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Supplemental Information

Mesoscale Modeling of Nucleosome-Binding Antibody PL2-6: Mono- versus Bivalent Chromatin Complexes

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Additional Methods

Model Constituents

Histone tails are modeled at a resolution of 5 amino acids per bead. Similarly, LHs are represented as 6 beads for the globular head (GH) and 22 beads for the flexible C-terminal Domain (CTD) as described in Ref. (1). See Ref. (2) for further model details and validation of equilibrium and dynamic properties.

Initial Starting Configurations

The initial 3D structure for all chromatin fibers are generated as ideal zigzag conformations with the long fiber axis oriented parallel to the z-axis. The z-rise per nucleosome (distance between successive nucleosomes along the long fiber axis) and fiber width (distance between successive nucleosomes when viewed in the plane perpendicular to the fiber axis) are assigned values proportional to the DNA linker length between nucleosomes such that DNA/DNA linker bead distances are less than the DNA bead radius (3 nm). Any overlaps between cores or linker DNA beads are removed. Nucleosomes are initially oriented perpendicular to the central axis, according to the zigzag structure found to be optimal in Ref. (3) (Fig. S1) due to stabilization by the H3 tail interactions with linker DNA.

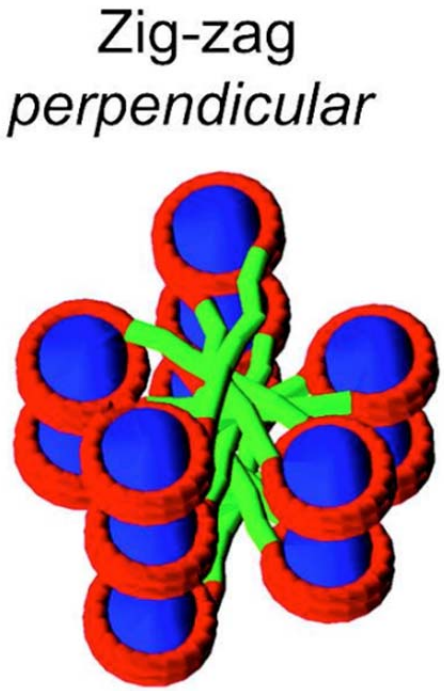

Figure S1. Initial perpendicular zigzag chromatin fiber structure (Ref. 3).

Initial coordinates for all monovalent and bivalent antibodies are placed along an approximate cylinder of 100 nm from each nucleosome, with 3 antibodies (each spaced at an additional 20 nm for the second and third antibodies per nucleosome). The first of each antibody triplet per nucleosome is translated 100 nm from the nucleosome center to the antibody center, along the *line of nodes*—defined as the x'-axis in the rotated reference frame determined by each nucleosome's initial Euler angle coordinate frame. Each monovalent antibody's long 'Fab' axis is oriented *parallel* with the nucleosome's *line of nodes* (Fig. S2) while each bivalent antibody's long 'Fc' axis is oriented *perpendicular* to the nucleosome's *line of nodes* (Fig. S3).

