Theoretical Modeling of Gene Silencing Induced by Active Enzymes

Yulong Dong
Supervisor: Prof. Bin Zhang
Department of Chemistry, MIT

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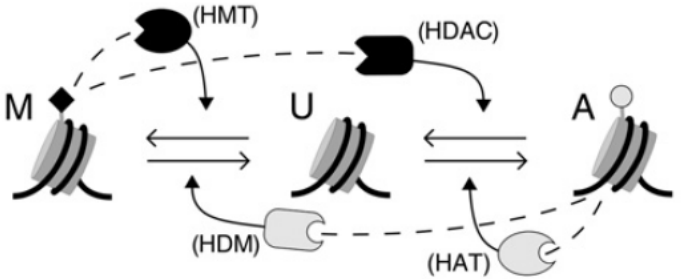
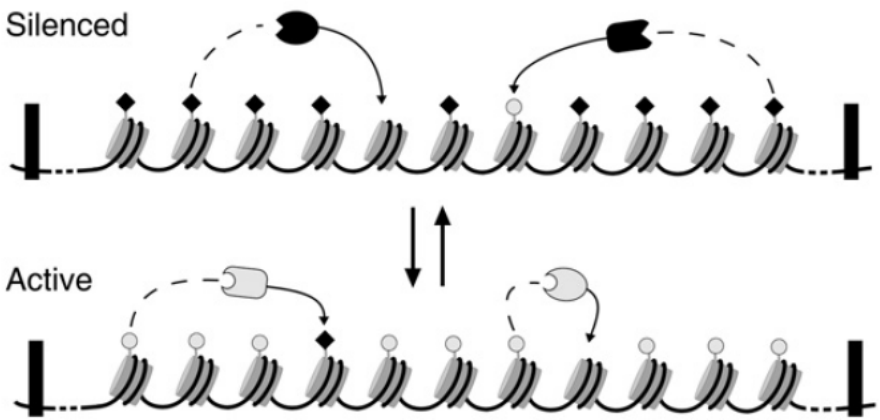
Introduction

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.

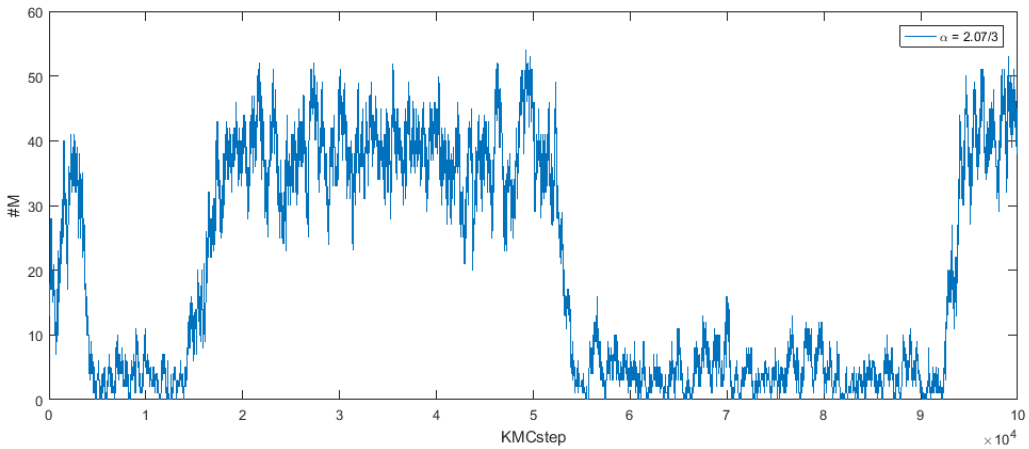


Figure: Time series of methylated sites.

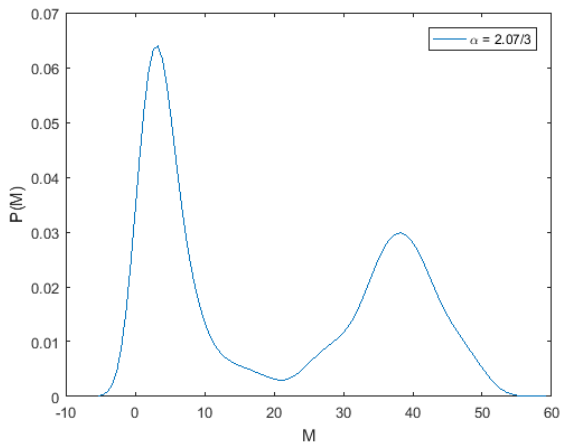


Figure: P.D.F. of methylated sites.

