Designing nucleosomal force sensors

M. Tompitak,[1] L. de Bruin,[2] B. Eslami-Mossallam,[3] and H. Schiessel[1]

[1]*Instituut-Lorentz for Theoretical Physics, Leiden University, P.O. Box 9506, 2300 RA Leiden, The Netherlands*
[2]*Section de Mathématiques, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland*
[3]*Department of Bionanoscience, Kavli Institute of Nanoscience, Delft University of Technology,*
Lorentzweg 1, 2628 CJ Delft, The Netherlands

About three quarters of our DNA is wrapped into nucleosomes: DNA spools with a protein core. It is well known that the affinity of a given DNA stretch to be incorporated into a nucleosome depends on the geometry and elasticity of the basepair sequence involved, causing the positioning of nucleosomes. Here we show that DNA elasticity can have a much deeper effect on nucleosomes than just their positioning: it affects their "identities". Employing a recently developed computational algorithm, the mutation Monte Carlo method, we design nucleosomes with surprising physical characteristics. Unlike any other nucleosomes studied so far, these nucleosomes are short-lived when put under mechanical tension whereas other physical properties are largely unaffected. This suggests that the nucleosome, the most abundant DNA-protein complex in our cells, might more properly be considered a class of complexes with a wide array of physical properties, and raises the possibility that evolution has shaped various nucleosome species according to their genomic context.

I. INTRODUCTION

DNA in eukaryotic cells is folded in a hierarchical series of steps into the chromatin complex. Whereas details of the higher levels are still debated, the first level of complexation is well understood: the basic repeated structure, the nucleosome, involves a short stretch of DNA, 147 base pairs (bp) in length, wrapped in 1 3/4 turns around a cylindrical aggregate of eight histone proteins. This results in a disk-shaped particle with a diameter of 11 nm and a height of 6 nm [1]. A short stretch of DNA, called the linker, connects to the next such protein spool.

DNA is a rather stiff molecule with a persistence length of about 150 bp, or 50 nm. Therefore, wrapping the DNA into nucleosomes costs energy, which is compensated by the binding of the DNA backbones to the histone octamer at 14 binding sites [1]. Because the deformation energy of the DNA depends on its nucleotide sequence, the affinity of a given DNA stretch to the nucleosome is dominated by the elasticity and geometry of that underlying sequence. This allows for mechanical cues to be written along DNA molecules, telling nucleosomes where to sit and where not to sit, sometimes called the "nucleosome positioning code" [2] (for earlier versions of this idea see, e.g., [3,4]).

Remarkably, these cues can even be written on top of genes, because the degeneracy of the genetic code allows for multiplexing [5,6]. Beautiful examples are nucleosome depleted regions before transcription start sites in yeast facilitating transcription initiation [7,8], mechanically encoded retention of a small fraction of nucleosomes in human sperm cells allowing transmission of paternal epigenetic information [9] or the positioning of 6×10^6 nucleosomes around nucleosome inhibiting barriers in human somatic cells [10].

So far the role of the DNA sequence has mainly been seen in the positioning (or antipositioning) of nucleosomes. In other words, one scalar quantity is attributed to a 147-nucleotide stretch of DNA: its affinity to the nucleosome. (Histone proteins are evolutionarily well conserved, even though variants exist, and they can contain post-translational modifications.

Here we neglect these effects and focus exclusively on the role of DNA elasticity.) This, however, oversimplifies the possible roles that DNA mechanics can play for nucleosomes. Here we advocate the idea that nucleosomes form a highly diverse class of DNA-protein complexes whose diversity results from the mechanical properties of the DNA sequences involved. There are some first hints in the experimental literature that nucleosomes can have individual properties [11], especially in the case of a nucleosome wrapped with the 601 sequence (an artificial DNA sequence that was selected out of a large pool of random DNA for its high affinity to the histone octamer [12]). Recent micromanipulation experiments on this particular nucleosome have revealed its highly asymmetric response to force [13,14], reflecting an asymmetry in the bending energy of the wrapped DNA [15]. Such a nucleosome would act as a "polar barrier" for elongating RNA polymerases [16]. For this reason asymmetric nucleosomes may have evolved on real genomes as well, see also [17].

