Evaluating changes of writhe in computer simulations of supercoiled DNA

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We compute changes in the writhe of a polygonal space curve when one of the vertices is displaced. The resulting expressions can be used in simulations of supercoiled DNA. For Brownian dynamics simulations, the expressions can be used to eliminate the explicit twisting degree of freedom. For Monte Carlo simulations, they can be used in fast local moves. Preliminary Monte Carlo simulations using only such fast local moves show that these can be used to efficiently simulate small DNA supercoils. © *2005 American Institute of Physics*. [DOI: 10.1063/1.1846052]

INTRODUCTION

Supercoiling plays an important role in determining the large-scale structure of DNA in both prokaryotic and eukaryotic cells,[1] and a lot of effort has gone into developing algorithms for Monte Carlo,[2–5] Brownian Dynamics,[6,7] and Molecular Dynamics[8] simulations of supercoiled DNA. At a mesoscopic level, the DNA chain can be viewed as a ribbon $\{\mathbf{r}(s),\mathbf{n}(s)\}$ consisting of a spacecurve $\mathbf{r}(s)$ and a local normal $\mathbf{n}(s)$ pointing, for example, in the direction of the major groove. Indeed, many simulations of supercoiled DNA use some form of a discretized ribbon to represent the DNA chain.[4–8]

If the fluctuations in local twist angle are assumed to be Gaussian with zero mean, they can be integrated out (as described in detail by Gebe *et al.*[3]), and one can use a description in terms of a space curve $\mathbf{r}(s)$ only. This does require that the fluctuations in local twist angle do not couple to any other degrees of freedom, but this is the case in many models. After integrating out Gaussian fluctuations of local twist angles, the expression for the twist elastic energy is

$$\frac{H_{\text{twist}}}{kT}=\frac{2\pi^2 C}{L}(\Delta Tw)^2, \tag{1}$$

where $C\approx 75$ nm is the DNA twist persistence length, L is the contour length of the closed DNA molecule, and kT is thermal energy. At a fixed excess linking number ΔLk, the excess twist of the chain can be computed from White's theorem,

$$\Delta Lk=\Delta Tw+\mathrm{Wr}. \tag{2}$$

The writhe Wr is a function of the space curve $\mathbf{r}(s)$ only. A description in terms of a space curve $\mathbf{r}(s)$ only is convenient whenever one is not interested in the local twisting dynamics, or in the inhomogeneities of the distribution of the twist along the chain, and has been used in a number of Monte Carlo simulations of supercoiled DNA.[2,3]

However, numerically evaluating the writhe of a polygonal spacecurve is a slow operation. For a closed space curve of N vertices, most methods[9] give computation times $O(N^2)$. Recently,[10] algorithms have been developed with computation times $O(N^{1.6})$. In computer simulations, one often needs to evaluate small changes of Wr rather than absolute values. Evaluating small changes of Wr, or evaluating only the fractional part of Wr is known to be fast [$O(N)$ as compared to $O(N^2)$] but as far as we know, this has not yet been exploited in computer simulations of supercoiled DNA. In this paper we derive explicit expressions that can be used in fast evaluations of changes of Wr for closed polygons. We show how to use these expressions in both Brownian Dynamics and Monte Carlo simulations of supercoiled DNA.

Fuller[11] has given two formulas that can in principle be used for fast evaluation of changes of Wr. Consider a closed, nonintersecting space-curve with unit tangent $\mathbf{T}(t)$. The unit tangents trace out a closed curve on the unit sphere called the tangent indicatrix. The fractional part of Wr is related to the spherical area (or solid angle) A enclosed by the tangent indicatrix:

$$1+\mathrm{Wr}=\frac{1}{2\pi}A \bmod 2. \tag{3}$$

The enclosed area is only determined up to multiples of 4π, whence the modulo 2. A related formula gives an explicit expression for the difference in Wr of two space curves 1 and 2, with unit tangents $\mathbf{T}_1(t)$ and $\mathbf{T}_2(t)$,

$$\Delta\mathrm{Wr}=\frac{1}{2\pi}\int dt\frac{\mathbf{T}_1(t)\times\mathbf{T}_2(t)}{1+\mathbf{T}_1(t)\cdot\mathbf{T}_2(t)}\frac{d}{dt}(\mathbf{T}_1(t)+\mathbf{T}_2(t)). \tag{4}$$

