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Applications of the twist difference to DNA structural analysis

(DNA geometry/superhelical DNA/DNA surface winding/nucleosome)

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ABSTRACT **The twist is a fundamental geometric property of nucleic acids. Calculation of the twist in the most general case requires detailed specification of the three-dimensional path of each strand, but many important cases may be analyzed by considering only the twist difference. If C_1, C_2, and C_3 are three distinct space curves, the twist difference about C_1 is defined as $\mathrm{Tw}(C_3, C_1) - \mathrm{Tw}(C_2, C_1)$. We show here that this difference measures the rotation of the correspondence surface joining C_1 to C_2 about the correspondence surface joining C_1 to C_3. This result has application to DNA containing local nonuniformities, such as denatured regions, cruciforms, and other altered structures. It also facilitates the calculation of twist for three-stranded structures, including D-loops in mitochondrial DNA and replication and transcription intermediates. The twist difference may also be used to simplify greatly the analysis of twist changes in duplex DNA due to winding on surfaces, such as histones and certain enzymes. In such cases the strand-axis twist of DNA divides into two independent terms. The first term arises from the twist of the local reference frame, and the second arises from the rotation of either strand about the duplex axis as measured in the local reference frame. Twist changes consequent to nucleosome winding, for example, arise from the twist of the nucleosome axis, a straight line, about the DNA axis plus the rotation of either strand of the DNA about its axis in the reference frame of the cylinder.**

Undistorted duplex DNA is characterized by a linear axis and by regular winding of both strands; consequently the twist is simply the number of rotations of either strand about the axis. This is a highly idealized case, unlikely to occur commonly in nature. More biologically and biophysically interesting situations arise from perturbations of several different kinds (1, 2). We distinguish, among others, smooth axial distortions, such as bending (3–5) and rotations (6–8); local nonuniformities, such as denatured regions (9–11), cruciforms (12–15), and other types of altered structures (16–18); ordered windings about protein surfaces (19–22); and multistranded structures. This last category includes stable structures, such as D-loops and expanded D-loops in mitochondrial DNA (23), and theta (24) and bubble (25) structures. Also included are various types of transient structures, such as replicating or transcribing DNA molecules (see, for example, ref. 26). In these latter cases there is a systematic reduction of twist between the original strands and a corresponding increase in twist between the newly formed strands.

Since twist alteration is an obligatory accompaniment of both replication and transcription, it is of first-order importance to be able to calculate the twist for each structure involved and, ultimately, as a function of the progress of these reactions. In such complex structures, involving at least three oligonucleotide strands, geometric relationships exist among the various strand combinations taken two at a time. These relationships, which we denote as twist differences, are generally useful for simplifying the calculation of twist in complex cases. For example, the twist of any two curves about one another will be shown to be simply related to the twist of either curve separately about a common third curve.

The twist difference has further application to situations involving smooth distortions of duplex DNA due to winding about a surface. Such winding usually results in a change in the twist of either DNA strand about the duplex axis (27). We show here that in general this twist can be analyzed in terms of two much simpler concepts: first, the rotation of either strand about the duplex axis measured in terms of a reference frame defined by the surface and, second, a term involving changes in the reference frame itself. In the case of nucleosome winding, for example, the first term depends only on the rotation of either strand about the DNA axis as it traverses the surface of the nucleosome cylinder; the second term is the twist of the axis of the nucleosome, a straight line, about the axis of the DNA. In a subsequent paper we will extend this treatment to include winding about arbitrary surfaces.

Calculation of the Twist for Two Curves Joined by a Correspondence Surface

We deal with the case of any two curves, C_1 and C_2, that are in one-to-one correspondence with each other. Taking into account the ordering of the curves, we denote the twist of C_1 about C_2 by $\mathrm{Tw}(C_1, C_2)$ and that of C_2 about C_1 by $\mathrm{Tw}(C_2, C_1)$. In order to calculate $\mathrm{Tw}(C_2, C_1)$, we let z_{12} be the correspondence vector joining a point q of C_1 to its corresponding point p on C_2. The ladder-like correspondence surface S_{12}, which is generated by the family of all such vectors, is assumed to be smooth (has no discontinuities or corners) and thus has a well-defined tangent plane at each point. (Cases in which there are corners can be dealt with by using piecewise smooth surfaces.) The resulting correspondence surface S_{12} is defined and illustrated in Fig. 1.

