Folding DNA into nucleosome and chromatin: dynamics.

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Abstract

A theoretical framework for evaluating the approximate energy and dynamic properties associated with the folding of DNA into nucleosomes and chromatin is presented. For this purpose experimentally determined elastic constants of linear DNA and a simple fold geometry are assumed to derive constants for the higher order folding. The model predicts the correct order of magnitude for the experimentally determined Young’s and shear modulus of condensed chromatin. Thus we have demonstrated that the elastic properties of DNA are the primary determinant of the elastic properties of each folded state. The derived elastic constants are then used to predict the speed of propagation of small amplitude waves. It is shown that extension/compression, twist, bend or shear waves can be excite in each folded state.

Introduction

The folding of DNA into higher order structures is readily observed, but the path of DNA through these folded structures has not been determined

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conclusively [1]. Only the structure of individual nucleosome particles that have been crystallized is available at atomic resolution [2]. The x-ray structures of the nucleosome reveal that DNA is wrapped around a histone core in a somewhat irregular, left-handed helical path, but these structures do not provide information on how multiple nucleosomes are arranged on a length of double stranded DNA in chromatin. For this purpose a variety of experimental techniques (see [1]) as well as computational modeling [3, 4, 5, 6] have been used. In our model the hierarchy of folding: DNA, nucleosomes, condensed chromatin, corresponds to the hierarchy of equilibrium conformations that exist for an elastic rod [7, 8, 9]. In elastic rod theory these folded states are unstable, but biologically we know that the first folding (nucleosomes) is stabilized by the histone octamer and the second folding (condensed chromatin) is stabilized by linker histone [10].

Both an extended and condensed form of chromatin exists. The extended conformation of chromatin is an irregular, 3-dimensional zig-zag pattern of what appears to be intact nucleosomes unevenly spaced along DNA. The degree of compaction of this zig-zag structure is known to be affected by the ionic environment [11]. The length of linker DNA between nucleosomes and the entry/exit angle of the linker from each nucleosome are important but nonetheless secondary determinants. The primary determinant of the structure of extended chromatin is the histone octamer, since under appropriate conditions the zig-zag can be condensed into a more or less continuous, irregular 11 nm fiber with essentially zero length linker. To obtain the next level of folding, what we refer to as condensed chromatin with a diameter of approximately 30 nm, requires the presence of linker histones [11]. Thus the primary determinant of the folding of extended chromatin into condensed chromatin is linker histone. The path of DNA in condensed chromatin is determined by the arrangement of nucleosomes within the fiber and in turn, it is expected that the arrangement of nucleosomes is determined by whether or not the linker DNA between nucleosomes bends or remains straight.

A recent review [1] favors straight linkers and an arrangement of nucleosomes that resembles the 2-start model over the solenoid [12] or coiled-linker models, (the latter two assume a bent linker), but the evidence is still inconclusive. Virtually all models assume the nucleosome maintains the x-ray structure. This does not seem justified when it is known that the two (H2A-H2B) dimers that form part of the octamer core can readily dissociate from the nucleosome in solution and can be reversibly dissociated by changing ion
concentrations [13]. Furthermore the affects of linker histone on the structure of the nucleosome, in particular the histone core, are not known. A "pear-shaped" structure is apparently induced in the nucleosome upon the binding of linker histones, as observed with electron microscopy [14, 15] and scanning force microscopy [14]. Single fiber pulling experiments demonstrate that there are discrete "jumps" as histones dissociate from extended chromatin fibers suggesting a simple on/off association of the histone octamer, but the data also indicate a linear force-extension relationship for the gross properties of the extended chromatin fiber, Figure 3b in [16].

Our view is that nucleosomes in particular is the arrangement of the core histones will likely be altered by both the addition of linker histones and the constraints imposed by folding or external forces. The latter occur during experimental manipulations, as well as, biological processes. The observed irregularities in extended and condensed chromatin result from a fluid-like motion of histones within nucleosomes and of nucleosomes along chromatin in a fairly smooth energy landscape with multiple local minima. The local minima are due in part to the sequence dependent nature of DNA, the particular state of modification of the DNA and the histones, and differences in the local environment. At the molecular level, the local environment has an inhomogeneous distribution of ions and/or DNA binding proteins. The barrier between these minima is relatively low thus well-defined regular structures do not exist. We assume that to a first approximation, i.e. we smooth out the energy landscape even further, the structures of extended and condensed chromatin are governed by the elastic properties of DNA and can be predicted based on the theory of elastic rods [7, 8, 9, 17, 18]. As noted by Bishop and Hearst [17], the "pear-shaped" or elliptic structures that are observed are a tell-tale sign that DNA is behaving as an elastic rod even when it is folded into nucleosomes and the energy landscape associated with a potential function describing chromatin folding is sufficiently flat to allow for the irregularities noted above. Furthermore the effect of combining a histone core that tends towards cylindrical symmetry with a wrapping of DNA that tends towards elliptic cross-sections, as predicted by elastic rod theory, produces an interaction that explains the deviation in the path of DNA as it passes over the dyad axis of symmetry of the nucleosome.

