Effect of replication on epigenetic memory and consequences on gene transcription

Mehari B. Zerihun,[1] Cédric Vaillant,[1] and Daniel Jost*[2]

[1] *École Normale Supérieure de Lyon, CNRS, Laboratoire de Physique, UMR 5672, Lyon, France*
[2] *Joseph Fourier University, CNRS, TIMC-IMAG lab, UMR 5525, Grenoble, France*

Abstract

Gene activity in eukaryotes is in part regulated at the level of chromatin through the assembly of local chromatin states that are more or less permissive to transcription. How do these chromatin states achieve their functions and whether or not they contribute to the epigenetic inheritance of the transcriptional program remain to be elucidated. In cycling cells, stability is indeed strongly challenged by the periodic occurrence of replication and cell division. To address this question, we perform simulations of the stochastic dynamics of chromatin states when driven out-of-equilibrium by periodic perturbations. We show how epigenetic memory is significantly affected by the cell cycle length. In addition, we develop a simple model to connect the epigenetic state to the transcriptional state and gene activity. In particular, it suggests that replication may induce transcriptional bursting at repressive loci. Finally, we discuss how our findings - effect of replication and link to gene transcription - have original and deep implications to various biological contexts of epigenetic memory.

keywords: epigenetic marks, DNA replication, stability, stochastic modeling, transcriptional bursting

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I. INTRODUCTION

Maintenance of cell identity implies a tight control of gene expression [1]. Different layers of regulation exist from transcriptional to post-translational regulation. In eukaryotes, epigenetic regulation represents a main player of gene regulation [2]. Biochemical tags, the so-called epigenetic marks, are dynamically deposited on histone tails or on DNA itself by modifying enzymes. Typically, two categories of marks could be distinguished: active marks that are set down on euchromatic loci containing expressed genes, and inactive marks that are present on heterochromatic - silenced - regions. At large scale, these marks are associated with the 3D organization of chromatin into the nucleus [6–8]. At the gene scale, they are involved in controlling the direct accessibility of chromatin to the transcription machinery or in recruiting important factors [3, 4].

A key question in the field of epigenetics is to understand the generic principles behind the transcriptional memory of single cells, in particular the establishment and transmission of the cellular identity, the so-called epigenetic memory. While part of these mechanisms involve cytoplasmic inheritance of transcription factors during cell division, it is now believed that some epigenetic marks are transmitted during replication and mitosis and participate directly in maintaining the cell behavior [5].

At the gene scale, many studies have started to address these questions both experimentally [9–16] and theoretically [17–32]. For the modeling part, the seminal work of Sneppen, Dodd and coworkers [17, 21, 24] has shown that long-range or cooperative interactions between epigenetic marks are needed for the maintenance of a stable and coherent local epigenetic identity. Such concepts have been applied successfully to describe the epigenetic regulation in various biological contexts like in the vernalization of plants [10, 13, 23], in the silencing of the locus *MAT* in yeasts [17, 19, 22, 29] or in the propagation of heterochromatin in human cells [28]. In a recent paper [31], we illustrate the capacity of such models to account within the same framework for the robustness and plasticity of epigenetic regulation observed during development, proliferation and diseases. In particular, we suggested a possible mechanism for developmental transitions where the system is shifted closed to a critical point to benefit from the ultra-sensitivity to external cues.

* Correspondence: daniel.jost@imag.fr

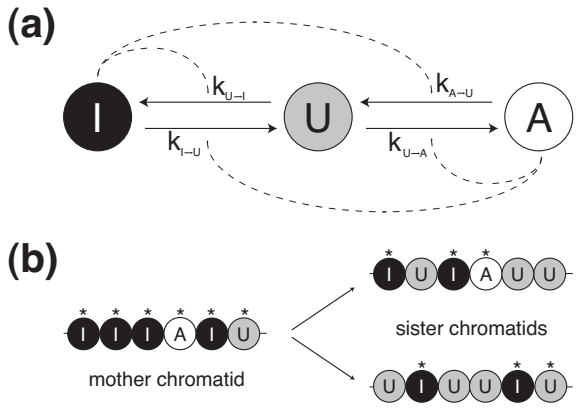

FIG. 1: (a) 3-states model for the local epigenetic state of one nucleosome. Transition rates between states depend on the total density of active and inactive marks (Eqs1-4). (b) Random distribution of the maternal marks (*) among the sister chromatids during replication. Empty spaces are filled with U-type nucleosomes.

