Efficient chain moves for Monte Carlo simulations of a wormlike DNA model: Excluded volume, supercoils, site juxtapositions, knots, and comparisons with random-flight and lattice models

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We develop two classes of Monte Carlo moves for efficient sampling of wormlike DNA chains that can have significant degrees of supercoiling, a conformational feature that is key to many aspects of biological function including replication, transcription, and recombination. One class of moves entails reversing the coordinates of a segment of the chain along one, two, or three axes of an appropriately chosen local frame of reference. These transformations may be viewed as a generalization, to the continuum, of the Madras–Orlitsky–Shepp algorithm for cubic lattices. Another class of moves, termed $T_{\pm 2}$, allows for interconversions between chains with different lengths by adding or subtracting two beads (monomer units) to or from the chain. Length-changing moves are generally useful for conformational sampling with a given site juxtaposition, as has been shown in previous lattice studies. Here, the continuum $T_{\pm 2}$ moves are designed to enhance their acceptance rate in supercoiled conformations. We apply these moves to a wormlike model in which excluded volume is accounted for by a bond-bond repulsion term. The computed autocorrelation functions for the relaxation of bond length, bond angle, writhe, and branch number indicate that the new moves lead to significantly more efficient sampling than conventional bead displacements and crankshaft rotations. A close correspondence is found in the equilibrium ensemble between the map of writhe computed for pair of chain segments and the map of site juxtapositions or self-contacts. To evaluate the more coarse-grained freely jointed chain (random-flight) and cubic lattice models that are commonly used in DNA investigations, twisting (torsional) potentials are introduced into these models. Conformational properties for a given superhelical density $\sigma$ may then be sampled by computing the writhe and using White’s formula to relate the degree of twisting to writhe and $\sigma$. Extensive comparisons of contact patterns and knot probabilities of the more coarse-grained models with the wormlike model show that the behaviors of the random-flight model are similar to that of DNA molecules in a solution environment with high ionic strengths, whereas the behaviors of the cubic lattice model with excluded volume are akin to that of DNA molecules under low ionic strengths. © 2008 American Institute of Physics. [DOI: 10.1063/1.2899022]

I. INTRODUCTION

A knowledge of the structure and dynamics of double-stranded DNA (dsDNA) is important for understanding their biological functions and how they interact with other biomolecules such as proteins.\textsuperscript{1–3} In theoretical investigations, DNA molecules have been modeled with structural resolutions at a hierarchy of length scales. These efforts include high-resolution atomistic models,\textsuperscript{4–6} treatments at the base-pair level,\textsuperscript{6–9} coarse-grained continuum models designed to account for the elasticity and excluded volume of the DNA molecule without explicit reference to the basepairs,\textsuperscript{10–13} discrete “wormlike” models with segment units encompassing multiple basepairs\textsuperscript{14–16} but are considerably shorter than the Kuhn length\textsuperscript{17} of dsDNA, and more coarse-grained chain models configured on lattices\textsuperscript{18} or in the continuum\textsuperscript{19–26} with each segment unit length corresponding essentially to one Kuhn length. At an even higher degree of coarse graining, the segment unit in some models for large DNA molecules represents many Kuhn lengths,\textsuperscript{27–29} as for the $\sim 20–40$ Kuhn-length units in bead-spring models for studying the hydrodynamic properties of DNA molecules with contour lengths of $\sim 120 \mu m$ or longer.\textsuperscript{28,29}

Supercoiling, looping, and topological entanglements, including knots and catenanes, occur naturally in circular DNA and are critical for their biological function or malfunction.\textsuperscript{3,30–34} Computationally, DNA supercoiling and topology have been investigated using various models with different degrees of coarse graining as outlined above. These efforts include wormlike chain model studies of thermodynamic aspects of knotting probability, supercoiling, catenation, their interplay, and other conformational properties by Monte Carlo (MC) sampling,\textsuperscript{35–41} and kinetics of site juxtapositions\textsuperscript{42–45} and DNA-protein interactions\textsuperscript{46} by Brownian (Langevin) dynamics. More coarse-grained
random-flight (freely jointed) chain models\textsuperscript{19–26,47} have also been used, for example, to study knotting and writhe in confined spaces\textsuperscript{20,26,47} as in phage capsids, as well as the connectivities in knot space\textsuperscript{55} (see also Ref. 48)—a property that one may term “topology of topologies.” Another common class of models is self-avoiding walks or polygons (ring polymers) configured on cubic lattices.\textsuperscript{18,49–54} These models account for excluded volume, a physical constraint that is neglected in random-flight models. Because of their simplicity, lattice models are more amenable to rigorous mathematical analyses\textsuperscript{49–51} and have provided insights into statistical and thermodynamic aspects of knots,\textsuperscript{18,49,53,54} catenanes,\textsuperscript{52} and DNA denaturation transitions.\textsuperscript{55}

Extensive conformational sampling is required for many of these investigations. For MC simulations, efficient chain moves are especially important in situations with prevalent topological entanglements, which, in conjunction with excluded volume constraints, tend to diminish severely the success rates of attempted conformational transitions. As far as lattice models are concerned, MC techniques using the Madras–Orlitsky–Shepp (MOS) and Berg–Foerster–Aragão de Carvalho–Caracciolo–Fröhlich (BFACF; Refs. 57 and 58) algorithms are effective. The MOS moves of inversions, reflections, and interchanges can effect transformations of an arbitrarily long subchain between two sequentially and spatially nonlocal positions along the chain. The MOS move set is ergodic, and because the moves can entail very significant conformational changes, the MOS algorithm is efficient in exploring conformational space. By comparison, sampling by BFACF is slow\textsuperscript{56} because the moves are local. Moreover, the BFACF move set is nonergodic by itself. Although it is sufficient and useful for ergodic sampling of conformations belonging to a fixed knot type,\textsuperscript{54} because the BFACF ergodic class is equivalent to the knot classes,\textsuperscript{59} BFACF moves cannot change the knot type. Nonetheless, the BFACF algorithm enjoys the important advantage that it can vary chain length. This capability is particularly useful in studies of chain length dependence as well as in constrained simulations with a preformed juxtaposition, i.e., a chain-chain contact (Fig. 1), a methodology we have recently developed to investigate segment-passage mechanisms of type-II DNA topoisomerases wherein a combination of MOS and BFACF moves was used to ensure ergodicity and at the same time allow for sampling of different chain lengths and different knot types.\textsuperscript{53}

Recent interests in the statistics of conformations with a preformed juxtaposition\textsuperscript{53,60} arose from the biophysical question as to what local geometrical information of the DNA can be gleaned by type-II topoisomerase enzymes to discern the global knot versus unknot topology of a much larger DNA molecule (Ref. 61 and references therein). Earlier studies of the constraining effects of a preformed, or “presumed,” contact on conformational properties have provided insights into the emergence of proteinlike secondary structures in compact conformations as well.\textsuperscript{62} Length-changing moves at random positions are indispensable for MC sampling of constrained conformations with a juxtaposition that may be present anywhere along the chain. As illustrated in Fig. 1, such moves are required for simulating the relative populations of conformations with different lengths for the two subchains separated by the preformed juxtaposition. In our recent lattice model study,\textsuperscript{53} BFACF moves were adopted for this task. As discussed in Ref. 53, an effective way to apply BFACF moves to determine properties of constrained conformations of any given total chain length \( n \) is by restricting the BFACF moves to transitions between \( n \) and \( n−2 \). For example, conformations with different subchain lengths in Fig. 1 can be sampled in this manner for both \( n \) and \( n−2 \) by allowing total chain length to oscillate between these two values.

In contrast to the structurally low-resolution lattice models, wormlike models with bending and torsional energies provide a structurally more realistic account of DNA conformational features such as supercoiling and branching. The MC chain moves that have been applied in simulating these models include bead displacements\textsuperscript{39,42}—with or without\textsuperscript{49} global shifting of chain position, rotations of chain segments between two randomly chosen beads along an axis connecting the two beads (crankshaft moves),\textsuperscript{15,39,42} local-global rotations around a random axis passing through the position of a randomly chosen bead,\textsuperscript{39,42} and reptation moves.\textsuperscript{15} Also of relevance are algorithms designed to enhance sampling efficiency in simulations of biopolymers that entail concerted rotations of more than six bond and torsion angles with Jacobian weighting\textsuperscript{63,64} (see below). The methods were proposed in the context of polypeptide sampling and have also been applied to atomic simulations of nucleic acids.\textsuperscript{65–67} To our knowledge, however, they have not been used in the study of wormlike DNA chain models.

In practice, because of the rather severe structural and energetic constraints of wormlike DNA models, efficient sampling of certain slow processes in such models is often a challenge. For example, even with an improved algorithm using a combination of crankshaft and reptation moves, Yologodskii \textit{et al.}\textsuperscript{15} reported that the transition rate in branch number is as low as \( 10^{-6} \) (i.e., on average there is only one transition between conformations with different branch numbers in every \( \sim 10^{6} \) attempted moves).

Considering the advances made in MC techniques for lattice models versus that for continuum wormlike models, it raises the possibility that some of the effective algorithms in lattice sampling could be adapted to improve sampling.
efficiency in continuum models. In a similar vein, it might be worthwhile to incorporate certain energetic aspects of wormlike models into lattice and random-flight models to enhance their mimicry of supercoiled DNA. Pursuing these lines of inquiry, the objectives of our study and an outline of our subsequent presentation are as follows. First, we briefly review a wormlike chain model in which a segment-segment repulsive energy is introduced to explicitly account for excluded volume. Second, we generalize the MOS moves to the continuum and tune the simulation parameters for efficient sampling of the wormlike model. Third, inspired by the effectiveness of the lattice BFACF moves in simulations such as that of a topoisomeraselike knotting/unknotting by segment passages, as noted above, we develop a new transformation, termed $T_{\pm 2}$, that adds or subtracts two units of chain length at a time in a continuum wormlike DNA chain model. This effort is motivated by the prospect of applying our new length-changing moves to study conformational properties of wormlike models of DNA chains with a given juxtaposition, as outlined above, so as to evaluate the generality of our lattice model results on how global knot/unknot topology may be inferred from local geometries in a more realistic model of DNA. In this endeavor, the roles of the new generalized MOS and the $T_{\pm 2}$ moves in continuum wormlike chain models will be complementary, similar to the roles played by the corresponding MOS and BFACF moves in lattice models. The generalized MOS moves are designed to increase sampling efficiency. In contrast, as for the lattice BFACF moves, the $T_{\pm 2}$ moves are not very efficient by themselves, but the length-changing capability they embody is indispensable in conformational samplings with a preformed juxtaposition. In view of our scientific goal, we regard the $T_{\pm 2}$ moves as a success insofar as they provide a valid length-changing sampling algorithm and are sufficiently efficient to allow for interesting biophysical questions to be addressed. Fourth, with the above considerations in mind, we test the efficiency of our new MC chain moves and compare their performance with conventional chain moves for DNA simulations. As examples, we study branching relaxation and address general relationships between writhe and site juxtapositions. Fifth, motivated by how supercoiling is accounted for in terms of writhe and a global torsional energy so that Boltzmann ensembles of conformations with prespecified values of superhelicity and $\sigma$ may be sampled in these models as well. This added feature affords a more direct correspondence between supercoiled DNA and conformations in the random-flight and lattice models. The site juxtaposition statistics and knot distributions of these models are then compared with that in the structurally more realistic wormlike model. Finally, we use these comparisons to delineate the limitations of the highly coarse-grained random-flight and lattice models and to gain insights into the conditions under which these models would likely provide a biophysically reasonable description of DNA behaviors.

**II. MODEL**

The main DNA model of interest in the present study is based on the combined wormlike chain and bead model of Jian et al., which was developed from the formulations of Allison et al. and Chirico and Langowski, respectively, for linear and supercoiled DNAs. We will refer to this construct simply as the wormlike chain model below. Following these prior works, here a DNA molecule is represented by a chain of $n$ beads that may either be open ended or closed. Our focus, however, will be almost exclusively on circular DNA. The potential energy of the model consists of the following terms (Fig. 2).

(1) The bond-stretching energy,

\[ E_s = \frac{h}{2} \sum_i (l_i - l_0)^2, \]  

accounts for chain connectivity, where $l_i$ is the length of the $i$th segment, i.e., the magnitude $|s_i|$ of the bond vector $s_i$ from the $i$th bead to the $(i+1)$th bead, $h$ is the stretching force constant, and $l_0$ is the reference segment length. The summation is over all segments $(i=1,2,\ldots,n)$ for a closed chain, in which case $s_i$ is from the $i$th bead to the $i=1$ bead. With $l_0=5$ nm, each segment is approximately 1/20 the Kuhn statistical length of DNA. The value of $h$ is chosen to be $100 k_B T/l_0^2$, where $k_B$ is Boltzmann’s constant and $T_0$ is a reference absolute temperature; we use $T_0=298$ K for the present simulations.

(2) The elastic bond angle or bending potential is given by

\[ E_b = g \sum_i \theta_i^2, \]  

where $\theta_i$ is the angular displacement of bond vector $s_i$ relative to bond vector $s_{i+1}$, i.e., $\theta_i = \cos^{-1}(s_i \cdot s_{i+1})$ ("." represents scalar product of vectors). The quantity $g$ is the bending rigidity constant, which depends on the reference segment...
length as \( g = p k_B T_0 / l_0 \), where \( p \) is the DNA persistence length; we take \( p = 50 \) nm in our simulations.

(3) The electrostatic interaction is approximated as

\[
E_e = \sum_{j > i + 1} \frac{\mu^2 \phi^2}{D} \exp\left( -\kappa r_{ij} \right),
\]

where \( \nu \) is the effective linear charge density of the DNA molecule, \( D \) is the dielectric constant of the aqueous medium, \( D=80 \) in our simulations, \( \kappa \) is the reciprocal of the Debye length, \( r_{ij} \) is the distance between the \( i \)th and \( j \)th beads, and the \( \sum_{j > i + 1} \) summation is over every pair of bead positions. Because of screening and other counterion effects, both \( \nu \) and \( \kappa \) are dependent on the salt concentration. We use three sets of \( \nu, \kappa \) values in the present study: \( \nu = 0.243, 8.2, \) and \( 78.8 \, \text{e/Å} \) (\( e \) is the electronic charge) and \( \kappa = 0.326, 1.29, \) and \( 3.26 \, \text{nm}^{-1} \). These values correspond, respectively, to solution environments with monovalent salt concentrations (e.g., \([\text{NaCl}]\) of 0.01, 0.15, and 1.0M. The above parameter choices for Eqs. (1)–(3) follow that of Refs. 43 and 71.

(4) For closed circular DNA, a torsional potential energy is also included to account for the energy entailed by over-twisting or undertwisting the two strands of the double-helix DNA. In general, this energy may be modeled by a quadratic term

\[
E_t = \frac{C}{2l_0} \sum_i (\phi_i - \phi_0)^2,
\]

where \( C \) is the torsional rigidity constant, \( \phi_i \) is the twist angle of segment \( i \), i.e., \( \phi_i / 2 \pi \) is the number of times the two strands of the dsDNA intertwine around each other in the double helix along the length of the segment, and \( \phi_0 \) is the corresponding equilibrium twist angle for a double-helix DNA in the “relaxed” state (see below). In this description of double-helix twist energy, the value of \( C \) is set to \( 2 \times 10^{-13} \text{erg cm} \) (Ref. 72) or, equivalently, 48.0 \( k_B T_0 \) nm.

For the Brownian dynamics studies in Refs. 43 and 68, the twist angle \( \phi_i \) of individual segments is treated explicitly by a body-fixed coordinate frame. In those cases, an explicit accounting of local twist is necessary to provide the dynamic forces for model kinetics. In MC studies of thermodynamic properties, however, supercoiling may be modeled by a simpler “implicit” approach that does not require a local frame but accounts only for the global torsional energy via the writhe (Wr) of the chain.\(^5 \) In general, the writhe of any closed curve is defined as a double line integral,

\[
W_r = \frac{1}{4 \pi} \int \int_C \frac{(dr \times d\mathbf{r}_1) \cdot \mathbf{r}_2}{r_{12}^2},
\]

where \( \mathbf{r}_1 \) and \( \mathbf{r}_2 \) are position vectors along the closed curve, “\( \times \)” denotes vector (cross) product, and \( \mathbf{r}_2 = \mathbf{r}_2 - \mathbf{r}_1 \). In the implicit approach to dsDNA torsional energy, which we adopt here, the internal structure of the DNA double helix is not modeled explicitly; thus, the (local) angle \( \phi_i \) for an individual segment is not defined. In other words, \( \phi_i \) is not a function of the other coordinate variables in Fig. 2. Instead, the twist energy is treated globally for circular DNA with a given double-strand linking number \( L_k \). The linking number \( L_k \) of a circular DNA is defined as the total number of times the two strands of the double helix intertwine. As \( L_k \) is an invariant in the absence of strand passages, now \( L_k \) of a circular DNA or its superhelical density \( \sigma = L_k / L_0 - 1 \) (\( L_0 \) is the linking number for the relaxed state) is treated as an input of the computation and is fixed at a freely chosen value for each simulation. During the course of the simulation, Wr is computed from the coordinates of each sampled conformation. Since \( L_k \) is given, once Wr is determined, the twist number Tw of the conformation is readily calculated via White’s formula\(^73 \) (Câlugăreanu–White–Fuller theorem\(^74,75 \))

\[
L_k = Tw + Wr.
\]

By definition, \( \Sigma_i \phi_i = 2 \pi (Tw) \). Hence, the torsional potential energy in Eq. (4) may be rewritten as

\[
E_t = \frac{C}{2l_0} \sum_{i=1}^{n} \left[ \phi_i - \frac{2 \pi (Tw)}{n} \right]^2 + \frac{C}{2l_0} \sum_{i=1}^{n} \left[ \frac{2 \pi (Tw)}{n} - \phi_0 \right]^2,
\]

\[
E_t = \frac{C}{2l_0} \sum_{i=1}^{n} (\Delta \phi_i)^2 + \frac{C}{2l_0} \left[ \frac{2 \pi (L_k - Wr) - \phi_0}{n} \right]^2,
\]

where \( \Delta \phi_i = \phi_i - \frac{2 \pi (Tw)}{n} \) satisfies \( \Sigma_i \phi_i = 0 \). In this expression for \( E_t \), the angles \( \Delta \phi_i \)’s are separated from the conformational coordinates \( \{ r_i \} \). Therefore, for any thermodynamic ensemble in which the \( \phi_i \) variables are integrated, the contribution of the \( \Delta \phi_i \) terms is a constant. This applies to our MC simulations, in which the \( \phi_i \) variables are implicitly integrated. Consequently, the contribution from the term involving \( (\Delta \phi_i)^2 \) in Eq. (7) has no effect on equilibrium properties. Therefore, it suffices to consider only the last term in Eq. (7), i.e., the effective torsional energy

\[
(E_t)_{eff} = \frac{nC}{2l_0} \left( \frac{2 \pi}{n} (L_k - Wr) - \phi_0 \right)^2
\]

\[
= \frac{nC}{2l_0} \left( \frac{2 \pi}{n} \left( \frac{nL_0}{l_h} - Wr \right) \right)^2,
\]

where \( l_h = 3.55 \, \text{nm} \) is the distance of a DNA double-helical repeat in the relaxed state (corresponding to \( \approx 10.5 \) basepairs). Thus, according to the definition of linking number noted above, each contour length \( l_h \) of a relaxed circular DNA contributes one unit to the total linking number and, therefore, \( nL_0 / l_h \) is the equilibrium linking number \( L_0 \) between the two strands of a circular dsDNA of total contour length \( nL_0 \). The last equality in Eq. (8) follows because \( L_0 \approx n \phi_0 / 2 \pi \) (see above). Equation (8) is identical to Eq. (4) of Ref. 15.

