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Supplemental Information

Irregular Chromatin: Packing Density, Fiber Width, and Occurrence of Heterogeneous Clusters

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Supporting Material

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1 Contact probability $I(k)$

We define $I(k)$ which is the probability that any nucleosome is in "contact" with its k^{th} neighbor. More precisely $I(k)$ is the probability of finding k^{th} neighbor nucleosome below a certain cut-off distance (here the cut off distance is taken as $2.5\sigma_h = 13.2$nm). To compute this probability, (similar to the procedure followed in ref [1]), we first define a square matrix $D^{i,j}$ which has elements 1 or 0 and is defined by:

$$D^{i,j}(n) = \begin{cases} 1 & \text{if } |\mathbf{r}_h^{(i)} - \mathbf{r}_h^{(j)}| < 2.5\sigma_h \\ 0 & \text{else} \end{cases} \tag{1}$$

where n is the n^{th} configuration (obtained from simulations), and $\mathbf{r}_h^{(i)}$ and $\mathbf{r}_h^{(j)}$ are the positions of i^{th} and j^{th} nucleosome. Let $\overline{D}(i,j)$ be the average of this matrix over different configurations (n), in stead-state. Then we compute I(k) which is nothing but the probability of k^{th} neighbor nucleosome below a cut-off distance of $2.5\sigma_h$, as:

$$I(k) = \frac{\tilde{I}(k)}{\sum\limits_j \tilde{I}(j)} \tag{2}$$

where $\tilde{I}(k) = \sum\limits_{i=1}^{N_h-k} \overline{D}(i, i+k)$ and N_h is total number of nucleosomes present in the chromatin.

2 Packing density and fiber width

We compute packing density p_d, which is roughly defined as the number of nucleosomes (N_h) packed in every 11nm effective length (L_{fiber}) of the chromatin fiber.

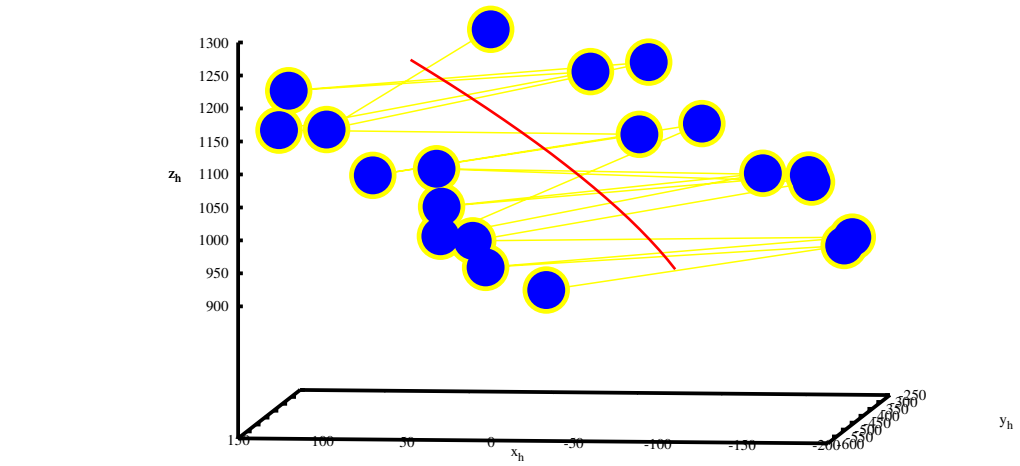
$$p_d = \frac{N_h \times 11\text{nm}}{L_{fiber}} \text{nucleosomes/11nm}, \tag{3}$$

To calculate effective length (L_{fiber}) of the chromatin fiber, (similar to the procedure followed in ref [1]), we define the fiber axis $\mathbf{r}_{ax} \approx (P_x^{(i)}, P_y^{(i)}, P_z^{(i)})$. $\mathbf{r}_{ax}$ is calculated by solving equations of polynomial $P_x^{(i)}, P_y^{(i)}$ and $P_z^{(i)}$ from least square method which is best fit with i^{th} nucleosome position $\mathbf{r}_h^{(i)} = (x_h^{(i)}, y_h^{(i)}, z_h^{(i)}$ in the x, y and z direction respectively (see Fig. S1). Then we computed fiber length L_{fiber} as follows:

