Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification

Project Report

Motivation

Nucleosome Modification by random as well as enzyme catalyzed processes serves as a tool for chromosomes to change their state despite losing the integrity of the DNA sequence. This ability of chromosomes to exist in alternate stable states is known as bistability. The paper aims to develop a stochastic model of these nucleosome modifications and determine how the bistability in this model is affected in the processes of DNA Replication and random nucleosome modifications due to noise in the system.

Basic Ideas

We consider each nucleosome to be in three possible states: A (Acetylated/ Anti modified), U(Unmodified) and M(Methylated/Modified). A nucleosome can convert from one state to another in two ways: Random system noise (Probability=1-alpha), Recruited Conversion (Probability=alpha). Recruited conversion involves modification enzymes that are recruited by other modified nucleosomes. Hence, the recruited conversion involves two nucleosomes whereas the random system noise can modify a nucleosome without depending on another nucleosome. We further assume that all these processes take place in a domain of 60 nucleosomes where the domain is isolated by inert segments on both sides.

We then check for bistability for different values of Feedback ratios using stochastic implementation. We introduce cooperativity in the system by introducing the dependence on another nucleosome for the recruited conversion with no adjustments to the random noise based conversion. We make changes to the recruited conversion in terms of selection of adjacent neighbours only to illustrate the fact that “beyond-neighbour” interaction is needed for higher bistability.

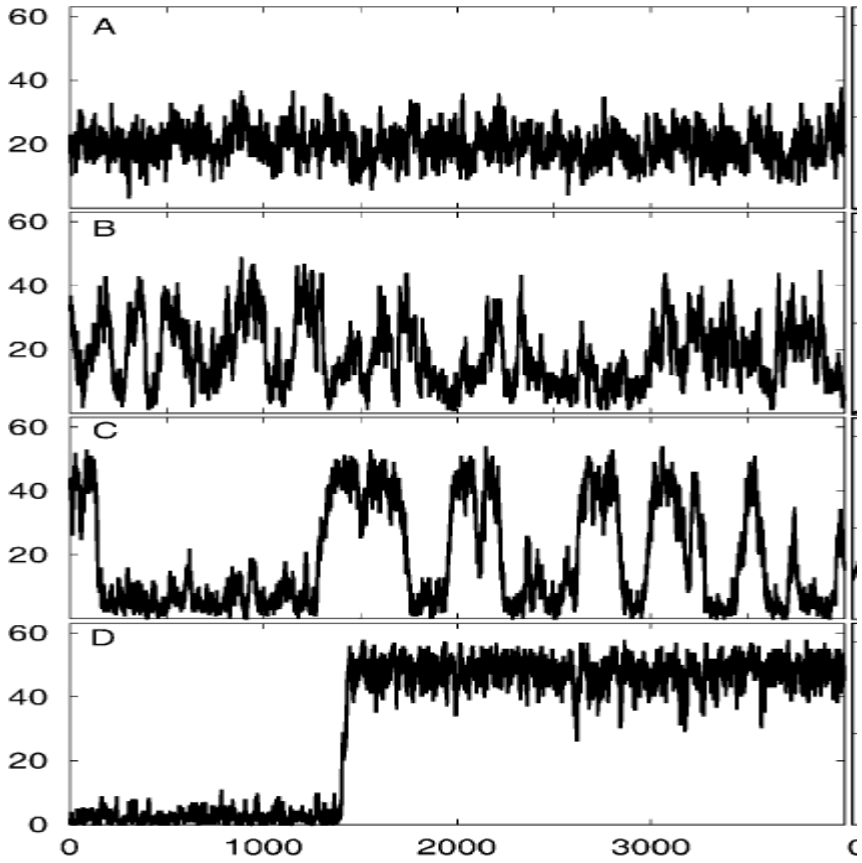
Results

The paper generates the following conclusions:

