

A Computer Simulation of the Unwinding of a DNA-Like Helix

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This paper investigates the use of a high-speed computer to simulate the unwinding of DNA. A Langevin equation of motion for the well-known bead-spring statistical macromolecule is written in difference form. An appropriate set of boundary conditions is developed to simulate a helical molecule and the resulting set of rules for the motion of the chain elements is used to produce the strand unwinding. The unwinding appears to proceed via initial end-unwinding followed by progressive unwinding inward. The latter process appears to occur by diffusion of twist outward from the central portion of the macromolecule. A computer simulation, using the Langevin equation, of linear tensile relaxation is compared with the appropriate analytical solution via the Rouse treatment of polymer dynamics, good agreement being obtained. The helical results are compared both with tensile relaxation and with Crothers' (1964) analytical treatment of the unwinding problem, which is analogous to the well-known temperature diffusion problem. The tensile results and Crothers' results are identical in form, and agree quantitatively remarkably closely with the computer-simulated helical unwinding, although the helical unwinding is somewhat slower.

KEY WORDS: DNA; helical molecule; computer simulation; biopolymers; Langevin equation; bead-spring macromolecule; polymer dynamics; unwinding of DNA; tensile relaxation; Rouse-Bueche model.

1. INTRODUCTION

There have been a number of attempts at a theoretical understanding of the unwinding of DNA.⁽¹⁻⁴⁾ The models all assume a specific torque acting in conjunction with a diffusion process to allow the unwinding to take place. They all show that the

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times involved for a torque-driven DNA molecule are within the range of those observed in cellular duplication. All models are one-dimensional and have simple boundary conditions for the ends as well as the central portions of the DNA. Furthermore they involve a simple exponential relaxation process. Clearly to represent a complex helical model such as DNA by simplified one-dimensional examples is not *a priori* justified. In reality one would have to solve a $6N$ -dimensional problem, $3N$ coordinates and $3N$ momenta, where each coordinate is that of a center of mass representing a nucleotide sugar combination. The problem is made difficult by the fact that one is dealing with helical geometry. Furthermore two strands are involved; the two strands cannot pass through each other, i.e., each strand appears to the other as an excluded volume, an infinite potential into which it cannot pass. One purpose of this paper is to investigate a model which includes more detailed considerations of the unwinding process and to compare the results to a one-dimensional theory.

The model chosen is the Rouse⁽⁵⁾–Bueche⁽⁶⁾ bead–spring model, that is, N elastic elements (springs) connecting $N + 1$ beads. Only one strand is considered explicitly, the other strand being represented as an excluded volume. The model set up here is a statistical model with the overall geometry of DNA. We will be concerned with the relaxation properties of this model. The analytical differential equation serving as a diffusion equation for an element of the chain is solved through a difference equation. In Section 2 we discuss the use of the Langevin equation. Section 3 will discuss the simulation of tensile relaxation of the end-to-end distance projected along the x axis for a series of chains. The extension of this method to the unwinding of DNA is carried out in Section 4, followed by a discussion of the results in Section 5.

2. THE LANGEVIN EQUATION

The diffusion equation for an element of a macromolecule in solution has been derived⁽⁷⁾ from consideration of the forces on that element. For a free-draining polymer,

$$\begin{aligned}\dot{x}_j &= -D \frac{\partial \ln \Psi}{\partial x_j} - \sigma(-x_{j-1} + 2x_j - x_{j+1}), & 0 < j < N \\ \dot{x}_0 &= -D \frac{\partial \ln \Psi}{\partial x_0} - \sigma(x_0 - x_1), & j = 0 \\ \dot{x}_N &= -D \frac{\partial \ln \Psi}{\partial x_N} - \sigma(x_N - x_{N-1}), & j = N\end{aligned}\quad (1)$$

where \dot{x}_j is the ensemble-averaged velocity of the j th bead at position x_j, y_j, z_j ; $\Psi(x_0 \cdots z_N)$ is the probability density of bead j at x_j , and similarly for y_j and z_j ; and $D = KT/\rho$ and $\sigma = 3KT/b^2\rho$, where b is a length parameter, ρ is the translational frictional coefficient of a single bead, T is the temperature, and K is the Boltzmann constant. This equation is a first-order differential equation for the motion of bead j which is harmonically bound to its nearest neighbors and which is acted upon by frictional and Brownian forces. It is formally equivalent to a modified Langevin

equation (inertial forces ignored), as seen by rewriting, calling $A(t)$ the fluctuating force due to Brownian motion,

$$\dot{x}_j = A(t) - \sigma(-x_{j-1} + 2x_j - x_{j+1}), \quad 0 < j < N \quad (2)$$

For use on the computer the difference form of this equation can be written:

$$\begin{aligned} \frac{[x_j(t + \Delta t) - x_j(t)]}{\Delta t} &= A(t) - \sigma(-x_{j-1}(t) + 2x_j(t) - x_{j+1}(t)) \\ \frac{[x_0(t + \Delta t) - x_0(t)]}{\Delta t} &= A(t) - \sigma(x_0(t) - x_1(t)) \\ \frac{[x_N(t + \Delta t) - x_N(t)]}{\Delta t} &= A(t) - \sigma(x_N(t) - x_{N-1}(t)) \end{aligned} \quad (3)$$

