**MPhys Draft Report**

**Molecular Dynamics Simulation of Chromosomes with Epigenetics**

**1 Introduction**

Epigenetics is the study of heritable modifications of gene expressions that occur without altering the genetic sequence within the DNA \cite{DNABook, probst2009}. Different classes of epigenetic modifications have been identified. One kind of modification involves biochemical changes on the nucleotides, the basic units within the DNA sequence. Another kind involves modifications of histones, which are proteins that the DNA coils around to form nucleosomes, the building blocks of the chromatin fibre. Epigenetic modifications are important as they facilitate the process of regulating gene expression.

It is clear that the epigenetic modifications must be established during developmental stage of an organism and these modifications must be maintained (or re-established) during major events in the cell cycle such as replications and cell division. A major research interest within the field of epigenetics is to understand the mechanisms which facilitate the establishment of epigenetic patterns and the stable inheritance of these modifications over generations of cells. This is particular important for differentiated cells in multi-cellular organisms (eukaryotes) to retain their identity.

A class of approach used to understand the mechanisms is through mathematical modelling. Many biophysical models have been proposed and have successfully explained some aspects of the establishment and inheritance of epigenetic marks \cite{dodd2007}. However, most of these models focus only on the epigenetic landscape of the chromatin fibre. It has long been recognised that epigenetic modifications are related to the dynamics and conformations of the chromatin fibre\cite{}. In addition, a lot of models only allow the proliferation of a single type of epigenetic modification on the modelled chromatin. It is clear that for additional information to be encoded one would need to allow a stable maintenance of multiple epigenetic marks. Hence, it is of interest to develop a model that is capable of describing the chr

Recently, the simulation work by Micheletto et. al. \cite{micheletto2016} has given some insights in coupling epigenetic modifications and chromatin dynamics. They used a polymer model to simulate the three-dimensional (3D) dynamics of the chromatin fibre and couple it with a Potts-like

The project focuses on investigating the coupling of another stochastic one-dimensional model proposed by Dodd et. al. (cite), which successfully characterise the spreading and maintenance of epigenetic marks, with a three-dimensional polymer model that describes chromatin dynamics.

The remaining sections of the report are as follows: Section 2 provides an overview o

**2 Background**

**2.1 Structure of the Chromosome**

To fully appreciate the discussion on epigenetic modifications and the simulation work performed in this project, it is important to understand how the DNA is stored within a (eukaryotic) cell. The DNA is located within the cell nucleus and is organised into highly compact structures called chromosomes. At the elementary level, the DNA is packaged into nucleosomes similar to a bead-on-a-string structure (see Figure XX). The core of each nucleosome is the histone octamer, which contains two copies of four kinds of histone proteins (H2A, H2B, H3, H4). The octamer is wrapped around by roughly 150 base pairs (bp) of DNA sequence. There are ~50 bp of DNA between two nucleosomes and the H1 histone protein binds to this region. The nucleosomes organise themselves into higher order structures by associating with each other to form the chromatin fibre. The fibre further compacts itself by proposed mechanisms such as forming loops and rosettes (cite). It is only during cell division (metaphase specifically) that the fibre condenses itself into the well-known X-shape structure to prepare for the separation of the genetic materials.

**2.2 Epigenetic Modifications**

As mentioned in the introduction, epigenetic modifications are heritable changes associated with gene expression without modifying the underlying sequence of the DNA. These modifications tend to be reversible, meaning that they can be added and removed from the genes throughout the lifetime of the cell. Two well-known types of epigenetic modifications are DNA methylation and histone modifications. Both have significant influence on the biological functions of a cell by regulating its genetic expression – whether a particular gene should be active or inactive.

DNA Methylation

DNA methylation refers to the addition of the methyl group (CH3) to a particular nucleotide, the basic unit of the genetic code, of the DNA. Most commonly, methylation occurs to the cytosine within the cytosine-guanine (CG or CpG) pair in the genetic sequence. Studies have shown that CpG methylation is associated with various biological processes including transcriptional repression, X-chromosome suppression in female mammals,

Histone Modifications

Histone modifications, which is the type of epigenetic modification of interest in this project, refer to the biochemical modifications that are applied to the histone proteins in the nucleosomes. As with other proteins, histone proteins are composed of amino acids, which are the basic building blocks any protein molecules. Each histone molecule has an extended tail which is composed of a thread of amino acids. Different functional groups can be bind to the amino acids of the tail to modify the histone protein. The three common types of modifications observed are acetylation (addition of CH3CO), methylation (addition of CH3), and phosphorylation (addition of PO43-). It can be seen that these modifications allow information to be stored in addition to the genetic sequence. These modifications have been thought as forming a “histone-code” which regulate gene expression.

**2.3 Relation between Epigenetic Modifications and Dynamics of Chromatin**

It is understood that epigenetic modifications have the function of regulating the activity of different genes within the DNA. A possible mechanism by which these modifications affect gene expression is through the control of how tightly the chromatin fibre is compacted together. An active gene means that it is possible for transcription factor. Indeed, there are evidences which support this proposed mechanism. For instance, it has been shown that acetylation of lysine 16 on histone H4 (H4K16Ac) hinders the compaction of nucleosomes into a very tight chromatin fibre and [knaak2006].

**2.4 Mechanisms for the Establishment and Maintenance of Epigenetic Marks**

**3 Methodology**

**Simulation Model**

In the project, we simulated a chromatin fibre as a semi-flexible “bead-and-spring” polymer of N beads. In line with common mappings employed in modelling chromatin dynamics [cite], each bead represents roughly 3 kbp, which corresponds to around 15 nucleosomes. Each bead

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The epigenetic modification is based on the model proposed by Sneppen et. al.

The modification is coupled to the chromatin dynamics.

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**Initialisation Procedure**

As in any molecular dynamics simulation, it is important to describe the initialisation procedure. The initial state of the chromatin fibre used in each simulation is created based on the random walk model. Each

**Program Structure and Software Used**

**Testing**

**Results**