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High-order discretization schemes for biochemical applications of boundary element solvation and variational electrostatic projection methods

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A series of high-order surface element discretization schemes for variational boundary element methods are introduced. The surface elements are chosen in accord with angular quadrature rules for integration of spherical harmonics. Surface element interactions are modeled by Coulomb integrals between spherical Gaussian functions with exponents chosen to reproduce the exact variational energy and Gauss's law for a point charge in a spherical cavity. The present work allows high-order surface element expansions to be made for variational methods such as the conductorlike screening model for solvation and the variational electrostatic projection method for generalized solvent boundary potentials in molecular simulations. © *2005 American Institute of Physics*.
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Two methods that have an important role in the arsenal of "multiscale" modeling techniques used to calculate the reactions of biomolecules are the smooth conductorlike screening model[1] (COSMO) and the recently introduced variational electrostatic projection (VEP) method.[2] The smooth COSMO model is based on a conductor variational principle originally proposed by Klamt and Schüürmann,[3] but differs from their original method in that the surface elements are modeled by the Gaussian functions that can be smoothly switched off or on as they become buried or exposed with changes in the molecular geometry. The smooth COSMO method has recently been extended to electronic structure and hybrid quantum mechanical/molecular mechanical (QM/MM) methods[4] and applied to phosphoryl transfer reactions in solution.[5] The VEP method[2] has been used to model the macromolecular electrostatic environment in stochastic boundary molecular-dynamics simulations.

The smooth COSMO and VEP methods are variational *boundary element* techniques that use discretized Gaussian surface elements that require specification of surface element position *and* properly calibrated Gaussian exponents to provide the correct variational response. In the present work, a prescription for the determination of the discretized surface elements and their Gaussian exponents is derived based on numerical quadrature rules for the integration of spherical harmonics. The data and relations presented here provide a convenient mechanism whereby boundary element methods such as smooth COSMO and VEP can be extended to a very high order.

ANGULAR QUADRATURE RULES

The surface discretization procedures used in the present work are based on angular quadrature rules[6] for spherical harmonic functions.[7] These rules are ideally suited for the smooth COSMO and VEP methods that may use constraints on high-order multipole moments in the variational procedure.

The set of N angular quadrature points $\{\theta_i, \phi_i\}$ and weights $\{w_i\}$ (normalized to 4π), for $i=1,\ldots,N$, for a particular order are determined to satisfy the integral relation

$$\int_0^{2\pi} d\phi \int_{-1}^{1} d(\cos\theta) f(\theta,\phi) = \sum_{i=1}^{N} w_i f(\theta_i,\phi_i), \tag{1}$$

where the function $f(\theta,\phi)$ can be represented in a basis of spherical harmonic functions up to a fixed order L as

$$f(\theta,\phi) = \sum_{l=0}^{L} \sum_{m=-l}^{l} C_{l,m} Y_{l,m}(\theta,\phi), \tag{2}$$

where $Y_{l,m}(\theta,\phi)$ is a spherical harmonic function and $C_{l,m}$ is the corresponding expansion coefficient.

Two types of angular quadrature rules[6] are considered: (1) a Gauss–Legendre product and (2) a Lebedev grid. The Gauss–Legendre product formula requires $L+1$ equally spaced points and uniform weights in ϕ, and $(L+1)/2$ Gauss–Legendre[8] quadrature points and weights in $\cos\theta$. This leads to a set of $N_{\mathrm{GL}}=(L+1)^2/2$ angular quadrature points that gives exact integration up to order L on the unit sphere. A more efficient set of angular quadrature for spherical harmonic functions, first pioneered by Lebedev,[9,10] involves formulas for specific points and weights determined algebraically. These angular quadrature grids were later extended[11,12] and recently to a very high order by Lebedev and Laikov.[13] For the Lebedev grid methods, the number of quadrature points required to satisfy exact integral relations up to order L is approximately $N_{\mathrm{Leb}}\approx(L+1)^2/3$, resulting in a computational cost reduction of about 33% relative to the Gauss–Legendre.