One important approximation used in this previous work, and in many other models, was to not account explicitly for the dilution of epigenetic information during replication. However, in actively dividing cells, epigenetic memory is periodically challenged during replication when maternal marks are distributed among the two sister chromatids. This represents a major perturbation to the system with typical time scales and statistical properties that might have deep implications in the stability of cell identity. Only few theoretical studies have quantified the destabilizing impact of replication on epigenetic memory [17, 20]. Here, we propose to characterize more deeply this impact by modeling the stochastic dynamics of the epigenetic state of single cells using kinetic Monte-Carlo simulations and by analyzing the role of model parameters on the epigenetic stability. We also develop a simple model to connect the epigenetic state to the transcriptional state and to study the propagation of epigenetics properties to the level of gene expression and bursting. Finally, we discuss the biological implications of our findings - effect of replication and link to gene transcription - in various contexts.

II. MODEL

A. Epigenetic level

We base our current work on a stochastic model of epigenetic regulation that we developed in a previous study [31] and that was inspired by the work of Dodd et al. [17]. We aim to describe the global epigenetic state of a specific DNA region containing n nucleosomes. We assume that each nucleosome can exist in one of three epigenetic flavors (see Fig.1a): active A that models epigenetic marks promoting expression of the underlying chromatin region (like H3K9ac), inactive I for epigenetic marks repressing gene expression (like H3K9me), and unmarked U in absence of marks. Interconversion between active and inactive states takes place through the unmarked state.

The stochastic dynamics of epigenetic state is assumed to be driven by three processes: (1) random transitions between states due to nucleosome turnover or to the leaky activity of modifying enzymes like (de-) methylases or (de-) acetylases; (2) long-range recruitment of these modifying enzymes by neighboring active or inactive marks; (3) dilution of marks due to replication. Transitions between successive states due to the first two processes can be described by four biochemical reactions. Noting n_X the number of nucleosomes with state X ($X \in \{A, U, I\}$ and $n_A + n_I + n_U = n$), the corresponding transition rates are given by (Fig.1a)

$$k_{A\to U} = k_0 + \epsilon_I \rho_I \quad (1)$$
$$k_{U\to A} = k_0 + \epsilon_A \rho_A \quad (2)$$
$$k_{I\to U} = k_0 + \epsilon_A \rho_A \quad (3)$$
$$k_{U\to I} = k_0 + \epsilon_I \rho_I \quad (4)$$

where k_0 and $\epsilon_X \rho_X$ are the contributions, respectively, of nucleosome turnover (process (1)) and of recruitment (process (2)), with $\rho_X = n_X/n$ the density of X nucleosomes and ϵ_X the strength of recruitment towards state $X \in \{A, I\}$.

During replication, it is believed that nucleosomes of the mother chromatid are randomly distributed among the two sister chromatids and that new unmarked nucleosomes are inserted at empty places [33, 34] (Fig.1b). This means that periodically, every T with T the length of the cell cycle, the state of the system (defined by n_A and n_I) is sampled from a binomial distribution[20]:

$$P(n_A, n_I) = \left(\frac{n_A^-!}{n_A!(n_A^- - n_A)!2^{n_A^-}} \right) \left(\frac{n_I^-!}{n_I!(n_I^- - n_I)!2^{n_I^-}} \right) \tag{5}$$

with $P(n_A, n_I)$ the probability to have state (n_A, n_I) just after the replication if there are (n_A^-, n_I^-) just before.

