The development and implementation of a tree code (TC) and fast multipole method (FMM) for the efficient, linear-scaling calculation of long-range electrostatic interactions of particle distributions with variable shape and multipole character are described. The target application of these methods are stochastic boundary molecular simulations with polarizable force fields and/or combined quantum mechanical/molecular mechanical potentials. Linear-scaling is accomplished through the adaptive decomposition of the system into a hierarchy of interacting particle sets. Two methods for effecting this decomposition are evaluated: fluc-splitting and box-splitting, for which the latter is demonstrated to be generally more accurate. In addition, a generalized termination criterion is developed that delivers optimal performance at fixed error tolerance that, in the case of quadrupole-represented Drude water, effects a speed-up by a factor of 2-3 relative to a multipole-independent termination criteria. The FMM is shown to be approximately 2-3 times faster than the TC, independent of the system size and multipole order of the particles. The TC and FMM are tested for a variety of static and polarizable water systems, and for the the 70S ribosome functional complex containing an assembly of transfer and messenger RNAs.

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I. INTRODUCTION

Computational chemistry and biology techniques continue to improve in their ability to tackle complex chemical phenomena. One area where this is particularly well illustrated is in the development and application of so-called multi-scale quantum models to study chemical reactivity of biological molecules.\(^1\) Simulations of biological reactivity using multi-scale models requires the integration of a hierarchy of methods working synchronously to assemble a network of interactions that reasonably mimic a realistic biological environment. These simulations can be considerably costly, especially when highly charged systems such as DNA and RNA are involved and the chemical events are intimately coupled with large-scale conformations changes. Despite the graduation in complexity of the methods contributing to the multi-scale quantum models, one of the main computational bottleneck for these simulations still derives from the evaluations of long-range electrostatic interactions as with conventional molecular mechanical force field simulations.\(^2\)–\(^4\) However, unlike the traditional static point charge models and fairly uniform distribution of atoms in force field simulations, the charge distributions in multi-scale quantum models involve added levels of complexity. A combined quantum mechanical/molecular mechanical model of an enzyme or ribozyme active site may require a fairly sophisticated representation of the quantum charge distribution based on the single-particle density-matrix.\(^5\),\(^6\) Some of the developing polarizable force fields\(^7\),\(^8\) may additionally require atom or off-center sites to have higher-order multipole character.\(^9\)–\(^15\) Finally, boundary element method used to mimic the electrostatic and linear-response effects of the medium require a set of surface points or Gaussians that encapsulate the macromolecule.\(^16\)–\(^19\) Together, the assembly of these heterogeneous, non-uniform charge distributions present a challenge for the design of
efficient, robust linear-scaling electrostatic algorithms.

In this paper we develop, implement and compare two different adaptive linear-scaling electrostatic methods: a tree code (TC) and a fast-multipole method (FMM). These methods utilize a non-grid based recursive bisection method that adaptively allows subdivision of multipolar particles into localized sets used to evaluate direct and multipolar interactions for a broad range of non-uniform particle distributions such as those encountered in multi-scale quantum simulations. The main features that comprise the methods have been for the most part described in other seminal papers on linear-scaling electrostatic methods in the literature. The accuracy and efficiency of the present implementations are tested and characterized for a variety of systems. Particular detail is spent on achieving an optimum balance between accuracy and efficiency as a function of multipole expansion order, the so-called “well-separateness” criteria, and adaptive termination condition. In addition, two methods for adaptive particle set splitting procedures are examined and compared. The methods are demonstrated to be considerably robust, and for non-periodic systems, provide an attractive alternative to either direct $O(N^2)$ calculation or more approximate spatial decomposition methods that employ electrostatic cutoffs.

The paper is outline of the paper is as follows. Sec. II describes the FMM and TC methods and our implementation, including the description of 2 different adaptive splitting conditions and termination conditions. Sec. III provides FMM and TC parameters corresponding to several levels of accuracy, which are examined as a function of system shape, size, and particle composition. The adaptive splitting procedures are compared and deficiencies are identified. Finally, the use of a generalized termination condition developed in Sec. II is examined. The paper concludes in Sec. IV
with a summary of the key results.

II. METHODS

Sec. II A provides the mathematical description of the FMM energy and derivatives, and Sec. II B describes our hierarchical implementation. Sec. II C discusses the relationship between FMM and tree-code methods and how this effects the implementation. The well-separatedness criteria, adaptive splitting procedures, and termination criteria are described in Sec. II D.

A. FMM energy

The Coulomb energy of a system, $J$, can generally be written

$$ J = \frac{1}{2} \int \int \frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d^3rd^3r' = \frac{1}{2} \int \rho(\mathbf{r})\phi(\mathbf{r})d^3r, \quad (1) $$

where $\rho(\mathbf{r})$ is the charge density of the system and $\phi(\mathbf{r})$ is its electrostatic potential. Suppose that $\rho(\mathbf{r})$ is composed of a set of $N$ sites (e.g., atoms), with the charge density of each site represented by a set of basis functions $\varphi_{i,(l,m)}(\mathbf{r})$, i.e.,

$$ \rho(\mathbf{r}) = \sum_{i=1}^{N} \rho_{i}(\mathbf{r} - \mathbf{R}_{i}) = \sum_{i=1}^{N} \sum_{l=0}^{l_{\text{max},i}} \sum_{m=-l}^{l} q_{i,(l,m)} \varphi_{i,(l,m)}(\mathbf{r} - \mathbf{R}_{i}), \quad (2) $$

where $i$ indexes sites, $\mathbf{R}_{i}$ is the position of the $i^{th}$ site, $(l, m)$ indexes the angular momentum of the basis function, and $q_{i,(l,m)}$ is the corresponding multipole moment of the site, i.e.,

$$ q_{i,(l,m)} = \int \rho_{i}(\mathbf{r} - \mathbf{R}_{i}) R_{l,m}(\mathbf{r} - \mathbf{R}_{i}) d^3r, \quad (3) $$

where $R_{l,m}(\mathbf{r})$ is a scaled real regular solid harmonic,$^{23,40,41}$ and is discussed further in the appendix. Eq. (1) can then be written

$$ J = \frac{1}{2} \sum_{i=1}^{N} q_{i}^T \cdot \mathbf{p}_{i}, \quad (4) $$
where \( q_i \) is the vector of multipole moments for site \( i \), and \( p_i \) is a corresponding set of “multipolar potentials”, i.e., the \((l, m)\)th element of the vector \( p_i \) is

\[
P_{i, (l, m)} = \frac{dJ}{dq_{i, (l, m)}} = \sum_{j=1}^{N} \sum_{l_j=0}^{l_{\text{max}, j}} \sum_{m_j=-l_j}^{l_j} \int \int \frac{\varphi_{i, (l, m)}(r - R_i) \varphi_{j, (l_j, m_j)}(r' - R_j)}{|r - r'|} d^3r d^3r'.
\]

The term multipolar potential is sometimes referred to in the literature as a Taylor expansion of the electrostatic potential.

