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A relationship between the helical twist of DNA and the ordered positioning of nucleosomes in all eukaryotic cells

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ABSTRACT **A large number of measurements of nucleosome repeat lengths are analyzed and are found to exhibit preferential quantization to a set of values related by integral multiples of the helical twist of DNA. This implies that the nucleosomal DNA content is preferentially quantized, which in turn implies that linker DNA lengths are preferentially quantized. This study confirms and extends previous observations in the literature that had suggested, but not firmly established, that linker lengths might be quantized. The quantization of repeat lengths applies even for very long repeat lengths. This suggests a model for the origin of the quantization, in which the quantization arises from the requirements of higher-order chromatin structure.**

The nucleosome is the repeating subunit of chromatin structure (for reviews, see refs. 1–3). In the nucleosome, a short stretch of DNA, typically from ≈165 to 245 base pairs (bp), is locally folded and compacted by interaction with proteins known as histones. Of this nucleosomal DNA, 166 bp or 146 bp are considered to be included in subparticles known as chromatosomes or nucleosome core particles, respectively, that have invariant DNA lengths; the remainder of the DNA associated with each nucleosome is called linker DNA and varies in length from ≈0 to ≈80 bp (if measured relative to the chromatosome). It has been firmly established that the length of linker DNA varies about a well-defined average from one nucleosome to the next even along a single DNA chain (4); this average itself varies between cell types and organisms.

Three sets of results in the literature have suggested, but not firmly established, that linker DNA lengths might be preferentially quantized. (*i*) Digestion of chromatin by DNase I or DNase II produces a large number of bands that can be assigned to two sets of cleavages at sites spaced ≈10 bases apart, but with the two sets shifted relative to each other by ≈5 bases (5–7). By assuming that one series arises from a pair of cleavages within one chromatosome or core particle, whereas the other series arises from one cleavage on each of two consecutive nucleosomes, linker DNA must be quantized in length, at values of $10n + 5$ bp, with n an integer. (*ii*) Single-strand DNA products ≈2 nucleosomes long (fragments that span two consecutive chromatosomes and include their intervening linker) were examined (8) and revealed a set of bands spaced at multiples of ≈10 bases; this implies that linkers must be quantized, with lengths differing by integral multiples of ≈10 bp. (*iii*) Dinucleosomes were produced with micrococcal nuclease, and their ends were trimmed precisely to the chromatosome locations using exonuclease III and S1 nuclease. Single-stranded DNA products were found to fall within a broad band that exhibited a set of shoulders spaced ≈10 bases apart (6). The set of shoulders must arise from quantized lengths of linker DNA, differing in length by integral multiples of ≈10 bp.

Each of these experiments has some limitations. The interpretation of the cleavage patterns in experiments *i* is not unique. Moreover, closely related experiments fail to confirm the $10n + 5$ bp result. One study observed a shift of the cleavage pattern on the neighboring nucleosome of −1 to −3 bp (9); this implies a quantized linker, but not of length $10n + 5$ bp. In other studies, the ≈10-bp periodic pattern of intracore particle cleavage extends onto and across the linker without any detectable shift (10–12); these results do not require any linker length quantization or, alternatively, they are consistent with quantization, but at still different lengths. The $10n + 5$ bp result was obtained only for a limited number of cell types, and of these, one failed to show a detectable pattern shifted by $10n + 5$ bp in one of the studies (5, 7). Experiment *ii* was carried out with only a single organism, has not been extended to other organisms or cell types, and has not been confirmed by another laboratory. Experiment *iii* follows two other virtually identical studies in which there was no resolution of shoulders or subbands (4, 13). Finally, as pointed out previously (1), all of these experiments at most demonstrate quantization of linker lengths within dinucleosomes.