The geometrical interpretation of this equation is that the right-hand side represents the spherical area of the ribbon traced out by $\mathbf{T}_1(t)$ and $\mathbf{T}_2(t)$ on the unit sphere. For the expression to be valid there should be a family of nonintersecting curves $\mathbf{T}_\lambda(t)$ for $\lambda=1,\ldots,2$ that interpolates between $\mathbf{T}_1(t)$ and $\mathbf{T}_2(t)$ without $\mathbf{T}_1(t)$ and $\mathbf{T}_\lambda(t)$ ever being oppositely directed.

It is not immediately clear how to use Fuller's formulas to compute changes of Wr for the N-sided polygons typically encountered in simulations of supercoiled DNA. In this paper we focus on a simple case: the change of Wr of an N-sided polygon when one of its vertices is displaced. Starting with Fullers equations, we first derive a simple closed expression for the case of infinitesimal displacements. This expression could, for example, be used in Brownian Dynam-

ics simulations of supercoiled DNA, to eliminate the explicit twisting degree of freedom. Then we show how to compute changes of Wr for finite displacements. This is useful in Monte Carlo simulations of supercoiled DNA. To illustrate this latter point, we present some preliminary results of Monte Carlo simulations of a small closed DNA molecule, using a simple algorithm that exploits fast evaluation of changes in writhe.

INFINITESIMAL DISPLACEMENTS AND BROWNIAN DYNAMICS

Consider a circularly closed DNA molecule with excess linking number ΔLk, that we model in terms of a polygonal space curve with N vertices $\mathbf{r}_1,\ldots,\mathbf{r}_N$ and $\mathbf{r}_{N+1}=\mathbf{r}_1$. We assume Gaussian fluctuations of local twist angles have been integrated out, such that the twist elastic energy is given by Eq. (1). Bond vectors $\mathbf{s}_i$ and unit tangents $\mathbf{t}_i$ are defined as

$$\begin{aligned}\mathbf{s}_i &= \mathbf{r}_{i+1}-\mathbf{r}_i,\\ \mathbf{t}_i &= \mathbf{s}_i/|\mathbf{s}_i|.\end{aligned} \tag{5}$$

For Brownian dynamics simulations, we need expressions for the forces on each of the vertices. Calculating forces due to bending, bond stretching and nonbonded interactions is straightforward, but what about forces due to the twist elastic energy given by Eq. (1)? Since the explicit twisting degree of freedom has been integrated out, we prefer to use the term "writhing force" for the forces due to the elastic energy given by Eq. (1). The excess twist is $\Delta\mathrm{Tw}=\Delta Lk-\mathrm{Wr}$, whence the writhing force on vertex n is

$$\mathbf{f}^{(n)}_{\mathrm{writhe}} = -\frac{\partial H_{\mathrm{twist}}}{\partial \mathbf{r}_n} = \frac{4\pi^2 C}{L}(\Delta Lk-\mathrm{Wr})\frac{\partial \mathrm{Wr}}{\partial \mathbf{r}_n}. \tag{6}$$

Clearly we need to evaluate the derivative of Wr of a closed polygonal space curve with respect to the position of the vertices.

Starting from Fuller's expression (4), Aldinger *et al.*[12] have derived an expression for the rate of change of Wr of a closed curve $\mathbf{R}(t,\lambda), t=0,\ldots,1$ that depends on some deformation parameter λ,

$$\frac{\partial \mathrm{Wr}[\mathbf{R}(t,\lambda)]}{\partial\lambda} = -\frac{1}{2\pi}\int_0^1 dt\left(\frac{\partial \mathbf{T}(t,\lambda)}{\partial\lambda}\times\mathbf{T}(t,\lambda)\right)\cdot\frac{\partial\mathbf{T}(t,\lambda)}{\partial t}, \tag{7}$$

where we have introduced the unit tangent

$$\mathbf{T}(t,\lambda) = \frac{\partial\mathbf{R}(t,\lambda)/\partial t}{|\partial\mathbf{R}(t,\lambda)/\partial t|}. \tag{8}$$

