Antagonistic histone post-translational modifications improve the fidelity of epigenetic inheritance - a Bayesian perspective

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Histone Post-Translational Modifications (PTMs) are important epigenetic marks regulating gene expression. The specific pattern of histone PTMs across the gene is critical for turning on/off the expression of the corresponding gene. During DNA replication in mitotic cells, the histone PTMs are dislodged from the mother chromatid, ahead of the replication fork, and distributed uniformly at random among the daughter chromatids. Building on our previous work which modelled the inheritance of a single PTM, the current work considers the effect of an additional antagonistic PTM. We model the joint PTM sequence as a Hidden Markov Model (HMM) and the DNA replication fork as a noisy communication channel. The optimal Bayesian sequence estimator is employed at the daughter chromatids to reconstruct the mother. A high-fidelity reconstruction, aided by the enzyme machinery, is shown to be possible in the presence of epigenetic memory. The structural properties derived for the optimal estimator are then verified through simulations, which show the improvement in fidelity of inheritance in the presence of antagonism. This is further validated through recent experimental data.

1 INTRODUCTION

Epigenetic markers regulate gene expression without altering the genetic sequences. They are inherited stably across cell generations and influenced by external factors such as diet, environment, and stress leading them to be reversible [1]. Histone Post-Translational Modifications (PTMs) are one of the prominent sets of markers whose patterns across the chromatin play significant roles in gene activation or repression [2]. Certain histone PTMs such as H3K27me3 are known to silence the chromatin region in which they are enriched while a few others like H3K36me3, and H3K4me3 are known to activate the underlying gene for transcription [3, 4].

During DNA replication, the histone PTMs are dislodged as tetramers $(H3\text{-}H4)_2$ from the mother chromatin ahead of the replication fork and are equally distributed between the two daughter chromatids [5, 6] (in mitotic cell division). The positions at which half of the parental histone tetramers are placed in one daughter chromatid are random, akin to a discrete signal being corrupted by an i.i.d. (independent and identically distributed) noise [7]. Thus, a daughter chromatid has two types of nucleosomes immediately after DNA replication - one set that is directly inherited from the mother chromatin with its PTMs, and another set from a histone pool, without any PTMs. Recent experiments have suggested that silencing modifications such as H3K27me3 are distributed closer to the loci of DNA replication fork than the activating modifications [8]. Additionally, certain modifications such as H3K9me3 and H3K27me3 are known to serve as templates for stable inheritance of heterochromatin, along with associated read-write enzymes [9, 10].

Since the patterns of the histone PTMs across the promoter and gene body play a critical role in the transcriptional regulation [11, 12], it is essential that the distribution of histone PTMs in the parental chromatin is replicated with sufficient fidelity in the daughter chromatids, even if they have only half the information (tetramers) from the parental chromatin. The histone PTMs and several histone chaperones are known to interact with one another to aid the

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effective inheritance of the regulating markers in the daughter chromatids from the mother chromatin, during DNA replication [10, 13]. The newly generated tetramers are modified based on the sequential pattern of modifications directly inherited from the parental chromatin [14, 15].

Our previous work modelled the DNA replication process by a noisy communication channel, where the inheritance of a specific modification was aided by localized interactions amongst nucleosomes. Since different histone PTM marks often interact with one other, we ask the question if the inheritance of a specific histone PTM such as H3K27me3 is aided by the presence of another histone PTM that is antagonistic to it (such as H3K36me3). If yes, how much does the presence of an antagonistic mark improve the fidelity of the original mark? We extend our previous model to accommodate this antagonistic mark and apply the principles from estimation theory to address this question.

2 MODEL AND METHODS

Along a region of the chromatin, we define the presence or absence of a histone PTM as a binary 1 or a 0 respectively. We consider two antagonistic histone PTMs (say A and B), with PTM A being the primary mark. Let $M^A = (m_1^A, m_2^A, \ldots, m_n^A)$ and $M^B = (m_1^B, m_2^B, \ldots, m_n^B)$ be the binary sequences representing the presence or absence of the histone PTMs A and B respectively across n nucleosomes in the mother chromatin. We model M^A as a first-order Markov chain similar to our previous work [16], whereas M^B is modelled as a Hidden Markov Model (HMM) driven by the Markov process M^A. Therefore, we have the conditional probability for M^A given by

$$\Pr(m_i^A | m_{i-1}^A, m_{i-2}^A, \ldots, m_1^A) = \Pr(m_i^A | m_{i-1}^A). \tag{1}$$

An example chromatin segment is shown in Fig. 1A. For the HMM M^B, the value m_i^B is conditionally independent of others, given m_i^A.

$$\Pr(m_i^B | M^A, m_j^B, j \neq i) = \Pr(m_i^B | m_i^A). \tag{2}$$

In the single modification model, we showed that the inheritance of a histone PTM from the mother to the daughter chromatin has high fidelity when it follows a threshold-$\hat{k}$ filling algorithm in certain regions of the chromatin (long islands of 1s interspersed by long islands of 0s). In the current work, we analyse how the presence of an antagonistic modification (PTM B) in the same region of the chromatin influences the fidelity of the histone PTM A's inheritance.