B. Transcriptional level

Gene transcription needs the DNA to be accessible to the transcriptional machinery including RNA polymerase and other transcription factors. While the coupling between local epigenetic state and transcriptional activity is now well established [3, 4] and recent experiments have started to quantify the relation between histone modifications and gene expression [11, 35], the mechanistic description of such coupling is still unclear and remains to be quantitatively investigated. An interesting hypothesis is that epigenetic markers are controlling the local density of chromatin allowing the formation of more or less condensed domains (the so-called topologically-associated domains). Heterochromatic - silenced - domains are more dense and transcription factors cannot penetrate and diffuse in these domains [36]. The formation of such dense - impenetrable - domains is cooperative and requires a critical number of inactive epigenetic marks [8].

Therefore, assuming that the inactive marks penalize gene activity by inducing chromatin compaction [4] and/or by recruiting RNA degradation pathways [37], we consider that the transcription rate α of the underlying genomic locus depends on the variable $m = (n_A - n_I)/n$, that we will subsequently name "magnetization" in reference to the analogy between our epigenetic model and a Ising-like model [31]. At low magnetization, chromatin is dense and the gene cannot be transcribed, while at high magnetization it is fully accessible. In between, we model the transcription rate by a cooperative switch that occurs at a given critical magnetization $\bar{m}$ (Fig.5a):

$$\alpha = \alpha_0 \left(\frac{\tanh[(m - \bar{m})/d] - \tanh[(-1 - \bar{m})/d]}{\tanh[(1 - \bar{m})/d] - \tanh[(-1 - \bar{m})/d]} \right) \tag{6}$$

where α_0 is the maximal transcription rate when all marks are active and d defines the sharpness of the switch.

C. Simulations

Investigation of the model was performed using exact stochastic simulations with the Gillespie algorithm [38]: between two replications the system is evolving accordingly to reactions 1-4 and at replication, the number of nucleosomes are redistributed following Eq.5. We let the system reaching a periodic steady-state ($P(n_A, n_I; t + T) = P(n_A, n_I; t)$) before taking any measurements.

In the next, we will present our results for a typical transcriptional unit ($n = 100$) and in terms of the magnetization m. Previously, we and others have already studied the effect of asymmetry in the recruitment strength between active and inactive marks [20, 26, 31]. Therefore to focus only on the effect of replication on epigenetic regulation, we will consider a symmetric regime with $\epsilon_A = \epsilon_I \equiv \epsilon$. We also fix $\alpha_0/k_0 = 10$.

III. RESULTS

A. Phase diagram

In the limit of very long cell cycles ($T \to \infty$), we know from our previous work that the system experiences a phase transition at a critical point given by $\epsilon_c \approx 3k_0$ [31]. This ferromagnetic/paramagnetic-like bifurcation delimits a boundary between: (i) a region of monostability where the probability distribution of m is centered around $m = 0$ (for $\epsilon < \epsilon_c$), ie where the epigenetic state of the DNA region is random and not clearly defined, and (ii) a region of bistability where the distribution is bimodal around two symmetric non-zero magnetizations (for $\epsilon > \epsilon_c$), signature of coherent active and inactive epigenetic states.

