

# **Bistability and state switching in computational dynamic histone modification models**

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## Declaration

I hereby declare and confirm that this thesis is entirely the result of my own original work. Where other sources of information have been used, they have been indicated as such and properly acknowledged. I further declare that this or similar work has not been submitted for credit elsewhere.

Leipzig, February 28, 2021

Michel Krecké

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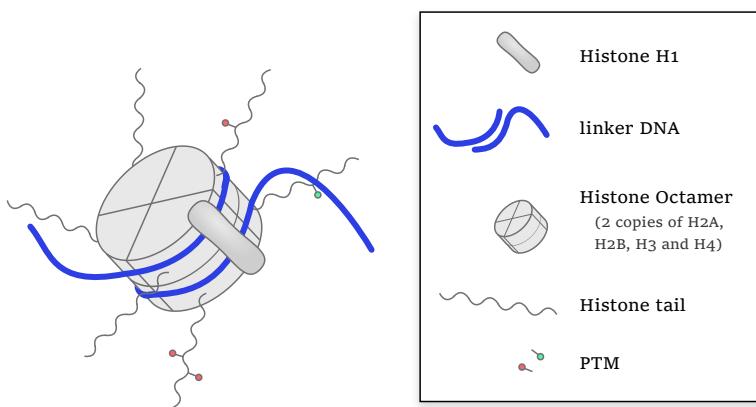
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# 1. Theoretical Background

## 1.1 Eukaryotic transcription regulation

### 1.1.1 Chromatin

Eukaryotic DNA is organized as chromatin in the cell nucleus, which consists of nucleosomes that mainly serve the increase of packing density and robustness of the DNA, but also play an important role in gene regulation. Nucleosomes are built out of DNA wrapped around an octamer of homologous, basic proteins, the histones. These proteins contain a great amount of the positively charged amino acids arginine (Arg, R) and lysine (Lys, K), which results in attracting the negatively charged DNA (phosphate backbone). The so-called histone tails on the amino end of the proteins stick out of the nucleosome core complex. Albeit not having a fixed secondary structure, the tails, as well as the rest of the histones are very well conserved throughout a large set of eukaryotes, from *Saccharomyces cerevisiae* all the way to *Homo Sapiens Sapiens* [2].



**Figure 1.1:** Schematic model of a nucleosome.

Chromatin can show higher order structure than the simple “beads on a string” variant. As such, nucleosomes that are not necessarily next neighbours along the DNA string can be in near proximity [2].

- The following higher order structures have been found by...

Chromatin structure plays an important role in eukaryotic gene expression. Some DNA segments close to and on an actively transcribed gene are more easily accessible by proteins due to a locally more open chromatin structure. These chromatin regions are

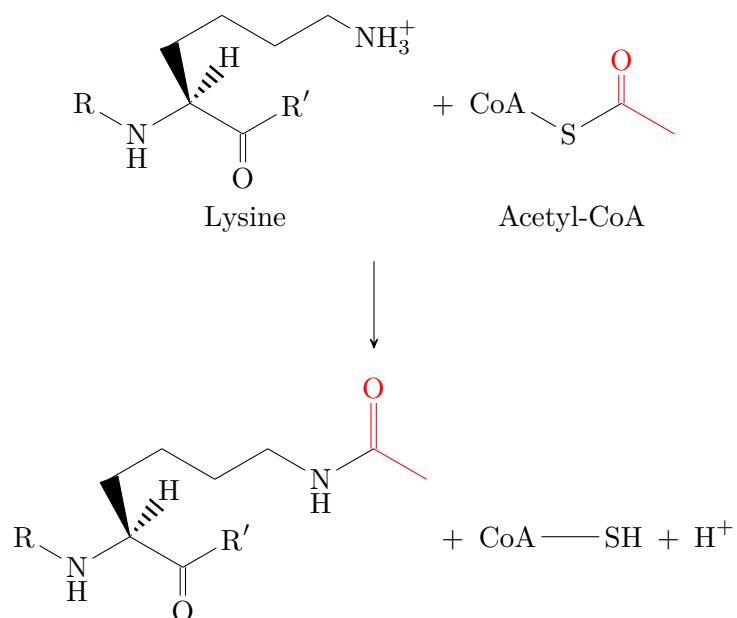
therefore called hypersensitive sites. [3] Logically, the location of hypersensitive sites depends on the set of active genes and is thus cell-type and age specific [2].

The complex process of chromatin remodelling which leads to activation or repression of gene transcription comprises a vast multitude of agents and their interaction network is still not fully understood.

### 1.1.2 Histone-modifying enzymes

This thesis is based on one aspect of the chromatin remodelling machinery, namely histone-modifying enzyme complexes (HME). These complexes are able to covalently bind or remove chemical groups on amino acids (mostly R and K) at very specific positions on the histone tail. These post-translational modifications (PTMs) are named according to the amino acid they have been bound to. H3K27ac, for instance, denotes an acetylation (ac) on lysine 27 (K27) of histone 3 (H3).

The presence of these chemical groups changes the charge or polarity of the modified amino acids and thus influence the histone's affinity to the DNA. Histone-acetyltransferases (HATs), for instance, add an acetyl group to lysine, thus neutralizing the positive charge on the ammonium cation at neutral pH (see figure 1.2). This neutralization decreases the attraction to the negatively charged DNA backbone significantly resulting in the occurrence of a hypersensitive site. [2]



**Figure 1.2:** Acetylation of lysine. This reaction is catalysed by the HAT enzyme which by means of the cofactor acetyl coenzyme A (Acetyl-CoA) is able to trigger the transfer (substitution reaction in chemical terms) of an acetyl group onto the nitrogen atom in the side chain of lysine. The latter can be part of a histone tail.

Apart from the acetyl group, a multitude of other markers have been found on histone tails, e.g. methylation (one-, two and three-fold), phosphorylation, ubiquitylation and so forth [1]. These groups can entail gene transcription activation, silencing (repressing), or completely different purposes [source].

This thesis will only feature acetylation as an activating modification and methylation as a silencing modification. Accordingly, the “state” of a nucleosome is defined as one of the following:

- **unmodified:** There has been no PTM on any histone tail of the concerning nucleosome.
- **active:** Every PTM found on the concerning nucleosome enables gene activation. In this thesis, every one of these PTMs is an acetylation.
- **silent:** Every PTM found on the concerning nucleosome disables gene activation. In this thesis, every one of these PTMs is a methylation.
- **bivalent:** see 1.1.3

### 1.1.3 Bivalency

In pluripotent stem cells, nucleosomes have been found to contain both activating and silencing markers on histone tails of one and the same octamer. This bivalent state is believed to maintain a “poised state”, being ready to induce a gene expression cascade as soon as the silencing marker is removed [source]. Others believe, that this bivalent state is connected to cell division and the ability of inheriting the active gene set for one daughter cell to induce differentiation while the other daughter cell remains a pluripotent stem cell [14].

## 1.2 Dynamic histone PTM models

### 1.2.1 Chemical master equation

The chemical master equation (CME) is the differential equation underlying the system that describes the time-dependent evolution of that system from a reactive point of view. Applied to the case at hand, we can establish the CME system made out of two equations for either the concentration of active (acetylated) and silent (methylated) nucleosome states.

In order to do this, one can establish the state occurrence dependent differential equation [11] for each HME type, as was already done by Mayer in [12].