The state transition diagram of the mother chromatin for histone PTM A alone is represented by Fig. 1B. We extend this original state diagram to include PTM B and represent the transitions in Fig. 1C. Here the states (m_i^A, m_i^B) takes values from the set $\{(0,0), (0,1), (1,0)\}$. In this manuscript, we make the assumption that the chromatin that we model for inheritance is not bivalent [17], i.e., we do not consider antagonistic modifications A and B to be present in the same nucleosome. Hence $(1,1)$ is not a permissible state. As can be seen from Fig. 1C, in addition to the transition probabilities α (Probability of staying in a modified state) and β (Probability of staying in an unmodified state), we define a new parameter μ as the probability of histone PTM B being present when histone PTM A is absent, in the same nucleosome. That is, $\mu = \Pr(m_i^B = 1 | m_i^A = 0)$. Notice that $\Pr(m_i^B = 1, m_i^A = 1) = 0$ and $1 - \mu = \Pr(m_i^B = 0 | m_i^A = 0)$. The transition probability $\Pr(m_{i+1}^A, m_{i+1}^B | m_i^A, m_i^B)$ is computed as follows:

$$\Pr(m_{i+1}^A, m_{i+1}^B | m_i^A, m_i^B) = \Pr(m_{i+1}^A | m_i^A, m_i^B) \Pr(m_{i+1}^B | m_{i+1}^A, m_i^A, m_i^B) \tag{3}$$

$$= \Pr(m_{i+1}^A | m_i^A) . \Pr(m_{i+1}^B | m_{i+1}^A). \tag{4}$$

Further details of the values of the transition probabilities are provided in the Supplementary Information (SI) Sec. 1.

The chromatin undergoes a loss of 50% of its nucleosomes during DNA replication while passing through the replication fork [18, 19]. For this study, we consider modifications A and B to represent the histone PTMs in the same histone type such as H3, for eg., A could be H3K27me3 while B could be H3K36me3, in the same nucleosome. From [20, 21], we know that these marks are antagonistic in functionality, i.e., H3K27me3 is a repressive histone PTM as opposed to H3K36me3 which is an activating one [4]. The presence of both of these marks together is rare, but not impossible and can be seen in 'poised' regions of the chromatin [22].

2.1 Modeling the replication with antagonistic histone PTMs.

In mitotic cells, the tetramers from the mother chromatin are placed in each of the daughter chromatids with equal probability with the help of histone chaperones such as MCM2 [23, 24]. There exist studies showing that both symmetric and asymmetric inheritance (where one daughter chromatid gets a larger share of the parental nucleosomes than its sister) are observed in different cell lines [25]. Additionally, symmetric inheritance is significantly hampered in cases where MCM2 is mutated [23]. We model the parameter for distribution between the daughter chromatids as ρ and analyze symmetric inheritance ($\rho = 0.5$) from the mother to the daughter chromatids, in this work.

The DNA replication fork is modelled as a noisy communication channel in which one of the two daughter chromatids is given a fraction $(1 - \rho)$ of the parental histones, with the remaining newly assembled from a histone pool. For the single modification case, the Z-channel model in Fig. 1D can be used to depict the DNA replication fork, where the daughter sequence $D^A = (d_1^A, \ldots, d_n^A)$ is obtained as $d_i^A = m_i^A Z_i$, where $Z_i \in \{0, 1\}$ is IID with $\Pr(Z_i = 0) = \rho$. The process of reconstruction of the mother-like pattern from the daughter is akin to estimating the original signal from the corrupted signal. The additional presence of antagonistic modifications allows us more choice in the observations. The model with antagonism having $d_i^{AB} = m_i^A Z_i + 2(1 - m_i^A) m_i^B Z_i$ as the daughter observations is shown in Fig. 1E, with the usual arithmetic. The latter model is called the Binary Erasure Channel (BEC) in information theory. Thus, for $d_i^{AB} \in \{1, 2\}$ values of the mother can be correctly guessed from the daughter. We now estimate the remaining daughter sequence and claim that the additional antagonistic information is improving the fidelity of inheritance of the primary modification PTM A.

