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Supporting Material

Computer Modelling Reveals That Modifications of the Histone Tail Charges Define Salt-Dependent Interaction of the Nucleosome Core Particles

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Supporting Material for the manuscript

"Computer Modelling Reveals That Modifications of the Histone Tail Charges Define Salt-Dependent Interaction of the Nucleosome Core Particles"

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i) Supporting computational methods for the "Sphere" model of the NCP

ii) Supporting computational methods for the "Sphere-Bead" model of the NCP

iii) Selected data on NCP-NCP interaction determined for the systems with Sphere-Bead model of the NCP

i) Supporting computational methods for the "Sphere" model of NCP

Description of the "Sphere" model of the NCP (Figure 1S, Table 1S)

The recombinant NCP was modelled as a spherical particle of effective radius 4.85 nm with net charge −236e combined with 8 strings of linearly-connected +1e charges of effective radius 0.25 nm and bond length 0.7 nm, which represent the histone tails (1). The charge of the central particle reflects the electrostatic balance between 147 base pairs of the double-stranded DNA (charge −294e) and the net positive charge +58e of the amino acids comprising the globular domains of the histones. The distance between charged groups of the histone tails (0.7 nm) was evaluated assuming extended conformation of the polypeptide chain and even distribution of the Lys^+/Arg^+ amino acids. The number of charged groups in each tail was set according to the charges of the real histone tails. The total charge of histone tails was +88e, which, together with the charge of the central unit, yields the total charge of NCP −148e.

The introduced coarse-grained model represents an "idealized symmetrical" approximation of the real structure of the NCP determined by X ray crystallography (2-4) (see Fig. 2 of ref. (4)). The distance from the first charged group of the tails to the center of the core was set to 5.5 nm for all tails. The points of exits for the four histone tails (H2B/1, H2B/2, H3/1, H3/2; see Supporting Fig. 1S) which protrude through the gears of the DNA superhelix in the real NCP, were set in the *x*,*y*-plane (*z*=0) with 90^o between them. The exit points of the H4/1 and H4/2 histone tails were placed 2.5 nm below and above the *x*,*y*-plane, opposite to each other and perpendicular to the dyad axis (Fig. 1S). Finally, the H2A/1 and H2A/2 tails exit the core particle 2.5 nm below and above the *x*,*y*-plane and are positioned between H2B/1 and H2B/2 tails. Distance constraints (shown in Fig. 1S) between the first particles of the histone tails were introduced to preserve the initial geometry of the histone tails' exits from the core particle.

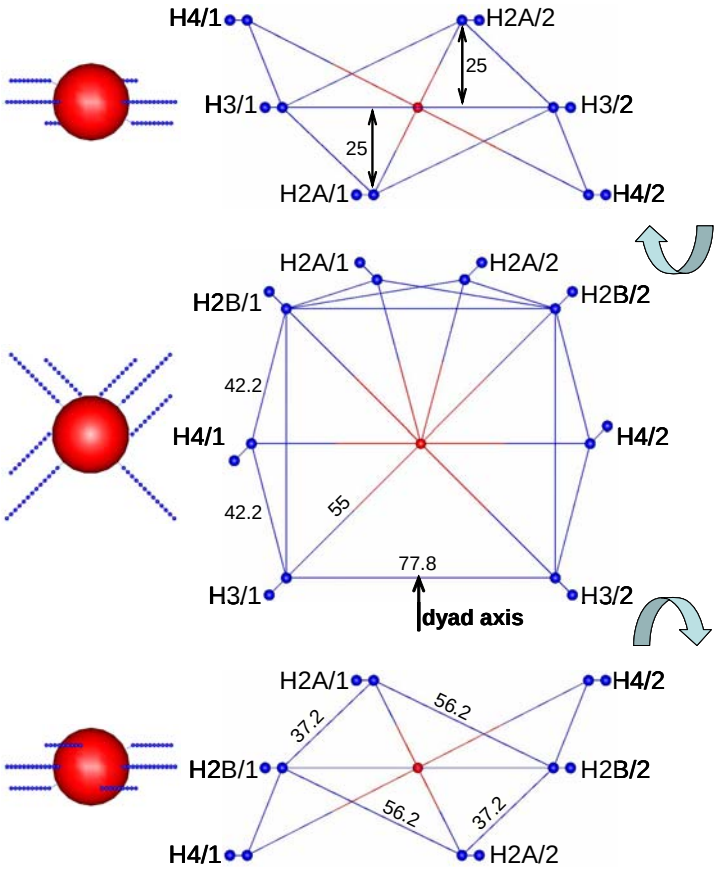

Figure 1S. Model of the NCP. The three schemes on the right hand side show the connection of the histone tails to the negatively charged core and to each other (2 groups of each tail closest to the core are shown as blue spheres). The centre of the core particle is drawn as a red ball. The coordinate system has its origin in the center of the core particle with exit points of the H2B and H3 tails forming the *x*,*y*-plane (*z*=0). The middle scheme shows the view from the top along *z*-axis; top and the bottom schemes display projections resulting from respective counter- and clockwise 90^{o} rotations of the scheme in the middle. The lines between particles indicate bonds described by harmonic potential with equilibrium distances in Ångströms indicated in the figure. The three pictures on the left hand side show views of NCP with all charges in the histone tails and the central core particle in the same projections as the corresponding schemes shown on the right hand side.

