

biomolecular simulations. The method has similar advantages to multigrid methods: $\mathcal{O}(N)$ scaling, ease of parallelization, flexibility for all types of boundary conditions, and the ability to handle inhomogeneous dielectric environments.

Better representation of electrostatics

More accurate representations of electrostatics can be achieved through the inclusion of higher-order multipoles, polarizability, and continuous electrostatics. Of course, the gain in accuracy has to be balanced with the increase in the cost of the simulations, and new algorithms are needed to make feasible the more physical representations of the electronic cloud. Here we review some of the recent developments.

Electrostatic interactions have traditionally been modeled using an atom-centered point charge (‘partial charge’) representation of the molecular charge density. The most popular methods for extracting charges from molecular wavefunctions are based on fitting atomic charges to the molecular electrostatic potential (MEP), computed with *ab initio*, density functional theory or semiempirical wavefunctions. The charge fitting procedure consists of minimizing the squared deviation between the Coulombic potential produced by the atomic charges and the MEP. These non-bond potentials are then expressed as a sum of spherically isotropic atom-atom potentials. Such representations are believed to be an important source of error in current force fields (35).

The fit to the MEP can be improved either by adding more charge sites (126) or by including higher order multipoles at the atomic sites or bonds. Even with these improvements the fit to the MEP remains poor in regions near the atomic nuclei, where the charge densities overlap. As a consequence, the electrostatic interaction energy must be corrected for “penetration” effects at close range (127) (usually this error is absorbed into the exchange repulsion term); and the optimal values of the point multipoles may be poorly determined (128, 129). Nevertheless the use of off-center charges and/or higher order atomic point multipoles can significantly improve the treatment of electrostatics (35, 130–134) and numerous schemes have been developed to partition the

electronic cloud into multipoles (131, 135–137).

In addition to fixed distributed multipoles, a better accuracy requires the inclusion of polarization and, when possible, of the charge density overlap. Polarization is the result of the change in the molecular charge density due to the presence of other molecules or to changes in the geometry of the molecule. These effects are known as inter- and intra-molecular polarization respectively (35). This effect can be introduced by the use of an explicit polarization energy contribution. Several methods have been developed including the Drude oscillator (138, 139), fluctuating charge (140, 141) and induced dipole model (142–144). This has given rise to several polarizable force fields (145–149).

The *distributed* multipole analysis first introduced by Stone assigns distributed multipole moments to several sites in the molecule (*i.e.*, atoms and bond midpoints), and gives a more accurate representation of the electrostatic potential than one-center, molecular multipole expansion. The generalization of Ewald summation to atomic multipoles up to quadrupoles was given by Smith (46). Since then, a few groups (47–49, 143) have extended the Ewald method to take into account multipoles at the atomic and other point sites. However, the multipoles greatly increase the cost of calculations within the Ewald framework. For instance, an electrostatic representation including charges, dipoles and quadrupoles costs approximately 100 times more than a representation with only charges, using the Ewald formalism, thus rendering multipolar representations in biomolecular simulations prohibitively expensive. In order to surmount this difficulty, PME-based methods have been introduced. A first approach for *large-scale* biomolecular simulations was introduced in 2000 by Toukmaji et al. (47), who developed –in addition to the classical Ewald treatment – a PME based treatment of fixed and induced point dipoles. Both methods have been implemented into the sander molecular dynamics module of AMBER (versions 6 to 11), along with several schemes for solving the induced dipoles (iterative, Car-Parrinello) The PME based implementation is quite efficient; for a 1 fs timestep it is only approximately 1.4 times more expensive than a calculation including only charges. Since then, a polarizable empirical force field based on the classical Drude oscillator model (150) was implemented in CHARMM in 2005. Even

these very simple representations of polarizability make a big difference for various biomolecular systems (*151–161*).

An efficient implementation of higher order multipoles in a Cartesian tensor formalism was introduced in 2004 by Sagui et al. (*49, 162*). The long-range electrostatic interactions are divided in two sums according to the usual Ewald scheme: the *direct* sum, which evaluates the fast-varying, particle-particle interactions, considered up to a given cutoff in real space; and the “*reciprocal*” sum, which evaluates the smoothly varying, long-range part of the interaction. When implementing multipoles, one has to take care of additional physics that is not present in the usual treatment of charges. First, the higher-order multipoles produce additional contributions to the reciprocal virial, that arise from the dependence of the structure factor on the reciprocal lattice vector. Second, all the multipolar components that appear in the expressions of energy, forces, etc. are given in a global coordinate system. It is necessary therefore to transform the local multipole moments – generally defined in reference to the molecule– to a global framework before any calculation starts. This is achieved by defining “frames” (local orthogonal coordinate systems). Third, to carry out molecular dynamics, the torques produced by every multipole need to be converted into atomic forces.

In order to accelerate the evaluation of the Ewald-like sums, the direct part was implemented using a McMurchie-Davidson formalism (*163*), while the reciprocal part was implemented in three different ways: using an Ewald scheme, a PME-based approach and a multigrid-based approach. The standard matrix implementation of multipole interactions up to hexadecapole-hexadecapole costs three orders of magnitude more than charge-charge interactions. Instead, due to the use of the SPME and the factorizability of B-splines, the multipolar SPME is very efficient. For instance, for the same grid density and spline order, calculating reciprocal sum interactions up to hexadecapole-hexadecapole is only twice as expensive as calculating charge-charge interactions. Therefore, by transferring more of the computation of the interactions to reciprocal space and using a small cut-off for the direct sum, it is possible to preserve the accuracy of the calculations at a moderate cost. In fact, a considerably accurate calculation of interactions up to hexadecapole-hexadecapole costs

only a factor of 8.5 more (for relative force errors of $\sim 5 \times 10^{-4}$) than a regular AMBER implementation with only charge-charge interactions. Furthermore, a ‘regular’ cutoff of 8 Angstroms for the Coulomb summation (with the acceleration provided by the McMurchie-Davidson scheme) is approximately six times more expensive and has a force error two orders of magnitude larger than the complete calculation for which most of the interaction is computed in reciprocal space via the PME method. This code has been adapted to achieve a fast implementation of the AMOEBA (Atomic Multipole Optimized Energetics for Biomolecular Applications) force field of Ren and Ponder (143, 164–166). The force field includes fixed atomic multipoles up to quadrupole level as well as inducible atomic dipoles using a Thole damping model. A PME-based implementation of the multipolar code for AMOEBA has been released through AMBER 9-11.