FMMs achieve linear scaling by partitioning a system into a hierarchy of sets, representing the charge distribution of each set by a single multipole expansion, and replacing explicit site-site interactions between well-separated sets by a single multipole-multipole interaction. In this context, the Coulomb energy is written

\[
J = \frac{1}{2} \sum_{a} \sum_{i \in a} q_{i_a}^T \cdot p_{i_a}^{fmm} + \frac{1}{2} \sum_{a} \sum_{i \in a} q_{i_a}^T \cdot p_{i_a}^{dir},
\]

where \( a \) indexes a set of sites, \( \sum_{i \in a} \) sums over all sites within set \( a \), \( i_a \) is the \( i^{th} \) site in set \( a \), and the multipolar potential has been separated into contributions arising from well-separated multipole-multipole interactions, \( p_{i_a}^{fmm} \), and explicit site-site interactions between non-well-separated sets, \( p_{i_a}^{dir} \).

In order to provide expressions for \( p_{i_a}^{dir} \) and \( p_{i_a}^{fmm} \) in a manner that includes concepts of hierarchy and well-separateness, it is notationally convenient to introduce the functions \( ws(ab) \) and \( dir(ab) \):

\[
ws(ab) = \begin{cases} 
1, & \text{if sets } a \text{ and } b \text{ are well-separated and do not interact at a superset-level} \\
0, & \text{otherwise}
\end{cases}
\]

(7)
\[ \text{dir}(ab) = \begin{cases} 1, & \text{if sets } a \text{ and } b \text{ are not well-separated and do not have subsets of particles} \\ 0, & \text{otherwise.} \end{cases} \] (8)

Using Eq. (8), the expression for \( p_{ia}^{\text{dir}} \) becomes analogous to Eq. (5)

\[
p_{ia,(l,m)}^{\text{dir}} = \sum_b \text{dir}(ab) \sum_{l_j=0}^{l_{\text{max},j}} \sum_{m_j=-l_j}^{l_j} q_{jb,(l_j,m_j)} \times \int \int \frac{\varphi_{ia,(l,m)}(r - R_{ia})\varphi_{jb,(l_j,m_j)}(r' - R_{jb})}{|r - r'|} d^3r d^3r',
\] (9)

i.e., \( p_{ia,(l,m)}^{\text{dir}} \) is the \((l, m)^{th}\) element of the vector \( p_{ia}^{\text{dir}} \). Similarly, \( p_{ia}^{\text{fmm}} \) is expressed with Eqs. (10)-(12)

\[
p_{ia}^{\text{fmm}} = W(R_{ia})^T \cdot v_a,
\] (10)

\[
v_a = \sum_b ws(ab) T(R_{ab})^T \cdot m_b,
\] (11)

\[
m_b = \sum_{j \in b} W(R_{jb}) \cdot q_{jb},
\] (12)

where \( m_b \) is the multipole moment of set \( b \), evaluated about its center \( R_b \), \( v_a \) is the electrostatic multipolar potential of the sites in set \( b \), evaluated at multipole expansion center \( R_a \), \( R_{jb} = R_{jb} - R_b \) is the vector between the \( j^{th} \) site in set \( b \) with set \( b \)'s expansion center, \( R_{ab} = R_a - R_b \) is the vector between the expansion centers of sets \( a \) and \( b \), and \( W(r) \) and \( T(r) \) are the real translation and interaction matrices, respectively. Expressions for \( W(r) \) and \( T(r) \), in terms of regular and irregular real solid harmonics, have been reported previously \(^23,40\) and are reproduced in the appendix, for completeness. We have also written the necessary Cartesian derivatives developed by Pérez-Jordá and Yang \(^{41}\) using a notation consistent with that used by Helgaker and collaborators \(^{23,40}\)

The derivative of the Coulomb energy with respect to the \( \alpha \)-Cartesian coordinate \([\alpha \in (x, y, z)]\)
of site $i_a$ is

$$\frac{dJ}{d\alpha} = q_{ia}^T \left( \frac{d}{d\alpha} p_{ia} \right),$$

where we have assumed that the multipole moments are static, and the remaining derivative is

$$\frac{d}{d\alpha} p_{ia} = \left( \frac{d}{d\alpha} W(R_{ia}) \right)^T \cdot v_a + \frac{d}{d\alpha} p_{ia}^{\text{dir}}.$$  \hspace{1cm} (14)

Formally, if the expansion center $R_a$ depends on $R_{ia}$, then the derivative of $T(R_{ab})$ appears from the chain-rule term associated with $v_a$, and therefore Eq. (14) is only approximate; however, FMMs are inherently approximate and additional chain-rule terms contribute negligibly to the derivative for the systems examined here.

Finally, we note that the charge densities considered in this work are point charges or point multipoles, in which case, the integral appearing in Eq. (9) is an element of the interaction matrix, i.e., $T_{(l,m),(l_j,m_j)}(R_{ij})$.

B. Hierarchical implementation

This section describes our FMM implementation and relates it to the formulas provided in Sec. II A. The description consists of a series of steps and pseudo-code used to aid the reader in understanding the program logic.

Our FMM implementation consists of the following steps:

- Recursively bisect the system into smaller sets to form a binary tree hierarchy and each site can be associated to 1 “childless” node. The binary tree is represented as a linked list, and each non-childless node contains references to 2 child nodes. The pseudo-code describing the logic used in the remaining steps of the algorithm notate a linked-list node as a variable,
e.g., A, and references its children by A%C1 and A%C2. The “parent-less” node consists of the entire system and is referred to as the “root” node.

- The binary tree is traversed and the multipole moments of each node is computed. For a childless node, the multipole moments are computed using Eq. (12). For nodes that have children, the multipole moments are computed from

\[ m_p = W(R_{c1p}) \cdot m_{c1} + W(R_{c2p}) \cdot m_{c2}, \]  

(15)

where \( p, c_1, \) and \( c_2 \) indicate parent, child 1, and child 2, respectively, and \( R_{ckp} = R_{ck} - R_p \) is the vector between the 2 expansion centers. In this way, the multipole moments of each node are built by traversing the tree from the bottom to the top using the procedure:

RECURSIVE SUBROUTINE ExpandMoments(A)
    – If the multipole moments of set A have already been computed, RETURN.
    – Else, if A has children,
        CALL ExpandMoments(A%C1)
        CALL ExpandMoments(A%C2)
        Translate the moments of the children onto set A using Eq. (15).
    – Else, translate the moments of each site in set A using Eq. (12).
END SUBROUTINE

- The binary tree is traversed, starting at the top, and all well-separated sets interact via multipole expansions. If the bottom of the tree is reached, the interaction is performed directly. The algorithm follows:
RECURSIVE SUBROUTINE BuildPotential(A,B)
  – If A and B are well-separated, then evaluate $v_a$ and $v_b$ using Eq. (11).
  – Else if A and B have children,
    * If sets A and B are the same set, then
      CALL BuildPotential(A%C1,A%C1)
      CALL BuildPotential(A%C2,A%C2)
      CALL BuildPotential(A%C1,A%C2)
    * Else
      · If child 1 of set A is well-separated from set B, then
        CALL BuildPotential(A%C1,B)
      · Else
        CALL BuildPotential(A%C1,B%C1)
        CALL BuildPotential(A%C1,B%C2)
      · If child 2 of set A is well-separated from set B, then
        CALL BuildPotential(A%C2,B)
      · Else
        CALL BuildPotential(A%C2,B%C1)
        CALL BuildPotential(A%C2,B%C2)
  – Else if A has children
    CALL BuildPotential(A%C1,B)
    CALL BuildPotential(A%C2,B)
  – Else if B has children
    CALL BuildPotential(A,B%C1)
    CALL BuildPotential(A,B%C2)
  – Else compute the site-site interactions directly [Eq. (9)].
END SUBROUTINE

BuildPotential takes 2 arguments, which may or may not be references to the same
node, and the recursion begins by passing in the root node as both arguments.

