# Supplementary Information for

## Physical Modeling of the Heritability and Maintenance of Epigenetic Modifications

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Figs. S1 to S8



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## 1. Supplemental figures for methylation over generations

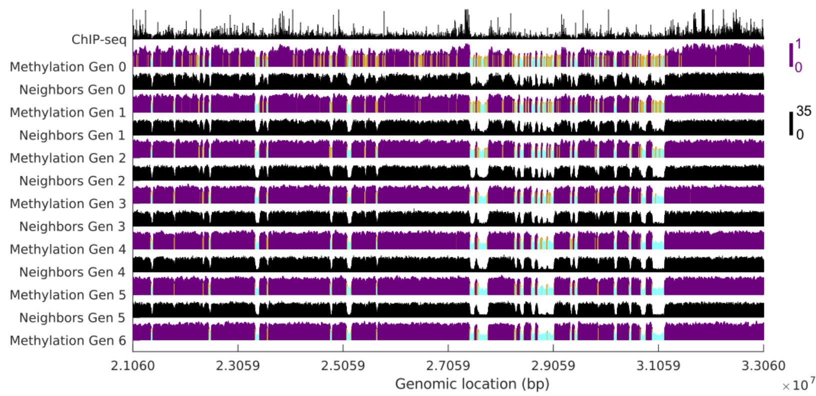


**Fig. S1.** The evolution of the methylation profile and number of neighbors at the optimal concentration of HP1 for a section of the chromosome that is approximately ten times longer than that shown in Fig. 3. As before, the height of the methylation profile corresponds to the fraction of methylated nucleosomes in the surrounding window of 101 nucleosomes. The color represents the condensation state of the nucleosome as predicted by the window fraction methylated and cutoffs established from Fig. 5. Cyan, gold, and purple colors designate nucleosomes that are in euchromatin, boundary between euchromatin/heterochromatin, and heterochromatin, respectively.

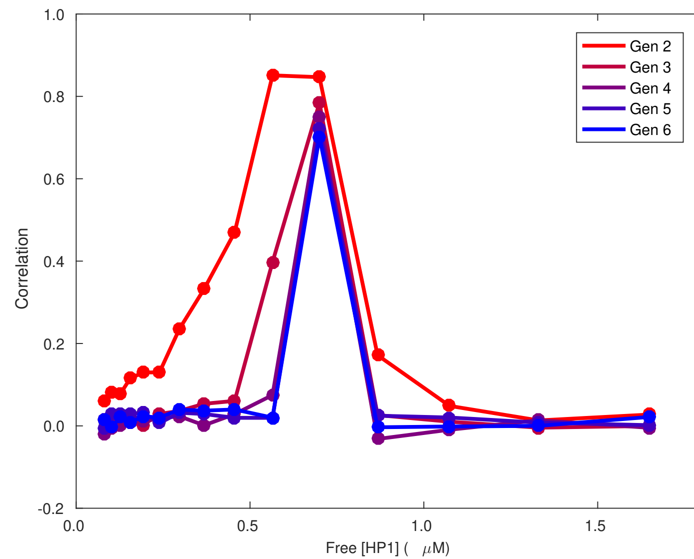


**Fig. S2.** Plot of the correlation coefficient $\chi$ versus free HP1 concentration for 5 generations of reestablishment of the methylation sequence using generation 1 as the reference generation, rather than generation 0 as shown in Fig. 4.

## 2. Modified methylation procedures for simultaneous methylation and reorganization

We have developed a modified procedure to more closely integrate chromatin organization and methyl spreading. While it is not currently possible to fully capture the dynamics of both processes simultaneously, our modified scheme presents a reasonable approximation. These procedures aim to describe the methylation process by capturing the chromosomal organization based on the instantaneous methylation throughout the methylation process. These additional analyses demonstrate the robustness of the methylation process as reproducing the original methylation sequence.
In Procedure S1, we take the following steps:

1. Begin with the same initial methylation sequence as before, derived from ChIP-seq data [39].
2. To mimic replication, randomly demethylate 50% of nucleosomes.
3. Using the diluted methylation sequence, run a Monte-Carlo simulation at several concentrations of HP1 to obtain equilibrium nucleosome positions and HP1 binding.
4. Using the configuration data from Step 3, solve the master equation for the steady-state methylation probabilities at each concentration of HP1.
5. Randomly determine the methylation sequences based on the methylation probabilities.
6. Identify a new optimal concentration of HP1 (call it $\mathrm{C}_{S1}^{opt}$) that maximizes the correlation between the original and final methylation sequences.