In order to use this expression we consider a deformed polygon $\{\mathbf{r}_1,\ldots,\mathbf{r}_n(\lambda),\ldots,\mathbf{r}_N\}$ in which the position of the nth vertex has been displaced along some direction ξ,

$$\mathbf{r}_n(\lambda) = \mathbf{r}_n + \lambda\xi. \tag{9}$$

The derivative of interest is

$$\frac{\partial \mathrm{Wr}[\mathbf{r}_1,\ldots,\mathbf{r}_N]}{\partial\mathbf{r}_n}\cdot\xi = \left.\frac{\partial \mathrm{Wr}[\mathbf{r}_1,\ldots,\mathbf{r}_n(\lambda),\ldots,\mathbf{r}_N]}{\partial\lambda}\right|_{\lambda=0}. \tag{10}$$

The problem in evaluating this for polygons is that the unit tangents change discontinuously at the vertices. Therefore we introduce a smoothed curve $\mathbf{R}_L(t,\lambda), t=0,\ldots,1$. This is a curve obtained by rounding off the corners of the polygon with vertices $\mathbf{r}_1,\ldots,\mathbf{r}_n(\lambda),\ldots,\mathbf{r}_N$. The parameter L is the distance from the vertices to the position where the rounded sections start and end. As remarked by Cantarella,[13] rounding off the corners leaves the tangent indicatrix unchanged, hence the rounding procedure does not affect Wr. For the continuous and differentiable curve $\mathbf{R}_L(t,\lambda)$, the integrand of Eq. (7) is nonzero only along the rounded corners of the vertices $n-1$, n, and $n+1$. The unit tangents of the rounded corners at the vertices $i=n-1$, n, and $n+1$ are denoted by $\mathbf{T}_i(t,\lambda)$. These start at $t=t_{i,1}$ and end at $t=t_{i,2}$. Expression (7) is invariant under a linear reparametrization of the curve. Without loss of generality we therefore choose $t_{i,1}=-1$ and $t_{i,2}=1$. Using the fact that the rounding procedure does not affect Wr, and applying expression (7) to the curve $\mathbf{R}_L(t,\lambda)$, we then write

$$\begin{aligned}&\frac{\partial}{\partial\lambda}\cdot\mathrm{Wr}[\mathbf{r}_1,\ldots,\mathbf{r}_n(\lambda),\ldots,\mathbf{r}_N]\\ &\quad= -\frac{1}{2\pi}\sum_{i=n-1}^{n+1}\int_{-1}^{1}dt\left(\frac{\partial\mathbf{T}_i(t,\lambda)}{\partial\lambda}\times\mathbf{T}_i(t,\lambda)\right)\cdot\frac{d\mathbf{T}_i(t,\lambda)}{\partial t}.\end{aligned} \tag{11}$$

Next we specify the unit tangents at the rounded corners. For convenience, we write $\mathbf{t}_i(\lambda)$ for all i, keeping in mind that only for $i=n-1,\ldots,n+1$ there is an actual λ dependence. At the boundaries,

$$\mathbf{T}_i(t,\lambda) = \begin{cases}\mathbf{t}_{i-1}(\lambda) & t=-1\\ \mathbf{t}_i(\lambda) & t=1.\end{cases} \tag{12}$$

For intermediate values of t we interpolate linearly,

$$\begin{aligned}\mathbf{T}_i(t,\lambda) &= f_i(t)[\mathbf{t}_i(\lambda)(1+t)+\mathbf{t}_{i-1}(\lambda)(1-t)],\\ f_i(t) &= |\mathbf{t}_i(\lambda)(1+t)+\mathbf{t}_{i-1}(\lambda)(1-t)|^{-1}.\end{aligned} \tag{13}$$