Table 1S. Coordinates (in nm) of the first bead of the histone tails in the NCP model.

Tail	x	y	z
H3	5.50	0.0	0.0
H3	–5.50	0.0	0.0
H2B	0.0	5.50	0.0
H2B	0.0	–5.50	0.0
H4	3.464	–3.464	2.50
H4	–3.464	3.464	–2.50
H2A	–4.243	–2.45	2.50
H2A	–4.243	–4.243	–2.50

Interaction and bond potentials used in the simulations with the NCP Sphere model

The interaction potential (force field) of the coarse-grained model consisted of three parts: electrostatic, short-range and bond potentials. The electrostatic interaction was defined in a standard manner, as a sum of Coulombic potentials from all the charges in the system, in dielectric media with dielectric constant ε=78. The particle-particle particle-mesh (PPPM) method was used to compute the long-range part of the electrostatic forces and energies. The short-range potential, acting between any pair of elements of the coarse-grained model (that is, NCP centre particles, histone tail monomers, and ions) has the following form:

$$U_{short}(r_{ij}) = \begin{cases} kT\left(\dfrac{a}{r_{ij}-\sigma_{ij}}\right)^9 & r_{ij} > \sigma_{ij} \\ \infty & r_{ij} < \sigma_{ij} \end{cases} \qquad \text{(S1)}$$

where r_{ij} is the distance between elements "i" and "j", $\sigma_{ij} = \sigma_i + \sigma_j$ is the sum of their hard core radii and a=0.3 nm - a parameter having the sense of effective thickness of the soft repulsion potential. For hard core radii, we used σ=4.7 nm for NCP central unit and σ= 0.1 nm for histone tail monomers and ions. The potential in Eq. S1 has effective interaction radius $\sigma_i+\sigma_j+a$, which is the sum of effective radii of each component $\sigma_i+a/2$. Thus the choice of parameters above provides the effective size of NCP core 4.85 nm and of ion (or tail monomer) 0.25 nm, together giving the effective NCP-core - ion interaction radius 5.1 nm.

The bond potential acting between neighbouring monomers of a histone tail has the form:

$$U_{bond}(r) = kT\left(\frac{r - r_{eq}}{\Delta}\right)^2$$

with equilibrium distance r_{eq}=0.7 nm and characteristic fluctuation Δ=0.1 nm. The same kind of potential acts between the NCP core and the first histone monomers of each tail (with

r_{eq}=5.5 nm). Some of the first histone monomers of different tails belonging to the same NCP are also bound by the harmonic bond potential to fix the positions of their attachment to the central core. The Figure 1S shows the geometry of their connections with the corresponding equilibrium distances.

ii) Supporting computational methods for the NCP "Sphere-Bead" model

Description of the "Sphere-Bead" model of the NCP (Figure 2S, Table 2S):

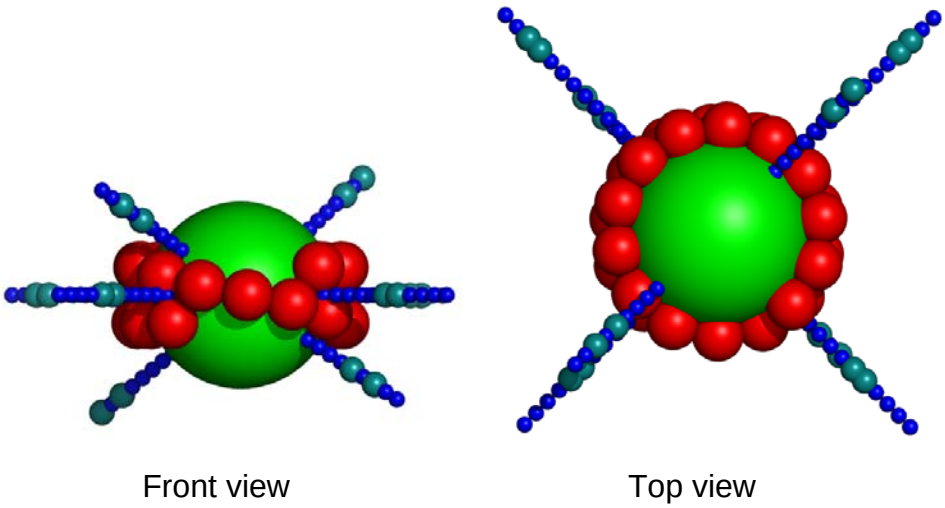

Figure 2S. Sphere-Bead model of the NCP. Top view and front view of the Sphere-Bead NCP model illustrated for the case with two acetylation sites in each of the histone tails. The non-acetylated (recombinant) model has the same geometry.

