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GBr⁶NL: A generalized Born method for accurately reproducing solvation energy of the nonlinear Poisson-Boltzmann equation

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The nonlinear Poisson-Boltzmann (NLPB) equation can provide accurate modeling of electrostatic effects for nucleic acids and highly charged proteins. Generalized Born methods have been developed to mimic the linearized Poisson-Boltzmann (LPB) equation at substantially reduced cost. The computer time for solving the NLPB equation is ~fivefold longer than for the LPB equation, thus presenting an even greater obstacle. Here we present the first generalized Born method, GBr⁶NL, for mimicking the NLPB equation. GBr⁶NL is adapted from GBr⁶, a generalized Born method recently developed to reproduce the solvation energy of the LPB equation [Tjong and Zhou, J. Phys. Chem. B **111**, 3055 (2007)]. Salt effects predicted by GBr⁶NL on 55 proteins overall deviate from NLPB counterparts by 0.5 kcal/mol from ionic strengths from 10 to 1000 mM, which is ~10% of the average magnitudes of the salt effects. GBr⁶NL predictions for the salts effects on the electrostatic interaction energies of two protein:RNA complexes are very promising. © *2007 American Institute of Physics*. [DOI: 10.1063/1.2735322]

I. INTRODUCTION

The Poisson-Boltzmann (PB) equation is widely used for modeling electrostatic effects and solvation of biomolecules.[1–11] For most applications on proteins, the linearized PB (LPB) equation is used; the solvation energy calculated from LPB can closely approach that calculated from the nonlinear PB (NLPB) equation.[12] However, for nucleic acids, accurate modeling of electrostatic effects requires NLPB.[13–24] Recent calculations have even shown that electrostatic enhancement of protein-protein association rates is more accurately predicted by NLPB than by LPB.[25] The computational cost of solving the LPB equation has prompted intensive efforts at developing generalized Born (GB) methods,[26–39] which, at orders of magnitude lower computational cost, aim to yield a solvation energy that is close to what is calculated from LPB. The computational cost for solving NLPB is even higher than for LPB, hence the payoff for a GB method that mimics the NLPB is greater than GB methods benchmarked against LPB. Here we report the first GB method that accurately reproduces the NLPB solvation energy.

This method is adapted from GBr⁶, which was found to reproduce well the LPB solvation energy.[39] The new method is referred to as GBr⁶NL. Like in the earlier study in which GBr⁶ was developed,[39] we test GBr⁶NL on a set of 55 representative proteins. In addition, we apply GBr⁶NL to two protein:RNA complexes, which were studied by NLPB recently.[24] We show that GBr⁶NL reproduces well NLPB salt effects on the electrostatic interaction energies of the two complexes.

The rest of the paper is organized as follows. In Sec. II we outline the GBr⁶ method and describe its adaptation into GBr⁶NL. This is followed by comparison of NLPB and GBr⁶NL salt effects in Sec. III. Concluding remarks are found in Sec. IV.

II. THEORY

A. GBr⁶

The GBr⁶ method was described fully in a recent paper.[39] Here we give a brief outline. In the GB model the electrostatic contribution to the free energy of solvation is given by[26]

$$\Delta G_{GB}^0 = - (1/\varepsilon_i - 1/\varepsilon_s) \sum_{i,j} q_i q_j /2f_{ij}, \tag{1}$$

where ε_i and ε_s are the solute and solvent dielectric constants, respectively, and f_{ij} is a function of the distance r_{ij} between the charges q_i and q_j on atoms i and j given by

$$f_{ij} = [r_{ij}^2 + B_i B_j \exp(- r_{ij}^2 /4B_i B_j)]^{1/2}. \tag{2}$$

The Born radii B_i are usually optimized for best reproduction of the PB solvation energy. The reason for the superscript "0" in ΔG_{GB}^0 of Eq. (1) will become clear shortly.

The conventional approach to determining the Born radii is based on the Coulomb-field approximation, which leads to

$$\frac{1}{B_i} = \frac{1}{4\pi} \int_{solvent} \frac{d^3 \mathbf{r}}{(\mathbf{r} - \mathbf{r}_i)^4}. \tag{3}$$

In GBr⁶, this is replaced by

$$\frac{1}{B_i^3} = \frac{3}{4\pi} \int_{solvent} \frac{d^3 \mathbf{r}}{(\mathbf{r} - \mathbf{r}_i)^6}, \tag{4}$$

as first proposed by Grycuk.[40] The solute is represented by the overlapping van der Waals (vdW) spheres of the atoms.

