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Editorial

Chromatin and epigenetics: current biophysical views

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Abstract: Recent advances in high-throughput sequencing experiments and their theoretical descriptions have determined fast dynamics of the "chromatin and epigenetics" field, with new concepts appearing at high rate. This field includes but is not limited to the study of DNA-protein-RNA interactions, chromatin packing properties at different scales, regulation of gene expression and protein trafficking in the cell nucleus, binding site search in the crowded chromatin environment and modulation of physical interactions by covalent chemical modifications of the binding partners. The current special issue does not pretend for the full coverage of the field, but it rather aims to capture its development and provide a snapshot of the most recent concepts and approaches. Eighteen open-access articles comprising this issue provide a delicate balance between current theoretical and experimental biophysical approaches to uncover chromatin structure and understand epigenetic regulation, allowing free flow of new ideas and preliminary results.

Keywords: chromatin; epigenetics; linker histones; nucleosome; DNA-protein binding; histone modifications; remodelers; topologically associated domains; DNA methylation; DNA supercoiling

1. Introduction

The interdisciplinary field of chromatin and epigenetics advances very fast. For example, in the last several months this research area has been highlighted in special issues in Journal of Experimental Biology [1,2], Molecular Plant [3], Plant Journal [4], Genome Biology [5,6], Genes [7], FEBS Journal [8], Journal of Physics: Condensed Matter [9], Chromosome Research [10], Proteomics [11], and now AIMS Biophysics (http://www.aimspress.com/newsinfo/133.html). It is fascinating to see how many faces this field has. Our special issue adds a new perspective to this field, considering new developments in chromatin and epigenetics from the point of view of classical

biophysics, both experimental and theoretical. Eighteen articles in this issue provide a snapshot of the established and emerging concepts in the field.

2. Protein-DNA Binding in Chromatin

The basic mechanical principles required to understand epigenetic regulation in chromatin are based on the classical views of interactions between nucleic acids, proteins and small ions in the crowded environment of the cell cytoplasm and the nucleus [12,13]. With the development of new experimental techniques, the current interest in this area has also shifted from model *in vitro* systems to *in vivo* functioning. Some of the basic mechanistic processes which need to be considered for this system include protein-DNA binding, wrapping of DNA double helices around the nucleosome core particle and the formation of chromatin fibers.

The generic problem of protein-DNA interactions in chromatin is addressed in two articles in this issue: a paper by Shubert and Längst proposing a new experimental method to study the thermodynamics of protein-DNA binding [14], and an extensive review of theoretical methods to describe such experiments using statistical-mechanical lattice models by Bereznyak et al. [15]. The work of Shubert and Längst introduces the MicroScale Thermophoresis (MST) as a method of choice to study the thermodynamics of protein-DNA binding in chromatin [14]. This is a rapid and precise method to characterize epigenetic interactions/linkages in solutions at microliter scale, requiring low concentrations of binding partners. The technology is based on the movement and diffusion of molecules through temperature gradients, a physical effect called thermophoresis (see e.g. [16]). This method allows measuring binding affinities in a broad range of molecular concentrations from pM to mM, which is important for the interactions of chromatin proteins with each other and with nucleic acids, taking into account the recognition of covalent epigenetic modifications. Once ligand binding curves are determined experimentally, e.g. using the MST method mentioned above, a quantitative analysis has to be performed to extract the thermodynamic parameters (binding constants, stoichiometry, cooperativity, etc) and allow further modelling. An extensive review by Bereznyak et al. [15] lists several classes of one-dimensional (1D) lattice binding models needed for such modelling and experimental data analysis. This review goes back to the classical models for the ligand-induced DNA melting and DNA-ligand binding and mentions some of the recent modifications of these methods which are being actively applied to the description of protein-DNA binding *in vivo* as reviewed elsewhere [17,18].

3. Chromatin Mechanics and Electrostatics

All interactions and processes in chromatin depend on the packing and 3D structure of the genome. One basic problem in this area concerns the physics of nucleosome formation. The work of Yanao and coauthors in this issue [19] presents a detailed computer simulation analysis of braiding of DNA molecules around uniform rods and spheres to mimic DNA wrapping which takes place in nucleosome core particles [20]. The right-handed DNA geometry appears as one of the major effects in this system, which gives rise to asymmetric coupling of elastic modes of DNA deformations, such as bending, stretching and twisting. The authors of Ref. [19] predict the preferred state of DNA wrapping to be a left-handed superhelix for both DNA-rod and DNA-sphere wrapping. This purely mechanical conclusion of the model [19] is in agreement with the predictions of electrostatic theory

of interactions of charged DNA double helices [21]. Two juxtaposed elastic DNA molecules prefer to form a left-handed braiding configuration for nearly all strengths of DNA-DNA interaction. As a next step, it would be interesting to understand the implications of helically positioned charges on the DNA in this elaborate elastic model, and the corresponding effects on gene regulation.

