A quantitative model of nucleosome dynamics and applications to hMSH2-hMSH6 nucleosome disassembly

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S1 Supplemental Figures

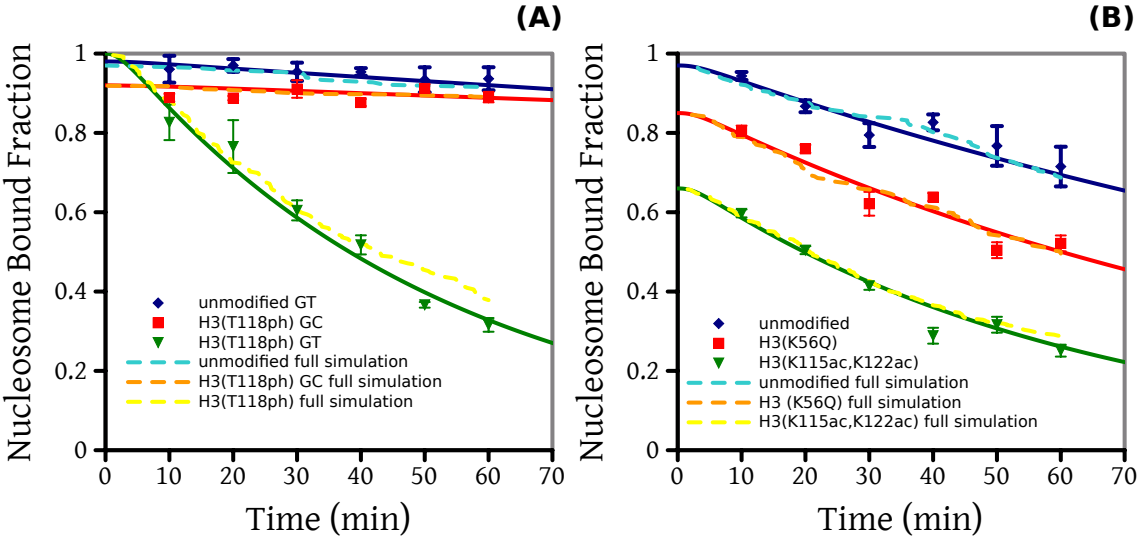

Fig. S1. Full simulations of nucleosome displacement which explicitly include each hMSH2-hMSH6 particle compared to our approximate solution using a one dimensional Tonks gas to represent the hMSH2-hMSH6 particles. The solid lines all show the result of our approximate solution and the symbols show experimental data. These approximate curves and data are identical to those shown in Fig. 2 of the main text. (A) Nucleosomes on the 601 sequence. The dashed light blue, orange and yellow dashed lines show full simulations for unmodified nucleosomes with a G/T mismatch, H3(T118ph) with no mismatch, and H3(T118ph) with a G/T mismatch, repectively. (B) Nucleosomes on the 5S sequence. The dashed light blue, orange and yellow dashed lines show full simulations for unmodified nucleosomes, H3(K56Q) and H3(K115ac,K122ac), respectively, all containing a G/T mismatch. In all cases the full simulations use identical parameters as in the corresponding approximate solution. The agreement is very good, but there is a slight systematic deviation. This is because in the full simulation it is possible for the nucleosome to undergo an unwrapping fluctuation, and then rapidly rewrap before the hMSH2-hMSH6 complexes have reached a new equilibrium, while in our approximation the hMSH2-hMSH6 complexes are assumed to reach equilibrium instantly. This causes our approximation to predict that displacement occurs slightly more rapidly than calculated by the full simulation.