Following Gallicchio and Levy,[36] Eq. (4) is implemented analytically.

Conventional GB methods do not have dependences on the solute and solvent dielectric constants beyond the prefactor in Eq. (1). The LPB solvation energy has more complex dependences on ε_i and ε_s. We found that these dependences can be modeled accurately by a scaling formula.[41] Based on that formula, the result of Eq. (1) is scaled to

$$\Delta G_{GB} = \Delta G_{GB}^0 f(\varepsilon_i/\varepsilon_s), \qquad (5)$$

as the final prediction for the solvation energy. The scaling factor is given by

$$f(\varepsilon_i/\varepsilon_s) = \frac{A + 2B\varepsilon_i/\varepsilon_s}{1 + 2\varepsilon_i/\varepsilon_s}, \qquad (6)$$

with

$$A = -1.63 \times 10^{-3}|Q|^{0.65} + 2.18 \times 10^{-6}N_{atom} + 1.016, \quad (7)$$

$$B = 3.31 \times 10^{-2}|Q|^{0.65} - 4.77 \times 10^{-5}N_{atom} + 0.683, \qquad (8)$$

where Q and N_{atom} are the net charge and number of atoms, respectively, of the solute molecule.

In GBr[6], salt effects are accounted for by modifying Eq. (1) to

$$\Delta G_{GB}^0 = -\sum_{i,j} [1/\varepsilon_i - \exp(-\alpha\kappa f_{ij})/\varepsilon_s]q_iq_j/2f_{ij}, \qquad (9)$$

where $\kappa = (8\pi e^2 I/\varepsilon_s k_B T)^{1/2}$ is the Debye-Hückel screening parameter (I is the ionic strength and $k_B T$ is the thermal energy). The parameter α depends on the ionic strength. Based on minimizing deviations between GBr[6] and LPB salt effects, the following fitting function was obtained:

$$\alpha = \frac{1 + 0.0169I^{1/2}}{1 + 0.075I^{1/2}}. \qquad (10)$$

The salt effect specifically refers to the change in the solvation energy from zero salt to a particular ionic strength and will be denoted as δG.

B. GBr[6]NL

The adaptation of GBr[6] for reproducing NLPB salt effects is straightforward. Salt effects are calculated according to Eqs. (5) and (9) for a range of α values. For each ionic strength, the α value that minimizes the difference from the NLPB salt effect is obtained. The optimal α values at various ionic strengths are then fitted to a function like as Eq. (10). This fitted function will be given in the next section.

C. Test systems

As before,[39] the test systems consist of 55 proteins collected from the Protein Data Bank (http://www.rcsb.org/pdb) using the following criteria: a sequence identity less than 10%, a resolution better than 1.0 Å, and a number of residues less than 250. The total number of atoms and net charges for each protein are listed in Table I.

We also apply GBr[6]NL to two protein:RNA complexes. These are formed by the A protein of the U1 small nuclear ribonucleoprotein particle and its stem-loop RNA target (U1hpII) and by the C-terminal domain of ribosomal protein L11 (L11-C76) and a 58-nucleotide domain of 23 S rRNA. The preparation of these complexes for NLPB calculations was described previously.[24]

The NLPB equation is solved by the UHBD program.[4] All UHBD calculations use a coarse grid with a 1.5 Å spacing followed by a fine grid with a 0.5 Å spacing. The dimensions of the coarse and fine grids are $160 \times 160 \times 160$ and $200 \times 200 \times 200$, respectively, for the 55 PDB structures, and are both $140 \times 140 \times 140$ for the two protein:RNA complexes. The solute and solvent dielectric constants are 4 and 78.5, respectively, and the ion exclusion radius is 2 Å. The dielectric boundary between the solute and solvent is specified as the vdW surface. Protein atoms are assigned charges of the Amber force field[42] and the Bondi radii.[43]

III. RESULTS

A. Difference in salt effects between NLPB and LPB among 55 proteins

The net charges of the 55 proteins from the PDB are listed in Table I, ranging from $-25e$ to $11e$. Five proteins have net charges higher than $10e$ in magnitude. These have PDB codes (with net charges given in parentheses) 1exr ($-25e$), 1iqz ($-17e$), 1eb6 ($-15e$), 1tg0 ($-12e$), and 1l9l ($11e$).

