Supporting Information

Atomistic Simulation of Stacked Nucleosome Core Particles: Tail Bridging, the H4 Tail and Effect of Hydrophobic Forces

Suman Saurabh[1], Matthew A. Glaser[2] , Yves Lansac[3,4,*] and Prabal K. Maiti[1,*]

[1]Center for Condensed Matter Theory, Department of Physics, Indian Institute of Science, Bangalore, India

[2]Department of Physics and Liquid Crystal Materials Research Center, University of Colorado, Boulder, CO 80309, USA

[3]GREMAN, Université François Rabelais, CNRS UMR 7347, 37200 Tours, France

[4]School of Materials Science and Engineering, Gwangju Institute of Science and Technology, Gwangju 61005, Korea

***To whom correspondence should be addressed.** Email: maiti@physics.iisc.ernet.in or yves.lansac@univ-tours.fr

Table S1: Properties of various histone tails. Hydrophobicity for an amino acid is calculated as the free energy change of transferring it from phenol to water. The H2B tail is the least hydrophobic, whereas the H2A tail is the most hydrophobic one. The numbers in the last column are sum over all residues of a given tail.[1,2] Amino acid sequences are given from N-termini (left) to histone core. Positively charged residues are represented in blue while the hydrophobic ones in orange. The vertical lines in the H4 tail sequence represent the two tail clipping positions for H4-tail clipped simulations. The first vertical line (from left) corresponds to the clipping position for H4-15-150 and the second one for H4-20-150.

Tail	Amino acid sequence	Total charge units	Charge Density	Total Hydrophobicity (kcal/mol)
H3	ARTKGTARKSTGGKAPRKQLATKAARKSAPATGGV KKPHR	**13**	0.325	-4.54
H4	SGRGKGGKGLGKGGA | KRHRK | VLRDN	**9**	0.36	-5.60
H2A	SGRGKQGGKTRAKAKTRSSRAGLQFP	**8**	0.308	-2.90
H2B	AKSAPAPKKGSKKAVTKTQKKDGKKRRKTRKESYA	**15**	0.428	-10.71

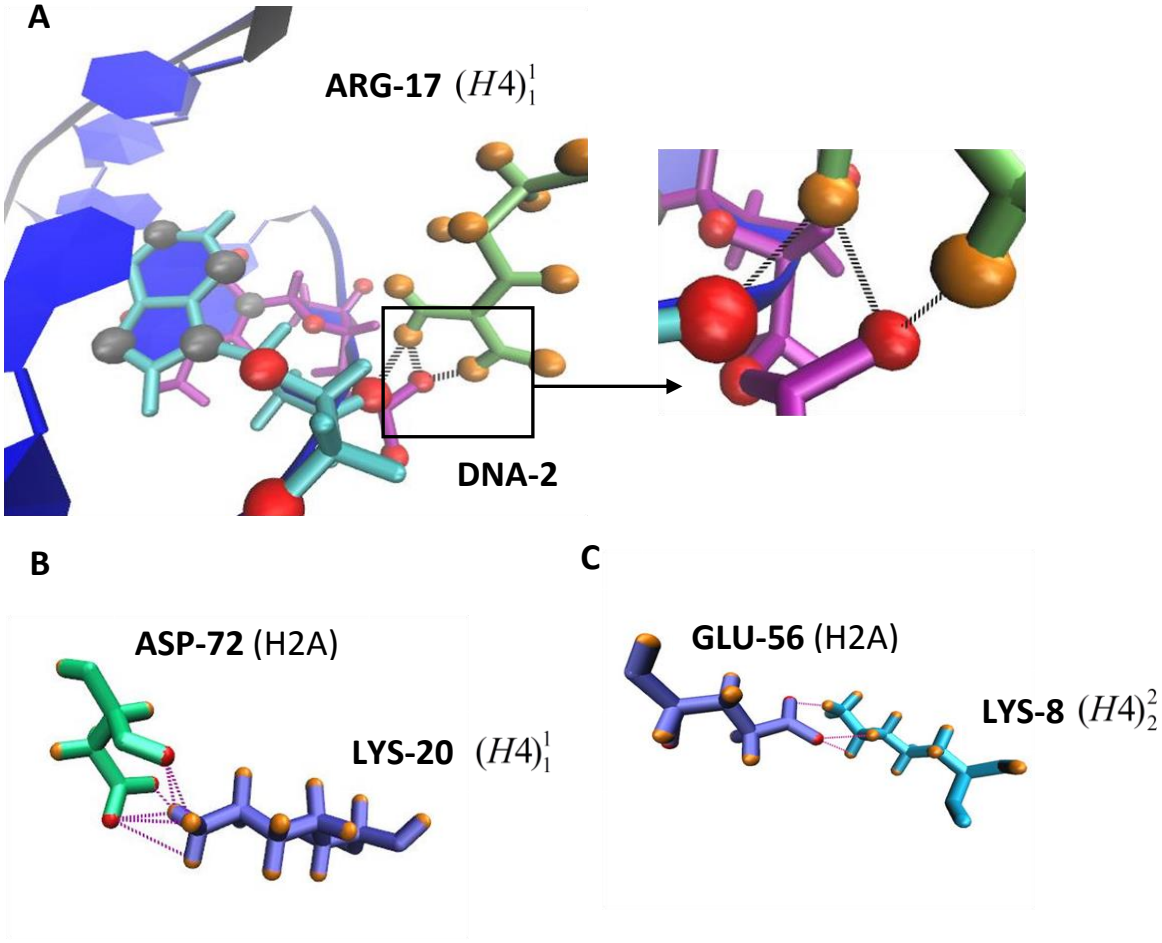


Figure S1: **(A)** ARG-17 of $(H4)^1_1$ interacting with DNA-2 backbone by donating hydrogen bonds. On the right is a zoomed view of the interaction site. **(B)** LYS-20 of $(H4)^1_1$ interacting with ASP-72 of histone H2A belonging to NCP2 through hydrogen bonds. **(C)** LYS-8 of $(H4)^2_2$ interacting with GLU-56 of histone H2A belonging to NCP1. The orange atoms are hydrogens and the red ones are oxygens. The snapshots correspond to AT-150.

