown. Bottom -the relative error. The parameters taken in to the calculations are as follow: $Q_1 = Q_1 = 10 \cdot e$. $R_1 = R_2 = 5\sqrt{2A}$, $\theta_1 = \pi/4$, $\theta_2 = 3\pi/4$, b=10A and r=1A. $\Delta G_0 = -5083.19$(kT) is analytical solution according [1].

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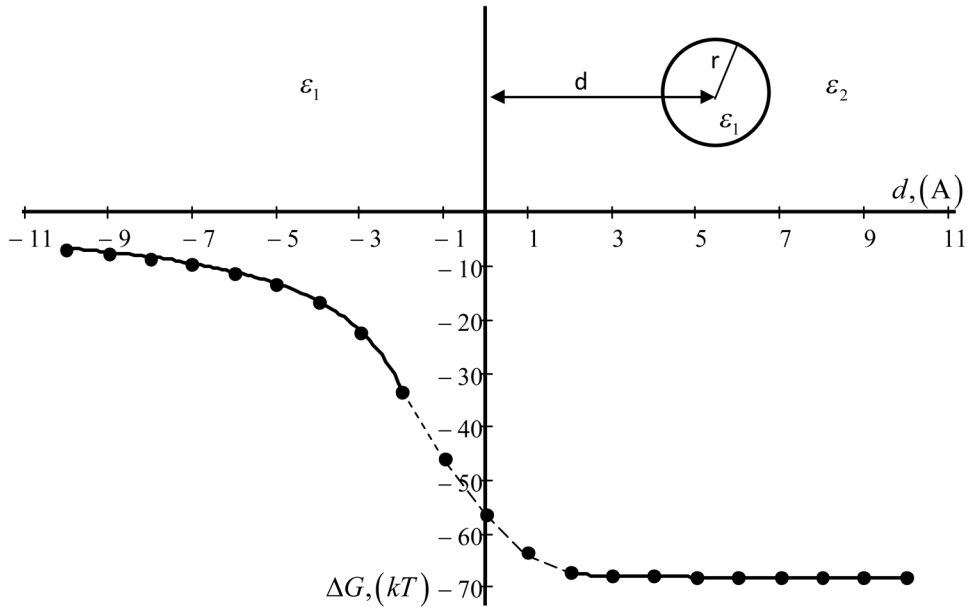


Figure 5.

Total energy of a spherical shell of charge as a function of it position relative to a planar dielectric boundary. $\varepsilon_2 = 80$, $\varepsilon_1 = 2$, $r = 2$A. Solid line is an analytical result (7) and (8), points are result from Delphi. Of course equations (7) and (8) are not valid for overlapping area in the region $-r < d < r$.