Mobile ions in the solvent redistribute around the charges in the solute and thus tend to favor the latter's solvation. This is reflected by an increase in the magnitude in the solvation energy (relative to the value in the absence of salt). The increase is generally more prominent for proteins with high net charges (either positive or negative). This is illustrated by the NLPB results for salt effects on the solvation energies of the 55 proteins at $I = 50$ mM. The magnitudes of the salt effects are greater than 10 kcal/mol only for the five proteins with net charges greater than $10e$ in magnitude. The NLPB slat effects for the five proteins in the ionic strength of $10-1000$ mM are shown in Fig. 1.

For comparison, in Fig. 1 we also show the LPB salt effects for the five proteins. LPB always underestimates the magnitude of the salt effects. It approaches NLPB at very high ionic strength, and is identical to NLPB at zero salt. The difference between LPB and NLPB is thus maximal at an intermediate ionic strength. The maxima occur at below 10 mM for the five highly charged proteins and shift to higher ionic strengths for proteins with lesser net charges. For example, for 1tqg (with a net charge of $-7e$), the maximum difference occurs at ~ 30 mM; for 1unq (with a net charge of $-3e$) it occurs at 75 mM. NLPB calculations take $\sim$five times longer than the LPB counterparts.

The differences in the salt effect between LPB and NLPB for the five highly charged proteins are all greater than 1 kcal/mol at $I = 50$ mM. Only two other proteins, 1tqg and 1unq, also belong to this category. The LPB and NLPB salt effects for all the 55 proteins at $I = 50$ mM are listed in Table I.

TABLE I. Number of atoms, net charge, and salt effects at $I=50$ mM for 55 proteins. Rows are arranged in descending order of $|Q|$.