We take $\Delta t = 1$, so that one computer cycle will correspond to a unit in t , the time; t now becomes a discrete integer variable. Then

$$x_j(t + 1) = x_j(t) + A(t) - \sigma(-x_{j-1}(t) + 2x_j(t) - x_{j+1}(t)) \quad (4)$$

The initial coordinates are given on data cards, a random number representing $A(t)$ is generated, and a new position is computed for each successive bead in any desired coordinate. Diffusion in the y and z directions can be handled simultaneously in an identical manner.

The magnitude of the random numbers is chosen as follows. Since the $A(t)$ term of Eq. (4) represents Brownian motion, consideration of the translational diffusion constant of a single free bead, δ , is necessary. For one-dimensional motion δ is given by the Einstein relation,

$$\delta = \nu \langle \Delta x^2 \rangle / 2 \quad (5)$$

where ν is the number of displacements of the center of mass per unit time, and Δx is the magnitude of each displacement along the x axis. We have chosen ν to be unity, so that

$$\Delta x = A(t)$$

From the definition of Δx^2 ,

$$\langle \Delta x^2 \rangle = \langle A(t)^2 \rangle = \int_{-a}^a x^2 p(x) dx / \int_{-a}^a p(x) dx \quad (6)$$

where a is an arbitrarily chosen upper limit to the range of displacements and $p(x)$ is the probability of finding a displacement at x . We take $p(x)$ to be unity, i.e., $A(t)$ is an evenly distributed random number. Since $\nu = 1$ (one impulse per computer cycle),

$$\delta = a^2/6 \quad (7)$$

From the Einstein model for bead motion, another equation can be written for δ :

$$\delta = kT/\rho$$

We make use of one other relation, that for σ as defined above, getting

$$b^2 = 3\delta/\sigma = a^2/2\sigma \quad (8)$$

where b is the equilibrium r.m.s. distance between beads. Thus σ , having the dimension of reciprocal time, is determined from the above relations.

3. TENSILE RELAXATION

To verify that the computer treatment was giving a representation of the analytical equation, simulation of tensile relaxation for a series of polymers was carried out. 31-, 61-, 81-, 121-, and 241-bead models were used with the following internally consistent parameters:

$$\sigma = 0.320, \quad b = 10, \quad a = \pm 8$$

To derive an expression for the average end-to-end projection along the x axis of a linear polymer we make use of a model⁽⁷⁾ in which equal and opposite forces of magnitude equal to f are applied to the ends of the chain. Then the average extension along the x axis between two elements of the chain, j and l , is

$$\langle x_j - x_l \rangle = \sum_{k=0}^N (Q_{jk} \bar{\mathcal{E}}_k - Q_{lk} \bar{\mathcal{E}}_k) \quad (9)$$

where

$$\bar{\mathcal{E}}_k = \frac{\int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \xi_k \Psi(\xi_0 \cdots \rho_N) d\xi_0 \cdots d\rho_N}{\int_{-\infty}^{\infty} \Psi d\xi_0 \cdots d\rho_N}$$

$\bar{\mathcal{E}}_k$ is the average of the normal coordinate ξ_k , Q_{jk} is an element of the normal-coordinate transformation matrix such that $\mathbf{x} = \mathbf{Q}\boldsymbol{\xi}$, etc. The time-dependent solution for $\bar{\mathcal{E}}_k$ is given⁽⁷⁾ (with an incorrect sign changed) as

$$\bar{\mathcal{E}}_k = \exp(-\sigma\lambda_k t) \int (f/\rho) \epsilon_k \exp(\sigma\lambda_k t) dt + C_k \exp(-\sigma\lambda_k t) \quad (10)$$

where

$$\epsilon_k = Q_{jk} E_j, \quad \mathbf{E} = \begin{bmatrix} -1 \\ 0 \\ \vdots \\ 0 \\ 1 \end{bmatrix}$$

C_k is a constant of integration, and λ_k are the eigenvalues of the free-draining chain, $\lambda_k = \pi^2 k^2 / N^2$. The problem chosen here requires that at $t = 0$ the chain is linearly extended; after $t = 0$ the chain relaxes to its equilibrium configuration. For $-\infty < t < 0$ assume a constant force f ; for $t > 0$, $f = 0$. Then for $t < 0$,

$$\begin{aligned} \bar{\mathcal{E}}_k &= \exp(-\sigma\lambda_k t) (f/\rho) \epsilon_k \int_{-\infty}^t \exp(\sigma\lambda_k t') dt' \\ &= f\epsilon_k / \rho\sigma\lambda_k \end{aligned} \quad (11)$$