The goal of this paper is to demonstrate the possibility of designing DNA sequences that lead to special nucleosomes with non-trivial physical properties. The asymmetry of the 601 nucleosome mentioned above is still a somewhat trivial example that simply splits the affinity of the sequence in two parts (and, since it is not particularly difficult to alter the affinities of the two halves, asymmetric nucleosomes may well be the rule rather than the exception). Here we aim to construct nucleosomes that show a set of physical properties that are unlikely to emerge randomly, because they require more careful tuning of the mechanical properties of the nucleotide sequence. We decided to construct nucleosomes that show unusual responses to external tensions.

There is a wide range of experiments on nucleosomes under tension [14,18,19]. Most remarkably, nucleosomes can generally withstand rather high tensions without unwrapping completely. This has been explained by the combination of spool geometry and DNA stiffness [15,20–31]. In order to completely unwrap, the nucleosome has to flip by 180 degrees around its symmetry axis. This leads to a high-energy

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transition state, the half-flipped nucleosome, between the single-wrapped and fully unwrapped nucleosome. The energy barrier arises due to two strongly bent DNA stretches in the transition state, which lead to a barrier with a height that increases like the square-root of the applied tension [20,29]. Nucleosomes, through this force-induced strengthening, are kinetically protected against transient tension.

In nature, nucleosomes will be subjected to tension through the actions of various molecular motors that interact with a cell's DNA [32]. Generally, this kinetic protection is valuable in maintaining the integrity of the chromatin. There are also cases, however, where it may be beneficial to undermine this protection. One such scenario is during the anaphase of cell division, when the mother cell's DNA and its newly produced copy need to separate. This separation can partially fail, because ultrafine DNA bridges between the two copies tend to form at certain fragile sites along the genome [33,34]. This causes tension on the DNA where the two copies remain connected. This tension pulls apart the chromatin structure, which is thought to be a signal for repair mechanisms to target the problematic section of DNA. The main mechanism is thought to be the exposure, due to the induced force, of bare DNA, which the repair mechanism has high affinity for [35]. During this repair process, all nucleosomes are expelled from the DNA; therefore, nucleosomes that easily unwrap under tension may be helpful in promoting this repair.

Using a new simulation technique, the mutation Monte Carlo (MMC) method [5], we demonstrate here that it is possible to construct, *in silico*, nucleosomes that behave perfectly "normal" with respect to their affinity to and their positioning along the DNA molecule, but that display a highly unusual feature in their response to force. When put under tension these nucleosomes fall apart rapidly (several orders of magnitude faster than "standard" nucleosomes) along a predefined unwrapping path. This nucleosome species serves as an example of our general idea: that nucleosomes constitute a class of DNA-protein complexes with a wide range of physical properties.

The use of the MMC method for this purpose is fundamentally no different from its application to the basic, fully wrapped nucleosome as in Ref. [5], but it does demonstrate the broad applicability of the method beyond its original purpose. One could imagine applying the same methodology to look for sequences with a range of properties: various other hypothetical nucleosome "species" that store twist defects or are easily invaded from one side (the "polar barriers" mentioned above); sequences that easily form DNA loops; and any other DNA system of interest.

This paper is structured as follows. In the next section, we will introduce the model that underlies our methods. In Sec. III, we describe how we use the MMC method combined with this model to design DNA sequences with the specific properties we are interested in. In Sec. IV we present the results of our attempts to engineer nucleosomes that unwrap easily under force. Finally, in Sec. V, we summarize our main conclusions.

II. MODEL

We employ the same nucleosome model as in our previous work [5,8,15], in which DNA is represented by the rigid base
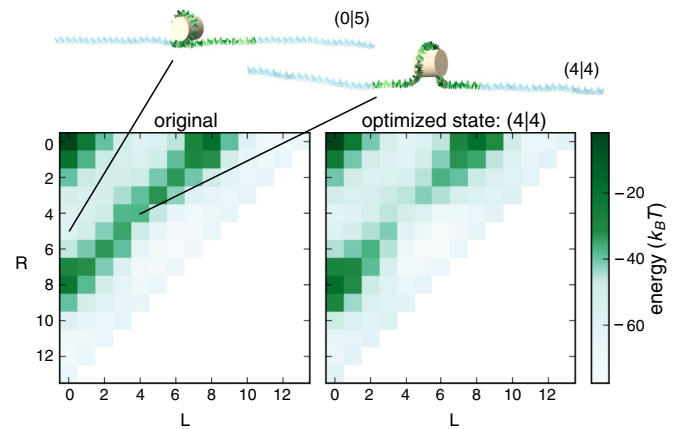

