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Heterochromatin and epigenetic memory from the viewpoint of polymer physics

Physical modeling of the heritability and maintenance of epigenetic modifications

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DNA is the primary information carrier of all known forms of life and at the same time being a huge flexible polymer chain with interesting conformation properties. In eucaryotes, i.e. cells equipped with a nucleus, DNA is compacted and wrapped around histone proteins thus forming chromatin, a flexible polymer consisting of nucleosomes which are DNA-sequences containing one histone octamer. While the base-pair sequence of DNA itself seems not to have an essential impact of DNA conformations on a larger scale, nucleosomes can carry additional information by chemical covalent modifications of their proteins. This can give rise to further spatial organization of chromatin on larger scales. Most notable is the formation of heterochromatin which can be related with the methylization of histone proteins [1, 2]. Heterochromatin, on the other hand, is essential for cell type identity, i.e. epigenetics. Heterochromatin is denser and less accessible part of chromatin, as compared to the more open euchromatin, in which most of the actively transcribed genes are located. Chromatin can be considered as multi-block copolymer consisting of sequences belonging to heterochromatin and euchromatin, which gives rise to micelle-type spatial organization of the chromatin on larger scales, where heterochromatin forms one (or several) dense cores and euchromatin forms a more fluffy corona (or matrix). It should be noted that this morphology can be changed for instance due to interaction with the nuclear membrane.

However, it is not the methylation of the histones itself which drives heterochromatin into a compact state in aqueous solution but its affinity to heterochromatin protein 1 (HP1)[1]. The interplay between the methylated sequences of the polymer, HP1, and water is essential to understand the formation of heterochromatin. In this respect it is important to know that HP1 can form clusters (oligomerize in the language of biology) and even phase segregate from water at sufficiently high concentrations *in vitro* [3, 4].

The recommended work by Spakowitz et al. starts with the assumption that HP1 binds preferentially to the methylated nucleosomes and at the same time energetically prefers

contact to other HP1 molecules, see the sketch in Fig.1. This is mathematically expressed by an adsorption order parameter ρ which quantifies HP1-bound nucleosomes. The affinity among the HP1 molecules is expressed by an energy gain, if two HP1-bound nucleosomes are close to each other leading to an energy gain $\sim J\rho^2$ with a coupling constant J. The latter is fixed by several k_BT in the simulations. Thus HP1 can be considered as a sticker or bridge element which favors methylated nucleosomes to be in close contact [5].

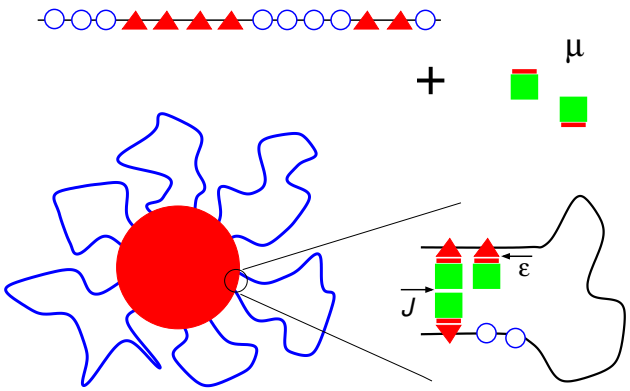

Figure 1: Sketch of the model for heterochromatin formation as proposed in the recommended work. Methylated units are indicated as red triangles and non-methylated units are drawn as blue circles. HP1 is displayed as green squares. The essential assumptions are: Adsorption of HP1 on methylated units is related with an energy gain of ϵ at a given chemical potential μ. HP1-tagged units can interact with each other with an energy gain of J. The latter causes compaction of the chain similar to the co-nonsolvency effect in polymer physics [6, 7]. The lower left part sketches the global phase separated micelle-like state as obtained in the simulations.

This ansatz is reminiscent of the analytical concepts developed for the collapse of polymers in a diluted co-nonsolvent, or in the presence of adsorbing nanoparticles [8, 6, 7]. The model is in turn applied by the authors to simulate a polymer which consists of about $400,000$ repeat units (corresponding to nucleosomes) and using an experimentally obtained methylation profile from a human chromosome. In order to simulate the huge chain various coarse-grained moves and soft interactions between repeat units are applied. The simulation method is described in a previous work of the authors in Ref. [5]. It is worth noting that HP1 is taken into account via the chemical potential of the bulk solution modeled by an ideal gas equation: $\mu = k_BT \ln([HP1]_{free})$. Bound (adsorbed) HP1 is modeled as a tag on the corresponding repeat unit. The simulation model is able predicting whether each nucleosome is segregated into the densely packed heterochromatic phase or the more lightly packed euchromatic phase based on the methylation profile from the experiment. Overall, a single chain micelle is obtained where the core is dominated by methylated chromatin and defines the heterochromatin phase in the simulations. The corona can be thus classified as euchromatin. Thus, the model can show the phase segregation of the copolymer (methylated/non-methylated) induced by a coupling between methylated monomers due to the presence of a binding cosolute.