To proceed we expand the unit tangents in powers of λ,

$$\mathbf{T}_i(t,\lambda) = \sum_{k=0}^{\infty}\lambda^k(\alpha_k^i(t)\mathbf{t}_i+\beta_k^i(t)\mathbf{t}_{i-1}+\gamma_k^i(t)\boldsymbol{\xi}). \tag{14}$$

This gives

$$\begin{aligned}&\left.\frac{\partial}{\partial\lambda}\mathrm{Wr}[\mathbf{r}_1,\ldots,\mathbf{r}_n(\lambda),\ldots,\mathbf{r}_N]\right|_{\lambda=0}\\ &\quad=\frac{1}{2\pi}\sum_{i=n-1}^{n+1}\int_{-1}^{1}dt\left(\frac{\partial\alpha_0^i(t)}{\partial t}\beta_0^i(t)-\alpha_0^i(t)\frac{\partial\beta_0^i}{\partial t}\right)\gamma_1^j(t).\end{aligned} \tag{15}$$

The zeroth order coefficients are

$$\alpha_0^i(t) = f_i(t)(1+t),$$
$$\beta_0^i(t) = f_i(t)(1-t). \tag{16}$$

The first order coefficients $\lambda_1^i(t)$ for $i=n-1,\ldots,n+1$ are

$$\gamma_1^{n-1}(t) = \frac{(\mathbf{t}_{n-2}\times\mathbf{t}_{n-1})\cdot\xi}{|\mathbf{s}_{n-1}|} f_{n-1}(t)(1+t),$$
$$\gamma_1^{n}(t) = \frac{(\mathbf{t}_{n-1}\times\mathbf{t}_{n})\cdot\xi}{|\mathbf{s}_{n-1}|} f_{n}(t)(1-t) - \frac{(\mathbf{t}_{n-1}\times\mathbf{t}_{n})\cdot\xi}{|\mathbf{s}_{n}|} \times f_n(t)(1+t), \tag{17}$$
$$\gamma_1^{n+1}(t) = \frac{(\mathbf{t}_{n}\times\mathbf{t}_{n+1})\cdot\xi}{|\mathbf{s}_{n}|} f_{n+1}(t)(1-t).$$

Substituting these into Eq. (11), and performing the integrations gives the final expression for the derivative,

$$2\pi\frac{\partial \mathrm{Wr}[\mathbf{r}_1,\ldots,\mathbf{r}_N]}{\partial \mathbf{r}_n} = \frac{1}{|\mathbf{s}_{n-1}|}\left\{\frac{\mathbf{t}_{n-2}\times\mathbf{t}_{n-1}}{1+\mathbf{t}_{n-2}\cdot\mathbf{t}_{n-1}} + \frac{\mathbf{t}_{n-1}\times\mathbf{t}_{n}}{1+\mathbf{t}_{n-1}\cdot\mathbf{t}_{n}}\right\} + \frac{1}{|\mathbf{s}_{n}|}\left\{\frac{\mathbf{t}_{n-1}\times\mathbf{t}_{n}}{1+\mathbf{t}_{n-1}\cdot\mathbf{t}_{n}} + \frac{\mathbf{t}_{n}\times\mathbf{t}_{n+1}}{1+\mathbf{t}_{n}\cdot\mathbf{t}_{n+1}}\right\}. \tag{18}$$

In practice, the value of Wr should be initialized at the beginning of the simulation, and then updated each time with the calculated changes. Since this may lead to some loss in accuracy over the course of many steps, it is probably wise to now and then recompute the actual Wr using one of the available algorithms.

FINITE DISPLACEMENTS

The above expression may not be accurate enough for steps in Monte Carlo simulations, which may be somewhat larger than in Brownian Dynamics simulations. Therefore, we consider next how to compute changes in Wr due to finite displacements.