In Procedure S2A, we take the following steps:

1. Begin with the same initial methylation sequence as before, derived from ChIP-seq data [39].
2. To mimic replication, randomly demethylate 50% of nucleosomes.
3. Using the diluted methylation sequence, run a Monte-Carlo simulation at $\mathrm{C}_{S1}^{opt}$ to obtain equilibrium nucleosome positions and HP1 binding.
4. Using the configuration data for $\mathrm{C}_{S1}^{opt}$ from Step 3 and starting from the diluted methylation sequence, integrate the master equation until the methylation level is 25% closer to the steady-state methylation level identified in Procedure S1.
5. Randomly determine the methylation sequence based on the methylation probabilities.
6. Using the partially reestablished methylation sequence, run a Monte-Carlo simulation at a concentration of HP1 that is reduced from $\mathrm{C}_{S1}^{opt}$ to be 25% closer to $\mathrm{C}_{0}^{opt}$ (the optimal concentration of HP1 identified in the paper).
7. Using the configuration data from Step 6 and starting from the partially reestablished methylation sequence, integrate the master equation until the methylation level is another 25% closer to the steady-state methylation level identified in Procedure S1.
8. Randomly determine the methylation sequence based on the methylation probabilities.
9. Repeat Steps 6 and 7 two more times until the methylation level reaches the steady-state level from Procedure S1. With each subsequent MC simulation, decrease the concentration of HP1 to be 25% closer to $\mathrm{C}_{0}^{opt}$. With each subsequent master equation solution, increase the methylation level to be 25% closer to the steady-state level from Procedure S1.

In Procedure S2B, we take the following steps:

1. Begin with the same initial methylation sequence as before, derived from ChIP-seq data [39].
2. To mimic replication, randomly demethylate 50% of nucleosomes.
3. Using the diluted methylation sequence, run a Monte-Carlo simulation at $\mathrm{C}_{0}^{opt}$ to obtain equilibrium nucleosome positions and HP1 binding.
4. Using the configuration data for $\mathrm{C}_{0}^{opt}$ from Step 3 and starting from the diluted methylation sequence, integrate the master equation until the methylation level is 25% closer to the steady-state methylation level identified in Procedure S1.
5. Randomly determine the methylation sequence based on the methylation probabilities.
6. Using the partially reestablished methylation sequence, run a Monte-Carlo simulation at $\mathrm{C}_{0}^{opt}$.
7. Using the configuration data from Step 6 and starting from the partially reestablished methylation sequence, integrate the master equation until the methylation level is another 25% closer to the steady-state methylation level identified in Procedure S1.
8. Randomly determine the methylation sequence based on the methylation probabilities.
9. Repeat Steps 6 and 7 two more times until the methylation level reaches the steady-state level from Procedure S1. Use $\mathrm{C}_{0}^{opt}$ for each MC simulation. With each subsequent master equation solution, increase the methylation level to be 25% closer to the steady-state level from Procedure S1.

We define the modified correlation coefficient $\chi_m$ (*i.e.* the Pearson correlation coefficient) for the current methylation state to the generation-0 methylation state

$$\chi_m = \frac{\langle m_i^{(j)} m_i^{(0)} \rangle - \langle m_i^{(j)} \rangle \langle m_i^{(0)} \rangle}{(\sigma_m^{(0)})^2}. \quad [1]$$

We note that this is slightly modified from the definition in the text as having only the variance for generation 0 in the denominator. This modification is made for showing the progression in the correlation throughout the methylation process (*i.e.* procedures S2A and S2B). Significant reduction in the methylation at the start of these procedures leads to low values of variance in the comparison and an artificially large correlation coefficient.

