**MPhys Project Report Outline**

**Title:** Investigating Chromosomal Dynamics with Epigenetics using Molecular Dynamics Simulations

1. **Introduction (~1 page)**

* Introduce epigenetic modification and its importance in biology
* State the key research question: understanding the mechanisms behind the establishment and maintenance of epigenetic patterns
* Summarise the work done to address this question, mainly focusing on computational and theoretical work (i.e. theories proposed and models studied) and mention recent advances that motivated the project (i.e. work done by Michieletto *et. al.)*
* State the main objectives of the project
* Outline the main structure of the report

1. **Background (6-7 pages)**
   1. DNA and Chromosome

* Introduce the key structures within the chromosomes that are relevant to the project: DNA, histones, nucleosomes, and the chromatin fibre

Figures:

* A figure showing the structures within the chromosome (DNA, histones, nucleosomes, chromatin fibre)
  1. Epigenetic Modifications
* Define epigenetic modifications and list two main types of modifications: DNA methylation and histone modifications
* (2.2.1) Discuss the mechanism of DNA methylation and its known biological roles
* (2.2.2) Discuss the mechanism of histone modification and its known biological roles

Figures:

* A diagram illustrating DNA methylation and histone modification
  1. Establishment and Maintenance of Epigenetic Marks
* State that establishment and maintenance of epigenetic patterns is a key topic to be understood
* Motivate the importance of studying the establishment and maintenance of epigenetic patterns by an important example: X-chromosome inactivation in the female mammalian cell
* (2.3.1) Outline the “read-write” mechanism and explain how it might allow stable establishment and maintenance of epigenetic patterns; provide a few examples which support this mechanism (e.g. spreading of H3K27me and H3K4me)

Figures:

* A figure illustrating the read-write mechanism, showing the coupled interactions between reader and writer enzymes
  1. Motivation of the Study
* Summarise the recent simulation work by Michieletto *et. al.* on the “read-write” mechanism
* State the objectives of the project:

1. Identify the possible phases/types of configuration of the system within the coupled model and characterise the transition nature between phases
2. Investigate mechanisms that allow establishment and maintenance of multiple epigenetic domains
3. **Methodology (7-8 pages)**
   1. Simulation Model

* (3.1.1) Discuss the model for the spatial dynamics of the chromosomes (the interaction potentials and the time integration schemes)
* (3.1.2) Discuss the model for epigenetic modifications (Sneppen model)
* (3.1.3) Discuss the initial conditions used for the simulations
* (3.1.4) Discuss the mapping between simulation and physical timescales

Figures:

* A cartoon illustrating the modification rules of the Sneppen model
  1. Model Implementation and Program Structure
* Discuss the main structure of the computer program created to run the simulation (i.e. main classes of the program and their responsibilities)

Figures:

* A UML diagram showing the program structure of the 1D epigenetic colour code
* A flowchart showing the coupling between the 1D epigenetic colouring code and the 3D chromosome dynamics LAMMPS code
  1. Program Testing
* Mention unit tests was created to verify the correctness of code
* Show that the 1D epigenetic code reproduced similar results to those described in the paper by Dodd *et. al.*

Figures

* Reproduced results (e.g. figure 2A-E in the paper by Dodd *et. al.*) (to be put in appendix?)

1. **Results (12-15 pages)**
   1. System Phases in the Coupled Model

* Describe the quantities used to characterise the phase of the system: radius of gyration () and effective magnetisation ()
* Discuss that there are at least three phases in the system: swollen-disorder (SD), compact-disorder (CD), compact-ordered (CO)
* (4.1.1) Analysis of the transition order for SD → CD (2nd order-like transition)
* (4.1.2) Analysis of the transition order for SD → CO (1st order-like transition)

Figures:

* Phase diagrams for and
* Combined result of the phase diagrams showing the transition lines (estimated from the peak of the variance) (also show images of the simulated chromosome in each phase)
* For SD → CD: probability distribution as a function of ; hysteresis results for N = 1000 (to be completed)
* For SD → CO: probability distribution as a function of and ; hysteresis in and for N = 1000 (if time permitted, perform a simulation which shows that the system would retain the same epigenetic pattern even after major events in cell-cycle (e.g. cell division))
  1. Formation of Multiple Epigenetic Domains
* (4.2.1) Domain formation by introducing permanent active/inactive states (bookmarks)
  + Identify the minimum frequency of bookmarks needed for domain establishment
  + Demonstrate that the explicit introduction of bookmarks can alter the 3D structure of the chromosome (i.e. mixed bookmarks result in more swollen configuration)
* (4.2.2) Domain formation by introducing non-modifiable regions (gene deserts)

Figures (for both bookmarks and gene deserts)

* Kemographs showing the formation of epigenetic domains
* Contact map indicating the strong coupling between like-coloured domains
* Probability distribution of beads along the chromatin fibre being in a particular state (to indicate domain size)

1. **Discussions (2-3 pages)**
   1. Significance and Implications of Simulation Results

* The simulation model further verifies that coupling 1D epigenetic modification and 3D chromosomal dynamics provides a reliable mean for the establishment and maintenance of epigenetic patterns
* Introducing “bookmarks” and “gene deserts” results in formation of stable epigenetic domains, indicating that these are effective mechanisms for maintaining multiple epigenetic domains in chromosomes
  1. Future Work
* Further improve the biological realism of this coupled model (e.g. adding active transcribing gene region and see its effect on the chromatin structure)

1. **Conclusion (~1 page)**

* Summarise the key results obtained in the project
* State the significance of the work and how it will contribute to this research field