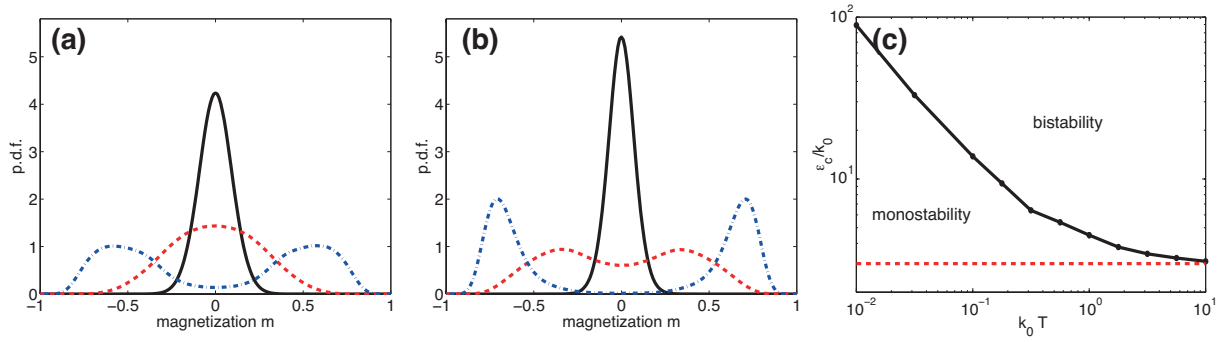

FIG. 2: (a,b) Probability distribution function (p.d.f.) of the magnetization m for a population of asynchronous cells for different values of recruitment ϵ and cell cycle length T. (a) $k_0T = 1$ and $\epsilon/k_0 = 1$ (full line), 4 (dashed line) and 6 (dotted and dashed line). (b) $\epsilon/k_0 = 5$ and $k_0T = 0.1$ (full line), 1 (dashed line) and 20 (dotted and dashed line). (c) Phase diagram. Critical point ϵ_c as a function of T, separating the bistable region (right hand) to the monostable region (left hand). The dashed line corresponds to the long cell cycle limit $\epsilon_c/k_0 \approx 3$.

For finite cell cycle, we observe the same type of bifurcation between the two regimes. As the recruitment strength increases, the average distribution of magnetization switches from a zero-magnetization centered distribution to a symmetric bistable distribution (Fig.2a). Identically, for a given recruitment strength, shorter cell cycles enhances the randomization of epigenetic state by information dilution of epigenetic marks. This leads to breaking of the "ferromagnetic" order for fast cycling cells (Fig.2b).

Figure 2c shows the demarcation between the mono- and bistability regions. For high T, the critical recruitment remains close to the long cell cycle limit ($\epsilon_c \approx 3k_0$). For small T, $\epsilon_c \propto 1/T$, ie bifurcation occurs when the typical time-scale $1/\epsilon$ of the ordering process (recruitment) is of the order of the time scale of the major source of randomness (the cell cycle).

B. Dynamics along the cell cycle

As the system is periodically perturbed by the replication, the distribution of epigenetic states is dynamically evolving along the cell cycle (Fig.3a,b). While for small T, the system is constantly out-of-equilibrium (a), for large T, the system converges to steady-state within the cell cycle (b), the post-replication distribution ($t = 0$) being given by the convolution of Eq.5 with the pre-replication distribution ($t = T$). In presence of bistability, we observe a fast convergence to the steady-state distribution (Fig.3c) that depends on the strength of recruitment: the convergence rate being an increasing function of ϵ (inset). Interestingly, we remark that as the peaks of the distribution converge to their steady-state values, the height of the peaks reaches a minimum value around $k_0 t_s \sim 1$. Indeed, cells with a higher magnetization at $t = 0$ will tend more quickly to steady-state that those with weak magnetization. This spreading of convergence speeds leads to a maximum of variance for the pools of active and inactive cells before each pool had reached the steady-state.

C. Epigenetic memory

To quantify the stability of epigenetic state, we study the mean first passage time (MFPT) to switch from an inactive to an active state. Previously [31], we showed that MFPT scales exponentially with the recruitment strength ϵ and the length of the cooperative unit n. Here we focus on the effect of cell cycle length T. MFPT is an increasing function of T that scales almost linearly for small values of T while converging to the long cell cycle limit for large T (Fig. 4). Indeed, switching is much more likely to occur just after the replication (inset) since magnetization is transiently diluted and in average divided by 2. Increasing the frequency of dilution leads to higher opportunities to switch and automatically to decrease the MFPT. For very large T this effect is reduced since the system has the time to equilibrate before the next replication. Interestingly, in these situations, we observe that the switch occurs preferentially at a given time along the cell cycle, just after the replication ($k_0 t_s \sim 1$). This time corresponds to the position when the height of the distribution of epigenetic states is minimal (Fig.3b), ie when the "energy barrier" between the inactive state and the transition state ($m = 0$) is the lowest.