At a larger scale, the mechanics of long chromatin fibers needs to be considered [22–27]. This problem is addressed in the current issue in the work of Norouzi and coauthors [28]. Their article unravels the implications of differences in the length of the linker DNA between nucleosomes on topological and folding properties of chromatin fibers, as well as their transcriptional behaviour. The analysis is based on two most common linker lengths L, with L = 10n and L = 10n + 5 bp, where n is an integer number. Very different structures of chromatin fibers distinguished by the orientation of individual nucleosomes with respect to the fiber axis have been obtained depending on the chosen n value in Ref. [28]. The authors have focused on the topological, deformation-invariant parameter called the linking number, and computed linking numbers per nucleosome for different arrangements of the core particle as a function of the chromatin fiber length. For the range of L = 10–70bp, energetically optimal fibers with L = 10n belong to the topological type T2, characterized by the linking number per nucleosome in the range [−1.4; −1.2], while fibers with L = 10n + 5 belong to the family T1 characterized by a smaller linking number in the range [-1.0; -0.8] (meaning less negative DNA supercoiling). The authors proposed a model that explains the role of such topological polymorphism of chromatin fibers in regulation of DNA transcription in yeast. Namely, as RNA polymerase (RNAP) gives rise to higher DNA twisting in front of the transcription complex, the model predicts that T1 fibers with L = 10n + 5 are formed downstream from the RNAP (because they are less negatively supercoiled). The analysis of baker yeast genes performed in the paper indeed shows that L = 10n + 5 chromatin fibers are getting transcribed more often, as compared to L = 10n fibers. It is an intriguing question whether these tendencies will persist in other species, often with longer DNA linker lengths.

This special issue also touches the classical question of the electrostatics of DNA and chromatin [29–32]. All chromatin objects are highly charged (negatively charged DNA and RNA, positively charged histones, the solution contains metal ions and charged proteins). Yet, this molecular soup is mostly neutralized. A delicate interplay between small changes of electroneutrality governs this tightly packed nucleoprotein system. Bohinc and Leu [33] provide in this issue a systematic review of simplistic electrostatic models required for the understanding of DNA-DNA and DNA-protein-DNA interactions in chromatin. These interactions were highlighted especially in situations where molecules possess spatially distributed charges such as those in three-valent spermidine and four-valent spermine cations strongly influencing DNA-DNA interactions [34,35]. Thus, the work presented in Ref. [33] follows a large number of articles offering electrostatic descriptions of this system, and it finishes with formulating an open question: how to model explicitly the electrostatics of nucleosome arrays? Despite many efforts of scientists in this field, more work is needed to understand e.g. the effects of long-range electrostatics, charge discreetness and heterogeneities, and low dielectric permittivity inside DNA and histones on the large scale properties of chromatin fibers.

4. Nucleosome Positioning

Another important problem in the field of chromatin and epigenetics is nucleosome positioning.

Nucleosomes are not positioned randomly along the genomic DNA, but rather bear a distinct signature of the underlying DNA sequence in their location sites [36,37,38]. Therefore, it is extremely important to know where each nucleosome is located on a particular stretch of the DNA, because this determines the accessibility of a given DNA site to transcription factors and other regulatory molecules. Three particular aspects of nucleosome positioning are reflected in this special issue of AIMS Biophysics: a novel type of columnar nucleosome arrangement determined by the DNA sequence, a recently introduced nucleosome repositioning mechanism known as kinetic proofreading, and a concept of nucleosome remodelling as a "buffer" for gene regulatory processes:

The first of these questions is addressed in this issue by one of the pioneers of the field, who proposed more than 35 years ago that DNA sequence at least partially encodes nucleosome positions on the DNA [39], the statement which later has been confirmed in a number of genome-wide studies. In an original work featured in this special issue, Trifonov describes a new structural entity called "columnar chromatin structure", which means that often several nucleosomes are regularly arranged organized by long periodic sequences, with the nucleosome DNA period of 10.4 bases [40]. This effect can be seen visually when the periodicity along DNA sequences is mapped using the consensus motif characteristic for "strong nucleosomes" previously developed by the author [41]. The columnar structures may have a range of implications, for example predicting the nucleosome switch positions at promoters when an array of nucleosomes sitting at their preferred sequence-determined positions is disturbed by transcription and then relaxes to the initial position.