2.2 Reconstructing the mother chromatin's pattern from the daughter chromatid

We only need to estimate the mother chromatin's pattern from the daughter chromatid where $d_i^{AB} = 0$ (newly deposited tetramers), between flanking $d_i^{AB} = 1$s or $d_i^{AB} = 2$s (parental tetramers). We perform a Sequential Maximum A-posteriori Probability (SMAP) based decoding, which is a Bayesian estimator calculating argmax $_{M^A} \Pr(M^A, d_1^{AB}, \ldots, d_n^{AB})$. Notice that

$$\begin{aligned}
\Pr(M^A, d_1^{AB}, \ldots, d_n^{AB}) &= \sum_{M^B} \Pr(M^A, M^B, d_1^{AB}, \ldots, d_n^{AB}) \\
&= \sum_{M^B} \prod_{i=1}^{n} \Pr(m_i^A, m_i^B, d_i^{AB} | m_{i-1}^A, m_{i-1}^B) \\
&= \sum_{M^B} \prod_{i=1}^{n} \Pr(m_i^A, m_i^B | m_{i-1}^A, m_{i-1}^B) \Pr(d_i^{AB} | m_i^A, m_i^B) \\
&= \prod_{i=1}^{n} \sum_{m_i^B} \Pr(m_i^A | m_{i-1}^A) \Pr(m_i^B | m_i^A) \Pr(d_i^{AB} | m_i^A, m_i^B). \qquad (5)
\end{aligned}$$

Since the unknown segment is flanked by known values from the mother sequence, for each run of k 0s, we have four possibilities depending on the flanking values.

Case 1 : $\{1, 0_k, 1\}$ - between flanking 1s ($d_i^{AB} = 1$) on both sides,

Case 2 : $\{1, 0_k, 2\}$ - between a flanking 1 ($d_i^{AB} = 1$) on the left and a 2 ($d_i^{AB} = 2$) on the right,

Case 3 : $\{2, 0_k, 1\}$ - between a flanking 2 ($d_i^{AB} = 2$) on the left and a 1 ($d_i^{AB} = 1$) on the right,

Case 4 : $\{2, 0_k, 2\}$ - between flanking 2s ($d_i^{AB} = 2$) on both sides.

We maximize Eq. (5) using the Viterbi decoding algorithm, which finds the optimal path that maximizes the joint probability $\Pr(M^A, D^{AB})$, from the trellis representing all possible paths. Each of the above four cases will yield a different Trellis diagram, this is illustrated in Fig. 2 where the branch metrics are marked on the graph edges. Notice that the branch metrics are evaluated using Eq. (5) for the appropriate states. In each Trellis, the winning path is the one with the highest end-to-end path metric.

3 RESULTS

Using simulations of antagonistic sequences, we first obtained the results of the SMAP decoding performed using the Viterbi algorithm. For each α, β and μ in the interval $[0.1, 0.9]$, binary daughter sequences of length 100 were generated and the corresponding mother sequences were estimated using SMAP decoding. The daughter sequences were obtained from the mother sequences with a ρ value of 0.5 i.e., 50% of the mother sequence's nucleosomes are transferred to one daughter (symmetric inheritance). The results were averaged over 10000 realizations.

We define the Bit Error Rate (*BER*) corresponding to M^A as the fraction of nucleosomes where the original and estimated mother sequences differ with respect to PTM A, i.e.,

$$BER = \frac{1}{n} \sum_{i=1}^{n} (m_i^A - \hat{m}_i^A)^2. \tag{6}$$

3.1 Presence of antagonistic modifications improves the fidelity of PTM A's inheritance

We plot the average *BER* as heatmaps for cases of $\mu = 0.2, 0.5$ and 0.8 in Fig. 3A, 3B and 3C respectively. The heatmap corresponding to the non-antagonistic ($\mu = 0$) case is available in SI Fig. S1A. The Hinton plots in Fig. 3D, 3E and 3F demonstrate the *BER* improvement for $\mu \in \{0.2, 0.5, 0.8\}$ over the non-antagonistic case. From these plots, we can observe that with an increase in μ, the average *BER* decreases. This is also evident from the Hinton plots - the number and size of black squares increase with μ, indicating that more regions have lower *BER* as compared to the non-antagonistic case.

Let us discuss the biological relevance of these simulations. We postulate that this near-perfect recovery for PTM A in the daughter chromatid obtained through SMAP decoding could be performed by an ideal enzyme machinery consisting of readers and writers that work in tandem with histone chaperones, transcription factors etc., while catering to the antagonistic modifications. It has to be noted that the estimation of the mother sequence from the daughter sequence requires the knowledge of the mother sequence's statistical parameters such as α, β and μ. This is possibly achieved through epigenetic memory effectors such as lncRNA, other PTMs such as H3K4me2, DNA methylation mechanisms and so on [26].