In order to extend our potential function representation of the folding of DNA into nucleosomes and chromatin, we seek first to determine to what degree DNA alone contributes to the observed properties of these structures.
For this purpose we analyze the elastic properties of an idealized nucleosome that results from folding DNA into a regular left handed helix. If this helix is extended beyond the 1.75 turns that correspond to a single nucleosome, it will form a linear array of nucleosomes aligned end to end, as has been suggested for the structure of telomeric DNA [19]. We propose that such a model approximates the properties of extended chromatin in the limit of a zero length linker even if it does not represent the actual structure [20]. In a like manner condensed chromatin is modelled as a regular right handed helix constructed from a linear array of nucleosomes, similar to the solenoid or coiled linker models and a close approximation to the helix-on-a-linear helix predicted by elastic rod theory. The model predicts that the elastic properties of DNA are the primary determinant of the elastic properties of each folded state. Our results can also be used to relate experimentally determined elastic properties to the velocity of propagation of mechanical disturbances in DNA and chromatin, which has direct relevance for molecular processes.

In the next section we present the equations of motion of an elastic rod and outline the derivation of our linear analysis [21]. We then demonstrate how to use the known elastic constants of DNA to evaluate the velocity of propagation of various mechanical disturbances through DNA. In subsequent sections we use the elastic constants for DNA to obtain effective elastic constants for nucleosomes, extended and condensed chromatin. For each fiber we calculate the speed of propagation of mechanical disturbances.

Our paper is based on a continuous medium model of DNA. Such an approach is well known and widely used to describe solids, liquids and gases (see, for example [22, 23]). Thus, when we speak of infinitely small elements of volume, we shall always mean those which are "physically" infinitely small, i.e. very small compared with wavelength or radius of curvature under consideration, but large compared with the distance between the atoms in DNA.

1 Dynamics of an Elastic Rod.

We utilize a uniform isotropic elastic rod model for which analytic solutions for the equilibrium configurations have been determined [8] and parameterized to represent the observed folding of DNA [18]. Such an elastic rod model is a suitable description for small deformations of any solid body that is long, slender and possesses uniform material properties. Here, small refers to the
length scale of the deformation in comparison to the length scale of the rod, but still large compared to the distance between atoms. Thus the results presented in this section apply to macroscopic objects such as cables and beams, as well as hair and cilia, actin filaments and DNA. Strictly speaking all experiments cited above silently suppose that DNA is a continuous media with no structure. One only needs to utilize the appropriate elastic constants for each entity to apply the results. The equations of motion [24] for such an elastic rod can be solved numerically and visualized in 3-dimensional space [25].

A natural coordinate system for expressing the equations of motion of an elastic rod is a so-called internal coordinate system that relates the translation, denoted by the three-vector $\vec{\Omega}$, and the rotation, denoted by the three-vector, of one cross-section with respect the adjacent one. These six coordinates have a one to one correspondence to the six helical parameters that describe DNA. In biologic terminology the three components of $\vec{\Gamma}$ correspond to the basepair parameters (shift, slide, rise) and the three components of $\vec{\Omega}$ correspond to (roll, tilt, twist). Formally, the components of $\vec{\Gamma}$ and $\vec{\Omega}$ are orthogonal and are defined only in the limit of infinitesimally thin “basepairs”. For an actual strand of DNA, $\vec{\Gamma}$ and $\vec{\Omega}$ will also be functions of time, $t$, and location along the strand of DNA, $s$. Each basepair will also possess translational and rotational velocity, denoted by $\vec{\gamma}$ and $\vec{\omega}$. The equations of motion expressed in such a coordinate system are as follows:

$$
\rho \left( \frac{\partial \vec{\gamma}}{\partial t} + \vec{\omega} \times \vec{\gamma} \right) = \hat{C} \cdot \frac{\partial (\vec{\Gamma} - \vec{\Gamma}_0(s))}{\partial s} + \vec{\Omega} \times \left( \hat{C} \cdot (\vec{\Gamma} - \vec{\Gamma}_0) \right) \tag{1}
$$

