Applying mean-field approximation to old and new model

1. Introduction

As the initial effort to model the spatio-temporal dynamics of centromere protein A (CENP-A) at centromere, we started from a mechanistic model based on information gathered from biological experiments. Hereafter, I will refer to this model as 'old model' to distinguish it from the model we are currently working on. The current model will be addressed as 'new model'. It is a stochastic cellular automata (CA) model built with the motivation of formalizing the old model. Details of the two models will be described in section 2.

After simulating the old model and analyzing the results, we had an qualitative view of the model. To analyze the model quantitatively, I wanted to apply analytical methods. Given the similarity of the old model to CA models, I chose mean-field approximation as suggested in a book[1]. Instead of specific states of the system, mean-field approximation re-describes the dynamics of the system as how individual cells interact with the 'average state' and how the 'average state' itself changes over time. We were also interested in how the new model will behave with this method. Therefore, I applied mean-field approximation to both old and new model and reported the results here.

2. Methods

2.1. Old model

The model describes centromere as a one-dimensional array of fixed number of cells. Each cell is either a 1, representing CENP-A nucleosome, or a 0, representing H3 nucleosome. Biological experiments showed that CENP-A nucleosomes are replenished through a self-templating feedback loop during either late mitosis[2] or early G1[3] and diluted by being randomly placed to daughter DNA strands during S phase[3]. Due to the temporal separation of replenishment and dilution *in vivo*, our model treat them as two distinct processes. A replenishment is consisted of ***rr*** rounds. In each round, each cell of 1 has a probability of ***af*** to initiate a transition event where a cell whose relative position to the original cell is determined by a discrete Gaussian function (μ=0 sd=***s***) is converted to 1 (Figure 1). To be noted, a transition event can have no effect if the chosen cell is already taken by a 1. Dilution is modeled by cells of 1 being converted to 0 with a probability of 0.5.

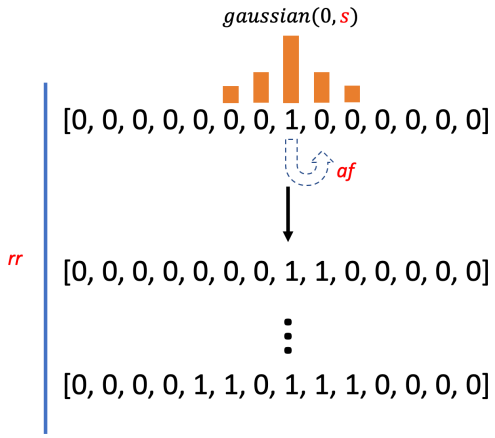


Figure 1: Schematics of replenishment. *af* denotes the probability of initiate a transition event; *s* denotes the standard deviation of distance-determining Gaussian function; *rr* denotes the rounds of replenishment.

2.2. Mean-field approximation of old model

By applying mean-field approximation, the system now only has one state variable D_t, the density of cells of 1 at time t. To monitor its change over time, one needs to enumerate all possible scenarios of individual

cells interacting with D_t and their probabilities. Here, I started from one round of replenishment (Table 1) for simplicity. I identified 3 possible scenarios:

current state	add a new 1	probability
0	0	$1 - D_t$
1	0	$D_t(1 - af) + D_t af(0) + D_t af(1 - f(0))D_t$
1	1	$D_t af(1 - f(0))(1 - D_t)$

Table 1: All possible scenarios in one round of replenishment of old model.

a. the cell state is 0 and it will not add a new 1 to the array. Since only cell of 1 can initiate a transition event, the probability of this scenario to happen is simply the probability of finding a cell of 0.

b. the cell state is 1 and it will not add a new 1 to the array. This scenarios can be further divided into 3 sub-scenarios. First, the cell of 1 fails to initiate a transition event, which is described as the first term of the probability function. Second, the cell of 1 initiates a transition event but itself is chosen as the cell to convert. Therefore no cell of 0 will be converted to 1. This sub-scenario is represented by the second term in the probability function. f here denotes the distance-determining function. Third, the cell of 1 initiates a non-self transition event but chooses another cell of 1 to convert, resulting in the third term of the probability function.

c. the cell state is 1 and it will add a new 1 to the array. For this scenario to happen, the cell of 1 has to initiates a non-self transition event and chooses a cell of 0 to convert.

After one round of replenishment, the density of cells of 1 equals to the sum of old (D_t) and newly added densities (scenario **c**). Hence, one-round replenish function R can be written as:

$$R(D_t) = D_t + D_t af(1 - f(0))(1 - D_t) \quad (1)$$

By defining a new parameter $\omega = af(1 - f(0))$, we get:

$$R(D_t) = -\omega D_t^2 + (1 + \omega)D_t \quad (2)$$

The next density of cells of 1 can then be calculated by implementing multiple rounds of replenishment as the recursion of function R and dilution as halving of density:

$$D_{t+1} = \frac{R^{rr}(D_t)}{2} \quad (3)$$

2.3. New model

New model keeps most of the old model except the replenishment step. As other CA models, new model updates the state of a cell by a state-transition function that reads the states of neighbour cells. To recapitulate old model, we set the function as that a cell of 1 will keep its state while a cell of 0 will be converted to 1 with the probability:

$$P_{0\to1} = \alpha \sum_{i=-n}^{n} x_i f_i \quad (4)$$

where α is an arbitrary parameter, n determines the size of neighbourhood, x is the state of cell and f is the weight function.