To elucidate how the biological enzymes may behave during cell replication in a realistic scenario, we observe how the Viterbi decoding strategy performs in different regions of α, β and μ. From Fig. 4A, we observe that distinct patterns of reconstruction emerge upon applying the Viterbi algorithm. In particular, for Case-1, Region A and Region B (marked

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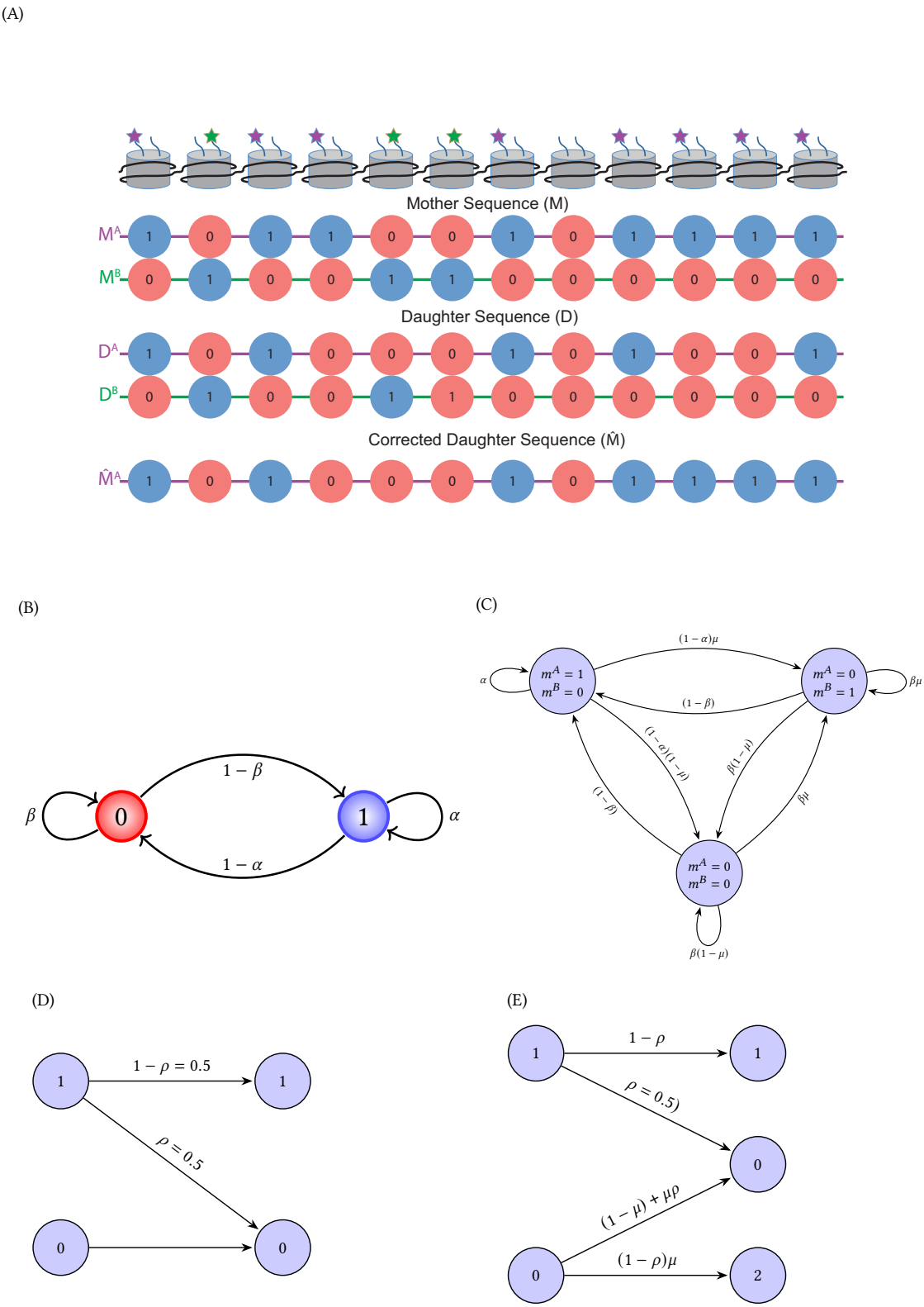

Fig. 1. (A) The schematic representation of the antagonistic model where 1s and 0s represent the presence and absence of modifications. (B) State diagram for the case considering only PTM A. (C) State diagram for the case considering antagonistic modifications PTM A and PTM B assuming non-bivalent chromatin, i.e. $\Pr(m_i^B = 1 | m_i^A = 1) = 0$. (D) DNA replication in the single modification case - modelled by a Z-Channel. (E) DNA replication in the antagonistic modification case - modelled by a Binary Erasure Channel