$$
\hat{I} \cdot \frac{\partial \vec{\omega}}{\partial t} + \vec{\omega} \times (\hat{I} \cdot \vec{\omega}) = \hat{D} \cdot \frac{\partial (\vec{\Omega} - \vec{\Omega}_0(s))}{\partial s} + \vec{\Omega} \times \left( \hat{D} \cdot (\vec{\Omega} - \vec{\Omega}_0) \right) + \vec{\Gamma} \times \left( \hat{C} \cdot (\vec{\Gamma} - \vec{\Gamma}_0) \right) \tag{2}
$$

$$
\frac{\partial \vec{\Gamma}}{\partial t} + \vec{\omega} \times \vec{\Gamma} = \frac{\partial \vec{\gamma}}{\partial s} + \vec{\Omega} \times \vec{\gamma} \tag{3}
$$

$$
\frac{\partial \vec{\Omega}}{\partial t} + \vec{\omega} \times \vec{\Omega} = \frac{\partial \vec{\omega}}{\partial s} \tag{4}
$$

The diagonal matrix $\hat{I}$ is the linear density of the inertia tensor for a cross-section of the rod. The matrix $\hat{C}$ contains the shear ($\mu$) and Young’s modulus ($Y$) as the diagonal elements and zeros everywhere else; $\hat{D}$ contains
the bend stiffness \((D_{1,2})\) and torsional rigidity \((D_3)\) as diagonal elements; and 
\(\rho\) is the linear density of the rod.

The first equation in (1-4) represents the balance of force and linear momentum and the second equation represents the balance of torque and angular as written in the reference frame of the rod. The use of Hooke’s Law to describe bending/twisting deformations with respect to some arbitrary intrinsic bend/twist state denoted by \(\vec{\Omega}_0\) is apparent. A similar statement applies to shear/stretch deformations with respect to some intrinsic shear/extension \(\vec{\Gamma}_0\). For ideal B-form DNA \(\vec{\Omega}_0 = (0, 0, 36^0/bp)\) and \(\vec{\Gamma}_0 = (0, 0, 3.4 \text{ Å}/bp)\). The third and fourth equations arise from geometrical considerations. More thorough descriptions can be found in [24, 25].

In subsequent sections we consider DNA as an elastic rod, extended chromatin as an elastic rod and condensed chromatin as an elastic rod. In each case we only have to determine appropriate values for each of the matrices in the above equations. Once these values have been determined the velocity of propagation of a mechanical disturbance through each structure can be evaluated as described below.

A linear analysis (small amplitude disturbances) of equations (1-4) indicates that four different types of waves can propagate through the elastic rod [21]. These are an extension/compression, bend, twist, or shear waves in the rod. In the limit of very short wavelength (wavelength is much smaller than scale parameters of the problem, e.g. much less than radius of curvature of the rod) these four types propagate independently of one another and independently of a shape of a rod. In this case expressions for speed of waves propagation will be obtained below.

The linear analysis assumes that the four three-vector functions \(\vec{\Gamma}(s, t)\), \(\vec{\Omega}(s, t)\), \(\vec{\gamma}(s, t)\) and \(\vec{\omega}(s, t)\) each have the functional form \(\vec{G}_i(s, t) = \vec{G}_{i0} \cdot \exp(-i\omega t + iks)\) where \(\vec{G}_{i0}\) is a constant. Upon substitution into the linearized equations of motion one obtains the following relations:

\[
\begin{align*}
&i\omega^2 \rho \vec{\Gamma} - ik^2 (\vec{C} \cdot \vec{\Gamma}) = 0 \quad (5) \\
&i\omega^2 (\vec{I} \cdot \vec{\Omega}) - ik^2 (\vec{D} \cdot \vec{\Omega}) = 0 \quad (6)
\end{align*}
\]

It is convenient to split the longitudinal and transverse components with help of the definitions \(\vec{\Gamma}_\perp \equiv (\Gamma_1, \Gamma_2, 0)\) and \(\vec{\Omega}_\perp \equiv (\Omega_1, \Omega_2, 0)\). In this way we can easily divide the four types of wave types which can propagate along the rod. The equations below correspond to four waves: shear, extension, bend and
We point out that in general case (arbitrary wavelength) bend and shear waves are coupled but extension and twist remain independent. Moreover it can be shown that for straight rod extension and twist waves have ”special” properties. They are independent of each other and of bend and shear waves even for not small wave amplitudes. Our assumption of a circular cross section \((D_1 = D_2, C_1 = C_2 \text{ and } I_{xx} = I_{yy})\) results in a equivalents speed of propagation for both components of bend and shear.