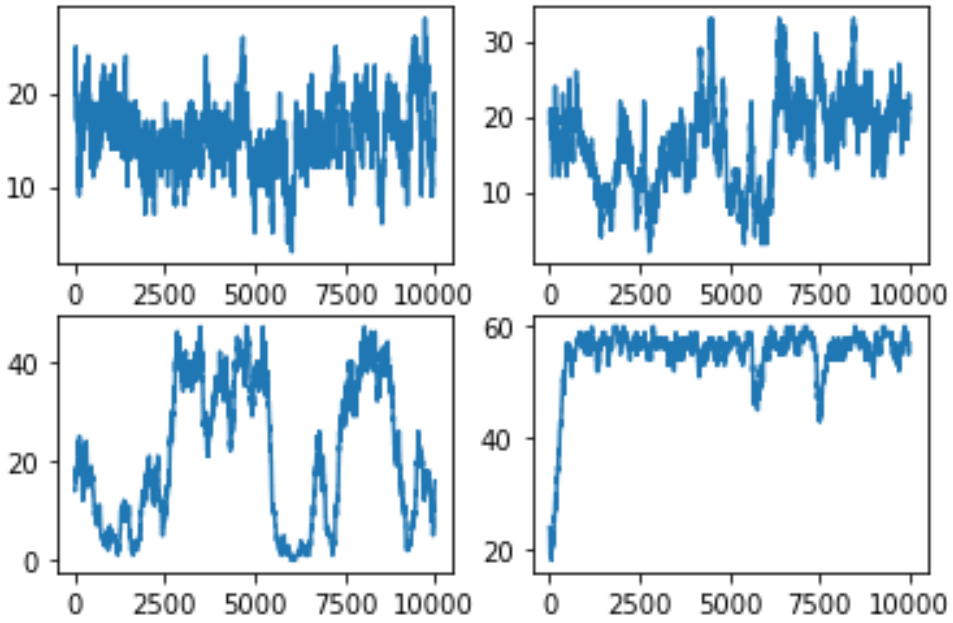
1. Higher feedback ratio denoted by F (alpha/1-alpha) produces higher bistability and noisier systems (low F value) produce lower bistability.
2. If recruitment involves only immediate neighbours then we get poor bistability and hence there is a need for the recruitment process to involve nucleosomes in a certain region around the originally selected nucleosome.
3. Bistability is also dependent on the system size and the symmetry of the A->U and U->M processes.
4. Nucleosome conversion can be modelled as a stochastic process without causing a loss in predicted bistability as in the model employed in the paper where the nucleosome conversion is randomized

Reproduced Plots

1. The dependence of M values as time progresses for different F values



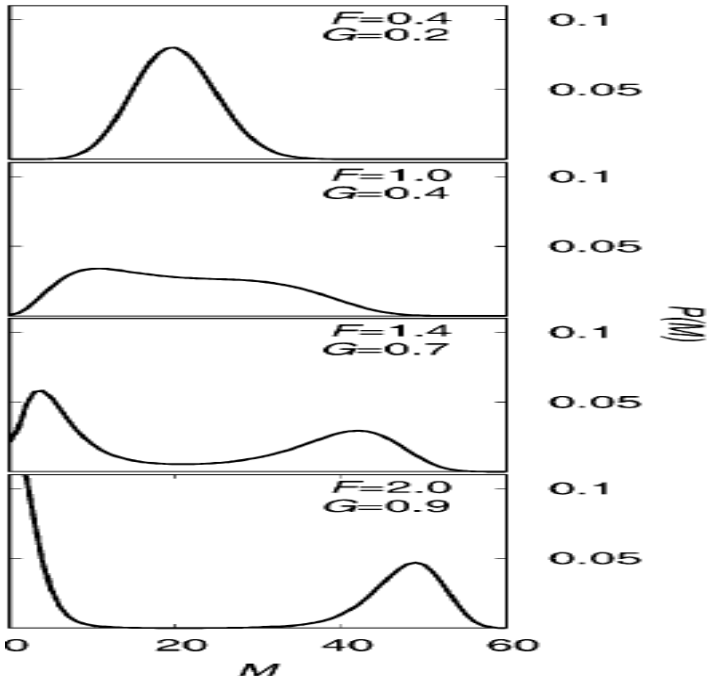
(Dependence of M values on F with A,B,C,D representing F values of 0.4,1,1.4,2 respectively from the paper)