While this concept can in principle explain the formation of heterochromatin as a co-condensed denser phase of chromatin in equilibrium, there is a second crucial aspect related

with heterochromatin: epigenetic memory. The latter means that daughter cells should inherit the same cell identity from the parental cell. The issue here is the fact that in the process of duplication of the chromatin each daughter polymer contains only 1/2 of the epigenetic marks, i.e. methylated histones, and new un-methylated histones are added randomly. In contrast to the genetic code which has to be preserved to high precision epigenetic memory which is based on the physics described above can only be conserved statistically.

First of all, the deletion of every second methylation tag reduces the average interaction between the tagged monomers in the presence of HP1 by a factor of two. Any model for epigenetic memory should be robust with respect to this drastic change of average interaction and recover the original phases. Furthermore, a dynamic process must be introduced to reestablish the methylation level within the cell-cycle. Indeed, it has been experimentally discovered that the enzyme methyltransferase which is known to reestablish the methylation of the histones has a preference to be located together with HP1 which suggests a feedback-mechanism between higher concentrations of HP1 and further methylation in this region.

This is exactly what the authors assume to extend their polymer-based model of the chromatin-HP1 system. In detail they have chosen a master equation approach which describes the conversion of the repeat units between the two states (methylated/non-methylated) according to the equation

$$\frac{dp_i}{dt} = k_m^{(0)} \langle n_{HP1} \rangle (1 - p_i) - k_a p_i \tag{1}$$

where p_i denotes the probability of methylation of a repeat unit i, and n_{HP1} denotes the number of methylated repeat units in a given spatial environment of the repeat unit. The essential parameter of the kinetic model is the relative rate of methylation to demethylation $\alpha_d = k_m^{(0)}/k_a$. The authors now solve the master equation based on Monte-Carlo sampled conformations to readjust the methylation tags accordingly. Afterwards the polymer conformations in space are resampled based on the stochastic re-labeling of the monomers according to the prediction of Eq.(1).

Using this concept the authors are able to simulate the evolution the epigenetic pattern due to the interplay of local conformation properties of the polymer and the amount of bound HP1. Starting always with the experimentally obtained methylation profile which has a fraction of about 0.6 of methylated units, already after a few simulated cell-cycles this fraction shifts to either higher or lower values depending on the HP1 concentration. However, the authors found an intermediate level of the simulated HP1 concentration where indeed a conservation of overall methylation pattern can be observed. This proves that the model is in principle able to reproduce epigenetic memory.

The important aspect of the work is the interplay between the epigenetic code (methylation pattern) and the conformation statistics of chromatin. In this aspect it goes beyond naive concepts where re-methylation of nucleosome units is thought of as a process which proceeds only along the neighborhood of the existing methylated units along the chain, i.e. considering the process as purely one-dimensional. Here, HP1 plays a role of a mediator which attracts methyltransferase. A major advantage of the model by Spakowitz et al. is that the heterochromatin phase defines a natural boundary in space for the methylation reaction at the same time concentrating the activity of methyltransferase in regions of high

HP1-content which correlates with the heterochromatin phase.

Several aspects of the presented model should be further elaborated. First, the affinity of HP1 with itself leads to spontaneous phase segregation at higher concentrations *in vitro*. The presented model does not consider free HP1 molecules in the simulation which excludes the possibility of oligomerization of free and bound HP1. This would give rise to an increase of the HP1 content inside the heterochromatin phase and in turn to a higher affinity to and stronger confinement of methyltransferase. A point which certainly deserves discussion is the instability of the numerical model with respect to the HP1 concentration in bulk. The simulation data as a function the number of cell-cycles, Fig.2 in the recommended work, indicate that the conserved state of the methylation pattern is an unstable fixpoint of the map in time. Thus, the nucleus must control the HP1 level very precisely. It would be also interesting to investigate in more detail under which conditions and model assumptions the phase-separated micelle-like state is indeed stable, i.e. spontaneously reformed, upon deletion of half of the methylated units.

To conclude, the recommended work is an excellent example of how the interplay between conformation properties and sequence in biopolymers can explain biological functions. In particular coupling the kinetics of changing the monomer properties with the conformation state of the polymer opens interesting perspectives in the theory of polymers.

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