Explicit expressions for the wave velocities are:

- **Shear waves \(\vec{\Gamma}_\perp\):**
  \[
  V_{\text{Shear}} = \frac{\sqrt{\mu}}{\sqrt{\rho}}
  \]
  \(\text{Eq. 11}\)

- **Extension waves \(\Gamma_3\):**
  \[
  V_{\text{Extension}} = \frac{\sqrt{Y}}{\sqrt{\rho}}
  \]
  \(\text{Eq. 12}\)

- **Bend waves \(\vec{\Omega}_\perp\):**
  \[
  V_{\text{Bend}} = \sqrt{\frac{D_{1,2}}{I}}
  \]
  \(\text{Eq. 13}\)

- **Twist waves \(\Omega_3\):**
  \[
  V_{\text{Twist}} = \sqrt{\frac{D_3}{2I}}
  \]
  \(\text{Eq. 14}\)

We point out that expressions (11-14) are rightly for a rod of arbitrary shape because in the short wave limit all terms that define the rod shape in equations (1-4) were vanished.

It is well known that the measurement of wave velocities is a usual method for determining elastic properties of solids. Just so the DNA elastic properties were studied in [29].
2 Dynamics of linear DNA.

Having obtained expressions (11-14) we evaluate the propagation velocities of each type of mechanical disturbance for linear B-form DNA using the elastic properties listed in Table 1. The results are listed in Table 3. For our calculations we have used a linear density of DNA of $\rho_{\text{DNA}} = 660 \text{Da/basepair} \cdot \text{basepair}/0.34\text{Å}$, and assumed a DNA radius of $1.0 \text{ nm}$ with a circular cross-section for determining the moment of inertia tensor.

| Elastic Constant       | Symbol | Value                   |
|------------------------|--------|-------------------------|
| Young’s modulus        | $Y$    | $1.09 \cdot 10^{-9}[\text{KM}/\text{S}^2]$ |
| Shear modulus          | $C$    | $8.16 \cdot 10^{-9}[\text{KM}/\text{S}^2]$ |
| Torsion rigidity       | $\mu$  | $2.02 \cdot 10^{-28}[\text{KM}^3/\text{S}^2]$ |
| Bend stiffness         | $A$    | $2.7 \cdot 10^{-28}[\text{KM}^3/\text{S}^2]$ |
| Linear density         | $\rho$ | $3.22 \cdot 10^{-15}[\text{K}/\text{M}]$ |
| Moment of inertia      | $I_{xx,yy}$ | $8.05 \cdot 10^{-34}[\text{K.M}]$ |
|                        | $I_{zz}$ | $1.61 \cdot 10^{-33}[\text{K.M}]$ |

Table 1: Elastic Constants for linear DNA [26, 27, 29, 30].

Here we have used the quantities $Y^* = Y \cdot A$ where $Y$ is the Young’s modulus as expressed in the text, $A$ is the area of the cross-section, and $Y^*$ is the stretch modulus. Similarly $\mu^* = \mu \cdot A$.

3 Effective Elastic Constants for Nucleosomes and Chromatin.

In this section we demonstrate how to determine effective elastic constants for nucleosomes and condensed chromatin. For this purpose we analyze the nucleosome as a regular helical spring made of DNA and condensed chromatin as a regular helical spring made of a linear array of nucleosomes. In case of the ”nucleosome spring” we consider two limiting cases. In the first case, we imagine that the histones stably fold the DNA into a helix, yet the DNA is free to undergo small deformations independent of the histones. For this
case the histones are completely ignored, and the nucleosome is really a spring made from DNA. In the second case we imagine that the DNA is rigidly attached to the histones but that the elastic properties of the nucleosome are still governed by DNA. In this case the nucleosome is a spring made from DNA but it is filled with a core material made of histones. For the analysis we need to know the elastic constants of DNA, the linear density of DNA and the histones and the fold geometry. Since each fold is a simple helix, the pitch and radius of the helix define the geometry. The radius of each helix is defined as the centerline path of the DNA in case of the nucleosome and the center line path of the nucleosomes in case of condensed chromatin.