• The binary tree is traversed, starting at the top, and the multipole potentials of each node is
translated and added to each of it’s children, i.e.,

$$v^T_{c_1} = v^T_{c_1} + v^T_p \cdot W(R_{c_1 p})$$ (16)

$$v^T_{c_2} = v^T_{c_2} + v^T_p \cdot W(R_{c_2 p})$$ (17)
Eqs. (16)-(17) are equivalent to the summation appearing in Eq. (11). When the bottom of the tree is reached, the node has no children, and the potential is translated to each of the sites associated with the childless node using Eq. (10). The pseudo-code is:

```
RECURSIVE SUBROUTINE CollapsePotential(A)

  - If A has children, translate the potential of A into its children [Eqs. (16)-(17)]
    CALL CollapsePotential(A%C1)
    CALL CollapsePotential(A%C2)

  - Else, translate the potential of A onto each site [Eq. (10)].
END SUBROUTINE
```

- The energy is evaluated using Eq. (6).

C. Relationship between FMMs and Tree Codes

The Coulomb energy in a Tree Code is similar to the FMM expression [Eq. (6)] and is written

\[
J = \frac{1}{2} \sum_a \sum_{i \in a} q_i^a \cdot P_i^{tc} + \frac{1}{2} \sum_a \sum_{i \in a} q_i^a \cdot P_i^{dir},
\]

where

\[
P_i^{tc} = \sum_b \text{ws}(ab) T(R_{bia}) \cdot m_b,
\]

and \(m_b\) is given in Eq. (12). A Tree Code requires minimal storage, e.g., the multipole moments of a set \([m_b\text{ in Eq. (19)}]\) are computed whenever needed and then immediately discarded, and the multipolar potentials \(v_a\) are never computed. As a consequence, the algorithm is greatly simplified, i.e., the tree traversals ExpandMoments and CollapsePotential, described in Sec. II B, are not performed. However, the advantages of storage and algorithmic simplifications come at the cost of increased number of floating point operations.
D. Adaptive splitting procedures and well-separateness criteria

Secs. II B and II A made frequent use of the term “well-separateness”. We deem the sets $a$ and $b$ to be well-separated if

$$R_{ab}^2 \geq 2(W_S + 1)^2 \left( \langle R^2 \rangle_a - \langle R \rangle_a^T \cdot \langle R \rangle_a + \langle R^2 \rangle_b - \langle R \rangle_b^T \cdot \langle R \rangle_b \right)$$

(20)

where $W_S$ is a parameter, and

$$\langle R \rangle_a = \frac{1}{N_a} \sum_{i \in a} R_{ia}$$

(21)

where $N_a$ is the number of particles in sets $a$. Eq. (20) is very closely related to the criteria used in Ref. 24, except the latter weighted the particle positions by the magnitude of its partial charge.

In the present work, we consider more general charge distributions, including the possibility that sites may have higher-order multipole moments and no charge. Note that other well-separatedness criteria exist. For example, it is common in so-called “oct-tree” methods to prevent sets from interacting via multipole expansions unless they are separated by 2 intervening boxes; however, this approach inherently assumes a uniform cubic grid, which is not guaranteed in the binary splitting procedure described below. We note that for chemical applications, the rigorous error bounds originally derived for gravitational problems, are often found to be too conservative for most chemical applications where charge is largely balanced, leading to much less efficient algorithms in practice. We treat the $W_S$ as an empirical parameter, which is discussed in more detail in Sec. III. For additional discussion of error estimates in fast multipole methods, see reference 44.

The remainder of this section describes 2 adaptive schemes used to split a system of sites into a hierarchy of sets. Both schemes follow the same basic procedure: 1) Given a set of sites, define
a splitting center, $R_a$, which will also serve as the location of the multipole expansion of the set.

2) Define a “splitting plane” passing through $R_a$, with normal vector $\hat{R}_s$. 3) Partition the set into 2 child sets by assigning each particle to one side of the splitting plane, i.e., site $i$ is in child 1 if

$$\hat{R}_s^T \cdot R_i < \hat{R}_s^T \cdot R_a,$$

or else site $i$ is in child 2. The 2 schemes discussed below differ in their definitions of $R_a$ and $R_s$, but both are adaptive because these definitions depend on the spatial distribution of the sites within the set.

The first scheme, termed “fluc-splitting”, defines $R_a$ as the center of distribution, i.e.,

$$R_a = \langle R \rangle_a.$$

(23)

The splitting vector, $R_s$, is chosen as the eigenvector corresponding to the largest eigenvalue of the $3 \times 3$ covariance matrix, $X$

$$X_{j,k} = \frac{1}{N_a} \sum_{i \in a} (R_{ia,j} - R_{a,j})(R_{ia,k} - R_{a,k}),$$

(24)

where $j$ and $k$ index the Cartesian component. Note that this definition of $\hat{R}_s$ is also the principle axis of smallest inertia moment (treating each site as having unit mass). By splitting at the center of distribution, fluc-splitting tries to partition a set such that each of the 2 children contain approximately the same number of particles, and consequently forms a well-balanced binary tree, and the choice of splitting plane attempts to minimize spatial fluctuations.

The second scheme, termed “box-splitting”, defines boundaries of the distribution, $R_{max}$ and $R_{min}$, where, for example, the $x$-component of $R_{max}$ is the maximum $x$-component of any $R_{ia}$.
in the set \(a\). \(R_{\max}\) and \(R_{\min}\) therefore define a non-cubic rectangular Cartesian box enclosing the sites. The expansion center is the center of the Cartesian box, i.e.,

\[
R_a = \frac{1}{2} (R_{\max} + R_{\min}),
\]

and the splitting vector is either \(\hat{x}\), \(\hat{y}\), or \(\hat{z}\), corresponding to the longest edge of the Cartesian box. In this way, box-splitting tries to partition a set such that each of the 2 children enclose similar spatial volumes.

An important aspect common to either of the above described splitting procedures is termination, i.e., how many sites the childless nodes should contain. Excessive splitting is undesirable because this would require additional multipole moment and multipolar potential translations through the tree structure, and formation of the interaction matrix can exceed the time required for direct interactions between “small” sets. Therefore, there exists some childless set size where direct interactions yield more accurate results with less computational effort, and is therefore preferred. It is also undesirable to have childless nodes containing too many sites, which would artificially limit the number of possible well-separated interactions, and thus the benefits of the method are not effectively exploited.