It is clear from the above development that the analysis is generally applicable to any model of closed chain conformations, including random-flight and lattice models. We will explore such applications below. A key ingredient in this general approach to global torsional potential energy is the writhe calculation. Several algorithms are available in the literature for computing writhe in continuum\(^76-78 \) as well as lattice\(^79,80 \) chain models. We use method 2a in Ref. 76 for the
wormlike chain model here. While the algorithm in Ref. 78 for evaluating the differential of writhe with respect to bead position is useful for Brownian dynamics, we elect not to pursue it in the present MC simulations.

(5) The covalent nature of DNA molecules forbids passage of one segment through another. This is a physical constraint that should be captured in realistic models.81 In early Monte Carlo studies of wormlike DNA chain models, excluded volume was strictly enforced by discarding conformations with any point along one virtual bond separated by less than a distance cutoff from any point along another virtual bond.15 However, excluded volume is not strictly enforced in more recent wormlike chain and bead models developed for Brownian dynamics,45 perhaps because a sharp distance cutoff constraint is difficult to translate into a force for dynamics simulation. Helpful attempts have been made to address this limitation, for example, by introducing a short range repulsion between beads.45 However, even with such improvements, the frequency of unphysical segment passing events, \(-10^{-7}\) per simulation step,45 is not negligible for long simulations. The problem may be even more acute in simulations of experimental studies of DNA under a stretching force.83 Steric effects of excluded volume are of critical importance also for modeling DNA conformations in crowded environments.13,84

One straightforward way to implement a better account of excluded volume and suppress unphysical segment passing events is to use more beads and a shorter segment length \(l_0\) so that bead-bead electrostatic interaction and bead-bead excluded volume would raise the energy barrier against segment passage. However, this would greatly increase computational cost. Here, we take the approach of introducing a direct bond-bond repulsive interaction (or, equivalently, segment-segment or spring-spring repulsion81) between virtual bond pairs [Fig. 3(a)] in the form of an \(r^{-12}\) potential commonly used in molecular dynamics for excluded volume repulsion,

\[
E_{\text{rep}} = K_{\text{rep}} \sum_{j>i+1} \left( \frac{r_{ij}}{s_{ij}} \right)^{12},
\]

where \(K_{\text{rep}} = 1.0k_BT_0\) is used in the present simulations; in view of the \(\sim 2.4\) nm diameter of dsDNA, we have chosen the value of \(r_{\text{rep}} = 2.0\) nm. In Eq. (9), \(s_{ij}\) is the minimum distance between two virtual bonds.

To determine \(s_{ij}\), let \(r_{ij}\) be the vector from the position \(r_i\) for bead \(i\) to the position \(r_j\) for bead \(j\), i.e., \(r_{ij} = r_j - r_i\); the bond vectors \(s_i = r_{i+1} - r_i\) and \(s_j = r_{j+1} - r_j\) are defined as before [Fig. 3(a)]. Let the shortest distance between the two bond vectors be given by the distance \(|r_u - r_v|\) between two positions,

\[
\begin{align*}
\mathbf{r}_u &= r_i + u s_i, \\
\mathbf{r}_v &= r_j + v s_j,
\end{align*}
\]

for some values of \(u\) and \(v\). A straightforward minimization of \(|r_u - r_v|\) leads to the relation

\[
\begin{align*}
\mathbf{r}_u &= r_i + u s_i, \\
\mathbf{r}_v &= r_j + w s_j,
\end{align*}
\]

\[
\begin{align*}
\begin{vmatrix} s_i^2 - s_i \cdot s_j \\ s_i \cdot s_j - s_j^2 \end{vmatrix} &= \begin{vmatrix} u \\ v \end{vmatrix},
\end{align*}
\]

which is solved to yield values of \(u\) and \(v\). The determinant of the \(2 \times 2\) matrix in Eq. (12) is equal to \(-|s_i \times s_j|^2\). If it is equal to zero, i.e., if \(s_i\) is parallel to \(s_j\), \((s_i)^2 = |r_{ij}|^2 - |r_{ij} \cdot s_j|^2/|s_j|^2\). Otherwise, \(u\) and \(v\) can be determined uniquely. In general, when the values of \(u\) and \(v\) are not restricted, they define the shortest distance between two infinite lines along the directions of \(s_i\) and \(s_j\). For the question at hand, however, we require the shortest distance to be be-
between two points along two bonds of finite lengths. Accordingly, if \(0 \leq u, w \leq 1\), the shortest distance \(s_{ij} = |r_u - r_w|\) between the two bonds is given by directly substituting the \(u\) and \(w\) values solved from Eq. (12) into Eqs. (10) and (11) to yield:

\[
s_{ij} = \frac{|(s_i \times s_j) \cdot r_{ij}|}{|s_i \times s_j|}.
\]  

(13)

On the other hand, if either \(u\) or \(w\) or both is \(< 0\) or \(> 1\), a different set of considerations is needed for the following cases. (i) For \(u < 0\) and \(0 \leq w \leq 1\), the shortest distance between the two bonds is from one of the endpoints, \(r_u\) (\(r_w\) for \(u = 0\)), of the first bond to some point \(r_w = r_u + w s_i\) along the second bond. Minimizing \(|r_u - r_w|\) leads to \(w' = -r_{ij} \cdot s_j/|s_j|^2\). Then, if \(0 \leq w' \leq 1\),

\[
s_{ij} = \frac{|(s_i \times r_{ij})|}{|s_i|},
\]  

(14)

if \(w' < 0\), set \(w' = 0\) and \(s_{ij} = |r_u|\), and if \(w' > 1\), set \(w' = 1\) and \(s_{ij} = |r_u + s_i|\). (ii) For \(u > 1\) and \(0 \leq w \leq 1\), \(s_{ij}\) is given by applying the substitutions \(r_u \rightarrow r_u + s_i\), and, thus, \(r_u \rightarrow r_u + s_i\) to the expressions for case (i) above. (iii) For \(w < 0\) and \(0 \leq v \leq 1\), \(s_{ij}\) is given by applying \(i \rightarrow j\) interchanges to the expressions for case (i) above. (iv) For \(w > 1\) and \(0 \leq v \leq 1\), \(s_{ij}\) is given by applying \(i \rightarrow j\) interchanges to the expressions for case (ii) above. (v) For \(u < 0\) or \(v > 1\) and \(w < 0\) or \(w > 1\), \(s_{ij}\) is given by the smaller of the two \(s_{ij}\) values for two of the above (i)-(iv) cases whose respective first \(u\), \(w\) range condition coincides with the given condition for the present case (v). For example, if \(u < 0\) and \(w < 0\), \(s_{ij}\) is the smaller of the two \(s_{ij}\) values for cases (i) and (iii). We note that the optimized \(u\) and \(w\) values from Eq. (12) in the above analysis for the different cases are analogous to the \(t_1\) and \(t_2\) quantities derived by Kumar and Larson,\(^{81}\) though exact expressions for \(s_{ij}\) were not provided in their study.

The impact of the new excluded volume repulsion term\(^{86}\) in Eq. (9) is illustrated in Fig. 3 using an example of two infinitely long straight chains perpendicular to each other [Fig. 3(b)]. In the absence of the \(E_{rep}\) term, the energy barrier against unphysical segment passage is quite high under low ionic strength (=50\(\text{mM}\) \(\text{NaCl}\)) but the barrier height is nonetheless finite. By contrast, with the incorporation of the \(E_{rep}\) term, unphysical segment passage is impossible because of an infinite energy barrier [Fig. 3(c)]. Furthermore, the results in Figs. 3(c)–3(f) contrasting the energy barriers as well as the forces \(-\partial E_r/\partial y\) and \(-\partial E_r + E_{rep}/\partial y\) at two ionic strengths clearly show that with increasing ionic strength, the repulsion caused by the \(E_r\) term diminishes, resulting in a dramatic decrease of the energy barrier. In those situations, the \(E_{rep}\) contribution would be crucial because relying solely on \(E_r\) to account for excluded volume may result in an unacceptable high rate of unphysical segment passage. These quantitative comparisons are instructive in view of the aforementioned common usage of wormlike DNA chain models with no insurmountable excluded volume repulsion term.

Although the focus of the present study is on thermodynamic sampling, not on dynamics, we expect the \(E_{rep}\) term developed here to be applicable to dynamic simulations because Eqs. (9), (13), and (14) are amenable to differentiation with respect to conformational coordinates to yield the necessary dynamic forces. For cases when Eq. (13) does not apply because either the two virtual bonds are parallel or the shortest distance between them involves one or more endpoints, as described above, the shortest distance is nonetheless always given by a function of conformational coordinates and therefore can be differentiated to yield dynamic forces.

### III. CONFORMATIONAL SAMPLING

#### A. Generalized MOS moves

The MOS algorithm is an effective algorithm for sampling self-avoiding chain conformations with a given length on square, cubic, and hypercubic lattices.\(^{86}\) In each attempted MOS chain move, a pair of beads \(k<l\) are first randomly chosen. Then, one of three classes of transformations that were designed to allow for large conformational changes is randomly chosen and applied to the bead positions \(r_{k+1}, r_{k+2}, \ldots, r_{l-1},\) with respect to an \((x, y, z)\) reference frame fixed within the lattice, between bead \(k\) and \(l\), while leaving the positions of the beads in the rest of the chain unchanged (Fig. 4). Thus, the resulting conformational change, with new positions for the corresponding beads at \(r_{k+1}, r_{k+2}, \ldots, r_{l-1},\) can be local (when \(k\) is close to \(l\) along the chain sequence, i.e., \(l-k\) is small) but can also be extensive (when \(l-k\) is large). Here, we briefly summarize the lattice MOS algorithm and reformulate the moves with respect to a variable \((\alpha, \beta, \gamma)\) reference frame, in a notation which is more amenable to generalizing to the continuum (Fig. 5). The \((\alpha, \beta, \gamma)\) coordinate system is defined as one in which the \(x\) axis is in the \(r_{id} = r_i - r_d\) direction and the origin is the midpoint between \(r_k\) and \(r_l\). Because all MOS moves leave the positions of \(r_k\) and \(r_l\) unchanged, they are point group transformations in the \((\alpha, \beta, \gamma)\) framework (see below).

#### 1. Inversions

The inversion transformation is defined\(^{56}\) [Fig. 4(a)] for any \(k<l\) by

\[
r'_i = r_k + r_l - r_{k+l-i}, \quad k \leq i \leq l.
\]  

(15)

In terms of the \((\alpha, \beta, \gamma)\) reference frame in Fig. 5, let the position vectors before and after a MOS transformation be, respectively, \(\mathbf{R}\) and \(\mathbf{R}'\). Therefore,

\[
\mathbf{R}_i = r_i - (r_k + r_l)/2,
\]  

(16)

\[
\mathbf{R}'_i = r'_i - (r_k + r_l)/2.
\]  

(17)

In this notation, the inversion transformation is equivalent to

\[
\mathbf{R}' = -\mathbf{R},
\]  

(18)

where the transformed position of bead \(i\) is given by \((\mathbf{R}')_i = -(\mathbf{R})_{k+l-i}\) or the inversion transformation may be defined simply by Eq. (18) if bead numbering is immaterial to the application at hand. In the form of Eq. (18), the inversion transformation can be applied to a continuum chain model.
amounts to reversing all three axes of the $(\alpha, \beta, \gamma)$ frame. Thus, we denote the inversion transformation as $T(\alpha, \beta, \gamma)$. Figure 5(a) illustrates the effect of an inversion transformation in the continuum. This schematic shows that an inversion (thick dashed curve) tends to result in a larger conformational change for the bead positions between $k$ and $l$, from that of the original conformation (solid curve), than the conformational change resulted from a rotation (thin dashed curve) along the $\alpha$ axis. This is so even if the rotation was through a large angle such as $180^\circ$ because an inversion changes the shape of the chain between positions $k$ and $l$ (by reversing the $\alpha$ axis) but a rotation does not.

2. Reflections

On square and cubic lattices, a reflection transformation\textsuperscript{56} is possible when the coordinates of beads $k$ and $l$ along two of the orthogonal axes satisfy the condition

\[
(r_k^{(1)}) - (r_l^{(1)}) = m[(r_k^{(2)}) - (r_l^{(2)})],
\]

where the superscripts “(1)” and “(2)” denote components along the two axes, named as 1 and 2 here without loss of generality, and $m = \pm 1$. The reflection transformation is then defined as\textsuperscript{56}

\[
(r_k^{(1)}) = r_k^{(1)} - m[r_{k+l}^{(2)} - r_l^{(2)}],
\]

\[
(r_l^{(2)}) = r_l^{(2)} - m[r_{k+l}^{(1)} - r_k^{(1)}].
\]
\[(r'_i)^{(3)} = r_i^{(3)} + r_i^{(3)} - r_i_{k+l-i}^{(3)}. \quad (22)\]

For the two-dimensional square lattice, Eq. (19) is satisfied if and only if \(r_{kl} \) is along the x-y or x=-y directions \([-45^\circ, 135^\circ]\) from either axes: See Fig. 4(b)(i)), in which case the reflection transformation is given only by Eqs. (20) and (21), because a third axis does not exist. For the cubic lattice, Eq. (19) may be satisfied with beads \(k\) and \(l\) on the same \(x\)-y or \(x\)-z or \(y\)-z plane (one of the three lattice planes), i.e., \((r_i)^{(3)} = (r_i)^{(3)} \) [Fig. 4(b)(i)]. Equation (19) may also be satisfied with beads \(k\) and \(l\) on none of the three lattice planes together, i.e., \((r_i)^{(1)} \neq (r_i)^{(1)} \) and \((r_i)^{(2)} \neq (r_i)^{(2)} \) and \((r_i)^{(3)} \neq (r_i)^{(3)} \) [Fig. 4(b)(ii)]. It is nonzero for the above two cases. Finally, when beads \(k\) and \(l\) have the same coordinates for two of the axes, i.e., \((r_i)^{(1)} = (r_i)^{(1)} \) and \((r_i)^{(2)} = (r_i)^{(2)} \) [Fig. 4(b)(ii)], Eq. (19) is satisfied because in that case, \((r_i)^{(1)} - (r_i)^{(2)} = (r_i)^{(2)} = 0 \) (see below).

The lattice reflection transformation may be described with respect to an \((\alpha, \beta, \gamma)\) reference frame consisting of unit vectors \((e_{\alpha}, e_{\beta}, e_{\gamma})\) along the three axes defined in terms of the unit vectors \((e_1, e_2, e_3)\) for the coordinate system in Eqs. (20)–(22) as follows:

\[e_{\alpha} = e_3, \quad e_{\beta} = (e_1 + me_2)/\sqrt{2}, \quad e_{\gamma} = (e_1 - me_2)/\sqrt{2}. \quad (23)\]

In this system, the reflection transformation is given by \((\alpha, \beta, \gamma)\) components indicated by superscripts

\[(R')^\alpha = -R^\alpha, \quad (R')^\beta = -R^\beta, \quad (R')^\gamma = R^\gamma. \quad (24)\]

i.e., it amounts to reversing two of the axes \((\alpha, \beta). In more compact form, Eqs. (26)–(28) are equivalent to

\[R' = -[R - (R \cdot e_{\gamma})e_{\gamma} + (R \cdot e_{\gamma})e_{\gamma}] = -R + 2(R \cdot e_{\gamma})e_{\gamma}. \quad (29)\]

As for inversion, the position for bead \(i\) after a reflection transformation corresponds to the \(R'\) position obtained from the transformation of the \(R\) position for bead \(k+l-i\) by Eq. (29).