| PDB	N_{atom}	Q	LPB δG (kcal/mol)		NLPB δG (kcal/mol)	
			UHBD	GBr^6	UHBD	GBr^{6}NL
1exr	2240	−25	−39.69	−39.60	−46.18	−45.42
1iqz	1171	−17	−20.38	−20.37	−23.29	−23.62
1eb6	2572	−15	−14.87	−15.84	−18.23	−18.46
1tg0	1029	−12	−11.33	−11.03	−13.83	−13.04
1l9l	1230	11	−9.78	−9.40	−11.50	−11.17
1j0p	1597	8	−4.40	−4.17	−4.70	−4.88
1ssx	2750	8	−4.02	−4.22	−4.14	−4.88
1vbw	1058	8	−4.65	−4.62	−4.99	−5.42
1yk4	770	−8	−4.91	−4.81	−5.31	−5.68
2fdn	731	−8	−4.88	−4.67	−5.21	−5.48
3lzt	1960	8	−4.46	−4.41	−4.73	−5.16
1gqv	2143	7	−3.81	−3.59	−4.17	−4.27
1m1q	1265	−7	−4.13	−3.97	−4.66	−4.79
1nls	3564	−7	−3.42	−4.29	−3.70	−5.34
1tqg	1660	−7	−5.02	−4.55	−6.09	−5.63
1k4i	3253	−6	−2.76	−2.95	−3.54	−3.66
1nwz	1912	−6	−2.78	−2.92	−3.03	−3.56
2erl	573	−6	−2.92	−2.82	−3.13	−3.35
2fwh	1830	−6	−2.68	−2.78	−2.85	−3.34
1c7k	1929	−5	−2.57	−2.73	−3.12	−3.46
1f9y	2535	−5	−1.89	−2.02	−1.97	−2.50
1ok0	1076	−5	−2.10	−2.15	−2.26	−2.63
1w0n	1756	−5	−2.07	−2.24	−2.66	−2.80
1byi	3383	−4	−1.80	−1.90	−1.95	−2.48
1c75	987	−4	−1.46	−1.47	−1.54	−1.83
1p9g	529	4	−1.33	−1.32	−1.40	−1.59
1pq7	3065	4	−1.11	−1.19	−1.14	−1.47
1u2h	1526	4	−1.61	−1.53	−1.73	−1.94
1od3	1900	−3	−1.06	−1.11	−1.18	−1.47
1ufy	1926	−3	−1.25	−1.07	−1.37	−1.44
1unq	1966	−3	−3.57	−3.00	−4.86	−4.13
1vb0	921	3	−0.78	−0.77	−0.81	−0.95
2a6z	3432	−3	−1.12	−1.28	−1.23	−1.77
2chh	1624	−3	−1.43	−1.48	−2.41	−2.01
2cws	3400	−3	−0.90	−0.92	−0.97	−1.22
1a6m	2435	2	−0.80	−0.73	−0.90	−1.03
1aho	967	−2	−0.63	−0.63	−0.74	−0.86
1g66	2794	−2	−0.95	−1.29	−1.15	−1.85
2bf9	560	−2	−0.80	−0.72	−0.88	−0.96
1cex	2867	1	−1.15	−0.97	−1.31	−1.41
1f94	982	1	−0.22	−0.24	−0.24	−0.36
1g4i	1842	−1	−0.54	−0.57	−0.66	−0.88
1hje	179	1	−0.14	−0.13	−0.15	−0.18
1iua	1207	−1	−0.31	−0.27	−0.34	−0.40
1tt8	2676	1	−0.94	−0.78	−1.04	−1.13
1wy3	560	1	−0.23	−0.22	−0.25	−0.32
1x8q	2815	−1	−0.52	−0.87	−0.88	−1.33
1xmk	1268	1	−0.70	−0.54	−0.76	−0.78
1zzk	1252	1	−0.84	−0.65	−0.98	−0.97
1ejg	678	0	−0.08	−0.07	−0.08	−0.12
1etl	145	0	−0.09	−0.07	−0.10	−0.11
1kth	894	0	−0.33	−0.34	−0.38	−0.54
1r6j	1230	0	−0.22	−0.23	−0.23	−0.36
1ucs	997	0	−0.24	−0.24	−0.28	−0.38
1x6z	1741	0	−0.77	−0.69	−0.86	−1.02
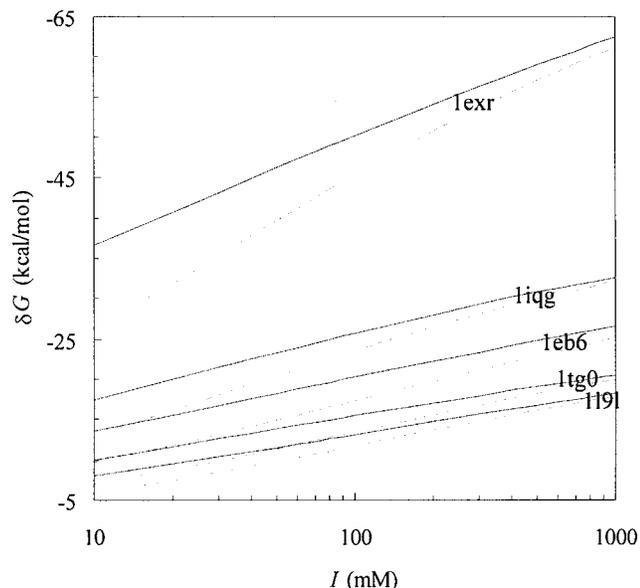
FIG. 1. Salt effects calculated from solving the NLPB (solid curves) and LPB (dashed curves) equations for five highly charged proteins.