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DISCRETIZED SURFACE ELEMENTS

The discretized surfaces (henceforth be designated by γ) used in the smooth COSMO (Ref. 1) and VEP (Ref. 2) methods are based on discretized unit spheres that can then be dilated using exact scaling relations, translated, and assembled. The surface elements are represented by smooth Gaussian functions of the form

$$g_i(\mathbf{r}) = \left(\frac{\zeta_i^2}{\pi}\right)^{3/2} e^{-\zeta_i^2|\mathbf{r}-\mathbf{r}_i|^2}, \tag{3}$$

where $\mathbf{r}_i$ is the position of the ith surface element and ζ_i is the Gaussian exponent. The electrostatic interaction between surface elements i and j are modeled by the Coulomb integrals

$$J_{ij} = \int\int \frac{g_i(\mathbf{r})g_j(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|} d^3r d^3r' = \frac{\mathrm{erf}(\zeta_{ij}r_{ij})}{r_{ij}}, \tag{4}$$

where $\zeta_{ij}=\zeta_i\zeta_j/\sqrt{\zeta_i^2+\zeta_j^2}$, $r_{ij}=|\mathbf{r}_i-\mathbf{r}_j|$, and $\mathrm{erf}(x)$ is the error function.[7] The surface element self-interaction is determined in the limit that $\zeta_i=\zeta_j$ and $r_{ij}\to 0$, and is given by

$$J_{ii} = \int\int \frac{g_i(\mathbf{r})g_i(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|} d^3r d^3r' = \sqrt{\frac{2}{\pi}}\zeta_i \tag{5}$$

and the interaction of the Gaussian surface elements at $\mathbf{r}_i$ with a unit point charge at $\mathbf{R}_j$ can be calculated from Eq. (4) in the limit that $\zeta_j\to\infty$ to give

$$B_{ij} = \int\int \frac{g_i(\mathbf{r})\,\delta(\mathbf{r}'-\mathbf{R}_j)}{|\mathbf{r}-\mathbf{r}'|} d^3r d^3r' = \frac{\mathrm{erf}(\zeta_i|\mathbf{r}_i-\mathbf{R}_j|)}{|\mathbf{r}_i-\mathbf{R}_j|}. \tag{6}$$

The matrix elements of Eqs. (4)–(6) correspond to the matrix elements of Eqs. (66), (67), and (72), respectively, in the smooth COSMO method,[1] and Eqs. (9) and (12), and (13) respectively, in the VEP method.[2]

These Gaussian exponents, ζ_i, satisfy a simple relation with the angular quadrature weights w_i on the unit sphere:

$$\zeta_i = \zeta/\sqrt{w_i}, \tag{7}$$

where ζ is a scale factor chosen for each quadrature rule to reproduce the variational energy and the Gauss's law surface charge for a point charge Q at the center of a unit sphere [Eq. (7) is appropriate for rules where $w_i>0\ \forall i$]. The relation between the surface element and the Gaussian exponent [Eq. (7)] results in a nearly uniform variational surface charge distribution γ_i

$$\gamma_i = Qw_i/4\pi. \tag{8}$$

For spheres of different radii R, the discretization points, weights, and the Gaussian exponents obey the exact scaling relations

$$\zeta_i(R) = \zeta_i/R = \zeta/\sqrt{w_i(R)}, \tag{9}$$

$$\mathbf{r}_i(R) = \mathbf{r}_i R, \tag{10}$$

$$w_i(R) = w_i R^2, \tag{11}$$

where $\mathbf{r}_i$, w_i, and ζ_i correspond to the discretized unit sphere. The purpose of the present work is to present the scale factors ζ for a wide range of high-order quadrature rules such that they can be used to generate systematic sets of discretized γ surfaces for smooth COSMO, VEP, and other boundary-element methods.

TABLE I. Optimized scale factor for the Gaussian exponents for Gauss–Legendre product quadrature rules.