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

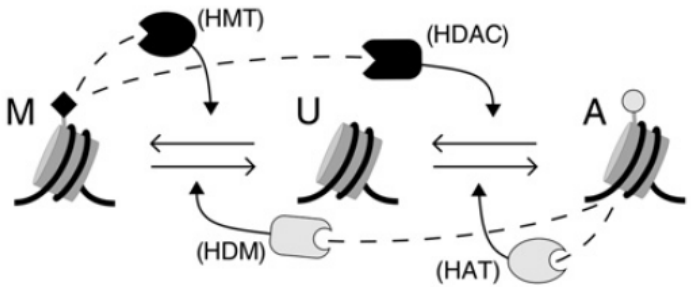
4. This approach, however, does not consider the spatial structure of chromatin. Without diffusion, it is hard to understand the essence of those patterns.
5. Therefore, we propose a reasonable method to simulate gene silencing induced by active enzymes.

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_mO	open methylated enzyme
E_mC	closed methylated enzyme	E_a	acetylated enzyme
E_r	removal enzyme		

1. Um $\underset{E_r}{\overset{E_mO}{\rightleftharpoons}}$ Me
2. Um $\underset{E_r}{\overset{E_a}{\rightleftharpoons}}$ Ac
3. $E_mO \rightleftharpoons E_mC$

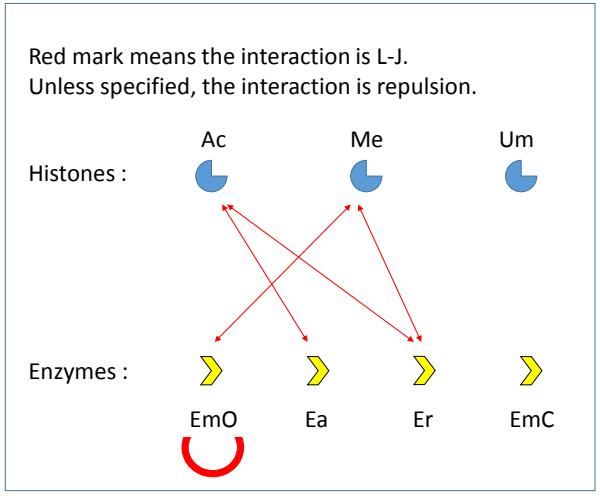


4 Schoneberg J, Noe F (2013) ReaDDy - A Software for Particle-Based Reaction-Diffusion Dynamics in Crowded Cellular Environments. PLOS ONE 8(9): e74261.

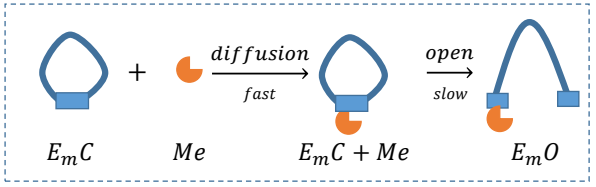
Methods

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



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

5 Daniele Canzio, Maofu Liao, Nariman Naber, et al. A conformational switch in HP1 releases auto-inhibition to drive heterochromatin assembly. Nature 496, 377 381.

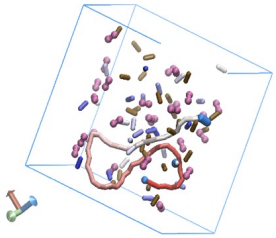
Methods

Simulation

Diffusion Process

LAMMPS

Dynamics on phase space
position, momentum, etc



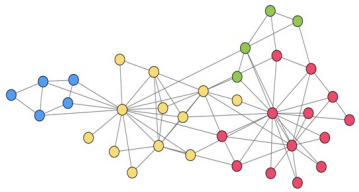
$$X_t = x_0 + \int_0^t b(s, X_s)\mathrm{d}s + \int_0^t \sigma(s, X_s)\mathrm{d}B_s$$