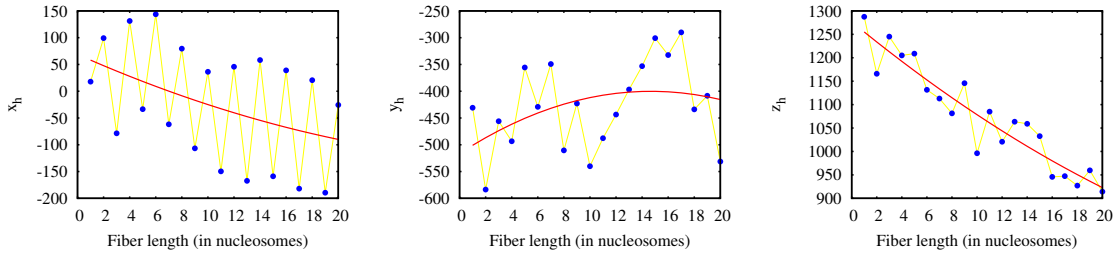
$$L_{fiber} = \sum_{i=1}^{(N_h-1)/2} |\mathbf{r}_{ax}^{(2i-1)} - \mathbf{r}_{ax}^{(2i+1)}|, \tag{4}$$

We also calculate fiber width (w_d) which is Following:

$$w_d = \frac{2}{N_h} \sum_{i=1}^{N_h} |\mathbf{r}_h^{(i)} - \mathbf{r}_{ax}^{(i)}| + 5.5\text{nm}. \tag{5}$$



(a)



(b) (c) (d)

Fig. S 1: (a) Fiber axis (red curve) is calculated using least square method which is best fitted with nucleosome center positions (blue dots). Yellow lines are connections between two consecutive nucleosomes. (b),(c) and (d) Fiber axis decomposition (red curve) with center position of nucleosomes (blue dots) into x, y and z directions respectively.

3 Cluster of nucleosomes

When a few nucleosomes come within a certain cutoff distance (we took 2.5 times its diameter, $2.5\sigma_h$), they are defined as a cluster of nucleosomes. If a nucleosome has no neighbor within the cutoff distance, it is considered to be a cluster of size 1. Similarly if a nucleosome has $N_h - 1$ neighbors within the cutoff distance, it is considered as a cluster size N_h.

4 Simulation parameter description

Parameter	Description	Value
q_d	Charge on DNA bead	$-21.14\,e$ [1]
q_h	Charge on core-histone bead	$52\,e$ [2]
q_t	Charge on histone tail bead	$2\,e$
q_l	Charge on linker histone(H1) bead	$13.88\,e$ [1]
σ_d	Diameter of DNA bead	34 Å [1]
σ_h	Diameter of core-histone bead	52.5 Å [3]
σ_t	Diameter of histone tail bead	15.6 Å [1]
σ_l	Diameter of linker histone(H1) bead	29 Å [4]
m_d	Mass of DNA bead	$6000\,\mathrm{g\,mol^{-1}}$ [3]
m_h	Mass of core-histone bead	$22\,089\,\mathrm{g\,mol^{-1}}$
m_t	Mass of histone tail bead	$579\,\mathrm{g\,mol^{-1}}$
m_l	Mass of linker histone(H1) bead	$5118\,\mathrm{g\,mol^{-1}}$
k^{spring}	Stretching stiffness for any type of bead	$0.17\,\mathrm{kcal/mol/Å^2}$ [5]
k^{bend}	Bending stiffness of DNA bead	$8.8\,\mathrm{kcal/mol}$ [5]
Δt	Time-step for BD	359.5 fs

Table 1: Parameters used in our simulations

5 Calculation of DNA density

The ratio of the length of DNA and the volume of the packaged chromatin can be called as DNA density. Unit of this density is basepairs per nm^3. We define density (ρ) as

$$\rho = \frac{L}{\pi(w_d/2)^2 L_{fiber}},$$

where L is the total length of the DNA in basepairs, w_d is the fiber width, and L_{fiber} is the effective length of fiber in nm. This is equivalent to DNA concentration measured in experiments having units of $\mathrm{g\,ml^{-1}}$. Note that $1\mathrm{bp/nm^3}$=$1\,\mathrm{g\,ml^{-1}}$.