N_γ	Order	ζ	$\sigma_\gamma^{\mathrm{rel}}$	σ_γ
8	3	4.814 222 866 57	5.6E−08	7.0E−09
18	5	4.803 553 176 23	1.4E−02	7.8E−04
32	7	4.789 291 822 20	2.2E−02	7.3E−04
50	9	4.780 461 940 39	2.6E−02	5.4E−04
72	11	4.774 419 394 71	2.6E−02	3.8E−04
98	13	4.769 877 570 37	2.4E−02	2.7E−04
128	15	4.766 273 396 59	2.3E−02	1.9E−04
162	17	4.763 310 340 85	2.1E−02	1.4E−04
200	19	4.760 811 640 22	2.0E−02	1.1E−04
242	21	4.758 664 343 29	1.8E−02	8.1E−05
288	23	4.756 792 421 21	1.7E−02	6.4E−05
338	25	4.755 142 294 20	1.6E−02	5.1E−05
392	27	4.753 674 654 48	1.5E−02	4.1E−05
450	29	4.752 359 679 33	1.4E−02	3.4E−05
512	31	4.751 174 118 75	1.3E−02	2.8E−05
578	33	4.750 099 448 40	1.3E−02	2.4E−05
648	35	4.749 120 648 99	1.2E−02	2.0E−05
722	37	4.748 225 368 75	1.1E−02	1.7E−05
800	39	4.747 403 329 38	1.1E−02	1.5E−05
882	41	4.746 645 892 70	1.0E−02	1.3E−05
968	43	4.745 945 736 94	9.9E−03	1.1E−05
1058	45	4.745 296 610 02	9.6E−03	9.9E−06
1152	47	4.744 693 138 24	9.2E−03	8.8E−06
1250	49	4.744 130 675 76	8.9E−03	7.8E−06
1352	51	4.743 605 184 77	8.5E−03	7.0E−06
1458	53	4.743 113 138 92	8.3E−03	6.2E−06
1568	55	4.742 651 444 83	8.0E−03	5.6E−06
1682	57	4.742 217 377 74	7.7E−03	5.1E−06
1800	59	4.741 808 528 38	7.5E−03	4.6E−06
1922	61	4.741 422 758 78	7.3E−03	4.2E−06
2048	63	4.741 058 165 25	7.1E−03	3.8E−06
2178	65	4.740 713 047 36	6.9E−03	3.5E−06
2312	67	4.740 385 881 61	6.7E−03	3.2E−06
2450	69	4.740 075 299 10	6.5E−03	2.9E−06
2592	71	4.739 780 066 50	6.3E−03	2.7E−06
2738	73	4.739 499 069 75	6.2E−03	2.5E−06
2888	75	4.739 231 300 02	6.0E−03	2.3E−06
3042	77	4.738 975 841 58	5.9E−03	2.1E−06
3200	79	4.738 731 861 40	5.7E−03	2.0E−06
3362	81	4.738 498 599 98	5.6E−03	1.8E−06
3528	83	4.738 275 363 45	5.5E−03	1.7E−06
3698	85	4.738 061 516 64	5.3E−03	1.6E−06
3872	87	4.737 856 477 01	5.2E−03	1.5E−06
4050	89	4.737 659 709 29	5.1E−03	1.4E−06
4232	91	4.737 470 720 83	5.0E−03	1.3E−06
4418	93	4.737 289 057 39	4.9E−03	1.2E−06
4608	95	4.737 114 299 49	4.8E−03	1.2E−06
4802	97	4.736 946 059 16	4.7E−03	1.1E−06
5000	99	4.736 783 976 99	4.6E−03	1.0E−06

SCALE FACTORS FOR GAUSSIAN EXPONENTS

Tables I and II list the optimized values of the scale factors, ζ of Eq. (7), for each discretization level, along with

TABLE II. Optimized scale factor for Gaussian exponents for the Lebedev quadrature grids with octahedral symmetry. Grids of order 13, 25, and 27 (N_γ=74, 230, and 266 points, respectively) were neglected due to negative quadrature weights that are not appropriate for use in Eq. (7).

N_γ	Order	ζ	$\sigma_\gamma^{\mathrm{rel}}$	σ_γ
6	3	4.845 660 778 68	2.2E−06	3.6E−07
14	5	4.864 587 143 34	9.0E−04	6.5E−05
26	7	4.854 782 262 19	6.6E−03	2.5E−04
38	9	4.901 058 126 85	1.8E−02	4.8E−04
50	11	4.892 506 732 95	3.8E−03	7.8E−05
86	15	4.897 413 725 80	1.3E−03	1.5E−05
110	17	4.901 010 609 87	5.1E−03	4.7E−05
146	19	4.898 251 873 92	1.4E−02	9.9E−05
170	21	4.906 855 177 25	1.2E−03	7.1E−06
194	23	4.903 376 442 48	3.6E−03	1.9E−05
302	29	4.904 980 881 69	3.2E−03	1.1E−05
350	31	4.868 794 748 32	3.3E−02	9.4E−05
434	35	4.905 673 490 80	2.3E−03	5.3E−06
590	41	4.906 240 713 59	2.0E−03	3.4E−06
770	47	4.906 564 357 79	1.5E−03	2.0E−06
974	53	4.906 851 679 98	1.3E−03	1.4E−06
1202	59	4.907 040 982 16	1.0E−03	8.7E−07
1454	65	4.907 210 238 69	9.6E−04	6.7E−07
1730	71	4.907 332 706 91	7.6E−04	4.5E−07
2030	77	4.907 444 991 42	7.2E−04	3.6E−07
2354	83	4.907 530 828 25	5.8E−04	2.5E−07
2702	89	4.907 609 727 66	5.6E−04	2.1E−07
3074	95	4.907 672 823 94	4.6E−04	1.5E−07
3470	101	4.907 731 413 71	4.4E−04	1.3E−07
3890	107	4.907 779 659 81	3.7E−04	9.7E−08
4334	113	4.907 824 695 26	3.6E−04	8.5E−08
4802	119	4.907 491 255 53	5.0E−04	1.1E−07
5294	125	4.907 620 734 52	4.2E−04	8.0E−08
5810	131	4.907 929 025 22	2.6E−04	4.6E−08