Even if polarization is taken into account, the neglect of the charge density overlap when point charges or multipoles are used gives rise to the so-called penetration errors (35, 167, 168) in the Coulomb interactions at close distances. This effect may be compensated to an extent by the use of damping functions (169–172). Another possibility to avoid the penetration errors is by using continuous representations of the molecular charge density. Several methods have been introduced to include better descriptions of the electron density. The Hansen-Coppens formalism describes the static density of a molecular fragment by a superposition of aspherical pseudoatoms composed of nuclei-centered density units (173–175). Gavezzotti introduced a method to adapt electron densities from molecular orbital calculations to calculate intermolecular energies by direct numerical integration (176).

Recently, Cisneros et al. (168, 177, 178) introduced a force field based on density fitting, termed the Gaussian electrostatic model (177) (GEM). In this method, the molecular charge density obtained from quantum mechanical (QM) calculations is fitted to a linear combination of Gaussian functions centered at specific sites. The fitted densities of the fragments are employed to calculate each of the components of the intermolecular interaction separately, thus also including many-body effects such as non-additivity. The philosophy of GEM is to carry out the fitting in order to reproduce only the gas phase *ab initio* QM intermolecular interaction results from the constrained

space orbital variation (CSOV) energy decomposition scheme (179, 180).

The initial formalism in this approach involved the analytical fitting of QM densities to s-type functions (GEM-0) (177). This enabled the calculation of intermolecular interactions with average errors well below 0.2 kcal/mol for each component of the energy as well as the total intermolecular energy. The formalism was subsequently extended for the Coulomb and exchange-repulsion terms to enable the use of Gaussian fitting functions of arbitrary angular momentum (178). The use of higher angular momentum functions required the improvement of the fitting methods to reduce numerical instabilities. Normalized Hermite Gaussian basis sets were employed for the fit of the molecular densities. The use of Hermite Gaussian functions has the additional advantage of facilitating a point multipole decomposition determination at each expansion site. Since the basis functions with higher angular momentum have directionality, a reference molecular frame formalism similar to that defined in Ref. (49) was employed for the rotation of the fitted expansion coefficients.

The use of molecular densities results in the need to compute a large number of two center integrals for the intermolecular interaction. A significant computational speedup can be achieved by using reciprocal space methods based on Ewald sums. In this way, the integrals are calculated in direct and reciprocal space depending on the exponent of the Gaussian charge densities.

Here we describe how the Ewald formalism can be extended to take into account the Gaussian distribution. As before, let U denote a unit cell whose edges are given by the vectors \mathbf{a}_1 , \mathbf{a}_2 and \mathbf{a}_3 . An idealized infinite crystal can be generated by all periodic translations $\mathbf{n} = n_1\mathbf{a}_1 + n_2\mathbf{a}_2 + n_3\mathbf{a}_3$ for all integer triples (n_1, n_2, n_3) , with n_1, n_2, n_3 not all zero. Now, consider a collection of N normalized spherical Gaussian charge densities $\rho_1 \dots \rho_N$ (e.g. GEM-0) centered at $\{\mathbf{R}_1 \dots \mathbf{R}_N\} \in U$ with exponents α_i , i.e. $\rho_i(\mathbf{r}) = (\alpha_i/\pi)^{3/2} \exp(-\alpha_i(\mathbf{r} - \mathbf{R}_i)^2)$, and let $q_1 + \dots + q_N = 0$. Note that N need not be limited only to atomic positions, e.g., GEM-0 includes sites on the oxygen lone pairs and the bisector line between the two hydrogens (177). The Coulomb energy of the central unit cell within a large spherical crystal, due to the interactions of the Gaussian charge distributions with each other and all periodic images within the crystal can be calculated using Ewald methods.

In particular, to determine the reciprocal part in the Ewald sum it is necessary to grid the Gaussian densities. However, this can become intractable for Gaussian functions with large exponents (compact Gaussians). In the initial implementation the charge densities were classified into compact or diffuse Hermite Gaussians based on a given Ewald exponent β . Therefore, if the exponent of a given Hermite was above the cutoff it was considered compact, and diffuse ($\alpha_i < \beta$) otherwise. With this, the contributions involving diffuse Hermites can be calculated in reciprocal space exclusively (178).

This was later improved by the realization that the Ewald exponent, β may be different for each pair ij (181). Thus, β is chosen to be infinite for ij pairs where at least one of the Gaussians is diffuse. In this way, all pairs that involve diffuse Hermites are evaluated in reciprocal space. That is, given $\beta > 0$ a Gaussian distribution $q_i \rho_i$ is classified as compact ($i \in c$) if $\alpha_i \geq 2\theta$ and diffuse ($i \in d$) otherwise. Subsequently, for $i, j \in \{c\}$, select β so that $1/\theta = 1/\alpha_i + 1/\alpha_j + 1/\beta$, otherwise $\beta = \infty$. With this, the Ewald expression becomes

$$\begin{aligned}
E = & \frac{1}{2} \sum_{\mathbf{n}}' \sum_{(i,j) \in c \times c} q_i q_j \left\{ \frac{\text{erfc}(\theta^{1/2} |\mathbf{R}_{ij} - \mathbf{n}|) - \text{erfc}(\mu_{ij}^{1/2} |\mathbf{R}_{ij} - \mathbf{n}|)}{|\mathbf{R}_{ij} - \mathbf{n}|} \right\} \\
& + \frac{1}{2\pi V} \sum_{\mathbf{m} \neq 0} \sum_{(i,j) \in c \times c}^N q_i q_j \frac{\exp(-\pi^2 \mathbf{m}^2 / \theta)}{\mathbf{m}^2} \exp(-2\pi i \mathbf{m} \cdot \mathbf{R}_{ij}) \\
& + \frac{1}{2\pi V} \sum_{\mathbf{m} \neq 0} \sum_{(i,j) \notin c \times c}^N q_i q_j \frac{\exp(-\pi^2 \mathbf{m}^2 / \mu_{ij})}{\mathbf{m}^2} \exp(-2\pi i \mathbf{m} \cdot \mathbf{R}_{ij}) \\
& - \frac{\pi}{2V} \sum_{i,j=1}^N q_i q_j \left(\frac{1}{\theta} + \frac{1}{\alpha_i} + \frac{1}{\alpha_j} \right) - \sum_{i=1}^N q_i^2 \left(\frac{\theta}{\pi} \right)^{1/2} - \sum_{i=1}^N q_i^2 \left(\frac{\alpha_i}{\pi} \right)^{1/2} + \frac{2\pi \mathbf{D}^2}{3V} + \varepsilon(K),
\end{aligned} \tag{13}$$

where the first term corresponds to the direct part of the Ewald sum, the second and third terms to the reciprocal part, $\mathbf{R}_{ij} = \mathbf{R}_i - \mathbf{R}_j$, the term involving the unit cell dipole $\mathbf{D} = q_1 \mathbf{R}_1 + \dots + q_N \mathbf{R}_N$ is the surface term, $\varepsilon(K)$ denotes a quantity that converges to 0 as $K \rightarrow \infty$, \mathbf{m} denotes the reciprocal lattice vectors, and $1/\mu_{ij} = 1/\alpha_i + 1/\alpha_j$.