If linker DNA lengths were preferentially quantized, then the length of DNA associated with each nucleosome [considered as a fixed core length of 166 (or 146) bp plus the quantized linker DNA] would be similarly quantized. An average measure of the length of DNA in each nucleosome is known as the nucleosome repeat length; this is defined as the average length by which the length of DNA (representing all or most of the DNA in a population of cells) in oligonucleosomes containing $N + 1$ nucleosomes exceeds the length of DNA in oligonucleosomes containing N nucleosomes. In practice, the nucleosome repeat length is generally calculated from the slope in plots of average DNA size in N-mer oligonucleosomes versus N. The nucleosome repeat length for any cell type is thus a highly averaged quantity. If the DNA content of nucleosomes were indeed quantized, then nucleosome repeat lengths should be quantized too. Because of the preaveraging inherent in a measurement of the nucleosome repeat length (together with other effects; see below), this quantization might be obscured. Conversely, if nucleosome repeat lengths were found to be quantized, this would imply that the DNA content of nucleosomes must be quantized.

Are nucleosome repeat lengths quantized? Previous studies have examined the distribution of nucleosome repeat lengths only for relatively long length scales. For example, one study prepared (for other reasons) a histogram of repeat lengths using a 10-bp sampling period (1); this is adequate only for spectral analysis of periods of length 20 bp or greater. In this study, I reconsider a large body of data for nucleosome

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repeat lengths, with the goal of testing whether there is quantization on length scales as short as 2 bp.

RESULTS AND DISCUSSION

Probability Distribution Function for Nucleosome Repeat Lengths. Nucleosome repeat lengths have been measured in many laboratories, for a large number of cell types, tissue types, and organisms. van Holde (1) has abstracted 185 such measurements from the literature and presented them in tabular form; the measured (average) nucleosome repeat length obtained in each study is reported, and error bars are reported when available. To reduce the possibility of inadvertent bias in my selection of data, I have restricted the analysis to only these data. I consider them collectively and also in statistically defined subgroups and ask whether the reported nucleosome repeat lengths for all of these cell types, tissue types, and organisms are related to one another by some fundamental periodicity? The data have been rounded to the nearest (integer) 1 bp; therefore, periodicities to 0.5 bp^{-1} (i.e., 2 bp) may be analyzed.

Each measurement was represented as a Gaussian function of probability versus nucleosome repeat length (L), having unit integrated probability, with a mean equal to the reported repeat length and a standard deviation (σ) equal to the reported error bar for that measurement. When no error bars are given, that repeat length measurement was (in separate calculations) either skipped or assigned a σ of 10 bp or 3 bp. The measurements were then combined by summation of their Gaussians to give a probability distribution function for the set of nucleosome repeat length measurements. This is effectively an averaging procedure, which suppresses possible errors in individual measurements. The probability distribution function was evaluated only for the interval $1 \leq L \leq 512$ bp. Six calculations were performed, in which the data were considered collectively or in subgroups. Plots of the resulting functions are shown in Fig. 1.

The probability distribution functions are broadly centered around 190–200 bp, and they exhibit multiple peaks or shoulders. In Fig. 1*a*, the curve calculated using all 134 measurements for which error bars were reported shows peaks or shoulders at 159, ≈171, 178, 188, 192, 196, and ≈206 bp repeat lengths; in Fig. 1*b*, the curve calculated using all 55 measurements having error bars of ≤4 bp shows peaks or shoulders at 159, 170–171, 178, 188, 196, 206–207, and ≈217–218 bp. Thus, the probability distribution functions show an imperfect but pronounced quantization, with a preference for a set of repeat lengths differing from each other by multiples of ≈10 bp.

Fourier Transforms of Probability Distribution Functions. To analyze quantitatively the spatial periodicities present in these plots, Fourier transforms of the distribution functions were calculated (14). The results for the six calculations are shown in Fig. 2. The transforms are dominated by a large peak centered at zero periodicity, arising from the envelope of the repeat length distribution. There are numerous subsidiary maxima; the most pronounced (measured as the height, or integrated area, above the envelope of the transform) is a broad peak occurring at a periodicity of 0.10–0.11 bp^{-1} that is present in all six transforms. The reciprocal of this range of periodicities is ≈9–10 bp; it is this maximum in the Fourier transforms that is responsible for the set of roughly evenly spaced peaks or shoulders detected in the probability distribution functions. There are numerous smaller maxima. Possibly the most prominent of these occurs at a periodicity of ≈0.04 bp^{-1}; however, this peak is prominent only in limited subsets of the data. In Fig. 2*b*, it weakens or disappears, with a concomitant increase in the amplitude at ≈0.10–0.11 bp^{-1}, when the data are restricted successively to $\sigma \leq 4$ bp, $\sigma \leq 3$ bp, and $\sigma \leq 2$ bp. It is only weakly present