the root-mean-square (rms) error [$\sigma_\gamma=\langle(\gamma^{\mathrm{calc}}-\gamma)^2\rangle^{1/2}$] in the variational γ surface charge distribution [Eq. (8)], and the relative rms error ($\sigma_\gamma^{\mathrm{rel}}=\sigma_\gamma/\langle\gamma^2\rangle^{1/2}$). All of the surface element discretization schemes beyond eight points give numerical values for the variational energy and Gauss's law surface charge to at least 12 significant figures. The surface elements derived from all of the quadrature rules produce nearly uniform variational surface charge distributions. The σ_γ values for the Gauss–Legendre surface elements fall below 10^{-4} with 242 points (order 21) or greater and fall below 10^{-5} with 1058 points (order 45) or greater, reaching the lowest σ_γ value of 10^{-6} at 5000 points (order 99). The Lebedev grids converge more quickly in terms of the integration order and require less discretization points than the Gauss–Legendre product rules. The σ_γ values for the Lebedev surface elements fall below 10^{-4}, 10^{-5}, and 10^{-6} with 50, 434, and 1202 points, respectively, corresponding to orders 11, 35, and 59, respectively. The lowest σ_γ value of 4.6×10^{-8} occurs at 5810 points (order 131).

The scale factors, ζ, can be fit to the number of surface elements N_γ with the empirical equation

$$\zeta = c_0 + c_1/(N_\gamma + c_2)^{1/n}, \tag{12}$$

where c_0, c_1, and c_2 are unitless empirical parameters and n is an integer. Plots of the Gaussian exponent scale factors for the Gauss–Legendre and Lebedev surface elements as a function of $N_\gamma^{1/2}$ are shown in Fig. 1. Although the fit to Eq. (12) is very good, it is recommended that the scale factors from Tables I and II be used for quantitative work.

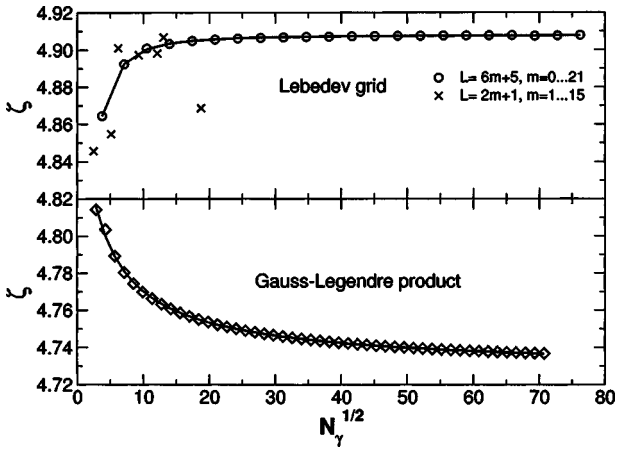

FIG. 1. Optimized scale factors for the surface element Gaussian exponents derived from the Gauss–Legendre and Lebedev quadrature formulas. The black diamonds are the optimal zeta values calculated for the Gauss–Legendre surface elements. The black circles and × symbols are the optimal zeta values calculated for the Lebedev grids of order L given by $L=6m+5$, $\{m=0,1,\ldots,21\}$ and $L=2m+1$, $\{m=1,2,\ldots,15\}$, respectively. The latter did not fit to the empirical relation of Eq. (12) used to produce the trendlines. The values for the parameters in Eq. (12) for the Gauss–Legendre surface elements are $n=3$, $c_0=4.723\,827\,4$, $c_1=0.219\,217\,30$, and $c_2=5.642\,918\,6$. The corresponding values for the Lebedev surface elements are $n=1$, $c_0=4.907\,834\,1$, $c_1=-0.845\,688\,67$, and $c_2=5.553\,785\,4$.

The present work offers a prescription for the generation of discretized surface elements for variational boundary element methods such as smooth COSMO and VEP that are important for modeling reactions of biomolecules with multiscale models. Extension to high-order discretization allows the accuracy of the methods to be systematically improved, the convergence properties to be characterized, and the benchmark quality calculations to be performed.

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