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Slow Chromatin Dynamics Allow Polycomb Target Genes to Filter Fluctuations in Transcription Factor Activity

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[1]John Innes Centre, Norwich Research Park, Norwich NR4 7UH, UK
[2]Present address: Institute of Molecular Life Sciences, University of Zurich, 8057 Zurich, Switzerland
[3]Lead Contact
*Correspondence: martin.howard@jic.ac.uk
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SUMMARY

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INTRODUCTION

Models of chromatin-based epigeneticndONthuTJTh

RESULTS

Previous mathematical models of epigenetic memory based on

Box 1. Fitting Quantitative Experimental Data Indicates that Sub-saturating H3K27me2/me3 Is Sufficient for Full Gene Repression

Nascent chromatin capture together with time-resolved stable isotope labeling by amino acids in cell culture (SILAC) was recently used to experimentally measure the dynamics of histone modification accumulation after DNA replication (Alabert et al., 2015). These data demonstrate that H3K27me3 accumulates very slowly on newly incorporated histones in dividing human somatic cells. In fact, within one cell cycle, H3K27me3 levels on newly incorporated histones do not reach the pre-replication level on parentally inherited histones. In contrast, previous mathematical models of histone-modification-based epigenetic memory have employed histone modification rates significantly faster than this, with each histone tail typically undergoing many modification reactions per cell cycle (Angel et al., 2011; Dodd et al., 2007; Sneppen and Dodd, 2012). Here we use these quantitative experimental data to constrain our model, in particular the methylation rate k_{me}. Throughout this box, we set the histone exchange rate as $p_{ex} = 10^{-3}$ histone^{-1} transcription^{-1}

In this case, transcriptional output shows dependence on the initial chromatin state over an even greater range of α, and the difference in transcriptional output between the two initial states occurs at higher α values (Figure 2C). This indicates that chromatin can instruct gene expression over a wider range of transcriptional activation levels (i.e., a wider cis memory window). Furthermore, mean first passage times are greater within the cis memory window for

The model therefore suggests a rationale for why experimental H3K27me3 accumulation is slow: genes that change H3K27me3 levels slowly in response to varying trans-factor inputs offer more stable memory storage than genes with faster chromatin dynamics because neither prolonged absences nor pulses of transcriptional regulators are sufficient to change chromatin states. Interestingly, a previous study of mammalian heterochromatin also used modeling to suggest that fluctuations of chromatin

- METHOD DETAILS
  - Computational Methods and Simulation Details
  - Two-State Model
  - Processivity in Methylation or Demethylation
  - Transcriptional Bursting
  - Additional Details of the Main Model
  - Fitting Triple-SILAC Mass Spectrometry Data
  - Stochastic Model of a Noisy Transcriptional Regulator

SUPPLEMENTAL INFORMATION

Supplemental Information includes eight figures and five tables and can be found with this article online at http://dx.doi.org/10.1016/j.cels.2017.02.013.

AUTHOR CONTRIBUTIONS

S.B. and M.H. conceived the study and constructed the model. S.B. performed simulations and analyzed results. S.B., C.D., and M.H. wrote the manuscript.

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STAR★METHODS

KEY RESOURCES TABLE

CONTACT FOR REAGENT AND RESOURCE SHARING

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Martin Howard (

Each histone i undergoes noisy removal of methyl groups (one methyl group at a time) with propensity,

$$r_i^{dem} = \gamma_{dem}\left(\delta_{S_i,me1} + \delta_{S_i,me2} + \delta_{S_i,me3}\right). \quad \text{(Equation S4)}$$

Demethylation is also coupled directly to transcription, which itself has propensity given by Equation 3. Each transcription event can result in removal of methyl groups (one methyl group at a time) at each histone (with probability p_{dem} per histone) and also replacement of each nucleosome (mex/mex→ me0/me0, with probability p_{ex} per histone). Since p_{ex} is a probability per histone and histone exchange actually results in replacement of a pair of H3 histones, the average rate of loss of histones through exchange is $\approx 2fp_{ex}$.

To replicate DNA, the Gillespie algorithm simulation was interrupted if the projected time for the next reaction exceeded the time at which DNA would have been replicated. In this case, system time was updated to the forecast time of DNA replication. After replication of DNA, reaction propensities were then re-calculated and the Gillespie algorithm was repeated for another cell cycle. A similar approach was previously used to incorporate reactions with delays in Gillespie algorithm simulations (Bratsun et al., 2005).

Quantities Calculated from Simulations

Time-Averaging. For an individual simulation time-course comprising K reactions, the Gillespie algorithm determines the state of the system at K simulation time-points t_i

First Passage Times. Mean first passage times, $t_{FP(me0)}$ and $t_{FP(me3)}$

model was due to a lack of nonlinearity in the reactions converting between H3K27me0 and H3K27me3. It is therefore interesting to consider the ability of the full model to maintain both the active and repressed expression states when either methylation or demethylation (but not both) occur processively (Figure S2).

Processive Methylation

To investigate if bistability in our full model is dependent on non-processivity of the methyltransferase, we modified the model structure so that PRC2 catalyses the conversions me0 → me3, me1 → me3 and me2 → me3 instead of adding methyl groups one at a time (Figure S2B). All reaction propensity calculations remain unchanged. The model retains the relative catalytic activity of PRC2 on

With $f_{min} = 10^{-4}\ s^{-1}$ (Figure 1D), we therefore obtain,

$$f_0 ==$$

Additional Details of the Main Model

In the main text, we presented an overview and brief justification for features included in the model. For the sake of brevity, some

the model, we therefore chose to couple histone exchange to transcription. That is, each passage of Pol II in the model has the capacity to remove an H3/H4 tetramer. Actual histone exchange rates in the model depend on both the probability of histone exchange per transcription event, and the transcription initiation rate, f. Because histone exchange is directly coupled to transcription, the maximum fold-change in the transcription initiation rate, $F = f_{max}/f_{min}$ provides an upper bound on the fold-change in histone residence times between the active and repressed states. To break this linear coupling would require a more complicated function relating transcription and histone exchange. Without additional information about how histone exchange changes as a function of

Stochastic Model of a Noisy Transcriptional Regulator

The following model was used in (Ozbudak et al., 2002) to investigate how rates of transcription and translation affect variability in protein abundance over time. In the present work it is used as an arbitrary 'noisy' input function representing the expression of a trans-regulator:

$$DNA \xrightarrow{S_R}$$