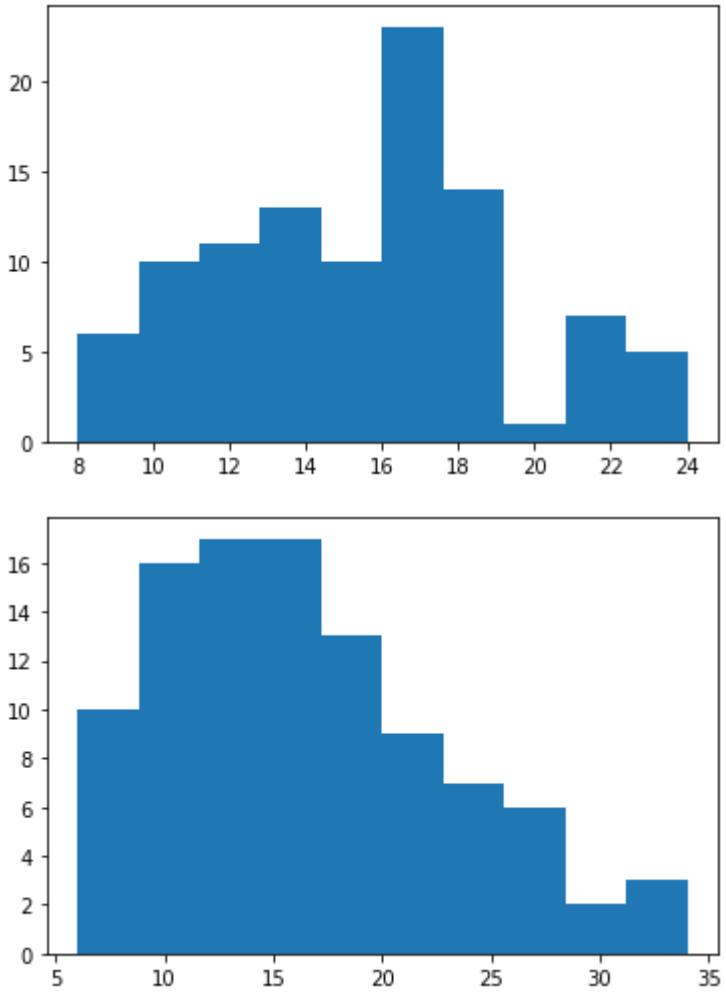
(Reproduced Plots with F values: 0.33,1,3,19
(top-left,top-right,bottom-left,bottom-right)

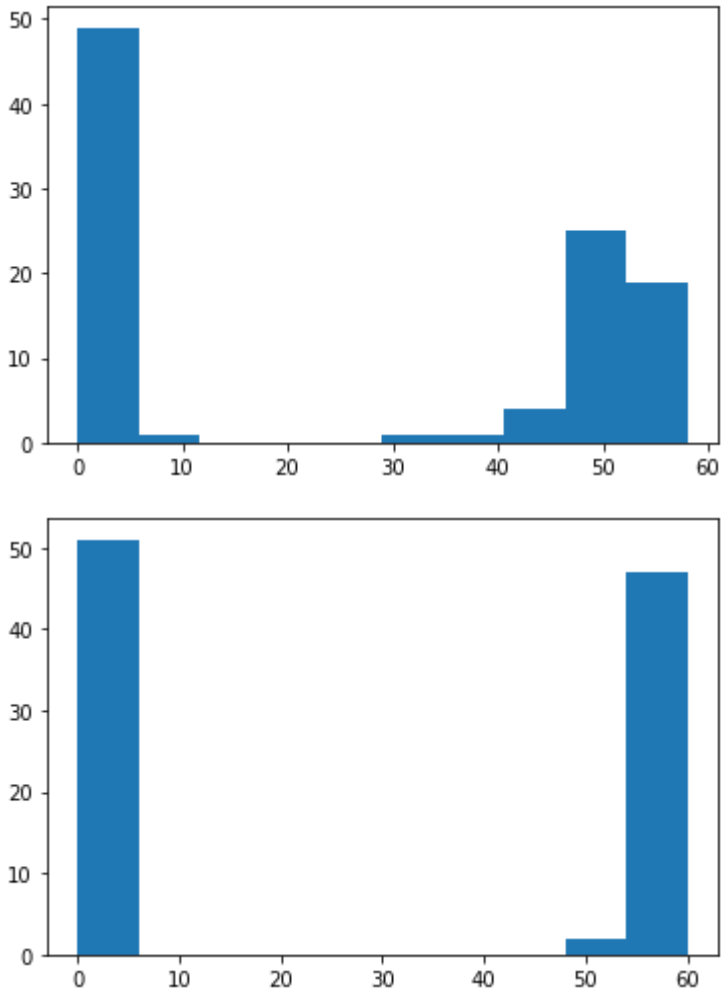
The graphs illustrate the fact that at higher values of F we can see the system in a bistable state and low bistability at lower F values or higher noise values.