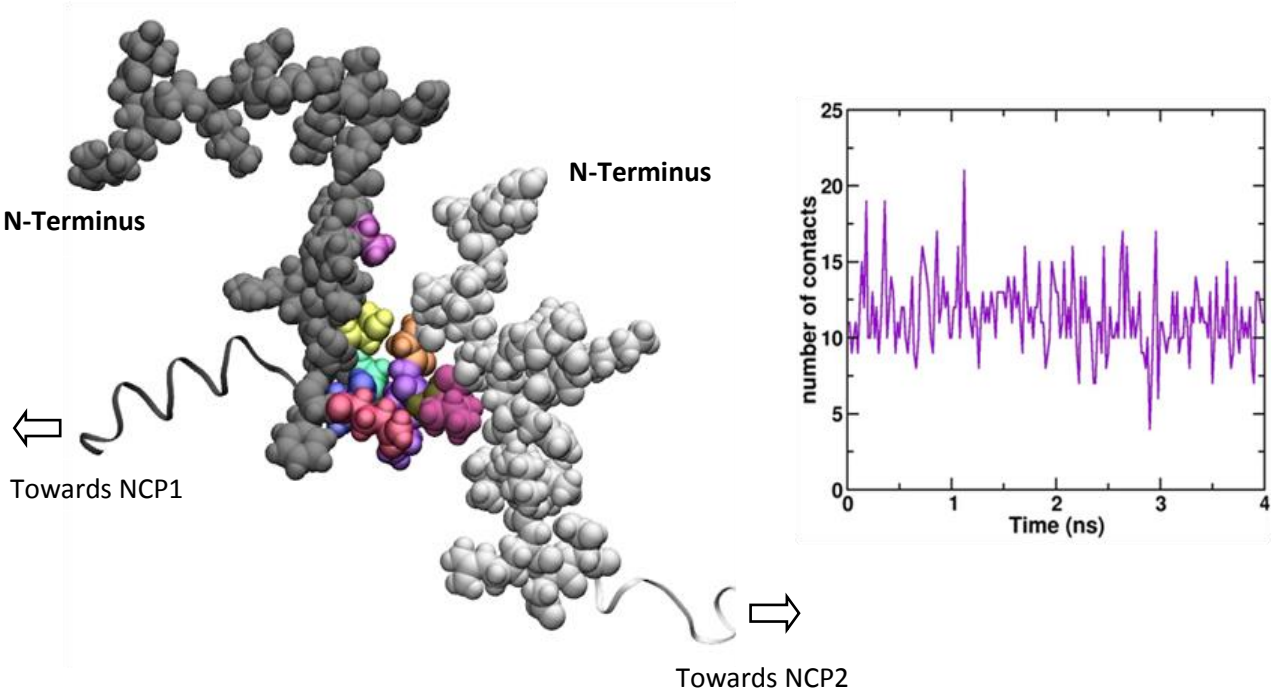
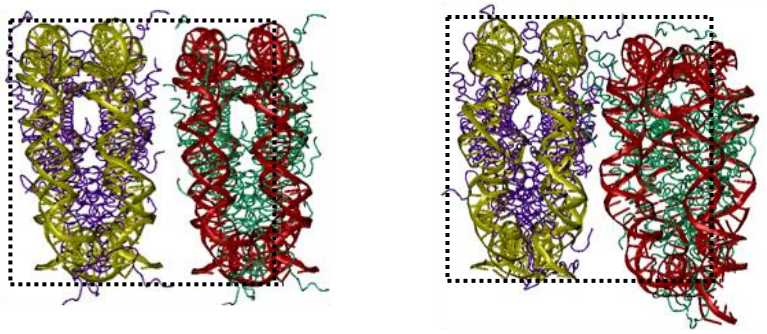
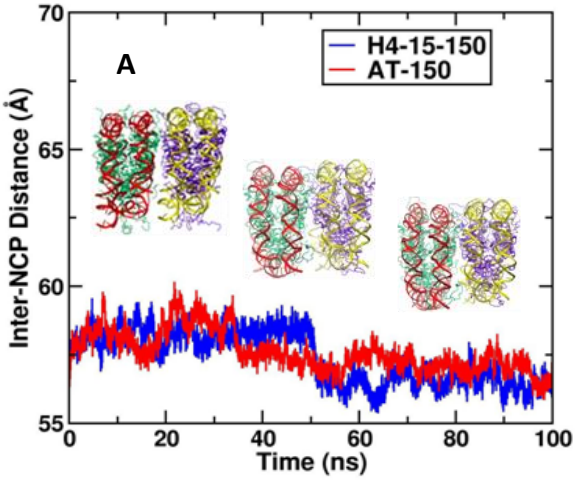


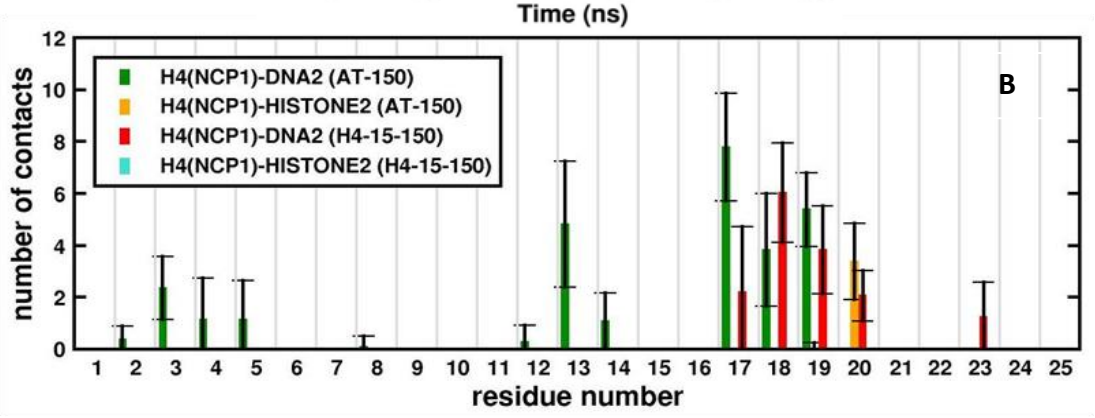
Figure S2: Equilibrium conformation of $(H2A)_1^1$ (grey) and $(H4)_2^2$ (white) for the AT-150 system. The snapshot shows the two tails in contact with each other. The residues involved in contacts are colored. The number of contacts for the last 4 ns of MD trajectory is shown. One can observe that the two tails form considerable number of contacts with each other. Consequently, the configuration of $(H2A)_1^1$ is affected by the absence of $(H4)_2^2$, as discussed in Figure S5 below.

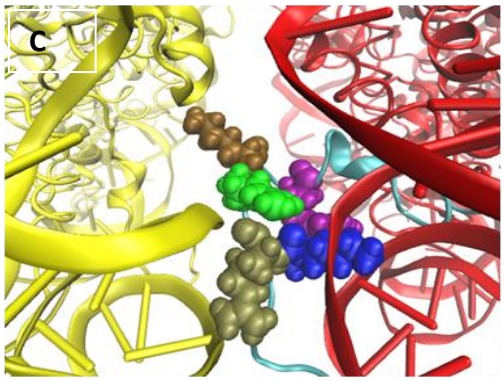


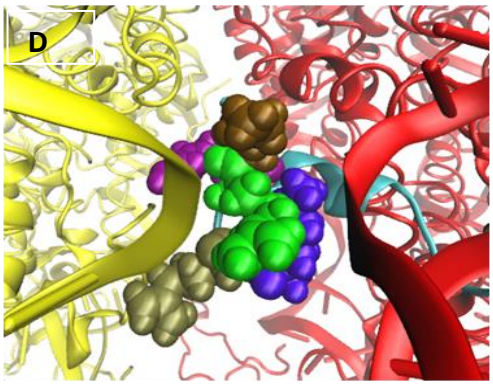
H4-20-150 (initial) **H4-20-150 (84 ns)**