Equation (13) applies only to spherical ($l = 0$) Gaussians. This expression can be further gen-

eralized for the case when the auxiliary and optimized bases used for the fitting include Gaussians with $l > 0$ (*178*). In this case, the direct space contributions can be efficiently evaluated by using the McMurchie-Davidson (MD) recursion (*163*). This recursion was used to calculate the required erfc and higher derivatives for the multipoles (*49*). This approach was also employed for the Hermite Gaussians (*178*), where it was shown that the MD recursion is applicable to other types of operators besides $1/r$. For the reciprocal sums two methods were implemented: SPME (*42*) and FFP (*43*).

These methods were applied to simulate a series of water boxes of 64 to 1024 molecules under periodic boundary conditions (*178, 181*). These calculations showed a significant computational speed improvement when FFP and PME were used compared to full Ewald sums. Alternative methods for fitting have been also explored. Numerical fitting of molecular properties, in particular electrostatic potential, have given good results. The numerical fitting has resulted in two improvements. The first is the reduction of numerical instabilities in the calculation of the coefficients. The second is a reduction in the number of fitting sites needed for accurate reproduction of the molecular electrostatic potential (*182*). Overall, the use of numerical fits produces results similar to the analytical fits with errors around 0.2 kcal/mol. More recently the numerical fitting has been improved by introducing spherical grids coupled to a Gaussian type weighting function for discarding points near the core (*183*). The reduction in the number of fitting sites results in significant computational speedups. For example, an extremely accurate calculation with GEM using a 3 site fitting model for water with interactions up to d-type Hermite Gaussians was carried out in a box of 4096 waters in PBC using the A1 auxiliary basis set (*184*) with coefficients fitted to the electrostatic potential. The resulting energy/force calculation costs (in one processor) only one order of magnitude more than the calculation using a TIP3P water model (*182*).

Perspective

At present, the performance of traditional classical codes, where electrostatics is represented by point charges, is driven by the successive generations of computer architectures with parallelization issues dominating the game. At the frontier, very large systems and mili-second time scales are now feasible (82, 185). It is to be expected that simulations on such scales will become more commonplace with improvements in hardware prompting questions regarding the validity of the force fields on these scales. Interesting work remains to be done to characterize the effect of point-charge electrostatics in extremely long molecular dynamics simulations. There is a good chance that undesired artifacts will be discovered as more and more systems are studied. Future studies will likely need more accurate representations of non-bonded interactions. This, in turn, will require the development of new parallel implementations to allow for the efficient evaluation of long-range electrostatic interactions with more accurate representations of the molecular charge density.

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References

1. Alper HE, Levy RM (1989) Computer-simulations of the dielectric-properties of water – studies of the simple point-charge and transferable intermolecular potential models. *J. Chem. Phys.* 91:1242–1251
2. Alper HE, Bassolino D, Stouch TR (1993) Computer-simulation of a phospholipid monolayer-water system – the influence of long-range forces on water-structure and dynamics. *J. Chem. Phys.* 98:9798–9807

3. Alper HE, Bassolino-Klimas D, Stouch TR (1993) The limiting behavior of water hydrating a phospholipid monolayer – a computer simulation study. *J. Chem. Phys.* 99:5547–5559
4. Feller SE, Pastor RW, Rojnuckarin A, Bogusz A, Brooks BR (1996) Effect of electrostatic force truncation on interfacial and transport properties of water. *J. Phys. Chem.* 100:17011–17020
5. Mark P, Nilsson L (2002) Structure and dynamics of liquid water with different long-range interaction truncation and temperature control methods in molecular dynamics simulations. *J. Comp. Chem.* 23:1211–1219
6. Yonetani Y (2006) Liquid water simulation: A critical examination of cutoff length. *J. Chem. Phys.* 124:204501
7. Smith PE, Pettitt BM (1991) Peptides in ionic solutions: A comparison of the Ewald and switching function techniques. *J. Chem. Phys.* 95:8430 – 8441
8. Schreiber H, Steinhauser O (1992) Cutoff size does strongly influence molecular-dynamics results on solvated polypeptides. *Biochemistry* 31:5856–5860
9. York DM, Darden TA, Pedersen LG (1993) The effect of long-range electrostatic interactions in simulations of macromolecular crystals – a comparison of the Ewald and truncated list methods. *J. Chem. Phys.* 99:8345–8348
10. York DM, Yang WT, Lee H, Darden T, Pedersen LG (1995) Toward the accurate modeling of DNA – the importance of long-range electrostatics. *J. Am. Chem. Soc.* 117:5001–5002
11. Cheatham III TE, Kollman PA (1997) Molecular dynamics simulations highlight structural differences among DNA:DNA, RNA:RNA, and DNA:RNA hybrid duplexes. *J. Am. Chem. Soc.* 119:4805 – 4825
12. Auffinger P, Westhof E (1998) Molecular Dynamics Simulations of Nucleic Acids. Encyclopedia of Computational Chemistry. John Wiley and Sons, New York