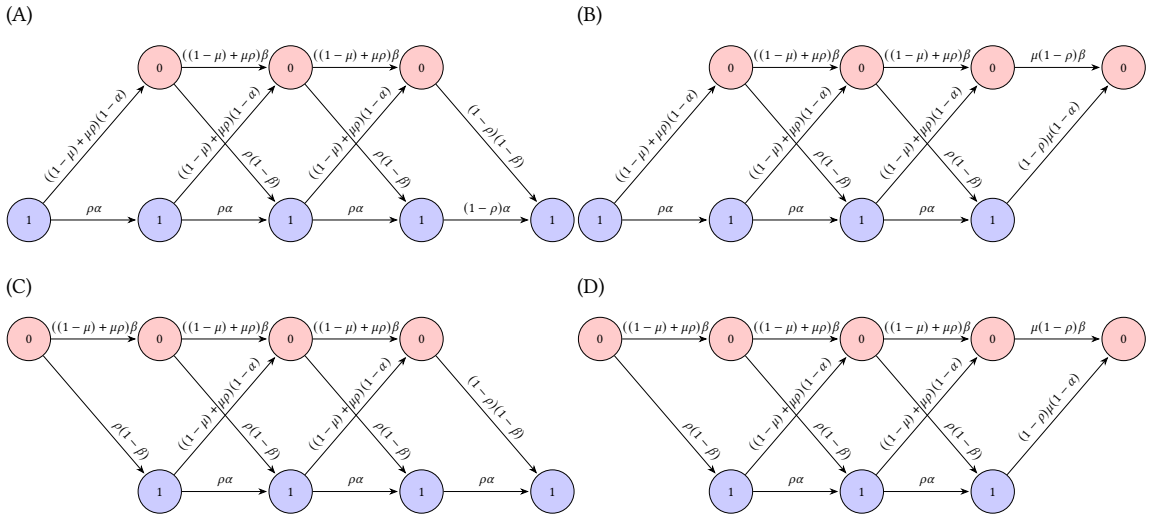

Fig. 2. Trellis diagrams for the antagonistic modification cases 1-4 (for 5 nucleosomes) as listed in Sec 2.2. The Viterbi algorithm is used to obtain the reconstructed sequences

by blue and white squares respectively) will obey:

$$\frac{\alpha^2}{2} - (1-\alpha)(1-\beta)\left(1-\frac{\mu}{2}\right) \geq 0. \tag{7}$$

In addition, $\alpha - (2-\mu)\beta \geq 0$ is true in Region A, whereas the reverse inequality is true in Region B. This implies that in Region A, every 0 is converted to a 1 whereas only shorter runs of 0s are modified to 1s in Region B. In Region C (green), the daughter sequence remains unchanged while partial modification is optimal in Region D (yellow).

It has to be noted that except for Case 1, there are only three regions present in the Viterbi reconstruction patterns. Specifically, Region B of Case 1 is replaced by Region C (unfilled 0s) due to the presence of the antagonistic modification in the nucleosome ($m_i^B = 1$) (Fig. 4B).

3.2 Higher antagonism leads to more filling of gaps during reconstruction

The threshold-$\hat{k}$ parameter indicating the cut-off for the filling or no-filling decision in Region B of Fig. 4A is given by:

$$k = \frac{\log\left(\frac{(1-\alpha)(1-\beta)}{\alpha\beta}\right)}{\log\left(\frac{\frac{\alpha}{2}}{(1-\frac{\mu}{2})\beta}\right)} \tag{8}$$

It can be understood from the above equation that the threshold-$\hat{k}$ decreases with μ, this can be inferred from Fig. 4C as well. Additionally, from the figure, one could infer that for the chromatin region defined by a high α and moderate β, a higher level of antagonism may shift the behaviour of reconstruction from Region B (threshold-$\hat{k}$ filling) to Region A (zero threshold-$\hat{k}$). The threshold-$\hat{k}$ filling is akin to a realistic reconstruction of the mother chromatin's PTM pattern by the enzyme machinery as the first step in the PTM inheritance process [16].