It is now straightforward to generalize Eq. (29) to the continuum. Unlike the restrictive situation on cubic lattices in which Eq. (19) is not always satisfied, one advantage of continuous space is that it is always possible to choose a set of appropriate axes for reflection. However, when applied to a wormlike chain model, the acceptance probability of a reflection move would be very low if it leads to too much changes in bond angle at bead \(k\) and at bead \(l\). We therefore develop the following strategy to choose an \((\alpha, \beta, \gamma)\) frame to minimize changes in these bond angles for a generalized MOS reflection. As discussed above, a reflection reverses two axes. The \(\alpha\) axis lies along \(r_{kl}\); thus, it is determined by the given \(k, l\) bead positions. However, we are free to choose the \(\beta\) axis when the reflection move is generalized to the continuum. Consider the \((\alpha, \beta, \gamma)\) components of the initial and transformed bond vectors at the \(k\) and \(l\) endpoint bead positions of the transformation. Because of \((s_i)^\alpha = (R_{i}^\alpha)^\alpha - (R_{k}^\alpha)^\alpha = -R_{k+l-i}^{\alpha} + R_{k}^{\alpha} = s_{k+l-i}^\alpha - s_k^\alpha\) from Eq. (26), and similar relations from Eqs. (27) and (26),

\[(s_i)^\alpha = s_{k+l-i}^\alpha, \quad (s_i)^\beta = s_k^\beta, \quad (s_i)^\gamma = -s_l^\gamma. \quad (30)\]

It follows that the scalar product between the initial and transformed bond vectors at \(k\) and \(l\) is

\[s_k^\gamma = s_{k+l-i}^\gamma = s_k^\gamma, \quad s_l^\gamma = s_{k+l-i}^\gamma = s_l^\gamma. \quad (31)\]

Hence, minimizing the bond angle changes at \(k\) and \(l\) is equivalent to maximizing \(s_k^\gamma, s_l^\gamma\). This aim may be achieved by setting the \(\beta\) axis for reflection (unit vector \(e_\beta^R\)) along an angle bisector \(s_k^\gamma, s_l^\gamma\) for the vector pair \(s_k^\gamma\) and \(s_l^\gamma\) [Fig. 5(b)], where \(s^\gamma\) is the vector projection of \(s\) onto the \(\beta-\gamma\) plane,

\[s_k^\gamma = s_k - (s_k \cdot \hat{r}_{kl})\hat{r}_{kl}, \quad (32)\]

\[s_l^\gamma = s_l - (s_l \cdot \hat{r}_{kl})\hat{r}_{kl}, \quad (33)\]

where \(\hat{r}_{kl} = r_{kl}/|r_{kl}|\). The unit vector for a \(\gamma\) axis orthogonal to \(e_\beta^R\) is then provided by

\[e_\gamma^R = \frac{s_k^\gamma - s_l^\gamma}{|s_k^\gamma - s_l^\gamma|}, \quad (35)\]

where \(s_k^\gamma = |s_k^\gamma|/|s_k^\gamma|\) and \(s_l^\gamma = |s_l^\gamma|/|s_l^\gamma|\). We denote this generalized MOS reflection transformation as \(T(\alpha, \beta), \) wherein \(e_\gamma^R\) defined in continuous space now takes the place of the lattice-defined \(e_\gamma\) in Eq. (29).

\[R' = -R + 2(R \cdot e_\gamma^R) e_\gamma^R. \quad (36)\]

3. Interchanges

On square and cubic lattices, if Eq. (19) is satisfied, an interchange transformation is defined as \(56\)

\[(r_i)^{(1)} = r_i^{(1)} + m[r_i^{(2)} - r_i^{(2)}], \quad (37)\]

\[(r_i)^{(2)} = r_i^{(2)} + m[r_i^{(1)} - r_i^{(1)}], \quad (38)\]

\[(r_i)^{(3)} = r_i^{(3)}. \quad (39)\]

Figure 4(c) illustrates interchanges that do [Fig. 4(c)(i)] and do not [Fig. 4(c)(ii, iii)] leave the transformed beads on the lattice plane they originally occupy, with the latter two examples corresponding to situations in which Eq. (19) is satisfied because \((r_i)^{(1)} - (r_i)^{(2)} = (r_i)^{(2)} - (r_i)^{(2)} = 0\), as discussed above for reflection transformations. It should be noted that the relative positions of \(k\) and \(l\) in all the examples in Figs. 4(b) and 4(c) satisfy Eq. (19) and thus admit both reflections and interchanges. Figure 4(c) shows that some interchanges are, while some are not, equivalent to rotations [Fig. 4(c)(ii) and (iii)]. Using the \((e_\alpha, e_\beta, e_\gamma)\) reference frame in Eqs. (23)–(25) above as for reflections, the lattice interchange transformation is given by
\[ (R')^\alpha = R^\alpha, \quad (R')^\beta = R^\beta, \quad (R')^\gamma = -R^\gamma, \]
i.e., it amounts to reversing one axis (\( \gamma \)) perpendicular to \( r_{ij} \). Equations (40)–(42) are equivalent to
\[ R' = \left[ R - (R \cdot e_\gamma)e_\gamma \right] - (R \cdot e_\gamma)e_\gamma = R - 2(R \cdot e_\gamma)e_\gamma, \]
where the position for bead \( i \) after an interchange transformation is the \( R' \) position obtained from the transformation of the \( R \) position for bead \( i \) using Eq. (43).

We generalize Eq. (43) to the continuum using a procedure similar to the one applied above to reflection to minimize bond angle changes at \( k \) and \( l \) so as to enhance the acceptance probability. For an interchange move, it follows from Eqs. (40)–(42) that
\[ (s_k')^\alpha = s_k^\alpha, \quad (s_k')^\beta = s_k^\beta, \quad (s_k')^\gamma = -s_k^\gamma, \]
\[ (s_{l-1}')^\alpha = s_{l-1}^\alpha, \quad (s_{l-1}')^\beta = s_{l-1}^\beta, \quad (s_{l-1}')^\gamma = -s_{l-1}^\gamma. \]
Hence,
\[ s_k \cdot s_k = (s_k^\gamma)^2 + (s_k^\beta)^2 - (s_k^\alpha)^2, \]
\[ s_{l-1} \cdot s_{l-1} = (s_{l-1}^\alpha)^2 + (s_{l-1}^\beta)^2 - (s_{l-1}^\gamma)^2. \]
Now, we seek to maximize these two bond-vector scalar products at both endpoint positions \( k \) and \( l \). This entails solving a quadratic equation to obtain an optimal \( e_\gamma^{(l)} \) for \( e_\gamma \) that minimizes the components of \( s_k \) and \( s_{l-1} \) along it because these components contribute negatively to Eqs. (46) and (47). Because we are free to choose the \( \beta \) and \( \gamma \) axes, however, to reduce the number of computational steps, we may approximate this optimization by choosing
\[ e_\gamma^{(l)} = \hat{r}_{ij} \times \frac{s_k^\alpha + s_{l-1}^\alpha}{s_k^\alpha + s_{l-1}^\alpha}, \]
as illustrated in Fig. 5(c). We denote the resulting transformation as
\[ R' = R - 2(R \cdot e_\gamma^{(l)})e_\gamma \]
as \( T(\gamma) \), which simply replaces the lattice-defined \( e_\gamma \) in Eq. (43) by the approximately optimized \( e_\gamma^{(l)} \) in continuous space.

Both the \( T(\alpha, \beta) \) reflections [Eq. (36)] and \( T(\beta) \) interchange [Eq. (49)] are effective for chain segments whose endpoint bond vectors at \( k, l \) have similar large components along \( r_{ij} \) (the \( \alpha \) axis) and similarly small projected amplitudes (even though their directions may be different) on the plane perpendicular to \( r_{ij} \). Thus, these moves should be useful for sampling supercoiled wormlike DNA conformations.

4. Further generalizations

As shown above, the three classes of MOS moves correspond to reversing one, two, or three axes in the \( (e_\alpha, e_\beta, e_\gamma) \) reference frame. This consideration leads naturally to two additional classes of generalized MOS moves. First, we may only reverse the \( \alpha \) axis and denote this transformation as \( T(\alpha) \),
\[ R' = R - 2(R \cdot \hat{r}_{ij})\hat{r}_{ij}, \]
wherein the position for bead \( i \) after the transformation is the \( R' \) position from transforming the \( R \) position for bead \( k+l-i \). Second, we may reverse both the \( \beta \) and \( \gamma \) axes and leave the \( \alpha \) axis (\( r_{ij} \)) unchanged and denote this transformation as
\[ R' = -R + 2(R \cdot \hat{r}_{ij})\hat{r}_{ij}, \]
wherein the position for bead \( i \) after the transformation is the \( R' \) position resulting from transforming the \( R \) position for bead \( i \). Because the \( \beta \) and \( \gamma \) axes are either both unchanged or both changed for \( T(\alpha) \) and \( T(\beta, \gamma) \), unlike the \( T(\alpha, \beta) \) reflection and \( T(\gamma) \) interchange but similar to the \( T(\alpha, \beta, \gamma) \) inversion, we do not have any choice to tune the changes in the \( e_\alpha \) and \( e_\gamma \) directions for \( T(\alpha) \) and \( T(\beta, \gamma) \). To improve computational efficiency, one may also evaluate the changes in endpoint bond vectors \( s_k' - s_k \) and \( s_{l-1}' - s_{l-1} \) after every attempted generalized MOS move and reject moves for which the bond-vector changes are too large for a certain criterion. It is straightforward to see that microreversibility is satisfied by the generalized MOS scheme described above.

B. A new class of length-changing moves in continuous space

A lattice BFACF move changes the chain length by adding or removing two adjacent beads;\textsuperscript{57,58} concomitantly, the bond angles at the new connecting points are changed from 180° to 90° or vice versa [Fig. 6(a)]. In designing moves that lengthen or shorten a wormlike chain, however, we realize that it is often energetically unfavorable to add or remove two adjacent beads in a similar manner because the resulting changes in bond angles at the new connecting points may be too large for a physically likely conformation tolerated by the bending potential in Eq. (2). Therefore, we explore instead a scheme that add or remove two beads from different parts of the chain, as illustrated by the lattice drawing in Fig. 6(b). We envision that such a move, when implemented in a wormlike DNA chain model (Fig. 7), would be reasonably effective when applied to the two dsDNA segments of a supercoiled conformation (Fig. 8).

An overview of the new length-changing moves, which we term \( T_{\pm 2} \), is given in Fig. 7. The \( T_{+2} \) transformation shortens the chain length by two units, whereas the \( T_{-2} \) (or, equivalently, \( T_{+2} \)) transformation lengthens the chain length by two units [Fig. 7(a)]. In order to enhance acceptance of these transformations, we devise a root-mean-square deviation\textsuperscript{88,89} (RMSD) procedure to minimize the changes in bond angle at the new connecting points.

For \( T_{+2} \), an initial conformation is chosen, as shown in Fig. 7, such that bead 1 is connected to bead \( a \) and bead 5 is connected to bead \( e \) [Fig. 7(a), upper drawing]. This initial conformation is then divided into two parts [Fig. 7(b)], beads 2, 3, 4, and 3′, 4, 5, and beyond and beads 2, 3′, 4, 5, and beyond in the upper drawing]. To shorten the chain conformation, we
then optimally overlap two sets of four bead positions [the eight positions enclosed in the dotted box in the lower drawing of Fig. 7(b)] by minimizing their RMSD. Subsequently, beads 3, 3', c', and c are discarded, bead 2 is connected directly to bead 4, and bead b is connected directly to bead d, resulting in a new conformation with two fewer beads [the conformation with beads 1, 2, 4, 5 and a, b, d, e in the lower drawing of Fig. 7(a)].

For \( T_2 \), which adds two beads and is the reverse of \( T_{-2} \), each step of the transformation is designed to be the exact inverse of a corresponding step in \( T_{-2} \) to ensure detailed balance. To add two beads, the initial conformation [lower drawing in Fig. 7(a)] is first split into two parts. Then, four new beads, 3, 3', c', and c', are grown subject to a minimum RMSD constraint. Subsequently, the two parts of the chain are moved apart and their relative orientation adjusted so that the position of bead 3 coincides with that of bead 3', and the position of bead c coincides with that of bead c', resulting in a conformation with two additional beads [the conformation with beads 1, 2, 4, 5 and a, b, c, d, e in the upper drawing of Fig. 7(a)]. Note that in addition to pushing out and pulling in the two parts of a conformation, the \( T_{\pm 2} \) moves can also change their relative orientation, as shown by the thick dashed-dotted lines in the lower drawings in Figs. 7(a) and 7(b). Examples of \( T_{\pm 2} \) actions in the wormlike chain model are provided in Fig. 8.

In general, the Metropolis acceptance criterion for any attempted move is implemented by a transition probability:

\[
P(a \rightarrow b) = \min \left\{ \frac{B(b \rightarrow a) \rho(b)}{B(a \rightarrow b) \rho(a)} \right\},
\]

from state \( a \) to state \( b \) via the given transformation, where \( \rho(a) \) and \( \rho(b) \) are the equilibrium population densities of the
corresponding states and \( B(a\rightarrow b) \) and \( B(b\rightarrow a) \) are, respectively, the differential volume elements for choosing (the path-choosing probability for) the \( a\rightarrow b \) and \( b\rightarrow a \) transitions. For the \( T_{\pm 2} \) transformations, a careful analysis is required to determine the equilibrium population density ratio between two conformations with different chain lengths because their densities are defined in configurational spaces of different dimensions. The technical details for such an analysis as well as an exact expression for Eq. (52) in terms of model quantities are provided in the Appendix.

C. MC procedure for wormlike, random-flight, and lattice models

The above algorithmic developments are applied in our work below to MC simulations of equilibrium properties and to test the efficiency of the new chain moves in the wormlike chain model. To this end, we use a combination of conventional chain moves and our newly constructed moves as follows:

1. A local bead displacement, whereby one vertex (bead) \( i \) is randomly selected and a small perturbation is applied to its position vector: \( \mathbf{r}_i \rightarrow \mathbf{r}_i + \mathbf{\delta r} \), with a uniform distribution of \( \mathbf{\delta r} \) within a three-dimensional cube of volume \( [2\Delta r^{(0)}]^3 \) centered at the origin.

2. A global rotation around a randomly chosen axis that passes through a randomly chosen bead for a chain with free ends or a crankshaft move, i.e., a rotation of the chain segments between two randomly chosen beads around the axis that passes through the beads [Fig. 5(a)], thin dashed curve], for a closed chain (circular loop). In both cases, the rotation angle is uniformly distributed within \( [-\Delta \theta_{\text{rot}}^{(0)}, \Delta \theta_{\text{rot}}^{(0)}] \). In our algorithm, the simulation parameters \( \Delta \theta_{\text{rot}}^{(0)} \) and \( \Delta \theta_{\text{rot}}^{(0)} \) are automatically optimized after an initial period of test run so that the acceptance ratio of each move is around 50%. These two conventional moves are widely used in MC simulations. We compare their efficiency with that of our new moves.

3. The generalized MOS moves described above. To initiate such a move, a pair of beads is randomly chosen. Then, a list of all possible transformations among the \( T(a,\beta,\gamma), T(a,\beta,\gamma), T(a,\beta), T(\gamma,\beta), \) and \( T(\beta,\gamma) \) transformations is made. Subsequently, a particular transformation is chosen from the list with uniform probability to conduct an attempted move. The Metropolis acceptance criterion is simply \( P(a\rightarrow b)=\min\{1,\exp(-\Delta E/k_B T)\} \), where \( \Delta E \) is the change in total potential energy. This is because for the generalized MOS moves, the differential volume element of choosing a particular transition or the path-choosing probability is identical for the forward and backward transitions, i.e., \( B(a\rightarrow b)=B(b\rightarrow a) \).

4. The length-changing \( T_{\pm 2} \) moves outlined above and detailed in the Appendix. In the present work, as in our recent application of the BFACF moves to study lattice knots,\(^{33}\) we restrict the procedure so that only conformations of loop sizes \( n \) and \( n-2 \) are sampled, where \( n \) is the chain length of a ring polymer, or loop size, chosen to be studied. Namely, when the loop size is \( n \), we only allow \( T_{\pm 2} \) moves which lead to loop size \( n-2 \), whereas when the loop size is \( n-2 \), we only allow \( T_{\pm 2} \) moves which lead to loop size \( n \). The conformational properties of interest are then computed separately for chain lengths \( n \) and \( n-2 \). The generalized Metropolis criterion in Eq. (52) is used to determine whether an attempted \( T_{\pm 2} \) move is accepted.

In the discussion below, the attempt probabilities \( P_{\text{MC}} \) of the above four classes of moves are given in the notation \( P_{\text{MC}}=\{P_{\text{bead}}, P_{\text{rot}}, P_{\text{MOS}}, P_{\pm 2}\} \), where \( P_{\text{bead}}, P_{\text{rot}}, P_{\text{MOS}}, \) and \( P_{\pm 2} \) are the attempt probabilities, respectively, of the local bead displacement, rotation (crankshaft), generalized MOS, and \( T_{\pm 2} \) moves.

We also compare results from simulations of circular DNA in the wormlike chain model with the corresponding predictions for ring polymers from the random-flight and lattice models. For the random-flight model, the only term in the potential energy is of the same form as Eq. (1), now with \( l_k \) replaced by the Kuhn length \( l_k^{(\text{Kuhn})} \) of DNA, and \( l_k^{(\text{Kuhn})} = 100 \text{ nm} \) is used in our simulations. To better mimic the behavior of a chain of freely jointed rigid rods, we use a stretching force constant \( k_B T/\ln(l_k^{(\text{Kuhn})})^2 \), which is proportionally much stiffer than that for our wormlike chain model. Conventional moves, generalized MOS, and \( T_{\pm 2} \) moves are used in the simulation of the random-flight model. For the lattice model, we apply the lattice MOS moves\(^{56}\) in the context of a general setup we recently published.\(^{52,53}\) Because the present lattice simulations do not involve preformed juxtapositions (see Fig. 1 and related discussion above), the lattice MC procedure used here is equivalent to that we have used for simulating the conformations of an unconstrained loop.\(^{53}\) With the values of cubic lattice chains are computed using the algorithm of Lacher and Summers.\(^{79}\)
D. Model testing: Comparing simulations against available analytical results

To ensure that our wormlike chain model is properly implemented, we first subject a simplified version of it to evaluation against available analytical results (Fig. 9). For this purpose, we consider open chains and turn off the electrostatic, torsional, and excluded volume interactions in the full model. Probability densities, normalized by their respective horizontal scales, are shown for (a) the bond length $l$, (b) the bond angle $\theta$, and (c) the end-to-end distance $L$ in unit of the reference contour length $L_0=(n-1)\ell_0$. The MC results for $n=11$ (open squares) and $n=101$ (filled circles) are compared to the corresponding results from analytical treatments (solid curves, see text for details). Simulation results for $n=11$ in (a) and (b) are not plotted separately because they are practically identical to that for $n=101$. The analytical curves in (c) are adapted from Fig. 3 of Samuel and Sinha (Ref. 96). A total of $8 \times 10^8$ steps of attempted conventional moves are used in the simulation for each chain length ($R_{MC}=(0.6,0.4,0,0)$).

expression for the case with stretching freedom is not available. Figure 9(c) compares our simulation results with the analytical results in Refs. 96–98. Apparently, the stretching freedom allowed by Eq. (1) in our model leads to larger end-to-end distances for short chains [$n=11$; open squares in Fig. 9(c)] but the simulated distribution for longer chains is practically indistinguishable from that predicted analytically for nonstretchable wormlike chains [$n=101$; filled circles in Fig. 9(c)].

IV. RESULTS AND DISCUSSION: SUPERCOIL PROPERTIES

We now proceed to test the efficiency of our new moves in sampling writhe and other features of closed-chain (ring-polymer) conformations. In particular, we assess the ability of the new moves to effect transformations between supercoils with different numbers of branches. The simulation techniques are then applied to delineate the physical relationship between writhe and site juxtapositions and to ascertain the differences and similarities among common approaches of wormlike, random-flight, and cubic lattice modeling of supercoiled and knotted conformations.

