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Decoding Chromatin: The Synergy of Structure Dynamics, and Function

DNA choreography: correlating mobility and organization of DNA across different resolutions from loops to chromosomes

Authors: M.K. Pabba, J. Meyer, K. Celikay, L. Schermelleh, K. Rohr and M.C. Cardoso
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Recommended with a Commentary by Yuval Garini,
Biomedical Engineering Faculty, Technion, Israel Institute of Technology, Haifa, Israel

The relations between structure and dynamics is fundamental across nearly all scientific disciplines, particularly in the life sciences. Waddington's renowned depiction of the epigenetic landscape (Fig. 1) [1] illustrates this beautifully, both on the surface and beneath it.

This is precisely the focus of the work by Pabba, Meyer, Celikay et al.: understanding chromatin structure within the nucleus alone is insufficient for grasping its function, and these two factors, structure and dynamics, influence one another and works together to ensure proper nuclear functions such as gene expression, replication, and integrity maintenance. In their work, Pabba, Meyer, Celikay et al. correlates the dynamics of chromatin to different nucleus scales and structures, from sub-loops of topologically associated domains (TADs) to whole chromosomes.

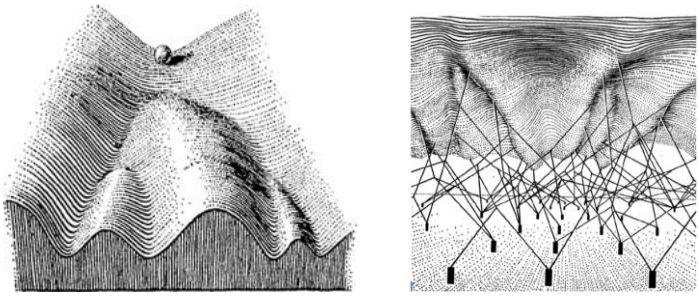

Figure 1. Waddington's epigenetic landscape (left) and its underlying 'hidden' source [1].

The exploration of nuclear and chromatin organization has experienced significant growth over the past decade [2]. Several studies have previously highlighted the interplay between structure and dynamics. Ochs et al. [3] describes a dynamic mechanism that occurs in a double-stranded break site in the nucleus. The broken site is mobilized mainly by two proteins in order to shield it against further resection. Another work studied the formation of TADs chromatin loops. A major protein that takes part in TADs formation is the CCCTC-binding factor (CTCF). CTCF marks the end-points of a TAD loop and takes part in its formation. It was found that its stability allows interactions of DNA inside the loop to become more frequent and persist for a longer duration [4].

Various insights were identified in the recommended work, including the correlation between chromatin size and its diffusion coefficient. It was found that sub-TAD loops had the highest diffusion coefficient of

~8.3×10^{-5} cm^2/sec while TADs as a whole were 'slower' (D ~ 5.4×10^{-5} cm^2/sec). The dynamics was also found to be higher in G1/G2 phases versus S phase (D ~ 13×10^{-5} cm^2/sec and 8×10^{-5} cm^2/sec in correspondence). Overall, the findings suggest that the size of DNA and chromatin directly influences their dynamics, with smaller structures exhibiting greater dynamics. While it seems obvious, a proof is still required. What does this imply for the functionality of the nucleus? This remains somewhat unclear, and requires further investigation. On one hand, higher mobility could accelerate search processes, such as the enhancer-promoter theme. On the other hand, it might cause disruption, as in the case of double-strand breaks mentioned above [3].

In a more recent study by W. R. Legant [5], the dynamics of single nucleosomes was measured and analyzed in relation to local chromatin density. The findings showed that nucleosome dynamics increase with lower chromatin density and that the dynamics in the nucleus periphery is slower than in the center, both in agreement with the results of the work described here.

The work by Pabba et al. represents a line of studies that is taken by various labs employing advanced imaging techniques to enable local dynamic studies in the nucleus with correlations to various parameters, including density, genomic properties, viscoelasticity, gene activity and more.

These studies necessitate the use of advanced imaging methods including labeling techniques for single molecules and blinking assays, the use of super resolution and optical sectioning, single molecule detection methods and statistical analysis. It is interesting to note that since the 2009 groundbreaking publication by Lieberman-Aiden, van Berkum and Williams et al. [6], chromosome conformation capture methods have driven significant progress in the field of nuclear organization. At the same time, we witness a growing number of advanced imaging studies that are becoming increasingly important to the field [7].

Data from both structural (molecular) and imaging methods should be integrated to provide insight into the structure–dynamics–function trio. This information will be crucial for developing chromatin models that can reveal the complexities of nuclear function. Various models have been proposed to explain the chromatin structure, dynamics, and function [8], ranging from liquid-like or solid-like behavior [9], incorporation of phase separation theories, polymer models [10], polymer-flow models [11] and others. The wealth of models highlights the need for further experimental data that can aid in focusing on the most relevant model.

In summary, this work serves as an example of a comprehensive study utilizing advanced imaging techniques in order to explore the spatially-related dynamics of the chromatin in the nucleus. As more data from similar studies are gathered, they may offer valuable insight for formulating a comprehensive theoretical model of the nucleus. Such a model would significantly enhance both our fundamental scientific understanding and advancement in healthcare.

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