The effective radius of the central neutral particle representing the globular part of the histone octamer (core) is 3.5 nm. The DNA wrapped around the core is modeled by 25 beads of effective radius 1.0 nm. Each DNA bead represents a 6 bp DNA fragment. The original –12e charge of each DNA bead is reduced to –9.44e assuming that DNA phosphate groups contacting the NCP core are neutralized by positive charges of the histone core, which by this reason carries no charge. Totally the 25 DNA beads carry –9.44e*25=–236e charge, which is equal to that of the sum of the charges on 147 bp DNA (–294e) and the globular part of the histone octamer (+58e). The DNA beads are separated by 2.4 nm. They wrap around the core for about 1.7-1.75 rounds. The first and the last DNA beads were placed correspondingly close to the root of H3/1 histone tail and to the root of H3/2 tail. The z-coordinates of the DNA beads from 1 to 9 are –1.2 nm; whereas for the DNA beads from 15 to 25, z = +1.2 nm; DNA beads 10-14 bridge two segments by being equally positioned between –1.2 nm and +1.2 nm in z-direction. The described combination of the bead sizes and positioning closely represents the crystallographic structure of the NCP (2, 5).

Table 2S. Coordinates (in nm) for the central particle, start/end DNA beads and the first particle at the root of each tail in the Sphere-Bead NCP model.

Particle	*x*	*y*	*z*
Core	0.0	0.0	0.0
DNA(Start)	4.45	0	–1.20
DNA(End)	0	4.45	1.20
H3/1	4.80	0.0	0.0
H3/2	0.0	4.80	0.0
H2B/1	–4.00	0.0	0.0
H2B/2	0.0	–4.00	0.0
H4/1	3.10	–0.10	1.60
H4/2	–0.10	3.10	–1.60
H2A/1	–3.40	–0.10	2.10
H2A/2	–0.10	–3.40	–2.10

Interaction potential used in the simulations with the NCP Sphere-Bead model

We employed a short-range variant of a Lennard-Jones potential as inter-particle potential function:

$$U_{short}(r_{ij}) = \begin{cases} \infty & r_{ij} < \sigma_{ij} \\ 4\varepsilon\left(\left(\frac{\sigma}{r_{ij}-\sigma_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}-\sigma_{ij}}\right)^{6} + shift\right) & \sigma_{ij} < r_{ij} < cutoff \\ 0 & r_{ij} > cutoff \end{cases}$$

with
$\varepsilon = kT$
$\sigma = 0.4\ nm$
$cutoff = \sqrt[6]{2}\,\sigma + \sigma_{ij}$
$shift = 0.25\ \varepsilon$

As in the short-range potential of the sphere NCP model, the interaction hard-core radius is defined as the sum of radius of each component, $\sigma_{ij} = \sigma_i + \sigma_j$, and the soft radius parameter σ defines the total effective interaction radius as σ_{ij} + σ. The following values of the hard core radii σ_i were used: Core – 3.3nm; DNA Bead – 0.8nm; Tail Bead – 0.1nm; Acetylated Tail Bead – 0.2nm; Cl^- - 0; Mg^{2+} - 0.05nm; K^+ - 0.

iii) Selected data on NCP-NCP interaction determined for systems with the Sphere-Bead NCP model