A. Writhe and branching of superhelical wormlike chains

The writhe [Wr, Eq. (5)] of a DNA molecule is a key measure of self-entanglement of its supercoiled structure. For models consisting of a finite set of beads and bonds—this encompasses the present wormlike model as well as the random-flight and cubic lattice models in this work—the double line integral in Eq. (5) for writhe is over a polygon of $n$ segments. Thus, it reduces to a double summation,

$$\text{Wr} = \frac{1}{4} \sum_{i=1}^{n} \sum_{j=1}^{n} \Omega_{ij} \sum_{i=1}^{n} \sum_{j=1}^{n} \text{Wr}(i,j),$$

where $\Omega_{ij}$ is the partial double line integral along segment $i$ and segment $j$, the expression of which is provided by Eqs. (16a) and (16b) of Kleinin and Langowski (Ref. 76) and Wr$(i,j)$
superhelical density
chain corresponds to a DNA circle with
therein
number Br  for this conformation is 4 and the number of trunks is 0.

Electron microscopy showed that branching is a salient
feature of superhelical DNA conformations. A branch point
is more clearly defined when the region of proximity of three
or more segments is small [e.g., the single branch point in
Fig. 11(d)] than when the region of proximity is extended
[e.g., Fig. 10(a)]. Nonetheless, geometrical features pertinent
to the recognition of superhelical branches may be deduced
from the Wr(i,j) pattern. Take the conformation in Fig. 10(a)
as an example. By visual inspection, roughly four branches
can be discerned in this supercoil (the branch point junction
corresponds to the region about 1/4 from the top, where the
two lower branches making up an inverted V shape come
together). This conformation’s Wr(i,j) map in Fig. 10(b)
shows that Wr(i,j) = 0 for a majority of i,j (flat areas) ex-
cept for several “mountain ranges” perpendicular to the i=j
diagonal. Each of these regions is made up of sequentially
consecutive segment pairs that are in spatial proximity be-

FIG. 10. Writhe and parameters for characterizing branching properties. (a) A typical branched, negatively supercoiled conformation generated in the simulation of our wormlike DNA model with all the interaction terms in Sec. II. The model chain here has n=233 segments (each with \(l_0=5\) nm; thus, the chain corresponds to a DNA circle with \(\approx 3.5\) kb or 3500 basepairs, the same contour length as for a model used for studying branching in Ref. 15) and superhelical density \(\sigma= -0.06\) (effective salt concentration [NaCl]=0.01M). (b) Three-dimensional graphics of the write map for the conformation in (a) showing contributions from individual segment pairs \(i,j\) to the pairwise writhe \(\text{Wr}(i,j)\) in Eq. (53); the plot provides values for \(-\text{Wr}(i,j)\) and is symmetric upon reflection by the \(i=j\) diagonal because, by definition, \(\text{Wr}(i,j)=\text{Wr}(j,i)\). (c) Contour plot of the \(-\text{Wr}(i,j)\) in (b). The dashed square and rectangular boxes illustrate, respectively, the ranges of \((i,j)\) contributing to the subchain writhe \(-\text{SWr}1\) (Ref. 15) and the transverse writhe \(-\text{SWr}2\) in Eqs. (54) and (55). (d) The four peaks in the \(-\text{SWr}1(i)\) scan (solid curve, \(b_1=48\)) and the \(-\text{SWr}2(i)\) scan (dotted curve; with \(b_2=10\)) of the conformation in (a) indicate that the branch number \(B_r\) for this conformation is 4 and the number of trunks is 0.
cause the integrand $r_{12}/r_{12}^3$ [Eq. (5)] is insignificant for large $r_{12}$, and these site juxtapositions or contacts are arranged along two subchains running in opposite directions. Hence, each mountain range corresponds, essentially, to either a superhelical branch that has a free end (when the mountain range touches the diagonal) or a superhelical “trunk” that is connected to two branching vertices (when the mountain range does not touch the diagonal). Therefore, the number of branches and trunks may be determined by detecting such mountain ranges from the Wr$_{i,j}$ map using, for instance, the subchain writhes

$$\text{SWr}_1(i) = \sum_{1-b_1/2 < j, k < 1+b_1/2} \text{Wr}(j,k),$$

which is introduced by Vologodskii et al. to count the number of superhelices at which the chain undergoes a sharp turn.\textsuperscript{15} SWr$_1(i)$ is the sum of Wr$_{i,j}$ within a $(b_1+1) \times (b_1 + 1)$ window sliding along the diagonal [Fig. 10(c)]. With an appropriate choice of $b_1 > l_{\text{Kuhn}}/l_0$, each superhelix end should coincide with a peak $-\text{SWr}_1(i)$ value for a negatively supercoiled chain. For instance, the $-\text{SWr}_1(i)$ function for the conformation in Fig. 10(a) has four peaks [Fig. 10(d), solid curve], corresponding to the conformation’s four branches. The choice of $b_1$ in Fig. 10(d) is equivalent to that used in Fig. 5 of Vologodskii et al.\textsuperscript{15} Following these authors, here we also define the number of branches Br as the number of peaks in the $-\text{SWr}_1$ function. We note, however, that the present notation for the subchain writhes is different from theirs. Our SWr$_1(i)$ is equivalent to the subchain writhes Wr$_{(-b_1/2, i+b_1/2)}$ defined in Ref. 15. We use SWr$_1$ for the multiple segment subchain writhes in Eq. (54) instead of their notation to avoid it being confused with the Wr$_{i,j}$ in Eq. (53) for a single segment pair.

It is apparent from Fig. 10(c) that the branch detector SWr$_1$ was not designed to detect trunks (or “interior branches”) because it only takes account of superhelix ends. To detect trunks from a Wr$_{i,j}$ map, we define a “transverse writhes,”

$$2\mathcal{P}(-\text{SWr}_2) - \text{Br} = 3N_3 + 4N_4 + \cdots .$$

Given two numbers Br and $\mathcal{P}(-\text{SWr}_2)$, the solution of Eq. (56) for $N_5$’s $\geq 0$ is, in general, not unique. However, in simple cases, e.g., when $2\mathcal{P}(-\text{SWr}_2) - \text{Br} = 4$ as for Figs. 10(a), 11(c), and 11(d), the only solution for Eq. (56) is that there is only one branching vertex and it is a 4-vertex ($N_4 = 1$, all other $N$’s equal zero). We may also truncate the series on the right-hand side of Eq. (56) leaving only the first two or three terms because it is very likely that higher order vertices are energetically and sterically disfavored. In this case, when $\mathcal{P}(-\text{SWr}_2) = 5$, $\text{Br} = 4$, and thus $2\mathcal{P}(-\text{SWr}_2) - \text{Br} = 6$, as for Figs. 11(a) and 11(b), the only solution for a modified equation [Eq. (56)] with terms for $N_6$ and higher truncated would be two branching vertices and each is a 3-vertex.

B. Efficiency of the generalized MOS and $T_{s2}$ algorithms

1. Generalized MOS moves speed up conformational equilibration of ring polymers and enhance writhe sampling

Figure 12 compares the efficiency of conventional versus generalized MOS moves in simulations using several combinations of the moves on a closed chain as well as an open chain. In these computations, the probability $P_{\text{read}}$ of the single-head displacement, which is the only move in our simulations that affects the bond length $l$, is kept constant, while the probabilities $P_{\text{tor}}$ of conventional rotation and $P_{\text{MOS}}$ of generalized MOS moves (Fig. 5) vary between 0.01 and 0.39. The sampling efficiency of the moves is evaluated by autocorrelation functions of the form
where $A$ is a conformational property of interest (bond length $l$, bond angle $\theta$, writhe $W_r$, etc.), $t$ is a "time" variable measured in units of MC time steps (i.e., number of attempted moves), and $\langle \cdots \rangle$ represents statistical averaging obtained from extensive sampling. Results in Fig. 12 indicate that the autocorrelation functions are well approximated by single exponentials,

$$C_A(t) = \langle A(0)A(t) \rangle, \quad (57)$$

where $\tau$ is the MC relaxation time. As another measure of conformational relaxation, we also compute the averaged RMSD between two conformations sampled at time steps apart,

$$\text{rmsd}(t) = \langle \text{RMSD}([\mathbf{r}(0)], [\mathbf{r}(t)]) \rangle, \quad (59)$$

where $[\mathbf{r}(t)]$ is the set of bead positions at time $t$. The mean-square distance of two sets of equal number of bead positions along two chains is the sum of square distances between pairs of corresponding beads (pairs with the same number label, see below) divided by the total number of beads, computed after appropriate rigid translation and rotation to optimize the relative positions and orientations of the two sets such that the mean-square distance is minimized. RMSD is the square root of this minimized mean-square distance, as is commonly used for measuring similarity in protein structure comparison (see also related discussion in the Appendix). Note that after a generalized MOS move in our simulation, the beads within the transformed part of the chain are renumbered if necessary such that the numbering of beads is always consecutive (1, 2, 3, ..., $n$) along the chain contour (including the ..., $n$, 1, ... sequence in the case of a closed chain), while bead numbering for the rest of the chain remains unchanged, as stated after Eqs. (18), (29), (50), and (51) in the discussion above.

It is clear from Fig. 12 that for closed chains, MC relaxations of $l$, $\theta$, and $W_r$ in simulations with the generalized MOS moves are significantly faster, with approximately five to seven times speed up, than that of the conventional moves alone [Figs. 12(a)–12(e)]. Root-mean-square deviation rmsd($t$) also increases faster by $\approx 25\%$ when the generalized MOS moves are included [Fig. 12(d)]. However, for the relaxation of end-to-end distance in open chains, the generalized MOS moves are much less efficient than the conventional rotations [a 27-time slowdown for the example in Fig. 12(e)] because, by design, the MOS moves do not change the end points of the subchain being transformed. As well, the generalized MOS moves are slightly less efficient than the conventional moves in increasing RMSD between sampled open-chain conformations [Fig. 12(f)].

Taken together, the test results in Fig. 12 indicate that the generalized MOS moves are effective for closed chains but not effective for open chains. Apparently, the reason underlying the success of the generalized MOS moves in sampling closed-chain conformations is that they can sequentially reverse the geometric features of a subchain and do so with a high acceptance probability. By reversing the $\alpha$ axis (Fig. 5), the geometric properties at bead $i$ is exchanged with that at bead $k + l - i$. Therefore, conformational characteristics along the chain can be rapidly reshuffled and randomized. Indeed, when we switch off $\alpha$-axis reversing, i.e., when the $T(\alpha, \beta, \gamma)$, $T(\alpha, \gamma)$, and $T(\alpha)$ transformations are disallowed while leaving only the $T(\gamma)$ and $T(\beta, \gamma)$ transformations in the generalized MOS move set, the $l$ and $\theta$ relaxations slow down to essentially the level attained by the conventional moves alone (data not shown).

Unlike the conventional bead displacement and rotation moves which are continuously connected in the space of transformations to the identity transformation such that the simulation range parameters $\Delta r^{(0)}$ and $\Delta \theta^{(0)}_{\text{rot}}$ can be freely adjusted to yield an acceptance probability $\approx 50\%$ (see above), the generalized MOS moves are not continuously connected to the identity transformation. Hence, the acceptance probabilities of the generalized MOS moves are not tunable once we have taken the procedure described in Fig. 5 to optimize the $T(\alpha, \beta)$ and $T(\gamma)$ transformations. In Fig. 12, the acceptance probabilities of the generalized MOS moves are reasonable for the simulations of $n=100$, $\sigma=0$ closed chains, with the following acceptance probabilities for the

![FIG. 12. Efficiency of the generalized MOS moves. Autocorrelation functions of (a) bond length $l$, (b) bond angle $\theta$, and (c) writhe $W_r$ as well as (d) the time-dependent root-mean-square deviation rmsd($t$) for closed circular wormlike chains with $n=100$ and $\sigma=0$ (effective salt concentration $[\text{NaCl}]=0.01 M$), computed using three different combinations ($P_{\text{rot}}, P_{\text{MOS}}$) = (0.01, 0.39) [circles], (0.2, 0.2) [squares], and (0.39, 0.01) [diamonds], of conventional crankshaft/rotation and generalized MOS moves with the probability of conventional bead move $P_{\text{rot}}=0.6$ in all cases. The variable $t$ is number of MC time steps (attempted moves). (e) The corresponding autocorrelation functions for the end-to-end distance $L$ and (f) the time-dependent RMSD functions rmsd($t$) for open chains with $n=101$. Each curve is obtained from a simulation of $2 \times 10^4$ MC time steps. Solid curves in (a)–(c) and (e) are single-exponential fits to the autocorrelation functions [Eq. (58)].](http://jcp.aip.org/jcp/copyright.jsp)
individual transformations: \( T(\alpha, \beta, \gamma), 4.9\%; T(\alpha, \beta), 38.0\%; T(\alpha), 18.0\%; T(\gamma), 18.0\%; T(\beta, \gamma), 2.2\% \). Not surprisingly, acceptance probabilities decrease generally with supercoiling (increasing \(|\sigma|\)), but the relative probabilities among individual types of generalized MOS moves are similar (data not shown).

2. Generalized MOS and \( T_{\pm 2} \) moves quicken the equilibration among different branching states

We now turn to the sampling of subchain writhe \( SW_{r1}(i) \) in Eq. (54) from which the branch number \( Br \) of a supercoil is deduced \(^{15} \) (see above). In this respect, we have compared the MC time evolution of the \( SW_{r1}(i) \) function for a supercoiled chain \( (\sigma = -0.06) \) in the absence versus that in the presence of our generalized MOS and \( T_{\pm 2} \) moves. \( SW_{r1}(i) \) profile changes very slowly when only the conventional moves are used. In contrast, after the generalized MOS and \( T_{\pm 2} \) moves are incorporated, the \( SW_{r1}(i) \) profile undergoes more rapid changes, indicating that the new moves entail a significant improvement in the sampling efficiency of supercoiled conformations with diverse writhe-related properties (detailed data not shown). Figure 13 highlights these effects by showing that the relaxation of \( SW_{r1} \) with the generalized MOS and \( T_{\pm 2} \) moves is much faster than that with the conventional moves alone. The solid curves in the figure are single-exponential fits indicating that the \( SW_{r1} \) relaxation time \( \tau_{SW_{r1}} = 4.3 \times 10^3 \) in the presence of the new moves, whereas MC relaxation is more than eight times slower \( (\tau_{SW_{r1}} = 3.6 \times 10^3) \) when only the conventional moves are used in the simulation.

Following Vologodskii \textit{et al.}, \(^{15} \) we set the branch number \( Br \) of a supercoil equal to the number of peaks in a \( -SW_{r1}(i) \) function with an appropriate \( b_1 \) [see Eq. (54) and above discussion], where a peak is identified by a continuous range of \( i \) in which \( -SW_{r1}(i) \) exceeds a certain threshold \( SW_{thr} \). The \( b_1 \) and \( SW_{thr} \) parameters used in the present analysis are chosen by optimizing the agreement between the branch number predicted using these parameters and that ascertained intuitively by visual inspection of hundreds of conformations. The resulting choices are \( (b_1, SW_{thr}) = (58, 0.6), (48, 0.7), (39, 0.8), \) and \( (33, 0.9) \), respectively, for \( \sigma = -0.04, -0.06, -0.08, \) and \( -0.1 \). With these parameters, the likelihood that a prediction agrees with visual inspection is in the range of 70\%–85\%, with higher percentages of agreement for conformations with larger \(|\sigma|\). It should be noted that, because of the differences in the underlying wormlike models, the values of \( b_1, SW_{thr} \) used here are similar but not identical to the corresponding parameters chosen by Vologodskii \textit{et al.} \(^{15} \).

To arrive at a MC relaxation time \( \tau_{Br} \), that provides a meaningful characterization of the efficiency in \( Br \) sampling, we found it problematic to simply account for the number of times a \( -SW_{r1}(i) \) value passes the \( SW_{thr} \) threshold. \(^{15} \) This is because fluctuations of the \( -SW_{r1} \) value around \( SW_{thr} \) can entail many such events but they may not result in long-lived change in branching. To circumvent this potential difficulty, which arises from the shortcomings of our current definition of \( Br \) (see above), we have used the following block-average \(^{100, 101} \) approach to estimate the branch number correlation time in our simulations. Let \( SD(Br)_t \) be the standard deviation of \( Br \) for a long simulation and \( SD(Br, \Delta t) \) be the standard deviation of the block averages of \( Br \) each simulated for a MC time interval \( \Delta t \). Because the expected number of independent \( Br \) values sampled during \( \Delta t \) is \( \Delta t / \tau_{Br} \), where \( \tau_{Br} \) is the correlation time for \( Br \),

\[
SD(Br, \Delta t) = \frac{SD(Br)_t}{\sqrt{\Delta t / \tau_{Br}}} \quad \text{for} \quad \Delta t \gg \tau_{Br}.
\]

By fitting simulation data to this relation, we obtain estimates for \( \tau_{Br} \). In general, we note that the block-average method offers computational advantages over analysis of exponential decay of the correlation function in estimating a long correlation time (\( \tau \)) such as the \( \tau_{Br} \) considered here. The correlation function method requires large memory because data for each time step have to be stored over several \( r \)'s. In contrast, the block-average method requires only one average value from each block to be stored. For large \( \tau \), the number of blocks needed for the computation can be orders of magnitude less than \( \tau \).