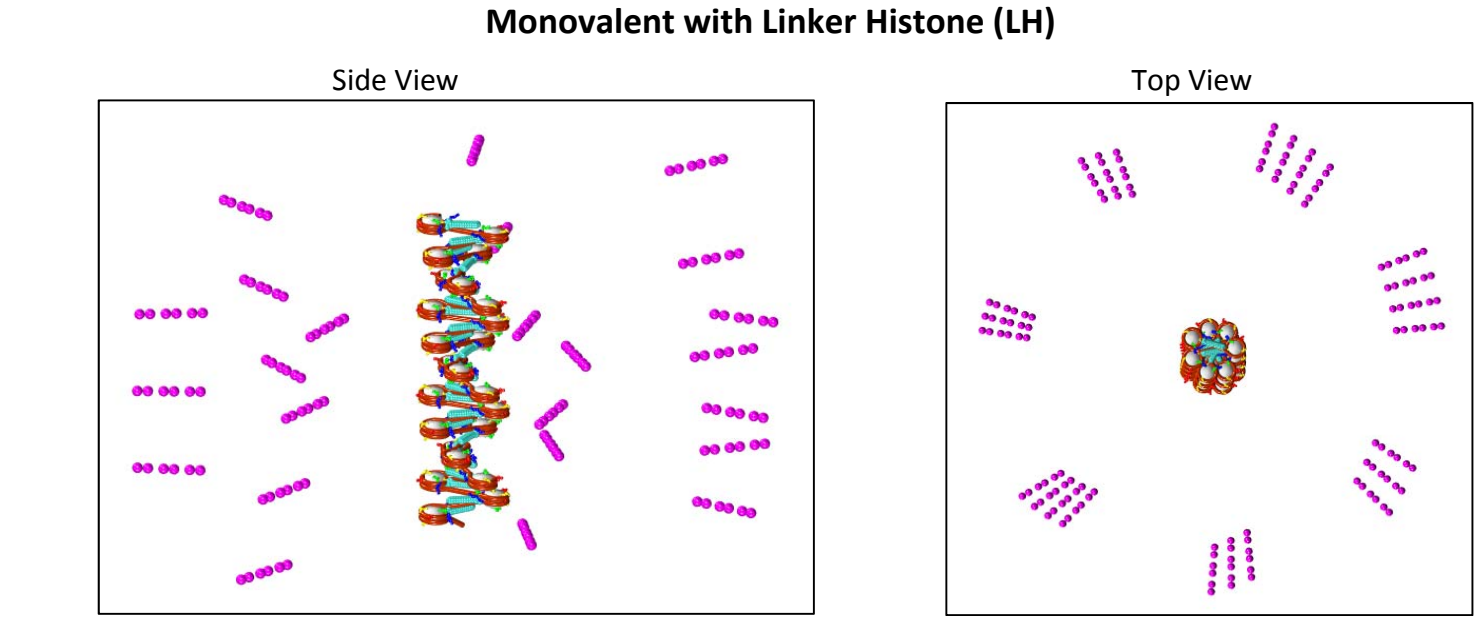

Figure S2. Initial positions for zigzag chromatin fibers with monovalent antibodies used in our MC simulations. Representative example with linker histone.

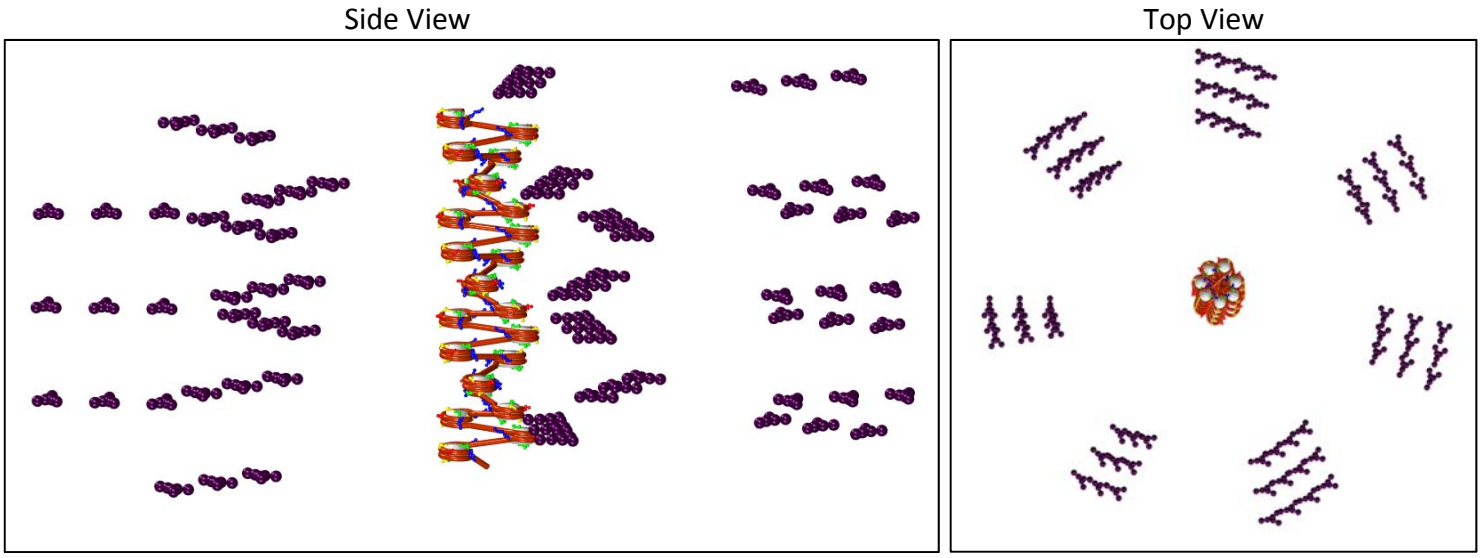

Figure S3. Initial positions for zigzag chromatin fibers with bivalent antibodies used in our MC simulations. Representative example without linker histone.

