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Abstract. Two separate regimes exist for the aspect ratio of DNA. A low aspect regime where DNA will twist further under strain and a high aspect regime where DNA will untwist under strain. The question of the overall geometry, i.e. the aspect ratio, of DNA is revisited from the perspective of a geometrical analysis of transcription. It is shown that under certain reasonable assumptions transcription is only possible if the aspect ratio is in the regime corresponding to further twisting. We find this constraint to be in agreement with long-established crystallographic studies of DNA.

Contents

1. Introduction

One classical way to characterize the overall geometry of DNA is through its aspect (pitch-to-width) ratio [1], see figure 1. Let A be the aspect ratio of DNA, and let A^* be the aspect ratio where DNA has a vanishing coupling between strain and twist. The coupling is negative below A^* and positive above A^*, i.e. below A^* strain leads to further winding rather than unwinding. Here, the restrictions inferred on the double-stranded DNA are studied in a geometrical analysis of the mechanics of transcription. We conclude that one must have $A < A^*$ for transcription to work.

The precise molecular mechanisms that control transcription are still to be fully explored, and represent a current theme of research in biology. In eukaryotes, a fundamental control point for the regulation of transcription is the structural adaptation of the chromatin fiber necessary to access the gene sequence. One scenario that has been proposed is based on the reversome (the mirror image of a nucleosome), explaining how transcription elongation can proceed within condensed chromatin [4].

Two criteria must be met for transcription to take place on a substring of a long string of DNA. The substring must melt into single-stranded DNA and in the untwisting of the two single strands, the remaining part of DNA must be able to absorb this twist, see figure 2. Without going into details here, this is one role of the reversome [5]. A mechanism for absorbing twist is the main point behind the present study. Of course there are various ways of absorbing twist, e.g. via topoisomerase [6]. However, when the number of rotations and counter-rotations become large the dependence on enzymes seems to us to be inefficient and to have the potential of slowing down the process. Another option is to form large plectonemic structures though this requires the availability of long and unrestricted stretches of DNA.

The topology of DNA in the chromosome has been studied in models taking into account possible local modifications and global constraints [7, 8]. For reviews on transcription and transcriptional regulation in relation to epigenetic phenomena, see [9, 10]. It has early been understood that the topology of DNA is essential to understanding transcription, in prokaryotes, one suggestion for this is the possible supercoiling of DNA during transcription [11, 12]. The mechanics of DNA and its topological supercoiling has been described using elastic models [13–15]. An elastic model has also been used to model DNA loops which play a role for the mechanics of transcription [16]; one suggestion is that transcription of a certain gene can be repressed or activated when a DNA loop is formed that contains that gene [17]. Constraints that involve the degree of twisting of DNA can have two origins. One origin is of topological nature, such as conservation of the linking number [18]. Another origin is longer-range interactions that are due to the range of the involved forces [19, 20]. An aspect of transcription involving the actual DNA geometry is the various stresses related to twist and strain when the B-DNA reorganizes itself before transcription. Experimental studies using magnetic tweezers and optical trapping suggest that DNA has a negative strain–twist coupling [21, 22]. Elongated DNA will therefore tend to rotate through a larger angle per set of base-pairs, i.e. to be twisting further. Recently, an analysis of the observed stick-slip melting of DNA under tension has revealed a zig-zag-like dynamics [23]. In [24], we have suggested a geometrical model that describes the phenomenon of winding of biological double helices as a generic phenomenon.
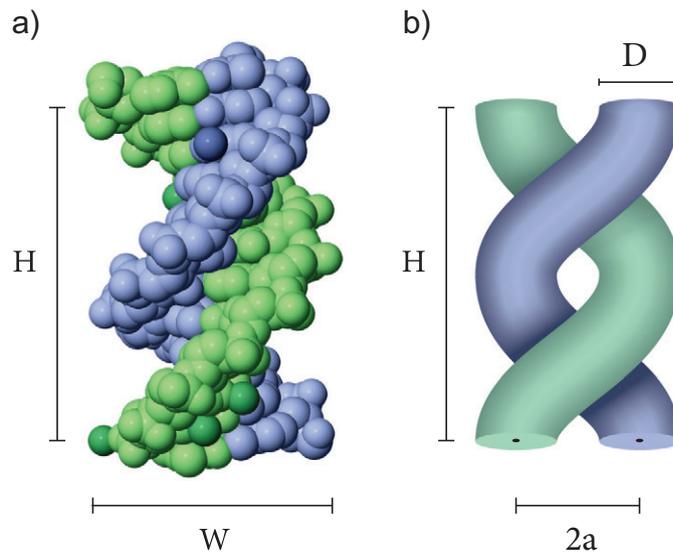
Figure 1. (A) B-DNA structure plotted using MATLAB R2011b (MathWorks) from crystallographic data deposited in PDB (The Protein Data Bank, see [2].). The entry id 425D was used, for additional information on the specific molecule, see [3]. Indicated in the figure is the pitch height, H, and the helix-packing diameter, W. The aspect ratio is $A = H/W$. (B) Sketch of tube model of DNA molecule discussed in section 2.
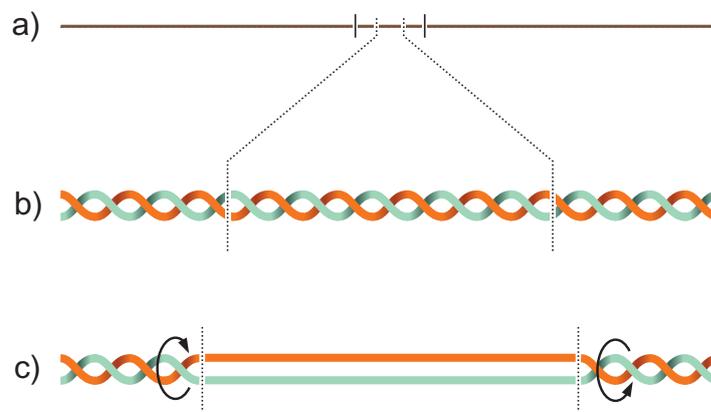
Figure 2. Transcription on (A) a long string of DNA; (B) a subsection of double-stranded DNA before melting takes place and (C) with strand separation having appeared. Also shown by arrows are the many rotations the DNA must be able to absorb.