3.1 DNA elastic properties.

3.1.1 Geometry of folding.

A length of linear DNA we shall designate by an $l$, a length of a linear array of nucleosomes by an $L$ and a length of the condensed chromatin by an $\mathcal{L}$. The radius of linear DNA is $a = 1.0 \text{ nm}$, the radius of the nucleosome is $R = 4.5 \text{ nm}$ and the radius of condensed chromatin is $\mathcal{R} = 9.5 \text{ nm}$. The nucleosome’s pitch is $h = 2.5 \text{ nm}$ and chromatin’s pitch is $H = 15 \text{ nm}$. Note that there are 1.75 turns of the helix for a single nucleosome, but for a linear array of nucleosomes there will be $n$ turns. Thus we can evaluate $L = n \cdot h$ and similarly for $N$ turns of the $30nm$ fiber $\mathcal{L} = N \cdot H$. The length of linear DNA contained within $n$ turns of a linear array of nucleosomes is $l_{\text{nuc}} = \sqrt{(n2\pi R)^2 + (nh)^2}$ and the length of a linear array of nucleosomes contained within $N$ turns of condensed chromatin is $L_{\text{cc}} = \sqrt{(N2\pi \mathcal{R})^2 + (NH)^2}$. This yields a factor of $l_{\text{nuc}}/L \sim 10$ for the compaction of DNA into nucleosomes and an additional factor of $L_{\text{cc}}/\mathcal{L} \sim 4$ for the compaction of nucleosomes into condensed chromatin.

3.1.2 Linear mass density and moments of inertia.

In the limit that the DNA functions independently of the histones, the linear density of the nucleosome is easy to calculate. The linear density of our ”nucleosome spring” is:

$$\rho_{\text{nuc}} = \rho_{\text{dna}} \cdot \frac{l_{\text{nuc}}}{L} \approx 3.66 \cdot 10^{-14}[K/M]$$

(15)
In the limit that the histones are rigidly attached to the DNA the linear density of the nucleosome is the sum of the linear density expressed above and the linear density of histones (108,500 Da/nucleosome). In this limit \( \rho_{\text{nuc}} = 1.1 \cdot 10^{-13}[K/M] \).

The linear density of condensed chromatin is accordingly \( \rho_{\text{cc}} = \rho_{\text{nuc}} L_{\text{cc}}/L \) with a value of \( 4.5 \cdot 10^{-13}[K/M] \) for the limiting case of the histones rigidly attached to the DNA. We point out that to vary the linker length the value of \( l_{\text{nuc}} \) should be changed accordingly.

For determining the moments of inertia we consider each spring as a hollow elastic rod. The walls are made of DNA in case of the "nucleosome spring" and of nucleosomes in case of the "condensed chromatin spring". Again, the nucleosome spring has two limits. In the limit that the DNA is rigidly attached to the histones, the core of the spring is filled with histones and the moments of inertia are calculated according to the expressions for rods. In the limit that the DNA is independent of the histones, the nucleosome spring is hollow, and the moments of inertia are calculated as for a tube. Analysis of the elastic constants in the latter limit is formally equivalent to our analysis of a condensed chromatin spring.

### 3.2 Elastic constants for Nucleosomes and Extended Chromatin.

#### 3.2.1 Extension/compression constant of the nucleosome.

Following the analysis of springs presented in Elmore and Heald [28], when our "nucleosome spring" is stretched along the axial direction the DNA in the nucleosome undergoes a twisting deformation. The twisting deformation of the DNA treated as a solid cylinder is related to its shear modulus, thus the nucleosome spring constant \( k_{\text{nuc}} = F/\Delta X \) relates to the shear modulus of the DNA, \( \mu_{\text{dna}} \), as follows:

\[
k_{\text{nuc}} = \frac{\pi \mu_{\text{dna}} a^4}{2 R_{\text{cent}}^2 l_{\text{nuc}}} \tag{16}
\]

Here \( a \) is the radius of the DNA, \( R_{\text{cent}} \) is the centerline radius of the nucleosome spring and \( l_{\text{nuc}} \) is the length of DNA in the nucleosome. We now treat the nucleosome spring as a cylinder with outer and inner radii, \( R_{\text{out}} \) and \( R_{\text{in}} \) and cross-sectional area, \( A = \pi \{(R_{\text{out}})^2 - (R_{\text{in}})^2\} \). The Young’s modulus for
such a hollow cylinder is (Young’s modulus is related to the stretch modulus $Y^* = Y \cdot A$):

$$Y_{\text{nuc}} = \frac{k_{\text{nuc}}L}{A} = \frac{\mu_{\text{dna}}a^4L}{2R^2(R_{\text{out}}^2 - R_{\text{in}}^2)l_{\text{nuc}}} \quad (17)$$