Interface
with proper time scale

Jump Process

Kinetic Monte Carlo
code

Master equation
Poisson process on complex
network

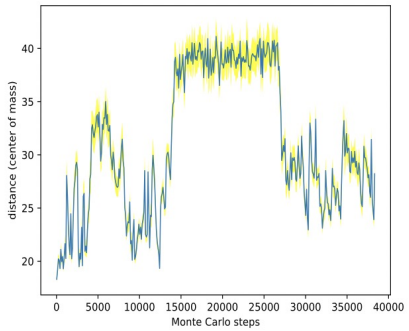


$$N = \bigcup_{j \neq i} N_j,\ N_j \sim \mathrm{Poi}(q_{ij})$$

Parameter refinement

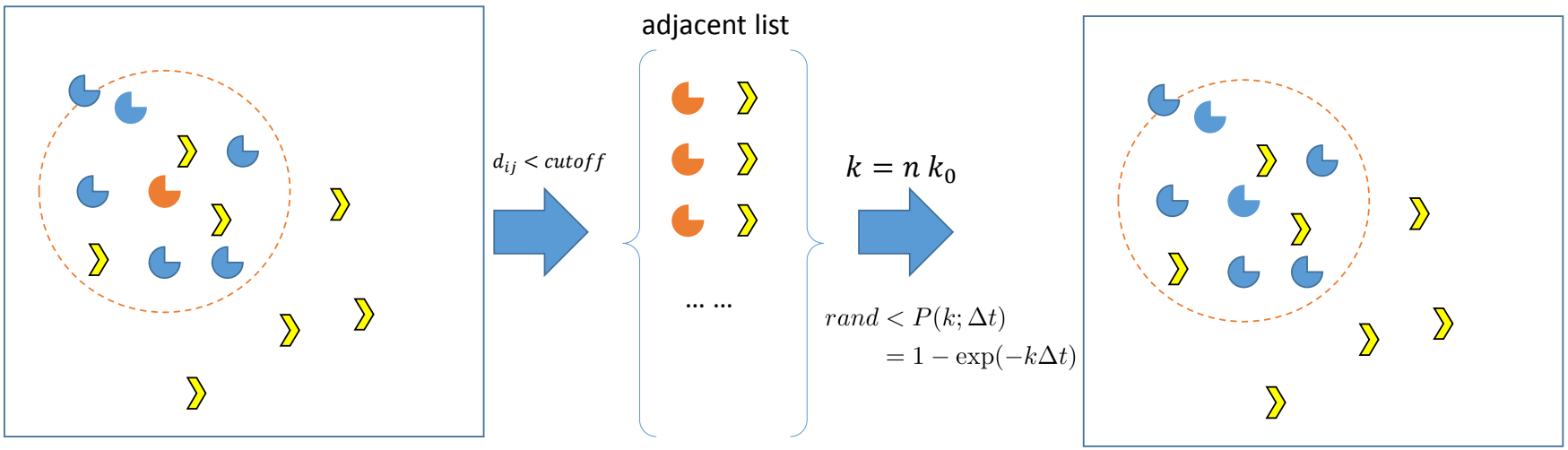
Data Analysis

Bistability



Methods

For each particle which can have reactions



Results

We validate our model on benchmark system with

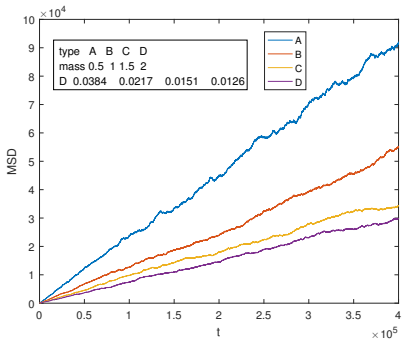
1. Diffusion

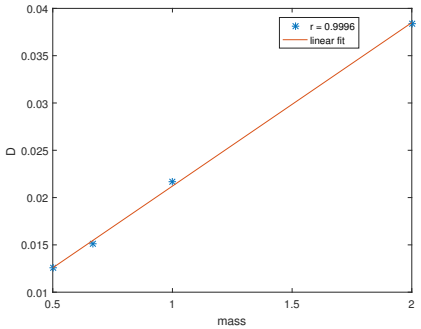
$$m\ddot{x} = -\gamma\dot{x} - \nabla U(x) + \xi$$