2. Mathematical model

For transcription, we consider DNA to be part of a structure that does not change on a large scale (figure 2). Within this structure we consider an intermediate structure which is allowed to change while being maintained as a double helix. Finally, we consider a relatively short stretch of DNA that separates (melt) to two single-stranded DNA (figure 2(C)). The first of these considerations
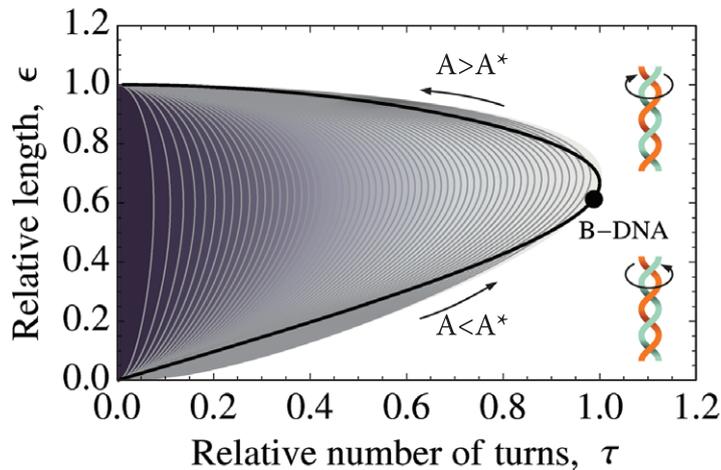
Figure 3. Relative length, ϵ, of double helix as a function of the relative number of turns, τ, on the strand. The solid curve is the configurations where the two strands are in contact. The aspect ratio increases along the curve from zero at the lower left corner, to 1.56 at the turning point, and approaching infinity at the upper left endpoint. In the present paper B-DNA is found to have an aspect ratio of 1.40 corresponding to the point below the turning point. The contour lines have constant volume fraction, along the outer contour its value is 0.597 corresponding to B-DNA.

requires that the length of DNA during transcription, L'_{DNA}, to be greater than the length of DNA before transcription, L_{DNA}, i.e.

$$L'_{DNA} > L_{DNA}. \tag{1}$$

Now, the twisting behavior of DNA depends on its aspect ratio, A. If the aspect ratio is such that DNA would simply unwind under strain, then equation (1) would not be fulfilled, as shown below. Instead the DNA would tend to get shorter during transcription. This is the origin of the constraint on A and shows that the behavior of B-DNA under strain must be opposite of that of a rope.

Here, we use an entirely geometrical approach and model DNA as a double helix of two flexible tubes with fixed thickness, D, see figure 1(B). For a geometry akin to the double-stranded DNA, the double helical structure has a length, $L_r(n)$, that depends on the number of twists, n [25] (see figure 3). When the strands are straight and parallel to each other, the length of the double helix is the same as the length of the strands, and as turns are added the double helix becomes shorter and shorter. Only up to a maximum number of turns can be added, resulting ultimately in a geometry which is maximally rotated. In addition, this structure has a vanishing strain–twist coupling [24]. As rotations are removed from the helix, the length becomes further reduced, see the lower part of the curve of figure 3. Here, the strands are twisted together on a cylinder which becomes bigger and bigger as one moves away from the tip. Therefore, $L_r(n)$ is shaped like a horizontal hairpin, see figure 3.