FIG. 1. Top: two unwrapping states of the model nucleosome under tension, state (0|5) (left) and state (4|4) (right). Bottom left: energy landscape (in units of $k_B T$) of the nucleosome at position 826 of the YAL002W gene of *S. cerevisiae* under an external force of 14 pN. Note that single wrapped states like (0|5) are located in a metastable valley. Nucleosomes with just half a turn of wrapped DNA [e.g., (4|4)] form a ridge in the landscape. Bottom right: designing a special nucleosome: result of a free MMC simulation on state (4|4).

pair model [36]. This model treats the base pairs that make up a DNA molecule as rigid plates, the spatial position and orientation of which are described by six (three translational and three rotational) degrees of freedom. It assumes only nearest-neighbor interactions, placing a quadratic deformation energy between successive base pairs:

$$E = \tfrac{1}{2}(q - q_0)K(q - q_0), \tag{1}$$

where the q and q_0 are six-component vectors that encode the relative degrees of freedom between two base pairs and their equilibrium values, respectively, and K is a six-by-six stiffness matrix.

The sequence-dependence of the model comes into play because every base pair step, depending on which two nucleotides compose it, has its own stiffness and intrinsic shape. These parameters can be found in the literature [36,37], and we use the same hybrid parametrization [38] as in Refs. [5,15].

The DNA, modeled with the rigid base pair (RBP) model, is forced into a superhelix through a set of 28 constraints that represent the 14 binding sites to the histone octamer and which were extracted from the nucleosome crystal structure without introducing free parameters [5]. In addition, we allow the binding sites of the nucleosome to be opened at the expense of some adsorption energy in the same way as detailed in Ref. [15]. We added 100-base-pair tails with sequence-averaged elastic properties as handles to apply a tension. Example configurations of our model nucleosome under a tension of 14 pN are provided in Fig. 1.

The model itself has been extensively tested. We have shown in Ref. [5] that our model reproduces the nucleosome positioning rules, gives good estimates of relative affinities, and predicts the rotational positioning of nucleosomes. In Ref. [15] we found that it reproduces details of the sequence-dependent response of nucleosomes to tension as reported recently [14]. We have also used an approximation to this

model [39] to perform genome-wide analyses of the nucleosome affinity of promoter regions [8].

In order to analyze the unwrapping of a nucleosome with a given sequence, we put the nucleosome in all possible unwrapping states $(L|R)$ that can be characterized by the number of binding sites opened from the left end, L, and from the right end, R. For each state $(L|R)$ we estimate the average energy from an ensemble of configurations produced by a Monte Carlo simulation. This leads to an energy landscape as a function of $(L|R)$.

III. DESIGNING SPECIAL NUCLEOSOMES

In Fig. 1 (bottom left) we depict the energy landscape for unspooling of a particular nucleosome under an external force of 14 pN. We chose 14 pN as the force to which to attune our designer nucleotide sequences, because we wished to work at significant tension, but not such that we leave the regime of stable nucleosomes, and nucleosomes have been found to be stable under tensions of up to about this magnitude [14]. We chose a nucleotide sequence that is associated with a "normal" well-positioned nucleosome, specifically the one at position 826 of the YAL002W gene of *S. cerevisiae*, which has been mapped with single-nucleotide resolution *in vivo* [40] and which we have used before to demonstrate multiplexing of mechanical cues and genetic information [5].

The unwrapping landscape shows the well-known overall features as already predicted with sequence-independent models [20,22]: (i) The most expensive state is the fully wrapped state $(L,R) = (0|0)$; (ii) a metastable valley for nucleosomes with a single wrap, $L + R = 5$; (iii) a ridge for half-flipped nucleosomes with $L + R = 8$; and (iv) the cheapest states, nearly unwrapped nucleosomes, $L + R = 12$. Nucleosomes that are put under an external tension for a short enough time will be stuck in states with $L + R = 5$, kinetically protected by the ridge, as has been observed recently for three other sequences [14]. We expect that this feature is typical for the vast majority of nucleosomes.