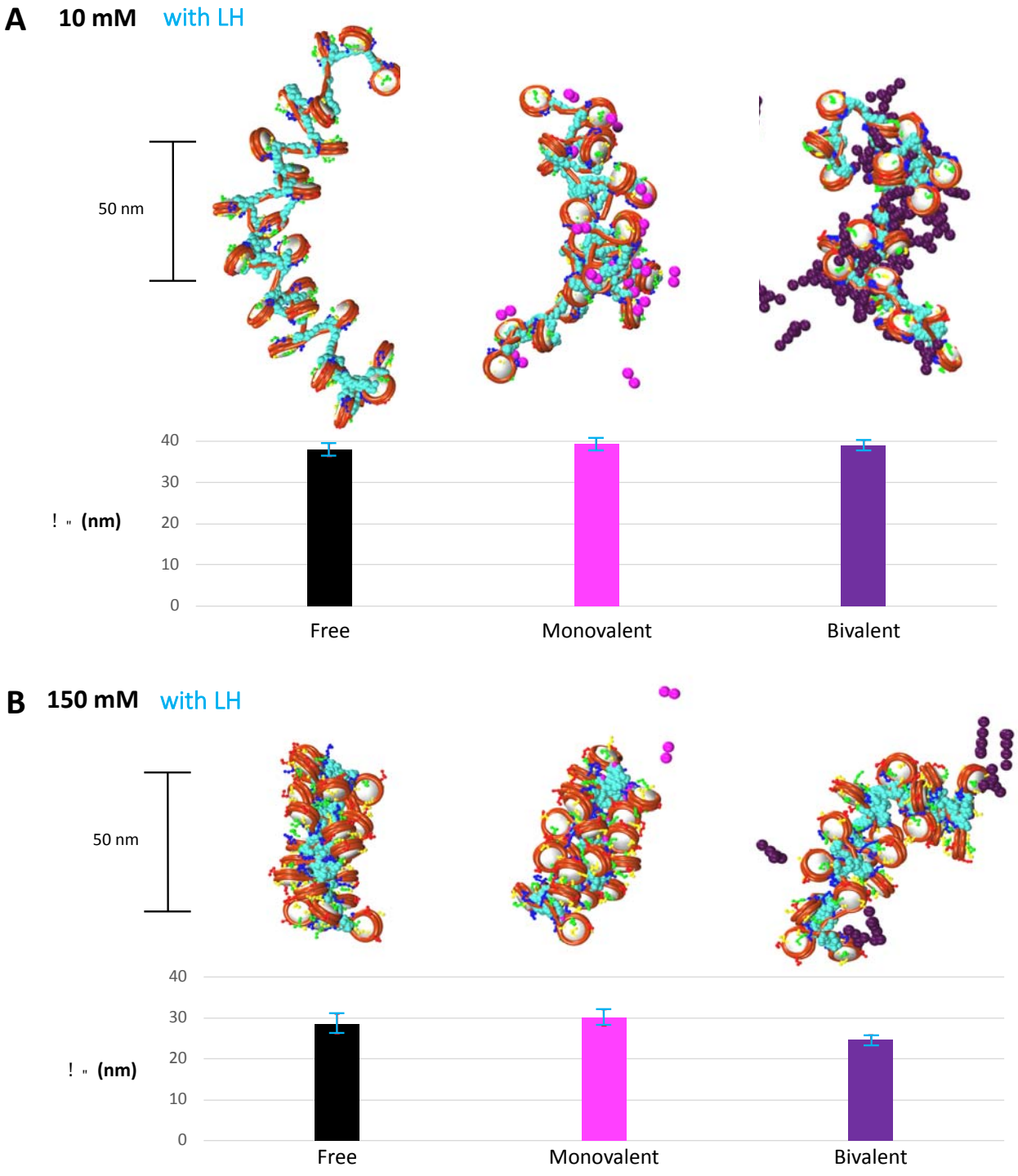

Figure S4. Snapshots of representative fibers from antibody/chromatin systems with linker histone (LH). All fibers consist of 24 nucleosomes and start from idealized zigzag configurations (Figs. S1-S2). For each condition (low salt / physiological salt) we show results for free fiber, monovalent PL2-6 Fab complex, and bivalent PL2-6 complex. Radii of gyration (R_G) of chromatin fibers are shown in nanometers (nm) for free (black), monovalent (magenta), and bivalent (purple) systems, with standard deviations shown as blue error bars. (A) Low salt. (B) Physiological salt. Both with LH.