While it might be possible to integrate expression (18) for the derivative, or even Fuller's Eq. (4) to arrive at closed expressions for finite displacements, we instead used a procedure inspired by the proof of Aldinger *et al.*[12] of Fuller's Eq. (4). To the tangents $\mathbf{t}_{n-2},\ldots,\mathbf{t}_{n+1}$ we attach unit normals $\mathbf{n}_{n-2},\ldots,\mathbf{n}_{n+1}$ such that $\{\mathbf{r}_i,\mathbf{n}_i\}$ for $i=n-2,\ldots,n+1$ forms a ribbon of zero twist. Translating the nth vertex amounts to deforming this ribbon into a new ribbon $\{\mathbf{r}_i^*,\mathbf{n}_i^*\}$. Since the excess linking number ΔLk is conserved, the change in Wr due to the deformation is

$$\Delta\mathrm{Wr} = -Tw^*, \tag{19}$$

where Tw^* is the twist of the deformed piece of ribbon, which can be easily calculated.[6] This procedure is generally applicable to calculating changes of Wr for arbitrary (but small) deformations of polygons.

Alternatively, one can use Fuller's expression Eq. (5) that relates the fractional part of Wr to the spherical area enclosed by the tangent indicatrix. For example, one can write the spherical area enclosed by the tangent indicatrix of a closed, N-sided polygon as a union of spherical triangles, as done by Starostin[14]

$$\mathrm{Wr} = \frac{1}{2\pi}\sum_{i=1}^{N-2} S(\mathbf{t}_N,\mathbf{t}_n,\mathbf{t}_{n+1}) \bmod 1, \tag{20}$$

where $S(\mathbf{t}_N,\mathbf{t}_n,\mathbf{t}_{n+1})$ is the signed spherical area of the spherical triangle on the unit sphere formed by the unit tangents $\mathbf{t}_k,\mathbf{t}_l,\mathbf{t}_m$,

$$S(\mathbf{t}_N,\mathbf{t}_n,\mathbf{t}_{n+1}) = \mathrm{sign}((\mathbf{t}_k\times\mathbf{t}_l)\cdot\mathbf{t}_m)[\alpha_{klm}+\alpha_{lmk}+\alpha_{mkl}-\pi]$$
$$\cos\alpha_{klm} = \frac{\mathbf{t}_k\cdot\mathbf{t}_m - (\mathbf{t}_k\cdot\mathbf{t}_l)(\mathbf{t}_l\cdot\mathbf{t}_m)}{|\mathbf{t}_k\times t_l||\mathbf{t}_l\times\mathbf{t}_m|}. \tag{21}$$

The change in Wr due to a translation of the nth vertex is

$$2\pi\Delta\,\mathrm{Wr} = S(\mathbf{t}_N,\mathbf{t}_n^*,\mathbf{t}_{n+1}) - S(\mathbf{t}_N,\mathbf{t}_n,\mathbf{t}_{n+1}) + S(\mathbf{t}_N,\mathbf{t}_{n-1}^*,\mathbf{t}_n^*) - S(\mathbf{t}_N,\mathbf{t}_{n-1},\mathbf{t}_n) - S(\mathbf{t}_N,\mathbf{t}_{n-2},\mathbf{t}_{n-1}^*) - S(\mathbf{t}_N,\mathbf{t}_{n-2},\mathbf{t}_{n-1}). \tag{22}$$

The choice of the last vertex is of course arbitrary, and in the above expression $\mathbf{t}_N$ can be replaced by any other tangent $\mathbf{t}_k$, as long as $k\neq n-2,\ldots,n+1$.

We have tested both approaches on supercoiled polygons obtained from preliminary Monte Carlo simulations (see below), and found that both approaches give accurate numerical values for the change in writhe, as compared with values obtained by calculating the actual writhe, using the explicit expressions for the Gauss integral of polygons.[9] Changes in Wr for very small displacements have been used to test the expression for the derivate of Wr.

Note that ΔWr is a purely local function that only depends on the positions of the vertices $\mathbf{r}_{n-2},\ldots,\mathbf{r}_{n+2}$. Both approaches can only compute changes $\Delta\mathrm{Wr}<1$. If larger changes need to be computed, one can subdivide the deformation of the curve into a series of deformations, and apply the above procedures to the smaller deformations.