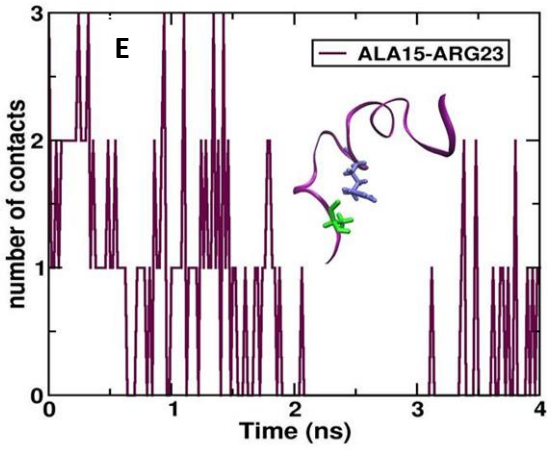
Figure S3: In-plane shift of one NCP with respect to the other. The shift is more prominent in H4-20-150, with the first 20 residues of the H4 tail removed. The shift is a characteristic feature of the NCP-NCP stacking observed in the columnar liquid crystalline phases and occurs due to DNA-DNA repulsion.


A
H4-15-150
AT-150
Inter-NCP Distance (Å)
Time (ns)


B
H4(NCP1)-DNA2 (AT-150)
H4(NCP1)-HISTONE2 (AT-150)
H4(NCP1)-DNA2 (H4-15-150)
H4(NCP1)-HISTONE2 (H4-15-150)
number of contacts
residue number


C


D


E
ALA15-ARG23
number of contacts
Time (ns)

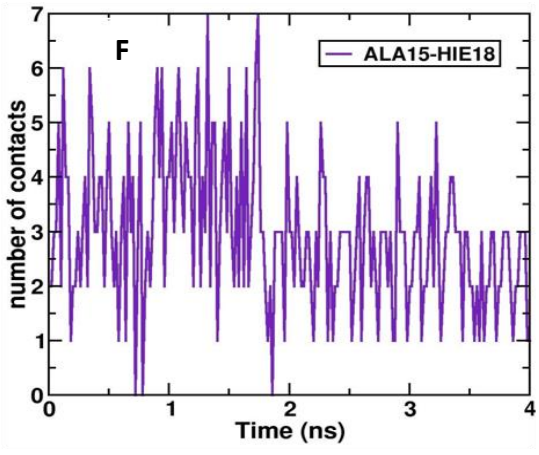

F
ALA15-HIE18
number of contacts
Time (ns)

Figure S4: (A) Inter-NCP distance for H4-15-150 compared to AT-150. One can see that there is a lot of overlap between the two. **(B)** Average number of contacts in case of AT-150 and H4-15-150 for the last 4 ns of MD trajectory. **(C)** Conformation of $(H4)_1^1$ tail in case of AT-150 simulation. **(D)** Conformation of $(H4)_1^1$ in case of H4-15-150. The residues shown with vdw representation are LYS-16 (blue), ARG-17 (tan), ARG-19 (green), LYS-20 (brown), and ARG-23 (purple) of $(H4)_1^1$. Contacts between ALA-15 and **(E)** ARG-23 and **(F)** HIE-18 over the last 4 ns of the 100 ns long MD trajectory for AT-150 system.