Eqns. 1.1 describe the non-cooperative (see 1.3.2) case for  $a = \frac{A}{N}$  and  $m = \frac{M}{N}$  with  $A$  the number of acetylated nucleosomes,  $M$  the number of acetylated nucleosomes and  $N$  the total number of nucleosomes.  $\alpha_i$  and  $\beta_i$  are coefficients taking into account the

types, association and dissociation ratios of the enzymes in the system.

$$\frac{\partial a}{\partial t} = \underbrace{-\alpha_1 a}_{\text{ac removal}} + \underbrace{\alpha_2 a * (1 - a - m)}_{\text{ac addition}} \quad (1.1\text{a})$$

$$\frac{\partial m}{\partial t} = \underbrace{-\beta_1 m}_{\text{me removal}} + \underbrace{\beta_2 m * (1 - a - m)}_{\text{me addition}} \quad (1.1\text{b})$$

Obviously, this would only be a usable model if the neighbour relations of the nucleosomes can be neglected. Given that the context from the enzyme rule sets is an important aspect of *EpiDynast* (see 1.2.3), an analytical solution of the CME would not be the best approximation. Also, as *EpiDynast*'s model strongly depends on discrete numbers such as the number of nucleosomes in the string, the analytical solution of the CME as a continuous system, makes it even more unfitting as an approximation.

A more fitting system would be to establish and solve the CME for every nucleosome while the CME for nucleosome  $i$  would depend on the number of neighbours equal to the biggest enzyme context in the system. So, if the rule set contains at least one rule including the next neighbours of the modified nucleosome  $i$ , the CME system would change to eqns. 1.2.

$$\frac{\partial a_i}{\partial t} = -\alpha_1(a_{i-1} + a_i + a_{i+1}) + \alpha_2(a_{i-1} + a_i + a_{i+1}) * (1 - a - m) \quad (1.2\text{a})$$

$$\frac{\partial m_i}{\partial t} = -\beta_1(m_{i-1} + m_i + m_{i+1}) + \beta_2(m_{i-1} + m_i + m_{i+1}) * (1 - a - m) \quad (1.2\text{b})$$

This differential equation system quickly increases in complexity and dimensionality with increasing number of nucleosomes in the system and higher reach of the enzyme models up to a point where an analytical solution is impossible to achieve. Mainly for this reason, it is convenient to numerically simulate the time-dependent evolution of the system.

### 1.2.2 Gillespie's algorithm

Gillespie's algorithm simulates the evolution in time of a spatially homogenous molecular mixture under specification of the coupled reaction channels (i.e. association and enzymatic reaction with dissociation) based on stochastic chemical kinetics [8, 9]. This is useful especially when solving the chemical master equation analytically is not ideal (see 1.2.1).

- next-neighbours
- rule-based, (paper from Arnold, Prohaska is basis for Nico's work, also basis for my work)
- Gillespie's
  - explain event based

– steps from his paper

- association and concentration are taken together.
- enzyme types

### 1.2.3 EpiDynast

The software used in this thesis is *EpiDynast*, developed by Herbig et al. The main working mechanism may be outlined as follows: After defining enzyme rule sets and a starting nucleosome string (defined as an array of nucleosomes reduced to their PTMs), *EpiDynast* simulates the stochastic time-dependent change of said modifications on the string, exactly one event at a time. The two events that can occur for each enzyme are either an association step or a reaction step that immediately entails dissociation of the enzyme from the nucleosome.

The enzyme rule sets simply describe a pattern (further on called “context”) on the string, that is then changed according to the rule. For instance, a linear acetylation extender enzyme would look for a pattern with two neighbouring nucleosomes, one acetylated and the other one unmodified, and acetylate the latter.

- explain the above with a picture or put a reference

## 1.3 Epigenetic fitness landscapes

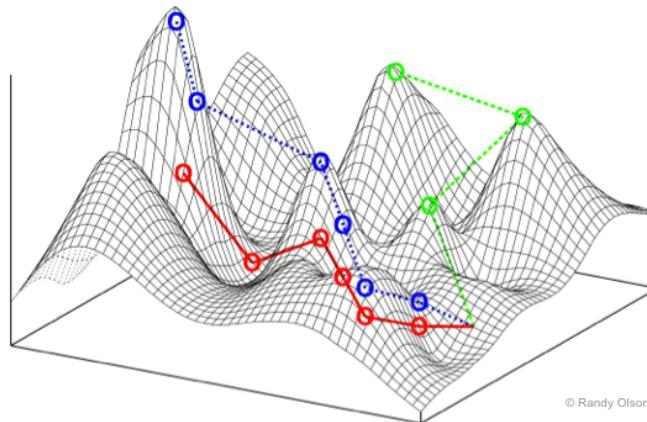
### 1.3.1 From landscape to vector field

The term of fitness landscape (referred to as landscape for the rest of this work) is mathematically defined as the triple  $(V, \chi, f)$  where  $V$  is a set of configurations,  $\chi$  refers to the neighbouring relationship or similarity among the configurations and  $f$  defines the fitness function of the landscape [source].

In this case, the epigenetic fitness landscape  $V$  comprises the entirety of active, silent and unmodified state distributions along the nucleosome string,  $\chi$  determines the modification of one nucleosome state, e.g. from silent to unmodified or vice versa and  $f$ , which indicates the relative height or depth  $f(v)$  of a specific configuration  $v \in V$ , is determined by all the association and dissociation rates, as well as the type of the enzymes in the system. In this specific landscape, the stochastic Gillespie’s algorithm will always tend towards configurations (fix points) at the very base of landscape basins. These configurations are those, that are adopted in the majority of time steps throughout Gillespie’s algorithm simulation.

Depending on the landscape, i.e. if there are deep and steep basins, it gets more and more difficult for the stochastic algorithm to exit the basin and adopt a configuration that lies outside. Each histone modifying enzyme thus induces a stability trend among the configurations which results in a vector field specific to each type of enzyme. In more complex systems with a multitude of different enzymes, these vector fields are combined and create the resulting landscape at hand containing one or more fix points.

In this thesis, there won’t be any numerical values given to  $f(v)$ . However, by modifying the relative enzyme rate ratios, one can easily see that  $f$  can change drastically



**Figure 1.3:** Fitness landscape example and 2D projection.

resulting in variation of ease for the system to maintain a certain state or move along the shape of the landscape to switch from one state to another.

### 1.3.2 Enzyme types and bistability

The number of fix points in the landscape can be analytically derived from the enzymes and their dependence on the frequency of nucleosome modifications (e.g. acetylation, methylation, ...) over time (see eqns. 1.1).

Mayer found 4 critical values for these equations [12]: 3 fix points at  $(0, 0)$ ,  $(0, 1 - \frac{\beta_1}{\beta_2})$ ,  $(1 - \frac{\alpha_1}{\alpha_2}, 0)$  and a separatrix whose gradient depends on the ratio between  $\frac{\alpha_1}{\alpha_2}$  and  $\frac{\beta_1}{\beta_2}$  and which connects the two non-trivial fix points. The separatrix always has a gradient towards one of the non-trivial fix points. If  $\frac{\alpha_1}{\alpha_2} = \frac{\beta_1}{\beta_2}$ , the separatrix has no gradient (see fig.1.4).

- Handle explanation for zero gradient separatrix.

