Nucleosome positioning by a periodic potential

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Abstract

In eukaryotes, DNA is compacted into nucleosomes that can also control the access of DNA-binding proteins to DNA. Experimental techniques of functional genomic provided high-accuracy maps of nucleosome positions. Recently a few methods have been proposed to predict positions of nucleosomes on DNA, most of them being based on sequence specificity, mechanical properties of the DNA and interaction with DNA-binding proteins. Steric exclusion of nucleosomes makes nucleosome positioning identical to discrete 1D gas of hard rods that are allowed to slide freely in an external potential. This model suggests an efficient way to position nucleosomes by creating a signal with a period finely tuned close to the characteristic period of the system. We demonstrate that this effect may lead to an ordering and compacting nucleosomes by a weak potential. We also check that this positioning is strongly robust to disorder of a compared amplitude.

1 Introduction

DNA in eucareots is compacted into nucleosomes. Each nucleosome consists of a core histone octamer with a 147 bp DNA wrapped around it [1]. Neighbouring nucleosomes are separated by a 5-10 bp linker, effectively increasing nucleosome length to $\approx$ 157 bp in Yeast. Apart from compacting DNA, nucleosomes carry a regulatory function by limiting DNA availability to cis-regulatory proteins. Experiments show that nucleosome positions

are not random: there are regions depleted of nucleosomes, stable and delocalized nucleosomes, and nucleosome occupancy locally often has a periodic structure[2].

Although nucleosomes show a weak sequence preference, there have been found few nucleosome positioning factors. They include chemical bonds, sequence-dependence of DNA bending properties[3] and exclusion/positioning of nucleosomes by a DNA binding factors. Apart from this, steric exclusion plays an important role in nucleosome positioning, leading to strong correlation between adjacent nucleosomes[4][5]. One of the effects of a steric exclusion is an ability of a single wall to position 3-4 nucleosomes at each side of the wall, introducing a so-called statistical positioning. Nucleosome positioning is mainly an equillibrium process, so this problem is easily reduced to a problem of 1D gas in an external potential. As hard rods, nucleosome may be positioned no closer that ≈ 157 bp to each other.

2 The model

We consider nucleosomes as a gas of rods in an external potential, each rod allowed to occupy a set of discrete positions starting at each basepair. Then a nucleosome occupancy at nth basepair is given by a formula

$$< p_n >= \frac{\sum_{conf[n]} exp(-\beta E^{(conf)})}{\sum_{conf} exp(-\beta E^{(conf)})},$$

where a sum over conf[n] denotes all conformation where nth basepair is covered by a nucleosomes.

We used a dynamic programming algorithm[3] that allows to compute a genomewide nucleosome occupancies within a few seconds.

2.1 Exact solution

For a case of a uniform potential this problem can be solved exactly. In the limit of large nucleosome length L this leads to an universal solution:

$$< p >= \frac{W(\mu_{eff})}{1 + W(\mu_{eff})},$$

where $W(x)$ is a Lambert function, that behaves as $\ln(x)$ for $x \gg 1$, and $\mu_{eff} = \ln(L) - U$ is an effective chemical potential.

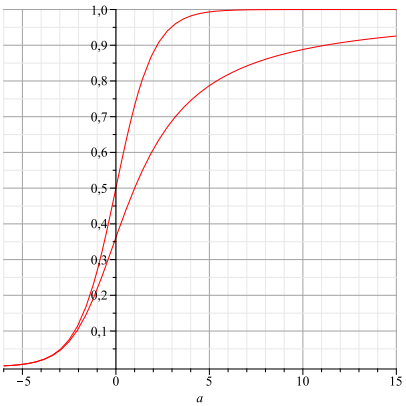


Figure 1: Occupancy as a function of effective energy μ_{eff} for an individual site (top) and gas of rods (bottom)

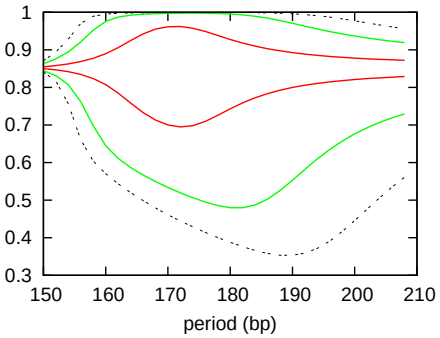
This solution strongly differs from the case of independent sites, where occupancy is given by $\exp(-U)/(1+\exp(-U))$ and will converge to one for a few k_BT binding energy (Fig. 1). For a gas of rods even $20k_BT$ binding energy will lead to 0.95 average occupancy, i.e. gas of nucleosomes is hard to compact. This is effect also known as a parking lot problem.

2.2 Positioning by a periodic potential

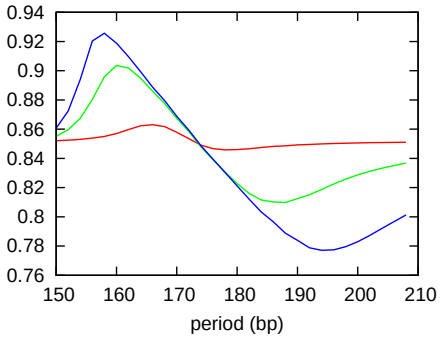
Consider a gas of rods subjected to a potential $U = U_0 + A\sin(2\pi n/T)$. Then nucleosome occupancy will be a periodic function. As a measure of ordering nuclesomes we use a maximal and minimal occupancy over the period. We plot them as a function of T for different amplitudes A. (Fig. 2(a)) Also we repeat the same plot for an average occupany. (Fig. 2(b))

This plots show that for a small A the min/max occupancies have a peak at $T = T_0 = L/ < p >$, i.e. when a period equals an average distance between nucleosomes. Periods smaller that T_0 serve as nucleosome-compacting, larger than T_0 - as nucleosome diluting. The effect of the compacting is so strong, that for a $U_0 = -3k_BT$ and $A = 1k_BT$ the resulting density is as large as it would be for $U_0 = -9k_BT$. As the density increases, even weaker signal is sufficient to induce ordering and/or compacting.

Compacting nucleosomes by creating a periodic structure may be seen as a transition from a gas of rods to a set of individual nucleosome sites (see Fig. 1), and even a weak potential is sufficient to impose nucleosome ordering



(a) Maxima and minima of occupancy for amplitudes 0.2,0.8 and 1.4 k_BT



(b) Average occupancy for amplitudes 0.2,0.8 and 1.4 k_BT

Figure 2: Effects of positioning (a) and compacting (b)

leading to a one-nucleosome-per-site arrangement.

2.3 Effects of noise

We also check a robustness of a periodic nucleosome positioning to noise. To check this we create a periodic potential with ampliute A and add it to two independent gaussian noise signals with a correlation length 150 and variance B. We position nucleosomes by both signals and measure the correlation coefficient between results. For a $U_0 = -3$ a ratio $B/A = 3$ is still sufficient to maintain the correlation coefficient > 0.5. This effect is also enhanced as the density increases.

3 Conclusion

We've shown that a weak periodic potential with a finely tuned period serves as an efficient nucleosome positioning and/or nucleosome compacting factor. We've checked that this positioning is robust to disorder that is few times stronger than the signal. We suggest that this effect should be taken into account in modeling nucleosome positioning, but requires a delicate balancing of a real nucleosome length (including linker) and a chemical potenatial, as this parameters control the strength of the effect.

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