Understanding of the twist requires specification of how the geometry of the curve C_1 relates to the geometry of the surface S_{12}. In particular, it is necessary to describe how the tangent line to the curve relates to the tangent plane to the surface S_{12} as the curve C_1 is traversed. Let $\boldsymbol{T}_1$ be the unit tangent vector to C_1 at the point q. Now z_{12} is not necessarily perpendicular to $\boldsymbol{T}_1$, and only its orthogonal component contains independent dimensional information. We therefore define ν_{12} to be the unit vector directed along that component of z_{12} that is perpendicular to $\boldsymbol{T}_1$ (Fig. 1). The vectors ν_{12} and $\boldsymbol{T}_1$ are orthogonal and together define the tangent plane to S_{12} in the vicinity of q. They contain information about the geometry of the curve C_1 and about the correspondence surface near C_1. A third vector that provides information about the curve C_1 is the unit normal vector, $\boldsymbol{N}_{12}$, given by the cross product $\boldsymbol{T}_1 \times \nu_{12}$. The unit vector $\boldsymbol{N}_{12}$ is perpendicular to the surface S_{12} (and hence to the curve C_1) at the

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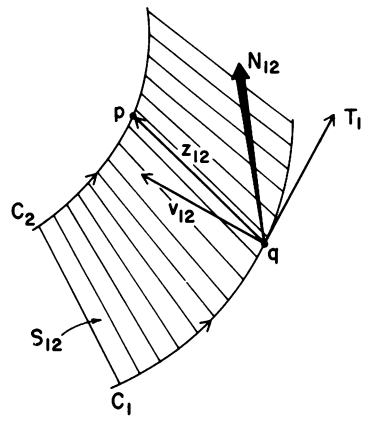

FIG. 1. Definition of the correspondence surface joining two curves, C_1 and C_2. Any point q on C_1 is joined to its correspondence point p on C_2 by the vector z_{12}. The correspondence surface, S_{12}, is formed from all lines along the z_{12} vectors. The unit normal vector N_{12} is equal to the product $T_1 \times v_{12}$, where T_1 is the unit tangent vector to C_1 at q and v_{12} is the component of z_{12} that is perpendicular to T_1. The vector N_{12} is perpendicular to S_{12}, and hence to C_1, at q. The vector v_{12} lies in the plane that is tangent to S_{12} at q and points to the interior of S_{12}. The twist of C_2 about C_1, $\mathrm{Tw}(C_2, C_1)$ is the total change of the vector v_{12} in the direction determined by the vector N_{12}.

point q. The twist of the curve C_2 about the curve C_1, using the correspondence surface S_{12}, is defined by (27)

$$\mathrm{Tw}(C_2, C_1) = (1/2\pi)\int_{C_1} T_1 \times v_{12} \cdot dv_{12}$$

$$= (1/2\pi)\int_{C_1} N_{12} \cdot dv_{12}. \quad [1]$$

The twist that results from the reversal in the order of the curves, $\mathrm{Tw}(C_1, C_2)$, also employs Eq. 1, except that the subscripts 1 and 2 are interchanged.

The choice of correspondence surface is usually dictated by the structural parameters of DNA, and in all applications described here the surface is to be understood to be S_{12} unless otherwise specified. We emphasize, however, that the definition of the twist $\mathrm{Tw}(C_2, C_1)$ is dependent upon the choice of correspondence surface and, indeed, can take on different values for different choices of the correspondence surface. Geometrically, the twist is a measure of the rotation of the tangent *plane* to S_{12} at C_1 about the tangent *line* to C_1 as the curve is traversed. The twist calculation must therefore take into account not only the rotation of the plane but also the configuration of the curve C_1. It is because of this latter fact that the twist of one closed curve about another is not necessarily an integer.