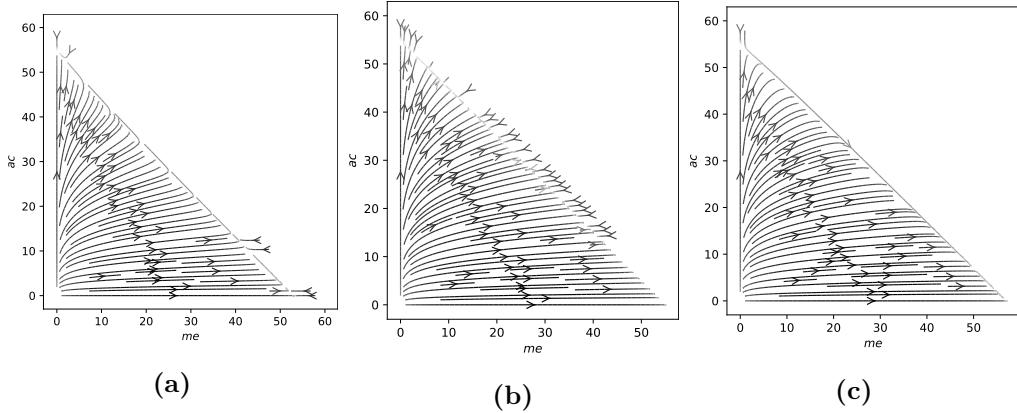
In order for a dynamic histone PTM system to be bistable, the enzymes have to show cooperativity [6, 12, 17]. According to Sneppen [16, p.48], “cooperative binding means that the probability of occupying a state increases more than linearly with the concentrations of the binding molecules”.

In [6], Dodd et al. specify the nature of cooperativity in order to reach ultrasensitivity<sup>1</sup> and thus a bistable system as follows<sup>2</sup>:

---

<sup>1</sup>From Dodd et al. [6]: “Ultrasensitivity is a nonlinearity that magnifies any numerical advantage of one nucleosome type over another, allowing positive feedback to strongly push the system away from intermediate states and towards a large majority of one or other type.”

<sup>2</sup>citations inside the quote changed their appearance in order to remain functional and to stylistically



**Figure 1.4:** Vector fields describing the noncooperative 60 nucleosome system with varying enzyme rates. These mainly define the parameters  $\alpha_n$  and  $\beta_n$  if the enzyme types are constant. The axes describe in absolute numbers the occurrence of methylation (x-axis) and acetylation (y-axis). (a) describes the case for  $\frac{\alpha_1}{\alpha_2} > \frac{\beta_1}{\beta_2}$  resulting in a separatrix with gradient towards  $(0, N(1 - \frac{\beta_1}{\beta_2}))$ . In (b), the equality  $\frac{\alpha_1}{\alpha_2} = \frac{\beta_1}{\beta_2}$  results in a zero-gradient separatrix. In (c),  $\frac{\alpha_1}{\alpha_2} < \frac{\beta_1}{\beta_2}$  results in a separatrix with gradient towards  $(N(1 - \frac{\alpha_1}{\alpha_2}), 0)$ . From [12]. Are the fix points denoted correctly?

“Cooperativity can be direct, where two modified nucleosomes act together to recruit an enzyme to modify a third nucleosome [7, 13, 15], or indirect, where each modified nucleosome catalyzes one of two separate modification reactions to fully convert a third nucleosome [5, 7]. A critical requirement for ultrasensitivity is that modified nucleosomes must act nonlocally, stimulating modification of nucleosomes located some distance away on the DNA. This long-range interaction is necessary for any nucleosome to be able to ‘sense’ the majority nucleosome type within the patch and cannot be provided by simple neighbor-to-neighbor contact [7, 13].”

In other words, cooperativity can only be achieved by allowing the enzymes to detect more than one nucleosome that, in order to reach bistability, must not be a direct neighbour of the nucleosome to be (un)modified. This allows the modification that is superiorly prevalent over the whole string at that moment to be accounted for and recognized by the enzymes.

On a sidenote, the definition of cooperativity might seem slightly counterintuitive from a biochemical point of view, where the notion of cooperativity is strongly associated to be an asset of the enzyme [4]. In contrast, according to Dodd et al., cooperativity is described as being a property of a set of nucleosomes being able to “cooperate” in order to recruit an enzyme and catalyse a reaction. Even though this is not ideally put from a biochemical point of view, the mathematical implications still remain valid.

- rephrase the biochemical side of cooperativity?

Mayer in [12] expressed the time dependent concentration of the modifications in the system in function of cooperative enzymes in the following differential equation system:

$$\frac{\partial a}{\partial t} = \underbrace{-\alpha_1 a}_{\text{ac rem}} + \underbrace{\alpha_2 \frac{1}{n} a^2 * (n - a - m)}_{\text{ac add}} \quad (1.3a)$$

$$\frac{\partial m}{\partial t} = \underbrace{-\beta_1 m}_{\text{me rem}} + \underbrace{\beta_2 \frac{1}{n} m^2 * (n - a - m)}_{\text{me add}} \quad (1.3b)$$

- Include Matilda's cooperative vector graphs
  - Mark the fix points and separatrix

## 1.4 Impact of this work

Although the mathematical foundation on whether a system can and cannot show bistability was already established, the execution in terms of building a model and rigorously identifying the influence of different factors within the model on the dynamics of a bistable system have, to my knowledge, not been explored yet.

Also, to date, bistable systems have not yet been modelled by means of a software that takes limited enzyme reach into account like *EpiDynastdoes*.

This thesis will show the potential and limitations of a model with fixed neighbour relations concerning bistability and the switching of stable states throughout the simulation. Furthermore, this work will provide proposed mechanisms of bistability occurring on a non-cyclic, as well as a cyclic nucleosome string.

## 2. Methods

### 2.1 Chromatin Model

The chromatin in *EpiDynastis* modelled as an array of half-nucleosomes (for simplicity, the the array of half-nucleosomes is referred to as nucleosome string in the rest of the work), meaning that they only contain a tetramer of H2A, H2B, H3 and H4. The nucleosomes hold their position on the string so that the neighbour relations are fixed. Furthermore, the nucleosomes are reduced to presence or absence of PTMs.

The model in this work can even be further reduced, that is to a nucleosome containing in most cases 1 ( $K_{27}$ ) single amino acid. In 3.6, every nucleosome possesses 2 modifiable amino acids, called  $K_x$  and  $K_y$ . All of these amino acids are monoacetylatable as well as monomethylatable. These two modifications are mutually-exclusive.

The nucleosome string is either modelled to be non-cyclic (as done in 3.1 and 3.2) or cyclic (3.3 to 3.6). In the cyclic case, the enzymes' context can include nucleosomes from the start as well as the end of the string simultaneously. The non-cyclic models contain 60 nucleosomes whereas the non-cyclic ones only contain 40 nucleosomes.

- limitations
- bistability impact on rule set
- what starting state?