2. Distribution of M values for different values of F (Using Histogram approach)

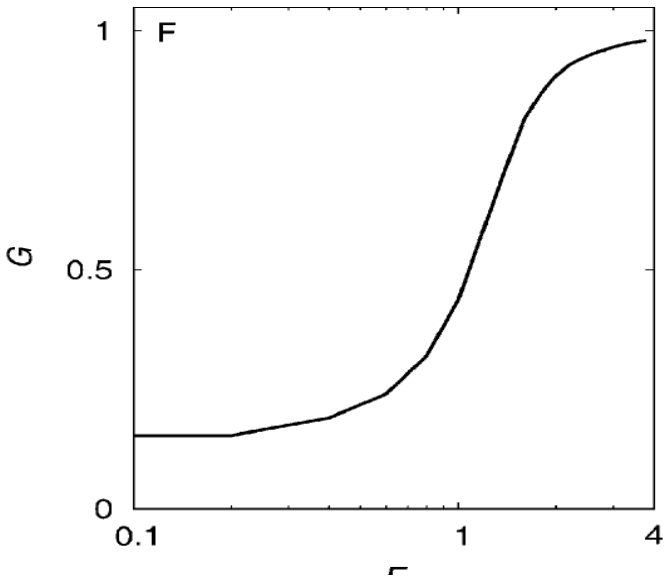


(Histogram showing rough probability distribution as a function of F corresponding to F values of 0.33,1,8,20 respectively)