However, the number of sequences into which a nucleosome can be wrapped is huge, 4^{147}, and each corresponding DNA double helix has different mechanical and geometrical properties. Could it be that among this huge sea of sequences there is a subset that leads to a very different unwrapping landscape? For example, suppose nature required a nucleosome that acted as a "force sensor", a nucleosome that is stably wrapped and positioned under normal conditions but that quickly falls off as soon as it is put under moderate tension, which might be beneficial in the detection of the ultrafine DNA bridges mentioned in the Introduction. We are not claiming here that such nucleosomes exist on real genomes but we want to check whether they could evolve in principle.

To design a nucleosome that does not get stuck in a set of metastable states we need to cut a trench through the ridge of metastable states. The ridge is caused to the largest extent by the strongly bent DNA portions of half-flipped nucleosomes, see, e.g., the (4|4) state shown in Fig. 1. What we need are nucleotide sequences that are soft or intrinsically bent in the right direction to substantially lower the cost of these bends.

Our strategy to create such sequences is to perform MMC simulations on nucleosomes that are in an unwrapping state

on top of the ridge, e.g., in state (4|4). A standard Monte Carlo simulation samples the Boltzmann distribution of a system across its state space,

$$P(\theta) = \frac{1}{Z_\theta} e^{-\beta E(\theta)}, \qquad (2)$$

where Z_θ is the partition function, θ encodes the conformational degrees of freedom of the system, β is the inverse temperature $1/k_B T$, and E is the energy of a given state.

The MMC method is a straightforward extension that includes the nucleotide sequence S of the DNA as additional degrees of freedom:

$$P(\theta,S) = \frac{1}{Z_{\theta,S}} e^{-\beta E(\theta,S)}. \qquad (3)$$

In the case of our nucleosome model, θ represents all the inter-base-pair degrees of freedom [the q in Eq. (1), for all 146 pairs of successive base pairs] and S is a 147-nucleotide sequence.

Such a simulation allows us, for example, to marginalize the spatial degrees of freedom in order to calculate the probability distribution of the system in sequence space (as in Refs. [5,8]),

$$P(S) = \frac{1}{Z_{\theta,S}} \int d\theta \, P(S,\theta) = \frac{1}{Z_S} e^{-\beta F(S)}, \qquad (4)$$

where $F(S)$ is the free energy of the sequence S wrapped into a nucleosome.

In the current work we wish to design specific sequences with certain properties. Therefore, we are not primarily interested in the thermal ensembles, but rather we wish to search sequence space for sequences with very high affinity for the state into which we force the system. We do so using simulated annealing, i.e., gradually lowering the simulation temperature while the algorithm searches the state and sequence space of the nucleosome.

We now apply this methodology to transition states that sit atop the energy barrier in the unwrapping landscape, like the state (4|4). Doing so gives us sequences that are favorable to this particular state, and that cut a trench through the barrier at the corresponding location in the landscape. We performed both free MMC, where any mutation is allowed, and synonymous MMC (SynMMC), where only mutations are allowed that do not alter the protein that the DNA sequence encodes for.

IV. RESULTS

In Fig. 1 (bottom right) is shown the landscape obtained from a sequence that we produced through an MMC simulation performed at state (4|4). The ridge now contains a trench at this position; see also the energy profile along the ridge, depicted in Fig. 2 (left). We also performed a SynMMC simulation of the same system, the result of which can also be seen in Fig. 2 (left), and shows that we can still dig such a trench on top of genes, albeit not as deep as in the freely mutated case. It is also possible to put a trench at an asymmetric position, see Fig. 2 (right), which resulted from free MMC and SynMMC on state (1|7). Taking the nucleosome on the YAL002W gene as reference, we find substantial decreases of the energy at the location of the trench, e.g., reductions of 18.4 for (4|4) and of
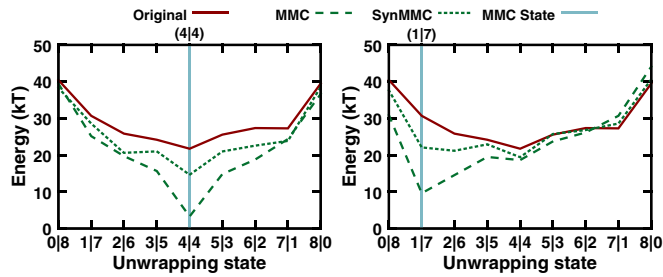
FIG. 2. Energy along the ridge for sequences found using MMC on position 826 of the YAL002W gene of *S. cerevisiae*, held in unwrapping states (4|4) (left) and (1|7) (right). The solid line represents the original ridge. The dashed line is the ridge after free MMC and the dotted line after SynMMC.

