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TOWARDS FORECASTING EPIGENETIC REPRESSION

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Abstract
Multicellular organisms form many different cell types from one genome, which requires differential gene activity. The Polycomb system upholds the correct gene expression programs by epigenetically silencing genes that encode critical transcription regulators. It is defined by the protein complexes Polycomb Repressive Complexes 1 and 2 (PRC1 and PRC2). PRC2 methylates lysine 27 on histone H3 (H3K27) on nucleosomes. This is necessary for the repression, but it is not known why. In *Drosophila melanogaster* both PRC1 and PRC2 bind to DNA elements called PREs near the target genes. In human cells, PRC2 are tethered to CpG islands, but PRC1 tethering is not well understood. In paper I of the thesis we uncover the first comprehensive catalogue of DNA elements, Polycomb Tethering Elements (PTEs), that target PRC1 to human developmental genes. PTEs and CpG islands may be intermixed—forming a PRE equivalent—or offset from each other. Genes equipped with PTEs have low transcription and are stochastically reactivated upon deletion of their PTE. In paper II, we used a computational model to stochastically simulate both the random and targeted methylation by PRC2, to understand the dynamics of H3K27 methylation. The model was constrained by data, such as the levels of methylation in cells, allosteric stimulation of PRC2 by H3K27 trimethylation, and the differing catalytic efficiency of each successive methyl transfer to H3K27. We used it to investigate PRC2's allosteric stimulation, the relationship between the rates of methylation and demethylation and cell cycle length, and how the rapid embryonic development of *D. melanogaster* affects the maternal contribution of H3K27me3 to the embryo. In paper III we used polymer modelling to investigate how chromatin folding by PRC1-H3K27me3 interactions affects contacts inside loci repressed by the Polycomb system. With these three studies, this thesis combines experimental and computational methods to further our understanding of epigenetic repression by the Polycomb system.

Keywords
epigenetics, Polycomb, PRC1, PRC2, H3K27 methylation, Monte-Carlo simulation, chromatin structure, *Drosophila*

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