Statistical model of intra-chromosome contact maps

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(Dated: December 2, 2013)

PACS numbers: 61.43.Hv, 87.15.Cc, 87.16.Zg, 87.18.Vf

The statistical properties of intra-chromosome maps obtained by a genome-wide chromosome conformation capture method (Hi-C) are described in the framework of the hierarchical crumpling model of heteropolymer chain with quenched disorder in the primary sequence. We conjecture that the observed Hi-C maps are statistical averages over many different ways of hierarchical genome folding, and show that the existence of quenched primary structure coupled with hierarchical folding can induce the observed fine structure of intra-chromosome contact maps.

The analysis of DNA folding in human genome based on the genome-wide chromosome conformation capture method \([1, 2]\) provides a comprehensive information on spatial contacts between genomic parts and imposes essential restrictions on available 3D genome structures. The Hi-C maps obtained in the experiments on various organisms and tissues \([2, 8]\) (some examples are shown in the Fig.1A-C) define the average contact probability, \(P(s)\) between two particular parts of genome separated by the (genomic) distance \(s\) along a chain. These maps display very rich structure in a broad interval of scales, where \(P(s) \sim 1/s\) (see the Fig.1D) in consistency with the so-called fractal (or ”crumpled”) globule \([9]\) model of polymer chain packing. The latter is characterized by two main features: (i) it has almost no knots, and (ii) it is self-similar in a wide range of scales, forming a fractal space-filling structure. Both these properties are essential for genome folding: fractal organization makes genome tightly packed at all scales, while the lack of knots ensures easy and independent opening and closing of genomic domains, necessary for transcription \([10, 11]\). In 3D this packing results in a space-filling conformation of a chain with fractal dimension \(D_f = D = 3\).

The Hi-C contact probability, \(P_{i,j}\), between two genomic units \(i\) and \(j\) depends in a complicated way on a combination of structural and energetic factors. However, in a fractal globule with \(D_f = 3\) the average contact probability, \(P(s) = (N - s)^{-1} \sum_{i,j=0}^{N-s} P_{i,j,s}\), between two units separated by the genomic distance \(s = |i - j|\) should decay as \(P(s) \sim s^{-1}\). This probability can be naively estimated as \(P(s) \sim 1/R^D(s)\), where \(R(s)\) is the typical size occupied by the \(s\)-fragment. For curves with the fractal dimension \(D_f\), one has \(R(s) \sim s^{1/D_f}\), hence, \(P(s) \sim s^{-D/D_f}\), and for \(D_f = D = 3\) one gets \(P(s) \sim 1/s\).

Apart from the averaged contact probability decay, one notes in Hi-C maps a chess-board-like intermittency in color intensity \([12]\), elements of a hierarchical structure on small scales \([8]\) (see the inset in the Fig.1C) and chromosome compartmentalization on the large scale. Below we propose a statistical toy model, which allows to reconstruct the \(1/s\) decay of the contact probability, and the typical fine structure of the experimentally observed Hi-C maps. Our model, on one hand, is based on sound physical principles dealing with the fractal globule formation, and on the other hand, is kept as simple as possible.

Figure 1: A-C: Typical samples of Hi-C maps (chromosomes 1 (A), 4 (B), and 13 (C), data used here provided to us by courtesy of M. Imakawa), the color encodes the contact probability between genome fragments, each pixel corresponds to 2kb genome length; D: Contact probability decay in doubly-logarithmic coordinates for the same Hi-C maps (s is the genomic distance form the main diagonal of a map) compared with \(1/s\) power law.

For the structural contribution to Hi-C probabilities, we assume a fractal globule model of genome packing \([10]\). The formation of a fractal globule (see \([9]\)) is a hierarchical process. In a collapsing polymer chain, there exists a certain chain-dependent critical length, \(g^*\), constituting...
the 1st-level fold (see the Fig.2A). As soon as 1st-level folds are formed, the “folds of folds” of the second level start forming, etc., producing a hierarchy of crumples, the process ends when all \( g^* \)-link folds are collected in a single (largest) fold.