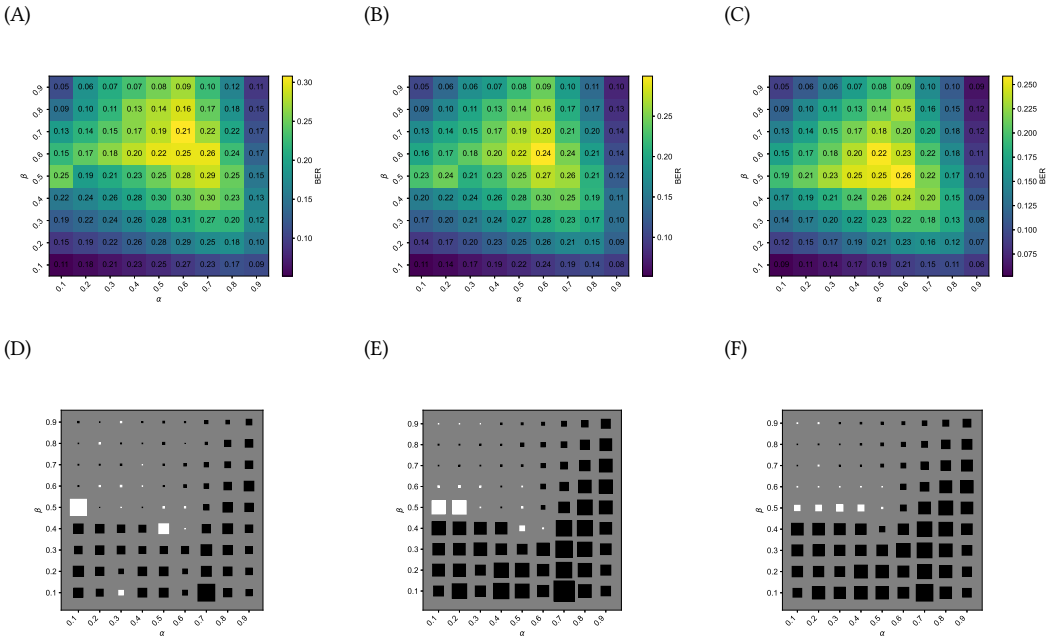

Fig. 3. **Simulation results for different α,β and μ combinations**: The top row (A, B and C) shows the average *BER* values for the different (α, β, μ) combinations. The bottom row (D, E and F) shows the corresponding Hinton plots highlighting the difference between *BER* with no antagonism and different levels of antagonism: (A, D - $\mu = 0.2$, B, E - $\mu = 0.5$, C, F - $\mu = 0.8$). The heatmap for the no antagonism *BER* case is provided in SI in Fig. S1A and is reproduced from our previous work [16]. In the Hinton plots, a black square shows that antagonism is providing a lower *BER* than the no-antagonism counterpart for that (α, β). In the Hinton plots, the largest square has a magnitude of $|0.0775|$ in (D), $|0.1152|$ in (E) and $|0.1532|$ in (F).

We then simulated 1000 sequences of length 1000 each, across different α, β combinations with varying antagonism (μ). These sequences were designed to be in Region B of Fig. 4C so that we can analyze the impact of antagonism on the threshold-$\hat{k}$ filling strategy using Eq. (8). The difference in BER (ΔBER) from the no-antagonism case ($\mu = 0$) is shown in Fig. 4D, demonstrating a clear advantage of having the antagonistic modification.

3.3 Verification of the model from the experimental data

We obtained the ChIP-seq data for the following 5 modifications from GSE135029 (Mus *Musculus*): H3K27me1, H3K27me2, H3K27me3, H3K36me2, H3K36me3. We binarized the data and obtained the sequences for the antagonistic modifications H3K27me3 (repressive modification) and H3K36me3 (activating modification) using the discretization algorithm explained in SI Sec. 3. We then associated an (α,β,μ) tuple with each nucleosome by considering a window of length 100 around it to calculate the transition probabilities. Further details are provided in SI Sec. 1.

In this data, we focus on chromatin segments with $0.7 \leq \alpha \leq 1.0, 0.5 \leq \beta \leq 0.8$ and $0.2 \leq \mu \leq 0.7$. A total of 29112 such segments spread across all chromosomes were identified. These sequences had modifications A (H3K27me3) or B (H3K36me3) or none at a specific nucleosome. We ignore the small fraction of nucleosomes where PTMs A and B were present together. We computed threshold-$\hat{k}$ for the daughter sequences (D^{AB}) with and without antagonism ($\mu = 0$) using Eq. (8) to facilitate threshold-$\hat{k}$ filling so as to yield $\hat{M}^{AB}$. We plot the distributions of the average *BER* for the antagonistic and non-antagonistic cases in Fig. 5A. We observe that the medians and the interquartile ranges