13. Norberg J, Nilsson L (2000) On the truncation of long-range electrostatic interactions in DNA. *Biophys. J.* 79:1537–1553
14. Feller SE, Pastor RW, Rojnuckarin A, Bogusz S, Brooks BR (1996) Effect of Electrostatic Force Truncation on Interfacial and Transport Properties of Water. *J. Phys. Chem.* 100:17011 – 17020
15. Patra M, Karttunen M, Hyvonen MT, Falck E, Vattulainen I (2004) Lipid bilayers driven to a wrong lane in molecular dynamics simulations by subtle changes in long-range electrostatic interactions. *J. Phys. Chem. B* 108:4485–4494
16. Anézo C, de Vries AH, Höltje HD, Tieleman DP (2003) Methodological issues in lipid bilayer simulations. *J. Phys. Chem. B* 107:9424–9433
17. Khelashvili GA, Scott HL (2004) Combined Monte Carlo and molecular dynamics simulation of hydrated 18:0 sphingomyelin-cholesterol lipid bilayers. *J. Chem. Phys.* 120:9841–9847
18. Patra M, Hyvonen MT, Falck E, Sabouri-Ghomi M, Vattulainen I, Karttunen M (2007) Long-range interactions and parallel scalability in molecular simulations. *Comp. Phys. Comm.* 176:14–22
19. Karttunen M, Rottler J, Vattulainen I, Sagui C (2008) *COMPUTATIONAL MODELING OF MEMBRANE BILAYERS*. Elsevier Inc.
20. Heyes DM, Barber M, Clarke JHR (1977) Molecular dynamics computer simulation of surface properties of crystalline potassium chloride. *J. Chem. Soc., Faraday Trans. 2*:1485–1496
21. Hautman J, Klein ML (1992) An Ewald summation method for planar surfaces and interfaces. *Mol. Phys.* 75:379–395
22. de Leeuw SW, Perram. JW (1979) Electrostatic lattice sums for semi-infinite lattices. *Mol. Sim.* 37:1313 – 1322

23. Nijboer BRA, de Wette FW (1957) On the calculation of lattice sums. *Physica* 23:309–321
24. Yeh IC, Berkowitz ML (1999) Ewald summation for systems with slab geometry. *J. Chem. Phys.* 111:3155–3162
25. Lekner J (1989) Summation of dipolar fields in simulated liquid-vapor interfaces. *Physica A* 157:826–838
26. Lekner J (1991) Summation of Coulomb fields in computer-simulated disordered systems. *Physica A* 176:485–498
27. Lekner J (1998) Coulomb forces and potentials in systems with an orthorhombic unit cell. *Mol. Sim.* 20:357
28. Sperb R (1994) Extension and Simple Proof of Lekner’s Summation Formula for Coulomb Forces. *Mol. Sim.* 13:189–193
29. Sperb R (1998) An Alternative to Ewald Sums part I: Identities for Sums. *Mol. Sim.* 20:179–200
30. Sperb R (1999) An Alternative to Ewald Sums, Part 2: The Coulomb Potential in a Periodic System. *Mol. Sim.* 22:199–212
31. Strebel R, Sperb R (2001) An Alternative to Ewald Sums. Part 3: Implementation and Results. *Mol. Sim.* 27:61–74
32. Arnold A, Holm C (2002) A novel method for calculating electrostatic interactions in 2D periodic slab geometries. *Chem. Phys. Lett.* 354:324–330
33. Arnold A, Holm C (2002) MMM2D: A fast and accurate summation method for electrostatic interactions in 2D slab geometries. *Computer Physics Comm.* 148:327–348
34. Baker NA (2005) Improving implicit solvent simulations: a Poisson-centric view. *Curr. Opin. Struct. Bio.* 15:137–143

35. Stone AJ (1996) *The Theory of Intermolecular Forces*. Clarendon Press, Oxford
36. Ewald P (1921) Die Berechnung optischer und elektrostatischer Gitterpotentiale. *Ann. Phys.* 64:253 – 287
37. DeLeeuw SW, Perram JW, Smith ER (1980) Simulation of electrostatic systems in periodic boundary conditions I: Lattice sums and dielectric constants. *Proc. R. Soc. Lond. A* 373:27 – 56
38. Boresch S, Steinhauser O (1997) Presumed versus Real Artifacts of the Ewald Summation Technique: The Importance of Dielectric Boundary Conditions. *Ber. Bunsenges. Phys. Chem.* 101:1019 – 1029
39. Hockney RW, Eastwood JW (1981) *Computer Simulation using Particles*. McGraw-Hill, New York
40. Pollock E, Glosli J (1996) Comments on PPPM, FMM, and the Ewald method for large periodic Coulombic systems. *Comp. Phys. Comm.* 95:93 – 110
41. Darden TA, York DM, Pedersen LG (1993) Particle mesh Ewald: An $N \log(N)$ method for Ewald sums in large systems. *J. Chem. Phys.* 98:10089 – 10092
42. Essmann U, Perera L, Berkowitz ML, Darden T, Lee H, Pedersen LG (1995) A smooth particle mesh Ewald method. *J. Chem. Phys.* 103:8577 – 8593
43. York D, Yang W (1994) The Fast Fourier Poisson (FFP) Method for Calculationg Ewald Sums. *J. Chem. Phys.* 101:3298 – 3300
44. Smith ER (1994) Calculating the Pressure in Simulations Using Periodic Boundary Conditions. *J. Stat. Phys.* 77:449 – 472
45. Caillol JP (1994) Comments on the numerical simulations of electrolytes in periodic boundary conditions. *J. Chem. Phys.* 101:6080 – 6090

46. Smith W (1982) Point Multipoles in the Ewald Summation. *CCP5 Information Quarterly* 4:13 – 25
47. Toukmaji A, Sagui C, Board JA, Darden T (2000) Efficient PME-based Approach to Fixed and Induced Dipolar Interactions. *J. Chem. Phys.* 113:10913 – 10927
48. Aguado A, Madden P (2003) Ewald summation of electrostatic multipole interactions up to the quadrupolar level. *J. Chem. Phys.* 119:7471–7483
49. Sagui C, Pedersen LG, Darden TA (2004) Towards an accurate representation of electrostatics in classical force fields: Efficient implementation of multipolar interactions in biomolecular simulations. *J. Chem. Phys.* 120:73 – 87
50. Smith W (1987) Coping with the pressure: How to calculate the Virial. *CCP5 Information Quarterly* 26:43 – 50
51. Alejandre J, Tildesley DJ, Chapela GA (1995) Molecular dynamics simulation of the orthobaric densities and surface tension of water. *J. Chem. Phys.* 102:4574 – 4583
52. Nose S, Klein M (1983) Constant pressure molecular dynamics for Molecular Systems. *Mol. Phys.* 50:1055 – 76
53. Brown D, Clarke JHR (1991) A loose coupling, constant-pressure, molecular dynamics algorithm for use in the modelling of polymer materials. *Comp. Phys. Comm.* 62:360 – 369
54. Reif MM, Kraeutler V, Kastenholz MA, Daura X, Huenenberger PH (2009) Molecular Dynamics Simulations of a Reversibly Folding beta-Heptapeptide in Methanol: Influence of the Treatment of Long-Range Electrostatic Interactions. *J. Phys. Chem. B* 113:3112–3128
55. Villarreal MA, Montich GG (2005) On the Ewald artifacts in computer simulations. The test-case of the octaalanine peptide with charged termini. *J. Biomol. Struct. Dyn.* 23:135–142
56. Monticelli L, Colombo G (2004) The influence of simulation conditions in molecular dynamics investigations of model beta-sheet peptides. *Theo. Chem. Acc.* 112:145 – 157