In the calculation of $L_r(n)$, the center lines of the two tubes are coiled with pitch H on a common cylinder of radius a. In terms of these parameters, the aspect ratio is $A = H/(2a + D)$. The pitch angle, $v_\perp$, measured from the horizontal is determined by $\tan v_\perp = H/2\pi a$. For these

idealized structures, the steric interactions of molecular DNA are described by letting the tubes be in contact with hard walls, i.e. the distance between the two helical lines should satisfy

$$\min(|\vec{r}_1(t_1) - \vec{r}_2(t_2)|) = D, \tag{2}$$

where $\vec{r}_1$, $\vec{r}_2$ describe the two helical center lines and t_1, t_2 parameterize the two helical lines of the double-stranded molecule.

Mathematically, the two helical center lines in equation (2) have the parametric equations

$$\vec{r}_1(t_1) = (a\cos t_1, a\sin t_1, (H/2\pi)t_1),$$
$$\vec{r}_2(t_2) = (a\cos t_2, a\sin t_2, (H/2\pi)t_2 + \Psi(H/2\pi)) \tag{3}$$

with t_1, $t_2 \in \mathbf{R}$. The parameter Ψ is a phase parameter that determines if the double helix is symmetric or asymmetric. For a symmetric double helix, e.g. A-DNA, Ψ is equal to π and for an asymmetric double helix, akin to B-DNA, we have $\Psi = \pi\,144°/180° = 2.513$. The phase difference of $144°$ for the minor groove in B-DNA is described in [26]. With D being the tube diameter, the points of tube–tube contacts obey the equation

$$D^2 = a^2(\cos t - 1)^2 + a^2\sin^2 t + \left(\frac{H}{2\pi}\right)^2 (\Psi + t)^2, \tag{4}$$

where $t = t_1 - t_2$. The solutions to the condition of minimum distance, equation (2), is found from a numerical study of the equation, $\mathrm{d}D^2/\mathrm{d}t = 0$; for further details, see [27–29]. These solutions can also be found with the help of a non-Euclidian geometry [30].

3. Constraint on the aspect ratio

Figure 3 shows how the (relative) length of the double helix depends on the number of turns in the twisted strands using equation (4); the specific curve is for the asymmetric double helix with $\Psi = 2.513$. The vertical axis is the relative length, ϵ, of the double helix, where $\epsilon = L_r/L_s$ and L_s is the strand length. The horizontal axis is the relative number of turns, $\tau = n/n_{max}$, where n_{max} is the number of turns at the turning point for $L_s = 1$. At the turning point, where τ is maximal, the aspect ratio takes a unique value, $A = A^*$, at which the double helix has zero strain–twist coupling. Below this turning point the double helix tends to twist further under strain, and above to untwist as indicated by the arrows on the two helices to the right. In [24] it was found that $A^* = 1.56$ for an asymmetric double helix (B-DNA) corresponding to $\epsilon = 0.6665$. The contour plot in figure 3 shows lines of constant volume fraction, f_V. The volume fraction is defined locally as the volume of the two strands relative to the volume of a smallest enclosing cylinder [27]. The boundary of the contour plot has $f_V = 0.597$ which is the maximal volume fraction for the asymmetric double helix. The contour plot shows that when straining DNA, its geometry tends to follow the solid curve—at this point its tangent is also tangent to lines of constant volume fraction.