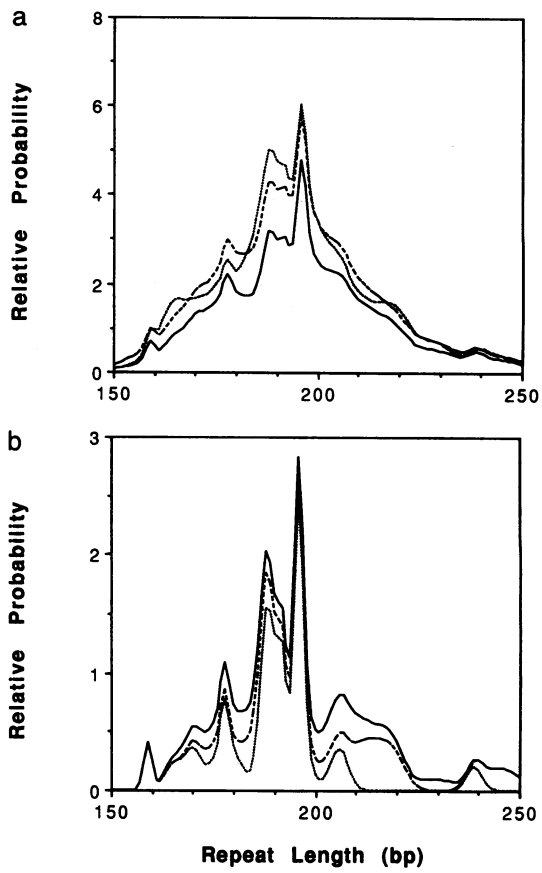

FIG. 1. Nucleosome-repeat-length probability distribution functions, $P(L)$, for distinct sets or subsets of the data. (*a*) $P(L)$ functions obtained using most or all of the data. Solid lines, data for which error bars are reported (n = 134); dotted lines, data (n = 185) when error bars are not reported, σ is set equal to 3 bp; dashed lines, data when error bars are not reported, σ is set equal to 10 bp. (*b*) $P(L)$ functions obtained using restricted subsets of the data. Solid lines, data having error bars ≤4 bp (n = 55); dashed lines, data having error bars ≤3 bp (n = 43); dotted lines, data having error bars ≤2 bp (n = 29). Only the range L of 150–250 bp is shown. The probabilities are relative: their integrals (if extended to the range $-\infty \leq L \leq \infty$) are equal to the number of measurements on which they are based.

(again, measured as the height, or integrated area, above the envelope of the transform) in the curve in Fig. 2*a* that was calculated using all of the repeat length data for which error bars were reported. The existence of narrower peaks in other regions of the transforms indicates that the breadth of the peak at 0.10–0.11 bp^{-1} must be due in part to the presence of multiple spectral components in that range of spatial periodicity.

The Fourier transforms are naturally defined in reciprocal space; however, it may be more convenient to analyze them plotted on a real-space axis. Fig. 3 shows the region of the six transforms from Fig. 2 centered on the peak at 0.10–0.11 bp^{-1}, plotted against the reciprocal of the abscissa used in Fig. 3, i.e., against spatial periods measured in bp. All six transforms show a broad maximum spanning the region of the 9- to 10-bp period, centered at a ≈9.5-bp period. In Fig. 3*a*, the single broad maximum appears to split (slightly) into two components; in two of the curves (corresponding to all data having error bars reported, and all data with σ set equal to 10 bp when not reported) the two components are centered at periods of ≈9 and ≈10 bp, with the component at ≈10 bp slightly higher. In one of the curves (corresponding to all data, with σ set equal to 3 bp when not reported), the two components occur at ≈9 and ≈10.5 bp, with the ≈10.5-bp period having considerably higher amplitude.