Termination has previously been discussed by Pérez-Jordá and Yang (PJY),\(^{24}\) and we interpret their discussion as suggested that, for reasons similar to above, optimal performance is obtained by choosing to split a set if

\[
\frac{T_{\text{dir}}(N_a)}{T_{\text{mult}}(N_a, L)} > 2K, \tag{26}
\]

where \(K\) is a parameter, \(T_{\text{dir}}(N_a)\) and \(T_{\text{mult}}(N_a, L)\) are measures of time that would be required to compute the interaction between 2 sets of this size directly and via multipole expansions, re-
pectively, \( N_a \) is the number of sites in the current set (denoted set \( a \)), and \( L \) is the multipole expansion order, respectively. PJY developed a tree-code specific to systems containing monopolar sites only. In this context, the multipole moments, \( q_i \), and multipolar potentials, \( p_i \), reduce to scalar quantities, and the translation and interaction matrices used in Eqs. (12) and (19) reduce to vectors corresponding to the regular and irregular solid harmonics, respectively. Thus, PJY used the scaling arguments: \( T_{\text{dir}}(N_a) \propto N_a^2 \) and \( T_{\text{mult}}(N_a, L) \propto N_a(L + 2)^2 \), which, when used in the termination criteria [Eq. (26)] yields childless sets containing \( N_0 \) sites

\[
N_0 \approx K(L + 2)^2, \tag{27}
\]

where the factor of 2 in Eq. (26) is removed since the last split satisfying the inequality approximately halves the distribution.

The present work introduces an adaptive FMM and considers more complicated charge densities, therefore, we must introduce a new, more general, termination criteria. In considering sites with nonzero multipole character, the execution timing estimates in Eq. (26) now depend on site multipole order, \( L_p \), and therefore

\[
\frac{T_{\text{dir}}(N_a, L_p)}{T_{\text{mult}}(N_a, L, L_p)} > 2K. \tag{28}
\]

We choose to “normalize” the ratio in Eq. (28), i.e., choose \( K \), by noting that when a set contains sites with \( L_p = L \) only, then that set should continue to split until all childless nodes arising from that set contain exactly 1 particle, and thus,

\[
K(L) = \frac{T_{\text{dir}}(1, L)}{T_{\text{mult}}(1, L, L)}, \tag{29}
\]
which yields the termination condition used in the present work:

$$\frac{T_{\text{dir}}(N_a, L_p)}{T_{\text{dir}}(1, L)} > 2$$

(30)

In order to apply Eq. (30), one must either use scaling arguments or perform empirical timing measurements to deduce forms for $T_{\text{dir}}(N_a, L_p)$ and $T_{\text{mult}}(N_a, L, L_p)$, which is now discussed. $T_{\text{mult}}(N_a, L, L_p)$ is different for FMM and TC methods, and are henceforth denoted $T_{\text{mult,fmm}}(N_a, L, L_p)$ and $T_{\text{mult,tc}}(N_a, L, L_p)$, respectively.

We empirically measured $T_{\text{dir}}(N_a, L_p)$ for a series of $N_a$ and $L_p$, using the `SYSTEM_CLOCK` Fortran 90 intrinsic, and found it satisfactory to decompose $T_{\text{dir}}(N_a, L_p)$ according to

$$T_{\text{dir}}(N_a, L_p) = T_{\text{dir}}(L_p)T_{N_a}(N_a)$$

(31)

and represent the component functions by simple parametrized forms:

$$T_{N_a}(N_a) = t_{0}^{\text{dir}} N_a^2$$

(32)

and

$$T_{L_p}(L_p) = 1 + t_{1}^{\text{dir}} L_p^2 + t_{2}^{\text{dir}} L_p^3 + t_{3}^{\text{dir}} L_p^4,$$

(33)

where the $t_{n}^{\text{dir}}$ parameters are given in the caption of Fig. 1. In other words, given 2 identical sets, each containing $N_a$ sites of particle multipole order $L_p$, Eq. (31) returns the time required to compute the Coulomb energy and derivatives directly. Of course, this is both implementation and computer architecture dependent; however, only the ratio between $T_{\text{dir}}(N_a, L_p)$ and $T_{\text{mult}}(N_a, L, L_p)$ is of importance and measuring a series of times is not difficult. In reviewing the times, we clarify that it is our convention is to compute all multipole interactions to some maximum order. For
example, when $L_p = 2$, each particle is treated as having monopole, dipole, and quadrupole components.

Following an analogous procedure for $T_{\text{mult,tc}}(N_a, L, L_p)$, we empirically measured the time required to compute the Coulomb energy and derivatives of each particle in 2 identical, well-separated sets using Eqs. (18)-(19), and fit the times to the function

$$T_{\text{mult,tc}}(N_a, L, L_p) = T_{\text{mult,tc}}(N_a)T_{\text{mult,tc}}(L)L_{\text{mult,tc}}(L_p)$$  \hspace{1cm} (34)

where

$$T_{N_a}(N_a) = t_{tc}^0 N_a$$  \hspace{1cm} (35)

$$T_{L}(L) = 1 + t_{tc}^1 (L - 6)$$  \hspace{1cm} (36)

$$T_{L_p}(L_p) = 1 + t_{tc}^2 L_p + t_{tc}^3 L_p^2$$  \hspace{1cm} (37)

which assumes $L \geq 6$. The $t_{tc}^n$ parameters are given in the caption of Fig. 1. From theoretical scaling arguments, it can be argued that $T_{L}(L)$ should depend quadratically on $L$, in general; however, in the range $6 \leq L \leq 12$, we have found the above form to perform satisfactorily, as is shown in Sec. III.

Before continuing with a discussion of $T_{\text{mult,frm}}(N_a, L, L_p)$, it is of interest to compare the original PJY termination criteria [Eqs. (26)-(27)] to our generalized form [Eqs. (30)-(37)], as it relates to the tree code evaluation of a system consisting of monopolar sites only. For such a system, PJY optimized the value of $K$ [as it appears in Eqs. (26)-(27)] and found $K = 0.4$. In order to compare our termination criteria, we ask the question, “What effective value of $K$, denoted
$K'$, does the generalized termination criteria yield?”, i.e.,

$$K'(L, L_p) = \frac{N_0(L, L_p)}{(L + 2)^2}$$  \hspace{1cm} (38)

where $N_0(L, L_p)$ are the number of sites in each childless node resulting from Eqs. (30)-(37), which can be analytically determined by solving the following equation for $N_0$:

$$T_{\text{dir}}(N_0, L_p) = T_{\text{mult}}(N_0, L, L_p) \frac{T_{\text{dir}}(1, L)}{T_{\text{mult}}(1, L, L)}.$$  \hspace{1cm} (39)

When $L_p = 0$ and $6 \leq L \leq 12$, $K'(L, L_p)$ varies from 0.38 to 0.48, which is in close agreement with PJY’s optimized value.