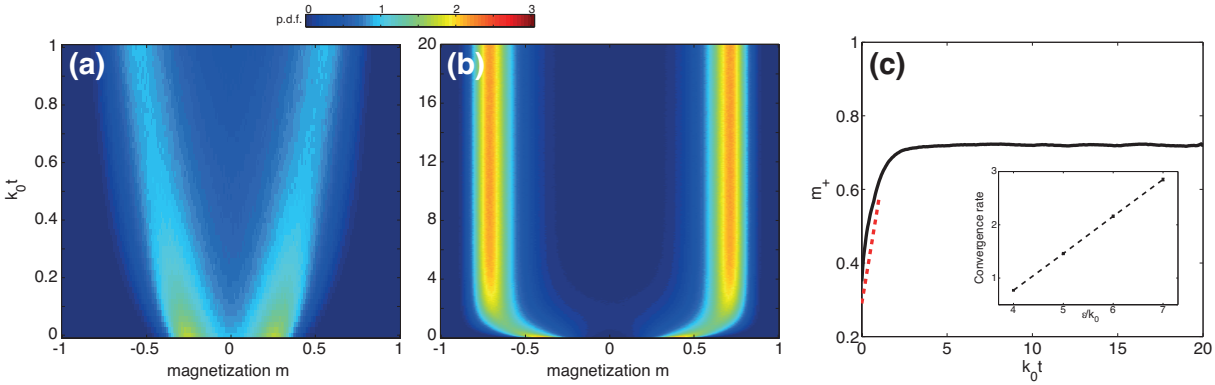

FIG. 3: (a,b) Probability distribution function (p.d.f.) of the magnetization m for a population of synchronized cells as a function of the time t along the cell cycle for $k_0T = 1$ (a) or 20 (b) and $\epsilon/k_0 = 5$. (c) Time-evolution of the positive position m_+ of the p.d.f. maximum value. Same parameters as in (a) (dashed line) and in (b) (full line). (Inset) Convergence rate β of m_+ (in k_0 units) as a function of ϵ/k_0 for $k_0T = 20$ obtained by fitting the full line in (c) by $m_0[2 - \exp(-\beta t)]$.

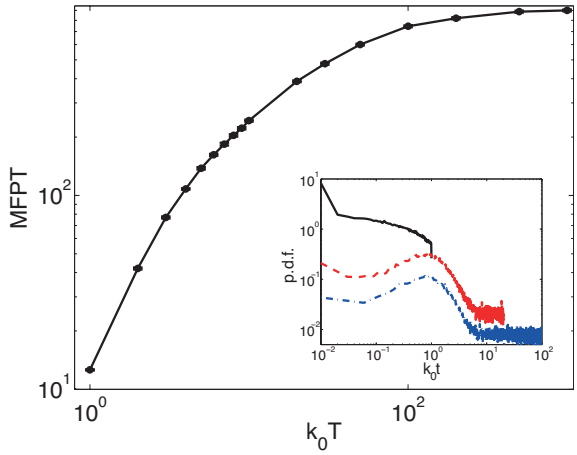

FIG. 4: Mean first passage time (in k_0^{-1} units) to switch from an inactive state ($m = -1$) to an active state ($m > 0$), as a function of T for $\epsilon/k_0 = 5$. (Inset) Probability distribution function of the first time t along the cell cycle when the switch occurs ($0 \leq t \leq T$) for $T = 1$ (full line), 20 (dashed line) and 100 (dotted and dashed line).

