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Transcriptional regulation by histone modifications

Transcriptional regulation in cells makes use of diverse mechanisms to ensure that functional states can be maintained and adapted to variable environments. Among these mechanisms are cis-regulatory modules and chromatin modifications. Unraveling the hierarchy of these different layers of regulation represents a challenge of Molecular Systems Biology. We here introduce a mathematical model of genome-wide transcriptional regulation governed by histone modifications. This model describes the binding of protein complexes to DNA which are capable of reading and writing histone marks. Cooperative molecular interactions between the protein complexes, the DNA and the modified histones create a regulatory memory and allow for switch-like changes of the expression state of the genome. We provide analytical results on the dependence of the regulatory states on i) the (de-) modification activity of histone (de-)methylases, ii) the accessibility of the DNA-binding regions of the protein complexes and iii) the number of histones that act cooperatively; and discuss the impact of the cellular environment on these properties. We demonstrate that according to our model proliferation activity per se can switch expression states of the genome as a consequence of suppressed inheritance of the histone marks. We apply our model to transcriptional regulation by trxG- and PcG-binding to DNA. By analysing ChIP-seq data of mouse ESC we provide evidence for cooperative modes of histone modifications. Thereby, our data suggest a threshold length of the cooperative chromatin regions of about 10kb which agrees with the loop length of an un-interrupted chromatin fibre. Our results provide new insights into genome-wide transcriptional regulation by histone modifications and represent a first step towards simulation studies on changes of the epigenome during ageing and disease.