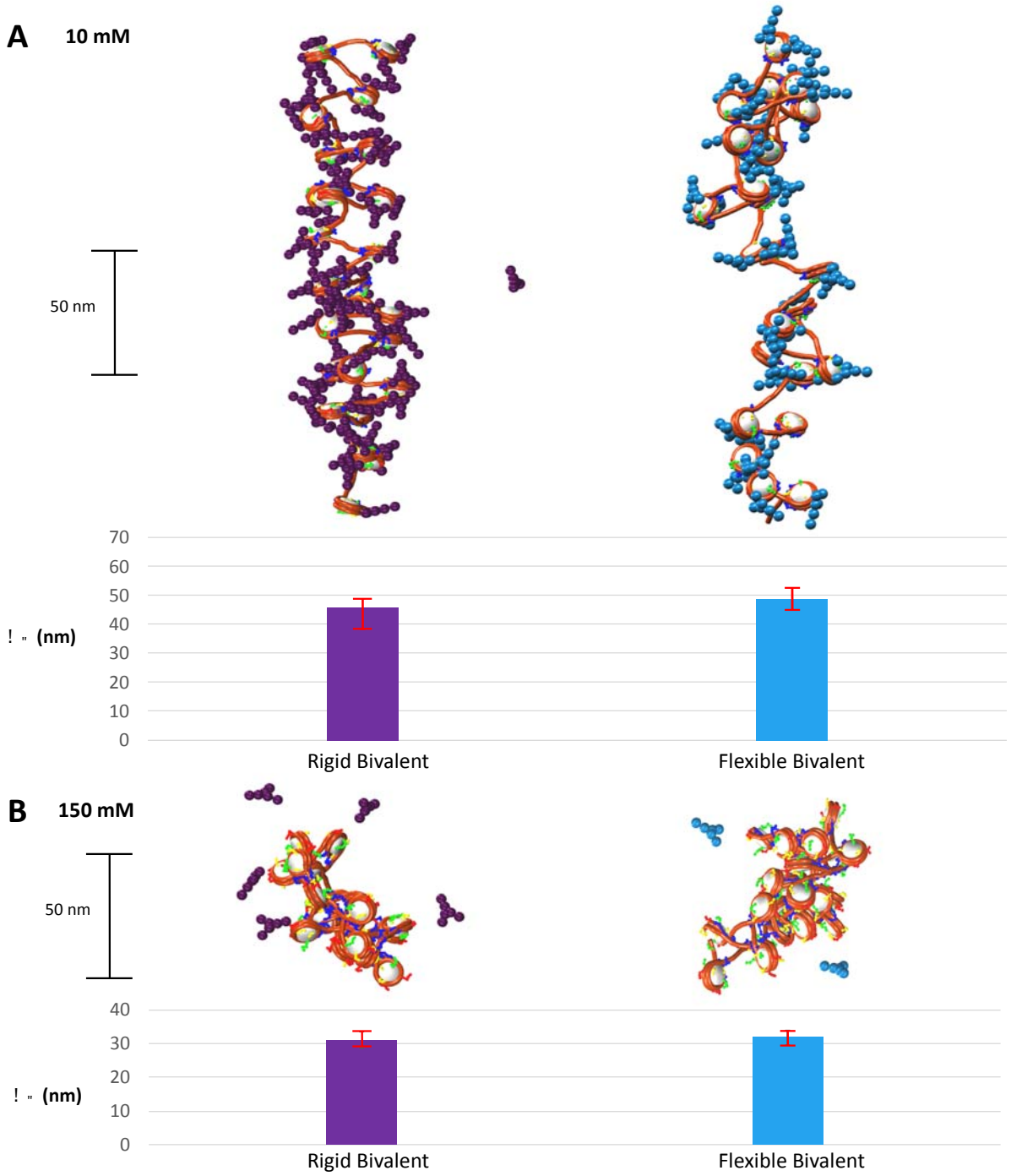

Figure S5. Snapshots of representative fibers of rigid vs flexible bivalent PL2-6/chromatin systems without LH. All fibers consist of 24 nucleosomes and start from idealized zigzag configurations (Figs. S1-S2). For each condition (low salt / physiological salt) we show results for rigid versus bivalent PL2-6 complexes. Radii of gyration (R_G) of chromatin fibers are shown in nanometers (nm) for rigid (purple) bivalent PL2-6 and flexible (blue) bivalent PL2-6 systems, with standard deviations shown as red error bars. (A) Low salt. (B) Physiological salt. Both without LH.