We computed this DNA density for different chromatin that we simulated (see Figs. S2(a) and (b)) for different parameter values. We also computed the same for different number of nucleosomes (N_h), where N_h =12, 20, 50, and 100. Since each nucleosome has 18 DNA beads (14 beads wrap around the core histone and 4 beads in the linker DNA) and each DNA bead size is 10.5 basepairs, the total length of L is $N_h \times 18 \times 10.5 = 189N_h$ bp. Results of density for L =2268, 3780, 9450, and 18900 basepairs of DNA are shown in Fig. S2(c) and (d). Value of DNA concentration reported by experiments, for regular zigzag structure is $0.06 - 0.15\mathrm{g\,ml^{-1}}$ and for irregular chromatin structure is $0.04 - 0.14\mathrm{g\,ml^{-1}}$ [6]. We compared these results from our simulations (20 nucleosomes) and got similar range (see Fig. S2(a) and (b)). Density of simulated long chromatin structure (18900 bp of DNA) is also comparable with density of human mitotic chromosomes. For human mitotic chromosomes DNA density is 0.14- basepairs/nm^3 (or $0.141\,\mathrm{pg\,nm^{-3}}$) [7].

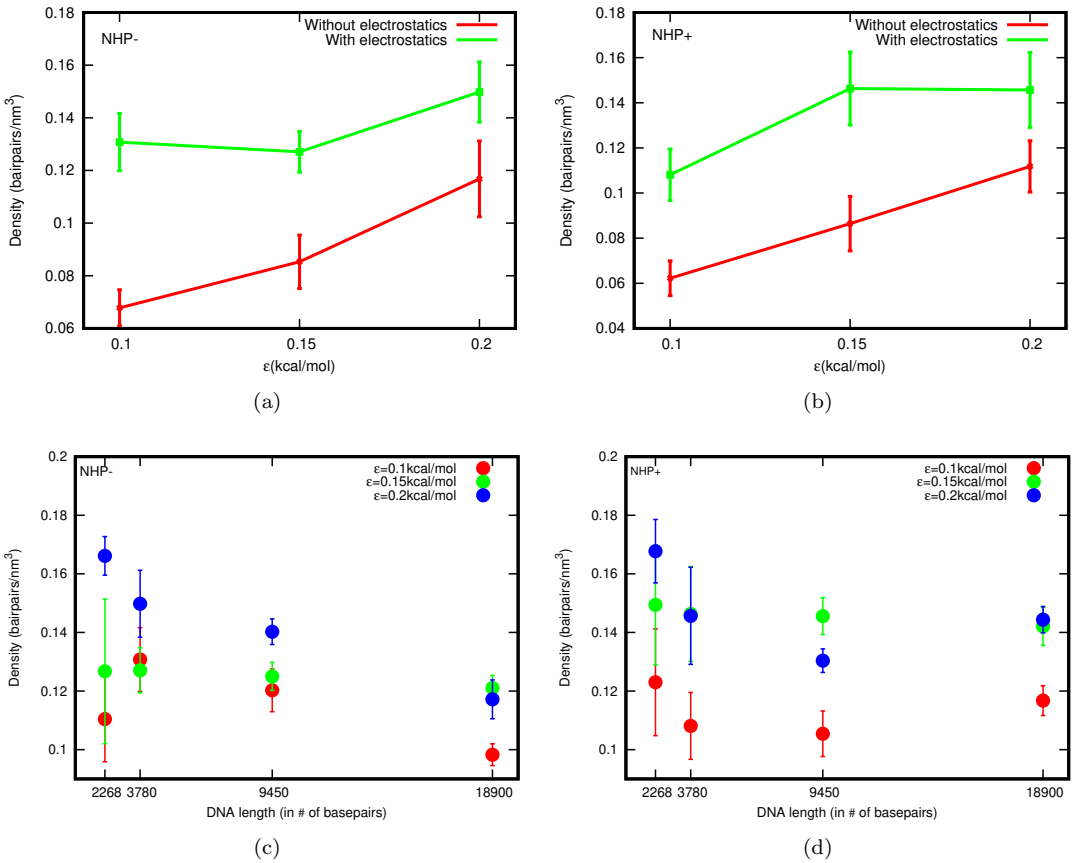
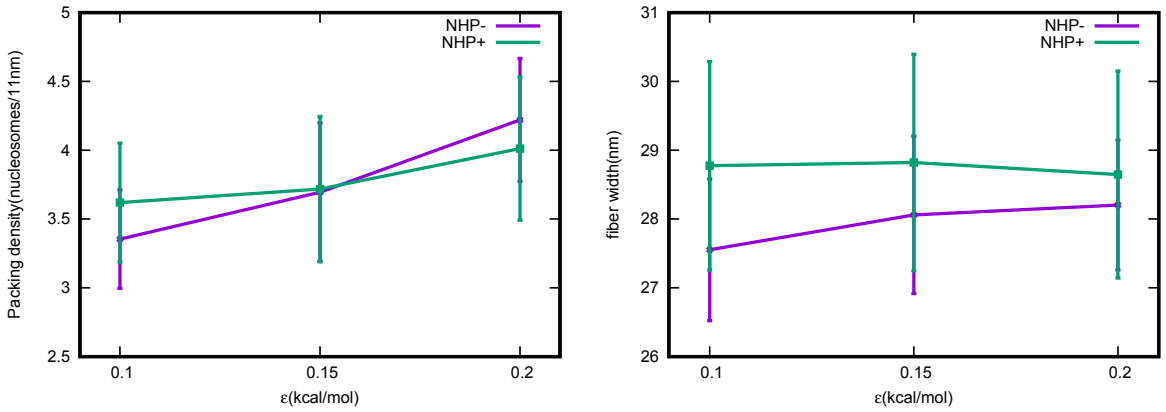


