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[1].

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

2 Experimental data and Methods

2.1 Analysis of the experimental data

We used the experimental 5C data generated by Nora et al.[4] for the chromosome contact frequencies of the X chromosome in a 4.5 Gb region encompassing the X inactivation center. In our work we focused on a subset of the data, including a 94,082 bp region, termed TAD D and E (see [4]).

The maps generated by the 5C experiments describes the contact between genomic loci of variable sizes over millions of nuclei. We followed data coarse-graining procedure, similarly to the one described in [2], to map segment encounter frequencies to that of evenly spaced, equal size 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 [2] Supplementary Material). This choice of bead size resulted in coarse-grained polymer of 307 beads.

The coarse-grained pair-wise bead encounter frequencies includes 14,509 data points and was used to calculate the bead encounter probability as a function of the distance in beads units. Encounter frequencies for equidistant beads were averaged to give the 'one sided' bead encounter frequency. The bead encounter probability was derived by dividing the bead encounter frequency by the total number of encounters of that bead.

We fitted the experimental bead encounter probability with a function of the form

$$p(d) = \alpha d^{-\beta} \tag{1}$$

with p the encounter probability, $\alpha = \frac{1}{\sum_{j=1}^{k} j^{-\beta}}$, d is the distance in bead units, and β is a parameter to be determined by the fitting procedure.

2.2 The polymer model

To explore the different polymer conformations that can explain the appearance of the TADs, we chose to use the Rouse chain. The Rouse chain 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 system of stochastic differential equations describing the time progression of a chain of N beads is given in the 3-dimensional case by

$$\frac{dR}{dt} = -\frac{3D}{b^2} K R + \sqrt{2D}\frac{dW}{dt} \tag{2}$$

where, $R(t) = [R_1(t), R_2(t), .., R_N(t)]^T$ describes the 3D coordinates of the N beads at time t, D is the diffusion constant, b is the standard-deviation of the distance between adjacent beads of the chain, W is an independent $N \times 3$ Brownian motion with mean 0 and variance 1 in each component, and K is the Kirchhoff bead connectivity matrix, which reflects different chain connectivities tested.

2.3 Simulations

Simulations were always carried out until the chain's relaxation time, in which any two beads were determined to have encountered if their distance at the end of the simulation satisfied $|R_j - R_k| < \epsilon < b, \quad (j \neq k)$. The chain's relaxation time is given by the slowest mode of the linear chain

$$\tau = \frac{b^2}{12D \sin(\frac{\pi}{2N})}$$

for which the number of simulation steps performed is $\frac{\tau}{\Delta t}$. The time step, Δt was set so to prevent simulation 'blow-ups' by demanding that the quotient of the norms of beads position at two subsequent steps would be smaller that unity, which resulted in $\Delta t = \frac{b^2}{12D}$.

For each tested polymer connectivity we summed up the bead encounter frequencies histogram and derived the bead encounter probability. The bead encounter probability was then fitted similarly to the fitting in eq. 1.

3 Results

4 Discussion

References

[1] Thomas Cremer and Christoph Cremer. Chromosome territories, nuclear architecture and gene regulation in mammalian cells. *Nature reviews genetics*, 2(4):292–301, 2001.

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