Nucleosome positioning on the DNA is not a static quantity, but rather undergoes perpetual changes driven by the DNA unwrapping from the histone octamer [42]. The work of Singh et al. in this special issue [43] offers an extensive coverage of the mechanisms of kinetic proofreading for the processes of chromatin remodelling. Chromatin remodelers of different families are known to control nucleosome positions in the genome [44,45,46] and the transcription of the corresponding genes [47]. The authors of Ref. [43] propose a system of rate equations for the formation of remodeler-nucleosome complexes, treating explicitly different binding events of this proofreading scenario. To quantify the implications of histone tail modifications, the authors compared the binding affinities of different bromodomains and modified histone tails using a combination of molecular dynamics, peptide docking and umbrella sampling techniques. In particular, the authors present new simulation results of pulling experiments of H3 and H4 histone tails bound to the bromodomain GCN5 in yeast and human, which are aimed at determining the free energies of binding and dissociation of the complexes. The authors discuss challenges of model parameterization using the experimental data and propose possible solutions.

In another paper of this issue Yuri Moshkin discussed nucleosome positioning and chromatin remodelling from a general point of view of the Jacob-Monod theory [48]. In a strict spirit of the classical works of Jacob and Monod [49], regulatory events can be tied to a specific gene orchestrated by a number of transcription factors [50]. However, genome-wide nucleosome remodelling offers more possibilities. The author argues that remodelers act not only locally, but also globally through genome-wide changes [48]. By modulating the concentrations of chromatin remodelers the whole nucleosome landscape can be changed. At the same time, the single-base pair specificity also remains, which makes the author to conclude that chromatin remodelling acts as a global buffer maintaining some average chromatin properties, while specifically regulating expression of individual genes.

5. Chromatin Domains

The next scale of chromatin organization is usually defined by so called chromatin domains characterized by some common physicochemical properties [51–57]. A systematic review by Bianchi and Lanzuolo in this special issue [58] lists a number of nuclear architecture elements and explains their interconnections. These structures include, for example, chromosome territories; topologically associated domains (TADs), which are defined as the regions characterized by a similar number of long-range DNA-DNA contacts revealed by high-throughput experiments; lamina-associated domains (LADs), which are defined by the proximity to the nuclear lamina; nucleolar-associated domains (NADs), etc. A specific focus of this review is on the nuclear periphery (lamina, nuclear pores, etc). This work introduces several open questions concerning chromatin domains, which are considered in more detail in the next articles:

The work of Caré et al. from this special issue considers the process of chromosome segregation in TADs based on two-colour block copolymer model introduced by Jost et al. [60]. This model was shown to reproduce a variety of selective chromatin folding patterns observed experimentally. In the present paper, Caré et al. use this model in Langevin dynamics simulations for predicting the compaction properties of chromatin fibers [59]. Interaction potentials of various intensity are used to describe the size-dependent coil-globule transition, with every bead representing 10 kb of chromatin or about 60 nucleosomes. The authors propose an expression for the finite-size Boltzmann-Gibbs distribution of chain conformations to describe a globule-like, coil-like, and stretched domain growth of the fiber, as based on their scaling properties with the chain length. The theory is in very good agreement with the results of computer simulations. The authors observe a size-dependent coil-globule transition for epigenomic domains (modelled as copolymer blocks), with the transition temperature (so called θ-point) increasing with the block length N. The main conclusion of the paper is that blocks of length N appear as globules if $\theta(N) > T$ (long blocks), whereas they are in a coil-like conformation for $\theta(N) < T$ (small blocks). This statement holds for homopolymers, block copolymers, and thus for epigenomic chromatin domains. A key prediction of the model is that chromatin compaction should increase with block size for a given epigenomic state (i.e. for a given interaction between beads of chromatin in a block). The results presented in this work open new perspectives linking epigenomes and chromosome conformation data.

Following a similar theme, the work of Moskalets et al. in this special issue [61] addresses the question of how the structure of topological domains of chromosomes is reflected in the loci colocalization data as obtained in the Hi-C experiments. In particular, the authors develop a method to extract the data about the natural separation of a chain into topological domains from the colocalization data. They also show that their algorithm is able to distinguish, based on the same data, the conformations with well-developed hierarchical domain structure from those where the domain structure is smeared and the position of domain walls somewhat arbitrary (as it is, e.g., in a regular equilibrium polymer globule [62]). The method employs modularity-based community structure detection algorithms developed in the complex network theory, but due to the linear structure of the underlying chain works substantially faster than for generic complex networks. The efficiency of the methods is checked on several artificially constructed chain conformations, including regular Peano curves, random fractal globule and equilibrium globule conformations.