57. Monticelli L, Simões C, Belvisi L, Colombo G (2006) Assessing the influence of electrostatic schemes on molecular dynamics simulations of secondary structure forming peptides. *Journal of Physics: Condensed Matter* 18:S329–S345
58. Babin V, Roland C, Darden TA, Sagui C (2006) The free energy landscape of small peptides as obtained from metadynamics with umbrella sampling corrections. *J. Chem. Phys.* 125:204909
59. Levy RM, Gallicchio E (1998) Computer simulations with explicit solvent: Recent progress in the Thermodynamic Decomposition of free Energies, and in Modeling Electrostatic Effects. *Ann. Rev. Phys. Chem.* 49:531 – 567
60. Hummer G, Pratt LR, Garcia AE (1996) On the free energy of ionic hydration. *J. Phys. Chem.* 100:1206 – 1215
61. Figueredo F, Buono GSD, Levy RM (1997) On finite-size Corrections to the Free Energy of Ionic Hydration. *J. Phys. Chem. B* 101:5622–5623
62. Hummer G, Pratt LR, Garcia AE (1997) Ion Sizes and Finite-Size Corrections for Ionic-Solvation Free Energies. *J. Chem. Phys.* 107:9275 – 9277
63. Sakane S, Ashbaugh HS, Wood RH (1998) Continuum Corrections to the Polarization and Thermodynamic Properties of Ewald Sum Simulations for Ions and Ion Pairs at Infinite Dilution. *J. Phys. Chem. B* 102:5673 – 5682
64. Darden T, Pearlman D, Pedersen L (1998) Ionic charging free energies: Spherical versus Periodic Boundary Conditions. *J. Chem. Phys.* 109:10921 – 10935
65. Herce D, Darden T, Sagui C (2003) Calculation of ionic charging free energies in simulation systems with atomic charges, dipoles and quadrupoles. *J. Chem. Phys.* 119:7621 – 7632
66. Ferrell R, Bertschinger E (1994) Particle-mesh methods on the connection machine. *J. Mod. Phys.* 5:933 – 956

67. Toukmaji A, Board JA (1996) Ewald Sum Techniques in Perspective: A Survey. *Comp. Phys. Comm.* 95:78 – 92
68. Darden T, Toukmaji A, Pedersen L (1997) Long-range electrostatic effects in biomolecular simulations. *J. Chim. Phys.* 94:1346 – 1364
69. Deserno M, Holm C (1998) How to mesh up Ewald sums I: A theoretical and numerical comparison of various particle mesh routines. *J. Chem. Phys.* 109:7678 – 7693
70. Sagui C, Darden TA (1999) Molecular Dynamics Simulations of Biomolecules: Long-range Electrostatic effects. *Annu. Rev. Biophys. Biomol. Struct.* 28:155 – 179
71. Sagui C, Darden TA (1999) P3M and PME: A Comparison of the two Methods. *Simulation and Theory of Electrostatic Interactions in Solution*. Pratt LR, Hummer G, Eds. AIP, Melville, NY
72. Case DA, Cheatham, III TE, Darden T, Gohlke H, Luo R, Merz, Jr. KM, Onufriev A, Simmerling C, Wang B, Woods R (2005) The Amber biomolecular simulation programs. *J. Comput. Chem.* 26:1668–1688
73. Brooks BR, Bruccoleri RE, Olafson BD, States DJ, Swaminathan S, Karplus M (1983) CHARMM: A Program for Macromolecular Energy, Minimization and Dynamics Calculations. *J. Comp. Chem.* 4:187 – 217
74. Phillips J, Braun R, Wang W, Gumbart J, Tajkhorshid E, Villa E, Chipot C, Skeel R, Kale L, Schulten K (2005) Scalable molecular dynamics with NAMD. *J. Comp. Chem.* 26:1781–1802
75. Hess B, Kutzner C, van der Spoel D, Lindahl E (2008) GROMACS 4: Algorithms for highly efficient, load-balanced, and scalable molecular simulation. *J. Chem. Theo. Comp.* 4:435–447
76. Bowers KJ, Chow E, Xu H, Dror RO, Eastwood MP, Gregersen BA, Klepeis JL, Kolossvary I, Moraes MA, Sacerdoti FD, Salmon JK, Shan Y, Shaw DE (2006) Scalable algorithms for

- molecular dynamics simulations on commodity clusters. In SC '06: Proceedings of the 2006 ACM/IEEE Conference on Supercomputing. ACM Press
77. Cerutti DS, Duke RE, Darden TA, Lybrand TP (2009) Staggered Mesh Ewald: An Extension of the Smooth Particle-Mesh Ewald Method Adding Great Versatility. *J. Chem. Theory Comput.* 5:2322–2338
 78. Chen L, Langdon AB, Birdsall CK (1974) REDUCTION OF GRID EFFECTS IN SIMULATION PLASMAS. *J. Comp. Phys.* 14:200–222
 79. Hockney RW, Eastwood JW (1988) *Computer Simulation using Particles*. Adam Hilger
 80. Cerutti DS, Case DA (2010) Multi-Level Ewald: A Hybrid Multigrid/Fast Fourier Transform Approach to the Electrostatic Particle-Mesh Problem. *J. Chem. Theory Comput.* 6:443–458
 81. Duke RE (2006) *Amber 9 manual: amber.scripps.edu/doc9/amber9.pdf*. AMBER 9, D. A. Case et al., University of California, San Francisco
 82. Schulten K, Phillips JC, Kale LV, Bhatele A (2008) In *Petascale Computing: Algorithms and Applications*, Bader D, Ed. Chapman & Hall / CRC Press
 83. Brandt A (1977) Multi-level adaptive solutions to boundary value problems. *Math. Comput.* 31:333 – 390
 84. Brandt A (1994) *SIAM J. Num. Anal.* 31:1695
 85. Brandt A (2001) Multiscale scientific computation: Review 2001. Multiscale and Multiresolution Methods: Theory and Applications. Barth TJ, Chan TF, Haimes R, Eds. Springer Verlag, Heidelberg
 86. Beck TL (2000) Real-space mesh techniques in density-functional theory. *Rev. Mod. Phys.* 72:1041–1080