For $t > 0, f = 0,$

$$\bar{E}_k = C_k \exp(-\sigma\lambda_k t) \quad (12)$$

For $t < 0$ from Eq. (11) the steady-state value of \bar{E}_k is $f\epsilon_k/\rho\sigma\lambda_k$. At $t = 0,$ (11) and (12) must be equal, giving

$$C_k = f\epsilon_k/\rho\sigma\lambda_k$$

Then for $t > 0,$

$$\bar{E}_k = (\epsilon_k f/\rho\sigma\lambda_k) \exp(-\sigma\lambda_k t) \quad (13)$$

The mean extension is

$$\langle x_N - x_0 \rangle = \sum_{k=0}^N (Q_{Nk}\bar{E}_k - Q_{0k}\bar{E}_k)$$

Since $Q_{Nk} - Q_{0k} = (8/N)^{1/2}$ for k odd and vanishes for k even, $\epsilon_k = (8/N)^{1/2},$ and

$$\langle x_N - x_0 \rangle = (8f/N\sigma\rho) \sum_{k \text{ odd}}^N \lambda_k^{-1} \exp(-\sigma\lambda_k t) \quad (14)$$

Then let

$$f = \frac{\langle x_N - x_0 \rangle|_{t=0}}{N}$$

so that

$$\langle x_N - x_0 \rangle = \frac{8\langle x_N - x_0 \rangle|_{t=0}}{\pi^2} \sum_{k \text{ odd}}^N k^{-2} \exp(-\sigma\lambda_k t) \quad (15)$$

Of particular importance are the relaxation times

$$\tau_k' = (\sigma\lambda_k)^{-1} = N^2/\sigma\pi^2 k^2 \quad (16)$$

It can be shown likewise that for the mean square end-to-end distance the relaxation times τ_k' are $\tau_k = (2\sigma\lambda_k)^{-1}.$

A plot of Eq. (15) and the results of a computer simulation for 121 beads is seen in Fig. 1. Table I is a comparison of theoretical and computer results for the principal relaxation time for a series of chain lengths; the computer relaxation times were determined from the slopes of semilog plots, ignoring the initial transient.

The linear tensile relaxation program makes use of Eq. (4) to generate new coordinates. $A(t)$ is produced through use of the random number generation routine. This computes random real numbers between 0 and 1.0 (which can be transformed to any suitable range) by a technique⁽⁹⁾ which will produce 2^{29} terms before repeating. Specifically, in FORTRAN notation, an odd integer number with nine or less digits called IX is used to compute IY,

$$IY = IX * 65539$$

If IY is less than zero it is augmented,

$$IY = IY + 2147483647 + 1$$

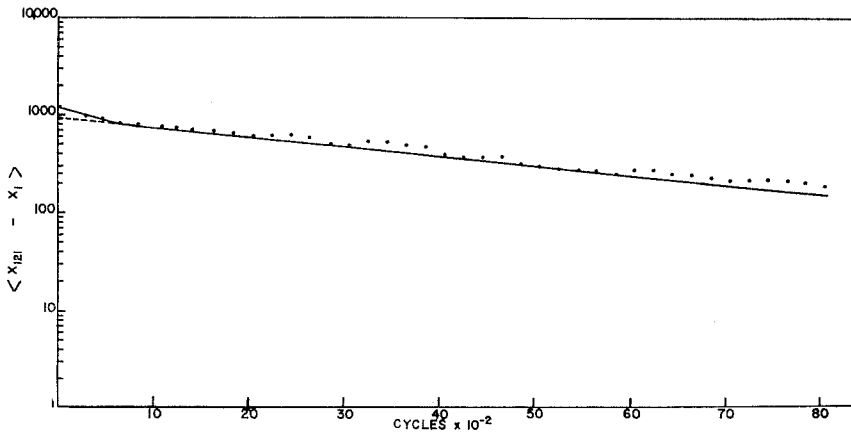


Fig. 1. Comparison of theoretical (line) and computer simulation (points) of linear tensile relaxation of the x projection of the mean end-to-end distance of a 121-bead chain with $\sigma = 0.32$. τ_1' (theory) equals 4760 cycles; τ from slope of best line through the points equals 5060. Points represent an average over two runs. $b = 10$.

It is then set equal to YFL, in order to change to floating-point mode,

$$YFL = IY$$

and the random number is formed,

$$YFL = YFL * 0.4656613E - 9$$

The new value of IX is the preceding value of IY.

Table I. Observed and Theoretically Expected Tensile Relaxation Times^a

	$N + 1$	Computer τ	S	Theory τ_1'
$\langle X_N - X_0 \rangle$	31	273	43	304
	61	1,204	86	1,178
	121	5,060	148	4,635
	241	16,600	1500	18,390
$\langle (X_N - X_0)^2 \rangle$				Theory τ_1
	31	141	11	152
	61	560	39	589
	121	2120	200	2317
	241	7000	2100	9195

^a The computer τ is determined from the slope of the average of semilog plots of the output (see Fig. 1). S is the standard deviation of τ . The theoretical τ_1 is the value of the slowest mode; see text. For all runs $\sigma = 0.320$; $b = 10$ units. $\langle X_N - X_0 \rangle$ and $\langle (X_N - X_0)^2 \rangle$ are the mean squared distances of the x component, respectively. $N + 1$ is the number of beads.