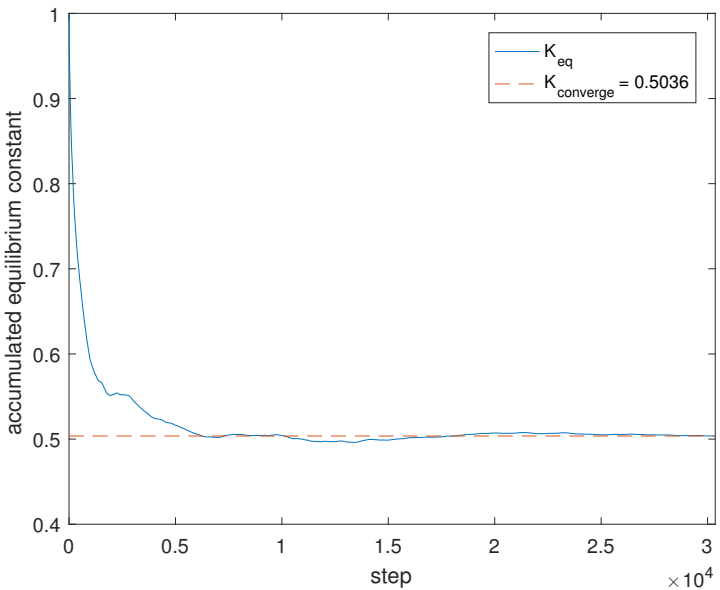
where the interaction between particles is L-J.

2. Reactions

$$\mathrm{A} + \mathrm{B} \underset{k_2 = 2 \times 10^{-3}}{\overset{k_1 = 1 \times 10^{-3}}{\rightleftharpoons}} \mathrm{C} + \mathrm{D}$$







1. With formula

$$k^{(2)}_{macro} = 4\pi(D_{E_1} + D_{E_2})(R_{12} - \sqrt{\frac{D_{E_1} + D_{E_2}}{k^{(2)}_{micro}}}\tanh(R_{12}\sqrt{\frac{k^{(2)}_{micro}}{D_{E_1} + D_{E_2}}}))$$

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 stablize this configuration.
2. In acetylated system, there will be higher close rate, making less methylated reactions happen.

bistablity is promising to occur in our system.