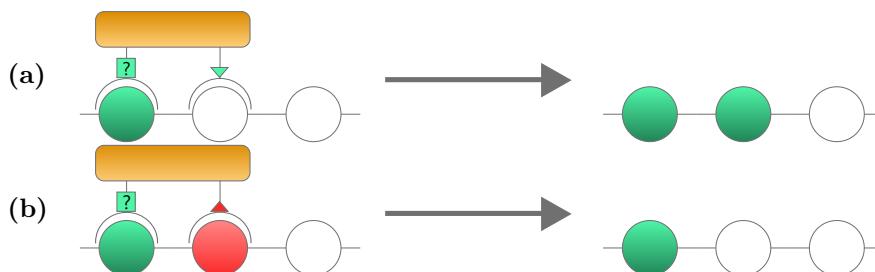
### 2.2 Enzyme models

#### 2.2.1 Enzymes in *EpiDynast*

- context
- rule definition
- only symmetric rules (concerning acetylation and methylation)
- association and reaction+dissociation rates
- side note on concentration depletion
- refer to Gillespie
- either put all the enzyme type reactions in one multifigure or put every type separately, then maybe put the mirrored reactions and/or the methylations

### 2.2.2 Enzyme types

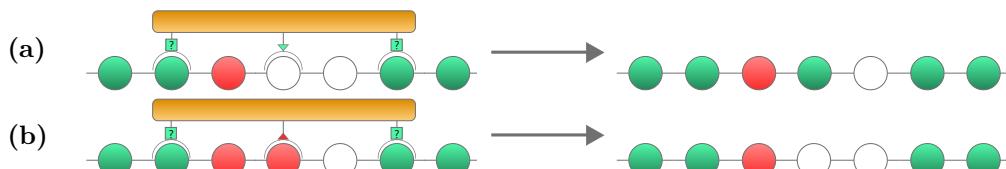
#### Linear enzymes



**Figure 2.1:** Graphical depiction of the possible linear enzyme acetylation addition (a) and removal (b) reactions. The reactions shown are also defined in the rule set to occur in the opposite direction. Linear enzyme methylators work analogically.

Linear enzymes can also be considered next-neighbour enzymes. They are used to extending sites containing a specific modification by either propagating the modification from nucleosome to neighbouring unmodified nucleosome or by deleting an opposing modification next to a nucleosome with the desired modification.

#### Cooperative enzymes

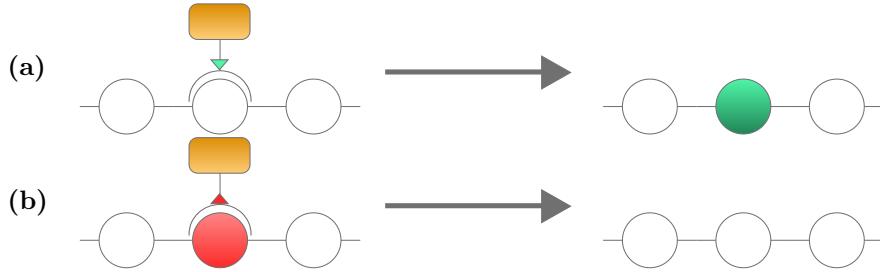


**Figure 2.2:** Graphical depiction of the possible cooperative enzyme acetylation addition (a) and removal (b) reactions. The reactions shown are also defined in the rule set to occur in the opposite direction. Cooperative enzyme methylators work analogically.

- spacing that is the same on both sides
- difference to linear enzymes

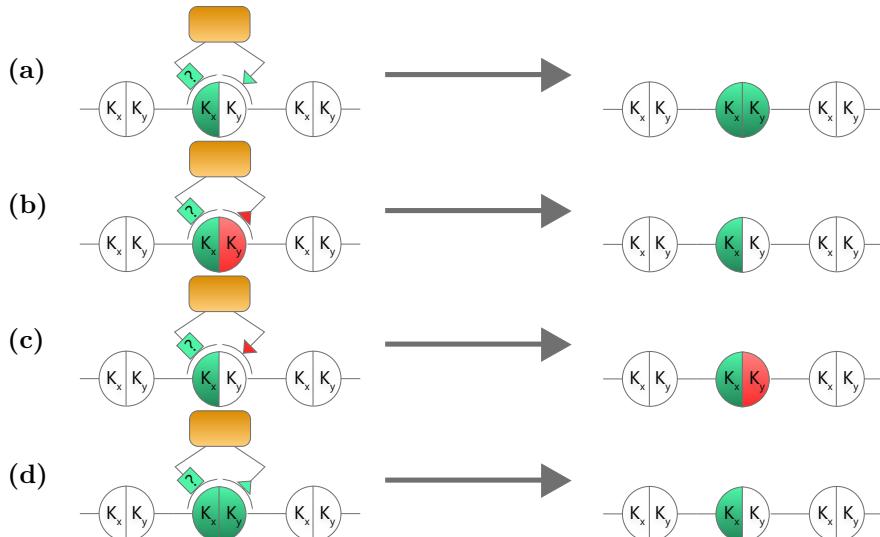
#### Random enzymes

- NOT contextless
- need very low rate (propensity sum)
- bring noise to the system
- not biological as enzymes, but noise is known to be in the system (source?)



**Figure 2.3:** Graphical depiction of the possible random enzyme acetylation addition (a) and removal (b) reactions. The reactions shown are also defined in the rule set to occur in the opposite direction. Linear enzyme methylators work analogically.

### Completer enzymes



**Figure 2.4:** Graphical depiction of the possible total enzyme acetylation addition (a) and removal (b) reactions. The reactions shown are also defined in the rule set to occur in the opposite direction. Total enzyme methylators work analogically.

- no known scientific background
- explain K<sub>x</sub> K<sub>y</sub> model

### 2.2.3 Enzyme rule sets

- Explain the sets later used? and enumerate them or sth so that the reader can easily refer to them. Explain them before.
- 3.1: linear extenders, linear removers, random adders, random removers
- 3.2: cooperative adders, cooperative removers (not for some), random adders, random removers (non-cyclic)

- 3.3: cooperative adders, cooperative removers (not for some), random adders, random removers (cyclic)
- 3.4: cooperative adders, random adders, random removers (cyclic)
- 3.5: cooperative adders, random adders, random removers (cyclic)
- 3.6:
  - BivalentBistability:
  - FavTotal:
  - FavBivalency:

### 2.3 Simulation parameters/details

- How did I change it?
- Time setting etc
- refer to exemplary state, rule and parameter files in appendix
- The simulations are run at two different length categories
  - short: Every step is plotted to see switching and meta data are used to plot association numbers and relative binding time
  - long: Only every 1000th step is plotted. Given that the system is stochastic/chaotic, regular plotting (f. ex. every 1000th data point) results in a smoothing of the histogram because the chosen points are more representative for the underlying distribution.

## 3. Results

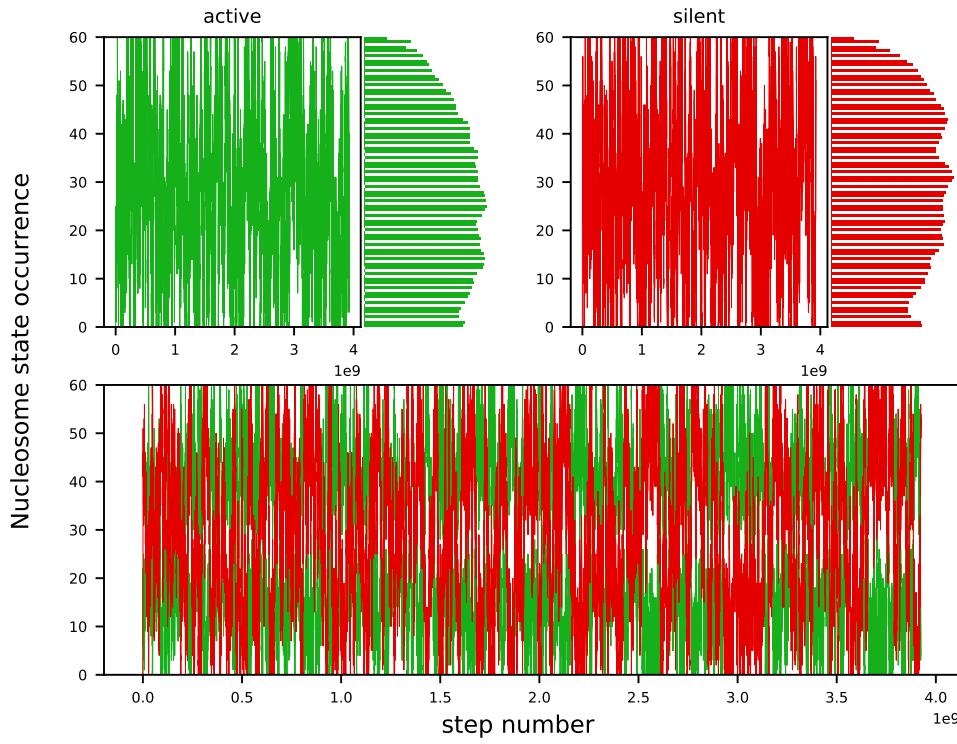
### 3.1 Non-cooperative enzymes do not entail bistable systems