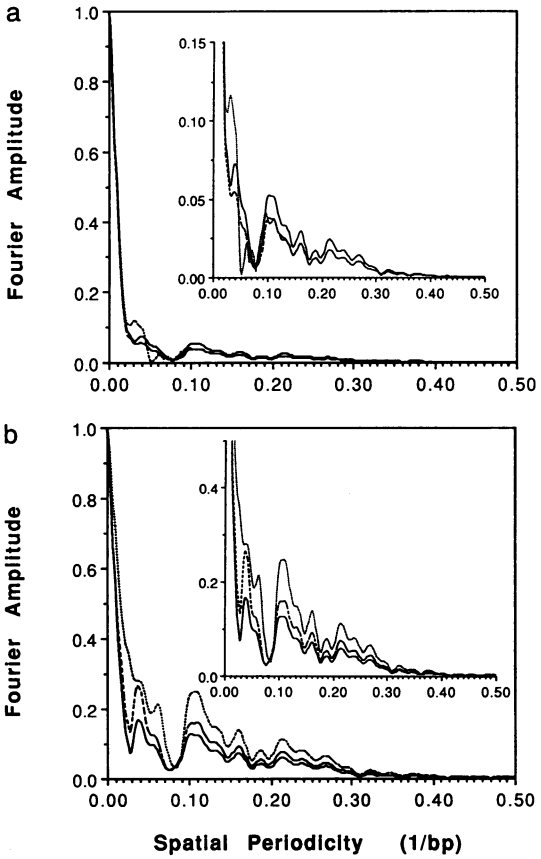

FIG. 2. Plots of Fourier transforms of the 6 nucleosome-repeat-length probability distribution functions $P(L)$. The curve designations in *a* and *b* are identical to those in Fig. 1. The Fourier transforms were calculated using the program FOUR1 (14). Only the amplitudes of the Fourier transforms are shown; they have been normalized by dividing by the integral (i.e., sum) of the corresponding $P(L)$. (*Insets*) Same results plotted on expanded scales.

Tests for Biased Rounding in Published Data. One possible explanation for the existence of a ≈10-bp period in the nucleosome-repeat-length probability distribution functions could be a tendency of investigators to bias their results by nonrandom rounding off of measured values. For example, rounding repeat lengths to the nearest 10 bp would impose a 10-bp period. If this had occurred in even just a relatively small fraction of the tabulated measurements, it could possibly account for the observed set of preferentially quantized repeat lengths. As a check for possible biased rounding, histograms of the last digits of the reported nucleosome repeat lengths were prepared for the four subsets of data used in Figs. 1–3 that are restricted to repeat length measurements having accompanying error bars. The results (not shown) indicate that biased rounding does not account for the observed ≈10-bp periodicity; instead, there is a tendency for nucleosome repeat length measurements to end with a digit in the range 5–0 (i.e., 5–10), with a maximum likelihood at 8.

Further Tests of Analysis. The shapes of the probability distributions and their transforms depend on the particular cells that have been investigated. Since cell types are not chosen randomly, the shapes of the distributions might not be representative of all cell types. In particular, two peaks present in each of the distribution functions, at 188 bp and 196 bp, have significantly greater amplitude than the others. The peak at 196 bp includes significant contributions from many very different cell types; but the peak at 188 bp includes a particularly large contribution from vertebrate cells grown in tissue culture.