D. Impact of epigenetics on gene transcription and bursting

In this section, we focus on situations where epigenetic regulation is operative, ie in presence of bistability. In presence of a coherent epigenetic state (in the bistable region of parameters, Fig.2c), we expect the switch-like nature of the epigenetic control of transcription (Eq.6; Fig.5a) to lead to a coherent transcriptional state depending on the underlying magnetization. Along each cell cycle, we compute the number of transcription events n_e and compare it to the corresponding average magnetization in the same cell cycle ($(1/T)\int dt\, m(t)$). Figure 5b-1 shows indeed that, for a symmetric switch ($\bar{m} = 0$, Fig.5a-1), the distribution of transcription activity is bistable and strongly correlated to the epigenetic state. In the active state, n_e is distributed according to a Poisson law with an average $\alpha_0 T$ and transcription occurs uniformly along the cell cycle (dotted and dashed line in Fig.5e-1). In the inactive state, n_e is essentially zero with very rare transcription events (Fig.5d-1). As expected, when transcription occurs, it mainly happens just after the replication when the magnetization is likely to be higher (full line in Fig.5e-1). Increasing the noise of the epigenetic state by decreasing ϵ or T leads to more transcription events in the inactive state (Fig.5c-1) that are more equally distributed along the cell cycle (dashed line in Fig.5e-1). Indeed, increased fluctuations of the magnetization in 'inactive' cells would lead to an increased probability to have a weak negative magnetization where α starts to be significant enough to fire transcription.

If the critical magnetization needed to silence the gene is lower ($\bar{m} < 0$, Fig.5a-2), we observe that the majority of the cell cycles now present a burst containing few transcription events (Fig.5b-2,c-2). These events are mainly located in a small time window after the replication (Fig.5d-2, e-2) when the magnetization is at the level of $\bar{m}$ before