Considering a system without cooperative enzymes, that thus only contains enzymes with a context that includes the next neighbours at most, bistability can not be achieved. Indeed, fig. 3.1 discloses a monostable system, as the histogram shows an unimodal distribution throughout the simulation.

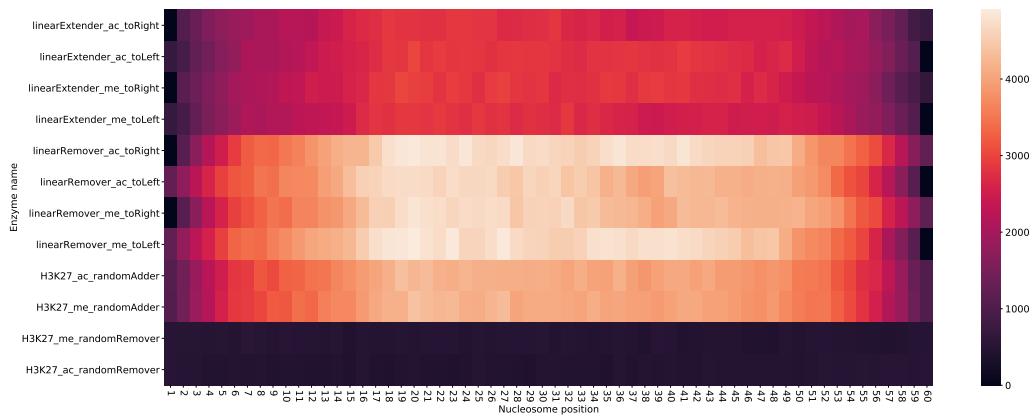
Fig. 3.1 exemplarily shows that the total number of active and silent states ambulate around one same value.

Fig. 3.2

- Include a boring graph that does not change much. Emphasis on the histogram.
- Renew the graphs
  - Gillespie time instead of step number on x-axis
  - remove bivalency window where it isn't needed
  - print (not plot) the total step number and indicate it in the caption
  - remove title
- run the heat map plots on these in order to see if there are two areas or if they are homogeneously mixed



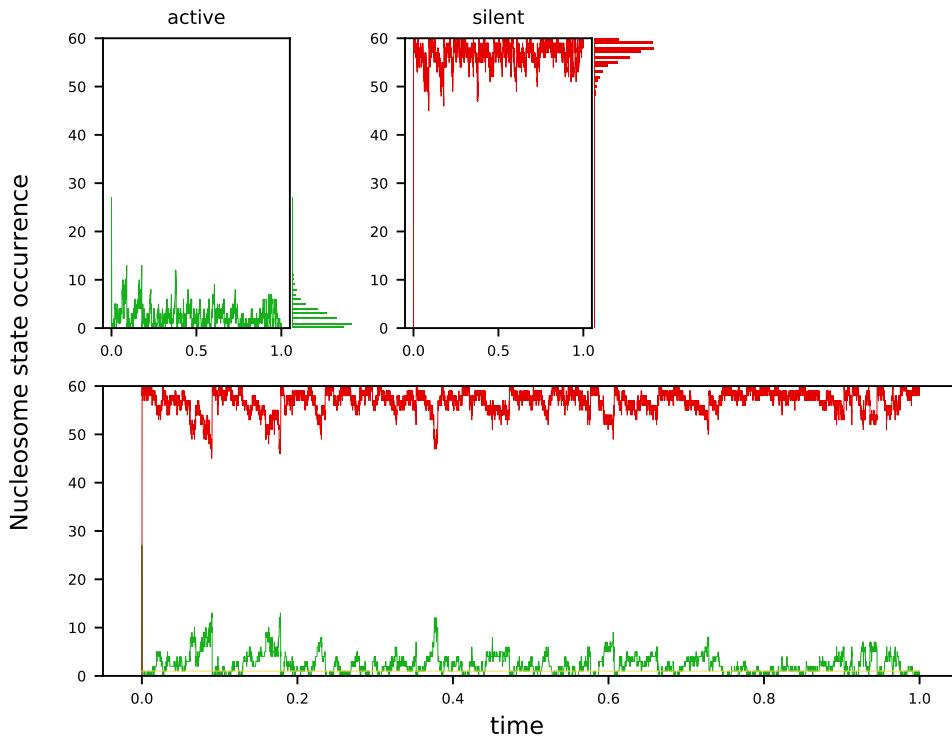
**Figure 3.1:** Absolute number of nucleosome states (active in green, silent in red) during the course of one long simulation (about 3.9 million reaction steps). The enzyme rule set contains linear extenders, linear removers, random adders and random removers. The rule set does not contain cooperative enzymes. (Rates and additional runs can be found in Appendix?)



**Figure 3.2:** Heatmap depicting the absolute numbers of enzyme associations per enzyme and per nucleosome on the nucleosome string. The numbers were summed up over 5 simulations, where each run was simulated over 750,000 time steps on average.

### 3.2 Bistability on a non-cyclic nucleosome string

With cooperative removers, no bistable switching can be observed: Figs. 3.3, 3.4 and 3.5.



**Figure 3.3**

Without the cooperative removers, frequent bistable switchings are observed with quite a bit of noise, meaning high variance around the bells in the histograms: figs. 3.6 and 3.7

- Describe difference between with coop removers and without
- Describe the heatmap figures and the trapez shape
- Describe, why the one coop Adder is much more active
- Describe, coopRemover activity at the borders
- Describe that random enzymes still have most activity
- Describe bistability and low frequency switching
- tell about the existence of runs where it is stuck in the middle state (“saddle point”) as can be seen in fig. 3.7
- Explain that we don’t want our enzymes to endure border effects and that we are thus switching to cyclic string (refer to discussion?)