MONTE CARLO SIMULATIONS

Below we describe preliminary Monte Carlo simulations of supercoiled DNA using a simple algorithm that exploits our procedures for fast evaluation of changes of Wr.

DNA MODEL

The circularly closed DNA chain is modeled as a polygon with vertices $\mathbf{r}_i$, $i=1,\ldots,N$, and $\mathbf{r}_{N+1}=\mathbf{r}_1$. The model Hamiltonian has contributions from bond stretching, bending, twisting, and interaction energy:

$$H = \frac{1}{2}k_s\sum_{i=1}^{N}(|\mathbf{s}_i|-l_b)^2 + \frac{1}{2}k_b\sum_{i=1}^{N}[\arccos(\mathbf{t}_i\cdot\mathbf{t}_{i+1})]^2 + \frac{2\pi^2k_t}{N}(\Delta Lk-\mathrm{Wr})^2 + \sum_{\substack{i=2\\ j<i}}^{N} u(|\mathbf{r}_i-\mathbf{r}_j|), \tag{23}$$

where k_s, k_b, and k_t are elastic constants for, respectively, stretching, bending, and twisting. The isotropic potential of

interaction $u(r)$ of the vertices is taken to be a sum of steric repulsion and longer ranged Debye–Hückel electrostatic repulsion,

$$\frac{u(r)}{k_BT} = \left(\frac{\sigma}{r}\right)^{12} + l_B\alpha^2\frac{\exp(-\kappa r)}{r}, \tag{24}$$

where σ is the DNA steric diameter, α is the strength of an effective Debye–Hückel point charge located on the vertices, $l_B = e^2/\varepsilon kT$ is the Bjerrum length, e is the elementary charge, and ε is the solvent permittivity. The Debye screening length of the electrostatic repulsion is $\kappa^{-1} = (8\pi l_B n_s)^{-1/2}$, where n_s is the concentration of monovalent electrolyte.

MONTE CARLO SIMULATIONS

Trial moves consist simply of a random translation of a randomly chosen vertex i,

$$\mathbf{r}_i \to \mathbf{r}_i + \delta\mathbf{r},$$
$$\delta\mathbf{r} = l_{\text{move}}\begin{pmatrix} \varsigma_x - \frac{1}{2} \\ \varsigma_y - \frac{1}{2} \\ \varsigma_z - \frac{1}{2} \end{pmatrix}, \tag{25}$$

where ς_x, ς_y, and ς_z are uniform deviates. Trial moves are accepted or rejected based on the Metropolis Monte Carlo criterium. We avoid explicit topology checking[15] by choosing l_{move} small enough such that strand crossing occurs with negligible probability. After every trial move we update the value of Wr using the value of ΔWr computed using one of the two methods for finite displacements discussed in the previous section. Both methods worked equally well. As expected, Eq. (18) for infinitesimal displacements was found to be too inaccurate for calculating changes of Wr in Monte Carlo simulations.

After every N_{save} Monte Carlo cycles (attempted trial moves per segment) we save the configuration and recompute the actual value of Wr using the explicit expressions for the Gauss integral of polygons.[9] No significant build up of errors in the value of Wr was detected.

PARAMETER VALUES

The bare DNA diameter is $\sigma = 2.4$ nm, and the Bjerrum length is $l_B = 0.71$ nm. At a concentration of monovalent ions of $n_s = 0.15$ M, the Debye length is $\kappa^{-1} = 0.77$ nm. For a bare DNA charge density of 4.2 elementary charges e per Bjerrum length, the far field of the DNA chain (at $n_s = 0.15$ M, computed from the Poisson–Boltzmann equation) is that of a line charge with $\xi_{\text{eff}} = 7.0$ elementary charges per Bjerrum length. There are $\alpha = \xi_{\text{eff}}\langle l\rangle / l_B$ effective point charges per vertex, where $\langle l\rangle$ is the average bond length. We use $\langle l\rangle = 3.0$ nm, which gives $\alpha = 30$. Mainly due to the electrostatic repulsion, the average bond length $\langle l\rangle$ is larger than l_b. We get $\langle l\rangle = 3.0$ nm and about 7% bond length fluctuations by setting $l_b = 1.8$ nm and $k_s = 25kT$. The bending elastic constant is $k_b \approx kTP/\langle l\rangle = 16.7$, where $P = 50$ nm is the DNA persistence length. The ratio of the twisting and bending elastic constants is taken to be $C/P = k_t/k_b = 1.5$. Configurations are saved every $N_{\text{save}} = 10^5$ MC cycles. We take $N = 150$, which corresponds to a 1.3 kb DNA molecule with a contour length $L = 450$ nm. The excess linking number is taken to be $\Delta Lk = -6$, which corresponds to a superhelical density of $\sigma = \Delta Lk/Lk_0 = -0.047$, where $Lk_0 = N\langle l\rangle/p$ and $p = 3.5$ nm is the helical period of double stranded DNA.