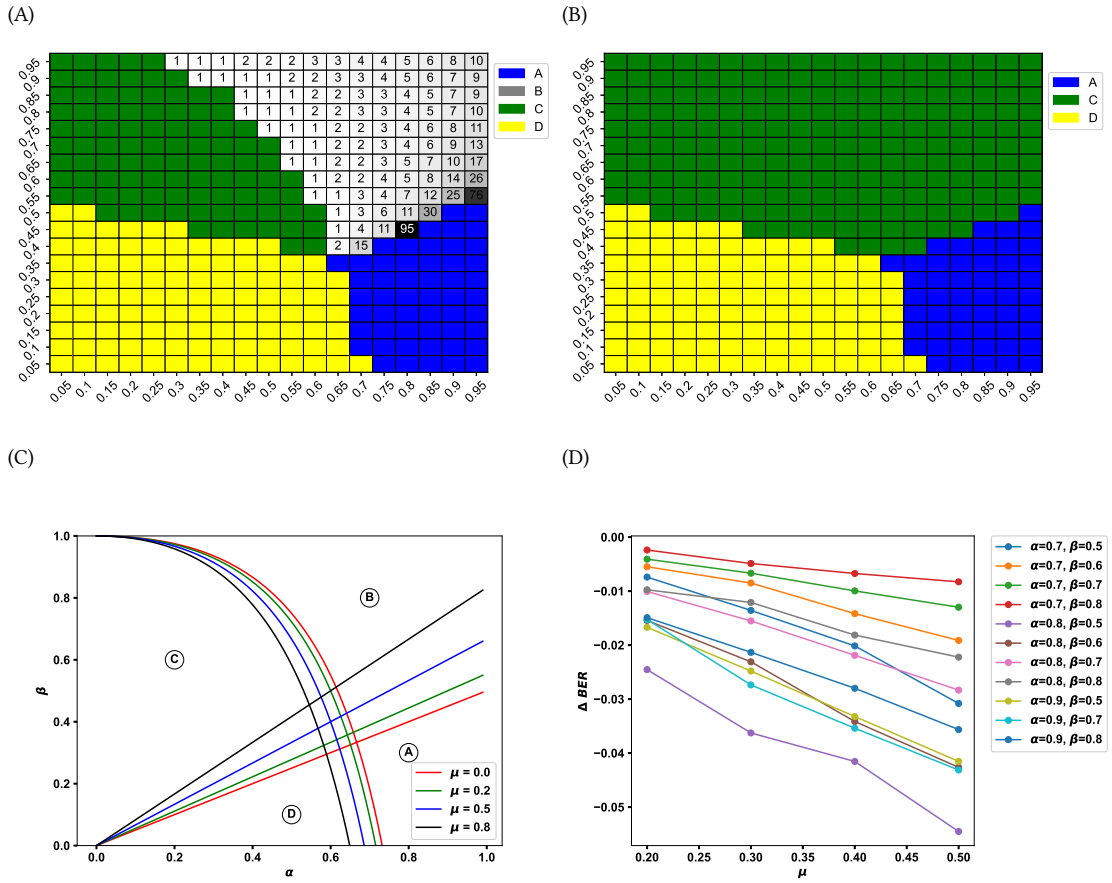

Fig. 4. Reconstruction patterns for (A) Case 1 for $\mu = 0.2$ and (B) Cases 2, 3, 4 for $\mu = 0.2$. Threshold-$\hat{k}$ filling is observed only for Case 1. The different regions in the pattern in (A) can be modelled by Eq. S14 and Eq. S17 in SI Sec. 4. (D) ΔBER between the reconstructed non-antagonistic sequences and the reconstructed antagonistic sequences for different values of α, β combinations, across μ. The simulations were performed for sequences of length 1000, with parameter values $\alpha \in [0.7, 0.9]$, $\beta \in [0.5, 0.8]$ and $\mu \in [0.2, 0.6]$ averaged over 1000 sequences for each combination.

are significantly lower for the antagonistic cases. These results validate our model suggesting that the presence of antagonistic PTM improves the fidelity of inheritance of the primary PTM.

4 DISCUSSION AND FUTURE WORK

There have been several models that aim to explain how these epigenetic marks are faithfully transferred from the mother chromatin to the daughter chromatids during DNA replication. Recently, Skjegstad *et al* proposed a 3D polymer configuration model in which they postulate that nucleosomes bind to one another in 3D configurations that affect phenomena such as epigenetic memory and bistability [27]. They employ partial confinement to explain the burst-like nature of certain epigenetic switches. Previously, Dodd *et al* [28] proposed a stochastic model in which cooperation between neighbouring nucleosomes leads to the spreading of modifications over distant regions. Using experimental