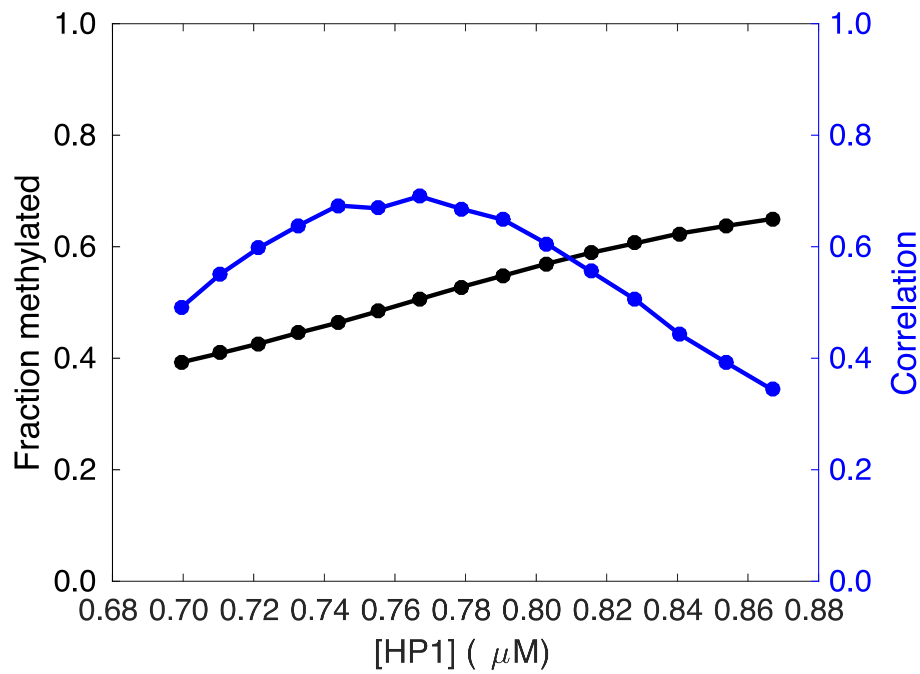


**Fig. S3.** Plot of the fraction of methylated nucleosomes and correlation coefficient $\chi_m$ versus free HP1 concentration for 1 generation of reestablishment of the methylation sequence, following Procedure S1.

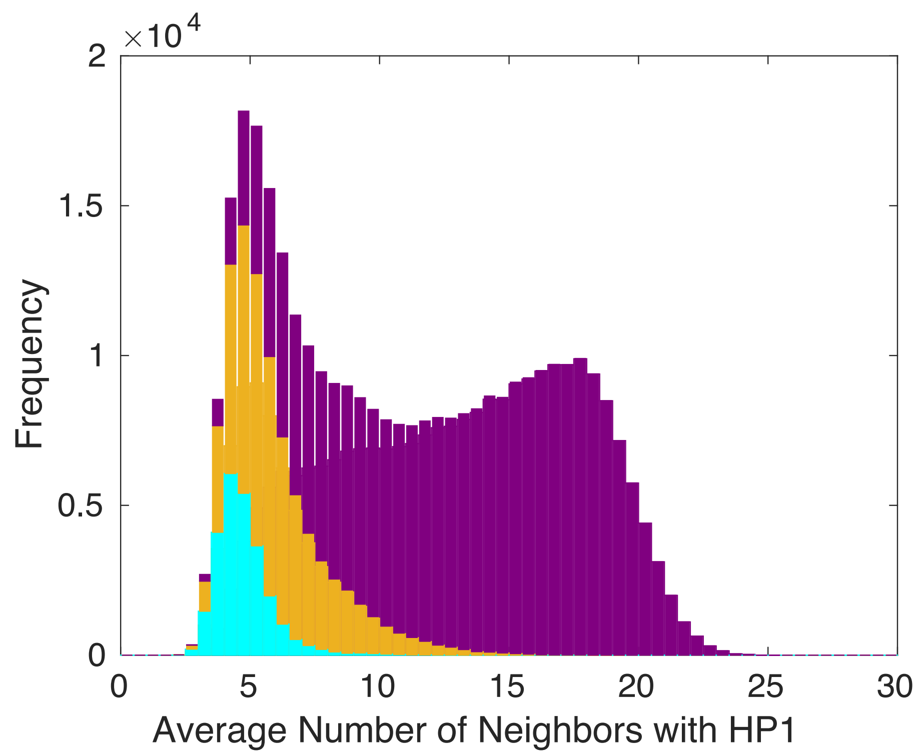


**Fig. S4.** Histogram of the average number of neighboring nucleosomes with HP1 bound for $C_{S1}^{opt}$ = 0.767 $\mu$M. Cyan, gold, and purple colors correspond to nucleosomes that are classified as originally residing in euchromatin, the boundary, and heterochromatin, respectively.