The individual tensile programs took approximately one minute to generate 10,000 complete cycles. Additional constraints were included to prevent any consecutive pair of beads from diffusing more than 1600 units apart; these constraints are discussed more fully in connection with the helical problem considered below.

4. COMPUTER TREATMENT OF THE HELICAL MODEL OF DNA

The present section considers the problem of representation of the Watson-Crick structure of DNA by a suitable model which can be treated on the computer. The model chosen for computer simulation is a simplified helix. Since the presence of two helices would greatly complicate both the computer program and the calculations, one helix is replaced by a stationary cylindrical boundary of infinite length. Wrapped around this in helical fashion is a bead-spring chain representing one strand of DNA (see Fig. 2). The boundary acts as an infinite potential to the chain, that is, a restricted area simulating the excluded volume presented by the other strand. The circular cylindrical boundary first used is later replaced by a square cylindrical boundary for practical reasons. Since there are no cross-terms connecting the motion in the z direction with those in the x and y directions, the z -axis motion reduces to that of an unrestricted chain, which can be solved analytically.⁽⁷⁾ Further, since the cylinder is infinite in the z direction, z -axis motion cannot lead to unwinding. For these reasons z -axis motion is ignored in the subsequent work.

The model thus reduces to motion of the chain throughout the xy plane, except for the interior of a circle or a square centered at the origin, and with the z -axis motion ignored. The actual movement of the bead-spring model is governed by a difference-equation representation of the Rouse-Bueche model of a free-draining

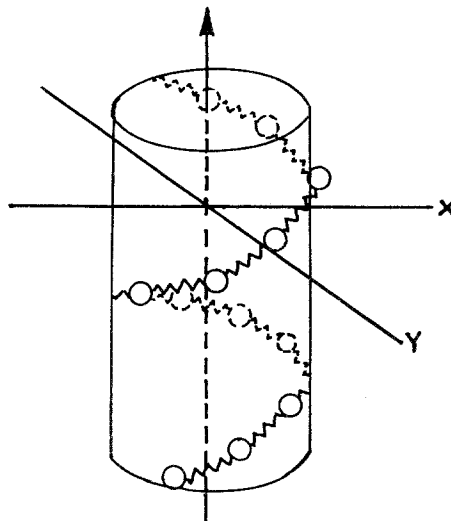


Fig. 2. Schematic representation of a section of the bead-spring model wrapped around an excluded-volume cylinder representing the complementary strand.

polymer as discussed above. (The treatment of base-base interactions, both stacking and hydrogen bonding, is not considered in detail in this paper. The present model is similar to DNA in which the base-base interactions have been disrupted, such as an alkali-treated sample.^(10,11,12)) The difference equation (4) is successively applied to each bead in the chain, starting with bead zero and ending with bead N . Thus in one cycle a new set of coordinates is generated for the entire chain. The initial set of coordinates is entered on data cards. Forty units was chosen as the diameter of the cylinder (or as the length of the side in the case of the square), and a distance of 16 units, equal to the value of b , was chosen as the initial separation between successive beads. Runs were made for chains of 31, 61, 81, and 121 beads. The quantity computed was the number of winds, defined as the sum of the angles, with respect to the cylinder axis, between successive pairs of beads divided by 2π . The number of winds was computed for those sections of the chain corresponding to each initial turn, as well as for the chain as a whole, at the end of each hundred computer cycles. The actual time taken was of the order of fifteen minutes for 40,000 cycles for the 121-bead chain.

When a bead interacts with the excluded volume a special operation must be performed on that chain element. Consider a reflecting barrier. If 1 (Fig. 3) represents the old coordinates and 2 the new position which is inside the excluded volume, then 3 would represent the coordinates of the bead reflected through a mirror angle. The coordinates of the new position are determined both by the position of the bead in the excluded volume 2 and also by the position of the previous coordinate 1. That is, in the case above one would determine coordinate pair 3 by the equations

$$x_3 = x_2, \quad y_3 = 40 - y_2 \quad (17)$$

However the move of $1' \rightarrow 2$ would be reflected to the new position $3'$ given by

$$x_{3'} = 40 - x_2, \quad y_{3'} = y_2 \quad (18)$$

Thus a test is needed to determine how the bead entered the excluded volume if

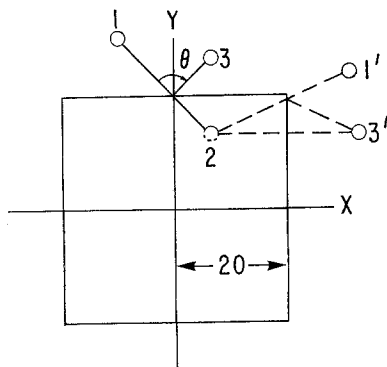


Fig. 3. Schematic representation of the interaction of a bead with the reflecting barrier. Two possible entrances 1 and 1' to the same resultant position 2 have the final positions 3 and 3', respectively.

reflecting walls are to be reproduced. The test chosen was simply to determine the y intercept on the line $x = 20$ or $x = -20$, i.e., extensions of two of the sides of the square. In Fig. 4 the move AC reflects to C' and the move AB reflects to B' by virtue of the fact that points 1 and 2 have y intersections on the line $x = 20$ greater and less than 20 respectively.