In the first limiting case the DNA moves independently of the histone core so we choose $R_{\text{out}} = R + a$ and $R_{\text{in}} = R - a$. In the second limiting case the DNA is rigidly attached to the histone core so we choose $R_{\text{out}} = R + a$ and $R_{\text{in}} = 0$. The corresponding values for the Young’s modulus are given in Table 2. There also one can find shear modulus, torsion rigidity and bend stiffness that will be evaluated below.

3.2.2 Shear constant.

Again, following the analysis of springs in [28], we determine the shear constant for the nucleosome by supposing that a pair of equal and opposite axial torques $M$ is applied to the ends of our nucleosome spring that has length $L$. Such a twisting distortion of the nucleosome causes the radius of the nucleosome to increase or decrease thus bending the DNA. So the twist constant of our nucleosome spring is a function of the bend stiffness of the DNA. The torsion constant for the nucleosome spring is:

$$k_{\varphi-\text{nuc}} = \frac{M}{\varphi} = \frac{2IY}{l_{\text{nuc}}} = \frac{\pi Y_{\text{dna}}a^4}{2l_{\text{nuc}}} \quad (18)$$

where $\varphi$ is twist angle of the nucleosome, $I = (\pi/4)a^4$, is the moment of the DNA cross-section, $Y_{\text{dna}}$ is the Young’s modulus of the DNA, and $l_{\text{nuc}}$ is the length of DNA in the nucleosome. We now consider the nucleosome as a cylinder with outer and inner radii, $R_{\text{out}}$ and $R_{\text{in}}$, and write an expression for the torsion constant as follows:

$$M = \frac{\pi}{2} \mu_{\text{nuc}} \frac{R_{\text{out}}^4 - R_{\text{in}}^4}{L} \quad (19)$$

Here $\mu_{\text{nuc}}$ is shear modulus of the nucleosome, and $L$ is its length. Equating these two expressions we obtain ($\mu^* = \mu \cdot A$ as for the Young’s modulus):

$$\mu_{\text{nuc}} = \frac{Y_{\text{dna}}a^4L}{(R_{\text{out}}^4 - R_{\text{in}}^4)l_{\text{nuc}}} \quad (20)$$
In the first limiting case the DNA moves independently of the histone core so we choose $R_{\text{out}} = R + a$ and $R_{\text{in}} = R - a$. In the second limiting case the DNA is rigidly attached to the histone core so we choose $R_{\text{out}} = R + a$ and $R_{\text{in}} = 0$. The corresponding values for the shear modulus are given in Table 2. In that table units are the same as in the Table [I].

### 3.2.3 Torsional rigidity constant.

Having obtained $\mu_{\text{nuc}}$ we can now evaluate the torsional rigidity constant of a cylinder as a function of shear modulus:

$$D_{\text{nuc}}^3 = \frac{1}{2} \mu_{\text{nuc}} \pi (R_{\text{out}}^4 - R_{\text{in}}^4)$$  \hspace{1cm} (21)

In the limiting case that the DNA moves independently of the histone core $R_{\text{out}} = R + a$ and $R_{\text{in}} = R - a$. In the other limit $R_{\text{out}} = R + a$ and $R_{\text{in}} = 0$. The values for the torsional rigidity are listed in Table 2.

### 3.2.4 Bend stiffness constant.

To complete the analysis, the bending stiffness of a hollow rod with circular cross-section is a function of its Young's modulus as follows:

$$D_{1,2}^{\text{nuc}} = \frac{1}{4} Y_{\text{nuc}} \pi (R_{\text{out}}^4 - R_{\text{in}}^4)$$  \hspace{1cm} (22)

In the limiting case that the DNA moves independently of the histone core $R_{\text{out}} = R + a$ and $R_{\text{in}} = R - a$. In the other limit $R_{\text{out}} = R + a$ and $R_{\text{in}} = 0$. The values for the bending stiffness are listed in Table 2.