B. Accuracy of GBr^{6}NL

GBr^{6}NL is parametrized by selecting the α value in Eq. (9) that minimizes the difference from the NLPB salt effect at each ionic strength. Following our earlier work on GBr^6,[39] the difference is taken to be the root mean square deviation (RMSD) between GBr^{6}NL and NLPB for the 55 proteins. The optimized α values in the ionic strength range of 10–1000 mM are shown in Fig. 2. These values are fitted to a function similar to Eq. (10), resulting in

$$\alpha = \frac{2.078 + 0.064I^{1/2}}{1 + 0.235I^{1/2}}. \quad (11)$$
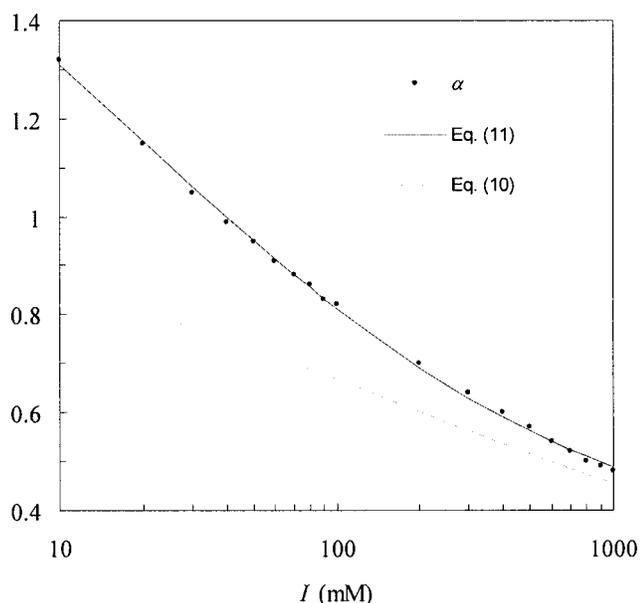
This fitted function is also shown in Fig. 2.

FIG. 2. Optimized α values (circles) for reproducing NLPB salt effects in the ionic strength range of 10–1000 mM and the fit to Eq. (11) (solid curve). For comparison, the prediction of Eq. (10), appropriate for LPB salt effects, is also shown (dashed curve).
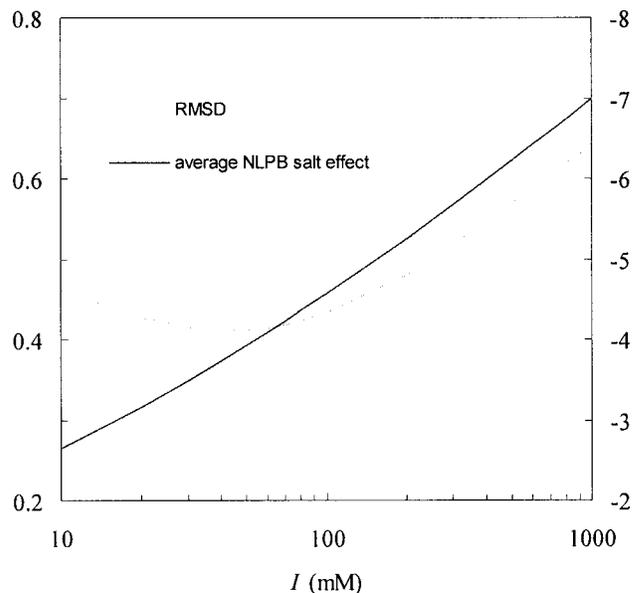

FIG. 3. Comparison of GBr^{6}NL and NLPB salt effects on the set of 55 proteins. The scale on the left ordinate, in kcal/mol, is for the RMSD of GBr^{6}NL from NLPB; the scale on the right ordinate, in kcal/mol, is for the average NLPB salt effect.

Compared to the counterparts in GBr^6, the optimized α values here are larger, as shown by the comparison between Eqs. (10) and (11) in Fig. 2. The increase in α is required by the stronger salt effects calculated from the NLPB equation (relative to the LPB counterpart). Note that the computational time for GBr^{6}NL is identical to that for GBr^6.

For the 55 proteins, the average NLPB salt effect changes from -2.6 kcal/mol at $I=10$ mM to -7.0 kcal/mol at $I=1000$ mM. The RMSD of GBr^{6}NL from NLPB falls in the range of 0.4–0.6 kcal/mol (Fig. 3). The salt effects for the 55 proteins at $I=50$ mM calculated by GBr^{6}NL and GBr^6 are listed in Table I.

C. Application to protein:RNA complexes

The accuracy of GBr^{6}NL is further tested on two protein:RNA complexes. The structures of these two complexes are shown in Fig. 4. In the U1A:U1hpII complex, the protein has a net charge of $6e$ and the RNA has a net charge of $-27e$. In the L11-C76:rRNA complex, the protein has a net charge of $3e$ and the RNA has a net charge of $-56e$.