Correlation times of branching number determined by the above block-average method for an effective \( [\text{NaCl}] = 0.01M \) in the left panel of Fig. 14 show that \( Br \) relaxations with 40\% generalized MOS moves (diamonds) are significantly faster than that simulated with other combinations of moves. Efficiency of \( Br \) relaxation in simulations with 95\% \( T_{\pm 2} \) moves (circles) are comparable to that with conventional moves alone (triangle) even though the acceptance probability of \( T_{\pm 2} \) moves, at \( \sim 2\% \) (see the Appendix), is much lower than the \( \sim 50\% \) acceptance probability of the conventional moves. When actual computer time is used for comparison (Fig. 14, right panel), the efficiency of the \( T_{\pm 2} \) moves is seen as superior to that of the conventional moves. Figure 14 also shows that branch relaxation is strongly dependent on supercoiling; relaxation is slower for higher \(|\sigma|\). With our generalized MOS moves, \( \tau_{Br} = 6 \times 10^4 \) MC steps for \( \sigma = -0.08 \) and \( \tau_{Br} = 5 \times 10^3 \) MC steps for \( \sigma = -0.04 \) (Fig. 14, left panel).
Branch relaxation is generally slower with increasing effective ionic strength, likely because the chain segments can then be closer to one another and therefore more tightly intertwined. For instance, when effective [NaCl]=0.15M, for the same n=233 chain length with superhelical density \( \sigma = -0.06 \), \( \tau_{Br} \) (in units of MC time steps) \( \approx 8.3 \times 10^6 \) with conventional moves alone, \( 2.3 \times 10^5 \) with \( T_{\pm 2} \) moves incorporated, and \( 2.3 \times 10^5 \) with generalized MOS moves. The latter correlation time with the generalized MOS moves is significantly lower than the average number of \( \approx 10^6 \) MC steps between branch transitions obtained previously using crankshaft and reptation moves for a chain of essentially the same length, for a range of \( \sigma \) values that covers \( \sigma = -0.06 \) and under a similar effective ionic strength.\(^\text{15}\)

C. Writhe and site juxtapositions: Local and global correlations

Because of the \( 1/(r_{12})^2 \) dependence in its definition [Eq. (5)], the writhe Wr of a conformation is contributed mainly by \( Wr(i,j) \) [Eq. (53)] for which the segment pairs \( i, j \) are in spatial proximity. This observation suggests that a necessary condition for a large \( Wr(i,j) \) contribution is that \( i, j \) are in contact or, equivalently, constitute a site juxtaposition. Therefore, some correlations between aspects of writhe, which is a measure of self-entanglement, and the probability of site juxtapositions are expected.\(^\text{15}\) Contacts between different parts of a DNA molecule can be important for its biological function (Ref. 15 and references therein); they can be binding sites for enzymes such as topoisomerases,\(^\text{52,53,61,102}\) for example. Here, for the wormlike chain model, Fig. 15 depicts a strong correlation between writhe and contact at the local level, with contacts defined by a bead-bead distance less than or equal to a critical separation \( d_c \). We use \( d_c = 30 \) nm in Fig. 15, which is approximately twice the effective diameter (15 nm) for the low effective ion strength \(^\text{35}\) under which the example conformations are simulated. In general, we note that the conformational properties characterized by Wr and contacts are not identical: Wr contains information about the relative directions of two local tangent vectors of the chain contour, whereas such information is not taken into account in the definition of a contact. Two bead positions in close contact can also have zero or negligible Wr if the directions of the two local tangent vectors are nearly parallel, as for \( \beta \)-sheet-like motifs in proteins.\(^\text{62}\) In view of these considerations, the resemblance between writhe and contact patterns in Fig. 15 in the context of a wormlike DNA chain model is quite remarkable.

Figure 16 provides global correlations between writhe and the compactness of wormlike chain conformations. In the present study, compactness is characterized by the number of bead-bead contacts (with spatial separation \( \leq d_c \) normalized by \( n(n-1)/2 \), which is the hypothetical maximum number of contacts. For random-flight chains without excluded volume, the number of contacts can, in principle, reach this maximum. For chains with excluded volume,\(^\text{62,103,104}\) however, the actual achievable maximum number of contacts is \( \sim O(n) \) [see, e.g., Eqs. (8.3)–(8.5) in Ref. 62 for the exact maximum number of contacts in self-avoiding walks on the simple cubic lattice]. Our choice for the \( n(n-1)/2 \) normalization serves to put different models on the same footing and thus facilitate their comparison. Here, we refer to the normalized number of contacts as \( Q \).

Several features in Fig. 16 are noteworthy. First, although there is some scatter in the dependence of \( Q \) on Wr (spread in \( Q \) values for a given Wr), the scatter is not wide and there is a generally good correlation between \( Q \) and Wr. Second, naturally, the \( Q \) values and the \( \langle Q \rangle \) values (computed from averaging conformations with similar Wr) depend on the threshold separation \( d_c \) used to define them, but a general trend of increasing \( Q \) with increasing Wr applies for diverse sets of \( d_c \) in at least two very different effective 

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**FIG. 14.** Comparing the correlation times, \( \tau_{Br} \), of branching number Br as functions of superhelical density \( \sigma \) in the simulations for an \( n=233 \) wormlike chain model with effective [NaCl]=0.01M, using attempt probabilities \( P_{MC} = (0.5, 0.5, 0, 0.0) \) (conventional moves only, triangles), \( 0.025, 0.025, 0, 0.95 \) (conventional and \( T_{\pm 2} \) moves, squares), \( 0.3, 0.3, 0.4, 0 \) (conventional and generalized MOS moves, diamonds), and \( 0.015, 0.015, 0.02, 0.95 \) (conventional, generalized MOS, and \( T_{\pm 2} \) moves, circles). The correlation time \( \tau_{Br} \) is provided in terms of number of MC time steps (attempted moves, left panel) as well as in units of actual computer time (in seconds, right panel). Each datapoint in this figure is obtained from \( 2.4 \times 10^5 \) MC time steps of simulation.

**FIG. 15.** Similarities between the writhe map \( Wr(i,j) \) (left) and the contact map (middle) for three example supercoiled conformations (right) in the simulation of the present wormlike chain model with \( n=233 \), \( \sigma = -0.06 \), and effective [NaCl]=0.01M. Here, points with \( Wr(i,j) < -0.001 \) are shown as black squares in the writhe map and pairs of bead positions spatially separated by \( \leq d_c = 30 \) nm are plotted as black squares in the contact map.
including bond fluctuation models on lattices, have been plotted by different symbols; scatter plot for conformations obtained from separate simulations of 2.4 effective ionic strength is weaker and 0.02, and 0.0 from left to right. Datapoints for different \( \sigma \) values are plotted by different symbols; \( d_s=30 \text{ nm} \); effective [NaCl]=0.01M. (b) Average \( \langle Q \rangle \) value of \( Q \) for three different contacting criteria (separation \( \leq d_j \)) as functions of Wr for the model in (a). \([c] \) and \([d] \) Same as (a) and (b) but for effective [NaCl]=1.0M and different \( d_s \) values as indicated. A simulation of 8.0\( \times \)10\(^3\) MC time steps is conducted for each \( \sigma \) value. Only 100 datapoints are shown for each \( \sigma \) in (a) and (b) but all simulated data from 800 and 1600 conformations, respectively, for each \( \sigma \) value for effective [NaCl]=0.01 and 1.0M are used to calculate the averages in (b) and (d).

D. Random-flight and cubic lattice models of supercoils: Contrasts and similarities with the wormlike model

Random-flight\(^{19,26,47,105}\) and lattice\(^{18,49,54,106-109}\) models, including bond fluctuation models on lattices,\(^{110}\) have been applied extensively to the study of DNA and related geometrical, topological, and dynamic properties of polymers. Indeed, more generally, self-avoiding walks on square and cubic lattices have provided critical insights into many aspects of biomolecular behaviors, most notably in investigations of general principles of protein folding.\(^{62,103,110,111-116}\) More recently, two-dimensional square\(^{117,118}\) and three-dimensional simple cubic\(^{118,119}\) and diamond\(^{120,121}\) lattice models emerged as a useful tool for understanding conformational properties of RNA as well.

Despite the important role of torsional energies in determining the conformational properties of circular DNA, torsional potentials and supercoiling were seldom addressed in random-flight and lattice modeling. To explore the prospect of extending the capability of these more coarse-grained and, therefore, computationally more efficient models, here we incorporate the torsional potential term in Eqs. (4) and (8) into the random-flight and lattice models. For both classes of models, we accomplished the task by using the same value of C as that for our wormlike chain model and replacing \( l_0 \) in Eq. (8) by \( l_{\text{Kuhn}} \).

Figure 17 shows distributions of Wr in the resulting lattice model for different values of the superhelical density \( \sigma \). For \( \sigma=0.0 \), the distribution is symmetric with respect to the origin. (The corresponding \( n=100 \) distribution without torsional potential is also symmetric with respect to the origin, with a slightly wider distribution width and an overall shape similar to early results of van Rensburg et al.\(^{106} \) for \( n=400 \) and 1100.) With more negative \( \sigma \) values, the peak of the distribution shifts to more negative values of Wr, and the width of the distribution narrows. Because the cubic lattice model entails a much smaller number of chain segments than that of the wormlike chain model with the same contour length measured in \( l_{\text{Kuhn}} \), the range of available writhes for the present cubic lattice model is modest in comparison (cf. Fig. 16). This feature is present as well in the random-flight model with torsional energy (data not shown). For the lattice model, Fig. 17 indicates that successive unit of negative change in \( \sigma \) brings about an ever smaller decrease in average Wr, and the negative movement of Wr appears to be saturating rather quickly even with a small decrease in \( \sigma \).

1. Model comparison: Site juxtapositions

Figure 18 shows the correlation between Wr and \( Q \) for the random-flight and lattice models with torsional energies. Here, the random-flight model with \( n=33 \) Kuhn lengths may be viewed\(^{25}\) as a caricature of the 10 kb DNA of bacterio-
phage P4 that has been used in experimental studies of DNA topology.\textsuperscript{20,37} The \( n = 100 \) lattice model corresponds to the one used extensively in our recent theoretical investigation of type-II topoisomerase mechanisms.\textsuperscript{53} The trends in Fig. 18 for these models are similar to that in Fig. 16 for the worm-like chain model. However, the scatter in Fig. 18 for the more coarse-grained models is considerably wider and thus the Wr-Q correlation is weaker than that in Fig. 16 for the wormlike chain model. Mathematically, the greater scatter in Figs. 18(a) and 18(c) may be related to the small numbers of chain units (small \( n \)) used in the present random-flight and lattice model simulations. Physically, this observation highlights the differences arising from the fact that a wormlike chain can bend within the contour of one Kuhn length, whereas the bonds representing one Kuhn length of DNA are always straight in the random-flight and lattice models. The example conformations in Fig. 18 show some characteristics of supercoiled structures, though they are not manifestly DNA-like. Intuitively, they bear some resemblance to pleonemic superhelices. In this regard, we note that lattice structures that share some geometric similarities with pleonoidal superhelices\textsuperscript{5} have also been observed (not shown). Taken together, the more coarse-grained models are seen as capturing to a reasonable degree the general averaged trends of the Wr-Q relationship in spite of their shortcomings in mimicking more detailed geometric features of individual DNA conformations.

Figure 19 investigates how the probability of contact between beads \( i \) and \( j \) depends on their sequence separation \(|i−j|\) (termed “contact order” in the protein literature\textsuperscript{62}). It shows that our wormlike chain model results for a high effective NaCl concentration (top) and a low effective NaCl concentration (bottom).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig18.png}
\caption{FIG. 18. [(a) and (c)] Normalized contact number \( Q \) and [(b) and (d)] the average \( Q \) vs writhe \( Wr \) for [(a) and (b)] the random-flight model and [(c) and (d)] the cubic lattice model, wherein a twisting energy is incorporated as described in the text. Random-flight data in (a) are for \( n = 33 \) and \( \sigma = -0.02, -0.015, -0.01, -0.005, \) and 0.0 (left to right, plotted by different symbols), with \( Q \) defined by a threshold contact distance \( d_c = \ell_{\text{Kuhn}} \). (b) Average \( Q \) according to three different \( d_c \) criteria for the model in (a). Cubic lattice model data in (c) are for \( n = 100 \) and \( \sigma = -0.015, -0.01, -0.005, \) and 0.0 (left to right, plotted by different symbols). In the lattice model, two beads not sequential along the chain contour but which are nearest lattice neighbors are defined to be in contact. (d) The corresponding \( Q \) for the model in (c). Example “supercoiled” conformations in the random-flight model (top, \( n = 33, \text{Wr} = -11.5 \)) and the cubic lattice model (bottom, \( n = 50, \text{Wr} = -5.25 \)) are shown on the right.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig19.png}
\caption{FIG. 19. Probability of site juxtaposition (i.e., contact) between two sites as a function of the sequence separation between the two sites along the contour of the chain. Left: \( n = 233 \) wormlike chain model, \( d_c = 10 \) nm, with effective [NaCl] = 0.01 M (top) and 1.0 M (bottom). Results for chains with different values of superhelical density \( \sigma \) are as indicated. Top right panel: \( n = 100 \) cubic lattice model for \( \sigma = -0.015, -0.01, -0.005, \) and 0.0 (top curve to bottom curve); minimum sequence separation \(|i−j|\) for a contacting pair is 3 for this model. Bottom right panel: \( n = 33 \) random-flight model, \( d_c = 0.1 \text{Kuhn} \), where contacts are defined by the bead-bead distance \( \leq d_c \) (dashed curves) or the shortest segment-segment distance \( \leq d_c \) (solid curves); minimum sequence separation \(|i−j|\) for a contacting pair is 2 for this model. The \( \sigma \) values are \(-0.02, -0.015, -0.01, -0.005, \) and 0.0 (top curve to bottom curve) in both cases. As an aid for comparing models, scales at the bottom convert \( n \) in the wormlike chain model to units of Kuhn length and kb (thousand basepairs) as discussed in the text. Same conformations as those used in Figs. 16 and 18 are used in the present analysis except additional simulations of \( 9.0 \times 10^7 \) MC time steps are used for each \( \sigma \) value of the wormlike chain model with effective [NaCl] = 0.01 M.}
\end{figure}
These earlier simulation results indicated that contact probability with increasing ionic strength of the effective ionic strength (Fig. 19, bottom left) are consistent with previous observations\textsuperscript{15} for negative $\sigma$ values up to $-0.08$. These earlier simulation results indicated that contact probability was lower for $|i-j|=0.5$ Kuhn length but was higher and stayed approximately constant for $|i-j|=1.0$ Kuhn lengths. This agreement between independent simulations of two similar models suggests that these aspects of the model predictions are robust. In this context, several novel features revealed by the full range of information in the present data are noteworthy. For instance, the wormlike model results in Fig. 19 predict a much stronger dependence of contact probability on sequence separation at lower ionic strengths (top left) and a similarly strong dependence even at high ionic strengths if the conformations are highly supercoiled (bottom left, $\sigma=0.1$ curve). The lattice and random-flight model results on the right capture some of the general trends of behavior of the wormlike chain model. These include an increase in contact probability with increasing $|\sigma|$ (as in Fig. 18). Because of the high flexibility of random-flight chains and that each segment represents a full Kuhn length, we found that it is physically more meaningful to define contacts in terms of the shortest segment-segment distance $s_{ij}$ [Eq. (13)] rather than the distance between beads. This distinction can lead to large differences (Fig. 20, bottom right, cf. solid and dashed curves) in the random-flight model, although such a distinction is insignificant for the wormlike model in which each Kuhn length is represented by many segments.

As expected, the lattice model (Fig. 19, top right), with its significant excluded volume, is more similar to the wormlike model in low ionic strengths (top left). Accordingly, the lattice model shows a steep rise in contact probability as the sequence separation decreases, a behavior which is more akin to that of unsupercoiled conformations\textsuperscript{65} because the superhelical densities achievable by the lattice models are relatively low (see above). In contrast, for the random-flight model, increases in contact probability as the sequence separation decreases are not as steep when contacts are defined by segment-segment distances (bottom right, solid curves), indicating once again that this class of models does share some similarities with wormlike chain models in high ionic strengths (Fig. 19, bottom left).

2. Model comparison: Knots in topological equilibrium

FIG. 20. Knot probabilities in the wormlike, random-flight, and lattice models, all with torsional energies as described in the text. Conformations with different $\sigma$ values are in topological equilibrium (Ref. 122). Datapoints plotted are for knot types with relatively higher probabilities among those sampled in our simulations. (a) Wormlike chain model, $n=400$, with effective NaCl concentration of 0.01 M (filled diamonds) and 0.15 M (open circles). (b) Wormlike chain model, $n=400$, with effective NaCl concentration of 1.0 M. (c) Cubic lattice model with $n=50$ (filled diamonds) and $n=100$ (open circles). (d) Random-flight model, $n=20$, i.e., with essentially the same number of $L_{\text{Kuhn}}$ as in (a) and (b). Data for the wormlike chain model with effective NaCl concentration of 0.01, 0.15, and 1.0 M are obtained, respectively, from simulations of 6.0, 9.0, and 2.0 $\times$ $10^7$ MC time steps; data for the lattice model are simulated using 4.5 $\times$ $10^9$ (for $n=50$) and 1.5 $\times$ $10^{11}$ (for $n=100$) MC time steps; data for the random-flight model are simulated using 2.4 $\times$ $10^9$ MC time steps.

Thus far, all of the above simulations were restricted to the unknot. We now relax this restriction to allow the MC chain to move to effect transitions between conformations with different superhelical densities as well as different knot types. The resultant ensemble is thus in topological equilibrium. Figure 20 provides the occurrence probabilities of various knot types in the wormlike, random-flight, and lattice models (all with torsional energies) under conditions of topological equilibrium.\textsuperscript{122} The knot-type notation in this figure is that of Rolfsen\textsuperscript{123} in conjunction with the common usage of an asterisk (*) to denote that a given knot is the mirror image of the version in the Rolfsen table. The wormlike chain results in Figs. 20(a) and 20(b) show that, consistent with experiments\textsuperscript{35,124} and previous model simulations,\textsuperscript{18} knot population increases with increasing ionic strength. Naturally, more screening of the electrostatic repulsions means that the chain can configure with its segments closer to one another and thus a higher degree of entanglement is likely. Figure 20 shows that the difference in knot population is large between effective NaCl concentration of 0.01 and 0.15 M [Fig. 20(a)] but the corresponding difference between effective NaCl concentration of 0.15 M [Fig. 20(a), open circles] and 1.0 M [Fig. 20(b)] is much smaller. As expected from the above discussion, the probabilities of various nontrivial knot types (all except the unknot, $0_1$) in the lattice model [Fig. 20(c)] are lower than but nonetheless exhibit a pattern similar to the corresponding knot probabilities in the wormlike model under low ionic strengths [Fig. 20(a), diamonds]. On the other hand, both the magnitude and knot-type distribution profile of the random-flight model in Fig. 20(d) are quite similar to that of the wormlike model under higher ionic strengths in Fig. 20(b).

Figure 21 shows further that knot population increases with chain length and with supercoiling, as predicted by theory\textsuperscript{38,49} and corroborated by experiment on DNA circles.\textsuperscript{37,38,124} Once again, as the behaviors of the random-flight model are more similar to that of wormlike chain models in high rather than low ionic strengths (see above), the data here show that knot probability is significantly higher in
E. Concluding remarks

In summary, we proposed in this work two new classes of efficient MC chain moves designed for simulating wormlike chain models of supercoiled DNA. Ideas for constructing these moves originated from related chain moves in lattice modeling. We have now developed the necessary formalisms for generalizing the move to the continuum and for adapting them to the conformational peculiarities of supercoiled conformations. For the test simulations of close chains we have conducted, the generalized MOS moves led to approximately five times speed up, vis-à-vis conventional moves, of relaxations in conformational properties including supercoil branching. The formulation for the length-changing moves is intricate. Nonetheless, once implemented, their computational efficiency is reasonable. Therefore, our $T_{\pm 2}$ moves offer a practical means to change the chain length in MC simulations of supercoiled conformations. Having such a tool is valuable as it is often needed in applications that involve conformational constraints, in the form of a preformed site juxtaposition, for example.