The y intersection, Y' , on the line $x = 20$ is given by the equation

$$Y' = y_A + \frac{(y_B - y_A)(20 - x_A)}{x_B - x_A} \quad (19)$$

Thus to determine the new coordinate one tests the y intersection of particles which penetrated the barrier with initial x values greater than 20 or less than -20 . The value of this intersection determines the operation performed on the particle to reflect it from the barrier. Particles whose y values are initially greater than $+20$ or less than -20 , but with x values not greater than $+20$ or less than -20 , and which penetrated the barrier are reflected without the intercept test. These procedures are seen in the FORTRAN program (Fig. 5).

When the distance between two successive beads becomes greater than 40 units (the length of a side of the square boundary) on or near the boundary, the spring connecting the two beads may pass through the excluded volume. This creates an artifact that we must exclude. The remedy is to measure the distance between successive beads and return the entire chain to its coordinates of the previous cycle when any spring length becomes greater than 39 units, thus guaranteeing that "passing through" cannot occur. To monitor the operation of this process the output indicates the cycle number at which the situation of exceeding 39 units occurred. It turned out that the maximal distance was exceeded up to ten times per hundred cycles for the 121-bead chain.

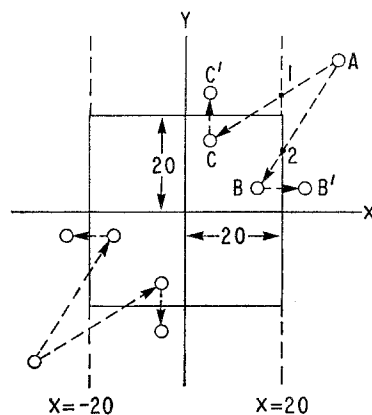


Fig. 4. More detailed schematic of the manner in which a bead is handled to simulate a reflecting barrier.

UNWINDING PROGRAM

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C
C THE FOLLOWING PROGRAM COMPUTES THE NUMBER OF WINDS OF A ROUSE-MODEL
C MACROMOLECULE ABOUT A CYLINDER. THE MODIFIED LANGEVIN EQUATION
C IS USED TO SIMULATE THE MOTION. SEE TEXT FOR FURTHER DETAILS .

      DIMENSION X(121,2),Y(121,2),R(121),D(121),P(121),
      *S(121),F(121),T(121),V(121)
      RNF(0)=8.-16.*RANF(0)
      READ 10,B
10  FORMAT (016)
      CALL RANFSET(B)
      AA=.125
      READ 17, (X(I,1),Y(I,1),I=1,121)
17  FORMAT(2F10,1)
      L10=0
      DO 2 I=1,20000
      DO 3 J=1,121,120
C THIS DO-LOOP COMPUTES THE NEW POSITIONS OF THE FIRST AND
C LAST SUB-MOLECULES.
      IF(J.EQ.1)4,5
4  J1=J+1 $GO TO 6
5  J1=J-1
6  X(J,2)=RNF(-1)-AA*(X(J,1)-X(J1,1))+X(J,1)
7  Y(J,2)=RNF(-1)-AA*(Y(J,1)-Y(J1,1))+Y(J,1) $GO TO 8
8  DO 9 J=2,120 $J1=J-1 $J2=J+1
C THIS LOOP COMPUTES THE NEW COORDINATES OF THE REST OF THE CHAIN.
9  X(J,2)=RNF(-1)+X(J,1)-AA*(-X(J1,1)+2.*X(J,1)-X(J2,1))
9  Y(J,2)=RNF(-1)+Y(J,1)-AA*(-Y(J1,1)+2.*Y(J,1)-Y(J2,1))
      GO TO 14
14  DO 414 J=1,121
C THE REFLECTING WALLED CYLINDER IS SIMULATED IN THIS DO-LOOP.
11  IF (ABSF(X(J,2)).GT.20..OR.ABSF(X(J,2)).EQ.20..OR.
      * ABSF(Y(J,2)).GT.20..OR.ABSF(Y(J,2)).EQ.20.) 11Z,200
200 IF(X(J,1).GT.20..OR.X(J,1).EQ. 20.) 310,307
307 IF (X(J,1).LT.-20..OR.X(J,1).EQ.-20.)305,308
308 IF(Y(J,1).GT.20..OR.Y(J,1).EQ.20.) 300,309
310 IF(Y(J,1)+(Y(J,2)-Y(J,1))*(20.-(X(J,1)))/(X(J,2)-X(J,1)).GT.20.)
      *300,312
312 IF(Y(J,1)+(Y(J,2)-Y(J,1))*(20.-(X(J,1)))/(X(J,2)-X(J,1)).LT.-20.)
      * 309,311
305 IF(Y(J,1)+(Y(J,2)-Y(J,1))*(-20.-X(J,1)))/(X(J,2)-X(J,1)) .GT. 20.
      * ) 300,316
316 IF(Y(J,1)+(Y(J,2)-Y(J,1))*(-20.-X(J,1)))/(X(J,2)-X(J,1)) .LT.-20.
      * )309,313
100 Y(J,2)=40.-ABSF(Y(J,2)) $ GO TO 12
309 Y(J,2)=-40.+ ABSF(Y(J,2)) $ GO TO 12
311 X(J,2)=40.- ABSF(X(J,2)) $GO TO 12
313 X(J,2)=-40.+ABSF(X(J,2)) $ GO TO 12
12  IF(J.EQ.1)414,415
415 J1=J-1
      IF (1+(X(J1,2)-X(J,2))**2+(Y(J1,2)-Y(J,2))**2).LT.1521.)414,408
408 GO TO 2
414 CONTINUE
7  DO 15 J=1,121
      X(J,1)=X(J,2)
15  Y(J,1)=Y(J,2)
      L10=L10+1
      IF(L10.EQ.100)202,2
C THE FOLLOWING PART OF THE PROGRAM COMPUTES THE ANGLE BETWEEN BEADS
C J AND J+1 IN THE FORM OF AN ARCTANGENT.
202 DO 213 J=1,120
203 R(J)=Y(J,1)
      D(J)=X(J,1)
205 P(J)=ARCTAN(R(J),D(J))
213 CONTINUE
214 DO 225 J=1,120 $ J1=J+1
      S(J)=Y(J1,1)
      E(J)=X(J1,1)
217 T(J)=ARCTAN(S(J),E(J))
225 CONTINUE
226 DO 208 J=1,120
227 V(J)=T(J)-P(J)
208 CONTINUE
209 DO 304 J=1,120
      IF (ABSF(V(J)).GT.3.14159) 301,304
301 IF (Y(J,1).LT.0) 302,303
302 V(J)=T(J)+(2.*3.14159-P(J)) $ GO TO 304
303 V(J)=- (P(J)+(2.*3.14159-T(J))) $GO TO 304
304 CONTINUE