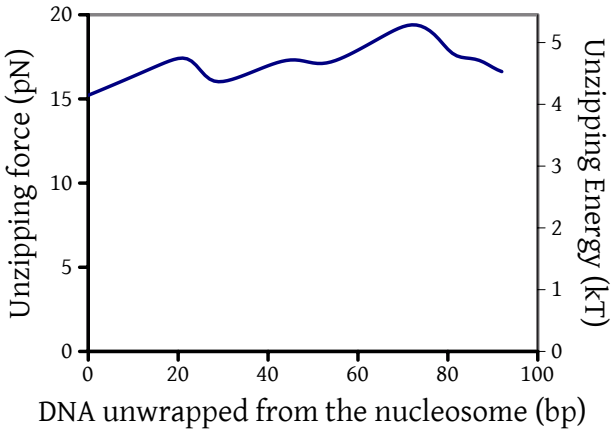

Fig. S2. The force $F_{unzip}(n)$ needed to unzip the base pairing and stretch the DNA is shown as a function of position for the 601 sequence, calculated using [1]. Since the free energy cost to break one base pair is linearly proportional to $F_{unzip}(n)$, we show $F_{unzip}(n)$ in pN on the left hand axis, and the free energy cost of breaking one base pair at this force in k_BT on the right hand axis. This free energy is just the force times the increase in length from breaking one base pair (1.12 nm) and then divided by 4.11 to convert from pN-nm to k_BT.

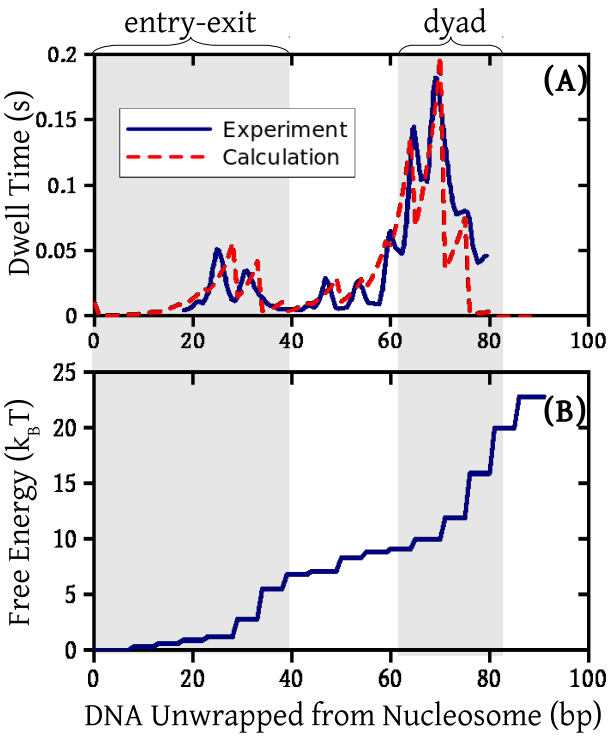

Fig. S3. A free energy landscape constrained to have steps separated by 5.25 bp, or half of one DNA helical repeat. (A) Dwell time as a function of the number of DNA base pairs (bp) unwrapped from the nucleosome. The solid blue line is determined from mechanical unzipping experiments, while the dashed red line is calculated from (B) a free energy landscape with exactly 5.25 bp separation between steps for DNA unwrapping from a nucleosome on the 601 positioning sequence. Because the separation between the peaks in the experimental unzipping data is not uniform, we are not able to accurately reproduce them with this landscape.