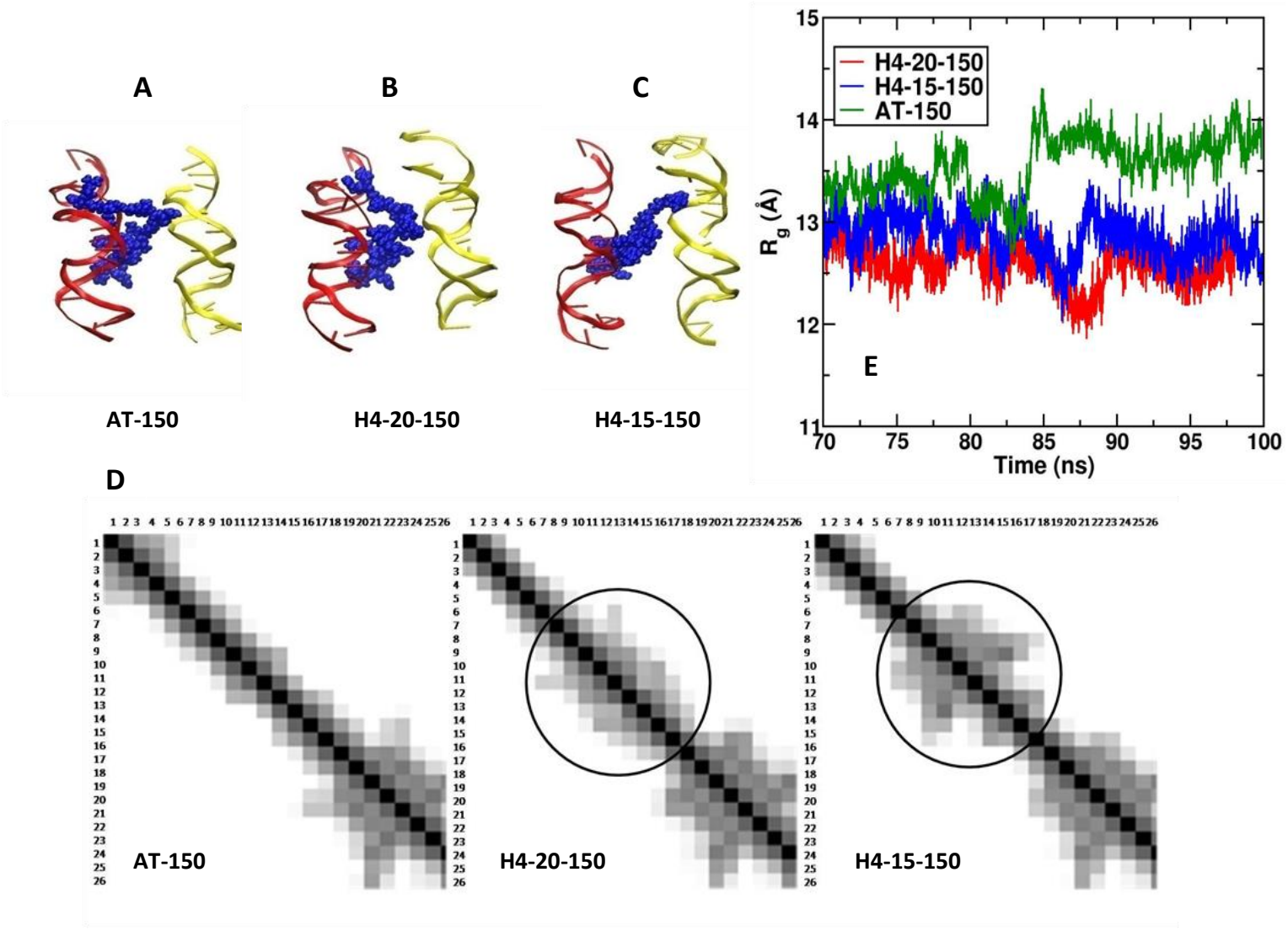


Figure S5: The equilibrium conformation of $(H2A)_1^1$ for **(A)** AT-150 **(B)** H4-20-150 and **(C)** H4-15-150. **(D)** Self contact map of $(H2A)_1^1$ for the three cases. One can see a significant increase in the number of self-contacts among residues of $(H2A)_1^1$ when $(H4)_2^2$ is removed. The circles on the contact map highlight the region of the tail that clusters on removal of a part of $(H4)_2^2$. It is to be noted that the two tails were in contact (see figure S2) in the intact NCP simulation at 150mM salt concentration (AT-150). The clustering occurs as $(H2A)_1^1$ tries to self-shield its residues from water. The residue numbers have been labeled. The corresponding amino acid sequence is provided in Table S1. **(E)** Comparison of radii of gyration of $(H2A)_1^1$ for the three different simulations. As a result of increase in clustering, the radius of gyration is lower for simulations with $(H4)_2^2$ partially removed (H4-20-150 and H4-15-150).

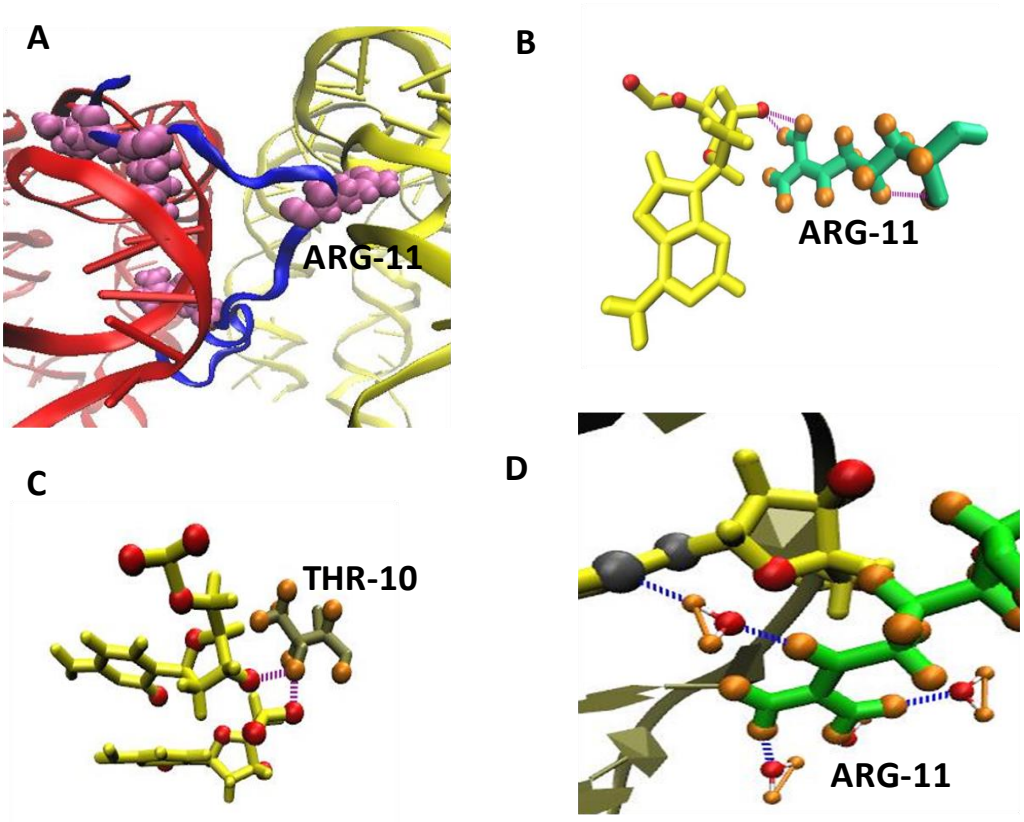


Figure S6: (A) ARG-11 of $(H2A)_1^1$ inserted into a minor-groove of DNA2. **(B)** ARG-11 interacting with a DNA-base of DNA2 in the minor-groove. **(C)** THR-10 of $(H2A)_1^1$ interacting with the DNA backbone. **(D)** Water-mediated interaction between an H atom of ARG-11 and an N atom of a DNA2 base. The snapshots are taken from AT-150.

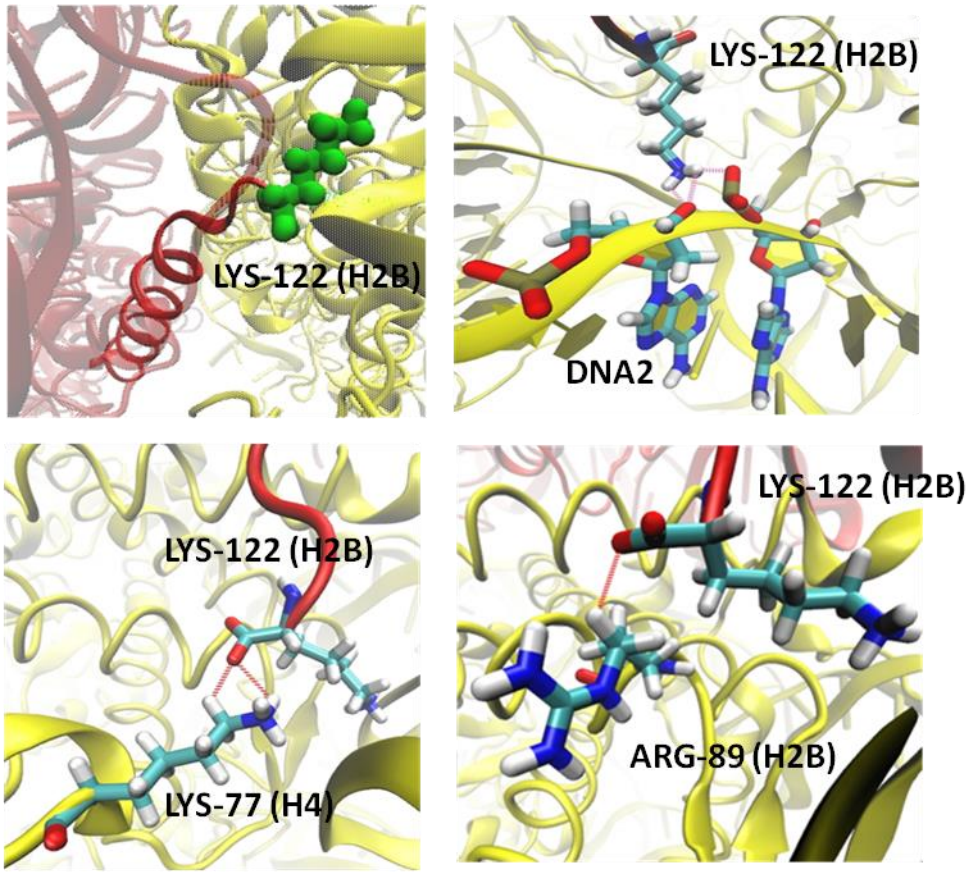


Figure S7: Contacts formed by LYS-122 at the extreme C-terminus of histone H2B of NCP1 with NCP2 (AT-150).