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C   THE ANGLE SUMMATION OVER ALL BEADS IS PERFORMED NEXT.
SUM=0
DO 228 J=1,10
228 SUM=SUM+ V(J)
ALPHA=SUM/(2.*3.14159)
SUM=0
DO 500 J=11,20
500 SUM=SUM+V(J)
ALEPH=SUM/(2.*3.14159)
SUM=0
DO 229 J=21,30
229 SUM=SUM+V(J)
BETA=SUM/(2.*3.14159)
SUM=0
DO 501 J=31,40
501 SUM=SUM+V(J)
DALED=SUM/(2.*3.14159)
SUM=0
DO 230 J=41,50
230 SUM=SUM+V(J)
GAMMA=SUM/(2.*3.14159)
SUM=0
DO 502 J=51,60
502 SUM=SUM+V(J)
GAMEL=SUM/(2.*3.14159)
SUM=0
DO 231 J=61,70
231 SUM=SUM+V(J)
DELTA=SUM/(2.*3.14159)
SUM=0
DO 503 J=71,80
503 SUM=SUM+V(J)
AMOUR=SUM/(2.*3.14159)
SUM=0
DO 232 J=81,90
232 SUM=SUM+V(J)
EPSILON=SUM/(2.*3.14159)
SUM=0
DO 504 J=91,100
504 SUM=SUM+V(J)
CROIS=SUM/(2.*3.14159)
SUM=0
DO 333 J=100,110
333 SUM=SUM+V(J)
CHI=SUM/(2.*3.14159)
SUM=0
DO 505 J=111,120
505 SUM=SUM+V(J)
ALORS=SUM/(2.*3.14159)
XI= ALPHA+BETA+GAMMA+DELTA+EPSILON +CHI
*+ALEPH+DALED+GAMEL+AMOUR+CROIS+ALORS
PRINT 1 ,ALPHA,ALEPH,BETA,DALED,GAMMA,GAMEL,DELTA,AMOUR,
*EPSILON,CROIS,CHI,ALORS,XI
1 FORMAT (1H0(13F5.2))
PUNCH 506,ALPHA,ALEPH,BETA,DALED,GAMMA,GAMEL,DELTA,AMOUR,
*EPSILON,CROIS,CHI,ALORS,XI
506 FORMAT (1H0(13F5.2))
L10=0
2 CONTINUE
CALL RANFGET (C) .
PUNCH 16, C
16 FORMAT (016)
PUNCH 18,(X(J,1),Y(J,1),J=1,121)
18 FORMAT (2F10.1)
END

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Fig. 5. The entire FORTRAN program. The new x and y coordinates of bead j are generated by the difference form of a Langevin equation of motion. $X(J, 1)$ and $X(J, 2)$ are the x coordinates of bead j at successive intervals of time. $Y(J, 1)$ and $Y(J, 2)$ are the corresponding y coordinates.

