Nuclear architecture and dynamics: chromatin, epigenetics, genomics

Review of Genome Organization and Function in the Cell Nucleus: Edited by Karsten Rippe

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The Project

Facing the hundreds of papers being published each month in one’s own field and given the fact that all of them can be downloaded with one click, you may ask: Why to buy and read a book? However, just considering chromatin, more than 78,000 citations are listed in Pubmed as of today, the first one being documented in this system in 1903, still a long time past after the term chromatin was coined by Walther Flemming in 1879. For me, a strong answer, why we still need books to understand what we do, was given by Wilfred Eade Agar in the preface of his book: Cytology—With special reference to the metazoan nucleus. He writes: “As must happen in any growing branch of science, the results of all this research are scattered through many publications, and any one whose duty it has been to lecture to students on this science must often have felt difficulty in recommending to inquirers a concise course of reading which will give a summary of the main results in the fields of research and at the same time indicate where more detailed information can be obtained. This book is an attempt to provide for this want.” “Cytology” was published in 1920 by Macmillan and Company, London, and obviously problems were the same for our past colleagues, though at a different level with respect to the amount of data published on the one side and without the availability of search engines on the other side.

Hence, the book edited by Karsten Rippe (Research Group Genome Organization and Function, German Cancer Research Center, Heidelberg, Germany) is of great value for students of life sciences as well as active researchers in biology of the nucleus to get a solid overview of the complexity of the interactions taking place in nuclear architecture, function and dynamics. Nowadays, you will hardly find such a comprehensive book written by a single author—one of the few exceptions was Peter Cook’s Principles of Nuclear Structure and Function in 2001.

The advantage and strength of the present book is that it provides in 20 chapters an authoritative view on this rather broad topic that received heavy attention and initiated competitive research over more than the past 100 years. Every chapter is written by internationally renowned authors and compiles insights obtained in the respective fields of expertise obtained over the past 20 years. Hence, Geneviève Almouzni, Peter Cook, Thomas Cremer, Job Dekker, Ronald Hancock, Heinrich Leonhardt, Nancy Kleckner, Angus Lamond, Eric Schirmer, Roel van Driel and Karsten Rippe himself, to name a few, have written concise but comprehensive articles that exactly manage to fulfill what Wilfred Eade Agar intended to reach: To provide balanced “starters” for entering a complex field and to perceive the nature of the respective problems.

The major topics presented, as stated in the preface by Karsten Rippe, are (1) sequence and epigenetic information; (2) chromatin organization and dynamics; (3) nuclear architecture and subcompartments; (4) transcription, RNA processing and the role of non-coding RNAs;
According to Arthur Kornberg, molecular crowding is one of the ten commandments, "Thou shall respect." Although the report provided by Ronald Hancock represents actually the shortest article of the series, it is nevertheless very informative. In particular, without going into too much detail, he is giving a very lucid picture of the problems one encounters when diving into a compartment with such a high concentration of DNA, proteins and ions as the nucleus. The concepts of "macromolecular crowding" on its way to "phase separation" is convincingly presented and optimally illustrated by very instructive figures. The problem of "Chromosomes as Polyelectrolyte Polymers" is introduced by considering the estimated concentration of nucleosomes that is stated to be 30 to 70 mg/ml and that may reach up to 400 mg/ml in some nuclear regions. This fact leads to the concept of the self-organization of nuclear components into chromosomes and an inter-chromatin compartment, i.e., the separation into discrete phases of the viscoelastic type. Along these lines, the formation and localization of transcription and replication "factories" is described as a result of entropic forces.

In the section "The Environment of the Genome during Mitosis," Ron Hancock points to the fact that the cellular components are somewhat more concentrated than in interphase, because the cell volume is decreased by around 30% during metaphase, and this crowding may affect the conformation of the chromosomes. As an example for a corresponding in vitro behavior of metaphase chromosomes, he adds an unpublished figure of his own, where the impact of decreasing concentrations of 8 kDa-PEG (12%, 6% and 0%) on the compaction state of isolated metaphase chromosomes is impressively demonstrated. In this situation, the presence of cations is not even required to prevent complete dispersion. Another interesting effect, the advantage of anomalous diffusion as produced under conditions of crowding, is presented as a way to increase the probability for small entities to find their targets.

Last but not least, in the outlook paragraph entitled "The Evolution of Genomes," Ron Hancock refers to the genome of dinoflagellates as being in a
liquid crystal conformation, citing a paper published in Chromosoma 1968. Here, Yves Bouligand and colleagues state in the English abstract of that French paper: 
"The arrangement of filaments in the chromosomes is compared with the structure of certain liquid crystals. A mathematical discussion is developed in the appendix and allows an estimate of the validity of the model and an interpretation of some of the morphological features of the chromosomes." This notion is brought into relation by Ron Hancock with chromosome segregation in bacteria, in view of the plethora of diseases caused by mutations in the corresponding genes, and lamin-binding proteins, in particular of reviews have been published on lamins as a Chromatin Organizer." It suggests that it may have played a "major role in evolution"—and not only as a platform for transcription factor and chromatin binding. The reference list is, as in practically all contributions of this book, comprehensive and the literature is covered up to 2010. More importantly, the real fundamental papers of the last decade as well as "classical" papers, in our todays view, are cited.

Quantitative Biology of Nuclear Architecture

The article of Job Dekker, Chapter 9, fits perfectly into the context of the two chapters discussed above. In principle, it deals with the chromosome conformation capture (3C) methodology for mapping long-range associations of genomic loci within a chromosome or between different chromosomes. Interestingly, besides Job Dekker and Martin Dekker, Karsten Rippe and Nancy Kleckner were engaged in establishing this method in 2002. The principal method of 3C, employing formaldehyde cross-linking of DNA and fragmentation by restriction enzymes, was later driven forward into 4C (3C on chip) in the labs of Bas van Steensel and Wouter de Laat, and eventually Job Dekker and colleagues introduced 5C, i.e., chromosome conformation capture carbon copy, in 2006. Of course, new developments such as Hi-C, building on the original 3C concept, were established and will allow us to gain further insight into chromosome architecture from the very DNA loop to the level of the whole nucleus. This article contributes, especially for me as a non-specialist in this field, all the important issues, technically and conceptually, one needs to understand the power of this approach, including FISH, 3C and deep sequencing.

In conclusion, without problems I could continue in highlighting the other chapters of the book as enthusiastically. However, I preferred to select three chapters that refer immediately to the bare bones of nuclear architecture and thereby form the basis of the complex functions performed within the nucleus. But be assured, this publication should sit on your bookshelf.
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