Table S2: Contacts between acidic and basic residues (AT-150) with snapshots.

Name	**HISTONE**	**CORE/ TAIL**	**RESIDUE**	**CONTACT WITH**	**HISTONE**	**CORE/ TAIL**
Saltbridge-1	H4 (NCP1)	TAIL $(H4)_1^1$	**LYS-20**	**ASP-72**	H2A (NCP2)	CORE
Saltbridge-2	H4 (NCP2)	TAIL $(H4)_2^2$	**LYS-8**	**GLU-56**	H2A (NCP1)	CORE
Saltbridge-3	H4 (NCP2)	TAIL $(H4)_2^2$	**LYS-8**	**GLU-110**	H2B (NCP1)	CORE
Saltbridge-4	H4 (NCP2)	TAIL $(H4)_2^2$	**ARG-23**	**GLU-64**	H2A (NCP1)	CORE
Saltbridge-5	H2A (NCP2)	CORE	**ARG-71**	**GLU-73**	H3 (NCP1)	CORE

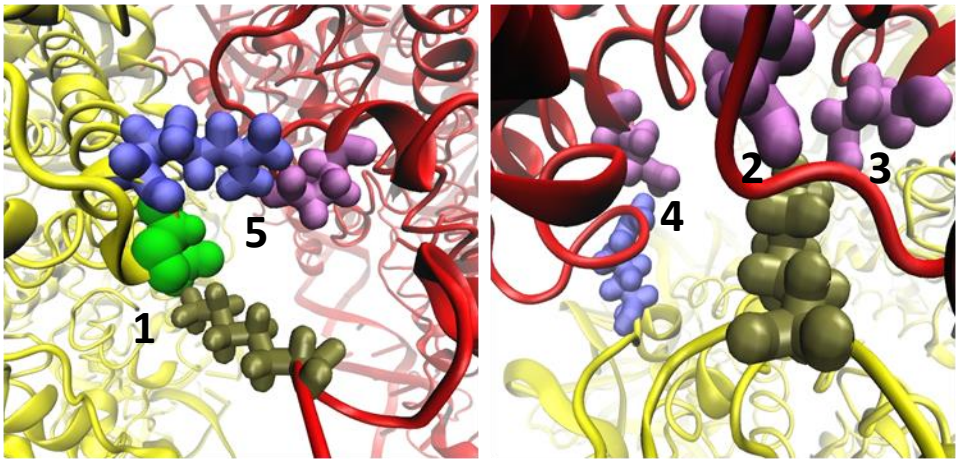
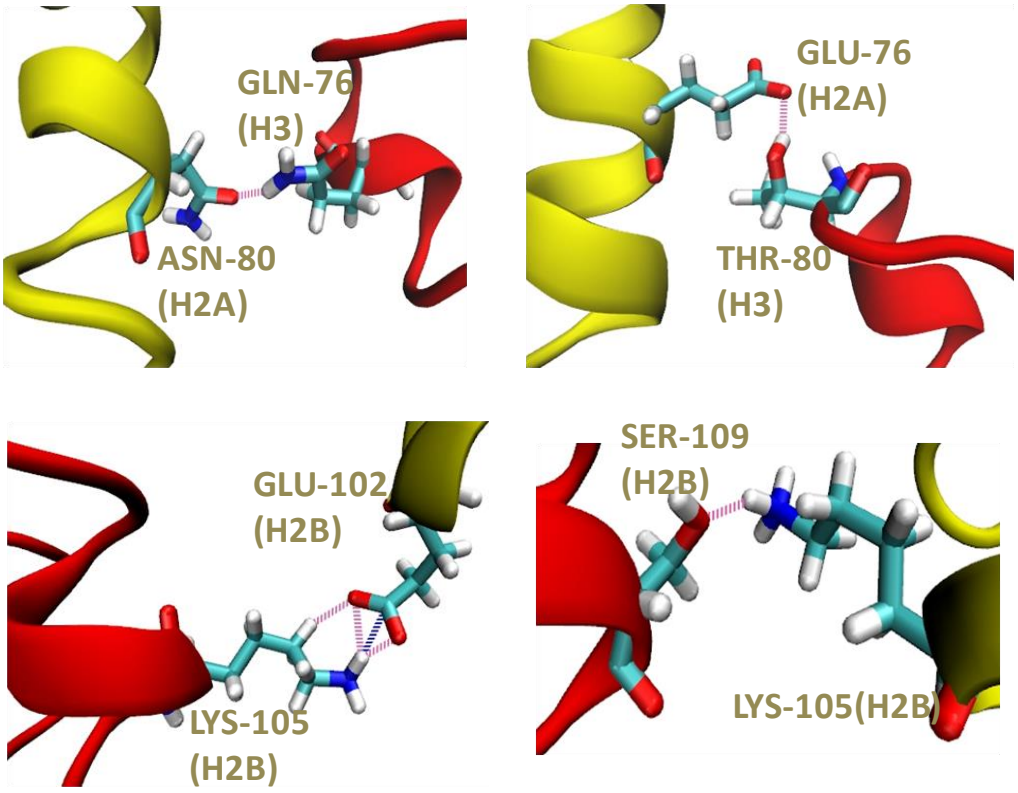


Table S3: Direct hydrogen bonds between NCP1 and NCP2 (AT-150) with snapshots showing some of the H-bond forming residue pairs.

S.no.	HISTONE	CORE/TAIL	RESIDUE	H-BOND WITH	HISTONE	CORE/TAIL
1	H3 (NCP1)	CORE	**GLN-76**	**ASN-80**	H2A (NCP2)	CORE
2	H2A(NCP1)	CORE	**GLU-76**	**THR-80**	H3 (NCP2)	CORE
3	H2B(NCP1)	CORE	**LYS-105**	**GLU-102**	H2B (NCP2)	CORE
4	H4 (NCP2)	TAIL $(H4)_2^2$	**ARG-23**	**GLU-64**	H2A (NCP1)	CORE
5	H2A (NCP1)	TAIL $(H2A)_1^1$	**GLY-22**	**LYS-8**	H4 (NCP2)	TAIL $(H4)_2^2$
6	H2B (NCP1)	CORE	**GLN-44**	**LEU-10**	H4 (NCP2)	TAIL $(H4)_2^2$
7	H2B (NCP1)	CORE	**PRO-47**	**LYS-20**	H4 (NCP2)	TAIL $(H4)_2^2$
8	H2B (NCP1)	CORE	**VAL-45**	**ARG-23**	H4 (NCP2)	TAIL $(H4)_2^2$
9	H2B (NCP1)	CORE	**LYS-122**	**LYS-89**	H2B (NCP2)	CORE
10	H2B (NCP1)	CORE	**LYS-122**	**LYS-77**	H4 (NCP2)	CORE
11	H2B (NCP1)	CORE	**SER-109**	**LYS-105**	H2B (NCP2)	CORE
12	H3 (NCP1)	TAIL $(H4)_1^1$	**SER-1**	**ARG-2**	H3 (NCP2)	TAIL $(H3)_2^1$


