500 words abstract of the dissertation of Christian Arnold

"The Eukaryotic Chromatin Computer – Components, Mode of Action, Properties, Tasks, Computational Power, and Disease Relevance"

Eukaryotic genomes are typically organized as chromatin, the complex of DNA and proteins that forms chromosomes within the cell's nucleus. Chromatin has pivotal roles for a multitude of functions, most of which are carried out by a complex system of covalent chemical modifications of histone proteins.
The propagation of patterns of these histone post-translational modifications across cell divisions is particularly important.
However, DNA replication constitutes a dramatic disruption of the chromatin state that effectively amounts to partial erasure of stored information. To preserve its epigenetic state the cell reconstructs the histone post-translational modifications using processes that are incompletely understood. A plausible hypothesis is that the different combinations of reader and writer domains in histone-modifying enzymes are capable of ``recomputing" the desired parental patterns.

Recent work suggests that during evolution, chromatin has been converted into a powerful cellular memory device capable of storing and processing large amounts of information. Eukaryotic chromatin may therefore act as a computational device, and even relatively simple models of chromatin computation are Turing-universal and hence conceptually more powerful than gene regulatory networks.

In this thesis, I establish a deeper understanding of the computational capacities and limits of chromatin, which have remained largely unexplored.
I analyze selected biological building blocks of the chromatin computer, particularly focusing on memory and the logical and arithmetical operations. I propose a cellular automata-like one-dimensional string as its computational paradigm on which sets of local rewriting rules are applied asynchronously with time-dependent probabilities. It furthermore provides volatile memory with a massive information content of several hundred megabytes of writable information per cell. Chromatin is therefore another representative of the growing number of non-standard computing examples.

As an example for a biological challenge that may be solved by the ``chromatin computer", I formulate epigenetic inheritance as a computational problem and develop a flexible stochastic simulation system for the study of recomputation-based epigenetic inheritance of individual histone post-translational modifications. I find that it is easy to evolve such a system of enzymes. However, the success of this task depends on several previously unanticipated factors, all of which also influence the accumulation of errors in the wake of cell divisions.

Chromatin-regulatory processes constitute a sensitive system, and any dysregulation may contribute to various diseases such as Alzheimer's disease, which is increasingly being recognized. I address the two hypotheses that a dysregulated chromatin computer plays important roles in Alzheimer's disease and that the disease may be considered as evolutionarily young. I identify numerous chromatin-associated, differentially expressed loci and found support for both hypotheses although it is very difficult to establish causalities due to the complexity of the disease.

For the identification of differentially expressed loci in Alzheimer's disease, I use a custom expression microarray. It was constructed with a novel bioinformatics pipeline because for complex transcriptomes, it is non-trivial to establish an appropriate probe design strategy because alternative splicing and transcription from non-coding regions are pervasive. Additionally, a user-friendly web server has been set up that makes the developed pipeline publicly available.