$T_{\text{mult,tc}}(N_a, L, L_p)$ depends linearly on $N_a$ because every well-separated set-set interaction requires construction of the set multipole moments and evaluation of $p_{ia}^{tc}$ [Eq. (19)]. FMMs construct the set multipole moments once, i.e., not for every set-set interaction, and only the childless sets construct the multipole moments directly from the sites [see Eq. (15)]. Therefore, in this context, FMM times involve the interaction between multipole expansions only, and thus $T_{\text{mult,fmm}}(N_a, L, L_p) \rightarrow T_{\text{mult,fmm}}(L)$. We empirically measured the time required to construct the interaction matrix and perform the dot product in Eq. (11) for a series of $L (L \geq 6)$ and fit the resulting times to the function

$$T_{\text{mult,fmm}}(L) = t_{\text{fmm}}^0 \left[ 1 + t_{1}^{\text{fmm}}(L - 6) + t_{2}^{\text{fmm}}(L - 6)^2 + t_{3}^{\text{fmm}}(L - 6)^3 + t_{4}^{\text{fmm}}(L - 6)^4 \right].$$  \hspace{1cm} (40)

The $t_{n}^{\text{fmm}}$ parameters are given in the caption of Fig. 1, which illustrates the functional dependencies of and relationships between $T_{\text{mult,fmm}}(L)$, $T_{\text{dir}}(N, L_p)$, and $N_0(L, L_p)$. 

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III. RESULTS AND DISCUSSION

Sec. III A applies the FMM and TC methods to the crystallographic structure of the 70S ribosome functional complex and establishes WS and L parameters at several set levels of relative force error accuracies that are later demonstrated to be transferable. Using these parameters, Sec. III B compares the box- and fluc-splitting procedures described in Sec. II D. Sec. III C compares the timings and relative force errors for the FMM and TC methods when applied to systems containing sites with variable size and multipole expansion orders, and illustrates the utility of the generalized termination criteria [Eq. 30] for the practical automation of linear-scaling calculations at constant error levels.

A. FMM and TC parameters

This section provides 2-dimensional scans of the WS and L parameters used in the TC and FMM methods and tabulates the timings and relative force errors (Tables I-II) as applied to the 7.8 Å resolution x-ray crystal structure of the 70S ribosome functional complex, which contains both messenger and transfer RNAs (53876 atoms). From these parameter scans, a set of optimal performance parameters are determined for a given tolerance in the relative force error, where the relative force error (RFE) is given by:

\[
RFE = \sqrt{\frac{\sum_{i=1}^{N} (\tilde{F}_i - F_i)^2}{\sum_{i=1}^{N} |F_i|^2}},
\]

where \(N\) is the number of sites, \(F_i\) is the vector of Cartesian force components (minus the electrostatic energy gradient) of site \(i\) computed exactly from direct interactions, and \(\tilde{F}_i\) is the corresponding vector of approximate force components computed from the FMM or TC algorithms.
The 70S assembly of RNAs provide a highly heterogeneous charge distribution spanning a large, irregular spatial domain and was therefore chosen as a test case representing real-world application of the methods. The errors in Tables I-II correspond to the box-splitting procedure described in Sec. II D. Parameters for the fluc-splitting procedure could not be obtained from this system due to the unsystematic accuracy of the fluc-splitting procedure, which is discussed in more detail in Sec. III B. The FMM and TC parameters corresponding to approximately $10^{-4}$, $10^{-5}$, and $10^{-6}$ RFE, as observed in Tables I-II, are provided in Table III. These parameters are only estimates of the error for the chemical systems studied, and do not deliver rigorous error bounds, hence, actual errors may vary depending on system composition, shape, particle multipole expansion order, splitting procedure, and termination criteria, as are discussed in the remaining subsections.

**B. Comparison of adaptive splitting procedures**

This section compares the timing and accuracy of the adaptive fluc- and box-splitting procedures, and from this comparison, we conclude that box-splitting is generally superior to fluc-splitting. This conclusion is reached by encountering 2 deficiencies in the fluc-splitting procedure when applied to systems of practical relevance, and much of the following discussion is devoted to describing these 2 deficiencies.

The first deficiency identified in the fluc-splitting procedure is deemed the “self-correction deficiency”, and is related to the discussion in Sec. III A, in which it was stated that we were unable to reliably determine WS and L parameters from 70S whilst employing fluc-splitting. Upon performing WS and L parameter scans using fluc-splitting and creating tables analogous to Tables I-II, it
was observed that the RFEs did not systematically decrease as WS and/or L increased, and generally yielded errors significantly larger than those observed in Tables I-II. In an effort to understand why this was so, we identified which atoms/childless sets contributed most to the computed RFE. Fig. 2 displays an example of one such childless set and the hierarchical binary genealogy of that set to the initial split. In this example, the childless set is described as having 3 distinct clusters consisting of 16, 5, and 3 atoms; the 2 larger sets are separated by \( \approx 12 \) Å and the smaller is separated from either of the 2 larger sets by \( \approx 50 \) Å. Tracing through the genealogy, the distal small cluster is severed from its backbone during the first split, and the fluc-splitting procedure is unable to remove this small cluster from the remaining bulk of the structure because it contributes negligibly to the fluctuation matrix and splitting center before termination is reached. The contribution of a cluster to the fluctuation matrix is increased as it becomes more separated from the rest of the system or as its size becomes larger relative to the rest of the system; however, this example demonstrates that this phenomenon may be problematic when applied to biomolecules, where small clusters may be formed in an intermediate region of separation and size in relation to its contribution to the fluctuation matrix. The box-splitting procedure overcomes this problem by choosing the splitting plane in a manner that is independent of particle weighting, i.e., it is based on extrema of the distribution. Therefore, if there is a set consisting of 2 separated clusters, their relative sizes and shapes are not important in choosing the splitting plane; it is only important that there is spatial length.

The second deficiency identified in the fluc-splitting procedure is “system shape dependence” which, unlike the self-correction deficiency, can be exhibited in spatially homogeneous systems. The shape of the system effects the fluctuation matrix, i.e., how the system is split, and thus effects
the shapes of the child subsystems throughout the entire tree structure. The quality of representing a
classic distribution with a finite multipole expansion is not independent of the charge distribution’s
shape, however. Oddly-shaped or anisotropic subsystems have a larger angular dependence and
thus require larger multipole expansion orders to achieve the same accuracy than what would be
required for systems with less angular dependence or contained few sites far from the expansion
center.