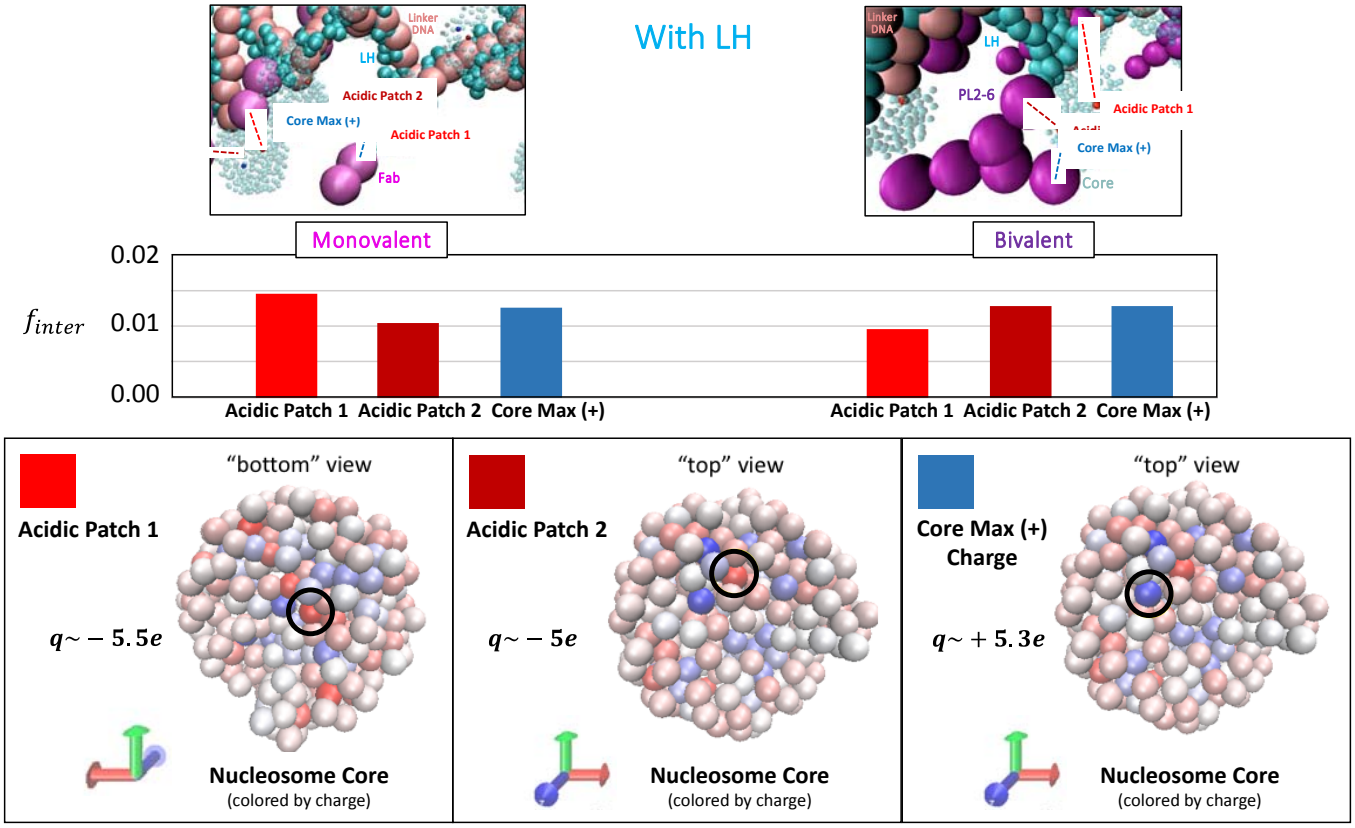

Figure S6. PL2-6 interactions with specific regions of the nucleosome core with LH. The three regions are the two sides of the negatively-charged acidic patch (arbitrarily labeled as Acidic Patch 1 and 2), and the largest positive charge on the nucleosome surface (Core Max (+)). Interaction frequencies (f_{inter}) are evaluated by measuring the number of simulation frames for which pairwise distances between elements are ≤5 nm, sampled over the last 1 million frames of the simulation and normalized across all sampled frames. Pairwise distances are measured from the center of the specified charged bead on the nucleosome core and from the center of the charged beads in both monovalent and bivalent systems. Acidic Patch 1 (red), Acidic Patch 2 (dark red), Core Max (+) Charge (blue).

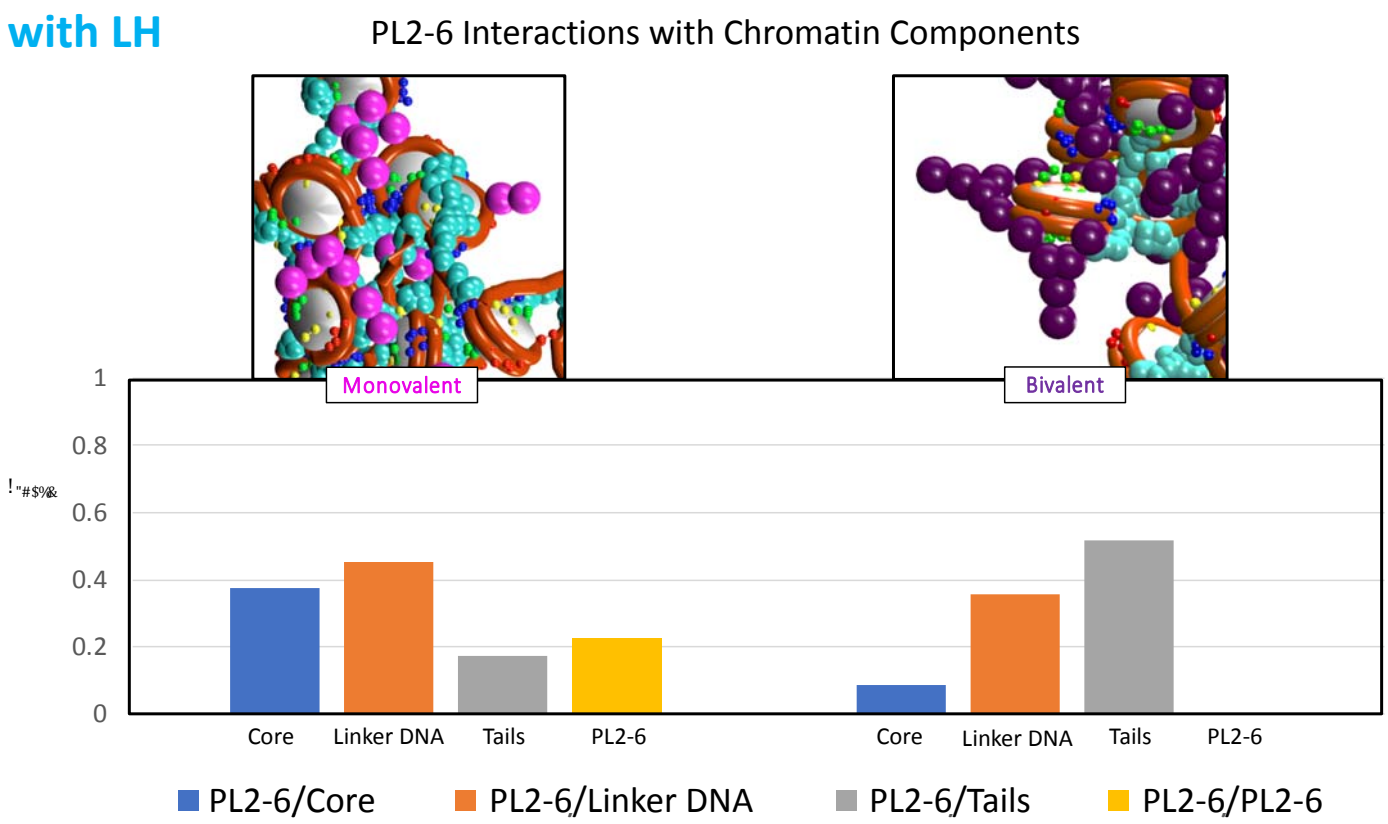

Figure S7. Overall antibody interactions with elements of open chromatin fiber (cores, DNA linkers, tails, and other PL2-6 antibodies) at low salt with LH. Interaction frequencies (f_{inter}) are evaluated by measuring the number of simulation frames for which pairwise distances between elements are ≤5 nm, sampled over the last 1 million frames of the simulation and normalized across all sampled frames. Interactions are averaged over all elements in the fiber for each category (core, linkers, tails, Fabs). Pairwise distances are measured from the center of the end tail bead, from the geometric center of the entire nucleosome core, from the center of each linker bead, and from the center of the charged beads in both monovalent and bivalent systems.