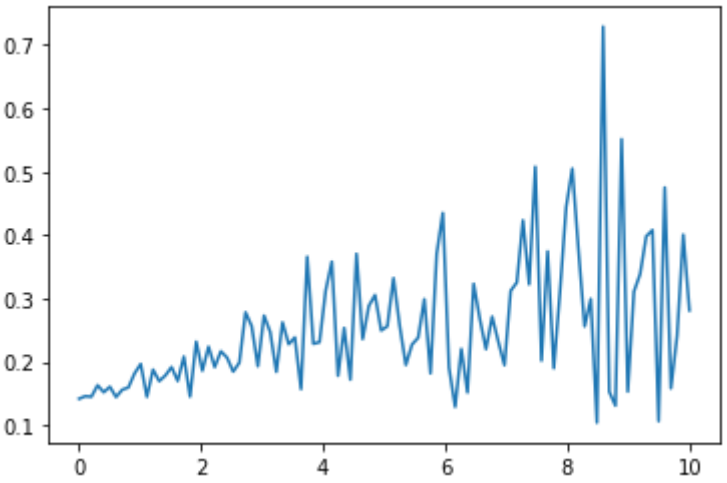




3. G vs F for normal non-cooperative non-restricted system



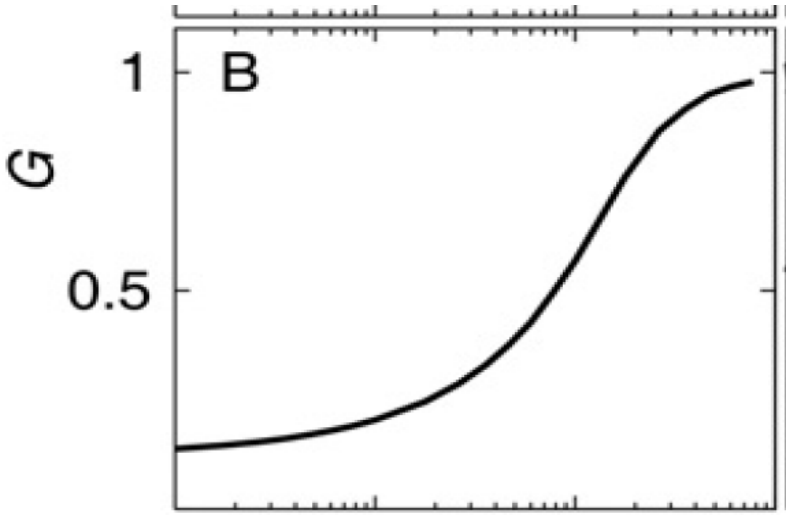
Paper plot

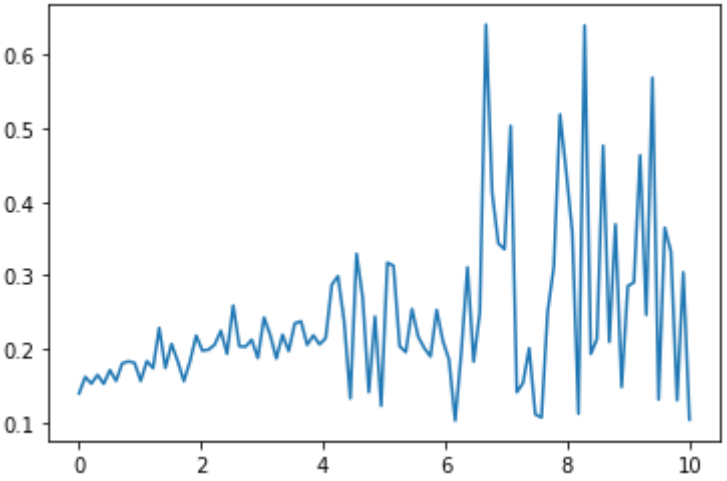


Reproduced Plot

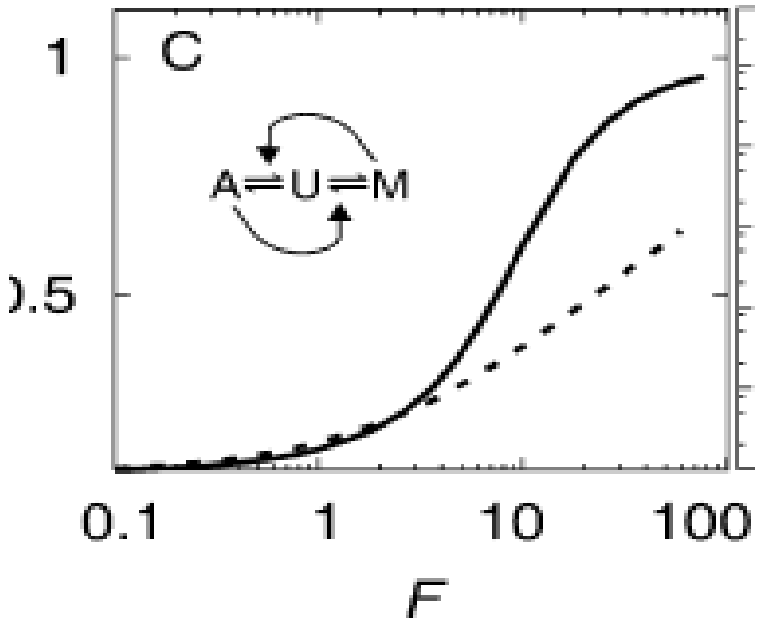
4. G vs F plot for neighbour only restriction excluding cooperativity approximation