Bistability in time series

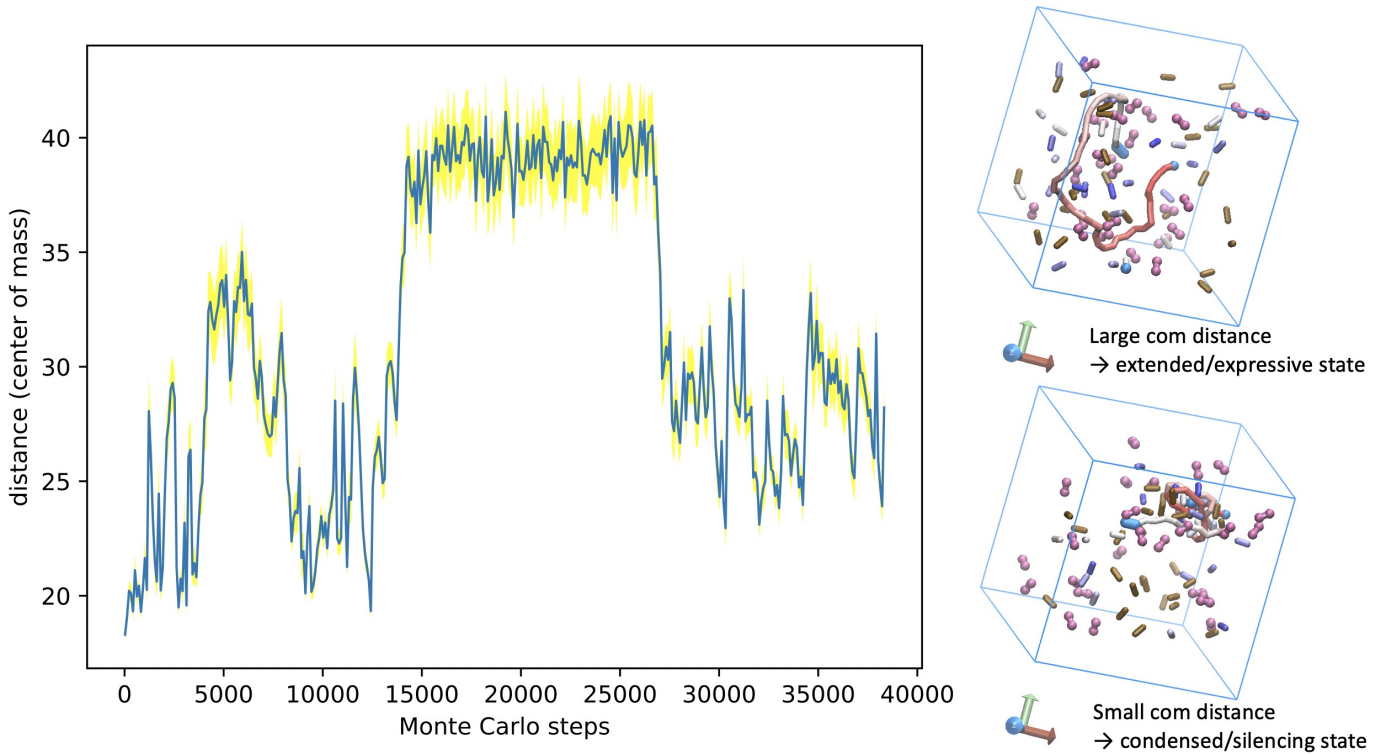


Figure: Bistability between condesed and extended states in simulation. Blue curve: time series filtered by moving average. Yellow shade: fluctuation.

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

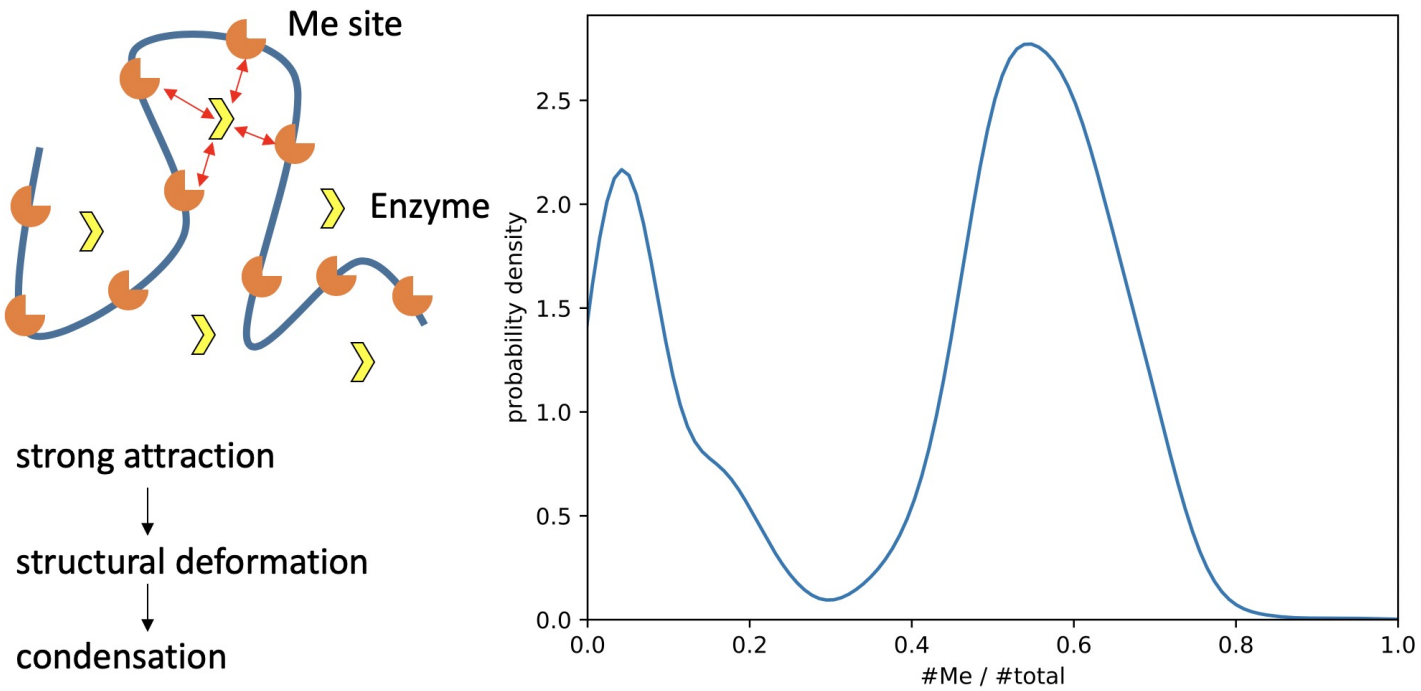


Figure: Probability density of Me site fraction with double-peak pattern and feedback scheme.

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!