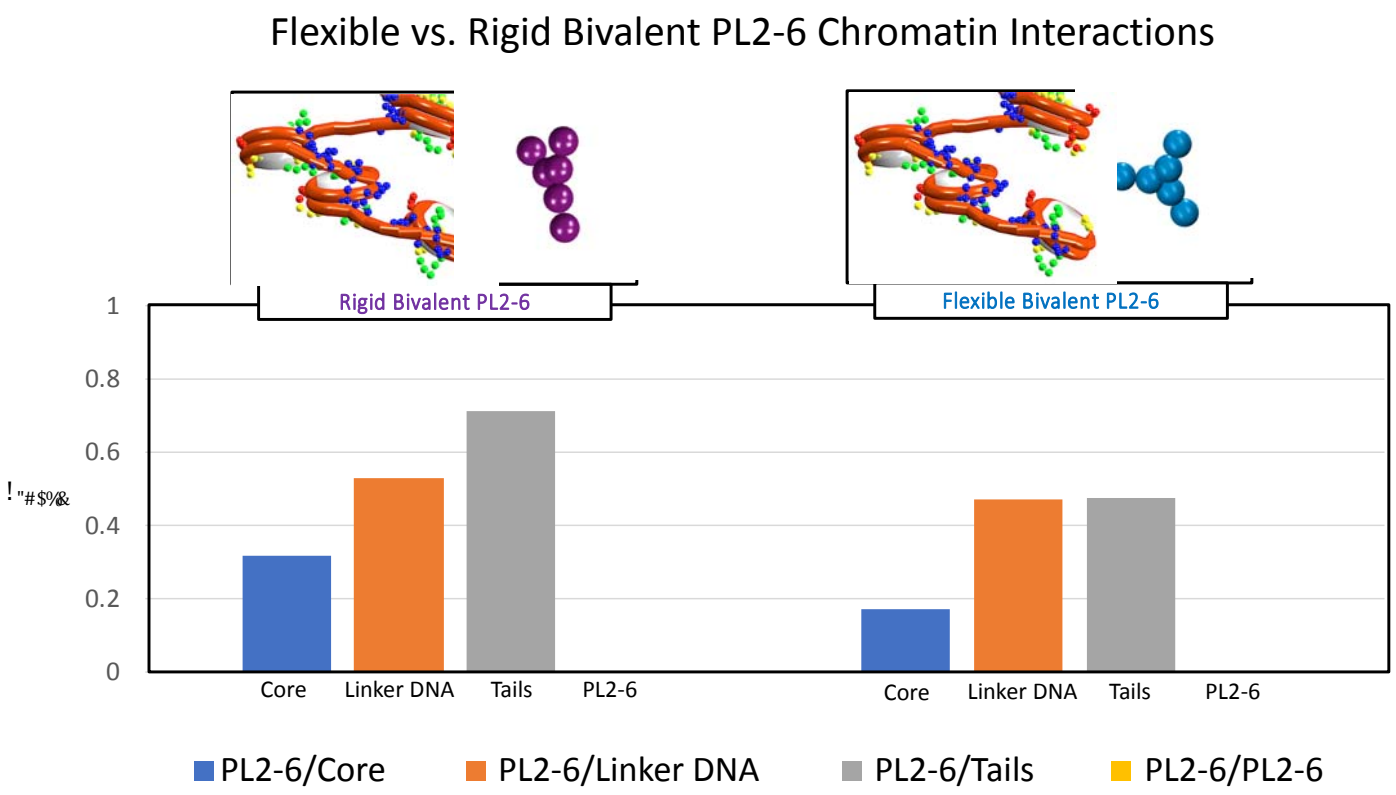

Figure S8. Rigid versus Bivalent PL2-6 Overall Chromatin Interactions. Comparing overall chromatin/antibody interactions between rigid versus flexible bivalent PL2-6 with elements of open chromatin fiber (cores, DNA linkers, tails, and other PL2-6 antibodies) at low salt. Interaction frequencies (f_{inter}) are evaluated by measuring the number of simulation frames for which pairwise distances between elements are ≤5 nm, sampled over the last 1 million frames of the simulation and normalized across all sampled frames. Interactions are averaged over all elements in the fiber for each category (cores, linker DNA, tails, Fabs). Pairwise distances are measured from the center of the end tail bead, from the geometric center of the entire nucleosome core, from the center of each linker bead, and from the center of the charged beads in both monovalent and bivalent systems.