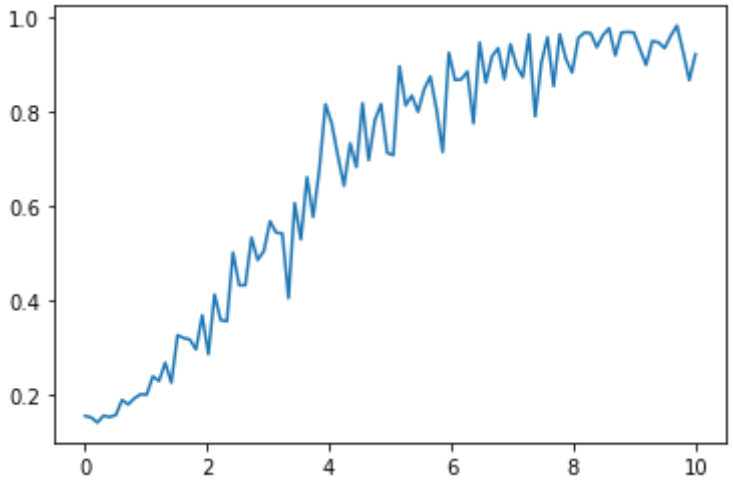
(Plot from the paper)



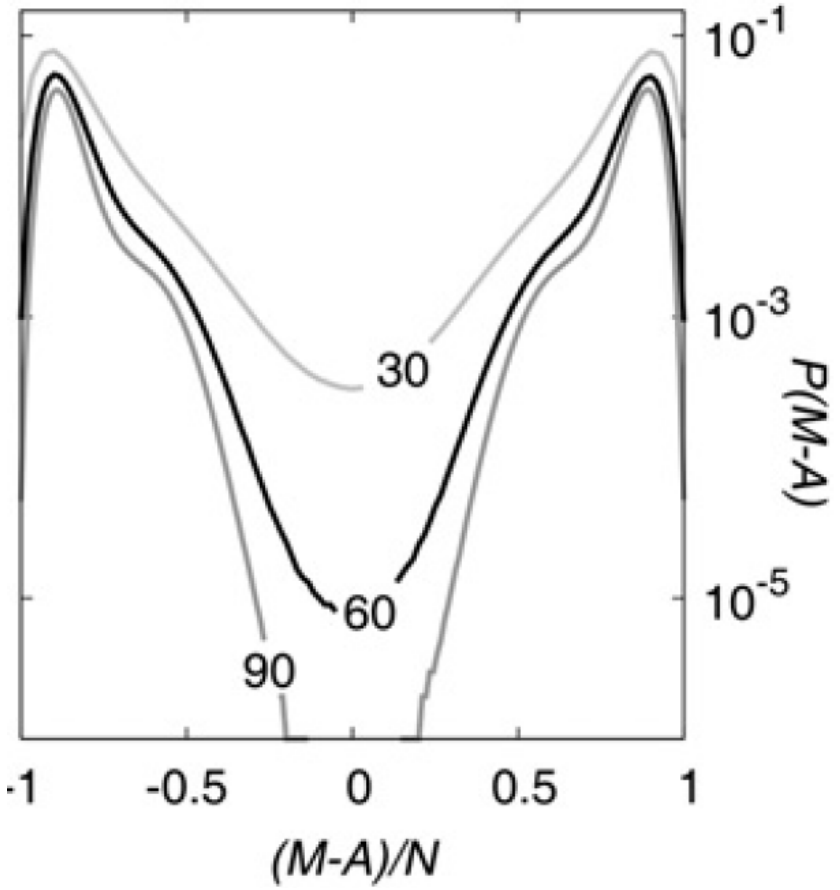


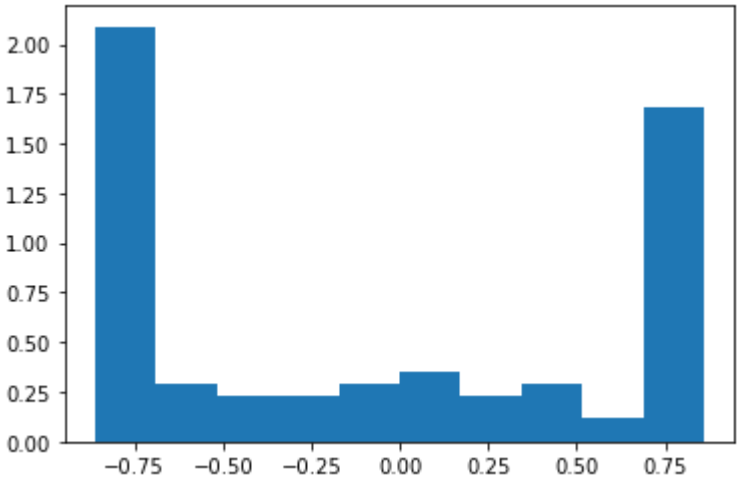
5. G vs F plot for non restricted cooperative model



