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Foreword. Biophysics in chromatin structure and nuclear dynamics

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The title of this special edition of *Chromosome Research* reflects an intersection of two worlds: biophysics and the nucleus. This is a volume to read if you want to get a taste of how biophysics is impacting modern cell biology, since the studies discussed here illustrate some of the key approaches that biophysics can bring to cell biological problems. But there is more to these articles than just biophysics, as biophysical approaches have led to some of the most interesting new concepts in nuclear cell biology.

What have biophysical approaches taught us about the nucleus, and what might they teach us in the future? This issue is focused on two very active areas: chromatin structure and nuclear dynamics.

The organization and the folding of chromatin in the interphase nucleus is a long standing problem that has yet to be resolved. Its importance derives from the fact that numerous molecules must interact with specific DNA sites in order to carry out transcription, repair, or replication. Determining chromatin folding patterns and their control is therefore vital for understanding how regulatory molecules can access DNA.

Controversy surrounds the folding of chromatin because at the moment there is no simple way to directly visualize it. The problem has been to obtain a 3D image encompassing several cubic microns of a nucleus at high enough resolution to follow the paths of 10 and 30 nm chromatin fibers. This may be attainable with the advent of fluorescence super-resolution techniques, which are now reaching or surpassing such 3D resolutions. The article by Weiland et al. shows a first path of how this goal of visualizing chromatin structure might ultimately be realized.

An alternate approach to visualize chromatin structure comes from Baù and Marti-Renom. They produce a predicted conformation of the α-globin locus consistent with chromosome conformation capture (3C-based) data. The resultant folding pattern includes several chromatin loops plus the clustering of adjacent genes in the locus. This novel computational approach to predicting chromatin structure is likely to become widespread, as a number of groups have, or are now generating, 3C-based data. The subsequent predictions for chromatin folding might be compared to what is eventually seen by super-resolution microscopy. Indeed, the modeling procedures described by Bau and Marti-Renom can be generalized to include microscopy data, and thereby provide an even more refined prediction of chromatin based on all of the available data.

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Even if we knew precisely how chromatin was folded throughout the genome, we would also like to understand both the governing rules and the practical consequences of that folding. Here, polymer models of chromatin are invaluable by providing insights into physical principles that must inevitably impact folding. In a polymer model, a segment of chromatin, for example a nucleosome, is viewed as a repeating unit, and then a chain of such "monomers" is formed subject to local interactions between them.

Entropy plays a role in polymer configuration. For example, a polymer will tend to increase its entropy by adopting more contracted configurations rather than extended ones. Finan et al. explain how these and other entropic forces can contribute to many features of chromatin organization, including the formation of chromosome territories and chromatin loops.

Mirny summarizes recent work showing how a particular type of polymer model, namely a fractal globule, is consistent with recent 3C-based data. As noted by Mirny, many of the intrinsic properties of a fractal globule are likely to be important for real chromatin. These include its spontaneous formation and relatively long-lived state, plus a low level of entanglement facilitating unfolding of the chromatin chain.

Fritsch and Langowski also use polymer models to consider the unfolding of a condensed chromatin fiber during interphase. As part of their analysis, these authors find that the simulated polymer network does not trap diffusing molecules as often as real chromatin does. These results therefore suggest that in real nuclei there must be some form of cross-linking between chromatin chains, or potentially another network altogether.

The Fritsch and Langowski article illustrates one of the connections between the two fields covered in this edition. The folding of chromatin influences how factors move and how they find their binding sites to engage in nuclear processes such as transcription, replication, or repair.

van Royen et al. review the different models for how a protein locates its target site amidst the vast number of non-specific sites in the genome. Relevant to this question of target site search is the measurement of protein diffusion and binding within the nucleus, and so these authors also review the application of fluorescence recovery after photobleaching (FRAP) to such measurements. The ability to measure the in vivo binding rates of proteins engaged in key nuclear functions has become an important tool in the emerging field of in vivo biochemistry, which analyzes molecular processes in the context of the live cell rather than a cell extract or reconstitution.

Erdel et al. discuss not only FRAP analysis of protein diffusion and binding, but also other types of photobleaching microscopy, plus various forms of fluorescence correlation spectroscopy (FCS). All of these approaches provide information about how molecules move through the nucleus, and how they interact with chromatin. The authors suggest how the different approaches can be integrated to provide a more accurate and complete picture of nuclear protein mobility and interactions with chromatin.

Further complementing the preceding approaches is single molecule tracking, as reviewed by Dange et al., who consider the tracking of single proteins or RNAs in the nucleus. Although for many years it has been possible to track single molecules at the cell surface, doing the same inside of a cell nucleus has only recently been realized. Single molecule tracking provides a richer data set than FRAP or FCS, since the latter techniques measure only the average behavior of many molecules. As a result, single molecule tracking of RNAs or proteins in the nucleus holds great promise for furthering our understanding of diffusion and binding interactions within the nucleus.

Virtually all of the work over the last decade on nuclear protein mobility by FRAP, FCS or single molecule tracking has painted a very dynamic picture of the nucleus. Notably, the components of many molecular complexes involved in transcription or repair appear to be only transiently bound, rather than forming a stable complex, as typically predicted by in vitro biochemistry.

Hemmerich et al. evaluate this dynamic world view by compiling the results of FRAP experiments from hundreds of nuclear proteins, representing the complete spectrum of nuclear structures and processes. Remarkably, they find that in each functional or structural category, there are some nuclear proteins that have very slow FRAPs, potentially reflecting very stable binding. Thus, a thorough analysis of the available data reveals that there may be significant exceptions to the rule of transient and dynamic nuclear interactions. The authors discuss the consequences of this for models of nuclear self-assembly and self-organization.

I hope that readers will find this collection of articles to be both an informative introduction and a valuable update to the current state of the art in this field. One take-home message is that while our understanding of the nucleus is itself in flux, biophysical approaches will remain a stable component in the arsenal of techniques used to investigate the nucleus. I wish to thank all of the authors for their contributions, the reviewers for their assistance, and the editor Herbert Macgregor for his oversight.