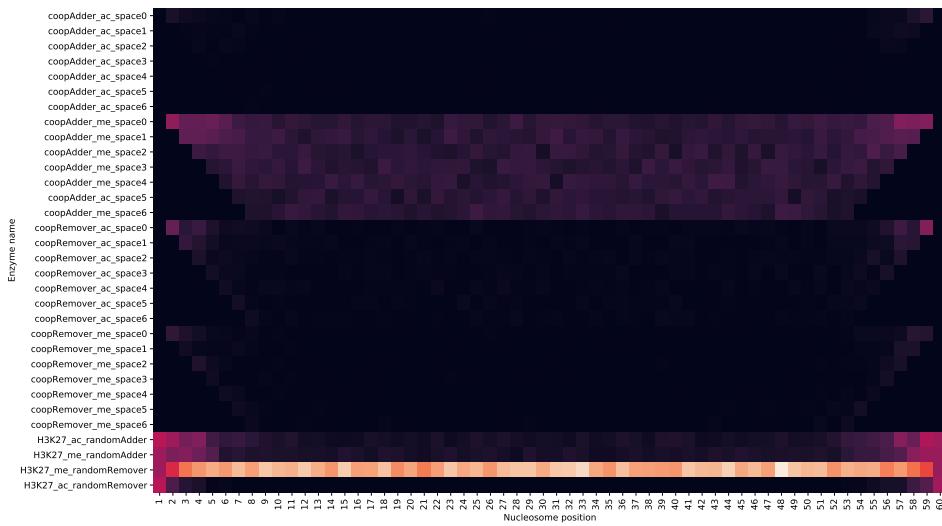


Figure 3.4

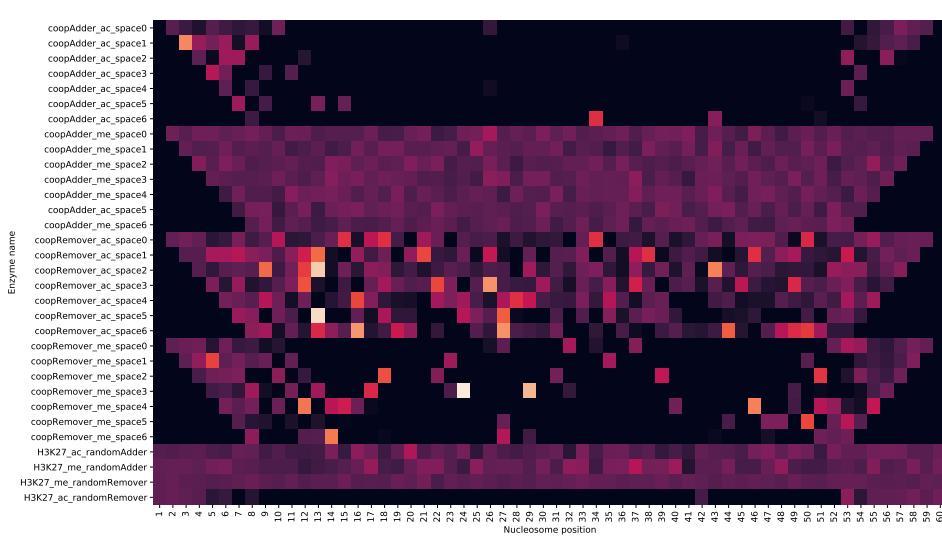
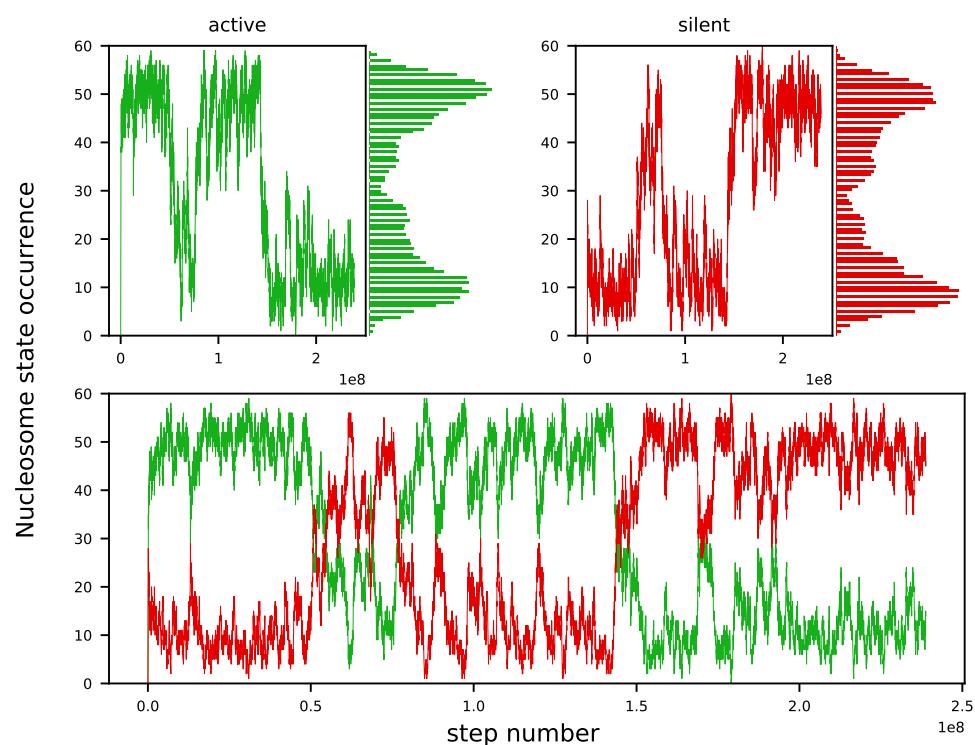
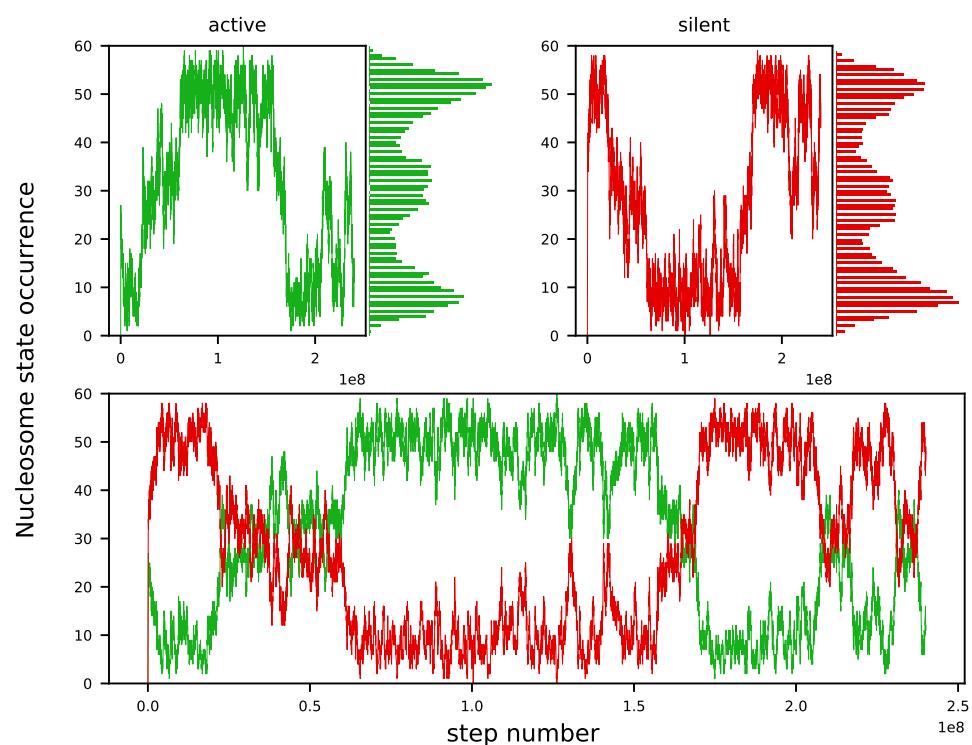