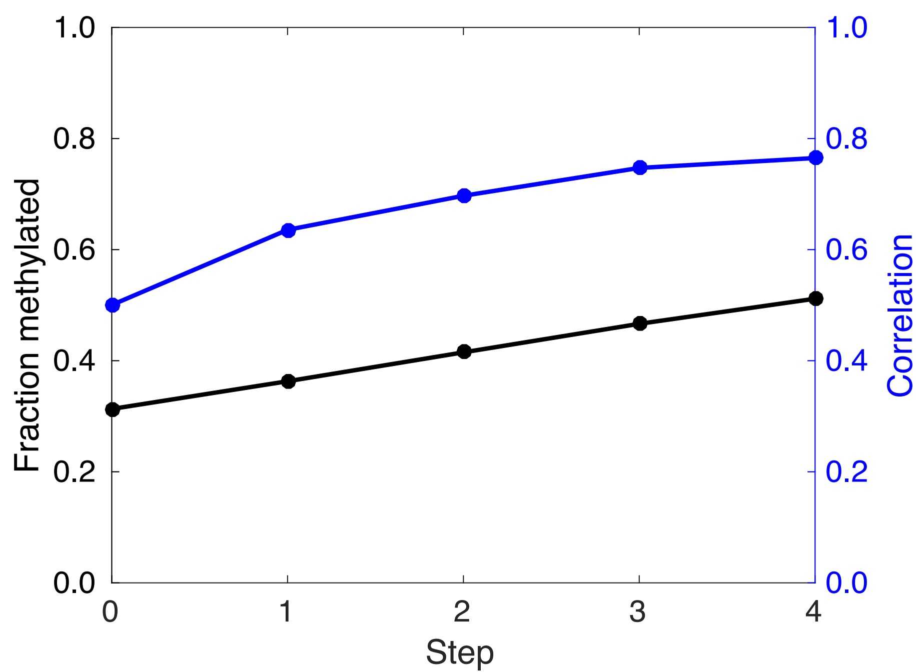


**Fig. S5.** Plot of the fraction of methylated nucleosomes and correlation coefficient $\chi_m$ versus free HP1 concentration for 1 generation of reestablishment of the methylation sequence, following Procedure S2A. Step 0 corresponds to the methylation level immediately after replication (*i.e.* 50% of the original methylation level). Steps 1 through 4 correspond to restoration of the methylation level to 25%, 50%, 75%, and 100% of the steady-state level (identified from Procedure S1), respectively.

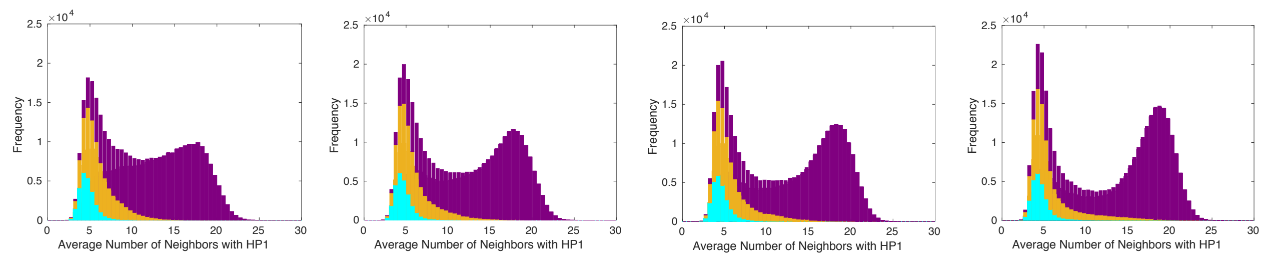


**Fig. S6.** Histograms of the average number of neighboring nucleosomes with HP1 bound in Procedure S2A. From left to right, the plots correspond to restoration of the methylation level to 25%, 50%, 75%, and 100% of the steady-state level (identified from Procedure S1) and HP1 concentrations of 0.767 $\mu$M, 0.750 $\mu$M, 0.733 $\mu$M, and 0.717 $\mu$M. Cyan, gold, and purple colors correspond to nucleosomes that are classified as originally residing in euchromatin, the boundary, and heterochromatin, respectively.