Let us assume that transcription is to take place on a short stretch of a long stretch of DNA without changing the total twist. The long DNA has strand length L, and the short stretch strand length l. The number of turns on the long DNA is $n_{DNA} = \tau_L n_{max} L$, and during transcription it is $n'_{DNA} = \tau_{L-l} n_{max} \cdot (L - l)$. Therefore, $\tau_{L-l} = \frac{L}{L-l}\tau_L$. On the stretch where transcription takes place, we have $\epsilon_l = 1$; that corresponds to the upper left endpoint of the curve in figure 3. The remaining part of the DNA has a relative length ϵ_{L-l}, which for now is undetermined.
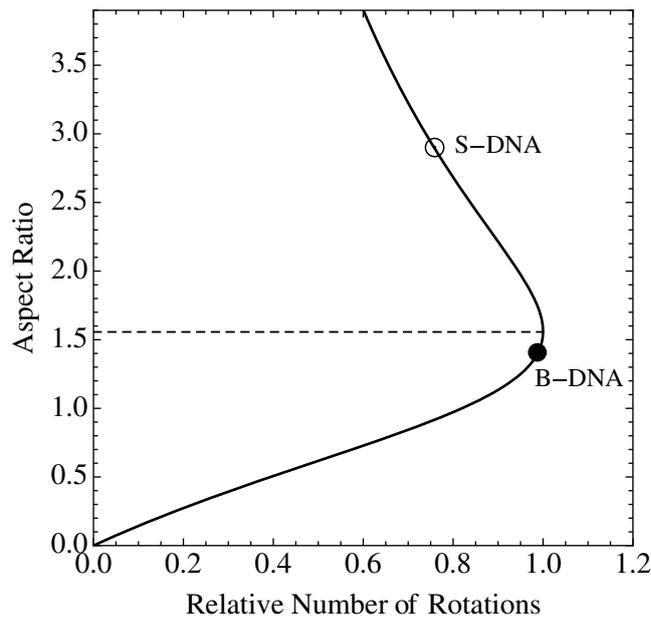
Figure 4. Aspect ratio of DNA versus number of rotations on the double helix (solid line). At the turning point the aspect ratio is $A^* = 1.56$ (dashed line), separating two regimes with low and high aspect ratio, respectively. The circle at $A = 2.90$ is the aspect ratio of an example of a stretched DNA, so-called S-DNA from [31].

The difference in the length of DNA after and before transcription is

$$L'_{\text{DNA}} - L_{\text{DNA}} = l\epsilon_l + (L - l)\epsilon_{L-l} - L\epsilon_L. \tag{5}$$

If this number is positive, then the DNA gets longer under transcription. If it is negative the DNA gets shorter. We will assume that the DNA is part of a much larger structure (e.g. chromosomes) and therefore it is advantageous not to get shorter as this can create undesirable, and perhaps even unhandleable strain. Now, let l be small compared to L, $l \ll L$, and series expand ϵ_{L-l} to obtain, $\epsilon_{L-l} = \epsilon_L + \frac{\partial \epsilon}{\partial \tau} \frac{l}{L-l} \tau_L$. Here is used the assumption that the total twist is constant and equal to $\tau_L n_{\max} L$. Therefore equation (5) can be rewritten as

$$L'_{\text{DNA}} - L_{\text{DNA}} = l \left(1 - \epsilon_L + \frac{\partial \epsilon}{\partial \tau} \tau_L \right). \tag{6}$$

Due to the convex nature of the curve in figure 3, the requirement that this difference is greater than zero cannot be obtained on the upper part of the curve where it is continuously bending downwards. We must be on the lower part of the curve in figure 3, so that the aspect ratio obeys $A < A^*$ for transcription to be possible.

In figure 4 is plotted the aspect ratio as a function of the number of turns, τ. The turning point is at $A = A^*$, the solid circle is the experimentally determined aspect ratio of B-DNA (see next section) and the circle is the aspect ratio of an example of a stretched DNA, S-DNA from [31] which unwinds under strain as opposed to regular B-DNA.

Table 1. Pitch height, H, and width, W, experimental values for crystallized A-DNA and B-DNA reproduced from [1]. Also given are derived values for aspect ratio A and pitch angle $v_\perp$. The corresponding A^* is obtained from [24].

	H(Å)	W(Å)	A	A^*	$v_\perp$
B-DNA	33.2	23.7	1.40	1.56	38°
A-DNA	24.6	25.5	0.96	1.32	28°

4. The aspect ratio and pitch angle of A- and B-DNA

What is the experimentally determined aspect ratio of DNA? The DNA pitch height, H, can accurately be determined by experiment. It is the height for which the helical structure progresses with precisely one full rotation. The helix-packing diameter [1], or simply the width, W, of the molecule, can also be accurately determined. A classical work that lists the values of H and W for crystal structures of DNA is the Cold Harbor Symposium contribution by Dickerson *et al* [1]. The results are reproduced in table 1, together with our calculated aspect ratios. Figure 1(A) depicts H and W for the B-DNA structure PDB 425D [3]. The helical geometry is clearly visible, however it is superficial to determine the pitch angle $v_\perp$ (the angle that the helical center line makes with the horizontal) by the naked eye from a two-dimensional projection. One needs to carry out a genuine three-dimensional geometrical study.