Fig. S2: (a-b): DNA density for 20-nucleosome chromatin is plotted for different LJ strengths (ϵ) having (a) absence and (b) presence of NHPs. (c-d): The density is plotted by varying the length of DNA (number of nucleosomes) for different ϵ in the (c) absence and (d) presence of NHPs.

6 Packing density and fiber width for a case with LJ attraction only among nucleosomes



(a) (b)

Fig. S 3: Results of our simulations with Lennard-Jones(LJ) attractive potentials only between nucleosomal beads; no attraction between DNA beads. (a) Packing density and (b) fiber width on varying chromatin fiber length in the absence and presence of NHPs for different LJ interaction strengths (ϵ). All data points here are computed with electrostatic interactions. Comparing with the results presented in Fig.3, we note the numbers are similar. For example, the width is $\approx$ 30nm. The packing density is slightly smaller as expected, but is of the similar magnitude.

7 Cluster size on varying chromatin fiber length

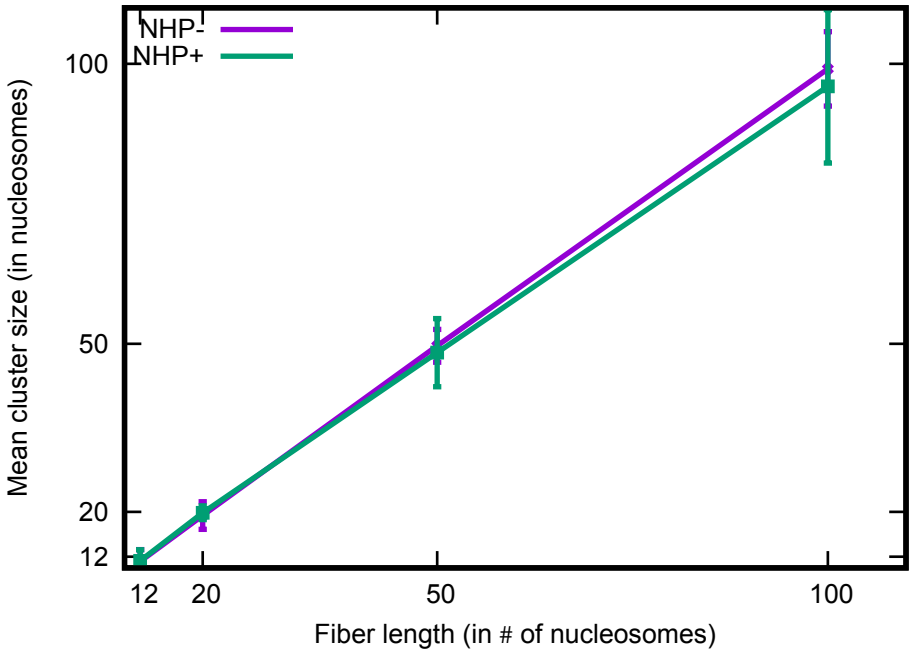


Fig. S 4: Cluster size on varying chromatin fiber length in the absence and presence of NHPs for LJ interaction strength $\epsilon = 0.15$ kcal/mol. Similar to the width, the cluster size is also increasing with length.

8 Globular chromatin structures varying κ and ϵ

Chromatin states can be affected by complex electrostatic interactions that include effect many cations and ions of higher valency [8]. In our model, this can be modelled by varying κ and ϵ . We varied the value from $1\,\mathrm{nm}^{-1}$ to $2.5\,\mathrm{nm}^{-1}$. Also we take large value of LJ strength ($\epsilon = 0.2\,\mathrm{kcal/mol}$) to show internucleosome interaction. For the large value of κ and ϵ, we simulated and chromatin and the resulting representative configurations are shown in Figs. S5 (a) and (b). It was seen that the fiber self-assembled into large globular structures; this appears similar to the interdigitated structure seen in experiments [8]. To check the chromatin properties, we calculated contact probability between two points that are s apart along the contour ($P(s)$) and it is fitted with s^{-1} (see Figs. S5 (c) and (d)).