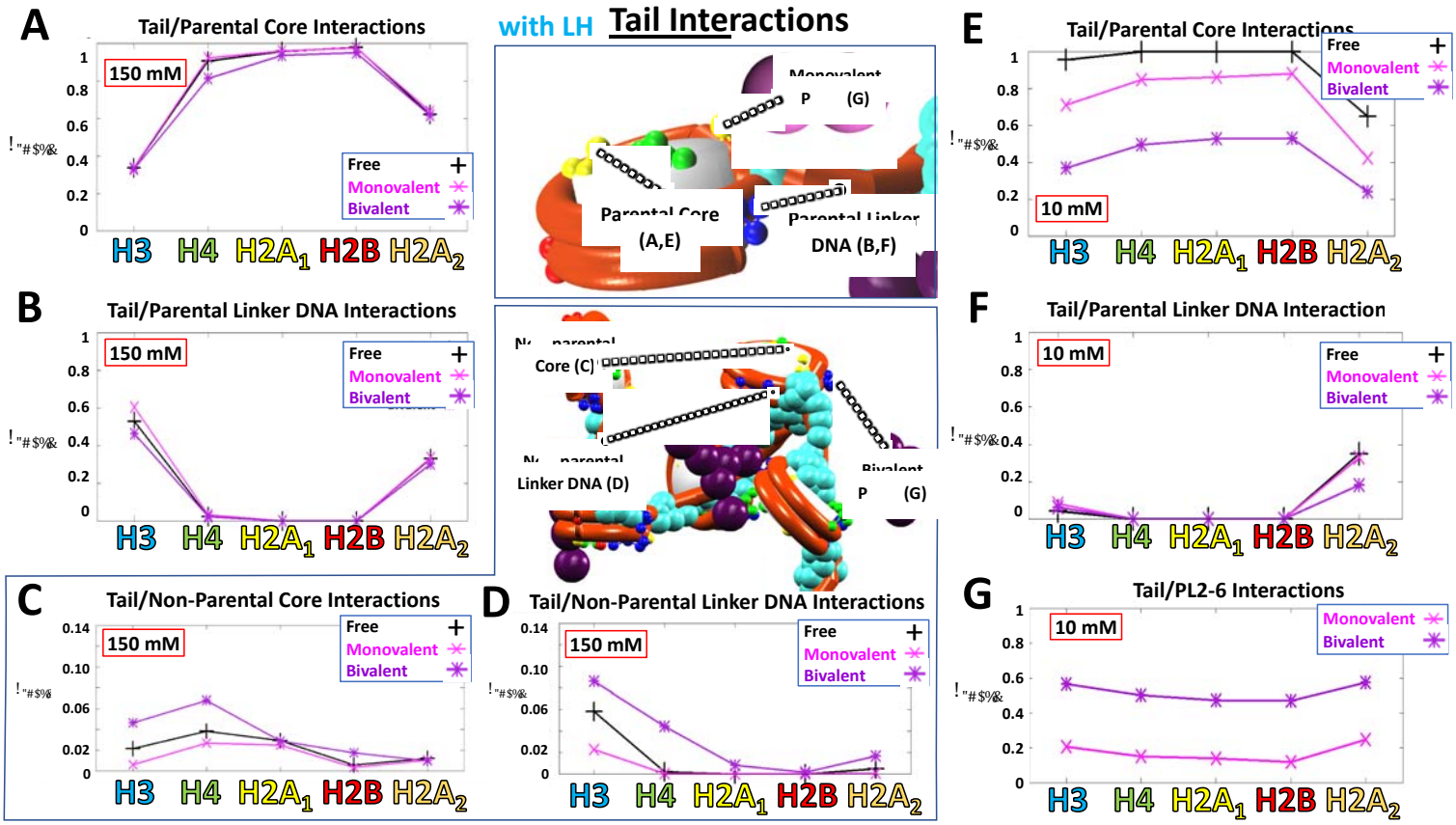

Figure S9. Tail interactions with chromatin and antibodies at physiological and low salt. Interaction frequencies (f_{inter}) are evaluated by measuring the number of simulation frames for which pairwise distances between elements are ≤5 nm, sampled over the last 1 million frames of the simulation and normalized across all sampled frames. Tail interaction frequencies are averaged over both copies of each C-terminal tail for H3, H4, and H2B. H2A1 and H2A2 refer to C-terminal and N-terminal H2A tails, respectively. Distances are measured from the center of the end tail bead, from the geometric center of the entire nucleosome core, from the center of each linker bead, and from the center of the charged beads in both monovalent and bivalent systems. (A) Tail interactions with parental cores at low salt. (B) Tail interactions with parental cores at low salt. (C) Tail interactions with parental linker DNA at physiological salt. (D) Tail interactions with parental linker DNA at low salt. (E) Tail interactions with nonparental cores at physiological salt. (F) Tail interactions with nonparental linker DNA at physiological salt. (G) Tail interactions with antibodies at low salt.