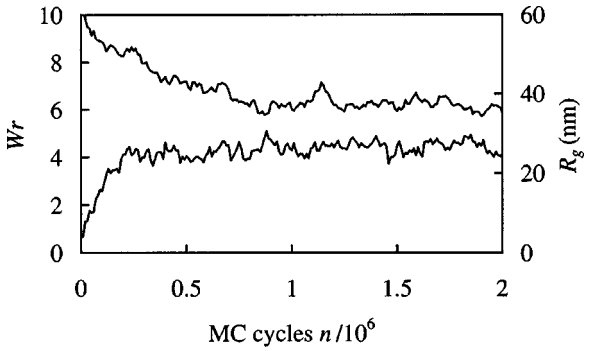

FIG. 1. Writhe (bottom curve, left axis) and radius of gyration (top curve, right axis) as a function of the number of MC cycles n for a simulation starting from a rectangular initial configuration.

RESULTS

We have performed a single long run of $300\cdot10^6$ MC steps, on an equilibrated initial configuration, using the above parameters. As shown in Fig. 1, starting from a rectangular configuration, equilibration takes about $1\cdot10^6$ MC cycles. The equilibrium ratio $\langle \text{Wr}\rangle/Lk$ is mainly a function of the ratio of twisting and bending elastic constants. We find $\langle \text{Wr}\rangle/Lk = 0.71\pm0.01$, which is close to results of previous simulations and to experimental data.[2] The average radius of gyration is $\langle R_g\rangle = 42\pm2$ nm. From the saved configurations we have calculated autocorrelation functions $g(n)$ for configurations separated by n Monte Carlo cycles, for both the writhe and for the radius of gyration, where

$$g(n) = \frac{\langle A(i)A(i+n)\rangle - \langle A(i)\rangle^2}{\langle A^2(i)\rangle - \langle A(i)\rangle^2} \tag{26}$$

and A is either the writhe Wr or the radius of gyration R_g. The autocorrelation curves are shown in Fig. 2. The number of MC cycles in which the correlation decreases by a factor of 2 is very much larger for R_g than for Wr: about $2\cdot10^6$ for

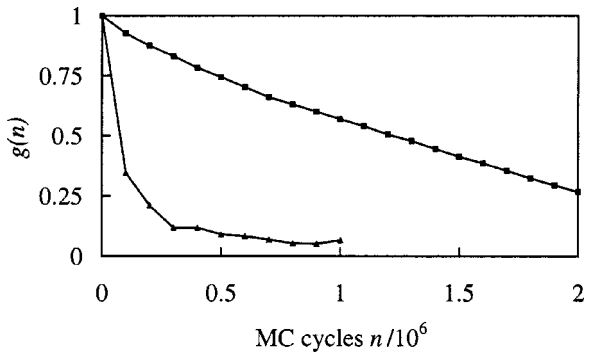

FIG. 2. Autocorrelation $g(n)$ of the Writhe (triangles) and the radius of gyration (squares) as a function of the number of MC cycles n. Computed from a run of $300\cdot10^6$ MC steps, that started from an equilibrated initial configuration.

FIG. 3. A typical configuration of the 1.3 kb model supercoiled DNA molecule as obtained from the Monte Carlo simulations. Vertices are represented as spheres with diameter $\sigma = 2.4$ nm.