The Twist Difference

We next consider the situation in which two curves, C_2 and C_3, twist about a third curve, C_1. We calculate the difference between their twists explicitly: $\mathrm{Tw}(C_3, C_1) - \mathrm{Tw}(C_2, C_1)$. Let v_{12} be the unit vector associated with the correspondence surface S_{12} joining C_1 and C_2; let v_{13} be the unit vector associated with the correspondence surface S_{13} joining C_1 and C_3; and let the associated unit normal vectors be $N_{12} = T_1 \times v_{12}$ and $N_{13} = T_1 \times v_{13}$.

$$\mathrm{Tw}(C_2, C_1) = (1/2\pi)\int_{C_1} N_{12} \cdot dv_{12}. \quad [2a]$$

$$\mathrm{Tw}(C_3, C_1) = (1/2\pi)\int_{C_1} N_{13} \cdot dv_{13}. \quad [2b]$$

Now at each point of C_1, v_{12} and v_{13} are unit vectors perpendicular to T_1; hence both lie in the plane perpendicular to T_1. This plane is spanned by the pair v_{12} and N_{12} and also by the pair v_{13} and N_{13}. We illustrate this in Fig. 2. Since all vectors in question are unit vectors, the pair v_{13} and N_{13} is obtained from the pair v_{12} and N_{12} by a rotation through an angle ϕ, which varies from point to point on C_1. These geometric considerations lead to the expressions

$$v_{13} = v_{12}\cos(\phi) + N_{12}\sin(\phi)$$
$$N_{13} = -v_{12}\sin(\phi) + N_{12}\cos(\phi).$$

Taking the derivative,

$$dv_{13} = [-v_{12}\sin(\phi) + N_{12}\cos(\phi)]d\phi + \cos(\phi)dv_{12} + \sin(\phi)dN_{12}.$$

Therefore,

$$dv_{13} \cdot N_{13} = \{[-v_{12}\sin(\phi) + N_{12}\cos(\phi)]d\phi + \cos(\phi)dv_{12} + \sin(\phi)dN_{12}\} \cdot [-v_{12}\sin(\phi) + N_{12}\cos(\phi)].$$

Now since $v_1 \cdot v_1 = 1$ and $N_{12} \cdot N_{12} = 1$, it follows that $dv_{12} \cdot v_{12} = 0$ and $dN_{12} \cdot N_{12} = 0$. Further, since N_{12} and v_{12} are perpendicular and $N_{12} \cdot dv_{12} = 0$, it follows that $dN_{12} \cdot v_{12} = -N_{12} \cdot dv_{12}$. Combining these results, we obtain

$$dv_{13} \cdot N_{13} = dv_{12} \cdot N_{12} + d\phi.$$

In order to calculate the twist, we integrate both sides of the above equation and obtain

$$\mathrm{Tw}(C_3, C_1) = \mathrm{Tw}(C_2, C_1) + \Phi(C_1), \quad [3]$$

where the twist difference $(1/2\pi)\int_{C_1} d\phi$ is denoted $\Phi(C_1)$. This result shows that the difference between the twists of two pairs of curves having one curve in common may be

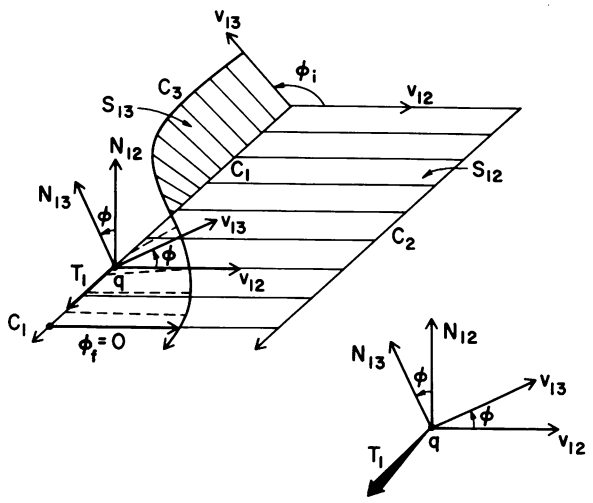

FIG. 2. Winding of one correspondence surface about another: the twist difference. Two correspondence surfaces, S_{12} and S_{13}, are shown connecting a curve C_1 to two different curves, C_2 and C_3. The associated unit vectors v_{12}, v_{13}, N_{12}, and N_{13} are also shown. The angle ϕ is the angle of rotation from v_{12} to v_{13}. All vectors at a point q are perpendicular to T_1 and therefore all lie in the same plane. This is shown separately in the *Inset*. The winding of S_{13} about S_{12} as the curve C_1 is traversed is measured by the total change in the angle ϕ, given by $\Phi = \phi_f - \phi_i$. In the example shown this change is negative.

