

Theoretical Modeling of Gene Silencing Induced by Active Enzymes

Yulong Dong

Supervisor: Prof. Bin Zhang

Department of Chemistry, MIT

September 1, 2017

1 Introduction

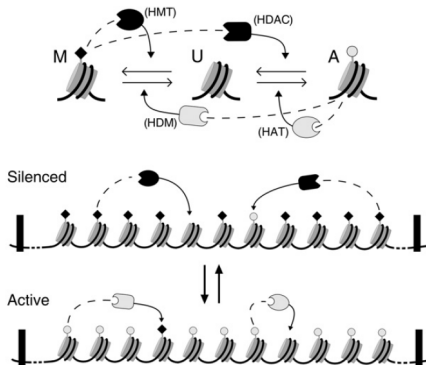
2 Methods

3 Results

4 Conclusions

Introduction

- 1 Chromosomal regions can have bistable gene expression associated with alternative covalent modifications of histones;
- 2 Because of the attraction between methylated enzymes and histones, methylated state is condensed and hard to express, which is silencing state.



- 1 Hathaway NA, Bell O, Hodges C, Miller EL, Neel DS, Crabtree GR. Dynamics and memory of heterochromatin in living cells. *Cell*. 2012 Jun 22;149(7):1447-60.
- 2 Dodd IB, Micheelsen MA, Sneppen K, Thon G. Theoretical analysis of epigenetic cell memory by nucleosome modification. *Cell*. 2007 May 18;129(4):813-22.

Introduction

- 3 In simple 1D model, this phenomenon can be described by analogous Ising model that will lead to the bistable pattern, transition between high methylated state and low methylated state.

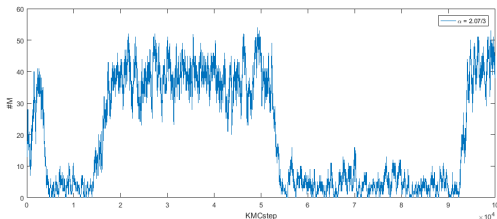


Figure: Time series of methylated sites.

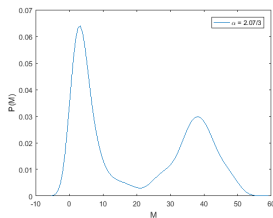


Figure: P.D.F. of methylated sites.

- 3 Zhang H, Tian XJ, Mukhopadhyay A, Kim KS, Xing J. Statistical mechanics model for the dynamics of collective epigenetic histone modification. Phys Rev Lett. 2014 Feb 14;112(6):068101.

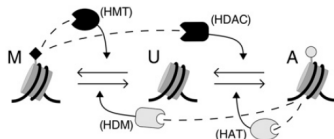
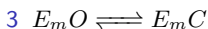
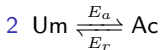
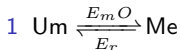
Introduction

- 4 This approach, however, does not consider the spatial structure of chromatin. Without diffusion, it is hard to understand the essence of those patterns.
- 5 Therefore, we propose a reasonable method to simulate gene silencing induced by active enzymes.

Methods

- 1 To simulate the system with diffusion and chemical reactions, we combined Monte Carlo (MC) and Molecular Dynamics (MD).
- 2 Poisson jump: reactions modifying histone site

Um	unmodified mark	Me	methylated mark
Ac	acetylated mark	$E_m O$	open methylated enzyme
$E_m C$	closed methylated enzyme	E_a	acetylated enzyme
E_r	removal enzyme		

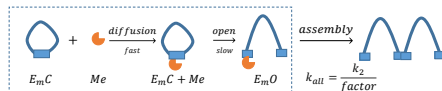
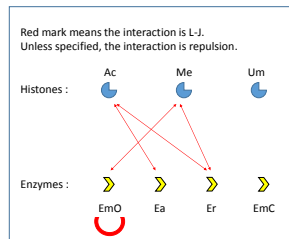


- 4 Schoneberg J, Noe F (2013) ReaDDy - A Software for Particle-Based Reaction-Diffusion Dynamics in Crowded Cellular Environments. PLOS ONE 8(9): e74261.

Methods

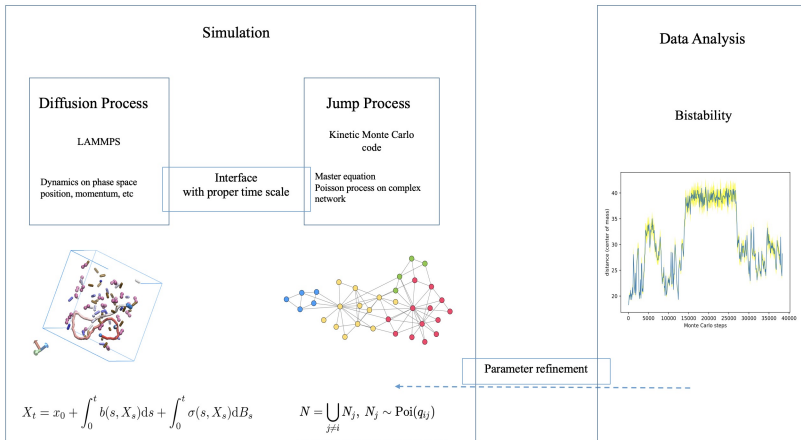
3 Rules:

- 1 The attraction between Me and E_mO is obviously stronger than others, resulting in condensation.
- 2 The attraction of open enzymes describes the collective behavior of HP1 enzymes according to experiments.
- 3 If there is Me near E_mO , the close reaction will be hard to happen. Because of the time limiting step, the overall reaction rate constant is approximately



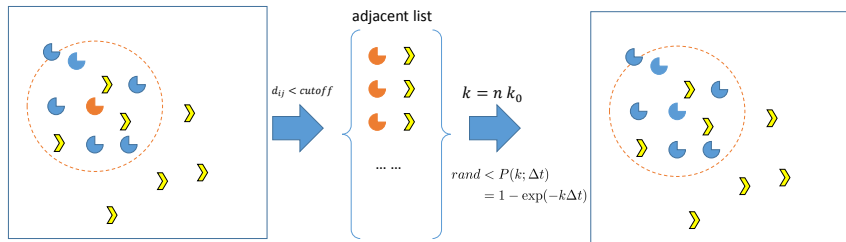
$$k_c = \begin{cases} k_2 & , \text{without Me} \\ k_2 / \text{factor} & , \text{with Me} \end{cases}$$

Methods



Methods

For each particle which can have reactions



Results

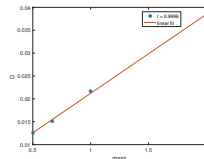
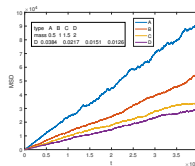
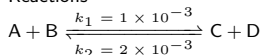
We validate our model on benchmark system with

1 Diffusion

$$m\ddot{x} = -\gamma\dot{x} - \nabla U(x) + \xi$$

where the interaction between particles is L-J.

2 Reactions



1 With formula

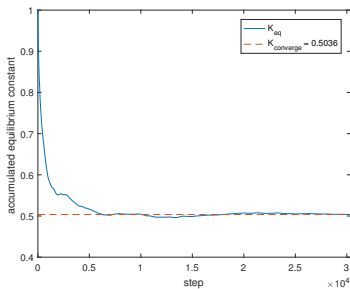
$$k_{macro}^{(2)} = 4\pi(D_{E1} + D_{E2})(R_{12} - \sqrt{\frac{D_{E1} + D_{E2}}{k_{micro}^{(2)}}})$$

$$\tanh(R_{12} \sqrt{\frac{k_{micro}^{(2)}}{D_{E1} + D_{E2}}})$$

we can calculate the equilibrium constant $K_{th} = 0.5122$.

2 relative error is

$$\omega = \frac{|K_{th} - K_{eq}|}{K_{th}} \times 100\% = 1.68\%$$



Results

With the feedback in our system,

- 1 In methylated system, there will be more Me near E_mO which can obviously decrease the close rate, leading to high concentration of E_mO .
Meanwhile, the condensed state can stabilize this configuration.
- 2 In acetylated system, there will be higher close rate, making less methylated reactions happen.

bistability is promising to occur in our system.

Bistability in time series

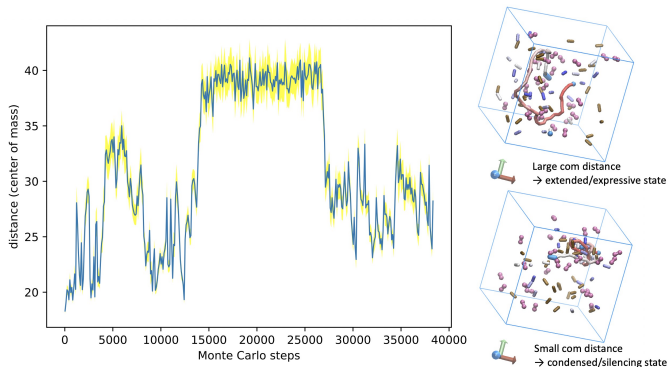


Figure: Bistability between condensed and extended states in simulation. Blue curve: time series filtered by moving average. Yellow shade: fluctuation.

Bistable pattern and sharp transition in P.D.F.

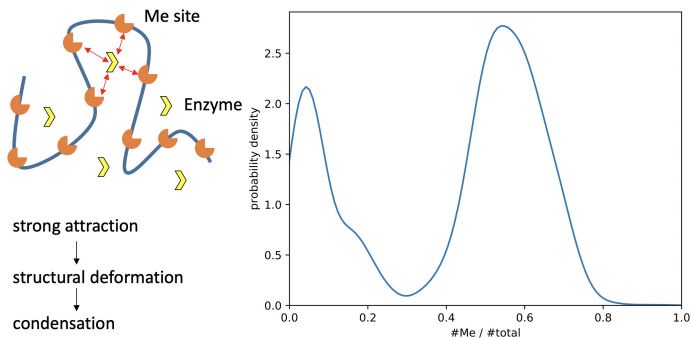


Figure: Probability density of Me site fraction with double-peak pattern and feedback scheme.

Conclusions

- 1 We have grasped the framework of reasonable methods to simulate gene silencing with diffusion and validated it on benchmark system.
- 2 Utilizing the experimental conclusions, we added reactions and feedbacks in our system.
- 3 Bistable patterns have been obtained by using the interface between MC and MD.

Thanks for your attendance!