Figure 3.5

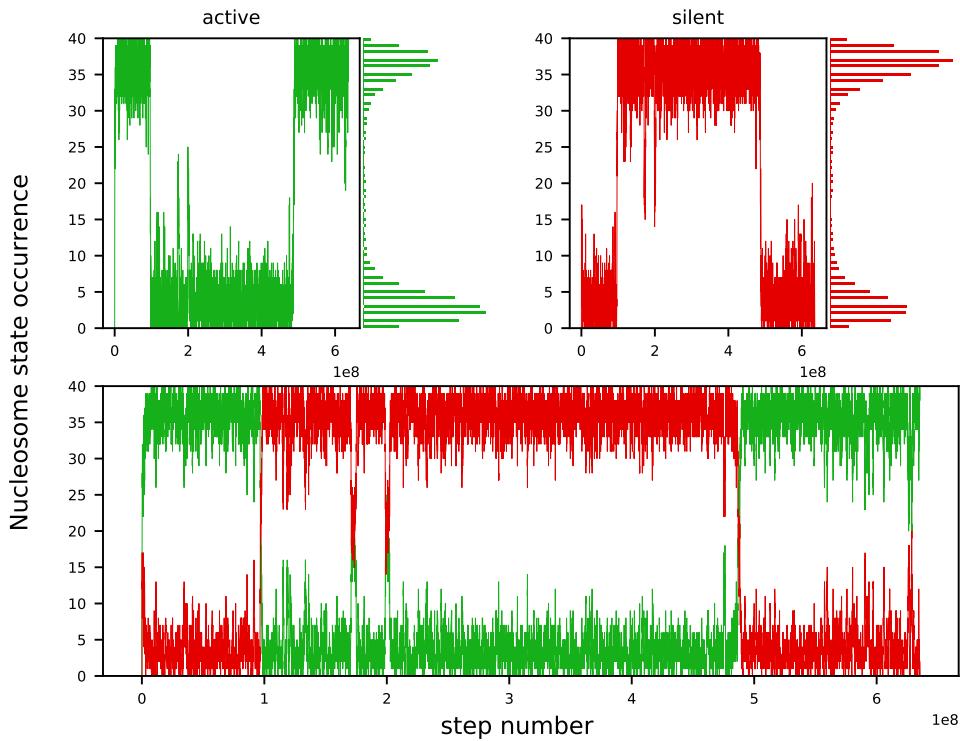


**Figure 3.6**



**Figure 3.7**

### 3.3 Bistable switching



**Figure 3.8**

- describe cyclic case without switchings (with coop removers)
- describe cyclic case with switchings (no coop removers)
- describe the low switching frequency
- describe the high variance in state length (that's why fig. 3.11 is asymmetric)
- maybe determine the frequency (cutoff at 30 etc.) with statistics?

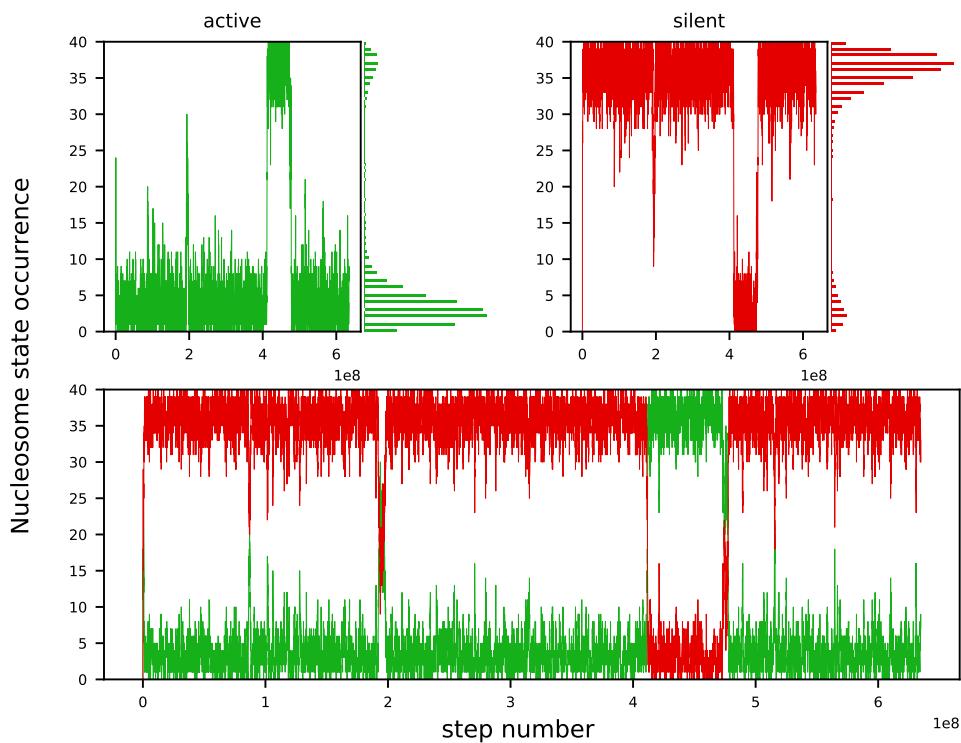


Figure 3.9

### 3.4 Influence of dissociation rate on system's noise

- high vs. low dissociation rate
- explain “protective groups” phenomenon
- discussion: discuss the biological significance of this

