Dynamic Random Loops Can Explain the Appearance of Topologically Associating Domain in Chromosome Capture Experiments

1   Introduction

The spatio-temporal organization of the chromatin plays an essential role in the regulation of sub-cellular activity such as gene expression and regulation [1].

3d structure of the Igh locus was suggested by [4] after tagging several position along the loci.

2   Experimental data and Methods

We use the experimental 5C data generated by Nora et al.[5] for the chromosome contact frequencies of the X chromosome in a 4.5 Gb region encompassing the X inactivation center. In our work we focus on a subset of the data, including a 94,082 bp region, termed TAD D and E (see [5]).

The maps generated by the 5C experiments describes the contact between genomic loci of variable sizes in many nuclei. Contacting loci are those resulted from the cross-linking created by the fixation of DNA in formaldehyde, which yields a contact distance of 10-100 nm [2]. We then follow data coarse-graining procedure performed by Giorgetti et al.[3] to map segment encounter data to that of beads. A bead size of 3000 bp was chosen according to the mean size of restriction segments resulted by HindIII enzyme digestion, used in the process of the 5C experiments (see [3] Supplementary Material). This choice of bead size resulted in coarse-grained polymer of 307 beads.

The coarse-grained pair-wise bead encounter frequency includes 14,509 data points and was used to calculate the bead encounter probability as a function of bead distance in the following way. Encounter frequencies for equidistant beads were averaged to give the 'one sided' bead encounter frequency, we then divide the bead encounter frequency by the total number of encounters for that bead to obtain the encounter probability. We use the bead encounter probability to display the bead encounter matrix. This is a 307 by 307 matrix containing the pair-wise encounter probabilities in each of its entries.

In our simulations we use a Rouse polymer to examine different polymer conformation that give rise to the appearance of a Topologically Associating Domain (TAD). The Rouse model describes the dynamics of a linear polymer as a collection of massless beads connected by harmonic springs and driven by the thermal forces of diffusion. The differential equation describing the time progression of the nth bead in a chain of N beads is given by

$$\frac{dR_n}{dt} = -\frac{K_B T}{b^2 \zeta}(2R_n(t) - R_{n-1}(t) - R_{n+1}(t)) + \sqrt{2D}\frac{dw_n}{dt} \qquad (1)$$

where $R_n(t)$ describes the 3D coordinates of bead n at time t, $K_B T/\zeta$ is the diffusion constant, b is the standard deviation of the distance between adjacent beads of the chain, and w_n is a white Gaussian noise.

The encounter probability was fitted with a function of the form $\alpha d^{-\beta}$, with $\alpha = \frac{1}{\sum_{j=1}^{k} j^{-\beta}}$, d is the distance in bead units, and β is a parameter to be determined.

3 Results

4 Discussion

References

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