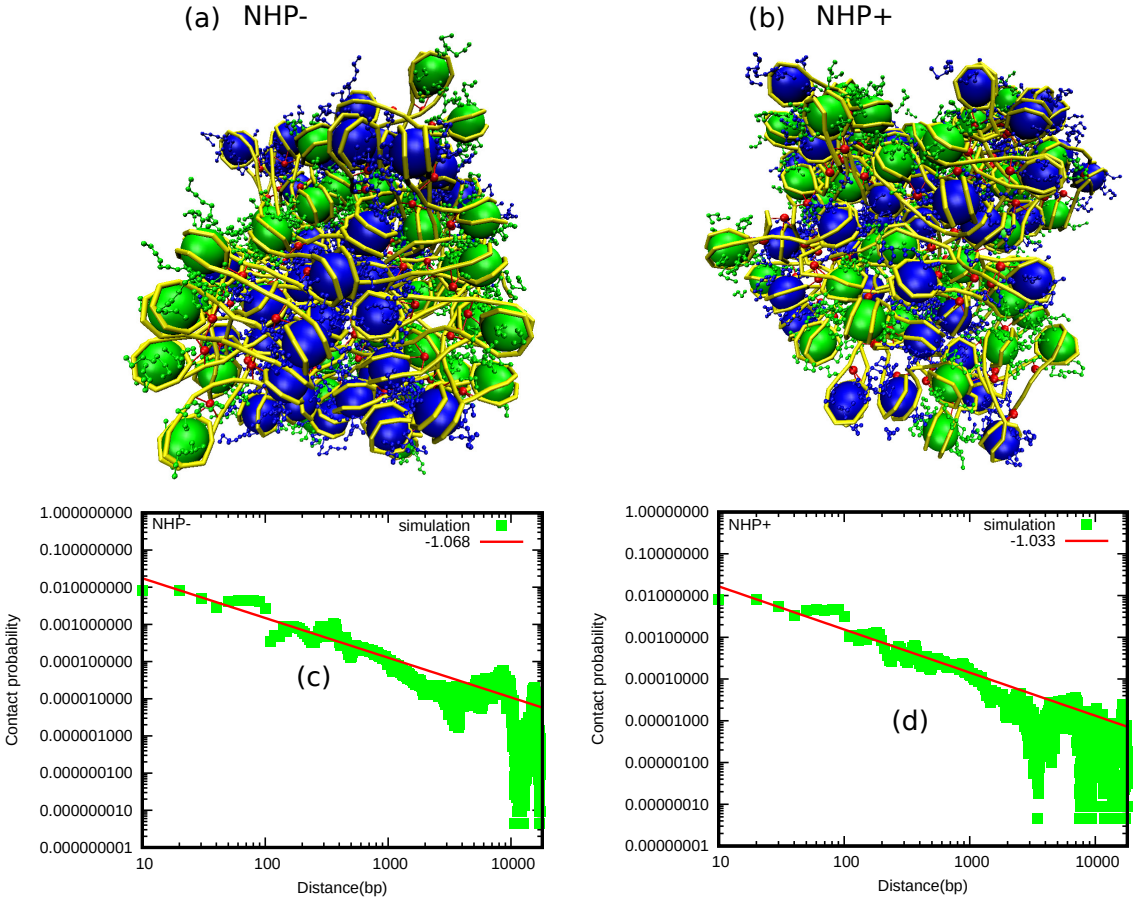


Fig. S5: (a), (b) Representative snapshots of chromatin structures in the absence and presence of NHP for higher values of κ and ϵ. (c),(d) Contact probability for the same case (high κ and ϵ) as a function of contour distance (distance along the DNA backbone) in the absence and