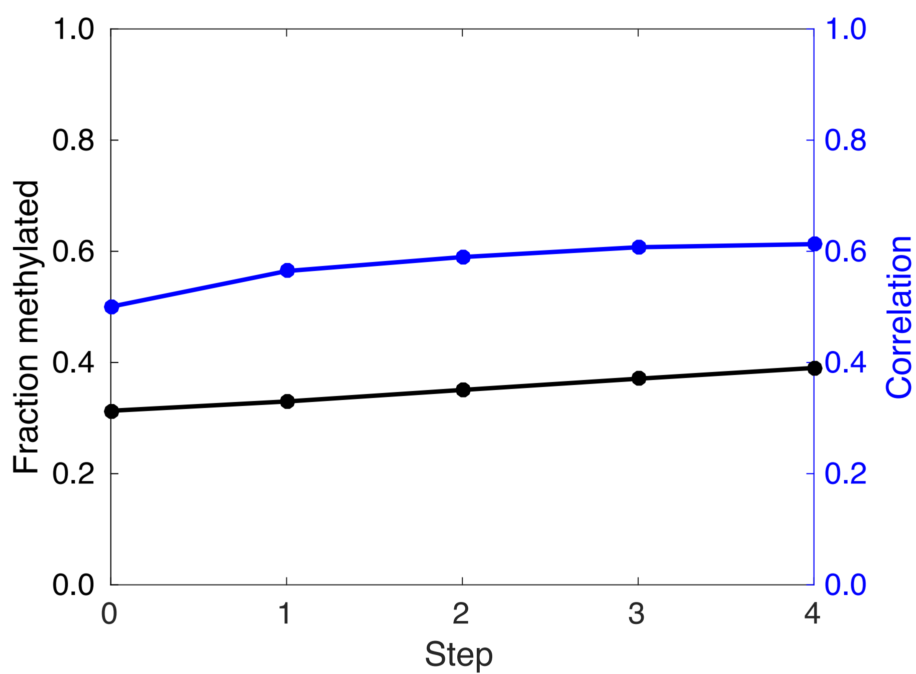


**Fig. S7.** Plot of the fraction of methylated nucleosomes and correlation coefficient $\chi_m$ versus free HP1 concentration for 1 generation of reestablishment of the methylation sequence, following Procedure S2B. Step 0 corresponds to the methylation level immediately after replication (*i.e.* 50% of the original methylation level). Steps 1 through 4 correspond to restoration of the methylation level to 25%, 50%, 75%, and 100% of the steady-state level (identified from Procedure S1), respectively.

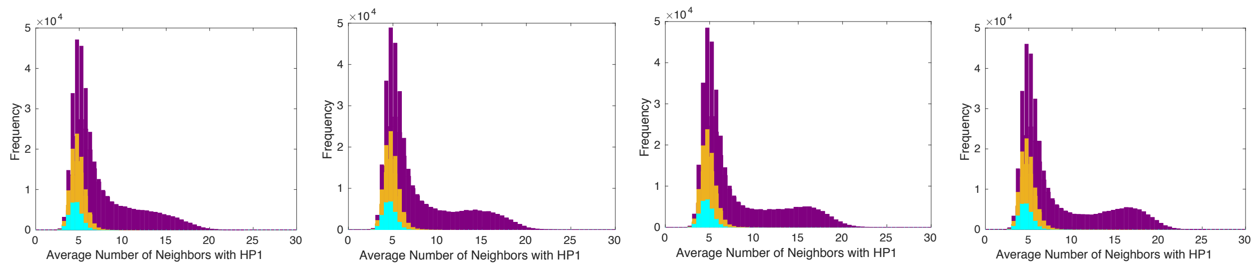


**Fig. S8.** Histograms of the average number of neighboring nucleosomes with HP1 bound for $C_0^{opt}$ = 0.700 $\mu$M in Procedure S2B. From left to right, the plots correspond to restoration of the methylation level to 25%, 50%, 75%, and 100% of the steady-state level (identified from Procedure S1). Cyan, gold, and purple colors correspond to nucleosomes that are classified as originally residing in euchromatin, the boundary, and heterochromatin, respectively.