Using the new simulation algorithm for conformational sampling, we found a close correlation between the writhe and site juxtaposition (contact) maps in the wormlike chain model and that the dependence of contact probabilities on sequence (contour) separation is sensitive to superhelical density and ionic strength. We have also extended the common random-flight and self-avoiding lattice chain models by augmenting them with a torsional potential, so as to enable questions regarding supercoiling to be addressed in these more coarse-grained constructs. An examination of the contact, writhe, and knotting patterns of the resulting models indicated that these random-flight and lattice models, respectively, are able to approximate aspects of behaviors of the wormlike chain model at high and low ionic strengths.

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APPENDIX: FORMULATION FOR THE LENGTH-CHANGING $T_{\pm 2}$ CHAIN MOVES

We now describe in more detail the $T_{\pm 2}$ moves introduced and applied to sampling studies in the main text (Fig. 7). The $T_{\pm 2}$ moves are designed to effect changes in chain length, particularly for but not restricted to close-loop DNA-like conformations (ring polymers) with significant supercoiling. Because the only strict requirement for MC moves is detailed balance, there is a latitude in choosing the moves. Nonetheless, we exerted considerable effort to arrive at a reasonable, albeit somewhat complex, choice (Fig. 22). The complexity arises because the moves are for continuous space—unlike the length-changing BFACF moves for simple cubic lattices—and, more importantly, because the moves have to be reasonably efficient to operate under energetic and conformational constraints such as long persistence lengths of wormlike chains. As emphasized in the main text, our interest in length-changing moves was motivated by biophysical and statistical mechanical questions in the study of unknotting mechanisms of type-II topoisomerases.

Length-changing moves are needed for the sampling of close-loop DNA conformations with a preformed juxtaposition (see Fig. 1 and related discussion). As we have demonstrated recently in a simpler lattice model the statistics of such constrained conformations is crucial in delineating how global knot/unknot topology can be inferred from local geometrical features that topoisomerase enzymes may detect from a juxtaposition. As shown below, our $T_{\pm 2}$ algorithm is computationally workable, despite its somewhat complex formulation. Therefore, as far as our scientific goal is concerned, the development of $T_{\pm 2}$ is a key advance toward addressing fundamental principles of topoisomerase mechanisms because these moves would facilitate extensions of the effective juxtaposition-centric conformational sampling approach to more realistic wormlike chain models for DNA. Here, Fig. 22 gives an overview of our $T_{\pm 2}$ moves; it depicts the individual computational steps that underlie the overall effect summarized by Fig. 7 in the main text. Below,
we will provide the mathematical basis for these individual steps, identify the free parameters that are randomly sampled in the MC simulations, and determine how the efficiency of the algorithm is affected by parameter choices.

1. Length-subtracting $T_{-2}$

Starting with two randomly selected chain segments 2-3-4 and $b\cdot c\cdot d$ (Fig. 22, top box), a length-subtracting move will be attempted if the following conditions are met. (i) The contour difference between the center beads on the two segments (absolute value of the difference in bead number of 3 and $c$) is larger than a threshold number $D_s$. (ii) The distance $r_{2b}$ between beads 2 and $b$ does not differ from the distance $r_{4d}$ between beads 4 and $d$ by more than a certain cutoff $\Delta r_{2b}^{(c)}$, i.e., $|r_{2b} - r_{4d}| \leq \Delta r_{2b}^{(c)}$. (iii) All the virtual bond lengths in the two segments (distances $r_{23}$ between beads 2 and 3, $r_{34}$ between beads 3 and 4, $r_{bc}$ between beads $b$ and $c$, and $r_{cd}$ between beads $c$ and $d$) do not differ from the equilibrium segment length $l_0$ in Eq. (1) by more than $\Delta r_e$, i.e., $|r_{23} - l_0|$. 

FIG. 22. Steps in the $T_{-2}$ (left) and $T_2$ (right) moves. Dotted lines represent the rest of the chain conformation, as in Fig. 7 (see the text for details).
As shown in Refs. 90 and 91, the minimized RMSD, denoted as $\text{minimizes the RMSD value}$, is achieved by a minimization of RMSD between the two rigid bodies defined by beads 2, 3, b, and c by beads 3', 4, c', d. After this procedure to optimally overlap the two sets of beads, bead 2 is connected to bead 4, bead b is connected to bead d, and beads 3, 3', c', e, and c are eliminated (Fig. 22, left, third step of $T_{-2}$). Consequently, the net result of the $T_{-2}$ steps is to transform the segment pair 2-3-4 and b-c-d (Fig. 22, top box) to a pair of segments 2-4 and b-d, each with one fewer bead than the original segment (Fig. 22, bottom).

RMSD at optimal superposition induces a metric for sets of rigid-body positions. A necessary condition for the minimization of RMSD between the positions in a pair of rigid bodies is that their centroids (barycenters) coincide. Therefore, we first shift the centroids of both the rigid bodies constituted by beads 2, 3, b and c and beads 3', 4, c', d to the origin. This operation entails a translation vector $X_0$ that brings the two centroids together. We then apply the quaternion method of Kearsley and Coutsias et al. to determine the optimal relative rotation that minimizes RMSD. We have chosen this method because it can be readily implemented; nonetheless, it should be noted that other mathematical procedures can also serve the same purpose, e.g., by a constrained optimization of the orthogonal transformation matrix itself. The following summarizes briefly the quaternion formalism in Ref. 91, which we have adopted for the present RMSD minimization. Let the coordinate vectors of the two sets of beads after both of their centroids are placed at the origin be, respectively, $\{X_k\}$ and $\{Y_k\}$, where $k=1,2,3,4$ labels the beads. Define

$$R_{ij} = \sum_{k=1}^{N} X_{i}^{(j)} Y_{k}^{(j)} ,$$

where $i,j=1,2,3$ refers to the x, y, and z spatial components, $N$ is the number of positions ($N=4$ in our case), and

$$\mathcal{F} = \begin{pmatrix}
R_{11} + R_{22} + R_{33} & R_{23} - R_{32} & R_{31} - R_{13} & R_{12} - R_{21} \\
R_{23} - R_{32} & R_{11} - R_{22} + R_{33} & R_{12} + R_{21} & R_{13} + R_{31} \\
R_{31} - R_{13} & R_{12} + R_{21} & R_{11} + R_{22} - R_{33} & R_{23} + R_{32} \\
R_{12} - R_{21} & R_{13} + R_{31} & R_{23} + R_{32} & R_{11} - R_{22} + R_{33}
\end{pmatrix} ,$$


As shown in Refs. 90 and 91, the minimized RMSD, denoted as $e_q$, is given by

$$e_q = \sqrt{\frac{\Sigma_{k}(|X_{k}|^2 + |Y_{k}|^2) - 2\lambda_{\max}}{N}} ,$$

where $|X_{k}|^2 = (X_{k}^{(1)})^2 + (X_{k}^{(2)})^2 + (X_{k}^{(3)})^2$ is the square of the magnitude of vector $X_k$ and $\lambda_{\max}$ is the maximum eigenvalue of the matrix $\mathcal{F}$. The corresponding rotation matrix $\mathcal{U}$, which acts on $X_k$ to bring the two rigid bodies to an optimal superposition that minimizes the RMSD value $\sqrt{\Sigma_{k}(|X_{k}|^2 - |Y_{k}|^2)/N}$, is given by

$$\mathcal{U}(q) = \begin{pmatrix}
q_0^2 + q_1^2 - q_2^2 - q_3^2 & 2(q_1 q_2 - q_0 q_3) & 2(q_1 q_3 + q_0 q_2) & 2(q_2 q_3 - q_0 q_1) \\
2(q_1 q_2 + q_0 q_3) & q_0^2 - q_1^2 + q_2^2 - q_3^2 & 2(q_2 q_3 - q_0 q_1) & 2(q_1 q_3 - q_0 q_2) \\
2(q_1 q_3 - q_0 q_2) & 2(q_2 q_3 + q_0 q_1) & q_0^2 - q_1^2 - q_2^2 + q_3^2 & 2(q_1 q_2 + q_0 q_3) \\
2(q_2 q_3 + q_0 q_1) & 2(q_1 q_3 - q_0 q_2) & 2(q_1 q_2 + q_0 q_3) & q_0^2 + q_1^2 - q_2^2 - q_3^2
\end{pmatrix} .$$
where \(q=(q_0,q_1,q_2,q_3)\) is the quaternion eigenvector of \(F\) for the maximum eigenvalue, viz.,

\[
F \begin{pmatrix} q_0 \\ q_1 \\ q_2 \\ q_3 \end{pmatrix} = \lambda_{\text{max}} \begin{pmatrix} q_0 \\ q_1 \\ q_2 \\ q_3 \end{pmatrix},
\]

and each \(q_i\), \((i=0,1,2,3)\) is a real number. This four-component quaternion \(q\) is directly related to the rotation axis \(\hat{e}\) (unit vector) along which a rotation angle \(\theta\) results in the same transformational effect as \(\hat{e}r\theta\hat{e}^{-1}\),

\[
q = (q_0,q) = (\cos(\theta/2), \sin(\theta/2)\hat{e}). \quad q = (q_1,q_2,q_3),
\]

as has been stated in Coutsias et al.\(^{91}\)

In our RMSD-minimization procedure, the rest of the conformation (chain segments beyond \(2, b\) and beyond \(4, d\)), as denoted by dotted lines in Fig. 22, is treated as two rigid bodies that are rigidly attached to sets \((2,3,b,c)\) and \((3',4,c',d)\). It follows that minimization of the RMSD between sets \((2,3,b,c)\) and \((3',4,c',d)\) will pull along the rest of the conformation and thus bring about a change in the relative position and orientation of the two sets of chain segments beyond \(2, b\) and beyond \(4, d\), as has been discussed in the main text (Figs. 7 and 8).

After the minimized RMSD value \(e_q\) is obtained, we compare it with a cutoff value \(\text{RMSD}_{c}\). The attempted \(T_{-2}\) move is rejected if \(e_q > \text{RMSD}_{c}\). For the simulations presented here, we set \(\text{RMSD}_{c}=1.5\) nm. Finally, we consider the positions of beads \(2, 4, b,\) and \(d\) at the minimal-RMSD superposition. Before connecting bead 2 to bead 4 and bead \(b\) to \(d\), we check the deviation of their separations, \(r_{24}\) and \(r_{bd}\), respectively, from the equilibrium segment length \(l_0\). The attempted \(T_{-2}\) is rejected if either \(|r_{24}-l_0|>\Delta r_c\) or \(|r_{bd}-l_0|>\Delta r_c\), or both. As discussed above for similar procedures before RMSD calculation, these tests aim to filter out conformations that are likely to have significantly unfavorable energies.

At this point, if the attempted \(T_{-2}\) move has passed all the above tests, we arrive at a putative new conformation with two fewer beads than the original. To maintain microreversibility, it is necessary to subject this conformation to further tests derived from the reverse \(T_2\) process to ensure that the reverse of the putative \(T_{-2}\) transformation is allowed by the parameter choices we make for the \(T_2\) transformation. This aspect of the final testing of the putative \(T_{-2}\)-transformed conformation will be addressed below under the discussion of the steps in the \(T_{-2}\) move.

2. Length-adding \(T_2\)

The starting point of \(T_2\), the reverse operation of the \(T_{-2}\) move above, is a randomly selected pair of chain segments as depicted in the bottom box of Fig. 22. A length-adding \(T_2\) (equivalent to \(T_{+2}\) in our notation) move will be attempted if the following conditions are met. (i) The contour difference (absolute value of the difference in bead number) between beads 2 and \(b\) and the contour difference between beads 4 and \(d\) are both larger than \(D_c-2\). (ii) \(|r_{2b}-r_{bd}|\approx\Delta l_{2b}\). (iii) The virtual bond lengths between beads 2 and 4 and between beads \(b\) and \(d\) \((r_{24} \text{ and } r_{bd})\) respectively do not differ from the equilibrium segment length \(l_0\) by more than \(\Delta r_c\), i.e., \(|r_{24}-l_0|\leq\Delta r_c\) and \(|r_{bd}-l_0|\leq\Delta r_c\). Note that conditions (i) and (ii) here for \(T_2\) correspond to the first two conditions [(i) and (ii)] for \(T_{-2}\) above, and condition (iii) here for \(T_2\) is identical to one of the last tests imposed above for \(T_{-2}\) after the chain has been shortened.

If the two segments pass these tests, we proceed to elongate each segment by one bead. First, four additional beads are grown: 3, \(3', c,\) and \(c',\) respectively, from \(2, 4, b,\) and \(d\). Second, this growing operation is to be followed by fusing 3 with \(3',\) and \(c\) with \(c',\) resulting in a net gain of two additional beads (Fig. 22, right, first and second steps of \(T_2\) from bottom). In the formal development below, the positions of the newly grown beads are described in terms of the vector \(r_{2b}=r_b-r_2\) for the relative positions between \(r_b\) and \(r_2\) for existing beads \(b\) and 2, and the position vector \(R_{2b}=(r_2+r_b)/2\) for the centroid of the two beads, as well as the analogous vectors \(r_{4d}=r_d-r_4\) and \(R_{4d}=(r_4+r_d)/2\) for existing beads \(d\) and 4. Vector variables \(r_{3c}, r_{3c'}, R_{3c},\) and \(R_{3c'}\) are similarly defined for the newly grown beads. Note that the vectors \(R_{2b}\), etc., here are different from and should not be confused with the \(R\) vectors defined in Sec. III of the main text with respect to a variable reference frame in our formulation of the generalized MOS transformations.

Consider \(r_{2b}, r_{3b}, \text{ and } r_{4d}\) and \((r_{2b}\times r_{4d})\times r_{2b}\), where \(\times\) denotes the usual cross product of three-dimensional vectors, as in the main text. Unless \(r_{2b}\times r_{4d}=0\), the directions defined by these three mutually orthogonal vectors may be used as a coordinate system. In the case \(r_{2b}\times r_{4d}=0\), which is extremely rare—practically impossible—in applications in continuum space, one may simply replace \(r_{2b}\times r_{4d}\) and \((r_{2b}\times r_{4d})\times r_{2b}\) with any two orthogonal vectors on the plane perpendicular to \(r_{2b}\). Using such a coordinate system, and a similar coordinate system set up with axes along \(r_{4b}, r_{2b} \times r_{4d}\), and \(r_{4d} \times (r_{2b} \times r_{4d})\) (with the same proviso for rare cases of \(r_{2b}\times r_{4d}=0\)), we may, in general, express the vector variables \(r_{3c'}, R_{3c'},\) and \(r_{3c}\) for the newly grown beads in the form

\[
r_{3c'} = \alpha_1 \frac{(r_{2b} \times r_{4d}) \times r_{2b}}{|r_{2b}|^2} + \beta_1 (r_{2b} \times r_{4d}) + \gamma_1 R_{2b},
\]

\[
r_{3c} = \alpha_2 \frac{r_{4d} \times (r_{2b} \times r_{4d})}{|r_{4d}|^2} + \beta_2 (r_{2b} \times r_{4d}) + \gamma_2 r_{4d},
\]

i.e., as sums of component variables \(\alpha_1, \beta_1, \gamma_1, \text{ for } r_{3c'}\) and \(\alpha_2, \beta_2, \gamma_2\) for \(r_{3c}\).

In general, growing four new beads entails adding 12 degrees of freedom in the vector variables \(r_{3c}, r_{3c'}, R_{3c},\) and \(R_{3c'}\). However, to satisfy microreversibility, these variables should not be all chosen independently because sets \((2,3,b,c)\) and \((3',4,c',d)\) should be constrained by the minimum-RMSD condition we implemented for the length-subtracting \(T_{-2}\) move above. As it will become clear below, in the present \(T_2\) transformation, the new beads have to be grown under minimum-RMSD conditions, i.e., they have to satisfy
\begin{align}
R_{3't'} + R_{4d} &= R_{3c} + R_{2b}, \\
R_{3't'} \times R_{2b} + \frac{1}{2} R_{3't'} \times r_{2b} + R_{3c} \times R_{4d} + \frac{1}{2} r_{4d} \times r_{3c} &= 0.
\end{align}
\tag{A10} \tag{A11}

Our aim here is to effect a process which is the reverse of moving two sets of beads from a general relative position and orientation to the optimized minimum-RMSD superposition, a task we have achieved for the length-subtracting \( T_{-2} \) operation by using a quaternion approach, as described above. Now, for the reverse length-adding \( T_{2} \) move, Eqs. (A10) and (A11) provide the necessary constraints to restrict the relative positions of the new beads to be grown such that sets \((2, 3, b, c)\) and \((3', 4, c', d)\) after beads 3, 3, \(c\), and \(c'\) have been grown will be already in a minimum-RMSD superposition with no further need for RMSD minimization. Specifically, Eq. (A10) states the well-known requirement that the centroids,

\[
\overline{R} = R_{3c} + R_{2b} \quad \text{and} \quad \overline{R'} = R_{3't'} + R_{4d},
\tag{A12}
\]

of the two sets of new beads need to coincide to minimize RMSD, a condition we have used as well in the RMSD-minimization procedure for \( T_{-2} \) above. Equation (A11) follows from a variational consideration of the rotational transformation as follows. For any two sets of bead positions with the same centroid, let \( A_k \) and \( B_k \) be the vectors from the common centroid to the two sets of beads. When the mean-square deviation, \( D = \sum_{k} |A_k - B_k|^2 \), between the two sets is minimized, \( D \) should be stationary with respect to infinitesimal rigid rotations of one set of beads relative to the other set. In other words, for a rotation of an angle \( |\Delta \omega| \rightarrow 0 \) (in radians) along an axis that passes through the common centroid in the direction of an arbitrary vector \( \Delta \omega \), the resulting change, \( \delta D \), in mean-square deviation should vanish. Hence,

\[
\delta D = \sum_{k} |A_k + \Delta \omega \times A_k - B_k|^2 - \sum_{k} |A_k - B_k|^2
= 2 \sum_{k} (A_k - B_k) \cdot (\Delta \omega \times A_k)
= 2 \sum_{k} (B_k \times \Delta \omega) \cdot \Delta \omega = 0.
\tag{A13}
\]

To yield the last equality, we discarded the \( O(|\Delta \omega|^2) \) term in view of the \( |\Delta \omega| \rightarrow 0 \) limit and utilized the vector identity \((A \times B) \cdot C = A \cdot (B \times C)\) for any three vectors \( A, B, \) and \( C \). It follows that

\[
\sum_{k} (B_k \times \Delta \omega) = 0
\tag{A14}
\]

for any two sets of beads satisfying minimum-RMSD conditions.\(^{125}\) For bead sets \((2, 3, b, c)\) and \((3', 4, c', d)\) being considered, applying Eq. (A14) yields

\[
(r_2 - \overline{R}) \times (r_3' - \overline{R'}) + (r_3 - \overline{R}) \times (r_4 - \overline{R'}) + (r_b - \overline{R}) \times (r_c' - \overline{R'}) + (r_d - \overline{R}) \times (r_{d'} - \overline{R'}) = 0,
\tag{A15}
\]

where the centroid positions \( \overline{R} \) and \( \overline{R'} \) are those defined in Eq. (A12). Starting from Eq. (A15), it is straightforward to verify Eq. (A11) by using the \( \overline{R} = \overline{R'} \) condition in Eq. (A10).