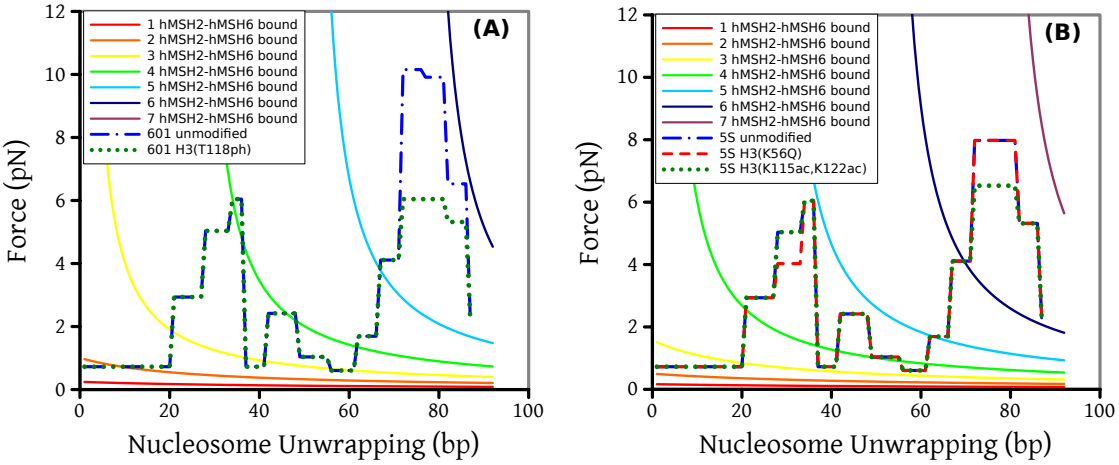

Fig. S4. Force exerted on the nucleosome as a function of the number of hMSH2-hMSH6 complexes bound and the number of DNA base pairs unwrapped from the nucleosome. This force is calculated using our one dimensional Tonks gas approximation and shown by solid colored lines for between one and seven hMSH2-hMSH6 complexes bound to the DNA. For comparison, we also show the force required to unwrap unmodified and modified nucleosomes for (A) the 601 construct, which has 75 base pairs of free DNA outside the nucleosome, and (B) the 5S construct, with 99 base pairs of free DNA. Note that the difference in the forces exerted by hMSH2-hMSH6 on 601 and 5S is due to the different lengths of free DNA. The force required to unwrap the nucleosome is calculated from the derivative of our free energy landscape averaged over the distance between steps in the landscape (5 base pairs). The system can be at equilibrium at any position where the force exerted by the hMSH2-hMSH6 complexes intersects the force needed to unwrap the nucleosome. Therefore, with 3 or 4 hMSH2-hMSH6 complexes bound, it is possible for the system to reach an equilibrium with about 40 or 60 base pairs of DNA unwrapped from the nucleosome. From these states, it is then reasonably probable for a fluctuation to the completely unwrapped state to occur.

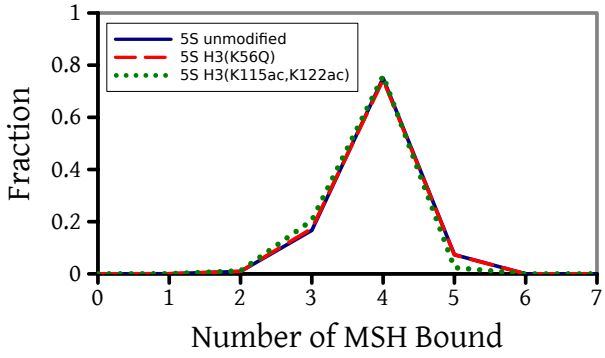

Fig. S5. Distribution of the number of bound hMSH2-hMSH6 complexes needed to displace nucleosomes from the 5S positioning sequence. The solid blue line shows the result for unmodified nucleosomes, the dashed red line for the modification H3(K56Q), and the dotted green line for the modifications H3(K115ac,K122ac). Note that more hMSH2-hMSH6 complexes (cf. Fig. 3 in the main text) are required to displace unmodified nucleosomes from the 5S DNA construct as compared to the 601 DNA construct because there is more free DNA outside the nucleosome (99 base pairs compared with 75 base pairs for the 601 construct). This allows up to three hMSH2-hMSH6 complexes to bind without unwrapping the nucleosome, and examination of Fig. S4 shows that four hMSH2-hMSH6 complexes are required to allow a partially unwrapped equilibrium with 40 or 60 base pairs of DNA unwrapped from the nucleosome. This is consistent with an average of four bound hMSH2-hMSH6 complexes required to displace nucleosomes from the 5S DNA construct.