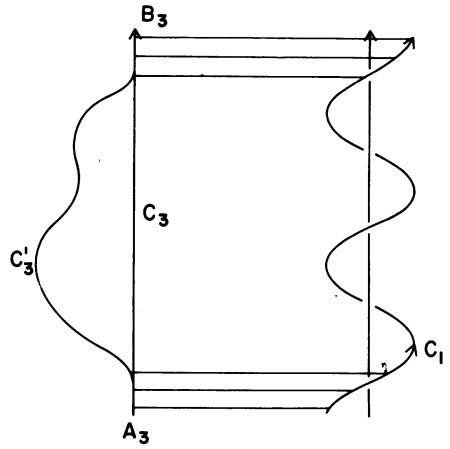

FIG. 3. Deformation of a curve C_3 into a second curve C_3'. The curve C_3' is obtained from C_3 by a deformation that leaves fixed (unaltered) segments near the endpoints A_3 and B_3. The correspondence surfaces joining C_1 and C_3 and joining C_1 and C_3' in these end regions are therefore identical. In all other regions the surfaces are different.

calculated simply from the change in the angle ϕ from the initial (i) point on C_1 to the final (f) point on C_1:

$$\mathrm{Tw}(C_3, C_1) - \mathrm{Tw}(C_2, C_1) = \Phi(C_1) = (1/2\pi)(\phi_f - \phi_i). \quad [4]$$

Thus, the twist difference, $\Phi(C_1)$, measures the number of times v_{13} rotates about v_{12} as the curve C_1 is traversed. An alternative way of interpreting Φ is in terms of surfaces, as also illustrated in Fig. 2. The two surfaces S_{12} and S_{13} have the curve C_1 in common, and $\Phi(C_1)$ measures the total rotation of S_{13} about S_{12} as the curve C_1 is traversed. Both the surface and the vector descriptions of $\Phi(C_1)$ are useful, and in the next two sections we give applications of each to DNA structure. The surface approach is used to calculate the twist in complex, nonuniform structures in DNA. The vector approach is used to calculate the change in twist of DNA due to surface wrapping.

The result stated in Eq. 4 has important applications to calculation of the changes in the twist of any DNA structure following deformation. In Fig. 3, we illustrate a simple deformation of curve C_3 into curve C_3'. The curves C_3 and C_3' are identical in the neighborhood of the endpoints A_3 and B_3. From this it immediately follows that the correspondence surfaces S_{13}, joining C_1 to C_3, and S_{13}', joining C_1 to C_3', are identical in the initial and terminal regions. Therefore, as long as C_3 is deformed into C_3' in such a way that the correspondence surface S_{13}' does not wind completely about S_{13} or intersect C_1, then it follows that $\phi_i = \phi_f = 0$ and $\Phi(C_1) = 0$; hence $\mathrm{Tw}(C_3', C_1) = \mathrm{Tw}(C_3, C_1)$.

Twist for Complex Structures: An Example

In this section we discuss how to use the twist difference to analyze the twist of a complex structure. Let C_1 be a right-handed circular helix of radius r and pitch $2\pi p$ that winds n times about a straight-line axis C_2. In Fig. 4 we illustrate the case in which C_2 lies along the z axis and C_1 winds about the cylinder $x^2 + y^2 = r^2$. If we express C_2 in terms of its arc-length parameter s, so that it can be written in vector form as $\{0, 0, s\}$ for the range $0 \le s \le 2\pi pn$, then C_1 may be written in vector form as $\{r\cos(s/p), r\sin(s/p), s\}$. The natural correspondence between C_1 and C_2 then associates the point $\{r\cos(s/p), r\sin(s/p), s\}$ on C_1 with the point $\{0, 0, s\}$ on C_2. We showed previously (27) that, with this choice of correspondence,