To account for the energetic contribution to the contact probability, we assume the elementary units of a genome to be different from each other. The chessboard intermittency in the contact probabilities typical for Hi-C maps (see Fig.1) suggests the existence of at least two distinct types of units which we denote A and B (for the discussion of possible biological meaning of this separation into different chromatin types see, e.g., [12]). The chess-board intermittency of darker and lighter regions is modelled by an Ising-type energy cost, \( E_{ij} \), associated with the spatial contact between two units \( i \) and \( j \):

\[
E_{ij} = \begin{cases} 
-1, & \text{if } i \text{ and } j \text{ are of same type} \\
-u, & \text{otherwise}
\end{cases}
\]  

where \( 0 \leq u \leq 1 \) is the ratio of the energies of favorable and unfavorable contacts (henceforth we use the energy of a favorable contact as the energy unit). Remind that the elementary units A and B represent rather long chromatin fragments, consistent with the resolution of the Hi-C method, which is of order of kilobases.

The probability \( P_{ij} \) of a contact between \( i \)th and \( j \)th units of a hierarchically folded heteropolymer chain should depend on the generation, \( \gamma_{ij} \), of the minimal common fold both these units belong to, and on the species of the two units. We define the corresponding statistical weight of the \( ij \) contact as

\[
w_{ij}(\gamma) = e^{-\beta E_{ij} P_{ij}^{str} + (1 - P_{ij}^{str})},
\]

where \( E_{ij} \) is the contact energy (11) between units \( i \) and \( j \), \( P_{ij}^{str} \) is an \( a \ priori \) (structural) contact probability between two units imposed by the hierarchy of folds, \( \beta \) is the inverse temperature, and the non-contact energy is assumed to be 0 by definition. The structural probability is a function of \( \gamma_{ij} \), and if the folding is space-filling, then

\[
P_{ij}^{str} \sim V^{-1}(\gamma_{ij}) \sim p^{-\gamma_{ij}},
\]

where \( V(\gamma_{ij}) \) is the volume of the fold, which for the space-filling folding is proportional to the number of elementary units in it. The proportionality coefficient in (3) can be absorbed into the definition of \( E_{ij} \) so, without the loss of generality, \( P_{ij}^{str} = p^{-\gamma_{ij}} \). In Fig.2C, D we depict binary matrix \( E \) with elements \( E_{ij} \) and a Parisi-type matrix \( P \) with elements \( P_{ij}^{str} \) for some particular chain with a quenched monomer sequence.

Although the hierarchical structure of folds emerges naturally within the fractal globule concept, its presence in the experimental Hi-C maps is not always very evident. We explain that by suggesting that smearing of the hierarchical block-diagonal structure occurs in experimental Hi-C maps due to the non-uniqueness of DNA folding.

Indeed, if the hierarchies of crumples are arranged differently in different folding realizations, then the distinct block-diagonal structure, typical for each realization, is

![Figure 2: A: Schematic representation of a hierarchical folding; B: Tree-like organization of crumples in a hierarchical folding; different translations are enumerated by the parameter \( m_f \); C: Block-hierarchical Parisi matrix of contact probabilities corresponding to a particular folding scheme with \( m_f = 0 \); D: Matrix of contact energies for a given primary structure.](image-url)
smeared out in the ensemble averaging, while the 1/s-decay of an average contact probability still holds. In what follows we demonstrate that combining the hierarchical heteropolymer folding with the averaging over different foldings, we can reproduce the typical behavior of experimentally observed Hi-C maps.

To introduce averaging over realizations we proceed as follows. Take a polymer chain with a given sequence of units and consider all possible ways to fold it into hierarchical structures. Since in our model the geometry of the tree of folds is fixed, and the chain fills all the folds sequentially, there is only one possible way to alter the folding structure from one realization to the other, that is, to change the position of the first elementary unit on the tree boundary – see Fig. 2A. This change of the starting position induces a cyclic shift of all monomers along the boundary: $i \to i + m \mod p_{\text{max}}$, $i = 1, 2, ..., N$, where $N$ is the length of the chain. The only parameter defining a particular folding configuration is the shift $m$, in Fig. 2B the samples corresponding to $m = 0$ and $m = 3$ are shown.