Figure 5 shows the complete set of FORTRAN IV statements which were used on the UCSD CDC 3600 computer. This particular program involves 121 beads with 20,000 impulses to each bead of the chain. The first set of statements is concerned with generation of new coordinates making use of a random number function RNF (-1) which has been defined to produce evenly distributed random numbers between -8.0 and $+8.0$ (see above). AA is the constant σ fixed at 0.125. This is consistent with an r.m.s. distance between elements of 16 units by Eq. (8).

The next do-loop (statement 414) first determines if any bead is within the excluded volume area. If it is not, then the distance to the preceding element is tested to see if it is equal to or greater than 40 units (a cylinder diameter). If this distance is exceeded, the entire cycle is thrown out (statement following 415). If the bead lies within the excluded volume, then a series of operations performs the reflection operation. Statements 200, 307, and 308 determine from what direction the bead entered the volume. Statements 310, 312, 305, and 316 determine the intersection with the extensions of the sides of the square [see Fig. 4 and Eq. (19)]. This, in turn, allows an appropriate move to a new position given in statements 300, 309, 311, and 313.

The next portion of the program determines the angle between beads j and $j + 1$. This is done by computing the angle made with respect to the positive x axis in the xy plane. (The ARCTAN routine can be replaced by a suitable power-series expansion if the routine is not available. However, to agree with the routine used here, the resultant angle must lie between 0 and 2π radians.) The do-loop started at statement 209 corrects for those infrequent cases where bead j lies below the x axis and $j + 1$ above the x axis, or *vice versa*. In these cases the arctangent calculation must be corrected so as to give the acute rather than the obtuse angle.

The final stage of the program sums over all the angles, in this case in twelve successive tiers, and divides by 2π in order to compute the number of winds. The last random number C is recorded as output; this may then be used as the initial random number B in a subsequent run, if desired.

5. RESULTS AND DISCUSSION

Chains of 31, 61, 81, and 121 beads with three to twelve turns were allowed to unwind. The total number of winds and a breakdown into tiers were computed as functions of computer cycles. An example which summarizes the study is discussed below.

5.1. 121-Bead Model

A 121-bead, 12-turn model of DNA with 16 units as the r.m.s. distance b serves as an example of the unwinding results (see Fig. 6). The total number of winds in each section of ten beads which corresponds to one initial turn ("tier") was computed as described above. Each result was then averaged over six independent computer runs. Each point is the running average over 1000 computer cycles. Specifically, ten successive values of the number of winds found at the end of every

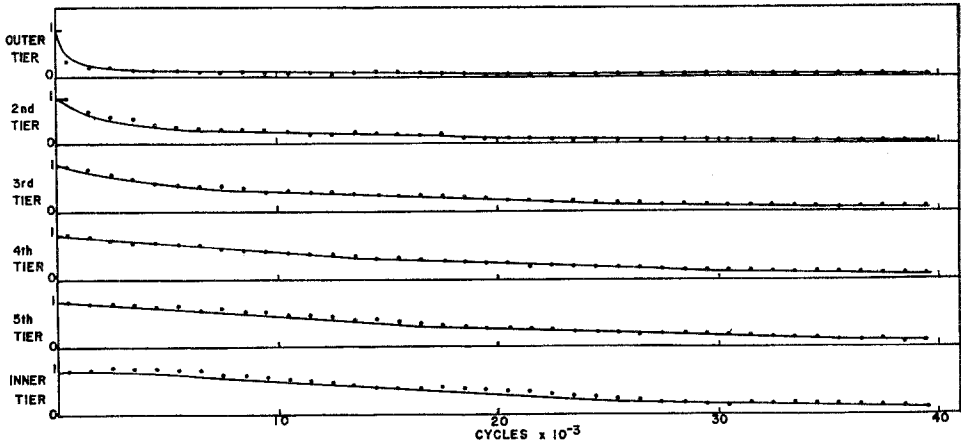


Fig. 6. Direct output of the computer simulation (points) for a 121-bead chain with 12 initial winds, $\sigma = 0.125$ and $b = 16$. The points for the outer tier are the averages of the results for tiers 1 and 12, those of the second tier are the averages of tiers 2 and 11, and so on. Each point is the running average over 1000 computer cycles. The curves represent the analytical solution of the tensile relaxation equation for a 121-bead chain with $\sigma = 0.087$. Each curve gives the length divided by the initial length of the appropriate twelfth of the chain.

100 cycles were averaged together to give one point for every 1000 cycles. Because of the symmetry of the chain with respect to its midpoint, it was possible to average the number of winds of tiers 1 and 12, 2 and 11, etc.

A plot of total winds *versus* cycles is shown in Fig. 7. The similarity to tensile relaxation, as shown in Fig. 1, is remarkable.