$$z_{12} = \{-r\cos(s/p), -r\sin(s/p), 0\} \quad [5a]$$

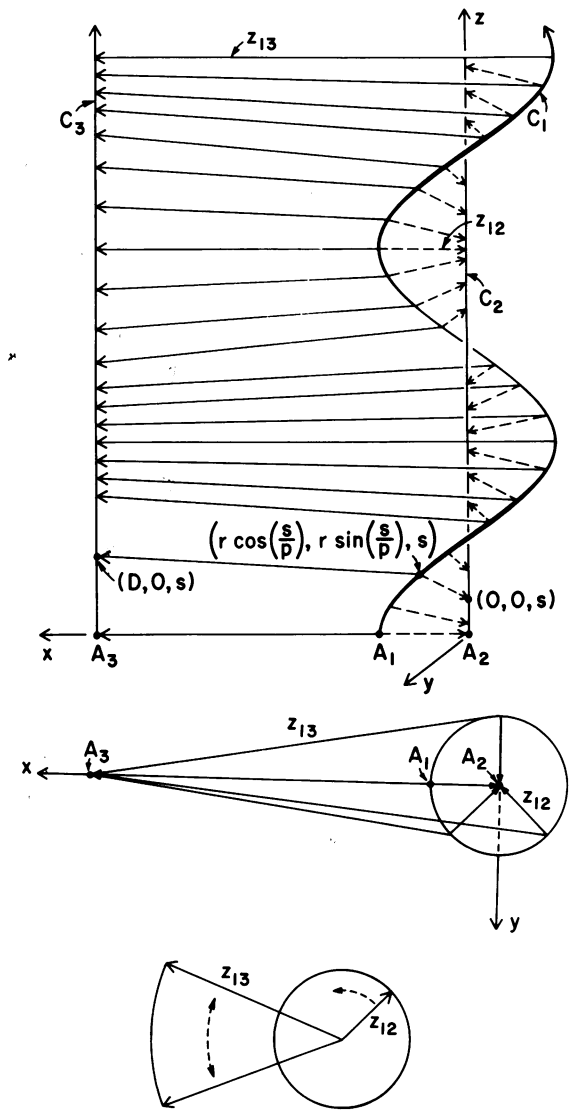

FIG. 4. Twist difference for a complex structure. (*Top*) Curve C_1 is a right-handed circular helix, of radius r and pitch $2\pi p$, that winds n times about the linear axis C_2. In order to obtain C_3, C_2 is displaced by a distance D along the x axis to a location outside the helix C_1. The correspondence vectors z_{12} and z_{13} connect C_1 to C_2 and to C_3, respectively. The initial points of the three curves are denoted A_1, A_2, and A_3. (*Middle*) A projection of the correspondence vectors, looking downward along the z axis. This projection illustrates the spinning or rotatory movement of the vector z_{12} and, in contrast, the simple oscillatory movement of the vector z_{13}. Four different positions of z_{13} are shown, as determined by the corresponding rotational locations of the terminus of z_{12}. (*Bottom*) Complete ranges of movement of the two vectors.

and $\mathrm{Tw}(C_2, C_1) = np/(r^2 + p^2)^{1/2}$.

We next make a parallel translation of the line C_2 by a distance D onto the line C_3, where $D > r$. This ensures that the line C_3 lies outside the cylinder. Then

$$z_{13} = \{D - r\cos(s/p), -r\sin(s/p), 0\} \quad [5b]$$

It is clear from Eq. 5a that as s varies from 0 to $2\pi p$ (i.e., C_1 makes one complete helical turn) the vector z_{12} spins counterclockwise as viewed from above exactly once about the z axis. However, since $D > r$, Eq. 5b shows that z_{13} always has a positive component along the x axis. Therefore z_{13} does not spin about the z axis but simply oscillates as shown in Fig. 4 *Middle* and *Bottom*. Since the vectors z_{12} and z_{13} are collinear at the initial point ($s = 0$) and at the final

point ($s = 2\pi p$), the net effect is that the surface S_{13} spins clockwise exactly once about the surface S_{12}. Thus the net change in the angle ϕ between these surfaces is -2π for each helical turn of the curve C_1, and the total change in ϕ over the whole of C_1 is $-2\pi n$, so that $\Phi(C_1) = -2\pi n$. Using Eq. 3, we obtain $\mathrm{Tw}(C_3, C_1) = np/(r^2 + p^2)^{1/2} - n$. We note that the twist obtained is negative.