GLN-76
(H3)
ASN-80
(H2A)
GLU-76
(H2A)
THR-80
(H3)
GLU-102
(H2B)
LYS-105
(H2B)
SER-109
(H2B)
LYS-105(H2B)

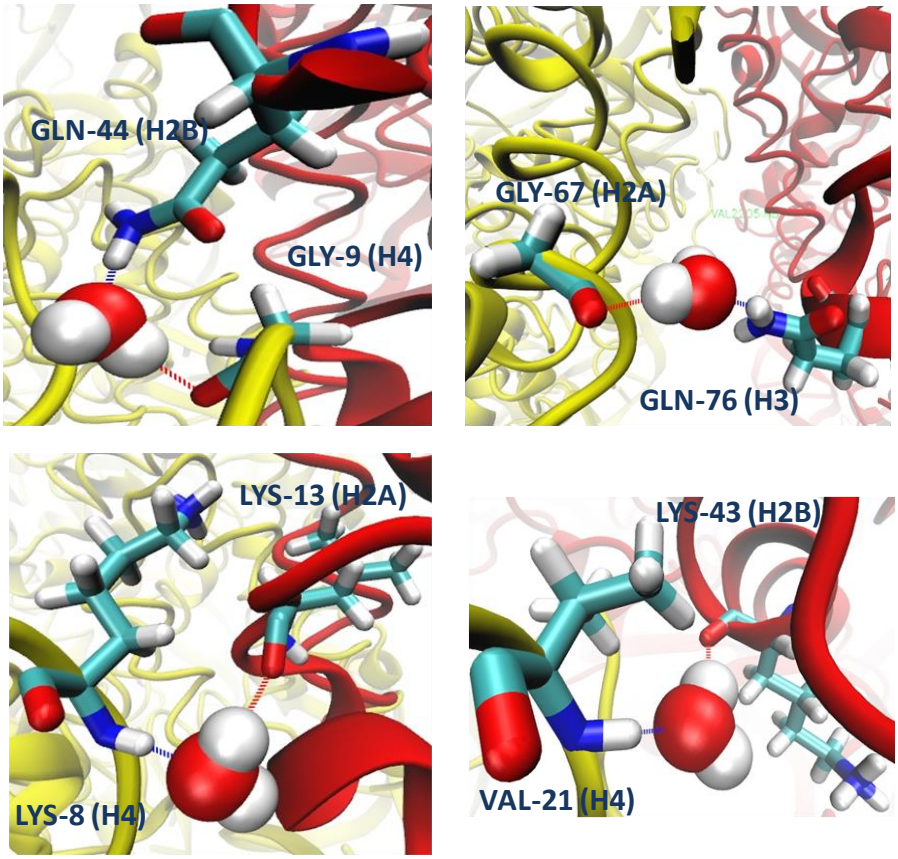


Figure S8: Figure showing some of the water-mediated hydrogen bonds between histone proteins of NCP1 and NCP2 for AT-150.

Table S4: Contribution of various energy terms for NCP-tripeptide complex.

For the calculation of binding energy, NCP1 (except the tripeptide) was removed from the equilibrated 2-NCP system. The resulting system was simulated at 150 mM salt using the protocol described in the text. Snapshots from well-equilibrated regions of this simulation were used as input structures for calculating energy. Various contributions to the total binding energy obtained from an MMPBSA calculation are listed (entropic contribution is not included). A large contribution to the negative binding energy comes from the electrostatic interactions. The DNA minor groove is a region of strong negative potential and hence arginine and lysine residues would bind strongly in these regions. For the MMPBSA calculation the generalized born model corresponding to igb=2 was used and the pbradii for atoms were set to mbondi2 parameter set.

Energy Component	**Mean ± σ (kcal/mol)**
VdW	-22.00 ± 2.95
Electrostatic	-1157.81 ± 42.88
GB Energy	1169.86 ± 42.19
ΔG_{gas}	-1179.81 ± 42.61
$\Delta G_{solvation}$	1167.01 ± 42.21
Surface Energy	-2.85 ± 0.43
Total	**-12.80 ± 4.2**

