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Geometric and computational models of chromatin fibre folding for human embryonic stem cells

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Abstract

In this study we analyze the chromatin state of human pluripotent stem cells by geometric and computational modelling of fibre conformation. The model takes into account local structure of chromatin organized into euchromatin, permissive for gene activation, and heterochromatin, transcriptionally silenced. Euchromatin was modelled using linear DNA while heterochromatin by means of a solenoid structure in which DNA winds onto six nucleosome spools per turn. Two geometric models are presented and are compared in terms of geometric quantities. The models are tested using in vivo data generated from chromatin human immunoprecipitation from embryonic stem cells. This study provides insight for identifying the relationships between chromosome geometry and epigenomic processes associated with chromatin remodeling, cellular reprograming and maintenance of cellular pluripotency.

Keywords: chromatin structure; pluripotency; epigenomics; geometric modelling; euchromatin; heterochromatin.

1. Introduction

The human genome is estimated to contain approximately 30,000 unique genes. Though every gene exists within every cell in the human body, only a small percentage of these genes is active in any given cell. What promotes the transcription of cell-specific genes and determines the cell identity? Chromatin structure and its ability for remodeling into different states.

Recent data show that stem cell chromatin differs from that of somatic or differentiated cells in several structural and functional aspects, such as global chromatin arrangement, condensation and compaction. Moreover,

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undifferentiated embryonic stem (ES) cells are characterized by hyperdynamic plasticity of chromatin proteins, supporting an open conformation model of chromatin in undifferentiated stem cells. Hence, chromatin state is currently being considered as one of the most important factors for self-renewal and pluripotency of ES cells. The chromatin state of a cell is defined through the establishment and the maintenance of localized open and closed states of the chromatin structure, determined by epigenomic interactors.
In fact mutations in epigenomic regulators have the potential to alter the chromatin structure, leading to mis-regulation of gene expression and contribute to cancer or other diseases.
Therefore understanding chromatin remodeling is of fundamental significance in understanding cancer and for regenerative medicine.
The focus of our research is on identifying and characterizing the chromatin state of Pluripotent Stem Cells (PSCs). PSCs are characterized by extensive self-renewal and multi-lineage differentiation potential. PSCs generate all functional tissues of the body during development and adult stem cells (SCs) that allow for regeneration of these tissues following injury or degenerative processes. In this study we present a summary of an extensive analysis on the chromatin state using in vivo data generated from chromatin immunoprecipitation of human embryonic stem cells with Oct4, Sox2 and Nanog transcription factors. The investigation is carried out using geometrical and computational models of the chromatin fibre conformation.

2. Measures and energetics of filament coiling

In this section we show how to investigate several geometric features of the DNA filament, such as writhing, inflexional configuration, torsion and twist localization, in relation to properties of physical interest, such as elastic deformation energy and filament compaction (Maggioni & Ricca, 2006; Ricca & Maggioni, 2008; Maggioni, Potra & Bertocchi, 2013, Maggioni, Alamri, Barenghi & Ricca 2013).
For this purpose we refer to an inextensible, smooth, simple closed curve C in the three-dimensional space $\mathbb{R}^3$, thought of as the central axis of a closed, double-stranded DNA filament. Each point on C is labeled by the position vector $\mathbf{X}=\mathbf{X}(\xi)$, where $\xi\in[0, L_{fin}]$, its curvature by $c(\xi)$, torsion $\tau(\xi)$ and $\hat{\mathbf{t}} = \dfrac{\mathbf{X}'(\xi)}{\left\| \mathbf{X}'(\xi) \right\|}$ the unit tangent to C at ξ and $l(\xi)$ the length function.
Coiling is measured by the *normalized total curvature* of C that is given by

$$\mathcal{K} := \frac{1}{l(\xi)} \int_0^{L_{fin}} c(\xi) \left\| \mathbf{X}'(\xi) \right\| \mathrm{d}\xi.$$

The folding process conserves topology. For a thin filament this means conservation of the linking number Lk (Călugăreanu, 1961; White, 1969), given by

$$Lk := Wr + Tw\,,$$

where Wr represents the *writhing number* (Fuller, 1971) and Tw represents the total twist of the filament fibres. These are assumed to be wound uniformly around the axis C.
Denoting by $\Omega = \Omega(\xi)$ the angular twist rate of the fibres, we have that the *normalized total twist* is given by

$$Tw := \frac{1}{l(\xi)} \left(\frac{1}{2\pi} \int_0^{L_{fin}} \Omega(\xi) \left\| \mathbf{X}'(\xi) \right\| \mathrm{d}\xi \right),$$

which is related to the geometry of the filament axis through the decomposition

$$Tw := \frac{1}{l(\xi)} \left(\frac{1}{2\pi} \int_0^{L_{fin}} \tau(\xi) \left\| \mathbf{X}'(\xi) \right\| \mathrm{d}\xi + \frac{1}{2\pi} [\Theta]_{\mathcal{F}} \right),$$