From the deformation analysis, as illustrated in Fig. 3, if C_3' is any deformation of C_3 that satisfies the conditions set forth there, then $\mathrm{Tw}(C_3', C_1) = \mathrm{Tw}(C_3, C_1)$. A structure of this type is found, for example, in the D-loop form of animal mitochondrial DNA. Typically the structure there consists of a 500-to 700-nucleotide-pair duplex region (23), formed by the D-loop strand and one of the linked complements. The other linked complement is single-stranded in this region. The curve C_3 corresponds to the single-stranded region, and the curve C_1 corresponds to either of the strands of the DNA.

Twist of Curves That Lie on a Surface: Application to DNA

We next apply the concept of the twist difference to calculate the twist of a DNA molecule constrained to lie on an arbitrary surface M; that is, the duplex axis traces out a curve A that lies on M. For example, the simplest model for linear DNA specifies a straight-line axis that lies on a plane surface. Similarly, the simplest relaxed closed circular DNA contains a circular axis that is also planar. In the generally accepted model for the nucleosome, the DNA wraps in a left-handed helix on the surface of a circular cylinder.

The surface M is assumed to be differentiable at every point, hence the tangent plane to M exists at all points and varies smoothly from point to point. M is also orientable, meaning that there exists a well-defined surface normal ν (termed the unit normal vector field) at every point of M. We require further that ν varies smoothly from point to point and that ν has unit length. Thus, in particular, ν is perpendicular to the tangent plane of M at each point. Let A be a smooth curve on M and let A_ε be a curve obtained by moving A a distance ε (where $\varepsilon \neq 0$) along the surface normal ν. Now ε may vary from point to point, but it is generated by a smoothly varying function so that A_ε remains a smooth curve (Fig. 5). We construct the correspondence between A and A_ε so that a point q on A is made to correspond to the point p on A_ε, obtained by moving q by a distance ε along ν. The correspondence vector is then just $\varepsilon\nu$ and, since ν is perpendicular to A, ν is also the vector ν_{12} used in Eq. 1 above. We let T be the unit tangent vector to A. Then, from Eq. 1, the twist of A_ε about A is given by

$$\mathrm{Tw}(A_\varepsilon, A) = (1/2\pi)\int_A T \times \nu \cdot d\nu. \qquad [6]$$

The argument of the integral in Eq. 6, $T \times \nu$, is called the geodesic torsion of the curve A on the surface S. This integral is a measure of the extent of rotation of the normal vector ν around the curve A.

The function ε may be chosen to be always positive or always negative. The positive case has been discussed immediately above. In case ε is negative, the correspondence vector is still $\varepsilon\nu$, but the twist vector is $\nu_{12} = -\nu$. Here Eq. 1 becomes $\mathrm{Tw}(A_\varepsilon, A) = (1/2\pi)\int_A T \times (-\nu)\cdot d(-\nu) = (1/2\pi)\int_A \mathbf{T} \times \boldsymbol{\nu} \cdot d\nu$. Thus, the twist of a curve moved along the surface normal about the original curve is independent of which side of the surface A_ε lies. We further specify that ε be chosen so as to prevent intersections of the curves A_ε and A. This is always possible, since the surface M is smooth.

We next let A represent the duplex axis of a DNA molecule. We wish to compute the twist of one of the strands, C, about the axis. We must first establish a natural correspondence between the axis A and strand C. The surface M provides the geometry necessary to do this. If we slice the DNA with a plane P that is perpendicular both to the surface M and to the axis curve A, we will obtain a cross-sectional piece (Fig. 6). This cross section contains a unique point (c) of the strand C and a unique point (a) of the axis A. This gives us a natural correspondence between A and C. Let ν_{AC} be the unit vector, perpendicular to A, that is determined by this correspondence. Then the twist of C about A is given by the formula $\mathrm{Tw}(C, A) = (1/2\pi)\int_A T \times \nu_{AC} \cdot d\nu_{AC}$. The relation for the twist difference, Eq. 3, provides the result $\mathrm{Tw}(C, A) = \mathrm{Tw}(A_\varepsilon, A) + \Phi(A)$, where $\Phi(A)$ is given by $(1/2\pi)\int_A d\phi$, ϕ being the angle between the surface normal and the vector ν_{AC}. Thus, $\Phi(A)$ measures how many times and in what sense the vector ν_{AC} rotates about the surface normal. The surface normal therefore provides a frame of reference in which to measure the turning of the backbone about the axis. In summary, the strand-axis twist $\mathrm{Tw}(C, A)$ divides into two parts: $\mathrm{Tw}(A_\varepsilon, A)$, which measures the change of local reference frame, and