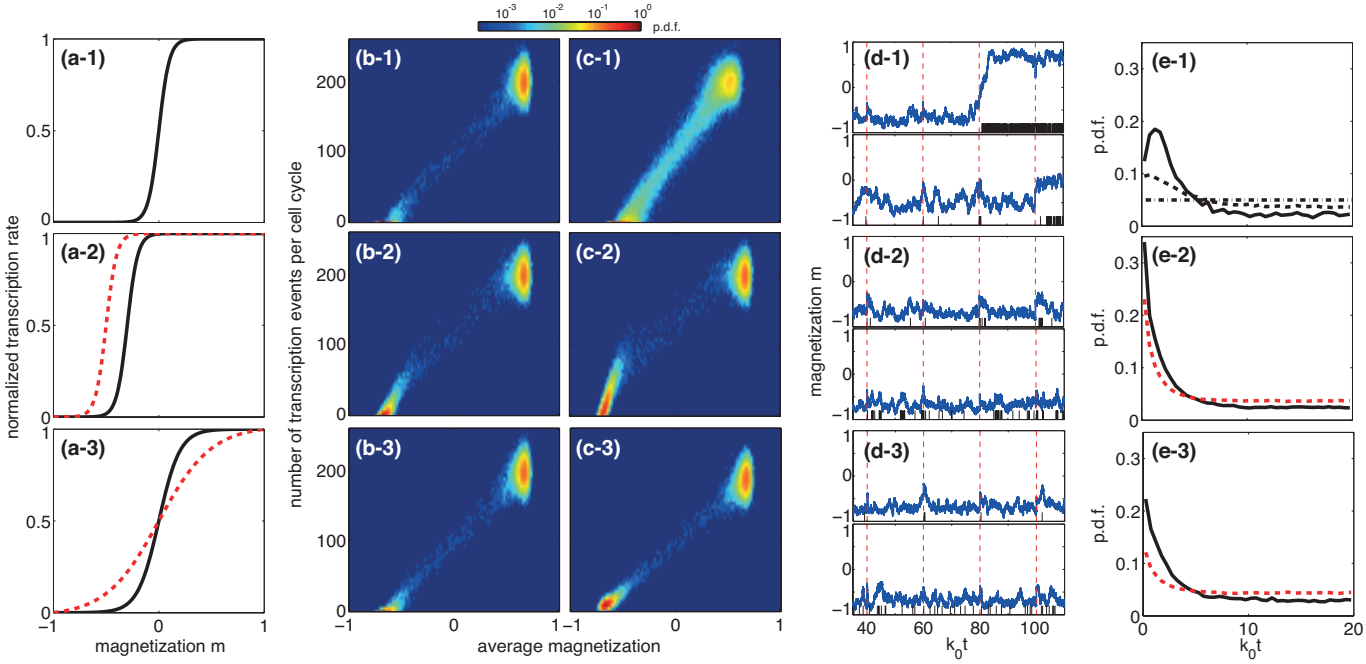

FIG. 5: (a) Normalized transcription rate α/α_0 (Eq.6) as a function of the magnetization m for $(\bar{m}, d) = (0, 0.1)$ (full line in a-1), $(\bar{m}, d) = (-0.3, 0.1)$ (full line in a-2), $(\bar{m}, d) = (-0.5, 0.1)$ (dashed line in a-2), $(\bar{m}, d) = (0, 0.2)$ (full line in a-3) and $(\bar{m}, d) = (0, 0.5)$ (dashed line in a-3). (b,c) Joint probability distribution function of the number of transcription events per cell cycle and of the average magnetization along the corresponding cell cycle, for $k_0T = 20$. (b-1): $(\epsilon/k_0, \bar{m}, d) = (5, 0, 0.1)$; (c-1): $(\epsilon/k_0, \bar{m}, d) = (4, 0, 0.1)$. (b-2): $(\epsilon/k_0, \bar{m}, d) = (5, -0.3, 0.1)$, (c-2): $(\epsilon/k_0, \bar{m}, d) = (5, -0.5, 0.1)$. (b-3): $(\epsilon/k_0, \bar{m}, d) = (5, 0, 0.2)$, (c-3): $(\epsilon/k_0, \bar{m}, d) = (5, 0, 0.5)$. (d) Examples of stochastic trajectories of magnetization (full lines) along several cell cycles. Same parameters as in (b-1) for (d-1, top), in (c-1) for (d-1, bottom), in (b-2) for (d-2, top), in (c-2) for (d-2, bottom), in (b-3) for (d-3, top) and in (c-3) for (d-3, bottom). Dashed lines represent replication events and small vertical stems at the bottom are transcription events. (e) Probability distribution function of the time along the cell cycle when a transcription event occured when the current magnetization is negative. Same parameters as in (b-1) for (e-1, full line), in (c-1) for (e-1, dashed line), in (b-2) for (e-2, full line), in (c-2) for (e-2, dashed line), in (b-3) for (e-3, full line) and in (c-3) for (e-3, dashed line). The dotted and dashed line in (e-1) represents the corresponding p.d.f. when the current magnetization is positive.

relaxing to the more negative steady-state magnetization where $\alpha \sim 0$. The burst size depends on the value of $\bar{m}$, more negative value leading to larger bursts.

This effect of bursting after replication also appears when we decrease the cooperativity in the transcriptional switch by augmenting d (full line in Fig.5a-3). For essentially the same reasons than for negative values of $\bar{m}$, in the inactive epigenetic state, bursts of transcription events are likely to be observed just after replication (Fig.5b-3,d-3 (top),e-3 (full line)). When the inactive epigenetic state is even more permissive to transcription (dashed line in Fig.5a-3), the transcription frequency is enhanced in the inactive state (Fig.5c-3) and the events are more equally distributed along the cell cycle (dashed line in Fig.5e-3).

IV. DISCUSSION

Figures 2 and 4 suggest that controlling the cell cycle length might represent a powerful global regulatory mechanism of epigenetic stability and sensitivity. For example, in fruit fly (*D. melanogaster*), the nucleosome turnover rate k_0 was estimated to be of order 1h^{-1} [39]. In embryogenesis, $T \sim 10$ minutes ($k_0T \approx 1/6$) [40]. This means that in early development, very strong recruitment ($\epsilon > 10\text{h}^{-1}$) is needed to maintain a coherent epigenetic state, and it is likely that lots of genes are below this threshold, ie close to criticality, and therefore might be highly sensitive to developmental or environmental cues that would drive differentiation and epigenetic identity [31]. For differentiated cells, cell cycles are much longer ($k_0T \approx 20$ [40]). Hence, maintenance of robust epigenetic state is possible for more physiological recruitment strength ($\epsilon > 3k_0$). Figure 3b and the inset of Fig.4 also suggest that along the cell cycle there is a preferential time-period just after the replication when the epigenetic state is more sensitive to perturbations. Misregulation of this transient time-window of increased sensitivity might lead to epigenetic instability and diseases

[41–43].