87. Honig B, Nicholls A (1995) Classical Electrostatics in Biology and Chemistry. *Science* 268:1144 – 1149
88. Holst M, Saied F (1993) Multigrid Solution of the Poisson-Boltzmann Equation. *J. Comp. Chem.* 14:105 – 113
89. Holst M, Kozack RE, Saied F, Subramaniam S (1994) Treatment of Electrostatic Effects in Proteins: Multigrid-Based Newton Iterative Method for Solution of the Full Poisson-Boltzmann Equation. *Proteins Struct. Fun. Gen.* 18:231 – 241
90. Holst M, Saied F (1995) Numerical solution of the nonlinear Poisson-Boltzmann equation: Developing more robust and efficient methods. *J. Comp. Chem.* 16:337–364
91. Ripoll DR, Vorobjev YN, Liwo A, Vila JA, Scheraga HA (1996) Coupling between folding and ionization equilibria: Effects of pH on the conformational preferences of polypeptides. *J. Mol. Biol.* 264:770–783
92. Vorobjev YN, Scheraga HA (1997) A fast adaptive multigrid boundary element method for macromolecular electrostatic computations in a solvent. *J. Comp. Chem.* 18:569–583
93. Qian X, Schlick T (2002) Efficient multiple-time-step integrators with distance-based force splitting for particle-mesh-Ewald molecular dynamics simulations. *J. Chem. Phys.* 116:5971–5983
94. Press W, Teukolsky SA, Vetterling WT, Flannery BP (1992) *Numerical Recipes in FORTRAN: The Art of Scientific Computing*. Cambridge University Press, Cambridge
95. Zaslavsky L, Schlick T (1998) An adaptive multigrid technique for evaluating long-range forces in biomolecular simulations. *Appl. Math. Comput.* 97:237 – 250
96. Sagui C, Darden TA (2001) Multigrid Methods for Classical Molecular Dynamics Simulations of Biomolecules. *J. Chem. Phys.* 114:6578 – 6591

97. Hackbush W (1985) *Multigrid Methods and Applications*. Springer-Verlag, Berlin
98. Briggs EL, Sullivan DJ, Bernholc J (1996) A Real-Space Multigrid-Based Approach to Large-Scale Electronic Structure Calculations. *Phys. Rev. B* 54:14362 – 14375
99. Skeel RD, Tezcan I, Hardy DJ (2002) Multiple Grid Methods for Classical Molecular Dynamics. *J. Comp. Chem.* 23:673–684
100. Goedecker S, Chauvin C (2003) COMBINING MULTIGRID AND WAVELET IDEAS TO CONSTRUCT MORE EFFICIENT MULTISCALE ALGORITHMS. *J. Theo. Comp. Chem.* 2:483–495
101. Izaguirre JA, Hampton SS, Matthey T (2005) Parallel multigrid summation for the N-body problem. *J. Parall. Distrib. Comp.* 65:949–962
102. Banerjee S, J. A. Board J (2005) Efficient Charge Assignment and Back Interpolation in Multigrid Methods for Molecular Dynamics. *J. Comp. Chem.* 26:957 – 967
103. Shan Y, Klepeis JL, Eastwood MP, Dror RO, Shaw DE (2005) Gaussian split Ewald: A fast Ewald mesh method for molecular simulation. *J. Chem. Phys.* 122:054101
104. Groot RD (2003) Electrostatic interactions in dissipative particle dynamics – simulation of polyelectrolytes and anionic surfactants. *J. Chem. Phys.* 118:11265–11277
105. Bishop T, Skeel R, Schulten K (1997) Difficulties with Multiple Stepping and Fast Multipole Algorithm in Molecular Dynamics. *J. Comp. Chem.* 18:1785 – 91
106. Greengard L, Rokhlin V (1987) A Fast Algorithm for Particle Simulations. *J. Comp. Phys.* 73:325 – 348
107. Board JA, Causey JW, Leathrum JF, Windemuth A, Schulten K (1992) Accelerated molecular dynamics simulation with the parallel fast multipole algorithm. *Chem. Phys. Lett.* 198:89 – 94

108. Schmidt KE, Lee MA (1991) Implementing the Fast Multipole Method in Three Dimensions. *J. Stat. Phys.* 63:1223 – 1235
109. Lambert CG, Darden TA, Board JA (1996) A multipole-based method for efficient calculation of forces and potentials in macroscopic periodic assemblies of particles. *J. Comp. Phys.* 126:274 – 285
110. Figueirido F, Levy R, Zhou R, Berne B (1997) Large scale simulation of macromolecules in solution: Combining the Periodic Fast Multipole Method with multiple time step integrators. *J. Chem. Phys.* 106:9835 – 9849
111. Greengard LF (1988) *The Rapid Evaluation of Potential Fields in Particle Systems*. The MIT Press, Cambridge MA
112. Greengard LF (1994) Fast Algorithms for Classical Physics. *Science* 265:909 – 914
113. Greengard L, Rokhlin V (1997) A new version of the Fast Multipole Method for the Laplace equation in three dimensions. *Acta Numerica* 6:229 – 270
114. Greengard L, Rokhlin V (1997) A Fast Algorithm for Particle Simulation. *J. Comput. Phys.* 135:280–292
115. Cheng H, Greengard L, Rokhlin V (1999) A fast adaptive multipole algorithm in three dimensions. *J. Chem. Phys.* 115:468–498
116. Fenley M, Olson W, Chua K, Boschitsch A (1994) Fast adaptive multipole method for computation of electrostatic energy in simulations of polyelectrolyte DNA. *J. Comp. Chem.* 17:976
117. Zhou R, Berne B (1995) A new molecular dynamics method combining the reference system propagator algorithm with a fast multipole method for simulating proteins and other complex systems. *J. Chem. Phys.* 103:9444 – 9459