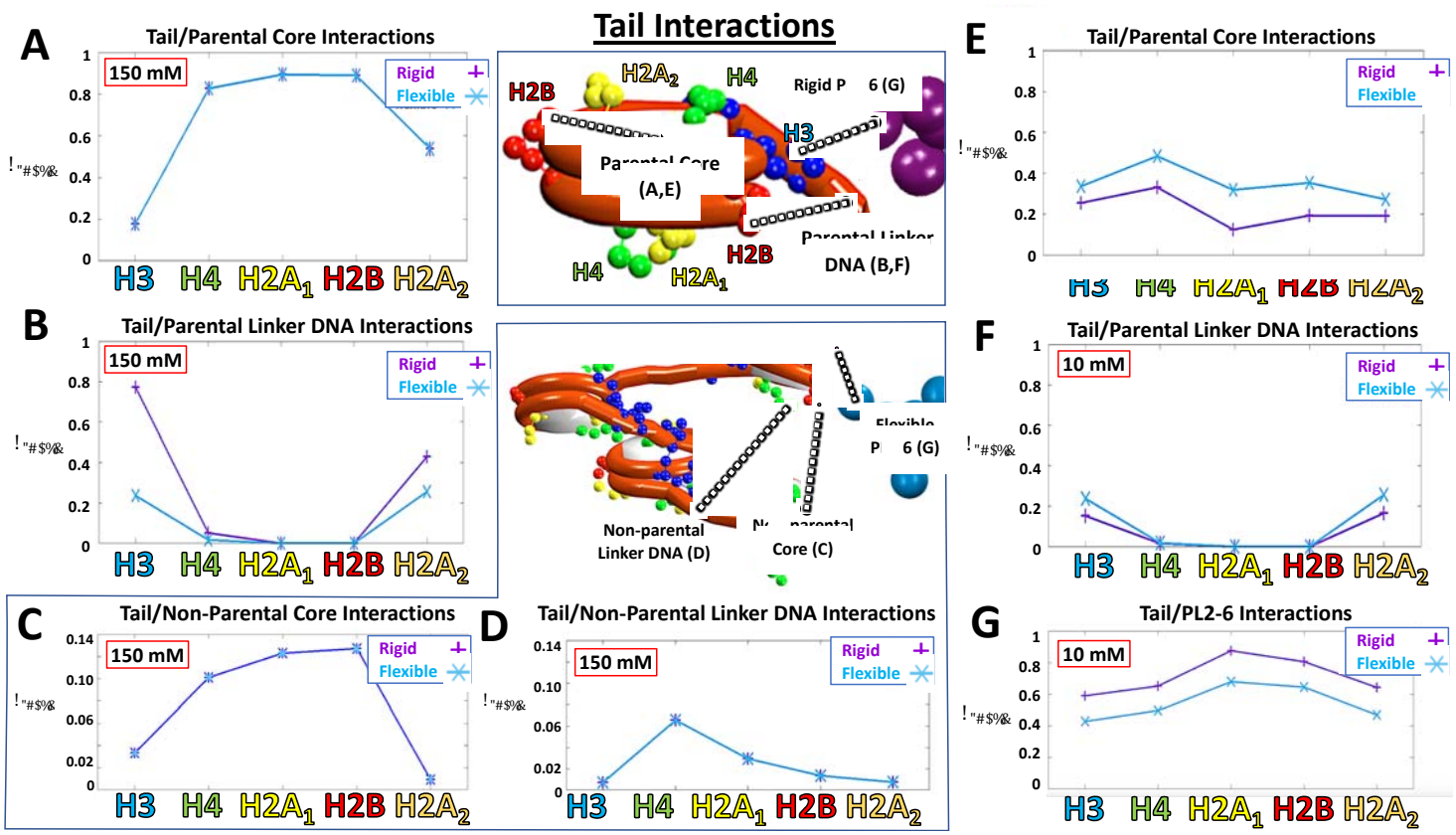

Figure S10. Flexible versus Rigid Bivalent PL2-6 IgG. Interaction frequencies (f_{inter}) are evaluated by measuring the number of simulation frames for which pairwise distances between elements are ≤5 nm, sampled over the last 1 million frames of the simulation and normalized across all sampled frames. Tail interaction frequencies are averaged over both copies of each C-terminal tail for H3, H4, and H2B. H2A1 and H2A2 refer to C-terminal and N-terminal H2A tails, respectively. Distances are measured from the center of the end tail bead, from the geometric center of the entire nucleosome core, from the center of each linker bead, and from the center of the charged beads in both monovalent and bivalent systems. (A) Tail interactions with parental cores at low salt. (B) Tail interactions with parental linker DNA at physiological salt. (C) Tail interactions with nonparental cores at physiological salt. (D) Tail interactions with nonparental linker DNA at physiological salt. (E) Tail interactions with parental cores at low salt. (F) Tail interactions with parental linker DNA at low salt. (G) Tail interactions with antibodies at low salt.

References:

1. Luque A, Collepardo-Guevara R, Grigoryev S, Schlick T (2014) Dynamic condensation of linker histone C-terminal domain regulates chromatin structure. Nucl. Acids Res. 42:7553–7560.
2. Bascom G, Schlick T (2018) Chromatin fiber folding directed by cooperative histone tail acetylation and linker histone binding. Biophys. J. 114(10):2376–2385.
3. Sun J, Zhang Q, Schlick T (2005) Electrostatic mechanism of nucleosomal array folding revealed by computer simulation. Proc. Natl. Acad. Sci. USA 102:8180—8185.