The system shape dependence of the fluc-splitting procedure is illustrated in Figs. 3 and 4,
which compare the timings and RFEs between TIP3P water boxes and spheres, respectively. The
fluc-splitting procedure produces RFE values that are 2-10 times larger in the water sphere systems
than the water boxes, whereas the box-splitting procedure produces very similar values. Identification
of the atoms which contribute largest to the RFE observed in the water spheres when using the
fluc-splitting procedure reveal that the errors are concentrated at the center of the sphere, whereas
the largest force errors in the water boxes are uniformly distributed throughout the system, and rel-
atively smaller in magnitude. In an effort to understand why the error is large and concentrated at
the center of the sphere, we traced the genealogy of a childless set near the center of the sphere, in
a manner analogous to Fig. 2. The initial cut forms 2 hemispheres, followed by a cut that quarters
the sphere, producing conical/wedge-like shapes in which the atoms near the center of the sphere
form the apex. Most of the atoms within these conical subsystems are located far from the sphere’s
center, therefore the atoms near the apex are furthest from the expansion center and, by virtue of the
conical shape, the spatial fluctuations leave the central atoms at a conical apex in near perpetuity
of the binary tree. The last cut before termination yields childless sets containing so few atoms
that their spatial anisotropy is not distinguishable from those obtained in the water box systems; the errors, however, arise from well-separated interactions between larger sets and are then propagated down the tree. The water sphere systems may pathologically intensify this phenomenon. This is important in practical applications of molecular simulations that utilize large spherical water drops with stochastic boundary conditions and generalized solvent boundary potentials. These methods are frequently employed, for example, in combined quantum mechanical/molecular mechanical simulations of biochemical reactions. In contrast, the box-splitting procedure is far less dependent on the system shape (see Figs. 3 and 4) because the shape of each set in the binary tree is a rectangular box, which is independent of the system’s shape (only the rectangular length can be changed).

In summary, at comparable performance levels, box-splitting is superior in accuracy to fluc-splitting because the latter suffers from unpredictable, system-dependent errors. We have identified 2 orthogonal undesirable features of the fluc-splitting procedure: a) the inability to adaptively-correct pathological superset splits in non-uniform spatial distributions (demonstrated with the 70S ribosome structure), and b) the ability to form spatially acute subsystems, due to a dependence on the global shape of the system, which may necessitate larger multipole expansion order for an expected accuracy (demonstrated with the water spheres).

C. Comparison of FMM and TC methods

This section compares the timings between the FMM and TC methods as a function of system size, composition (i.e., particle multipole order), and error-level (see Table III). In Sec. III B, it was concluded that box-splitting is superior to fluc-splitting and all comparisons in this section are
therefore with respect to box-splitting.

For the TIP3P water box systems (Fig. 3), FMM is 21.5 (10^{-4} RFE), 12.7 (10^{-5} RFE), and 8.7 (10^{-6} RFE) times faster than direct evaluation for a system of 100,000 atoms. The ratio of direct and FMM times is a linear function of $N$ and the FMM speedup relative to direct evaluation for $N \geq 10000$ can reasonably be approximated from the above data, e.g., for 10^{-4} RFE, the FMM speedup is $\approx 21.5 \times 10^{-5}N$. In comparison to the TC times, FMM is 2.65 (10^{-4} RFE), 2.53 (10^{-5} RFE), and 2.51 (10^{-6} RFE) times faster. The $N$ at which the FMM and direct evaluation times are approximately equal, i.e., the “break-even point”, range from 2000-5000 atoms for these error levels, whereas the TC break-even point ranges from 4000-10000 particles, which is consistent with the TC/FMM ratio of times described above.

It is of interest to compare the methods for systems consisting of sites with different distributions of multipole expansion orders. For the purposes of this comparison, we consider 3 different charge representations derived from a Drude (SWM4-DP) water model. The Drude model has static point charges located at the water H and M sites, and a point charge representation of a polarizable dipole function located at the O center, requiring the treatment of 5 point charges, in total. The systems hereto studied were constructed by replacing the waters in a pre-equilibrated box of 216 Drude waters (18.86 Å cube), fixing the nuclei, and minimizing the interaction energy through displacement of the Drude particles under periodic boundary conditions. From this 216 water system, larger boxes were constructed from explicitly replicating the unit cell. The charge density of each water was then represented in 3 different ways, which we will refer to as the 5S, 2S+1SP, and 1SPD models. The 5S model explicitly treats all 5 point charges, whereas the 2S+1SP model ex-
plicitly treats the H point charges and represents the O, M and Drude particle point charges together as a point monopole+dipole function (multipole expansion) located at the O position. The 1SPD model similarly represents the water’s charge density as a multipole expansion (up to quadrupole) located at the M-site position.

Fig. 5 (left) compares FMM, TC, and direct timings and RFEs of the water models using the $10^{-6}$ RFE parameters in Table III. The 2S+1SP and 1SPD models, when computed directly, are 1.10 times faster and 1.67 times slower than evaluation of the 5S model, respectively. Although higher multipole expansion orders are involved, there are also fewer sites to consider. FMM is approximately 2.35 (5S), 2.20 (1S+1SP), and 2.35 (1SPD) times faster than TC, which suggests that the performance benefits of the FMM is not sensitive to particle angular momentum.

Fig. 5 (right) compares the PJY [Eq. (26), $K = 0.4$, green] and generalized [Eq. (30), red] termination criteria for each water model using the box-splitting FMM. As discussed in Sec. II D these 2 criteria lead to very similar childless set sizes for monopole systems, and is illustrated by the close agreement in timings and RFEs in Fig. 5. The 2S+1SP timings and RFEs are also quite similar, and this is largely due to large percentage of monopole functions in the system. The 1SPD model yields a striking difference between the termination criteria, however. The generalized termination criteria leads to smaller childless set sizes (see Fig. 1), and therefore reduces the number of direct interactions. Alternatively stated, the PJY criteria nets too many direct interactions, yielding RFEs 10 times below the desired accuracy, and takes 2-3 times longer than the generalized termination criteria. The PJY termination criteria was not designed for treating sites with high particle multipole expansion order; Fig. 5 is an illustration of the generalization’s utility and not meant to imply
criticism of the PJY’s criteria in an application for which it was not designed.

IV. CONCLUSION

The present work describes the development, implementation and testing of adaptive linear-scaling FMM and TC methods extended to systems of particles with higher-order multipole character. The target application of these methods are molecular simulations with polarizable force fields and/or combined quantum mechanical/molecular mechanical potentials that are frequently performed under non-periodic boundary conditions (e.g., stochastic boundary simulations of enzyme or ribozyme active sites with generalized solvent boundary potentials). These simulations require methods that treat long-range electrostatics rigorously, but that are also highly efficient such that sufficient conformational sampling (e.g., for the calculation of multi-dimensional potential of mean force reaction profiles). Toward this end, we have developed generalized FMM and TC methods for particle systems of higher order multipole character, characterized their accuracy and computational efficiency, and derived a protocol for determination of the parameters for the methods at different accuracy levels to facilitate their automated use.

The methods described here are adaptive in that they recursive divide a particle system into a hierarchy of interacting sets so as to optimize the efficiency of the calculations. Two different adaptive techniques were explored: fluc-splitting based on the principal components of the fluctuation matrix, and box-splitting based on the Cartesian extremities of the particle distribution. The latter was found to be superior in terms of accuracy for a fairly wide range of particle distribution shapes and multipole orders.

Two different adaptive linear-scaling methods were developed: 1) a tree code (TC) that calcu-
lates multipole expansions and their interactions between sets “on-the-fly” and thus involves minimal memory storage and is algorithmically fairly simple, and 2) a fast multipole method (FMM) that utilizes multipole expansions of smaller “child” particle sets to build up the multipole expansions of the “parent” sets using translation theorems, and hence can be made to be more efficient than the TC, as the cost of higher algorithmic complexity. Both methods are demonstrated to be efficient and linear-scaling, with the FMM shown to be generally considerably faster (at fixed error tolerance) by a factor of around 2 for all of the system sizes and multipole orders considered.