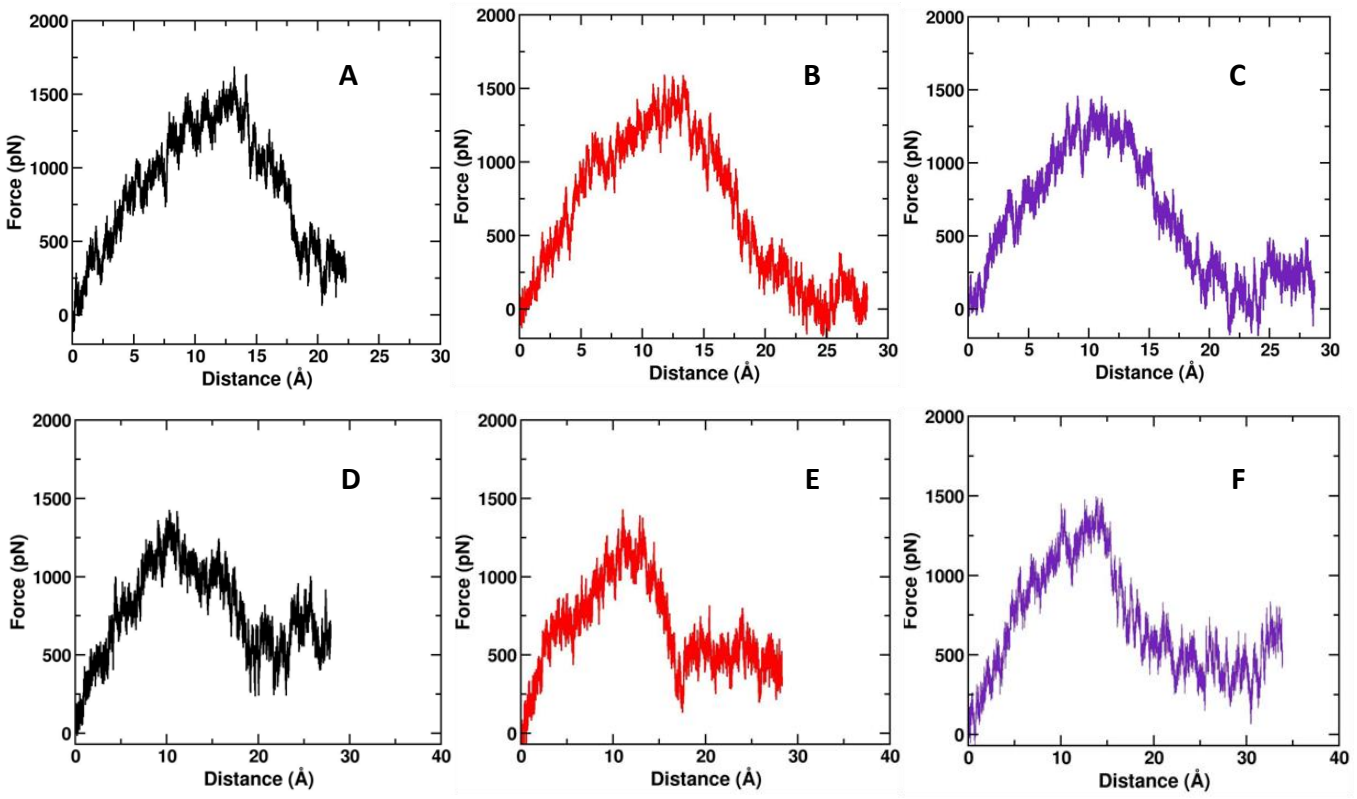


Figure S9: Force-extension plots for pulling two NCPs apart in presence of salt (AT-150) **(A)(B)(C)** and in absence of salt (AT-0)**(D)(E)(F)** at a velocity of 0.008Å/ps.

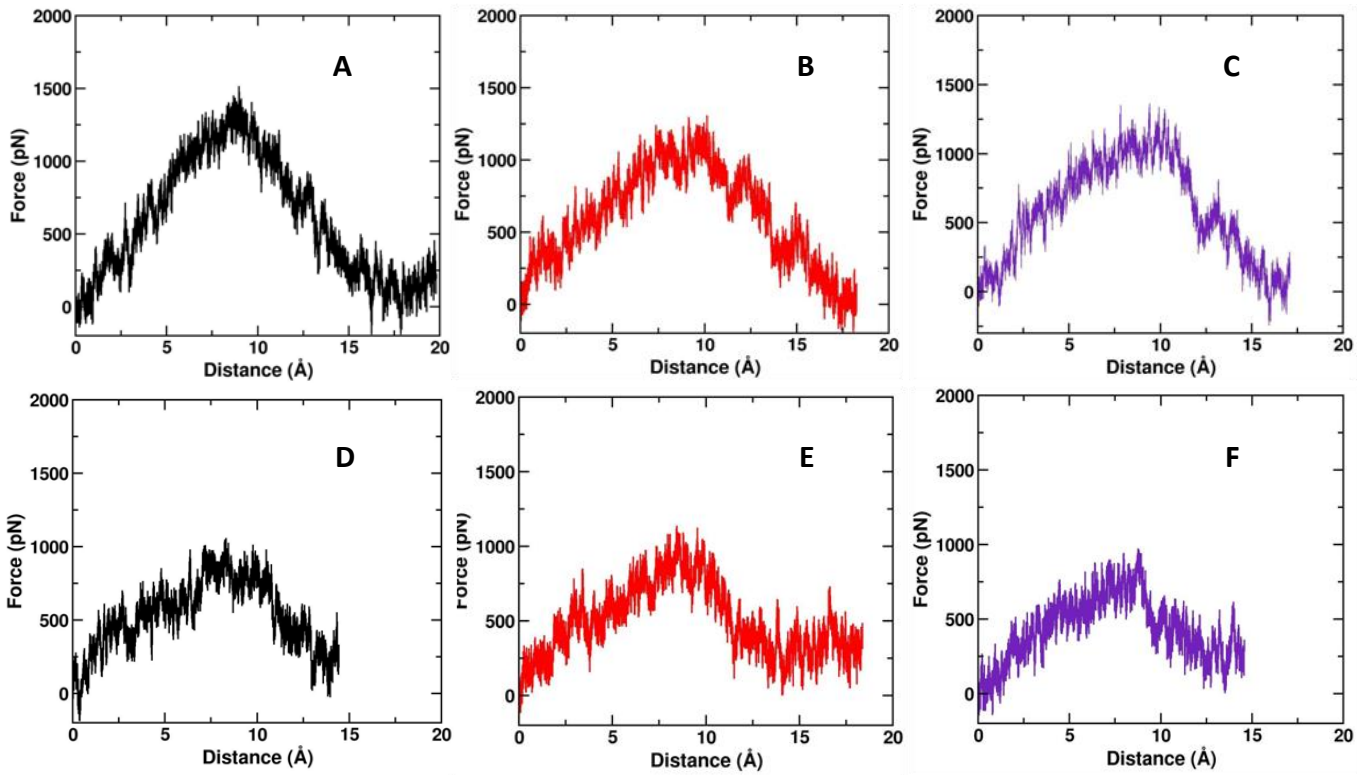


Figure S10: Force-extension plots for pulling two NCPs apart in presence of salt (AT-150) **(A)(B)(C)** and in absence of salt (AT-0)**(D)(E)(F)** at a velocity of 0.003Å/ps.