There is some debate in the scientific community about the interpretation and specific value of the pitch angle of B-DNA. In particular, some publications advocate a structure for DNA that has a pitch angle of 45° [32, 33] based on the *symmetric* double helix. This corresponds to a point on the upper part of the A-DNA symmetric version of the curve in figure 3 with $\epsilon = 0.707$. In fact, the pitch angle can be indirectly determined from the aspect ratio above. For the double helix with phase parameter Ψ, the equation (4) gives a unique curve for $2a/D$ as a function of pitch angle, that is monotonically decreasing. The relation between the pitch angle $v_\perp$ and the aspect ratio A reads

$$A(v_\perp) = \frac{\pi \tan v_\perp}{\phi(v_\perp)}, \tag{7}$$

where $\phi(v_\perp) = 1 + D/2a$. Figure 5 shows how the aspect ratio, A, depends on the pitch angle, $v_\perp$, for a tubular double helix by solving numerically equation (2). The solid curve in figure 5 is for an asymmetric double helix mimicking B-DNA. For an aspect ratio of 1.40 we obtain the pitch angle $v_\perp = 38°$ shown by a solid circle. The dashed curve is for a symmetric double helix such as A-DNA. It passes through the point $(45°, \pi/2)$. The experimentally determined aspect ratio for A-DNA is 0.96. This corresponds to a pitch angle of 28° as shown in figure 5 by a second solid circle.

In its crystallized form, B-DNA has ten base-pairs per turn, and using equation (7) one obtains a pitch angle of $\sim$38°. Non-crystallized DNA has about 10.5 base-pairs per turn. It is therefore further away from the turning point of the curve in figure 3 and consequently has a slightly lower pitch angle[2]. Table 1 summarizes our results for crystallized DNA.

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[2] For 10.5 bp/2π in B-DNA, the number of turns, τ, is reduced by a factor of 10/10.5, hence a quick estimate finds that the pitch angle is $v_\perp \sim 33°$, i.e. to be further below the zero-twist angle. Other sources, such as textbooks, differ slightly on the reported structural parameters and a typical number given is $2a = 20$ Å. This corresponds to a pitch angle of $v_\perp \sim 36°$.
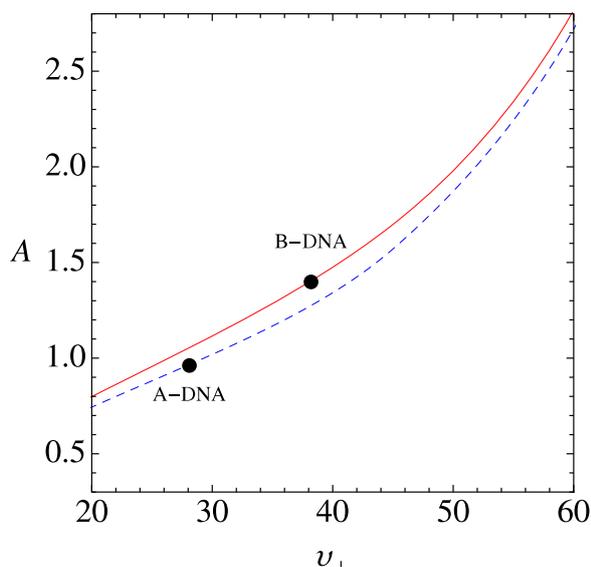
Figure 5. Aspect ratio A versus pitch angle $v_\perp$ plotted for double helix with minor groove (solid, red curve) and symmetric double helix (dashed, blue curve). The solid circles are for A-DNA and B-DNA using [1].

5. Discussion

In summary we have shown that the often visited question of excessive rotations (overwinding) of DNA under transcription [34] does not need to appear if transcription is initiated from the $A < A^*$ regime. Alternatively, changes in plectonemic structures can be invoked to release strain [35], enzymes can release overwinding as well as change the linking number [4]. Recently, the energetics of transitions in the supercoiling state have been studied in careful details [36], and the dynamics of supercoils have been observed directly in single-molecule studies [37]. The unfolding of the chromatin fiber remains an interesting subject where there currently is significant progress [38–40]. This field remains under ongoing debate [41–43].

In this paper we have discussed the hitherto little discussed possibility that DNA can itself absorb the additional rotations needed for transcription. Naturally, this will work in concert with enzymes plectonemic structure formations when available. Of course, the presented numerical results depend in detail on the tubular model. However, the phenomenon discussed depends only on the existence of the two regimes $A > A^*$ and $A < A^*$ and hence the ability to absorb twist does not depend in mathematical detail on the tube model.

In the presented considerations we had, in principle, an infinitely long string of DNA available. For finite-size systems one can expect a dependence not just on the length but also on the number of rotations being an integer or not as has recently been demonstrated [44].

Acknowledgment

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