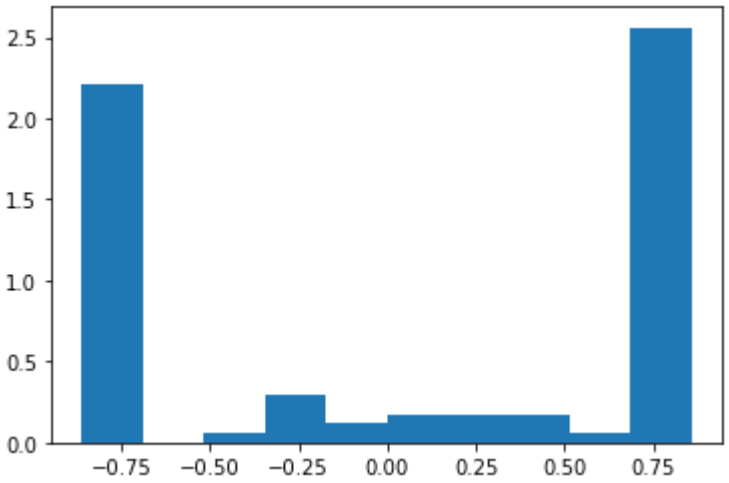


6. Plot illustrating probability distribution of normalized difference of M and A nucleosomes as a function of size of nucleosome region