118. Ogata S, Campbell T, Kalia R, Nakano A, Vashishta P, Vemparala S (2003) Scalable and portable implementation of the fast multipole method on parallel computers. *Comp. Phys. Comm.* 153:445–461
119. Kurzak J, Pettitt BM (2005) Massively parallel implementation of a fast multipole method for distributed memory machines. *J. Parall. Distrib. Comp.* 65:870–881
120. Kurzak J, Pettitt BM (2006) Fast multipole methods for particle dynamics. *Molecular Simulation* 32:775–790
121. Maggs AC, Rossetto V (2002) Paper1. *Phys. Rev. Lett.* 88:196402
122. Alastuey A, Appel W (2000) *Physica A* 276:508
123. Rottler J, Maggs AC (2004) Local Molecular Dynamics with Coulombic Interactions. *Phys. Rev. Lett.* 93:170201
124. Pasichnyk I, Duenweg B (2004) bla. *J. Phys.: Cond. Mat.* 16:S3999
125. Rottler J (2007) Local electrostatics algorithm for classical molecular dynamics simulations. *J. Chem. Phys.* 127
126. Dixon R, Kollman P (1997) Advancing beyond the atom-centered model in additive and non-additive molecular mechanics. *J. Comp. Chem.* 18:1632 – 1646
127. Wheatley R, Mitchell J (1994) Gaussian multipoles in practice: Electrostatic energies for Intermolecular potentials. *J. Comp. Chem.* 15:1187 – 1198
128. Bayly C, Cieplak P, Cornell W, Kollman P (1993) A well-behaved electrostatic potential based method using charge restraints for deriving atomic charges - the RESP model. *J. Phys. Chem.* 97:10269 – 10280

129. Francel MM, Chirlian LA (1999) The pluses and minuses of mapping atomic charges to Electrostatic potentials. *Reviews in Computational Chemistry*. Lipkowitz K, Boyd DB, Eds. VCH Publishers, New York, NY
130. Price S (1999) In *Reviews in Computational Chemistry*, Lipkowitz K, Boyd DB, Eds. VCH Publishers, New York, NY
131. Popelier P (2000) *Atoms in Molecules: An Introduction*. Prentice Hall, Harlow, England
132. Kosov DS, Popelier PLA (2000) Atomic Partitioning of Molecular Electrostatic Potentials. *J. Phys. Chem. A* 104:7339 – 7345
133. Popelier PLA, Joubert L, Kosov DS (2001) Convergence of the Electrostatic Interaction Based on Topological Atoms. *J. Phys. Chem. A* 105:8254 – 8261
134. Popelier PLA, Kosov DS (2001) *J. Chem. Phys.* 114:6539 – 6547
135. Proft FD, Alsenov CV, Peeters A, Langenaeker W, Geerlings P (2002) Atomic charges, dipole moments and Fukai functions using the Hirshfeld partitioning of the electron density. *J. Comp. Chem.* 23:1198 – 1209
136. Bader R (1990) *Atoms in Molecules: A Quantum Theory*. Clarendon Press, Oxford
137. Sagui C, Pomorski P, Darden TA, Roland C (2004) Ab initio calculation of electrostatic multipoles with Wannier functions for large-scale biomolecular simulations. *J. Chem. Phys.* 120:4530 – 4544
138. Yu H, Hansson T, van Gunsteren WF (2003) Development of a simple, self-consistent polarizable model for liquid water. *J. Chem. Phys.* 118:221–234
139. Lamoureux G, Alexander D, MacKerell J, Roux B (2003) A simple polarizable model of water based on classical Drude oscillators. *J. Chem. Phys.* 119:5185–5197

140. Rick SW, Stuart SJ, Berne BJ (1994) Dynamical fluctuating charge force fields: Application to liquid water. *J. Chem. Phys.* 101:6141–6156
141. Ribeiro MCC, Almeida LCJ (1999) Fluctuating charge model for polyatomic ionic systems: A test case with diatomic anions. *J. Chem. Phys.* 110:11445–11448
142. Caldwell J, Dang LX, Kollman PA (1990) Implementation of nonadditive intermolecular potentials by use of molecular dynamics: development of a water-water potential and water-ion cluster interactions. *J. Am. Chem. Soc.* 112:9144–9147
143. Ren P, Ponder JW (2003) Polarizable Atomic Multipole Water Model for Molecular Mechanics Simulation. *J. Phys. Chem. B* 107:5933 – 5947
144. Eling D, Darden TA, Woods RJ (2007) Gaussian induced dipole polarization model. *J. Comp. Chem.* 28:1261–1274
145. Ponder JW, Wu C, Ren P, Pande VS, Chodera JD, Schnieders MJ, Haque I, Mobley DL, Lambrecht DS, Robert A. DiStasio Jr., Head-Gordon M, Clark GNI, Johnson ME, Head-Gordon T (2010) Current Status of the AMOEBA Polarizable Force Field. *J. Phys. Chem. B* 114:2549–2564
146. Case DA, T.E. Cheatham III, Darden TA, Gohlke H, Luo R, K.M. Merz Jr., Onufirev A, Simmerling C, Wang B, Woods RJ (2005) The Amber biomolecular simulation programs. *J. Comp. Chem.* 26:1668–1688
147. Day PN, Jensen JH, Gordon MS, Webb SP, Stevens WJ, Krauss M, Garmer D, Basch H, Cohen D (1996) An effective fragment method for modeling solvent effects in quantum mechanical calculations. *J. Chem. Phys.* 105:1968–1986
148. Gagliardi L, Lindh R, Karlström G (2004) Local properties of quantum chemical systems: The LoProp approach. *J. Chem. Phys.* 121:4494–4500
149. Gresh N, Claverie P, Pullman A (1979) SIBFA. *Int. J. Quantum. Chem.* 253, Symp 11

150. Anisimov VM, Lamoureux G, Vorobyov IV, Huang N, Roux B, MacKerell AD (2005) Determination of electrostatic parameters for a polarizable force field based on the classical Drude oscillator. *J. Chem. Theory Comput.* 1:153–168
151. Jungwirth P, Tobias D (2002) Ions at the air/water interface. *J. Phys. Chem. B* 106:6361–6373
152. Baucom J, Transue T, Fuentes-Cabrera M, Krahn J, Darden T, Sagui C (2004) Molecular dynamics simulations of the d(CCAACGTTGG)₂ decamer in crystal environment: comparison of atomic point-charge, extra-point and polarizable force fields. *J. Chem. Phys.* 121:6998–7008
153. Vrbka L, Mucha M, Minofar B, Jungwirth P, Brown E, Tobias D (2004) Propensity of soft ions for the air/water interface. *Curr. Opin. Coll. Interface Sci.* 9:67–73
154. Herce D, Perera L, Darden T, Sagui C (2005) Surface solvation for an ion in a water cluster. *J. Chem. Phys.* 122:024513
155. Babin V, Baucom J, Darden TA, Sagui C (2006) Molecular dynamics simulations of DNA with polarizable force fields: Convergence of an ideal B-DNA structure to the crystallographic structure. *J. Phys. Chem. B* 110:11571 – 11581
156. Harder E, Anisimov VM, Whitfield TW, MacKerell AD, Roux B (2008) Understanding the dielectric properties of liquid amides from a polarizable force field. *J. Phys. Chem. B* 112:3509–3521
157. Vladimirov E, Ivanova A, Roesch N (2008) Effect of solvent polarization on the reorganization energy of electron transfer from molecular dynamics simulations. *J. Chem. Phys.* 129
158. Harder E, MacKerell AD, Roux B (2009) Many-Body Polarization Effects and the Membrane Dipole Potential. *J. Am. Chem. Soc.* 131:2760+