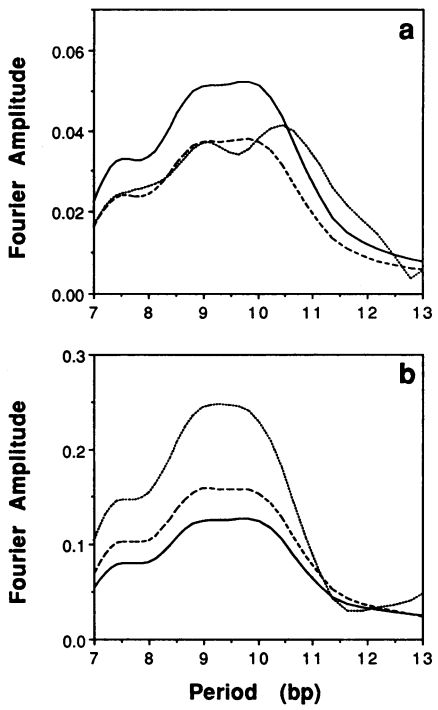

FIG. 3. Fourier transforms plotted against a real-space abscissa. The region of the six transforms centered on the peak at 0.10–0.11 bp^{-1} was plotted against the reciprocal of the abscissa. Thus, this figure plots the amplitude of the transforms against spatial periods measured in bp for periods from 7 to 13 bp. The curve designations in *a* and *b* are identical to those in Figs. 1 and 2.

Importantly, these peaks are not responsible for the chief result of this study, namely, the presence of a peak in the transform at a spacing of 0.10–0.11 bp^{-1} (≈9–10.5 bp). Indeed, these peaks, considered as a pair, detract from the amplitude in that region of the transform by shifting amplitude to the 8-bp region.

As a further check on the effects of nonrandom cell types in the data set, the results for the five most prevalent cell types were preaveraged, and the computations were carried out as before. With this preaveraging, the resulting probability distribution function (using all data with error bars) was still very similar to that of Fig. 1*a* (results not shown); the only apparent significant difference was that preaveraging reduced the magnitude of the peak at 188 bp to about two-thirds of its original value; the location of that peak remained unchanged. Importantly, the Fourier transform after preaveraging is virtually identical (results not shown). The peak at 0.10–0.11 bp^{-1} remains the prominent feature, and its magnitude is virtually unchanged (it decreases by 4%). This calculation includes 118 measurements from 99 different or potentially different cell types. Thus, the peak at 0.10–0.11 bp^{-1} is apparently representative of all cell types and is not an artifact of nonrandom selection.

Interpretation of Results. Importantly, the length scale of the observed quantization, ≈10 bp, is equal to the helical periodicity of DNA, ≈10 bp per turn. The implications of this are discussed in the following paragraphs. In fact, DNA is polymorphic, and its helical twist can depend both on its local sequence and on its environment (15, 16). Random sequence DNA in solution has a helical twist of ≈10.5–10.7 bp per turn (17, 18). On the nucleosome core particle, much of the DNA is overtwisted, to ≈10.2 bp per turn (10, 11), presumably because of interactions with the histone proteins. Fiber-diffraction experiments have revealed a range of allowed twists for random sequence DNA, with the A-, B-, and C-forms having twists of ≈11, ≈10, and ≈9 bp per turn,

respectively (16). It is important for an analysis of the structure of folded chromatin to determine the average helical twist of linker DNA. In principle, this value is obtained in the present study from the Fourier transforms of the repeat length probability distribution functions and is ≈10 bp per turn. It is not possible to specify this value more precisely at this time, because, depending on which subset of the data is considered, the maximum in the Fourier transforms appears at periodicities from 9.0 to 10.5 bp per turn. It may be possible in a future study to obtain an improved measure by first eliminating incorrect measurements of nucleosome repeat lengths from the data used to construct the repeat length probability distribution function. Suspect measurements can be identified based on the results of the present study.

One hypothesis for the existence of quantized linker lengths has previously been proposed (19); this hypothesis was developed to explain the $10n$ or $10n + 5$ bp quantization of linker DNA lengths detected in various studies (5–8). It was suggested that certain ranges of linker DNA length are forbidden because, as the linker leaving nucleosome i is lengthened progressively, the concomitant rotation of nucleosome $i + 1$ about the linker DNA axis (due to the helical twist of the linker DNA) leads to unacceptable steric clashes between the two nucleosomes for ≈5-bp stretches out of every helical turn (≈10 bp) of the linker DNA. This hypothesis, however, fails to explain the more general quantization observed in the present study, which extends at least to ≈208 bp and (although it is difficult to say because of a shortage of good data) may well extend out to the longest measured repeat lengths, ≈245 bp. For nucleosome repeat lengths greater than ≈178 bp, the linker DNA is sufficiently long that (if it is kept straight) nucleosome $i + 1$ need never contact nucleosome i, and all subsequent rotations caused by single base-pair increments of the linker DNA length would be permitted; thus, if this hypothesis were the origin of the observed quantization, quantization would not be observed for nucleosome repeat lengths beyond ≈178 bp, contrary to the findings of the present study.