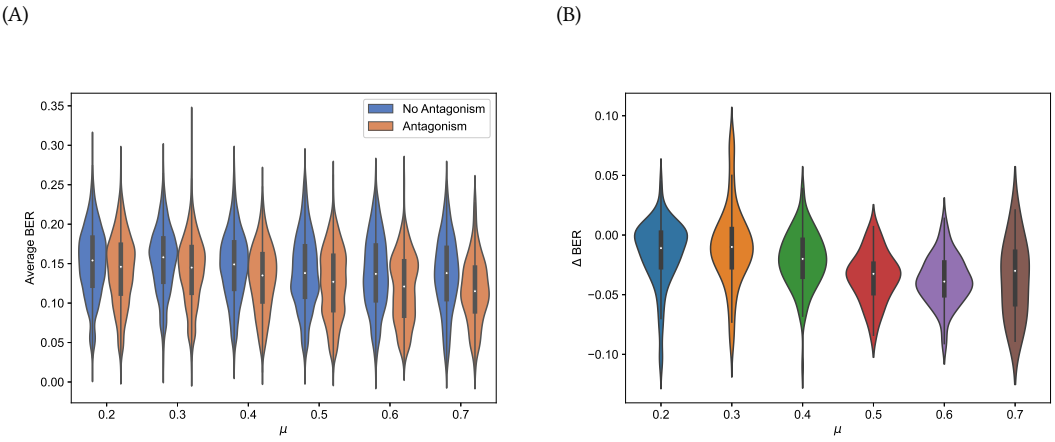

Fig. 5. **Experimental validation for the model**: (A) Average *BER* and (B) ΔBER for the non-antagonistic and antagonistic cases for the sequences binarized from the ChIP-Seq data from [20]. The selected chromatin regions were found to have the statistical parameters: $\alpha \in [0.7, 1.0], \beta \in [0.5, 0.8], \mu \in [0.2, 0.7]$

data from fission yeast, the authors in [29] suggest that heterochromatin propagates not in a linear manner but as bursts. Alabert *et al* [20] suggest that a domain model (in which methylation states are found in distinct domains) is more likely to explain the antagonism between H3K36me3 and H3K27me3 in mESCs.

Our proposed probabilistic model is not in disagreement with the above theories. While the above models focus on heterochromatin inheritance over long domains, we predict the mechanism (threshold-$\hat{k}$ filling) by which any modification (particularly silencing modifications) is inherited with high fidelity [16]. In this work, we claim that the antagonistic modifications aid in the inheritance of a given modification as can be seen by the improved fidelity of inheritance. Prior to our model, Ramachandran and Heinkoff [19] model each parental nucleosome assembling at a daughter chromatin as a Bernoulli trial - this is similar to our estimation theory based model.

There have been different theories proposed to explain the segregation of nucleosomes during DNA replication. In one model, the nucleosomes are dislodged ahead of the replication fork and the $(\text{H3-H4})_2$ tetramers are randomly placed along the daughter chromatids [7]. The parental tetramers serve as templates for the newly deposited unmodified tetramers (from the histone pool) that are placed adjacent to them. In another model (semiconservative), the nucleosomes are split into (H3-H4) dimers, guided by the chaperone Asf1. The dimers deposited from the parental nucleosomes aid in modifying the newly deposited dimers as an intraparticle process [6]. While both models are equally plausible[10], in this manuscript, we assume the former model. For computing the fidelity, it has to be noted that we consider the case of a single daughter chromatid individually.

The antagonistic roles of H3K36me3 and H3K27me3 have also been widely studied in the past. In Yang *et al* [30], the authors discuss how the antagonistic roles of the aforementioned modifications are necessary for the successful switching of epigenetic states in Arabidopsis for vernalization in winter. Their model and findings suggest a mutual antagonism between these modifications, similar to those in [31]. In [32], the authors propose that in HeLa cells, the nucleosomes containing H3K36me3 do not have the H3K27me3 except in newly synthesized H3. The authors also provide evidence that Ash1 (a Trithorax group protein) which is an H3K36-specific demethylase, antagonizes

PRC2-mediated H3K27 methylation. Our proposed work provides a model for explaining how the presence of H3K36me3 in neighbouring nucleosomes aids in the faithful inheritance of H3K27me3.

There have also been studies on the inheritance of the histone PTMs over several cycles of cell division. Our model not only quantifies the error in inheritance but also postulates the effect of antagonism on the fidelity of inheritance. The molecular mechanisms involved in the the faithful inheritance are not discussed in detail in our work - there could be a plethora of transcription factors, and chromatin remodelers including PRC2 domains, HP1 dimers, RNAi and so on [33]. It has been reported that DNA methylation is a critical factor in the faithful inheritance of gene expressions over large timescales [34, 35]. We have not considered the impact of replication-coupled DNA methylation factors in this model at present. Additionally, we assume a symmetric partition of the parental nucleosomes to the daughter chromatids. We aim to address these two concerns in our future work.

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