159. Vladimirov E, Ivanova A, Roesch N (2009) Solvent Reorganization Energies in A-DNA, B-DNA, and Rhodamine 6G-DNA Complexes from Molecular Dynamics Simulations with a Polarizable Force Field. *J. Phys. Chem. B* 113:4425–4434
160. Cieplak P, Dupradeau FY, Duan Y, Wang J (2009) Polarization effects in molecular mechanical force fields. *J. Phys.: Condens. Matter* 21
161. Yan T, Wang Y, Knox C (2010) On the Structure of Ionic Liquids: Comparisons between Electronically Polarizable and Nonpolarizable Models I. *J. Phys. Chem. B* 114:6905–6921
162. Sagui C, Roland C, Pedersen LG, Darden TA (2005) New distributed multipole methods for accurate electrostatics in large-scale biomolecular simulations. *New Algorithms for Macromolecular Simulations*. Leimkuhler B, Chipot C, Elber R, Laaksonen A, Mark A, Schlick T, Schuette C, Skeel R, Eds. Springer Verlag, Berlin
163. McMurchie L, Davidson E (1978) One- and Two-Electron Integrals over Cartesian Gaussian Functions. *J. Comput. Phys* 26:218 – 231
164. Ren P, Ponder JW (2002) A Consistent Treatment of Inter- and Intramolecular Polarization in Molecular Mechanics Calculations. *J. Comput. Chem.* 23:1497 – 1506
165. Ponder JW, Case DA (2003) Force Fields for Protein Simulation. *Adv. Protein Chem.* 66:27
166. Ren P, Ponder JW (2004) Temperature and pressure dependence of the AMOEBA water model. *J. Phys. Chem. B* 108:13427–13437
167. Qian W, Krimm S (2005) Limitations of the Molecular Multipole Expansion Treatment of Electrostatic Interactions for C-H...O and O-H...O Hydrogen Bonds and Application of a General Charge Density Approach. *J. Phys. Chem. A* 109:5608–5618
168. Cisneros GA, Piquemal JP, Darden TA (2005) Intermolecular electrostatic energies using density fitting. *J. Chem. Phys.* 123:044109

169. Piquemal JP, Gresh N, Giessner-Prettre C (2003) Improved formulas for the calculation of the electrostatic contribution to the intermolecular interaction energy from multipolar expansion of the electronic distribution. *J. Phys. Chem. A* 107:10353–10359
170. Cisneros GA, Tholander SNI, Parisel O, Darden TA, Elking D, Perera L, Piquemal JP (2008) Simple formulas for improved point-charge electrostatics in classical force fields and hybrid quantum mechanical/molecular mechanical embedding. *Int. J. Quantum. Chem.* 108:1905–1912
171. Freitag MA, Gordon MS, Jensen JH, Stevens WJ (2000) Evaluation of charge penetration between distributed multipolar expansions. *J. Chem. Phys.* 112:7300–7306
172. Wang B, Truhlar DG (2010) Including Charge Penetration Effects in Molecular Modeling. *J. Chem. Theo. Comp.* 6:3330–3342
173. Volkov A, Koritsanszky T, Coppens P (2004) Combination of the exact potential and multipole methods (EP/MM) for evaluation of intermolecular electrostatic interaction energies with pseudoatom representation of molecular electron densities. *Chem. Phys. Lett.* 391:170–175
174. Volkov A, Li X, Koritsanszky T, Coppens P (2004) *Ab initio* quality electrostatic atomic and molecular properties including intermolecular energies from a transferable theoretical pseudoatom databank. *J. Phys. Chem. A* 108:4283–4300
175. Volkov A, Coppens P (2004) Calculation of electrostatic interaction energies in molecular dimers from atomic multipole moments obtained by different methods of electron density partitioning. *J. Comp. Chem.* 25:921–934
176. Gavezzotti A (2002) Calculation of intermolecular interaction energies by direct numerical integration over electron densities I. Electrostatic and polarization energies in molecular crystals. *J. Phys. Chem. B* 106:4145–4154

177. Piquemal JP, Cisneros GA, Reinhardt P, Gresh N, Darden TA (2006) Towards a force field based on density fitting. *J. Chem. Phys.* 124:104101
178. Cisneros GA, Piquemal JP, Darden TA (2006) Generalization of the Gaussian electrostatic model: Extension to arbitrary angular momentum, distributed multipoles, and speedup with reciprocal space methods. *J. Chem. Phys.* 125:184101
179. Bagus PS, Hermann K, C. W. Bauschlicher Jr. (1984) A new analysis of charge transfer and polarization for ligand–metal bonding: model studies for Al_4CO and Al_4NH_3 . *J. Chem. Phys.* 80:4378–4386
180. Piquemal JP, Marquez A, Parisel O, Giessner-Prettre C (2005) A CSOV Study of the difference between HF and DFT Intermolecular Interaction Energy Values: the importance of the charge transfer contribution. *J. Comp. Chem.* 26:1052–1062
181. Darden TA (2007) In “*Dual bases in crystallographic computing*” in *International Tables of Crystallography*, Shmueli U, Ed. Kluwer Academic Publishers, Dordrecht, The Netherlands
182. Cisneros GA, Elking DM, Piquemal JP, Darden TA (2007) Numerical fitting of molecular properties to Hermite Gaussians. *J. Phys. Chem. A* 111:12049–12056
183. Elking DM, Cisneros GA, Piquemal JP, Darden TA, Pedersen LG (2010) Gaussian Multipole Model (GMM). *J. Chem. Theo. Comp.* 6:190–202
184. Godbout N, Andzelm J (1998) *DGauss Version 2.0, 2.1, 2.3, 4.0: the file that contains the AI and PI auxiliary basis sets can be obtained from the CCL WWW site at <http://ccl.osc.edu/cca/data/basis-sets/DGauss/basis.v3.html>*. Computational Chemistry List, Ltd., Ohio
185. Shaw DE, Maragakis P, Lindorff-Larsen K, Piana S, Dror RO, Eastwood MP, Bank JA, Jumper JM, Salmon JK, Shan Y, Wriggers W (2010) Atomic-Level Characterization of the Structural Dynamics of Proteins. *Science* 330:341–346