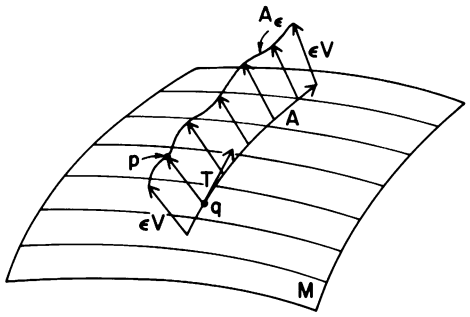

FIG. 5. Representation of the surface curve A and its displacement curve A_ε. Curve A lies on the surface M. The vector ν is the unit normal vector to the curve. The curve A_ε is obtained by moving the distance ε, from each point q and A to the corresponding point p, along the vector ν. T is the unit vector tangent to A at q.

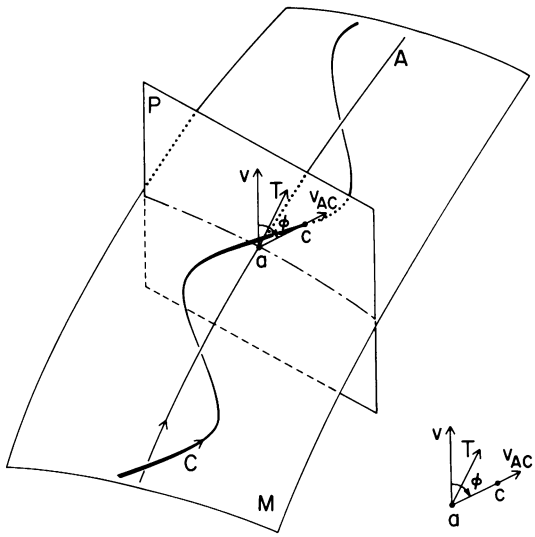

FIG. 6. Strand-axis correspondence of DNA on surfaces. The axis A of the DNA lies on the surface M. The backbone chain C winds about the axis A, alternately above and below the surface M. The plane P, perpendicular to A at the point a, passes through C at the point c, after which C lies above M but behind P (···). The vector ν_{AC} is the unit vector along the correspondence line joining point a on curve A to point c on curve C. ϕ is the angle from ν to ν_{AC}. The total change in ϕ as the axis is traversed, Φ, measures how many times the backbone turns about the axis in the reference frame, as shown separately in the *Inset*.

$\Phi(A)$, which measures how the backbone revolves about the axis in the reference frame. The first term, $\mathrm{Tw}(A_\varepsilon, A)$, is the reference-frame twist and the second is the total helical turning as generally understood.

One of the important problems in DNA geometry is to understand how it is that the helical pitch changes when DNA is wrapped on a surface. In a forthcoming paper we will present a general analysis of how DNA wraps on surfaces of revolution and of how the shape of such surfaces alters the helical pitch. At present we deal with one classical example, the winding of DNA in a nucleosome. Here the pitch changes from 10.45 base pairs per turn in dilute saline (28, 29) to 10.17 (30, 31). We showed previously, by a direct analysis, that this pitch change can be predicted solely from geometric considerations. Other factors, such as energy calculations (32), lend insight but are not required to explain the experimental observations. The nucleosome can be described as a cylindrical surface M of radius R on which the DNA axis A wraps as a left-handed helix of pitch $2\pi p$ (27). The central line of the cylinder is denoted L. The unit normal vector ν to M points radially outward from the surface; therefore, if we let $\varepsilon = -R$, then A_ε is simply the line L. Hence, the twist of DNA divides according to

$$\mathrm{Tw}(C, A) = \mathrm{Tw}(L, A) + \Phi(A).$$

We computed $\mathrm{Tw}(L, A)$ previously (27) from straightforward geometric considerations to be $-np/(p^2 + R^2)^{1/2}$. The second term, $\Phi(A)$, is the total helical turning, of which the best current experimental determination is (number of base pairs)/10.17. We emphasize that the local reference-frame twist can always be determined entirely from the local geometry, whereas the total helical turning must be experimentally measured.

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