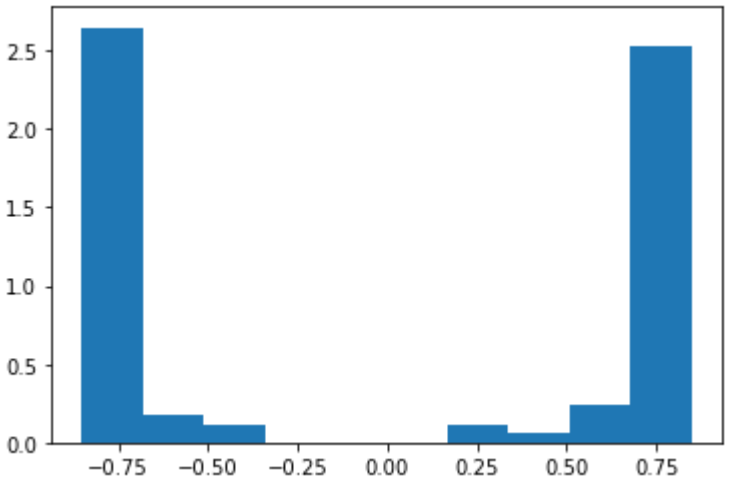




N=30 Reproduced distribution



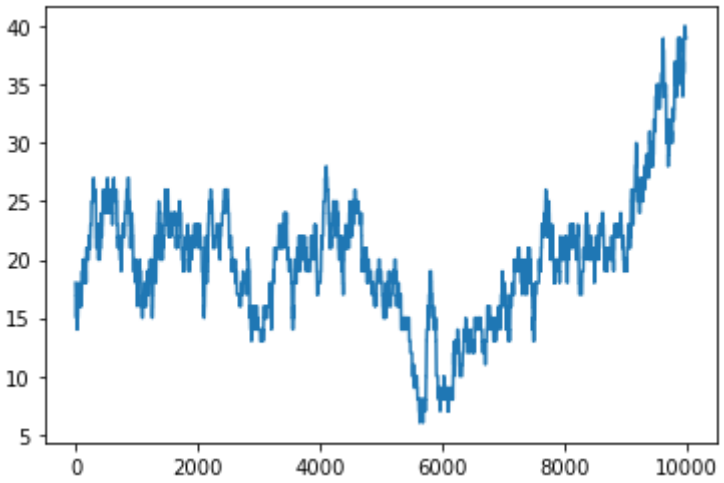
N=60 Reproduced distribution



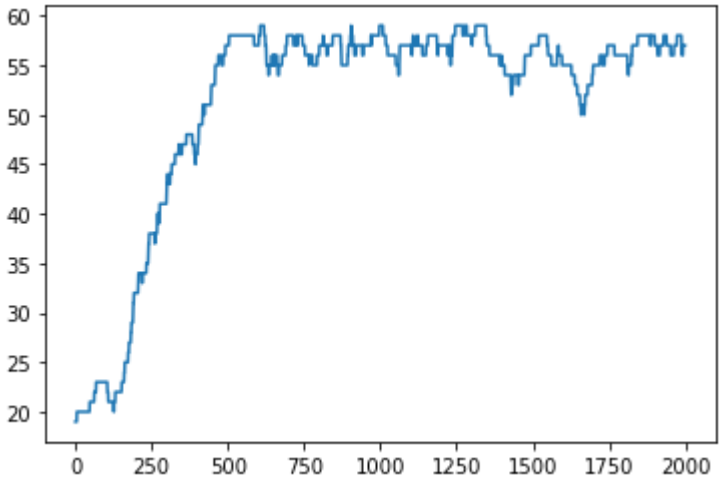
N=90 Reproduced distribution

Additional Plots

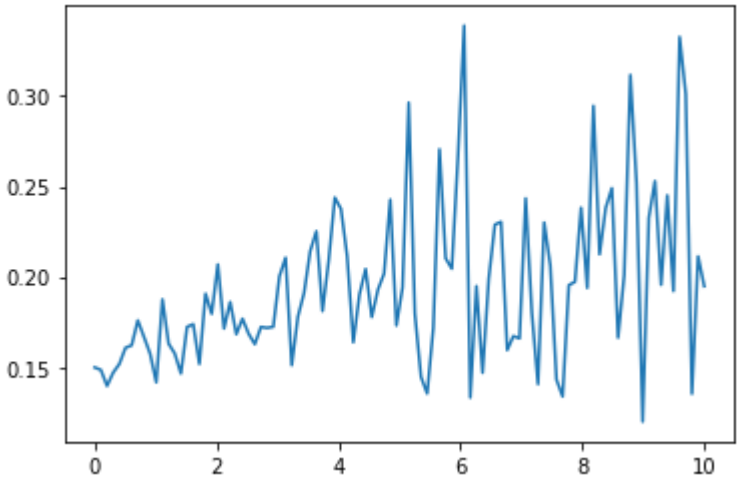
1. Inability of the system to achieve bistability in neighbour only approach for the same value as compared to non restricted approach



2. Bistability in cooperative conversion of nucleosomes



3. G vs F graph for neighbour only restriction with cooperative bistability



Remarks

For the G vs F graphs we are not getting precise distributions due to the fact that there is stochastic implementation in the model hence giving a random sort of distribution roughly replicating the graph.

For the probability distributions, histogram serves as an approximation and the figures presented here based on N=60 provide the best possible bin size with respect to distribution continuity.

The probability distribution of M for different values of F are partially accurate due to the fact that the G values have not been incorporated as the distribution is found using probabilistic modelling which prevents predefined setting of G which essentially is not in line with the stochastic model and keeps on changing randomly. Yet the histograms roughly approximate the probability distribution without taking G into consideration.

To illustrate the dependence of probability distribution on normalised difference of M and A, I did not combine the three histograms(rough approximations to probability distributions for N=30,60 and 120) to enhance readability.