

Organization

Umeå University
Department of Physics

Document type

Doctoral thesis

Date of publication

15 November 2024

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Title

Finding a target on DNA: Interplay between the genomic sequence and 3D structure

Abstract

Cells are complex systems of interconnected machinery that maintains, repairs and furthers the growth of themselves. In the center lies the instructions that coordinate it all - the DNA. This meter-long string of code carries the instructions that coordinate cell life, from basic maintenance to the specific function of the cell in the body.

These instructions are constantly used by different protein complexes, but the mechanisms behind several details of these processes are still not understood. For example - the size of a specific set of instructions on the DNA is a mere fraction of the whole genome - how can these instructions be quickly found, and how can the complexes know it found the right set of instructions? Is this search problem related to how DNA is folded and stored in our cell nucleus? These questions are further complicated by the fact that different cell types only use specific instructions, which can change as the cell is affected by, for example, external forces. How can the DNA control which instruction set is available, and how does this affect the other questions we just asked?

These are some questions this thesis tackles. To take a step towards a better mechanistic understanding, this thesis combines data from biology and methods from physics to formulate computational and analytic models to understand the mechanical principles of DNA folding, as well as protein search and binding. This entails finding new hierarchical clusters in DNA, proposing explanations for discrepancies in DNA regulation, connecting sequence specificity with DNA folding and investigating how multiple cooperating parts complicate the DNA search problem.

We find that we can improve our tools to better understand the data we base our models on, and that sequence specificity and folding connects in intricate ways, giving us a more complete view of cellular function.

Keywords

chromatin structure, DNA sequence, statistical physics, Monte-Carlo simulations, target-finding problems, network science, diffusion processes

Language

English

ISBN

print: 978-91-8070-517-2
PDF: 978-91-8070-518-9

Number of pages

69 + 5 papers