### 3.3 Elastic constants for Condensed Chromatin.

Since we treat condensed chromatin as a spring made from a linear array of nucleosomes, which contain a solid core of histones, the expressions for the elastic constants for condensed chromatin are identical in form to the previous section. The only differences are that instead of using the pitch and radius of the nucleosome and the elastic constants of DNA we use the pitch and radius for condensed chromatin (i.e. $L$ is replaced everywhere by $L$, $l_{\text{nuc}}$ by $L_{\text{cc}}$, and $a$ by $R$) and elastic constants for the nucleosome. We
only use the elastic constants for the nucleosome obtained in the limiting case of DNA rigidly attached to the histone core, and we analyze condensed chromatin with a hollow core (i.e. $R_{out} = R + R + a$ and $R_{out} = R - R - a$ where $R$, $R$ and $a$ are the centerline radii of condensed chromatin and the nucleosome and the radius of DNA, respectively). The resulting values for the elastic constants for condensed chromatin are given in Table 2. Alternatively experimentally determined values for extended chromatin can be used at this step to determine elastic constants for condensed chromatin, or experimentally determined elastic constants for condensed chromatin can be used to determine effective constants for extended chromatin.

| Elastic Constant | Extended Chromatin (no core) | Extended Chromatin (histone core) | Condensed Chromatin |
|------------------|-----------------------------|----------------------------------|---------------------|
| Young’s modulus  | $1.8 \cdot 10^{-12}$         | $1.8 \cdot 10^{-12}$             | $9.2 \cdot 10^{-14}$ |
| Shear modulus    | $2.3 \cdot 10^{-12}$         | $3.2 \cdot 10^{-12}$             | $7.6 \cdot 10^{-14}$ |
| Torsion rigidity | $4.8 \cdot 10^{-29}$         | $6.8 \cdot 10^{-29}$             | $9.2 \cdot 10^{-30}$ |
| Bend stiffness    | $1.9 \cdot 10^{-29}$         | $1.9 \cdot 10^{-29}$             | $5.5 \cdot 10^{-29}$ |
| Linear density   | $3.7 \cdot 10^{-14}$         | $1.1 \cdot 10^{-13}$             | $4.5 \cdot 10^{-13}$ |
| Moment of inertia| $3.9 \cdot 10^{-31}$         | $6.1 \cdot 10^{-31}$             | $9.0 \cdot 10^{-30}$ |
|                  | $7.8 \cdot 10^{-31}$         | $1.2 \cdot 10^{-30}$             | $1.8 \cdot 10^{-29}$ |

Table 2: Elastic constants for extended and condensed chromatin.

In this table we use the same units as in Table 1.

4 Wave Propagation in Extended and Condensed Chromatin.

In this section we use the derived elastic constants listed in Table 2 to evaluate the dynamics of extended and condensed suitable chromatin. The elastic constants for the nucleosome are for measuring the force and torque associated with distortions of individual nucleosomes. Propagating of mechanical disturbance through the single nucleosome will be problematic because of
length scale requirement. However we can consider the propagation of waves through a linear array of nucleosomes as an approximation to extended chromatin.

These results are valid for any shape in which the curvature of the rod is much greater than the wavelength of the disturbance. The velocities of propagation of mechanical disturbances for extended and condensed chromatin are listed in Table 3.

| Velocity     | Linear DNA | Extended Chromatin (no histone) | Extended Chromatin (histone) | Condensed Chromatin (histone) |
|--------------|------------|---------------------------------|-----------------------------|-------------------------------|
| Shear (Å/ns) | 5000       | 79                              | 46                          | 4.1                           |
| Bend (Å/ns)  | 5100       | 110                             | 89                          | 5.1                           |
| Twist (Å/ns) | 3600       | 79                              | 63                          | 3.6                           |
| Extension (Å/ns) | 5800 | 70                              | 41                          | 4.5                           |

Table 3: Shear, bend, twist and extension wave velocities.

5 Conclusions.

We briefly compare the predictions of our model to published experimental results. First the speed of sound in B-form DNA as measured by Brillouin scattering has been reported as 1.9km/s [29], which differs from the value listed in Table 3 by a factor of 3. Thus our calculations indicate that experimental results obtained from fundamentally different approaches agree quite well, and that relating the speed of sound in DNA to its elastic properties (i.e. equations (11-14)) is valid for DNA as it is for other macroscopic materials.

For the evaluation of the elastic properties of extended chromatin, we note that there is a linear relationship between the average stretching force and the extension of λ-DNA in Figure 3b of [16]. The corresponding spring constant is approximately 10pN/10µm. The sample contains core histones but no linker histones thus according to our model this system is extended.
chromatin. We note that the degree of compaction, 16um DNA/2um chromatin, is in close agreement with our value of 10 for the extended chromatin model. Converting the force constant to a Young’s modulus using Equation 17 gives a value of \( Y^* = YA = 2 \cdot 10^{-12}[KM/S^2] \) which is the same as listed in Table 2 for extended chromatin. Thus the gross properties of the stretching are determined by the elastic properties of the DNA, but the specific details remain dependent on the histone-DNA interactions as illustrated by the results in Figure 3c of [16].