12.1 for (1|7) for free MMC, and of 7.1 for (4|4) and of 2.3 for (1|7) for SynMMC (here and below all energies are given in units of $k_B T$).

In general, changing the sequence of course affects the entire energy landscape and not just the favored state. To learn about how much the rate of unwrapping at the given force of 14 pN is affected, we need to calculate the total barrier height, the difference between the lowest energy state on the ridge and that in the metastable valley. Defined as such, the reference nucleosome on gene YAL002W has an 18.5 barrier height. For free MMC, in all cases except (0|8) and (8|0), this difference was substantially reduced, e.g., to 7.4 for case (4|4) and to 13.1 for case (1|7). This suggests that the lifetime of the metastable state would be reduced by 2–4 orders of magnitude. For SynMMC, in five of the nine cases the lifetime is raised [e.g., twofold for case (1|7) as the barrier is now 19.2], in the other cases it is lowered, specifically to 14.5 for (4|4), shortening its lifetime by a factor of about 50.

What do sequences look like that feature such trenches in the landscape? To understand the typical changes in such sequences it is convenient to consider the properties of an ensemble of sequences produced by MMC [i.e., a thermal ensemble of sequences, with the probability distribution given in Eq. (4)]. Shown in Fig. 3 is the distribution of AA, AT, TA, and TT dinucleotides found in an ensemble of 10^4 sequences for the barrier state (4|4) and for the fully wrapped nucleosome. The characteristic ten-base-pair periodic signal for the fully
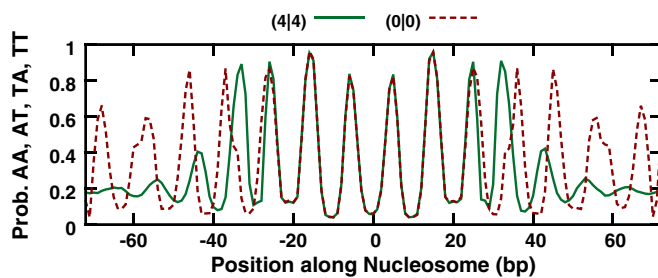

FIG. 3. Distributions along the nucleosome of AT-rich dinucleotides (AA, AT, TA, and TT, frequencies summed) from an ensemble of low-energy sequences of the fully wrapped nucleosome and of one in the (4|4) unwrapping state. The central part, which is wrapped in both cases, is identical. A phase shift occurs in the perpendicularly bent unwrapped tails.
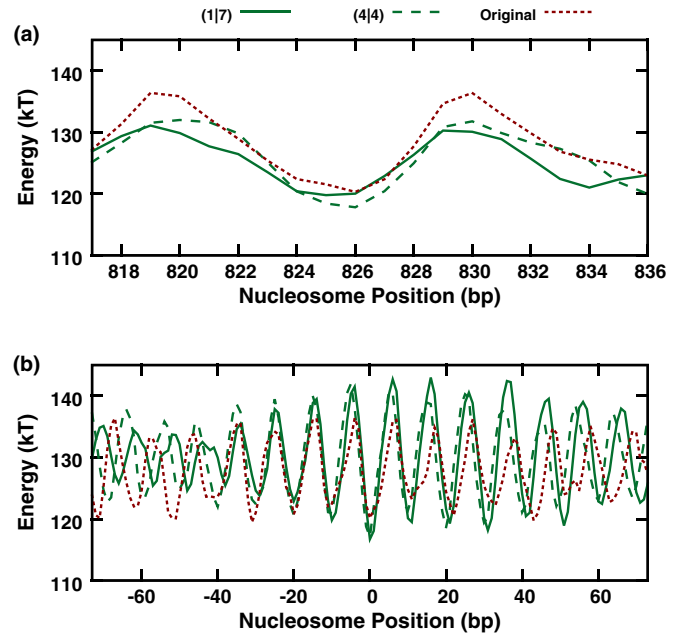