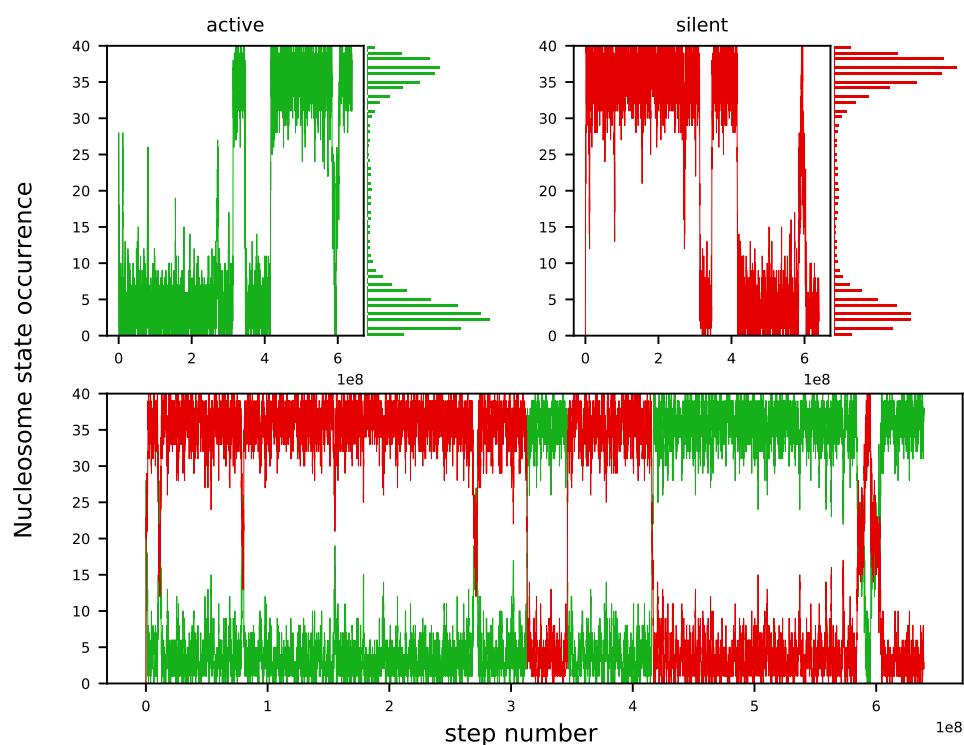
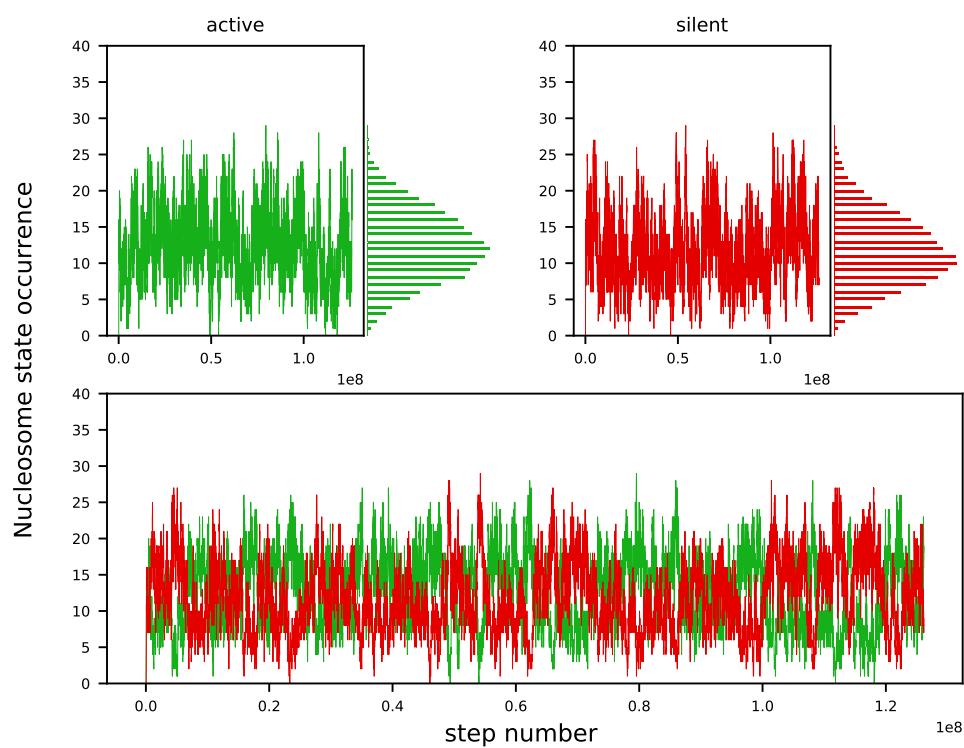
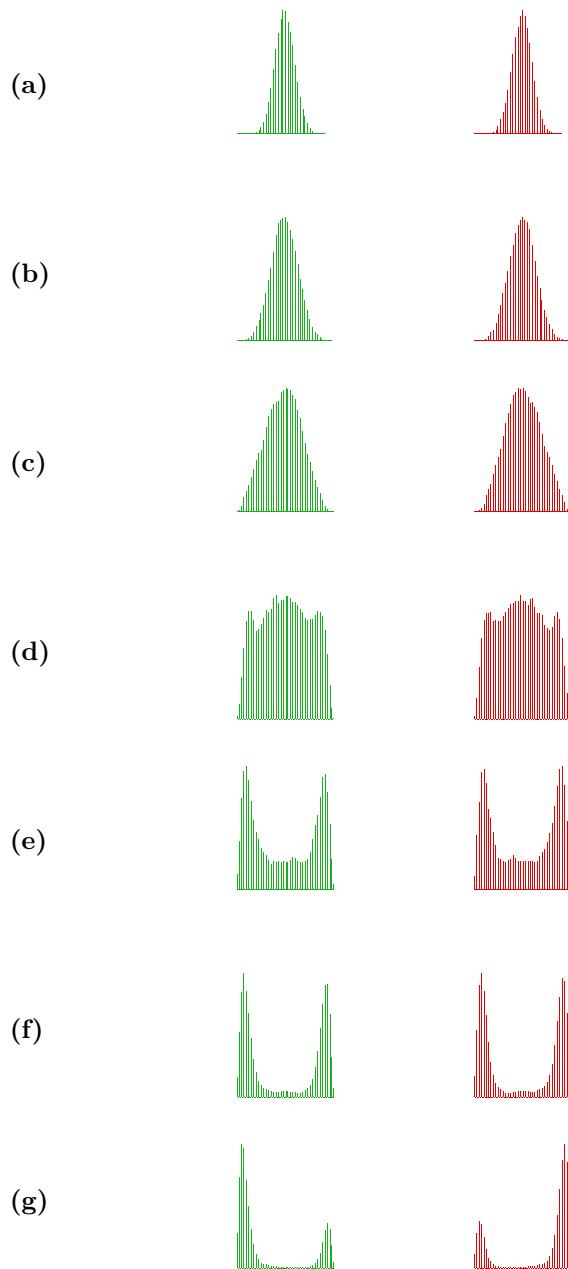


Figure 3.10



**Figure 3.11**

### 3.5 The boundaries of bistability



**Figure 3.12:** Graphical depiction of the possible cooperative enzyme acetylation addition (a) and removal (b) reactions. The reactions shown are also defined in the rule set to occur in the opposite direction. Cooperative enzyme methylators work analogically.

- describe loss of reach
- run without unmodified state?

### 3.6 Bivalency

- Here, we are at  $K_x+K_y$
- Two systems that either favour bivalency or total active/silent states as an introduction to bivalency
- Frequent switching and bivalency

## 4. Discussion

### 4.1 Conditions for bistability

- Bistability (condition: cooperativity) (Explain difference between biological and Sneppen coop.) (Errors in Sneppen's insights on the topic)

### 4.2 Proposed mechanism for bistable switching

#### 4.2.1 cyclic

#### 4.2.2 non-cyclic

- A state seed will immediately be extinguished by an opposing cooperative remover. In order to prevent this, there are two possibilities:
  - Build the seed in a corner where the coop Remover cannot be active
  - Remove coop Removers

## 5. Outlook

- Schuettengruber et al. in [14] (p44f) explain that PREs (Polycomb response elements) are responsible for the chromatin forming loops (TADs = topologically associating domains) and are thus able to form large silenced areas of condensed chromatin. These 3D-formations are critical for HOX gene regulation. It is also known that many active gene promoters interact with their enhancers and other promoters in a 3d-fashion. [10] These findings suggest that it might be beneficial for *EpiDynast* simulations to further explore possibilities to emulate fixed and dynamic 3D interactions within the nucleosome string.

## A. Run files and specifications

## B. Additional runs

# References

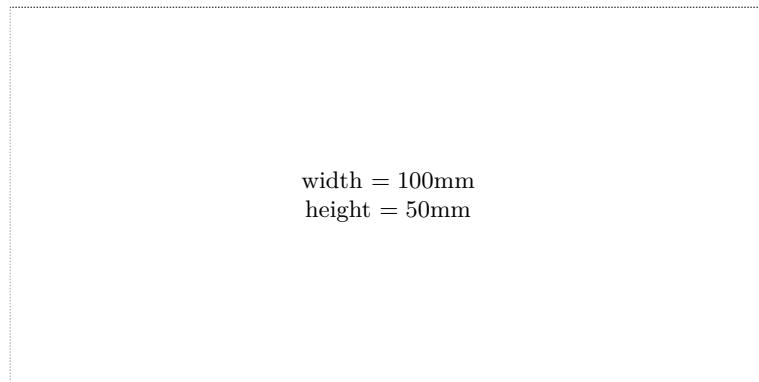
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