Our model of condensed chromatin yields a Young’s modulus and bend stiffness that closely predicts the persistence length and stretch modulus measured for chicken erythrocyte chromatin [30]. This sample contained linker histone so the folding should correspond to our model of condensed chromatin, however the reported degree of compaction (\( \sim 10 \)) corresponded to our model of extended chromatin. The reported persistence length, \( P = 30 \text{ nm} \), can be converted to a bending stiffness, \( D_{1,2} = P k_b T = 1.2 \cdot 10^{-28}[KM^3/S^2] \) which differs by a factor of 20 from the value listed in Table 2. The reported stretch modulus of approximately \( Y^* = 5 \cdot 10^{-12}N \) for condensed chromatin is a factor of 50 different than listed in Table 2. These values are actually much closer to our predicted values for extended chromatin differing by factors of 2 and 3, respectively. We offer two possibilities for explaining the discrepancy. One is that the degree of compaction reported in [30] indicates that the fiber should more closely resemble our model of extended chromatin than condensed chromatin. The other possibility is that the elastic properties of condensed chromatin are not determined primarily by the elastic properties of DNA as we have assumed in this manuscript, but that intermolecular interactions arising during the folding must also be considered. In this regard, we believe that our results which are based on a purely mechanical model provide good agreement with experiment.

Our main point has been to demonstrate how the folding of DNA leads to a hierarchy of time and energy as well as length scales. For this purpose we have evaluated elastic constants that correspond to ideal geometries of nucleosomes and extended and condensed chromatin and then evaluated the speed of propagation of mechanical disturbances through each of these structures. The hierarchy of lengths resulting from the folding of linear DNA into nucleosomes provides a factor of 10 reduction in length and the folding of nucleosomes into condensed chromatin provides another factor of 4 in compaction of linear DNA. Since the potential energy of deforming an elastic
body is directly proportional to the elastic constants simple ratios highlight the hierarchy of energy associated with the folding. For example the Young’s modulus for DNA divided by the Young’s modulus for extended chromatin is approximately $10^5$ while the corresponding ratios for torsional rigidity and bend stiffness are approximately 10. The velocities presented in Table 3 are an indication of the hierarchy of time scales. There is approximately a 100 fold reduction in the velocity of a mechanical disturbance propagating through DNA as compared to extended chromatin and less than a factor of 10 reduction between extended and condensed chromatin. Assuming that similar ratios occur for yet even higher order folding, the atomic scale of DNA can be folded into the macroscopic scale of the cell in as few as 6 or 7 folds. This is the same order of folding that exists for chromosomes during mitosis.

We emphasis that our model is an approximate model, it does not necessarily correspond to the atomic structure of any of the modeled structures or the sequence dependent nature of DNA. Experimentally measured elastic constants that correspond to a particular sample source and specific experimental conditions should be utilized in our velocity expressions to determine the speed of propagation of mechanical disturbances through extended and condensed chromatin. These speeds of propagation are of fundamental importance because they are literally the speed of sound in DNA. For comparison the speed of sound in water approximately $\sim 1.5km/s \ (15\AA/ps)$ and in steel is $\sim 5km/s \ (50\AA/ps)$. Mechanical disturbances associated with biological processes propagate at the speed of sound whether through the nucleus (water), DNA, or chromatin. Knowing these speeds of propagation enables us to identify through which medium a mechanical disturbance may be propagating.

The fact that twist disturbances propagate along DNA is readily observed during transcription and is implicit in DNA topological studies of twist relaxation. Disturbances exciting a bend, shear or extension are not as readily identifiable, but certainly the interaction of a DNA binding protein deep in the major groove of DNA will affect such disturbances.
6 Acknowledgement.

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[20] If we consider extended chromatin as consisting of nucleosome core particles connected via linker DNA the effective model in our approach is nucleosome springs connected via straight rods. The stretching force constant for the straight rod will be greater than for the nucleosome spring, thus when the fiber is pulled only the springs will extend. The straight rod segments only serve to lengthen the fiber. A similar statement holds for our model of condensed chromatin in which the stiffer spring consists of segments of extended chromatin.

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