FIG. 4. (a) Nucleosome energy landscapes in a small neighborhood of position 826 of the YAL002W gene, with the 826-sequence replaced by the sequences found through SynMMC at states (1|7) and (4|4). In each case, the replacement sequence still provides a local minimum. (b) Cyclical energy landscapes of sequences found through free MMC for states (1|7) and (4|4) compared to the sequence at position 826 of the YAL002W gene. There remains always a strong local minimum at position 0.

wrapped nucleosomes are due to the well-known nucleotide preferences of high affinity sequences [2,4,5,7]. For state (4|4) we see that in the center of the sequence, which is still wrapped, the preferences are unchanged, but in the bent tails, we have a phase shift by a quarter of a period. This reflects precisely the fact that the bending direction in the DNA arms is perpendicular to the one in the wrapped portion; see the (4|4) example configuration in Fig. 1.

We need to check that the sequences we designed actually have good affinities for nucleosomes. In the case of SynMMC, we are modifying a genomic sequence, and we indeed find that there is still a local minimum in the energy landscape along the DNA, see Fig. 4(a). For the sequences found using free MMC, there is no genomic context to compare to. Therefore, we shift the sequence through the nucleosome cyclically and check that the unshifted sequence is the most favourable one. In Fig. 4(b) we see that we still have strong local minima for the unshifted sequences.

Also note that in both plots in Fig. 4, the overall energy at the minima is similar to or reduced with respect to the original minimum. The lower energy is possible because the MMC method is not only adapting the sequence in the unwrapped part (this optimization is at odds with nucleosome affinity, as we have seen). It is also optimizing the still-wrapped part of the sequence to conform to the nucleosome, even better than the original sequence did. The result is that the sequences we designed, when fully wrapped, still give us nucleosomes which have equal or better overall affinity for the nucleosome as compared to the original sequence.
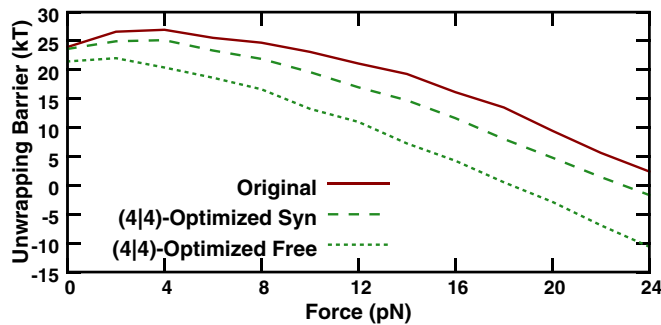
FIG. 5. The height of the unwrapping barrier as a function of the tension applied, for the original genomic sequence, and the sequences we found through optimization for state (4|4) at 14 pN, using both free and synonymous MMC. Though the sequences were optimized at a given force, they lower the barrier for the entire range of forces considered.

Finally we want to check that the results are not force-specific. The shape of the highly bent sections in the transition state will depend on the force: a higher force will lead to stronger, more localized curvature. Because the main feature of the sequences that facilitate crossing the barrier is likely to be the correct curvature direction, we expect our sequence optimized for 14 pN to also reduce the barrier at other forces. In Fig. 5 the effect is shown of the sequence modification on the barrier felt by the nucleosome at a range of forces. We see that, as expected, the barrier is significantly reduced across this entire range, and not only at the specific force at which we designed the sequence.

V. CONCLUSION

We have shown that the physical properties of nucleosomes, illustrated here through their response to an external force, depend strongly on the physical properties of the underlying nucleotide sequence. Not only can sequences position nucleosomes, but they can also equip them with special individual characteristics. Here we demonstrated this by engineering, via our mutation Monte Carlo algorithm, special nucleosomes that are easily unwrapped by an external force, while still being stably wrapped when no force is applied. Surprisingly, these two characteristics can be encoded into a single 147-base-pair nucleotide sequence.

One can imagine that a mechanical evolution of nucleosomes may also occur on real genomes, "speciating" nucleosomes to act as force sensors, polar barriers, twist storers, and so on. What makes such an evolution special compared to ordinary evolution is that we have here a very direct mechanical connection between the 147-base-pair sequence wrapped into a nucleosome—its "genome"—and the phenotype, i.e., the set of physical properties of the nucleosome. It will be interesting to scan whole genomes for special nucleosomes and to learn in which genomic context they occur. We are currently developing the methods necessary for this endeavour.

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