The observation that even long nucleosome repeat lengths are quantized by integral multiples of ≈10 bp, and hence by integral multiples of helical turns of linker DNA, suggests an alternative explanation. I propose here that nucleosome repeat lengths (i.e., linker DNA lengths) are quantized because of the need for a definite geometry of protein–protein or protein–DNA contacts between laterally adjacent nucleosomes in the folded chromatin fiber. This point is illustrated in Fig. 4 within the context of the solenoid model for folding of a chromatin filament into the next higher level of structure, the 30-nm filament (20–22). Equivalent arguments can be devised for other models of the higher-order folding of chromatin (for reviews of chromatin folding, see refs. 1, 2, and 23). Fig. 4*a* illustrates the solenoid model; DNA is shown in a heavy line, with the linker DNA that connects from nucleosome i to $i + 1$ shown as a dashed line. In Fig. 4*b*, the linker is considered in more detail. Addition of a short extra length of DNA to the linker causes a relative translation of i and $i + 1$ and, as indicated by the curved arrow, a right-handed rotation of nucleosome $i + 1$ about the local DNA helix axis. If the structure requires definite protein–protein or protein–DNA contacts between adjacent nucleosomes, then both the translation and the rotation must be undone. The translation may be undone by allowing the extra DNA to bend out of and then back into the page. There is a free energy penalty associated with such DNA bending, but the bending required of the linker need never exceed the bending that obtains on the nucleosome core particle (24). The rotation may be undone by underwinding or overwinding the linker, such that its integrated twist regains the original value. This requires that work be done against the torsional potential of DNA, which, for short linker lengths, has an accompanying large free energy penalty (17). Alternatively, one could simply restrict the linker lengths to any of a set of values having in common the property that they keep the integrated twist constant modulo the helical periodicity of the linker—in other words, to a quantized set of linker lengths that differ one from another by integral multiples of the helical repeat of the linker DNA. I propose here that this is the origin of the observed quantization of nucleosome repeat lengths. For very short nucleosome repeat lengths, the explanation proposed previously may apply as an additional constraint, as some repeat lengths that do not have the correct integrated twist may also be forbidden due to steric clash.

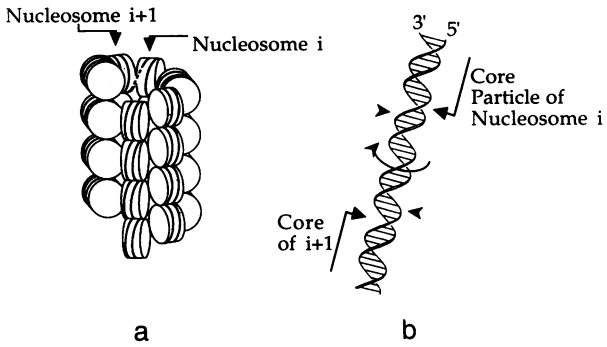

FIG. 4. (*a*) Solenoid model of chromatin folding (20–22). Nucleosomes are represented as disks, and the DNA is represented as a solid line wrapping about twice around each disk. Linker DNA (dashed line) connects consecutive nucleosomes i and $i + 1$. (*b*) The linker DNA shown as a dashed line in *a* is now shown in a frontal view with the DNA double-helix indicated. This figure needs to be considered as having the DNA bent out of the page and back in (see text). The large arrows indicate the position of enzymatic cleavage generating the end of nucleosome core particle i and the beginning of nucleosome core particle $i + 1$, for a linker length of $10n$; small displacements from these cleavage positions (e.g., arrowheads) account for linkers of length $10n + 5$ bp, or other lengths. The curved arrow indicates the sense of the helical twist of the (right-handed) DNA.