It should be noted that the condition in Eq. (A11) is independent of the choice of coordinate system provided that the condition in Eq. (A10) is met. Rewriting Eq. (A11) as

\[
r_{3't'} \times r_{2b} - r_{3c} \times r_{4d} = 4K,
\tag{A16}
\]

where the vector

\[
K = -R_{3't'} \times R_{2b} + R_{3c} \times R_{4d},
\tag{A17}
\]

and applying Eqs. (A8) and (A9) with identities such as \([r_{2b} \times r_{4d} \times r_{2b}] \times r_{2b} = -(r_{2b} \times r_{4d} \times r_{2b})^2\), we arrive at

\[
-(\alpha_1 + \alpha_2)(r_{2b} \times r_{4d} + \beta_1(r_{2b} \times r_{4d})
\times r_{2b} - \beta_2(r_{2b} \times r_{4d}) \times r_{4d} = 4K.
\tag{A18}
\]

Now, by taking the scalar (dot) product of both sides of this equation with \( r_{2b} \times r_{4d}, r_{2b}, \) and \( r_{4d} \), we obtain the following expressions, respectively, for the component variables \( \alpha_1 + \alpha_2, \beta_1, \) and \( \beta_2 \) in Eqs. (A8) and (A9) for \( r_{3't'} \) and \( r_{3c} \):

\[
\alpha_1 + \alpha_2 = -\frac{4K \cdot (r_{2b} \times r_{4d})}{|r_{2b} \times r_{4d}|^2},
\tag{A19}
\]

\[
\beta_1 = \frac{4K \cdot r_{4d}}{|r_{2b} \times r_{4d}|^2},
\tag{A20}
\]

\[
\beta_2 = \frac{4K \cdot r_{2b}}{|r_{2b} \times r_{4d}|^2},
\tag{A21}
\]

where the denominator in Eqs. (A20) and (A21) follows from applying the identity \((A \times B) \cdot C = A \cdot (B \times C)\) (see above) to \([r_{2b} \times (r_{2b} \times r_{4d})] \times r_{4d}\) and \([r_{2b} \times r_{4d}] \times r_{2b}\). Since the right-hand sides of Eqs. (A19)–(A21) are given in terms of \( K \) and vectors derived from existing positions of beads 2, 4, \( b, \) \( d \), once values are freely chosen for \( R_{3't'}, \gamma_1, \gamma_2, \) and \( \alpha_1 - \alpha_2 \) in the MC simulation, the value of \( R_{3c} \) is given immediately by Eq. (A10). Subsequently, with values for both \( R_{3't'} \) and \( R_{3c} \), the vector \( K \) is determined by Eq. (A17). Once \( K \) is known, the parameters \( \alpha_1 + \alpha_2, \beta_1, \) and \( \beta_2 \) are in turn determined by Eqs. (A19)–(A21). These parameters are then combined with the freely chosen values for \( \gamma_1, \gamma_2, \) and \( \alpha_1 - \alpha_2 \) to specify the vectors \( r_{3't'} \) and \( r_{3c} \) via Eqs. (A8) and (A9). This leads finally to the position vectors \( r_{3'y}, r_{3'z}, \) \( r_{3'e}, r_{3'c}, \) \( r_{3'f}, \) and \( r_{3'f'} \) for the newly generated beads 3, 3, \( c, \) and \( c' \), as they are readily calculated from \( R_{3't'}, \) \( R_{3c}, r_{3't'}, \) and \( r_{3c} \).

Each of the randomly chosen parameters for growing the new beads 3, \( c, \) and \( c' \) under the minimum-RMSD constraint is drawn with uniform probability within a range we set for the simulation,

\[
R_{3't'}^{(i)} \in [R_{2b}^{(i)} - \Delta R_{3't'}^{(0)}, R_{2b}^{(i)} + \Delta R_{3't'}^{(0)}],
\tag{A22}
\]

\[
\gamma_1 r_{2b} \in [r_{2b} - \Delta \gamma^{(0)} r_{2b} + \Delta \gamma^{(0)}],
\tag{A23}
\]

\[
\gamma_2 r_{4d} \in [r_{4d} - \Delta \gamma^{(0)} r_{4d} + \Delta \gamma^{(0)}],
\tag{A24}
\]

\[
(\alpha_1 - \alpha_2) r_{2b} \in [-\Delta \alpha^{(0)}, \Delta \alpha^{(0)}],
\tag{A25}
\]

where \( r_{3't'}^{(i)}, \) \( r_{3'c}^{(i)}, \) \( r_{2b}^{(i)} \), and \( r_{2b}^{(i)} \) \( (i=1, 2, 3) \) are the three spatial components, respectively, of \( R_{3't'}, \) \( R_{3c}, \) \( R_{2b}^{(i)} \) Without loss of gen-
erality, we use the known quantities (derivable from the initial conformation) \( r_{2b} = [r_{2b}]_1 = [r_{2d}]_1 \), and
\[
    r_a = \frac{1}{2} \left( \frac{(r_{2b} \times r_{4d}) \times r_{2b}}{r_{2b} \cdot r_{2b}} + \frac{(r_{2b} \times r_{4d}) \times r_{4d}}{r_{4d} \cdot r_{4d}} \right)
\]
(A26)
as normalizations to modulate variations in \( \gamma_1, \gamma_2 \), or \( \alpha_1 - \alpha_2 \) for a given range of \( \Delta \gamma(0) \) or \( \Delta \alpha(0) \) [Eqs. (A23)–(A25)].

We will explore below how the efficiency of \( T_2 \) moves depends on the choices for these range parameters and \( \Delta R_{\gamma, \alpha} \) in Eq. (A22).

Before proceeding to fuse beads 3 with 3’ and beads c with c’, we first check whether the minimized RMSD for the optimally superposed bead sets (2,3, b, c) and (3’,4, c’, d) is less than or equal to the cutoff RMSD, we introduce for \( T_2 \). If the minimized RMSD > RMSD, we terminate further attempts to make the \( T_2 \) move. We proceed only if the minimized RMSD ≤ RMSD. Then, as a prerequisite for the fusion operation, we next shrink/elongate the separations between 3 and c and between 3’ and c’, so that they are identical (Fig. 22, right, second step of \( T_2 \)). Let \( \Delta R_{3c} = r_{3c} - r_{3c} \) be the initial difference in separation (\( \Delta R_{3c} \) can be positive, negative, or zero). This procedure is the reverse of the \( T_{3c}, r_{3c} \)-perturbing step of \( T_2 \) (Fig. 22, left, second step of \( T_2 \)). Thus, as required by microreversibility, if \( \Delta R_{3c} \) of the present \( T_2 \) step is larger than \( \Delta R_{3c} \), where \( \Delta R_{3c} \) is given in Eq. (A1) for \( T_2 \) above, we reject the attempted \( T_2 \) move. In other words, we proceed further with the attempted \( T_2 \) move only if \( \Delta R_{3c} \leq \Delta R_{3c}^{(0)} \). In this case, the shrink/elongate procedure consists of the following operations: Change \( r_{3} \) to \( r_{3} - (\Delta R_{3c}/2) e_{3c} \), (i.e., \( r_{3} \rightarrow r_{3} - (\Delta R_{3c}/2) e_{3c}\), \( r_{c} \rightarrow r_{c} - (\Delta R_{3c}/2) e_{3c}\), \( r_{3} \rightarrow r_{3} - (\Delta R_{3c}/2) e_{3c}\), and \( r_{c} \rightarrow r_{c} - (\Delta R_{3c}/2) e_{3c}\)), where \( e_{3c} \) and \( e_{3c} \) are, respectively, the unit vectors in the directions of \( r_{3} \) and \( r_{c} \). To ensure microreversibility, we subject the new coordinates for beads 3, c, 3’, c’ to the following simple tests. We will proceed further with the attempted \( T_2 \) move only if \( |r_{3c} - l_0| \leq \Delta R_{3c}, |r_{3c} - l_0| \leq \Delta R_{3c}, \) and \( |r_{c} e_{c} - l_0| \leq \Delta R_{c} \), where \( l_0 \) is the equilibrium segment length; otherwise, the move is rejected. These tests correspond to the initial test (iii) at the beginning of the \( T_2 \) move (see above) and are implemented to enhance computational efficiency.

Finally, after the above shrink/elongate procedure, we are ready to fuse 3 with 3’ and fuse c with c’ to assemble the two parts of the conformation together. This step entails a rigid translation and rotation for the relative position and orientation of the two parts (3’,4,5,...; c’,d,e,...) and (3,2,1,...; c,b,a,...), where beads 1, 5, c, e in this representation for the rest of the conformation are bonded, respectively, to beads 2, 4, b, d. Clearly, only one degree of freedom is left for this last step—we are free to choose the rotation angle \( \omega_{3c} \) between the two parts of the conformation (Fig. 22, right, last step of \( T_2 \)). To enhance acceptance probability, we allow variation centered around a reasonable choice for \( \omega_{3c} \) that tend to minimize excessive local twisting and bending associated with high energetic penalties. To this end, we define \( \omega_{3c}^{(0)} \) as the average of four angles: The projections of \( \angle 3’45 \) (the angle between \( r_{3’4} \) and \( r_{45} \), other angles are similarly defined) and \( \angle c’de \) onto a plane perpendicular to \( r_{3d} \) and the projections of \( \angle 123 \) and \( \angle abc \) onto a plane perpendicular to \( r_{2b} \). The angle to be varied, \( \omega_{3c} \), is defined, after the fusion procedure, as the average of the projections of \( \angle 3’45 \) and \( \angle c’de \) onto a plane perpendicular to \( r_{3c} \). The angle \( \omega_{3c} \) is randomly selected with uniform probability,
\[
    \omega_{3c} \in [\omega_{3c}^{(0)} - \Delta \omega_{3c}, \omega_{3c}^{(0)} + \Delta \omega_{3c}]
\]
within a range defined by the simulation parameter \( \Delta \omega_{3c} \). The resulting conformation, with two more beads than the conformation at the beginning of the \( T_2 \) move, is now ready for further consideration.

3. Reversibility of \( T_{22} \) acceptance/rejection criteria

In the description of our algorithm thus far, we have implemented in reverse order in the \( T_2 \) move all the acceptance/rejection tests introduced for the \( T_2 \) move. Accordingly, it is clear that there is always a \( T_2 \) move that effects the reverse transformation of a \( T_2 \) move. On the other hand, as discussed at the end of the \( T_2 \) section, for a putative conformation we obtain from the above description for the \( T_2 \) transformation, there is no guarantee that there is a \( T_2 \) move that effects the reverse transformation. This uncertainty arises because such a reverse transformation may require choices for \( \gamma_1, \gamma_2, \alpha_1 - \alpha_2 \), and \( \omega_{3c} \), that lie outside the range prescribed by Eqs. (A22)–(A25) and (A27).

Therefore, every putative conformation obtained from the \( T_2 \) steps described above is subject to a final reversibility test, as follows, and we view this final test as an integral part of the \( T_2 \) acceptance/rejection criterion. The starting point of the reversibility test is the coordinates for beads (2, 3, b, c) and (3’,4, c’,d) after RMSD minimization. This information allows for immediate determination of whether the deviation of \( R_{3’4c} \) from \( R_{2b} \) lies within the range prescribed by Eq. (A22). The values for \( \gamma_1, \gamma_2, \alpha_1 - \alpha_2 \) are then computed from the coordinates. Whether these values lie within the range allowed by Eqs. (A23)–(A25) is checked. Finally, an \( \omega_{3c}^{(0)} \) value is computed from the coordinates. We compare this \( \omega_{3c}^{(0)} \) value against the \( \omega_{3c} \) value in the conformation before the \( T_2 \) transformation to check whether the condition in Eq. (A27) is satisfied. The putative \( T_{22} \)-transformed conformation is rejected if it fails any one of the above tests because such a failure implies that there is no reverse \( T_2 \) transformation for the putative \( T_{22} \) move. In adherence to microreversibility, the \( T_{22} \)-transformed conformation is further considered only if it passes all the above tests.

4. Detailed balance and \( T_{22} \leftrightarrow T_{22} \) Jacobian factor

Because the above-described \( T_2 \) and \( T_2 \) steps involve different variables, to ensure detailed balance of the transition probabilities, Jacobian weighting is required. A general discussion of Jacobian weighting was given in Sec. 1.7 of Green.126 for a recent application, see, e.g., Ref. 64. Here, we outline the derivation of the Jacobian factor and how it is computed in our simulations.

Recall that in effecting a length-subtracting \( T_2 \) move, the only parameter we are free to choose, within a prescribed
range, is $\Delta r_{3c}$ [see Eq. (A1)]. Therefore, the differential volume element of choosing a particular transition, normalized by the allowed range of variation, of the $T_{2}$ transition rate from the space of $n$-bead conformations to the space of $(n - 2)$-bead conformations [from $n$ to $(n - 2)$ space in short] is given by

$$B(n \rightarrow n - 2) = \frac{1}{2\Delta r_{3c}^2}d\Delta r_{3c}. \quad (A28)$$

For the length-adding $T_{2}$ move, there are seven degrees of freedom we can choose in $\mathbf{R}_{3c}^{(0)}, \mathbf{\gamma}_{1}, \mathbf{\gamma}_{2}, \mathbf{a}_{1} - \mathbf{a}_{2}$, and $\mathbf{w}_{3c}$. It follows that the corresponding differential volume element of the $T_{2}$ transition rate from the space of $(n - 2)$-bead conformations to the space of $n$-bead conformations, normalized by the ranges in Eqs. (A22)–(A25) and (A27), is given by

$$B(n - 2 \rightarrow n) = \frac{1}{8[\Delta \mathbf{R}_{3c}^{(0)}]^3[\Delta \mathbf{\gamma}_{1}^{(0)}]^2\Delta \alpha_{0}^{(0)}\Delta \alpha_{2}^{(0)}} \times d\Delta \mathbf{R}_{3c}^{(0)}d\mathbf{\gamma}_{1}d\mathbf{\gamma}_{2}d(\alpha_{1} - a_{2})d\alpha_{3c}. \quad (A29)$$

where $\Delta \mathbf{R}_{3c}^{(0)} = \mathbf{R}_{3c}^{(0)} - \mathbf{R}_{2b}$ is the deviation of the $\mathbf{R}_{3c}^{(0)}$ position in a given coordinate system; $\Delta \mathbf{R}_{3c}^{(0)}$ represents three independent variables in the step of growing two beads from an $n-2$ conformation under a minimum-RMSD constraint [see Eq. (A22)]. Note that the number of degrees of freedom of $T_{2}$ differs from that of $T_{2}$ by 6, as it should, because the addition of two beads introduces six extra degrees of freedom.

We now consider the population densities in the $(n-2)$ and $n$ spaces. The statistical weight $\rho(n-2)$ of any $(n-2)$ conformation is a product of its Boltzmann factor and the differential volume element for its chain geometry. For our purpose, the geometric factor for a complete $(n-2)$ conformation containing beads 2, 4, $b$, $d$, as in the bottom box of Fig. 22 may be expressed as a product of the following. (i) First are two geometric factors for the partial conformations encompassing two sets of beads $(2, 1; b, a, \ldots)$ and $(4, 5, \ldots; d, e, \ldots)$. We denote the product of these two factors collectively as $\rho_{\text{test}}$ (stands for “the rest of the conformation”). (ii) Second is a volume element for joining the two parts together to form a complete conformation. The operation of rigidly joining the two partial conformations $(2-4$ and $b-d)$ entails a translation and a rotation, which may be expressed in terms of a translation vector $\mathbf{X}_{0}$ and the quaternion variables (see above) in conjunction with a volume element factor $4/\sqrt{1 - |\mathbf{q}|^2}$ readily derived by changing the integration variables from the usual rotation angles to the $\mathbf{q}$ variables. Taken together, these analyses lead to

$$\rho(n - 2) = e^{-E_{n-2}/k_{B}T}\rho_{\text{test}}\frac{4}{\sqrt{1 - |\mathbf{q}|^2}}dq_{1}dq_{2}dq_{3}d\mathbf{X}_{0}$$

$$= e^{-E_{n-2}/k_{B}T}\rho_{\text{test}}\frac{4}{\sqrt{1 - |\mathbf{q}|^2}}d\mathbf{X}_{0}, \quad (A30)$$

where $E_{n-2}$ is the energy of the entire $(n-2)$-conformation. Note that the $\mathbf{X}_{0}$ and $q$’s in Eq. (A30) are general; they can take any value and do not necessarily correspond to a particular minimum-RMSD requirement. A similar geometric consideration leads to the $n$-space population density

$$\rho(n) = e^{-E_{n}/k_{B}T}\rho_{\text{test}}\frac{1}{2\Delta r_{3c}^2}d\Delta r_{3c}d\mathbf{X}_{3c}d\mathbf{\gamma}_{3c}d\mathbf{\gamma}_{4c}d(\alpha_{1} - \alpha_{2})d\alpha_{3c}. \quad (A31)$$

with the same $\rho_{\text{test}}$, where $E_{n}$ is the energy of the entire $n$-conformation. Note that the $\mathbf{R}_{3c}$, here is a variable for defining an $n$-conformation in general; thus, $d\mathbf{R}_{3c}$ is not identical to the $d\mathbf{R}_{3c}$ in Eq. (A29) above because $\Delta \mathbf{R}_{3c}$ operates under a minimum-RMSD constraint. Equation (A31) is derived from the fact that an $n$-conformation may be obtained by first growing beads 3, $c, 3'$, $c'$ and then fusing 3 with 3' and $c$ with $c'$. Because this procedure requires $\Delta r_{3c}$ $= r_{3c}$, the number of degrees of freedom in the above volume element is one fewer than that of $d\mathbf{r}_{3c}d\mathbf{R}_{3c}d\mathbf{\gamma}_{3c}$. Equation (A31) involves the differential of the unit vector $\mathbf{e}_{3c}$ along the direction of the vector $\mathbf{r}_{3c}$, but not its magnitude $r_{3c}$. To emphasize that $r_{3c}$ and $r_{3c}'$ have equal length in the upper expression, we rewrite $r_{3c}$ with an $(e)$ superscript, viz., $r_{3c}^{(e)}$, and recast $d\mathbf{r}_{3c}^e$ $= r_{3c}^{(e)}d\mathbf{r}_{3c}^e$ in the above equation as $(r_{3c}^{(e)})^{2}d\mathbf{e}_{3c}^e$.