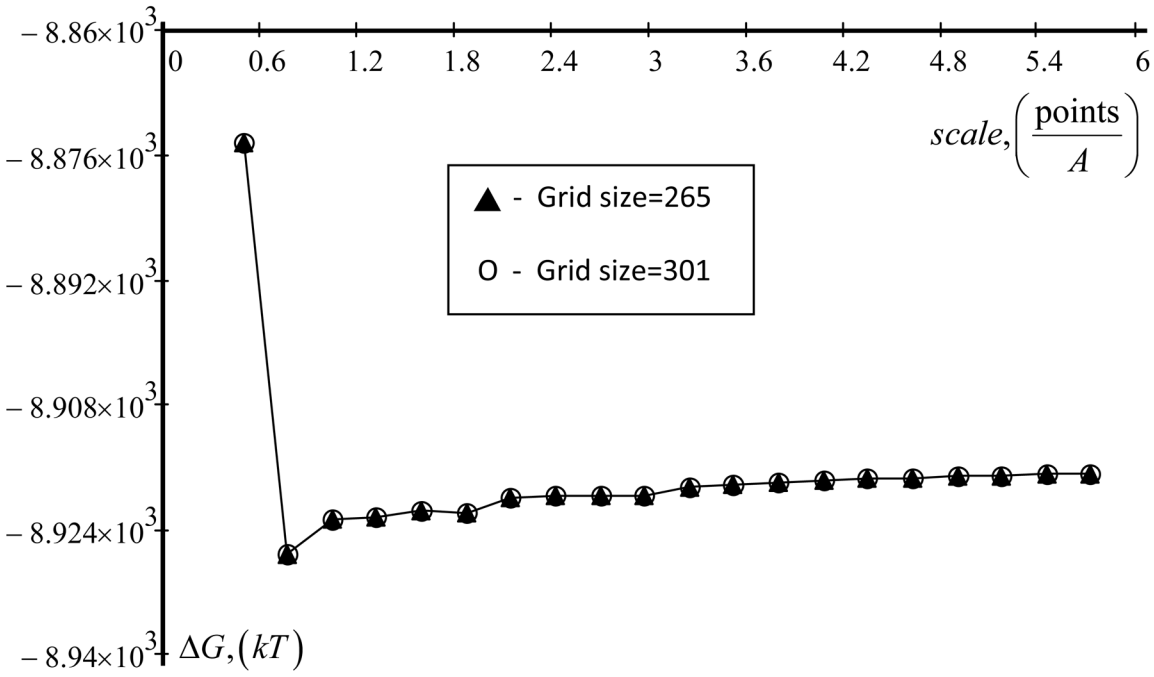


Figure 6.

Dependence of total energy of real protein (PDB ID 1A19)Δ*G* from scale (grid size fixed) is shown. Parameters are: internal dielectric permeability (indi) is 4, external dielectric permeability (exdi) is 80 and a radius of probe molecule (prbrad) is 1.4. Force field parameters is Parse set.

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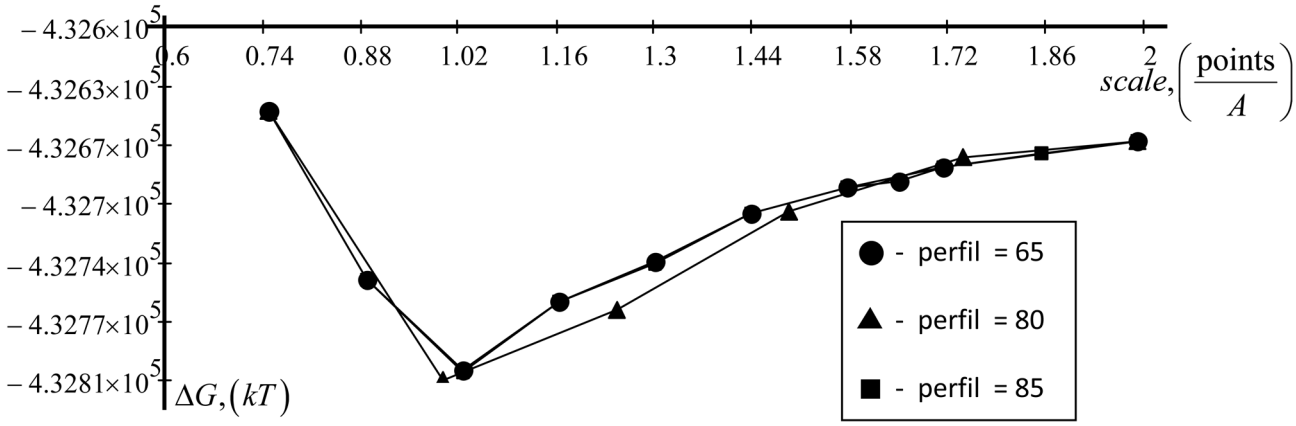


Figure 7.

Dependence of total energy of largest protein (PDB ID 2VZ8)Δ*G* as a function of scale is shown. A percentage of the object longest linear dimension to the lattice linear dimension size (perfil) is 65, 80 and 85. Parameters are: internal dielectric permeability (indi) is 2, external dielectric permeability (exdi) is 80 and a radius of probe molecule (prbrad) is 1.4. Force field parameters are Charmm22.

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