Chromatin reconstruction and dynamics using random Loops accounting for Chromosome Capture data

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Abstract

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References

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Figure 1: **Analysis of the experimental data** (a) Average contact histogram of the 2 replicates of the 5C experiments in 2 discrete genomic regions of high self interactions termed TAD D and E (Nora et al [6]) (b) The encounter probability graphs for each of the 307 beads show long range interactions between beads in TAD E and between TAD D and E, a fit of the form $\alpha d^{-\beta}$ to the mean encounter of each distance (red curve), was found to have a decay exp. $\beta = 0.729$, below the expected $\beta = 1.5$ for a linear Rouse polymer, implying compact configuration of the polymer and looping (c) The calculated decay exp. value for each of the 307 beads (circles) was fitted with a smoothing spline (black curve) to show a fluctuating pattern around the mean ($\beta = 0.729$, green dashed line) with sharp decrease in values for beads having long range interactions, e.g beads 25, 102, 165, 285.

Figure 2: **Simulation of a chain with connectors between beads corresponding to peaks of the encounter data**. (a) An illustration of a polymer connected between beads corresponding to peaks in the encounter data $(p_i, p_l), (p_j, p_m), (p_k, p_n)$ (b) The encounter histogram of the polymer with connectors does not show similarity to encounter histogram of the experimental data (Figure 1) (c) The encounter probabilities shows flat profile, indicating a compact polymer configuration. (d) the fitted decay exp. β values for each one of the profiles in box (c) display low value corresponding to long range interaction of beads along the chain.)

Figure 3: **Encounter profile for a polymer model with one fixed loop and 1-30 random internal loops.** (a) A sketch of the polymer model used in simulation. Beads 107 and 207 were connected to form a 100 beads fixed loop, while 1 to 30 random internal loops were sequentially added. Each loop was formed by randomly picking a bead pair (orange arrow) in the range 108-206 (B) The encounter histograms for 7 cases (number of loops indicated in white) resembles a TAD region.(c) For each number of random internal loops, a model of the form $\alpha d^{-\beta}$ was fitted to the encounter probability of each bead, the resulting decay exp. β values decreases sharply for beads in the loop range (107-207) with increased number of internal loops, whereas, beads outside the loop show similar behavior independent of the number of loops (D) The mean decay exp. β values as a function of number of internal loops decreases quadratically and allows to infer from the measured mean encounter probability the number of loops in the polymer.

Figure 4: **Encounter profile for a polymer model with two fixed loops and 1-30 random internal loops** (a) A sketch of the polymer model used in simulations. Beads 1,107 and beads 108,307 were connected to form two large loops corresponding to TAD D and E. One to 30 internal loops were sequentially added in each TAD (orange arrows) by randomly picking bead pairs in the range 2-106 and 108-306 (b) The encounter histograms for each number of loops (indicated in white in each box) resembles the TADs of the experimental data (Figure 1) as the number of loops increased. (c) For each number of internal loop, a model of the form $\alpha d^{-\beta}$ was fitted to the encounter probability of each bead. Beads on the edge between TADs (e.g beads 107, 108) show a decrease in the decay exponent due to frequent encounters with beads in both TADs. (d) A quadratic relationship was found empirically between the number of loops and the mean decay exp.(e) The anomalous exponent, α, extracted from the fitted mean square displacement of each bead in the case of 0 to 30 random loops in each TAD.

Figure 5: **Setting the weights in the connectivity matrix of the β polymer with loops**. (A) The weights in the matrix are determined by $A_{l,m} = 4\kappa\frac{2}{N}\sum_{p=1}^{N-1} sin^{\beta}(p\pi/(2N))cos((l-0.5)p\pi/N)\cos((m-0.5)p\pi/N)$, the curve is drawn for bead 1. (B) The polymer is treated as a graph with nodes representing beads (circles) and edges as springs (bars). An example of an architecture in which be beads 2 and 13 and 4 and 11 are connected (orange line). Arrows indicate that the new value for the weights for bead 1 in positions 13, 11, 9 are determined by the values of the original curve with no peaks at positions corresponding to the shortest distance on the graph between bead 1 to all others. (C) Connecting two beads in the polymer changes the weights such that the new weights are assigned by the values of the β polymer weights according to the closest distance between beads on the connected polymer graph.

Figure 6: **A comparison between simulations of two β models with loops corresponding to peaks of encounters in TAD D**. A uniform $\beta = 1.5$ model (left column) was compared to a variable β model (right column), with β values extracted from the experimental data. Encounter histograms (a-b) showed similar qualitative behavior with slightly more contacts in the variable β model, indicating a more compact configuration. This compaction was evident in the encounter probability signals (c-d) with a mean β value (red curves) of 0.75 in the uniform vs. 0.67 is the variable model. A qualitatively similar behavior was noted in the fitted decay exponents values of each bead (e-f) and for the decay exponent of the average of the encounters (horizontal lines) of 0.22 in the uniform vs 0.19 of the variable β model. Taken together, these observations suggest that a uniform β value for all beads is enough to capture the complexity in the experimental data.