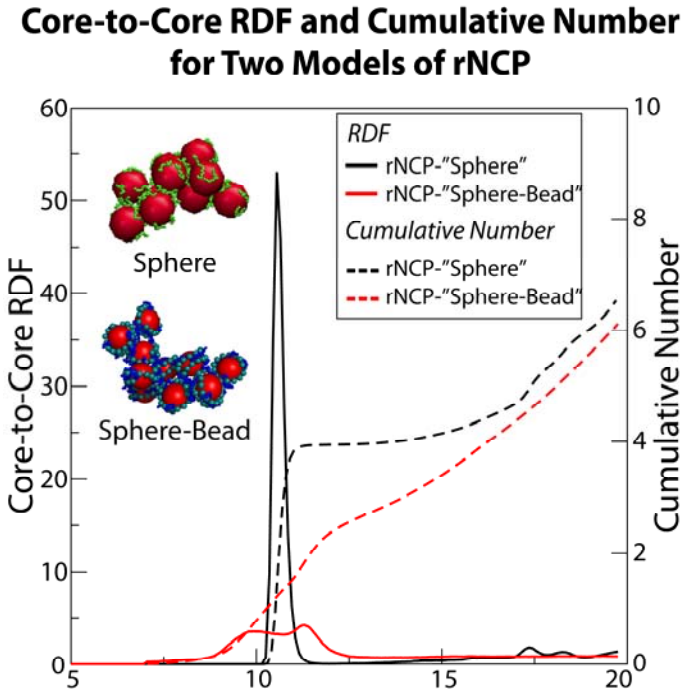

Figure 3S. Core-to-Core RDF (solid lines) and cumulative number (dashed lines) for the two rNCP models in the system with Mg^{2+} ions, rNCP-$MgCl_2$ (see main text for detailed description of the simulation system), computed from last 6×10^7 time steps of the simulation. "Sphere" NCP model (black curves) and "Sphere-Bead" NCP model (red curves). Representative snapshots shown in the graph illustrate aggregation of NCPs in the systems: top, Sphere model; bottom, Sphere-Bead model. The conditions for the simulation set up (including the number of mobile ions) are identical to those of the data presented in Fig. 2 and 3 and tabulated in Table 1 in the main text.

The RDF for the sphere-bead model is considerably broader than the corresponding RDF for the sphere model. It also displays two broad peaks. These features are caused by the difference in symmetry and the more varied packing alternatives in the sphere-bead model. E.g., two NCP can join either with the DNA chains adjacent to each other, or with the octamer cores in close proximity, giving rise to the two peaks. Integration of the RDFs can be made to compare the number of NCPs in clusters formed in the two models. The cumulative number of the NCP cores is defined from integration of the Core-to-Core RDF over the spherical space. It indicates how many NCP cores are inside a sphere of radius r centered at the core of one of the NCPs. On the average, for the NCP-$MgCl_2$ system with the Sphere NCP model, there are about four NCP cores within close distance from the central particle; whereas for the Sphere-Bead model, about three NCPs are coordinated to the central NCP. One can see that despite different intensities of the Core-to-Core RDFs of the systems with Sphere and Sphere-Bead models, the cumulative numbers are similar with small deviation around $r > 15$ nm which is the distance typical for the NCP-NCP separation in the second layer of densely aggregated NCPs.

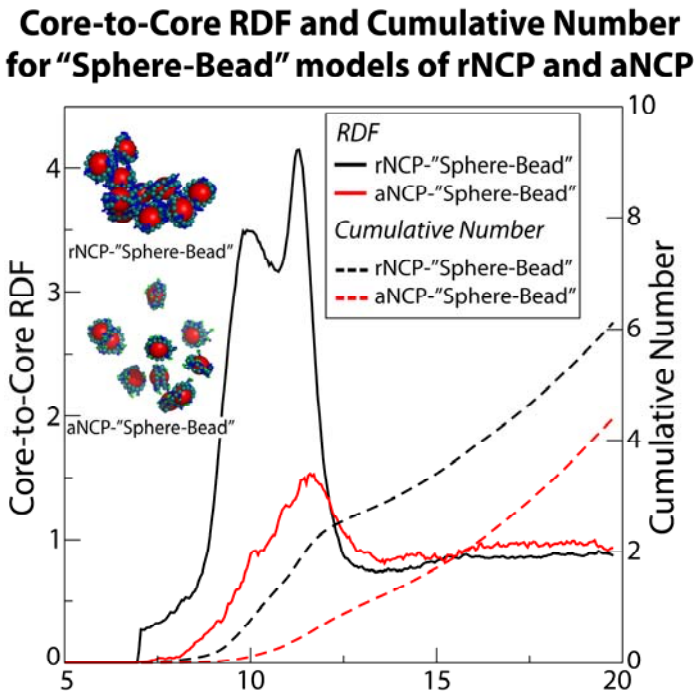

Figure 4S. Comparison of the Core-to-Core RDFs (solid lines) and cumulative numbers (dashed curves) for the "Sphere-Bead" model of rNCP (black curves) and aNCP (red curves) calculated in the presence of Mg^{2+}, computed from last 6×10^7 time steps and last 2×10^7 time steps respectively. Other conditions (box size, number of particles) are the same as for the systems rNCP-$MgCl_2$ and aNCP-$MgCl_2$ (see main text for detailed description of the simulation system).

RDFs and their cumulative numbers as well as representative snapshots indicate that "acetylation" of the tails significantly reduced NCP-NCP aggregation in the Sphere-Bead model. It can generally be concluded that the the simulations with the more detailed description of the nucleosome core particle in the Sphere-Bead model are in agreement with the those with the simpler Sphere model presented in the main text. Simulations conducted with full charges on the DNA beads, corresponding to the DNA structural charge and with a positively charged spherical histone octamer core gives similar result as described above.

References

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