A more dynamical view of large-scale chromatin organization [63,64] is considered in this special issue in the work of Lebaupin and coauthors [65]. This article focuses on the dynamical and

conformational properties of chromatin fibers and on the interplay between the chromatin dynamics and DNA repair mechanisms. The authors consider e.g. how recent chromatin polymer models combined with high-resolution spatio-temporal data analysis provide new insights regarding changes of the chromatin organization induced by DNA repair processes. After a short overview of experimental methods used for studying the chromatin dynamics on various length scales from several kbp (kilo base pairs) to Mbp (mega base pairs), the authors describe the anomalously slow diffusion of chromatin fragments. The enhanced chromatin dynamics and changes in the chromatin architecture in the context of DNA repair mechanisms in yeast and mammal cells are then compared and contrasted. In particular, the effects of chromatin repair machinery on the nucleosome destabilization and repositioning as well as on altering the inter-nucleosomal interactions within the chromatin fiber are discussed. A particular emphasis is put on active chromatin remodeling pathways. The models of chromatin organization including the fractal globule are also reviewed [66]. Finally, the authors explain the limitations of optical methods of tracking of tagged chromatin fragments.

6. Roles of Noncoding DNA and RNA

Regulatory regions can sometimes be very far away along the DNA from the gene they regulate. These are sensitive to the chromosomal environment and generally they work to limit expression of the genes to a specific tissue. Grant et al. [67] describe in this special issue several strategies to investigate the conserved noncoding DNAs. The authors note that introducing into the animal sensors capable of reporting on the regulatory potential of such chromosomal environments does little to associate the enhancer sequence on the chromosomal DNA with its long-range regulatory influence on a specific gene. This makes it difficult to examine the contribution of specific mutations in enhancers to a particular human disease. The authors of Ref. [67] argue in favour of the approach which is based on engineering large fragments of chromosomal DNA of known sequence and containing both the gene and its distant regulators with reporter genes, such as the Green Fluorescent Protein (GFP), before introducing them into the germ-line of zebrafish for expression. The use an example of the zebrafish amyloid precursor protein (*appb*) to demonstrate this approach, and show that the chromosomal context of the enhancer sequence is of utmost importance in specifying the tissue in which the gene is expressed.

Another emerging theme of epigenetic regulation is the noncoding RNA [68]. The article of Hamilton et al. in this special issue provides a comprehensive review of a particular class of noncoding RNAs, called long noncoding RNAs (lnkRNAs) [69]. Furthermore, the authors discuss in detail several interesting aspects of lnkRNA interaction with transcription factors by considering the case of a paradigmatic oncogene MYC. This article further reviews our current understanding of how MYC proteins regulate and are regulated by lnkRNAs in cancer.

7. Covalent Modifications of DNA and Histones

Covalent modifications of DNA and histones are believed to be at the core of epigenetic regulation [70,71], and are also in the focus of a number of recent biophysical studies [72]. This special issue contains several articles addressing covalent chromatin modifications and modifiers. For example, the article of Chen et al. [73] provides a systematic overview of an important chromatin modifier, MOF, which specifically deposits acetyl groups to histone H4 lysine 16. MOF plays

important roles in diverse processes ranging for stem cell identity and Xist repression to DNA damage repair, and has implications in cancers. Another acetyltransferase was featured in this special issue in the work of Kagansky and coauthors [74], who have performed a pilot RNAi screen for epigenetic silencing factors in mammalian cells and suggested new silencing proteins with unexpected roles. In particular, knock-down of the acetyltransferase Kat5/Tip60 (that is known to be down-regulated in many cancers) was found to affect the silencing in this system, likely due to the resulting changes to the lysine acetylation. The effects of DNA methylation are addressed in another article of this special issue, focusing on a controversial question of DNA methylation in insects [75]. The authors propose aphids and honey bees as an experimental model system to understand how the cytosine methylation is directly or indirectly linked to various environmental factors.

8. Linker Histones

Linker histones (H1) have been for some time understudied in comparison with the large amount of works devoted to the modifications of core histones. However, very recently several new important results connecting linker histones to epigenetic regulation have been obtained [76,77,78]. This issue has a special focus on linker histones. The article of Parseghian [79] provides a systematic and comprehensive review of linker histone variants followed by the author's original hypothesis of the role of H1 variants in chromatin organization and gene regulation. There appears to be a trend with organisms of greater multicellularity harboring a greater number of variants (11 in mammals) with the number and type of variants being conserved amongst the mammals throughout evolution. Each of the H1 subtypes varies in chromatin affinity, compaction ability and nucleosomal repeat length generation, providing a broad continuum of molecules capable of regulating transcriptional and replicational access to regions of chromatin in differentiated cells. Since H1 proteins are intrinsically disordered and take on different structural forms depending on their interactions with other cellular components, these proteins can have general effects on broad regions of chromatin and still evolve interactions with specific genes. This review provides a significant contribution to the histone H1 field and allows interested readers to understand both its history and unsolved challenges.

To summarize, eighteen articles of this special issue of AIMS Biophysics provide an exciting selection of research areas within the chromatin and epigenetics field. Of course, many important aspects of this large and rapidly progressing scientific field are not covered here, but at least some of the major current concepts are captured.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to this study.

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