Now, one can self-consistently define the weight of a particular hierarchical folding. Assume that all contacts within a given folding are formed independently (i.e. all correlations in formation of contacts are already encoded within a given folding are formed independently (i.e. all particular hierarchical folding. Assume that all contacts are shown. The boundary: $w_{ij} = w_{ij}(\gamma|m)$.

Here the weights $w_{ij}$ ($i, j = 1, N < p_{\text{max}}$) are given by Eq. (2), and one should make an additional assumption about the weights of the contacts between the chain folds and “outer space” (i.e., the chain parts surrounded by some other molecules), they are designated by open circles in Fig. 2A. Since the chromatin folding happens in a nuclei within a crowded environment, one assumes that these open circles are effectively filled by the units of other chromosomes. To account for this, we introduce a mean-field interaction between units of the chain under consideration and the “average” units of other chains exactly as in Eq. (2) where

$$E_{ij} = \begin{cases} -q - u(1 - q), & \text{if } i \text{ is of type A} \\ -(1 - q) - qu, & \text{if } i \text{ is of type B} \end{cases}$$

and $q$ is an average fraction of monomers of type A.

The total partition function accounting for all folds, reads now

$$Z = \sum_{m=0}^{p_{\text{max}} - 1} W(m)$$

(6)

The probability for each pair of units, $i$ and $j$ is, as usual

in equilibrium statistical mechanics

$$P_{i,j} = \sum_{m=0}^{N-1} \frac{W(m)}{Z} e^{-\beta E_{ij} P_{i,j}^{\text{struct}}(m)} e^{-\beta E_{ij} (1 - P_{i,j}^{\text{struct}}(m))},$$

(7)

where the first term defines the thermodynamic probability of a particular hierarchical folding realization, and the second term explicitly encounters the contact probability for this particular folding. The values of $P_{i,j}$ given by Eq. (7) are the contact probabilities that should be compared with the results of the Hi-C measurements for the intra-chromosome contact maps.

In the high-temperature limit, i.e. for $\beta = 0$, we have $w_{ij} = 1$ as it follows from Eq. (2), and $P_{i,j}$ are just the averages of $P_{i,j}^{\text{struct}}$ over cyclic permutations of indices along the Cayley tree boundary. Being averaged, all $P_{i,j}$ depend only on $s = |i - j|$, and in the limit $N \gg 1$ they are $P(s = |i - j|) \sim s^{-1}$. To reproduce this scaling, consider the values of $\mathcal{P}(s)$ for $s = p^m$, $m = 0, 1, 2, ...$. Let also $N$ be the power of $p$, i.e. $N = p^M$. Then

$$\mathcal{P}(p^m) = \frac{N}{N-1} \sum_{i=1}^{M-m} \frac{1 - p}{p^m} \simeq C p^{-m}$$

(8)

where $C = [p^2(1 + p)]^{-1}$. The last equation is valid for $(M - m) \gg 1$. Since $p^m = s$, we get $\mathcal{P}(s) \sim s^{-1}$. This corresponds (at least in the high-temperature limit) to the dependence typical for the real Hi-C data. This refines the naive arguments concerning space-filling curves: any fold containing $\sim p^3$ monomers is formed by a fragment of length $s \sim p^7$.

Let us summarize the main features of our model. Its input consists of a primary monomer sequence, and three numerical parameters: (i) the number of subfolds in each fold of the hierarchy, $p$ (this parameter, though being quantitatively important, does not influence the qualitative appearance of the resulting structure of Hi-C maps), (ii) the comparative affinity of alternating AB contacts versus AA/BB ones, $u$, and (iii) the inverse temperature, $\beta$, which essentially regulates the uniqueness of folding. Indeed, for $\beta = 0$ all foldings are equivalent and equally contribute to the resulting probability, while for $\beta \to \infty$ the folding with the lowest energy give the dominant contribution to the contact probabilities.