When introducing a simple model for the impact of epigenetics on transcription rate where a critical density of inactive marks is needed to prevent transcription, we remark that epigenetic regulation alone might already be strong enough to silence efficiently a gene over a long time period (Fig.5). Indeed, in the bistability region, far from the critical point, the propensity to switch is rare (Fig.4). A misregulation of the recruitment strength (Fig.5c-1), of this critical density (Fig.5b-2) or of the transcriptional cooperativity (Fig.5b-3) might lead to spurious transcription events, especially after replication, that might be deleterious for the cell. However, there are biological situations where such, a priori, unwanted events are part of the epigenetic maintenance. For example, the maintenance of a heterochromatin region at the pericentromers of fission yeast (*S. pombe*) involves the transient transcription of non-coding genes just after replication [44, 45]. The corresponding transcripts are then chopped into small non-coding RNAs that subsequently recruit modifying enzymes that will deposit inactive marks on pericentromers and therefore silence the underlying genes. Similar mechanisms of "silencing by transcribing" via RNA interference (RNAi) have been now identified in various organisms and systems, in particular in the control of transposable elements [37]. Considering that the replication-induced transient derepression of the gene activity might be a strong opportunity for such parasitic DNA to mobilize and proliferate, host genomes might have indeed developed, during evolution, defense strategy, like RNAi pathways, that takes benefit of these spurious - but unavoidable - transcription events [46].

Experimental testing of our predictions would be a crucial step to validate our model. In particular, recent experiments on the locus *MAT* in yeast *S. cerevisiae* have shown the dynamical epigenetic regulation of gene expression and the transient transcription of heterochromatic loci [12, 16]. Combining such techniques with live single cell mRNA microscopy [47] and precise measurement of the local epigenetic state [48] might represent a challenging but feasible task to study more deeply the mechanisms behind the dynamics (cell-cycle and transgenerational) of epigenetic state and its coupling with gene activity. By properly designed reporter gene constructs inserted at various genomic loci (heterochromatin vs euchromatin), we expect our working hypothesis (long-range recruitment, distribution of maternal marks at replication, switch-like nature of the epigenetic control of transcription (Eq.6)) and our predictions to be experimentally tested leading to model improvements and new insights into the epigenetic regulation.

V. CONCLUSION

In this study, we have tested the influence of replication on the epigenetic stability and gene transcription. Our results support the idea that replication represents a major perturbation of the epigenetic landscape and that maintenance mechanisms should be strong enough to avoid loss of information. We showed that this perturbation might have a strong effect at the transcriptional level by allowing transient transcription of inactive regions just after replication.

To derive our conclusions, we have used a simple but generic stochastic model of epigenetic regulation that can be upgrade to describe specific - in vivo - situations. In particular, in our model, the cell cycle is composed by a unique homogeneous phase between the two successive rounds of replication. The true biological situation is of course more complex: after the G1 phase, replication occurs during an extended period called the S-phase; only once full genome duplication has been completed, mother cells enter into G2 and M phases to end up with two daughter cells in the G1 phase. The reassembly and maintenance of the disrupted chromatin states is actually a multi-step process taking place throughout the cell cycle with molecular mechanisms that are likely to be locus and time specific [5, 34]. For example, peaks of expression of some chromatin enzymes just before the onset of the S-phase might result in effectively enhancing the recruitment mechanism over specific time-windows and hence in reinforcing the associated chromatin state [34].

Along the same line, titration effects that are induced by a limiting amount of active/repressive marks or of their associated chromatin enzymes [26] may introduce a coupling between epigenetic inheritance and replication timing: in this "timing" model, due to a competition in the reassembly process between loci that share the same chromatin state, earlier replicated loci tend to have a greater chance to be inherited [34, 49]. Moreover, the fact that active marks tend also to promote their early replication [50, 51] might lead to a positive feedback loop between epigenetic inheritance and replication timing. A challenging perspective will be to test this elegant but still speculative timing model by stimulating further experiments and developing an extended epigenetic model.

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