R_g as compared to about $0.1 \cdot 10^6$ for Wr. If we want to collect, say, 100 configurations with independent values of the radius of gyration, a typical run should therefore be about $200 \cdot 10^6$ MC cycles. On a desktop PC with an Intel Pentium IV processor of 2.3 GHz, our program executes about $0.44 \cdot 10^6$ MC cycles per hour. A typical configuration of a supercoiled DNA molecule as obtained from the simulations is shown in Fig. 3.

DISCUSSION

The present MC algorithm is useful when simulating small pieces of unbranched supercoiled DNA at a somewhat higher resolution than the 10 nm bond length commonly used in large-scale MC simulations of supercoiled DNA. Simulation time in our algorithm is dominated by evaluating the nonbonded interactions. Implementing techniques such as Verlet neighbor lists or linked lists would further increase the efficiency of the simulations, making the computing time per trial move independent of chain length.

At a more general level, we have shown that it is possible to evaluate changes in writhe without performing time consuming evaluations of the full writhe. Our approach could possibly be extended to the pivot moves that are commonly used in large scale MC simulations of supercoiled DNA. For example, by subdividing such moves in a finite number of smaller deformations, one could calculate changes in Wr for such moves, even if the changes are larger than one. Topology checking could be avoided by making sure that in each of the finite number of deformations, there is no strand crossing. If combined with efficient techniques for evaluating nonbonded interactions, it should then be possible to achieve a computing time per trial move that is independent of chain length for such moves too. Reptation moves—essential for equilibration of branches in large supercoiled DNA molecules—cannot simply be divided into a series of small deformations, hence for these moves, fast evaluation of changes in Writhe cannot be achieved using this strategy.

Although not shown here, it may be anticipated that by eliminating the explicit twisting degree of freedom, one can perform Brownian Dynamics simulations of supercoiled DNA more efficiently. At the very least the simulation algorithm will be much simpler.

[1] A. D. Bates, *DNA Topology* (IRL, Oxford, UK, 1993).
[2] K. V. Klenin, A. V. Vologodskii, V. V. Anshelevich, A. M. Dykhne, and M. D. Frank-Kamenetskii, J. Mol. Biol. **217**, 413 (1991); A. V. Vologodskii, S. D. Levene, K. V. Klenin, M. Frank-Kamenetskii, and N. R. Cozzarelli, *ibid.* **227**, 1224 (1992).
[3] J. A. Gebe, S. A. Allison, J. B. Clendenning, and J. M. Schurr, Biophys. J. **68**, 619 (1995).
[4] Yu. S. Velichko, K. Yoshikawa, and A. R. Khokhlov, J. Chem. Phys. **111**, 9424 (1999); Biomacromolecules **1**, 459 (2000).
[5] B. Mergell, M. R. Ejtehadi, and R. Everaers, Phys. Rev. E **66**, 011903 (2002).
[6] K. Klenin, H. Merlitz, and J. Langowski, Biophys. J. **74**, 780 (1998).
[7] D. A. Beard and T. Schlick, J. Chem. Phys. **112**, 7323 (2000).
[8] D. Sprous and S. C. Harvey, Biophys. J. **70**, 1893 (1996).
[9] K. Klenin and J. Langowski, Biopolymers **54**, 307 (2000).
[10] P. K. Agarwal, H. Edelsbrunner, and Y. Wang, Discrete Comput. Geom. **32**, 37 (2004).
[11] F. B. Fuller, Proc. Natl. Acad. Sci. U.S.A. **75**, 3557 (1978).
[12] J. Aldinger, I. Klapper, and M. Tabor, J. Knot, J. Knot Theory Ramif. **4**, 343 (1995).
[13] J. Cantarella, math.DG/0202236, SIAM J Numer. Anal. (to be published).
[14] E. L. Starostin, physics/0212095.
[15] A. V. Vologodskii, A. V. Lukashin, M. D. Frank-Kamenetskii, and V. V. Anshelevich, Sov. Phys. JETP **39**, 1059 (1975).