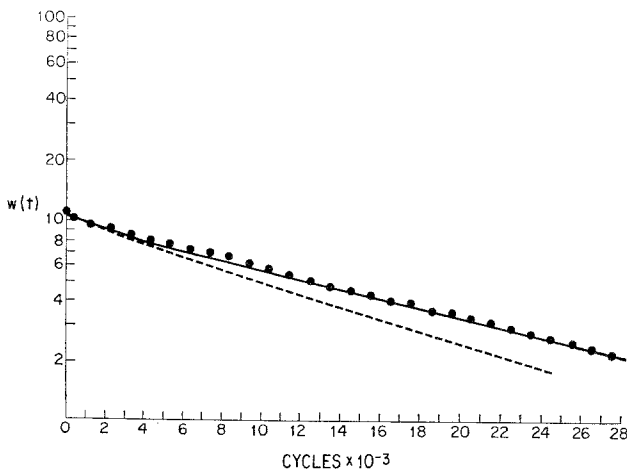


Fig. 7. Total winds *versus* time for the 121-bead model as in Figure 6. Points: computer simulation of the Langevin equation. Lower curve: tensile relaxation with $\sigma = 0.125$; upper curve: tensile relaxation with adjusted relaxation times, $\sigma = 0.087$.

The general features of these curves are similar to those found in runs with shorter chains. Runs for 31-, 61-, and 81-bead models were made, varying the number of initial twists about the cylinder for a constant number of beads. The results of this study showed that the relaxation time appeared to be independent of the number of twists for a given model but dependent on the parameter σ in a fashion very similar to that seen in tensile relaxation (Table I). These similarities suggested the model discussed below.

5.2. Tensile Relaxation as a Model for Unwinding

The equation for the relaxation of a chain initially linearly stretched is given by Eq. (15) with the relaxation times of (16). This equation for a 121-bead chain with $\sigma = 0.125$ is plotted as the lower curve in Fig. 7, taking the initial value to be 12 as if the length were the number of winds. The longest relaxation time here is given by Eq. (16) with k equal to unity, and is 11,862 cycles. If the curve is replotted with the change of substituting 17,600 cycles for this relaxation time, corresponding to $\sigma = 0.087$, and changing the other relaxation times by the same factor, we obtain the upper curve in Fig. 7, which is seen to be a remarkably good fit to the points representing the Langevin results.

The tensile result may also be compared to the detailed results of Fig. 6 if it is put in an appropriate form for comparison. From the results in Section 3 we may obtain the following result for the mean x coordinate of a bead, j , in a chain undergoing tensile relaxation:

$$\langle x(j, t) \rangle = \frac{4\langle x(j, 0) \rangle}{\pi} \sum_{k \text{ odd}}^{\infty} \frac{(-1)^{(k-1)/2}}{k} \frac{k\pi(2j - N)}{2N} \exp\left(-\frac{t}{\tau_k'}\right) \quad (20)$$

Integration over each of six equal parts from $j = 0$ to $j = N/2$, performing a running average over ten consecutive values of t , and summing over one hundred values of k puts Eq. (20) in suitable form for comparison to the Langevin results. The solid curves in Fig. 6 show the comparison, using 17,600 for τ_1' . Again the agreement of the two sets of results is noteworthy.

The molecular-weight dependence of the tensile relaxation times is second order. The molecular-weight dependence of the Langevin helical relaxation times is compared in Table II. The agreement with the tensile times is very close with the shorter chains, but there is a tendency for the helical times to become greater with the larger chains.

Table II. Observed Relaxation Times for a Series of Helical Chains Compared with the Corresponding Theoretical Relaxation Times of the Tensile Result (Eq. (16)) with $\sigma = 0.125$

$N + 1$	τ_1' tensile (theoretical)	τ computer (helical)
31	780	923 \pm 230
61	3,015	3,270 \pm 280
81	5,300	6,600 \pm 425
121	11,862	17,600 \pm 530

5.3. Discussion

In Crothers' model⁽³⁾ unwinding is considered to be a diffusion process; that is, there is a migration of twist outward from the central portions of the macromolecule. A one-dimensional diffusion equation analogous to the equation for temperature diffusion in a rod was derived. The solution to the diffusion equation for complete unwinding of DNA is

$$\nu(x, t) = \frac{4\nu_0}{\pi} \sum_{n=0}^{\infty} \frac{(-1)^n}{2n+1} \cos \left[\frac{(2n+1)\pi x}{2L} \right] \exp \left[-\frac{D(2n+1)^2 \pi^2 t}{4L^2} \right] \quad (21)$$

where ν is the number of winds per unit length, ν_0 is the initial (constant) value of ν , x is the linear distance from the center of the molecule, $2L$ is the total length, D is the rotational diffusion constant for the helix, and t is the time. Equation (21) is identical in form to our equation (20), and may be made to agree exactly with the results in Figs. 6 and 7 by a proper choice of the parameter D . Thus the agreement found above between Langevin helical results and the tensile model can be reinterpreted as an agreement between the same results and Crothers' model. The modest discrepancies in the cases of the longer chains would then represent a change of the twist diffusion constant D with molecular weight.

The present treatment has been extended to include strands with an adsorption interaction energy.^(13,14) The present analytical results must be appropriately modified.

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