Simulation of the Probability Distribution Function. The nucleosome-repeat-length probability distribution function was simulated, based on the hypotheses that the higher-order structure of chromatin requires that the integrated twist of the linker DNA remain constant modulo the helical twist and that linker DNA lengths will occur with a probability given by a Boltzman weighting of the free energy required to restore their integrated twist to an acceptable value. The exact results of the simulation will be sensitive to particular parameters that are chosen, but important conclusions will be general. The following assumptions were made. The overall probability distribution for nucleosome repeat lengths is assumed to be given by a product of two functions: a Gaussian envelope of observed nucleosome repeat lengths, with a mean of 200 bp and a standard deviation of 20 bp, and a Boltzman probability for correcting the integrated twist of the linker, given by:

$$P_B(L) = \exp[-\Delta G°(Tw^+)/RT] + \exp[-\Delta G°(Tw^-)/RT], \quad [1]$$

where Tw^+ and Tw^- represent the change in twist, measured in helical turns, necessary to correct the integrated twist by overwinding or by underwinding less than one turn, respectively; $\Delta G°(Tw^+)$ and $\Delta G°(Tw^-)$ are the corresponding free energies (17), which are proportional to the square of the required twist deformation divided by the length of DNA over which the deformation will be distributed; R is the gas constant; and T is the absolute temperature. Linker DNA is assumed to have a helical twist of 10.0 bp per turn, and its length is defined as the nucleosome repeat length minus 146 bp (the amount of DNA in the nucleosome core particle).

The simulated distribution function (data not shown) has very sharp peaks. Because of the relatively large free energy penalty for torsional deformation of DNA, linker lengths that differ from the local optimum by more than ±1–2 bp are predicted to occur with vanishingly low probability. As the linker length (i.e., the nucleosome repeat length) increases, the peaks broaden slightly, reflecting the fact that the required torsional deformation is distributed over longer lengths of DNA.

The peaks in the simulated distribution function are much sharper than those in the nucleosome-repeat-length distribution functions (Fig. 1). One reason for this is that the experimental distribution functions are artificially broadened when the error bars are incorporated in the representation of each measurement. However, one of the distribution functions in Fig. 2*b* was computed using only data having error bars ≤2 bp. The widths of the peaks in that function are still much broader than approximately ±2 bp. Three explanations for this seem likely. (*i*) Despite the narrow error bars, some of the experimental measurements may simply be incorrect. (*ii*) There may be instances when genetic constraints—perhaps involving proteins necessary for the regulation or the activity of transcription or replication or perhaps involving DNA sequences that happen to cause preferential positioning of two consecutive histone octamers—disallow the most desired linker length in some instances [e.g., by binding to a particular DNA sequence and thus sterically excluding a nucleosome (25) or by "phasing" the octamers (26, 27)] and, therefore, require a torsional deformation of the linker DNA to allow higher-order folding of the chromatin fiber. It is conceivable that a significant fraction of nucleosomes could be affected in this manner, particularly in cells that are active in transcription or replication. (*iii*) If a cell type has significant fractions of its genome packaged with two or more distinct (quantized) repeat lengths, the measured average repeat length will fall between the individually quantized values.

The simulated distribution function may also be compared to the experimentally determined distribution of linker DNA lengths in trimmed dinucleosomes. Two of those experiments (4, 13) revealed no detectable quantization at all. A third experiment (6) revealed a linker length distribution function having a set of shoulders at quantized spacings. This distribution could be approximated with a sum of Gaussians having quantized linker lengths at 10-bp intervals, but each Gaussian had a standard deviation of 4.5 bp. This is again much broader than the peaks approximately ±2 bp wide predicted from the present simulation. Two explanations seem likely. (*i*) As for the repeat length distribution functions, genetic constraints may force histone octamers to bind with suboptimal spacings in some instances. (*ii*) The helical twist of DNA depends on the local sequence, with variations of plus-or-minus several degrees of twist per base step quite common (15, 16). Positive and negative twist variations will cancel on average, but individual linker sequences may have integrated twists that are quite different from the average integrated twist for DNA of that length, requiring that extra base pairs be added to or subtracted from those particular linkers to restore their integrated twist to the desired value, thereby broadening the distribution of allowed linker lengths.

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