Key to the efficiency of both the TC and FMM algorithms is the determination of a generalized termination criteria that allows the methods, for a fixed error tolerance, to be performed with optimal efficiency. This will be a fairly complex function relating the number of particles in the terminal “childless” set, the multipole order of the particles themselves, and the the multipole expansion order used to allow particle sets to interact. Generalized termination criteria at fixed error tolerances have been derived for both the TC and FMM at relative force error tolerances of $10^{-4}$, $10^{-5}$ and $10^{-6}$ by scanning the various parameters and fitting the results to empirical functional forms inspired, in part, by scaling arguments. The result is an automated procedure for the determination of TC and FMM parameters for generalized multipole particles that, in the case of quadrupole-represented Drude water, effect a speed-up of approximately 2-3 times relative to a multipole-independent termination criteria. The methods developed here represent a potentially important contribution to the arsenal of linear-scaling techniques used for the efficient simulation of complex chemical events using multi-scale models.
ACKNOWLEDGMENTS

D.Y. is grateful for financial support provided by the National Institutes of Health (Grant GM62248), and the University of Minnesota Biomedical Informatics and Computational Biology program. Computational resources were provided by the Minnesota Supercomputing Institute and the IBM Blue Gene at the On-Demand Center in Rochester, Minnesota.
APPENDIX: The translation and interaction matrices

This appendix provides expressions for the translation and interaction matrices appearing in Sec. II A, which are conveniently expressed in terms of the scaled regular and irregular solid harmonics.

The complex representation of the scaled regular ($R_{l,m}$) and irregular ($I_{l,m}$) solid harmonics are separable into sine ($s$) and cosine ($c$) components\textsuperscript{23,40}

\begin{align}
R_{l,m}(r) &= R_{l,m}^c(r) + iR_{l,m}^s(r) \\
I_{l,m}(r) &= I_{l,m}^c(r) + iI_{l,m}^s(r).
\end{align}

The advantage of treating the cosine and sine components separately arises from the complex conjugate properties of spherical harmonics, e.g., $R_{l,m}^s(r) = (-1)^m R_{l,-m}(r)$; therefore,

\begin{align}
R_{l,-m}^{c/s}(r) &= \pm (-1)^m R_{l,m}^{c/s}(r), \\
I_{l,-m}^{c/s}(r) &= \pm (-1)^m I_{l,m}^{c/s}(r),
\end{align}

and thus, the $R_{l,-m}^{c/s}(r)$ and $I_{l,-m}^{c/s}(r)$ functions do not contribute to the completeness of the basis in real-representation. Therefore, real-valued arrays can be constructed that treat both the cosine and sine components, but for non-negative $m$ only. It is notationally convient to write summations using references to both negative and non-negative $m$, e.g. Eq. (5), and it is therein understood that the negative values of $m$ index the sine components of positive $m$. 

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The translation matrix is directly related to the addition theorem of solid harmonics, which is used to transfer the coefficients of a multipole expansion between expansion centers. Given an atomic density of atom \( a \), \( \rho_a(\mathbf{r} - \mathbf{R}_a) \), centered at \( \mathbf{R}_a \), the (scaled) multipole moments about its center is

\[
q_{l,m} = \int \rho_a(\mathbf{r} - \mathbf{R}_a) R_{l,m}(\mathbf{r} - \mathbf{R}_a) d^3r.
\]

The multipole expansion about the center \( \mathbf{R}_c \), denoted \( q'_{l,m} \), is related to \( q_{l,m} \) by a linear transfor-
mation, i.e.,

\[ q'_{l,m} = \int \rho_a(r-R_a) R_{l,m}(r-R_c) d^3r \]

\[ = \int \rho_a(r-R_a) R_{l,m}((r-R_a)+(R_a-R_c)) d^3r \]

\[ = \int \rho_a(r-R_a) \sum_{j=0}^l \sum_{k=-j}^j R_{l-j,m-k}(R_a-R_c) R_{j,k}(r-R_a)) d^3r \]

\[ = \sum_{j=0}^l \sum_{k=-j}^j R_{l-j,m-k}(R_a-R_c) q_{j,k}. \]  

(55)

Let the linear transformation [Eq. (55)] define the translation matrix, i.e.,

\[ W_{(l,m),(j,k)}(R_{ac}) = R_{l-j,m-k}(R_a-R_c). \]  

(56)

The real-valued elements of the translation matrix result from assigning the rows and columns of \( W(R_{ac}) \) into the corresponding cosine/sine components of \( R_{l,m}^{c/s}(r-R_c) \) and \( R_{j,k}^{c/s}(r-R_a) \), and using Eq. (44) to yield expressions involving \( m \geq 0 \) and \( k \geq 0 \) only,

\[ W_{(l,m),(j,k)}^{c/s,c}(R_{ac}) = \left( \frac{1}{2} \right)^{\delta_{ka}} \left[ R_{l-j,m-k}^{c/s}(R_{ac}) + (-1)^k R_{l-j,m+k}^{c/s}(R_{ac}) \right], \]  

(57)

\[ W_{(l,m),(j,k)}^{c/s,s}(R_{ac}) = \mp R_{l-j,m-k}^{s/c}(R_{ac}) \pm (-1)^k R_{l-j,m+k}^{s/c}(R_{ac}). \]  

(58)

In the event that \( m - k < 0 \), one again makes use of Eqs. (44). Note that the transformation [Eq. (55)] differs from Eq. (53) in Ref. 23 by the argument’s sign, and thus Eqs. (57) and (58) of the present work excludes the factor \((-1)^{l-j}\) appearing in Eqs. (55)-(58) of Ref. 23, i.e.,

\[ W_{(l,m),(j,k)}^{c/s,c/s}(R_{ac}) = (-1)^{l-j} W_{(l,m),(j,k)}^{c/s,c/s}(R_{ca}) \]

The derivative of a particle in the FMM algorithm [Eq. (14)] requires the derivative \( \frac{d}{da} W(R_{ac}) \), where \( \alpha_a \) is a Cartesian component of center \( a \). PJY have previously published the derivatives of
the scaled real regular solid harmonics as linear combinations of lower-order harmonics\textsuperscript{41}

\[
\frac{d}{dx} R_{l,m}^e/s(r) = \frac{1}{2} \left[ R_{l-1,m+1}^e/s(r) - R_{l-1,m-1}^e/s(r) \right], \tag{59}
\]

\[
\frac{d}{dy} R_{l,m}^e/s(r) = \pm \frac{1}{2} \left[ R_{l-1,m+1}^{s/c}(r) + R_{l-1,m-1}^{s/c}(r) \right], \tag{60}
\]

\[
\frac{d}{dz} R_{l,m}^e/s(r) = R_{l-1,m}^e/s(r), \tag{61}
\]

and substituting these expressions into Eqs. (57)-(58) yield

\[
\frac{d}{dx_a} W_{(l,m),(j,k)}^{e,c/s,c/s}(R_{ac}) = \frac{1}{2} W_{(l-1,m+1),(j,k)}^{e,c/s,c/s}(R_{ac}) - \frac{1}{2} W_{(l-1,m-1),(j,k)}^{e,c/s,c/s}(R_{ac}) \tag{62}
\]

\[
\frac{d}{dy_a} W_{(l,m),(j,k)}^{e,c/s,c/s}(R_{ac}) = \pm \frac{1}{2} W_{(l-1,m+1),(j,k)}^{s,c,c/s}(R_{ac}) \pm \frac{1}{2} W_{(l-1,m-1),(j,k)}^{s,c,c/s}(R_{ac}) \tag{63}
\]

\[
\frac{d}{dz_a} W_{(l,m),(j,k)}^{e,c/s,c/s}(R_{ac}) = W_{(l-1,m),(j,k)}^{e/c,s,c/s}(R_{ac}). \tag{64}
\]