The electrostatic contribution to the binding energy is $G_{bind} \equiv G(complex) - G(protein) - G(RNA)$, where G is the electrostatic interaction energy of a solute molecule. The salt effect on the binding energy is taken as the change in G_{bind} from zero salt to a particular ionic strength and denoted as δG_{bind}. Results on δG_{bind} for the two protein:RNA complexes were found by solving the NLPB equation in a previous study[24] and are used here for benchmarking GBr^{6}NL.

For the U1A:U1hpII complex, the NLPB salt effects are 32.0, 32.7, 33.5, and 34.2 kcal/mol at $I=160$, 230, 340, and 510 mM, respectively. The corresponding results calculated by GBr^{6}NL are 29.0, 30.1, 31.2, and 32.3 kcal/mol, respectively, which amount to underestimations of 5%–9%. For the L11-C76:rRNA complex, the NLPB salt effects changes
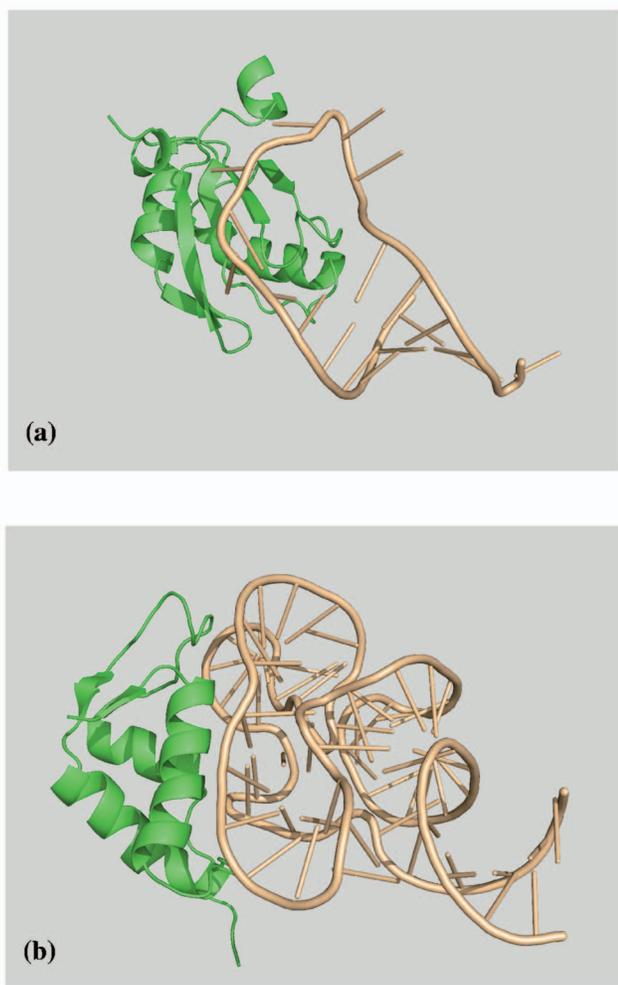
FIG. 4. (Color) Structures of two protein:RNA complexes: (a) U1A:U1hpII and (b) L11-C76:rRNA. Proteins are in green and RNA in gold.

from 25.1 kcal/mol at $I = 194$ mM to 27.1 kcal/mol at $I = 944$ mM. Over this range of ionic strength, the corresponding GBr^{6}NL results change from 31.7 to 35.9 kcal/mol. The larger errors, at ~30%, is likely related to the large net negative charge ($-56e$) on the RNA in this complex. Such a large net charge is far outside the range of net charges of the 55 proteins used for parametrizing GBr^{6}NL. With further refinements on nucleic acids, the accuracy of GBr^{6}NL will likely improve significantly.

IV. CONCLUSIONS

We have developed the first generalized Born method that is benchmarked against the nonlinear Poisson-Boltzmann equation. Salt effects are accurately predicted on test proteins and promising results are also seen for protein-:RNA complexes. We expect that GBr^{6}NL will spur the development of other GB methods. Highly charged large systems such as the ribosome are especially challenging;[6] GBr^{6}NL and similar GB methods present a very promising approach to tackling such a challenge.

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