presence of NHP, calculated from the simulations (green curve). The red line is a guide to the eye indicating power-law behavior suggesting the fractal nature of the self-organization.

9 Frequency distribution of lengths H3K9me3 modifications

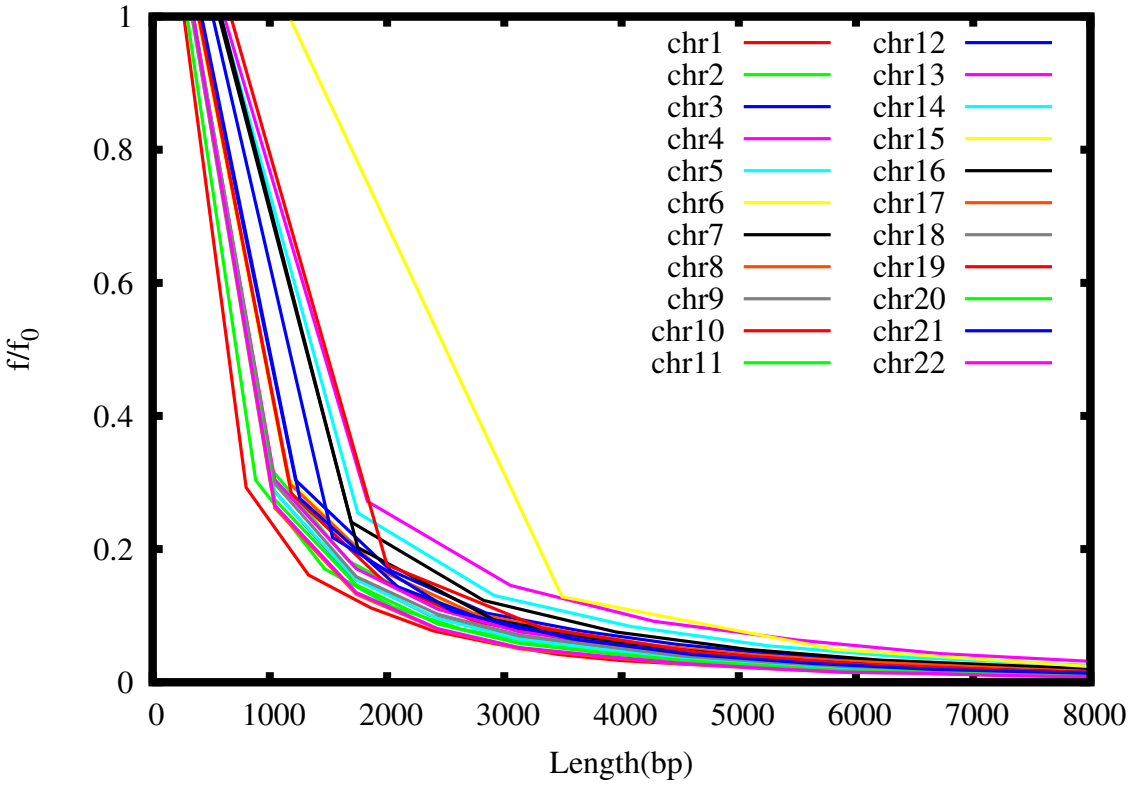
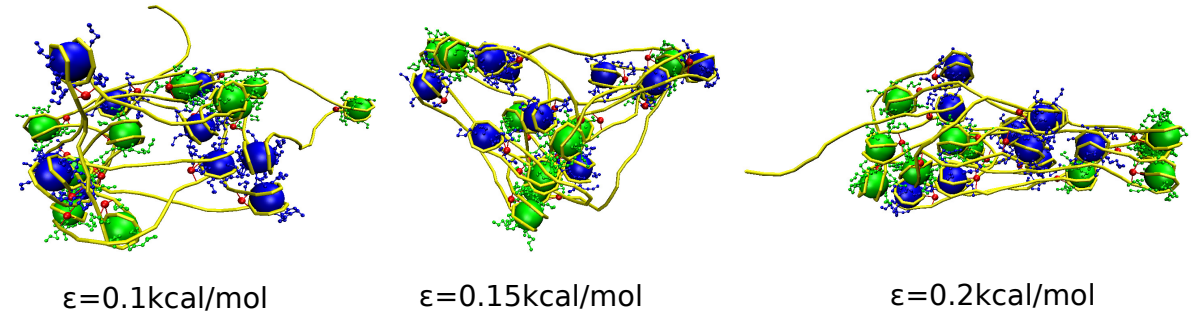