2.4. Mean-field approximation of new model

current state	new state	probability
1	1	D_t
0	1	$(1 - D_t)P_{0\to1}(D_t)$
0	0	$(1 - D_t)(1 - P_{0\to1}(D_t))$

Table 2: All possible scenarios in one round of replenishment of new model.

Next I applied mean-field approximation to the new model. Possible scenarios are listed in Table 2. Since the binary nature of cell state, the average value of a cell is just D_t. The probability of a cell of 0 to be

converted to 1 at D_t can then be calculated (note that it is always a cell of 0 at position 0):

$$\begin{aligned} P_{0\to1}(D_t) = \alpha(&D_t f(-n) + D_t f(-n+1) \\ &+ \ldots + 0 \cdot f(0) + \ldots + \\ &D_t f(n-1) + D_t f(n)) \\ &= \alpha(1 - f(0))D_t \end{aligned} \tag{5}$$

We can then calculate density of cells of 1 in the next time step, taking dilution into consideration:

$$D_{t+1} = \frac{D_t + (1 - D_t)\alpha(1 - f(0))D_t}{2} \tag{6}$$

Again, we can define a new parameter $\upsilon = \alpha(1 - f(0))$ to get:

$$D_{t+1} = \frac{-\upsilon D_t^2 + (1 + \upsilon)D_t}{2} \tag{7}$$

3. Results

3.1. One-round-replenishment old model is equivalent to new model

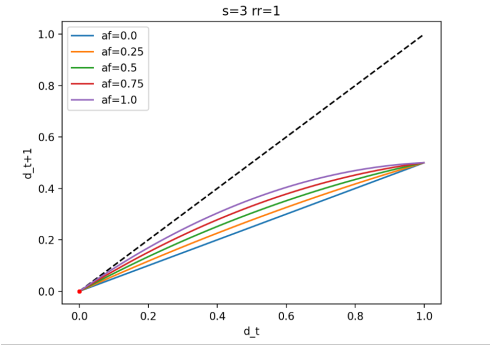
By letting $rr = 1$ in Equation 3, one can get:

$$D_{t+1} = \frac{-\omega D_t^2 + (1 + \omega)D_t}{2} \tag{8}$$

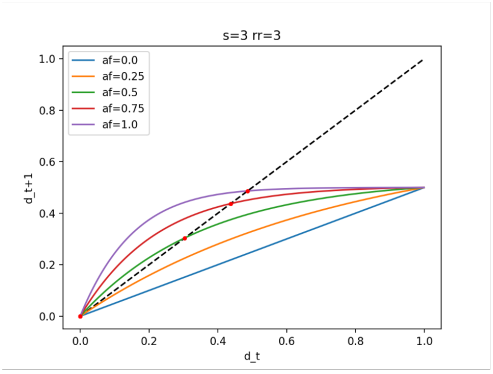
We can identify that it is the same as Equation 7. Given that $\omega = af(1 - f(0))$ and $\upsilon = \alpha(1 - f(0))$, if the distance-determining function in old model is the same as weight function in new model, af is equivalent to α.

3.2. Multiple rounds of replenishment is required for phase transition

I then numerically plotted cobweb diagrams of the difference equation of old model (Figure 2). For $rr = 1$, the system only has one stable equilibrium point at $D_t = 0$ regardless the value of af. For higher rr, for example $rr = 3$ here, the system's equilibrium point(s) depends on af values. Low af has only one stable point at $D_t = 0$ while it becomes unstable for high af. Meanwhile, a non-zero stable point starts to appear, indicating phase transition. The cobweb diagram also predicts that it is a first-order phase transition as the non-zero stable point can be very close to 0.



(a)



(b)

Figure 2: Cobweb diagrams of old model. (a) $rr = 1$; (b) $rr = 3$

4. Discussion

By applying mean-field approximation to old and new models, it is found that one-round-replenishment old model is equivalent to new model and that for old model, multiple rounds of replenishment is required to show phase transition. This

indicates that new model does not have phase transition.

Nevertheless, I learnt how to apply mean-field approximation to CA-like models through this practice, which should be useful for our further research.

References

[1] Hiroki Sayama. *Introduction to the modeling and analysis of complex systems*. eng. Deluxe color ed. OCLC: 942616166. Geneseo, NY: Open SUNY Textbooks, Milne Library, 2015. ISBN: 9781942341093 9781942341062.

[2] Anne Laure Pauleau et al. “The checkpoint protein Zw10 connects CAL1-dependent CENP-A centromeric loading and mitosis duration in Drosophila cells”. In: *PLoS Genetics* 15.9 (2019), e1008380. ISSN: 15537404. DOI: 10.1371/journal.pgen.1008380.

[3] Lars E.T. Jansen et al. “Propagation of centromeric chromatin requires exit from mitosis”. In: *Journal of Cell Biology* 176.6 (Mar. 2007), pp. 795–805. ISSN: 00219525. DOI: 10.1083/jcb.200701066.