John van Noort, J Proteomics Bioinform 2017, 10:8(Suppl)
DOI: 10.4172/0974-276X-C1-0100

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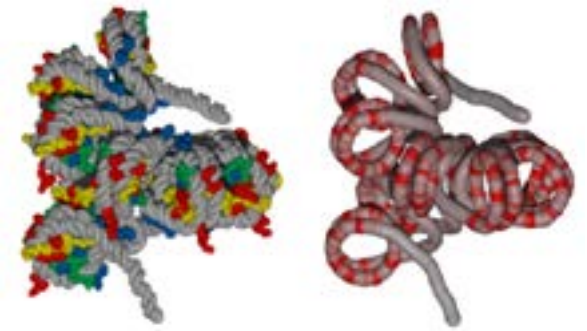
The structure of chromatin; single-molecule experiments on model fibers and real genes

The folding of chromatin defines access to our genes and therefore plays a pivotal role in transcription regulation. However, the structure of chromatin fibers is poorly defined and heavily debated. We used single-molecule techniques to probe and manipulate the dynamics of nucleosomes in individual chromatin fibers. These novel methods were initially applied to synthetic, highly homogeneous nucleosomal arrays and yielded unprecedented insight in the structure and dynamics of chromatin. With single pair Forster Resonance Energy Transfer, we showed that the nucleosome is very dynamic, unwrapping half of its DNA four times per second. Using single molecule force spectroscopy, it was possible to measure the kinetics of this unfolding, both in single nucleosomes and in well-defined arrays of nucleosomes that fold into a 30 nm fiber. Analysis of the unfolding pattern reveals a linker length dependence of the higher order folding. The linker length *in vivo* however varies, and to obtain insight the positioning of nucleosomes we developed a simple statistical physics model that captures sequence dependent positioning effects for both reconstitutions on synthetic DNA and chromatin *in vivo*. We recently developed a method to purify specific chromatin fragments from yeast without crosslinking the fiber while maintaining the complexity that provides functionality to our epi-genome. I will show the first single-molecule force spectroscopy results on intact, native fibers which uniquely probe chromatin structure, composition and variations in it at the single-molecule level.



Biography

Chromatin is the ubiquitous protein-DNA complex that forms the structural basis of DNA condensation in all eukaryotic organisms. Packaging and depackaging of chromatin, called chromatin remodeling, plays a central role in all cellular processes that involve chromosomes such as transcription, replication, recombination and repair. Detailed knowledge of the principles and mechanisms underlying this control of DNA condensation is thus vital for understanding many diseases, including neurological disorders and cancer. The physical mechanisms governing these processes however, are still largely unknown. I am interested in developing and using modern biophysical techniques to unravel the physics behind DNA condensation and its role in transcription regulation.

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