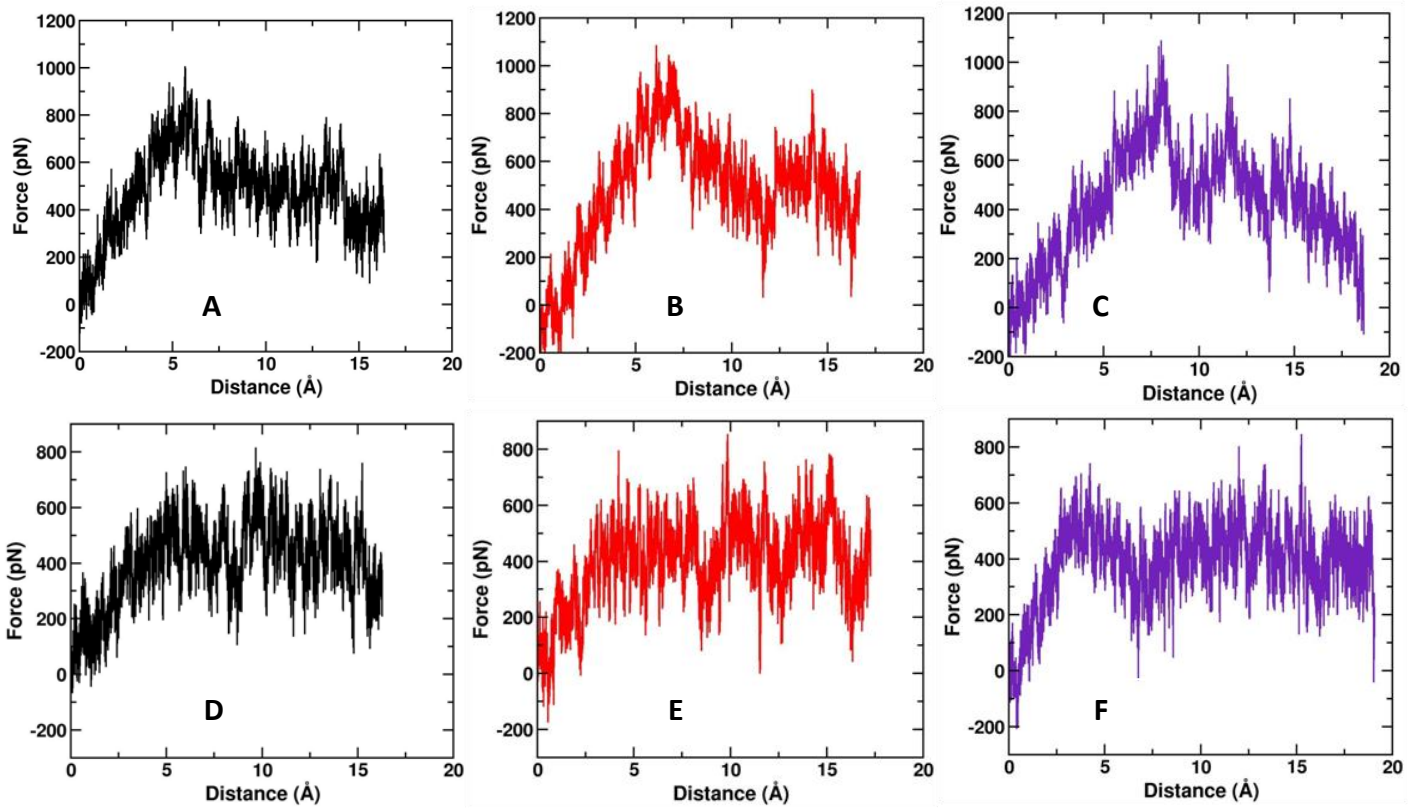


Figure S11: Force-extension plots for pulling two NCPs apart in presence of salt (AT-150) at the H4-binding site **(A)(B)(C)** and at the H2A-binding site **(D)(E)(F)** at a velocity of 0.0084Å/ps.

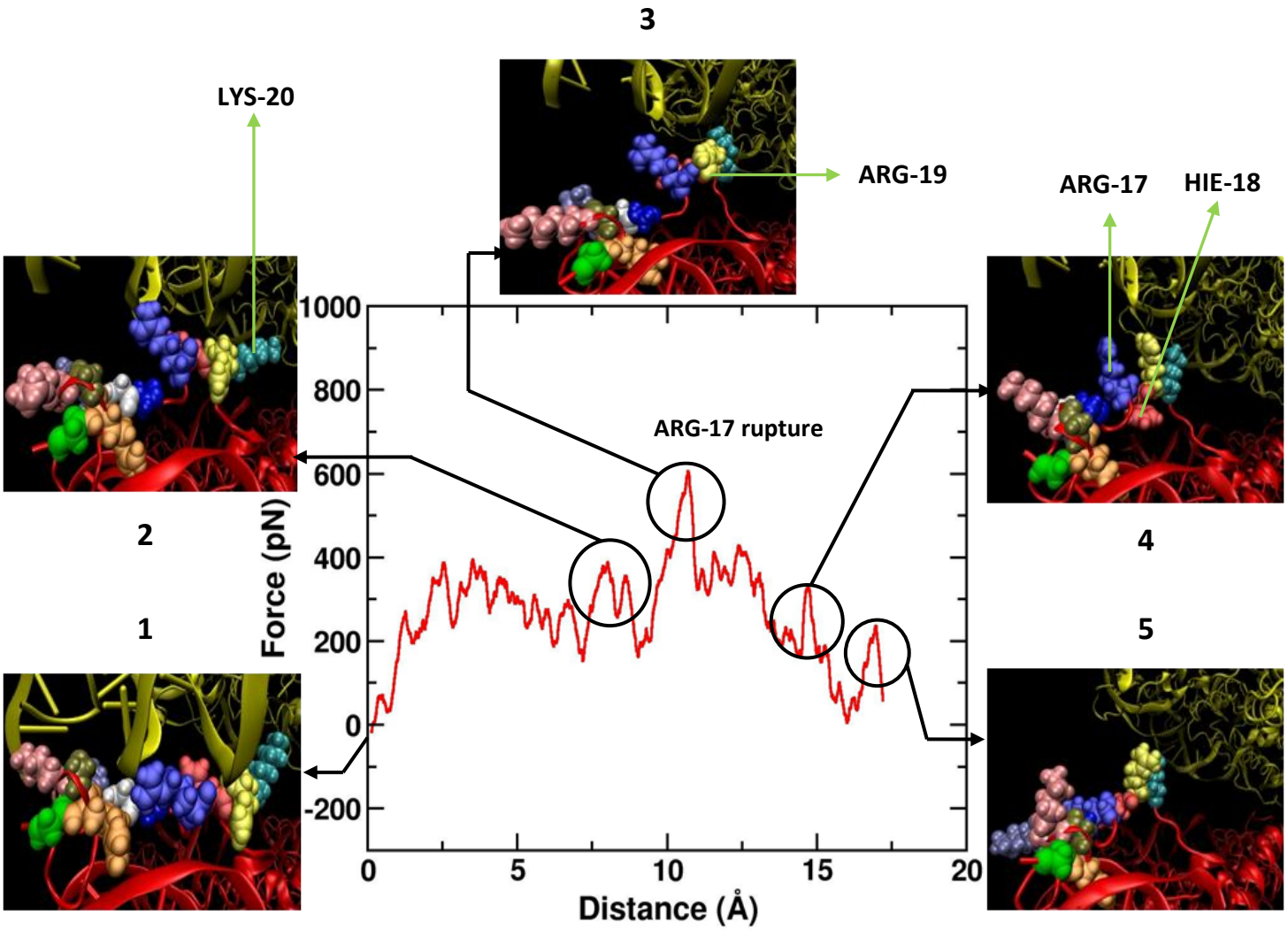


Figure S12: Figure showing the force v/s distance plot for an H4-binding site pulling run at 0.0033Å/ps, along with the snapshots corresponding to various rupture events. In this pulling run we observe the rupture of ARG17 mediated $(H4)_1^1$–DNA2 contacts. In most of the other pulling runs the contact between ARG17 $(H4)_1^1$ of and DNA2 did not break before the very end of the pulling process (See Figure 8). We observe that the largest jump corresponds to the final breaking of this contact. The correspondence between the various force peaks and rupture events is indicated by arrows. Snapshot 1 is the initial frame. Important residues of the H4 tail are labeled. Initially the contacts between the N-terminal residues of the H4 tail and DNA2 break. The presence of consecutively placed positively charged residues bestows residue-level cooperativity to the tail-DNA binding. Snapshots 2 and 3 show that when the ARG17-DNA2

contact is strained, the surrounding residues help to hold it intact. Similar cooperative effects are shown in snapshots 4 and 5.

REFERENCE

1. Arndt, K., Handbook of Proteins: Structure, Function and Methods. Edited by Michael M. Cox and George N. Philips, Jr. *ChemBioChem* **2008,** *9* (12), 2005-2006.
2. Matthews, B. W., Hydrophobic Interactions in Proteins. In *eLS*, John Wiley & Sons, Ltd: 2001.