It follows from Eqs. (A28) and (A31) that the volume element for the flux density from $n$ to $(n-2)$ space is given by

$$\rho(n)B(n \rightarrow n - 2) = e^{-E_{n}/k_{B}T}\rho_{\text{test}}\frac{1}{2\Delta r_{3c}^2}[(r_{3c}^{(e)})^{2}d\mathbf{r}_{3c}^e]$$

$$\times d\mathbf{e}_{3c}^e d\mathbf{R}_{3c}^e d\mathbf{\gamma}_{3c}^e d(\alpha_{1} - \alpha_{2})d\alpha_{3c}^e. \quad (A32)$$

Because the $\Delta r_{3c}$ variable from $B(n \rightarrow n - 2)$ allows for the difference between $r_{3c}$ and $r_{3c}'$, we may combine the effects of $d\Delta r_{3c}$ and $d\mathbf{e}_{3c}^e$ to obtain a more useful compact expression by changing variables from $(r_{3c}^{(e)}, \Delta \mathbf{r}_{3c})$ (in square brackets in the above equation) to the two independent variables $r_{3c}$ and $r_{3c}'$. We labeled them with a $(u)$ superscript, viz., $(r_{3c}^{(u)}, r_{3c}'^{(u)})$, to emphasize that they may take unequal values. From the relations $r_{3c}^{(u)} = r_{3c}^{(e)} + \Delta r_{3c}$ and $r_{3c}'^{(u)} = r_{3c}'^{(e)} - \Delta r_{3c}$ [see Eq. (A1)], the Jacobian $|\partial(r_{3c}^{(u)}, r_{3c}'^{(u)})/\partial(r_{3c}^{(e)}, \Delta \mathbf{r}_{3c})| = 2$; hence, $d\mathbf{r}_{3c}^{(u)}d\mathbf{r}_{3c}'^{(u)} = (1/2)d\mathbf{r}_{3c}^{(e)}d\mathbf{r}_{3c}'^{(e)}$. Since the angular integrations are not affected by this change of variables, $d\mathbf{e}_{3c}^{(u)}d\mathbf{e}_{3c}'^{(u)} = d\mathbf{e}_{3c}^{(e)}d\mathbf{e}_{3c}'^{(e)}$, $(r_{3c}^{(e)})^{2}$. Equation (A32) is equivalent to

$$\rho(n)B(n \rightarrow n - 2) = e^{-E_{n}/k_{B}T}\rho_{\text{test}}\frac{1}{4\Delta r_{3c}^2}[(r_{3c}^{(u)})^{2}d\mathbf{r}_{3c}^{(u)}]$$

$$\times d\mathbf{R}_{3c}^e d\mathbf{R}_{3c}'^e d\mathbf{\gamma}_{3c}^e d(\alpha_{1} - \alpha_{2})d\alpha_{3c}. \quad (A33)$$

Similarly, the volume element for the flux density from $(n - 2)$ to $n$ space follows from Eqs. (A29) and (A30). In certain applications, it would be desirable to have the capability to tune the relative sampling sizes for the $n$ and $(n-2)$ spaces. To this end, we introduce an additional adjustable parameter $\rho_{n-2}^{(0)}$ to the flux density.
\[
\rho(n-2)B(n-2 \to n) \\
= e^{-E_{n-2} + E_T} \rho_{\text{real}}B_{n-2} \frac{4}{\sqrt{1-|q|^2}} dq dX_0 \frac{1}{8|\Delta R_{3',c'}|^2 (|\Delta y_{0'}|^2)} \\
\times \left. \frac{1}{2\alpha(0)} \frac{1}{2\Delta \omega_3} d\Delta R_{3',c'} d\gamma_1 d\gamma_2 d(\alpha_1 - \alpha_2) d\omega_{3c}. \right)
\]

(A34)

A proper evaluation of the generalized Metropolis acceptance criterion in Eq. (52) in the main text requires the numerator and denominator of the forward and reverse flux ratio,

\[
\frac{\rho(n-2)B(n-2 \to n)}{\rho(n)B(n \to n-2)},
\]

(A35)

to be expressed in terms of the same differential volume element. As it stands, however, the differential volume elements in Eqs. (A33) and (A34) are different except the \(d\omega_{3c} \) factor that appears in both. To put them on equal footing, we change the variables in Eq. (A29) to that of Eq. (A33) by introducing a Jacobian factor,

\[
dq dX_0 d\Delta R_{3',c'} d\gamma_1 d\gamma_2 d(\alpha_1 - \alpha_2)
\]

= \[
\left| \frac{\partial(q, X_0, \Delta R_{3',c'}, \gamma_1, \gamma_2, \alpha_1 - \alpha_2)}{\partial(R_{3c}, R_{3',c'}, r_{3c}, r_{3',c'})} \right| dR_{3c} dR_{3',c'} dr_{3c} dr_{3',c'},
\]

(A36)

where for notational simplicity we have dropped the \((u)\) superscript from \(r_{3u} \) and \(R_{3u',c'} \) from Eq. (A33) as they are understood to be independent. It follows from Eqs. (A33) and (A34), after cancellation of their \(\rho_{\text{real}} \) factors, that

\[
\frac{\rho(n-2)B(n-2 \to n)}{\rho(n)B(n \to n-2)}
\]

= \[
e^{-E_{n-2} - E_T} \rho_{n-2}^{(0)} \frac{4}{\sqrt{1-|q|^2}} dq dX_0 \frac{1}{8|\Delta R_{3',c'}|^2 (|\Delta y_{0'}|^2)} \\
\times \left. \frac{1}{2\alpha(0)} \frac{1}{2\Delta \omega_3} d\Delta R_{3',c'} d\gamma_1 d\gamma_2 d(\alpha_1 - \alpha_2) d\omega_{3c}. \right)
\]

(A37)

The variables in the numerator of the above T_{n,2} Jacobian describe an \((n-2)\)- to \(n\)-space \(T_2\) transformation [Eq. (A34)] that results in a set of coordinates \(R_{3c}, R_{3',c'}, r_{3c}, \) and \(r_{3',c'}\) for an \(n\)-conformation before \(r_{3c}\) is set equal to \(r_{3',c'}\). Therefore, the Jacobian may be evaluated by determining the changes in the variables in the numerator of the Jacobian as a result of infinitesimal variations \(\delta R_{3c}, \delta R_{3',c'}, \delta r_{3c}, \) and \(\delta r_{3',c'}\) of the variables in the denominator of the Jacobian. Given these variations, the corresponding variations of the coordinates for beads 2, 3, 4, 3', 4', 5, 6 are:

\[
\delta r_3 = \delta R_{3c} - \delta r_{3c}/2.
\]

(A38)

\[
\delta r_3' = \delta R_{3',c'} + \delta r_{3',c'}/2.
\]

(A39)

\[
\delta r_3 = \delta R_{3',c'} - \delta r_{3',c'}/2.
\]

(A40)

\[
\delta r_3' = \delta R_{3',c'} + \delta r_{3',c'}/2,
\]

(A41)

and \(\delta r_3 = \delta r_3' = \delta r_{3c} = \delta r_{3'd} = 0\). These coordinate changes affect the minimum-RMSD transformation for optimally superposing \((2,3,b,c)\) and \((3',4,c',d)\) for \(T_2\): The \(\delta r\) coordinate changes in Eqs. (A38)–(A41) modify the translation vector \(X_0\) needed to bring the centroids of \((2,3,b,c)\) and \((3',4,c',d)\) together; the \(\delta r\)’s also modify the matrix \(F\) in Eq. (A3), which in turn changes the eigenvector \(q\) for the maximum eigenvector [Eq. (A6)]. These changes in \(X_0\) and \(q\) are straightforward to determine analytically as they are linear in the \(\delta r\)’s. Since the variations in \(X_0\) and \(q\) entail a varied minimum-RMSD transformation for \((2,3,b,c)\) and \((3',4,c',d)\), it leads also to changes in the \(T_2\) vector parameters \(R_{3',c'}, R_{2b}\) (and therefore \(\Delta R_{3',c'}\) \(R_{3c}, R_{2a}, r_{2b}, r_{2d}\) [and therefore \(K\) in Eq. (A17)], which are defined after the minimum-RMSD transformation, though the magnitudes \(r_{2b}\) and \(r_{2d}\) remain unchanged. After these changes are determined, the changes in \(\gamma_1, \gamma_2, \) and \(\alpha_1 - \alpha_2\) as a result of the \(\delta r\)’s in Eqs. (A38)–(A41) are readily deduced from Eqs. (A8), (A9), and (A19)–(A21). Finally, once all \(12 \times 12\) elements of the Jacobian matrix, \(\partial X_0^{(0)}/\partial R_{3c}, \partial X_0^{(0)}/\partial R_{3',c'}, \partial X_0^{(0)}/\partial r_{3c}, \partial X_0^{(0)}/\partial r_{3',c'}, \) etc., have been obtained in this manner, the Jacobian is calculated using standard computational method for matrix determinants.

5. Parameter choices and computational efficiency

As studies of MC moves that change the size of the system are relatively rare, here we discuss some general properties of the \(T_{n,2}\) moves, highlighting features that are special to this class of moves. The \(T_{n,2}\) move set is continuous in the sense that the choices of its parameters \((\Delta \alpha, \Delta y, \ldots)\) are continuous. We are also free to tune the ranges of variation for these parameters \((\Delta \alpha, \Delta y, \ldots)\) to enhance performance. However, because every \(T_{n,2}\) move either increases or decreases the chain length by two units, the \(T_{n,2}\) moves are separated from the identity transformation, i.e., they cannot be evolved into the identity by any continuous variation of the simulation parameters, unlike conventional transformations such as single-bead perturbation or rotations that preserve the chain length. As a result, we may optimize the simulation parameters for performance (e.g., to achieve as high an acceptance probability \(P_{\text{acc}}\) as possible for a given system) but, in general, we may not be able to achieve an \(a \ priori\) acceptance probability such as \(P_{\text{acc}}=0.5\).

Figure 23 shows how the performance of our \(T_{n,2}\) moves depends on the simulation parameter for an \(n=400, \sigma=-0.06\) wormlike supercoiled chain (ring polymer). Based on a common set of simulation range parameters \((\Delta \alpha(0) = 1.5 \text{ nm}, \Delta y(0) = 1.5 \text{ nm}, \Delta \omega_3(0) = 0.5, \Delta R_{3c}(0) = 2.0 \text{ nm}, \) and \(\Delta R_{3',c'}(0) = 1.0\) nm), we investigate the effect of each simulation range parameter by changing its value while keeping the others unchanged, and only allow moves between chain lengths \(n\) and \(n-2\) (Fig. 23, top panels). The value of \(r_{n-2}\) is chosen to be \(\approx 1760\) so that the population of chains with \(n=400\) is similar to that of chains with \(n-2=398\). For the set of simulation parameter values we explore in this example, the acceptance probability \(P_{\text{acc}}\) is quite low at \(\sim 1\%\). For all the
simulation range parameters, $P_{\text{acc}}$ increases from zero with increasing range, reaches a maximum value, and then decreases with further increase of the range parameter. For this system, an acceptance probability of about 1.5% is achieved when all the simulation range parameters adopt their respective optimized values. For ring polymers with less supercoiling, (smaller $|\sigma|$), acceptance probabilities are higher (data not shown).

After the simulation range parameters are specified, the transformation parameters may be generated to construct an attempted move. They can also be calculated from a constructed attempted move in reversibility checks, as discussed above. Take $\Delta \alpha$ as an example. For $T_2$, $\Delta \alpha$ is randomly generated in the range of $[-\Delta \alpha^{(0)}, \Delta \alpha^{(0)}]$ to construct an attempted $T_2$ move. For $T_{\text{c}}$, after the transformation is constructed (with a randomly generated $\Delta r_{3c}$), $\Delta \alpha$ can be calculated from the putative $T_{\text{c}}$-transformed conformation. As described above, if the calculated $\Delta \alpha$ value is outside the range $[-\Delta \alpha^{(0)}, \Delta \alpha^{(0)}]$, the putative conformation is rejected because the corresponding inverse transformation $T_2$ does not exist. Thus, $\Delta \alpha$ is a free parameter in $T_2$ and a calculated (constrained) parameter in $T_{\text{c}}$. The acceptance probabilities for different $\Delta \alpha$ values are different. The lower panels of Fig. 23 give the acceptance histograms of $\Delta \alpha$ and other parameters, for a simulation with optimized simulation range parameters determined from the upper panels of the same figure. In every case, the histogram decreases monotonically with the values of the transformation parameters. Unlike MC moves that can be connected continuously to the identity transformation, narrowing the distribution width of the $T_{\text{c}}$ range parameters does not necessarily enhance acceptance probabilities because the probability of accepting an attempted transformation depends not only on its parameters ($\Delta \alpha$, etc.) but also on the distribution width of the parameters $[\Delta \alpha^{(0)}$, etc.; see Eq. (A34)]. Moreover, increasing the other range parameters $\Delta r_c$, RMSD$_c$, and $\Delta R_{3c}^{(c)}$ only leads to small increases in $T_{\text{c}}$ acceptance rate that most likely are not computationally advantageous because energy would then be calculated more frequently. Using an $n=400$, $\sigma=0.06$ model as test case, we have compared the $T_{\text{c}}$ acceptance rate in a simulation using the original $\Delta \alpha^{(0)}$, RMSD$_c$, and $\Delta R_{3c}^{(c)}$ values listed above against the acceptance rate in a modified simulation using values ten times larger for each of these range parameters. We found that the $T_{\text{c}}$ acceptance rate (1.9%) in the modified simulation was only slightly higher than that (1.4%) in the original simulation. Apparently, the low acceptance rate for $T_{\text{c}}$ is mainly a consequence of the intrinsic difficulty in achieving an energetically favorable supercoiled wormlike chain conformation after the addition or deletion of two beads.
The equilibrium properties of the simulated system are expected to be independent of the parametrization of the MC moves. We have confirmed that this requirement is satisfied by the present \( T^2 \), move set by verifying that the population ratio between chains of lengths \( n-2 \) and \( n \) is well described by a constant, independent of the values of a set of simulation range parameters we tested. In our algorithm, an extra parameter \( \rho_{n-2}^{(0)} \) is introduced to adjust the relative populations of chains with lengths \( n-2 \) and \( n \) [Eq. (A34)]. Figure 24(a) shows more than four orders of magnitude variation of the simulated \( (n-2) \) versus \( n \) population ratio with different values of \( \rho_{n-2}^{(0)} \). The perfect logarithmic correlation (with essentially unity slope) confirms that the population of chains with length \( n-2 \) is proportional to \( \rho_{n-2}^{(0)} \), as it should, by construction. Figure 24(b) shows that the \( (n-2) \) versus \( n \) population ratio depends also on the potential energy of the system by providing its variation with \( \Delta L_k \), the linking number difference with respect to the equilibrium value. The result shows that \( \ln(P(n-2)/P(n)) \) decreases with increasing \( \Delta L_k \). Apparently, this trend follows from the fact that for the same given \( L_k \), a shorter loop \( (n-2) \) would entail a more unfavorable twisting energy than a longer loop \( n \). Consistent with the quadratic form of the twisting energy in the model, the dependence of \( \ln[P(n-2)/P(n)] \) on \( \Delta L_k \) in Fig. 24(b) is well fitted by a quadratic curve.

Figure 24. The ratio between the populations, \( P(n-2) \) and \( P(n) \), respectively, of chains with lengths \( n-2 \) and \( n \) as functions of simulation parameters. The simulation conditions are identical to that for the lower panels of Fig. 23 except for the variable \( \rho_{n-2}^{(0)} \) values in (a). The straight lines in (a) and the quadratic curve in (b) are fits to the data points from MC simulations.
Efficient chain moves for DNA


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Some of the present wormlike chain model results were simulated using an alternate algorithm with the same $s_{ij}$ for $0 \leq d_{ij} \leq 1$ but a different definition of $s_{ij}$ when either $v$ or $w$ or both is < $0$ or >1. Instead of the expressions for the five cases (i)-(v) enumerated in the text, the alternate algorithm sets $v=0$ if $v<0$, set $w=0$ if $w<0$, set $v=1$ if $v>1$, and set $w=1$ if $w>1$. A consequence of such a scheme is that the resulting $s_{ij}$ may not be the shortest distance between the two bonds. Nonetheless, the effects of this difference on the simulation results are minimal because the $E_{sim}$ term for a pair of bonds contributes significantly only when the two bonds are close to each other, mostly in relative positions and orientations corresponding to the $0 \leq v, w \leq 1$ condition. We have conducted long simulations comprising of $8.2 \times 10^5$ MC steps for an $n=400$, $\sigma=0.06$ model using both the alternate algorithm and the one described in the text. The difference in results obtained from the two algorithms is approximately indiscernible.

There is a typographical error in the equation at the bottom of p. 165 of Ref. 56 for the generalized cubic lattice reflection in three or more dimensions. The transformation for the component along the third and higher axes ($y$ in their notation) should be given instead by our present Eq. (22).


H. S. Chan and K. A. Dill, Macromolecules 22, 4559 (1989); see also a correction noted on p. 64 (Footnote No. 47) in Conformations and Forces in Protein Folding, edited by T. B. Nall and K. A. Dill (American Association for the Advancement of Science, Washington, DC, 1991).