Eq. (11) requires the interaction between 2 multipole expansions [defined by Eq. (54)]. The real-valued elements of the interaction matrix are related to the scaled real irregular solid harmonics by:\textsuperscript{40}

\[
T_{(l,m),(j,k)}^{e,c/s}(r) = 2(-1)^j \left( \frac{1}{2} \right)^{\delta_{k0} + \delta_{m0}} \left[ I_{l+j,m+k}^{e/s}(r) \pm (-1)^k I_{l+j,m-k}^{e/s}(r) \right], \tag{65}
\]

\[
T_{(l,m),(j,k)}^{s,c/s}(r) = 2(-1)^j \left( \frac{1}{2} \right)^{\delta_{k0} + \delta_{m0}} \left[ \pm I_{l+j,m+k}^{s/c}(r) + (-1)^k I_{l+j,m-k}^{s/c}(r) \right]. \tag{66}
\]

REFERENCES


**TABLE I: Tree Code WS and L parameter scan**

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*aCalculation CPU time (bold) in seconds, and RFE obtained from the TC algorithm using box-splitting, when applied to the 70S ribosome functional complex (Ref. 45). The notation \( X(\times Y) \) indicates \( X \times 10^{-Y} \). CPU times correspond to the computer described in the caption of Fig. 1.*
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\(^a\)Calculation CPU time (bold) in seconds, and RFE obtained from the FMM algorithm using box-splitting, when applied to the 70S ribosome functional complex (Ref. 45). The notation \(X(-Y)\) indicates \(X \times 10^{-Y}\). CPU times correspond to the computer described in the caption of Fig. 1.
TABLE III: Optimal FMM and TC parameters for different error tolerance\textsuperscript{a}

\begin{tabular}{c|c|c|c|c|c|c}
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\textbf{RFE\textsuperscript{b}} & \textbf{FMM} & \textbf{TC} & \textbf{FMM} & \textbf{TC} \\
\hline
$10^{-4}$ & 1.73 & 6 & 1.39 & 6 \\
$10^{-5}$ & 2.07 & 7 & 1.48 & 8 \\
$10^{-6}$ & 2.20 & 9 & 1.81 & 9 \\
\hline
\end{tabular}

\textsuperscript{a} All values in a.u.  \textsuperscript{b} Relative force error [see Eq. (41)] observed in the 70S ribosome functional complex (Ref. 45).
Figure Captions

• Figure 1: Left: Comparison between the timing functions $T_{dir}(N_a, L_p)$ [Eq. (31)] (colored lines) and $K(L)T_{mult,fmm}(N_a, L, L_p)$ [Eqs. (29) and (40)] (dotted lines) as a function of set size, $N_a$. The $N_a$ at which $T_{dir}(N_a, L_p) = K(L)T_{mult}(N_a, L, L_p)$ is the optimal number of particles in a childless set, $N_0$, for a given $L_p$ and $L$. Right: Optimal set size, $N_0$, as a function of particle angular momentum, $L_p$, for various expansion orders, $L$. The functional form of $N_0$ is found by solving Eq. (39) [using $K(L)T_{mult,fmm}(N_a, L, L_p)$] for $N_0$. By definition of $K(L)$ [Eq. (29)], all lines pass through $N_0 = 1$ at $L_p = L$. The timing parameters appearing in Eqs. (31)-(40) are: $t_{dir}^0 = 0.0801526\mu s$, $t_{1}^{dir} = 2.89598$, $t_{2}^{dir} = 0.234555$, $t_{3}^{dir} = 0.529349$, $t_{tc}^0 = 2.83\mu s$, $t_{1}^{tc} = 0.353347$, $t_{2}^{tc} = 0.830143$, $t_{3}^{tc} = 0.786382$, $t_{fmm}^0 = 35.2333\mu s$, $t_{1}^{fmm} = 0.302065$, $t_{2}^{fmm} = 0.234085$, $t_{3}^{fmm} = -0.0415405$, $t_{4}^{fmm} = 0.00502274$. All CPU times reported in this work were performed on a single Intel Xeon 2.66GHz processor (family 15, model 2, stepping 7) equipped with 512 KB cache and 1GB RAM.

• Figure 2: Genealogical ancestry of an example childless node displaying the symptoms of the self-correction deficiency expressed in the fluc-splitting procedure. The upper-left frame shows the initial split of the system and, moving left-to-right, top-down, all successive splits leading to the childless node. Green boxes indicate the zoom of the next frame. The highlighted areas indicate the atoms within the current set, and the child siblings are colored in red and blue, respectively. The blue highlighted set is the parent set in the succeeding frame.

• Figure 3: Comparison between FMM (blue), TC (red), and direct (black) timings (top), relative force errors (bottom), and box- (left) and fluc-splitting procedures (right), as a function of
number of atoms in a series of TIP3P water boxes. The number of waters is \( N/3 \). The FMM and TC timings are computed at various levels of accuracy [relative force error; Eq. (41)], corresponding to the parameters listed in Table III. The electrostatic energy, atom potentials, and atom forces are computed.

- Figure 4: Comparison of FMM, TC, and direct timings and RFEs for a series of TIP3P water spheres. See the caption of Fig. 3.

- Figure 5: Comparison of FMM (red), TC (blue), and direct (black) timings and RFEs for a series of model Drude water boxes. Dotted, dashed, and solid lines refer to the 5S, 2s+1SP, and 1SPD models described in the text. Only the \( 10^{-6} \) accuracy (see Table III) results are shown. Right: Comparison between the PJY (green) and generalized (red) termination criteria using the box-splitting FMM. Note that the red and black lines are the same in both the left and right plots.
FIG. 1: Giese et al

Comparison between direct and multipole timings

Optimal childless set sizes
FIG. 2: Giese et al
FIG. 3: Giese et al
FIG. 4: Giese et al.
FIG. 5: Giese et al

Drude Water Boxes
FMM vs TC FMM Termination

Time (s)

log(RFE)

-9 -8 -7 -6 -5 -4 -3 -2 -1 0

N_{wat}

5S 2S+1SP 1SPD

N_{wat}

4k 8k 12k 16k 20k

0 4k 8k 12k 16k 20k