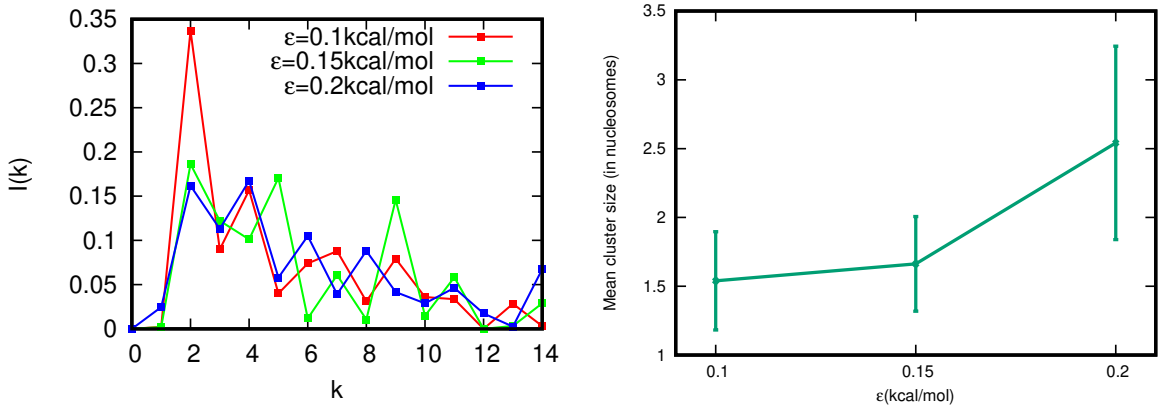
Fig. S6: Frequency (f) distribution of lengths of contiguous patches having H3K9me3 modifications, for different chromosomes, scaled with maximum frequency (f_0). Most of the patches are smaller in length; very long patches are rare.

10 Structure and contact probability $I(k)$ for irregular nucleosome spacing

Since, irregular nucleosome spacing or frequent nucleosome loss can change chromatin structure [9, 10], we did simulations taking non-uniform linker length between 21 bp to 147 bp. We assumed linker length is uniform randomly distributed between 2 to 14 DNA beads. Results are shown in Fig. S7.



(a)



(b) (c)

Fig. S7: (a) Configuration of chromatin ($N_h = 20$ nucleosomes) with non-uniform linker length (21 bp to 147 bp) for different LJ interaction (ϵ). Note the mixing of colors, implying irregular structure. (b) Calculation of $I(k)$ for irregular nucleosome spacing for different LJ interaction: $\epsilon = 0.1$ kcal/mol (red), $\epsilon = 0.15$ kcal/mol (green), and $\epsilon = 0.2$ kcal/mol (blue). $I(2)$ decreases while $I(k)$ increase for most other k values. This means, regular zigzag structure is destroyed for non-uniform linker length. (c) Mean cluster size values are small (1-3), suggesting many clusters of 1-3 nucleosomes on an average.

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