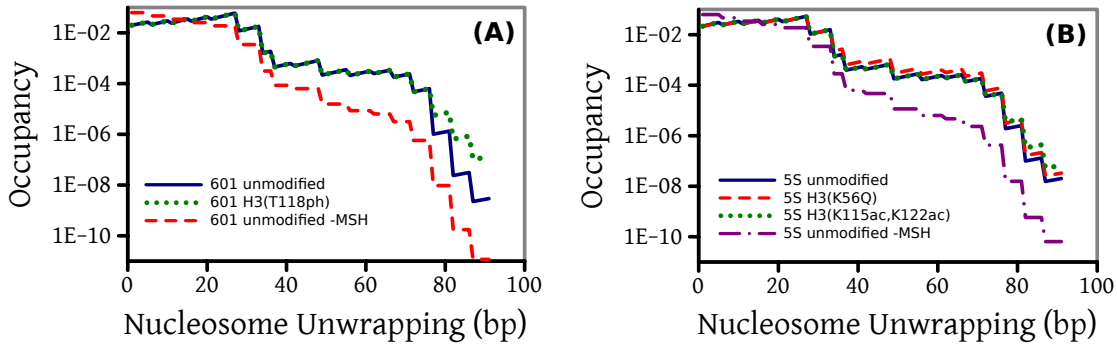

Fig. S6. Distribution of the number of DNA base pairs unwrapped from the nucleosome in the presence of hMSH2-hMSH6 on (A) the 601 DNA construct and (B) the 5S DNA construct. We show all modified nucleosomes considered in this work with a single G/T mismatch in the DNA construct at which hMSH2-hMSH6 can bind. We also show the occupancy with no hMSH2-hMSH6 binding allowed for unmodified nucleosomes on each construct (unmodified -MSH). While it is always most probable for the nucleosome to have less than 30 base pairs of DNA unwrapped, in the presence hMSH2-hMSH6 there is also a significant probability that between 30 and 70 base pairs of DNA are unwrapped from the nucleosome. The modification H3(K56Q) further increases the probability of such unwrapping by lowering the energy barrier to unwrap past 30 base pairs. In contrast, the dyad modifications H3(T118ph) and H3(K115ac,K122ac) do not change the probability of such modest unwrapping, but rather increase the chance of a large fluctuation which totally unwraps the nucleosome.

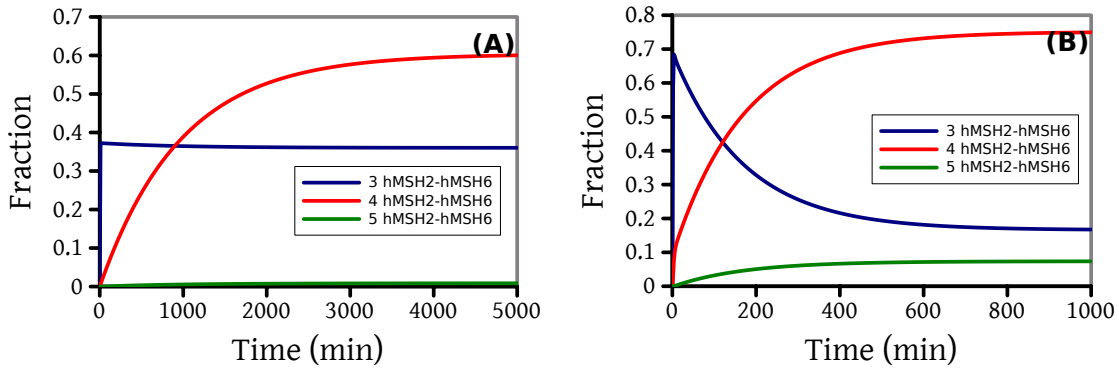

Fig. S7. Rate of binding three, four or five hMSH2-hMSH6 complexes to (A) the 601 DNA construct or (B) the 5S DNA construct containing an unmodified nucleosome. The distribution of hMSH2-hMSH6 complexes which can bind without displacing the nucleosome reaches equilibrium very rapidly, in about 1 minute. For both complexes three hMSH2-hMSH6 complexes can sometimes bind at equilibrium, with a larger probability for 5S because this construct contains more free DNA outside the nucleosome (99 base pairs compared to 75 base pairs for 601). For the 601 construct shown in (A), the probability of five hMSH2-hMSH6 complexes binding is insignificant, but the fraction of four hMSH2-hMSH6 bound increases very slowly with a characteristic time of 960 minutes. This is nearly equal to the characteristic time for displacement of the nucleosome from this complex. For the 5S construct shown in (B), the fractions of both four and five hMSH2-hMSH6 bound increase with a characteristic time of 170 minutes, which is again equal to the characteristic time for nucleosome displacement.

References

[1] Habib, F. and Bundschuh, R. (2005) Modeling DNA unzipping in the presence of bound proteins. *Phys. Rev. E,* **72**, 031906.