In Fig. 3 and Fig. 4 the examples of contact maps generated by our model are shown. To demonstrate the influence of a monomer composition on the contact probability, we have generated random Markovian heteropolymer sequences of $N = 150$ monomers with varying average block length (average lengths of blocks A and B are equal, thus the average fraction of units “A” is $q = 0.5$). The parameters $u = 0.25$, $\beta = 0.25$, and $p = 2$ are the same for all three sequences. One sees that the resulting contact map is essentially sequence-dependent, while the averaged contact probability decay plotted in the Fig. 3D as a function of genomic distance, $s$, still follows the $1/s$ power law for all selected sequences.
The contact probability is weakly temperature-dependent. The figure Fig.4D demonstrates that the averaged block-hierarchical structure with increasing temperature.

Figure 4: A-C: Dependencies of contact probability of the hierarchical crumpled globule on the primary sequence \((N = 150)\) for different realizations of primary sequences and fixed \(u = 0.25, \beta = 0.25\) and \(p = 2\); the average length of blocks is 10 for (A), 3.33 for (B) and 12.5 for (C); D: Averaged contact probability for sequences in A-C compared to the 1/s plot.

In Fig.4A,B and C we show the influence of \(\beta\) on the contact probability maps for a fixed Markov chain of length \(N = 150\) with average block length 12.5 and \(u = 0.25\). One sees the sequential degradation of the block-hierarchical structure with increasing temperature. The figure Fig.4D demonstrates that the averaged contact probability is weakly temperature-dependent.

Figure 3: A-C: Dependencies of contact probability of the hierarchical crumpled globule on the primary sequence (\(N = 150\)) for different realizations of primary sequences and fixed \(u = 0.25, \beta = 0.25\) and \(p = 2\); the average length of blocks is 10 for (A), 3.33 for (B) and 12.5 for (C); D: Averaged contact probability for sequences in A-C compared to the 1/s plot.

We see from Fig.4 and Fig.3 that our model indeed demonstrates a fine structure of the contact probabilities reminiscent of that obtained in the experimental Hi-C maps. Note that the existence of compartmentalization in the maps shown in the figures (i.e., large-scale block structure) is due to the quenched disorder primary sequence. The configuration of large-scale blocks is disorder-dependent (see figure Fig.4). In absence of any disorder all folding configurations have equal weights, so the average contact probability decays gradually as 1/s with genomic distance \(s\). Of course, the model presented above is a mere caricature of a real situation: the number of possible folding ways in our model grows linearly with the chain length, while it is bound to be exponential in real folding, when the hierarchical folding mechanism accounts for intrinsic randomness. However, we believe that the main result concerning the interplay of the uniqueness of folding and visibility of contact map fine structure will persist.

One possible way to generalize our model is as follows. Consider the hierarchy of folds, described by the terminal points at the Cayley tree boundary (see the Fig.2) as being entirely separated from the chain itself. In this case the hierarchy of folds plays a role of a specially prepared space of possible microstates (conformations), in which the chain is embedded. In such a description transitions between different folded conformations, i.e. transition between different terminal points at the Cayley tree boundary, are described by the “ultrametric” random walk, where the transition weight form one state to the other one is controlled by the highest barrier separating these two states [14]. Then, the coincidence of two folded configurations can be identified with the return probability of the ultrametric random walk.

In this letter we have proposed a statistical model which reproduces the principal features of the experimentally observed Hi-C maps. We have included into consideration the heteropolymer structure equipped by the hypothesis of hierarchical DNA folding. We tried to avoid as much as possible the specific “biological” details, sticking mainly to basic principles of statistical physics of disordered systems. Such a description, being less informative for concrete biological systems, allows us to conjecture the generic mechanism behind Hi-C map fine structure and could be considered as a complimentary for the probabilistic refinement of Hi-C experiments developed recently in [15].

We have assumed in our model that each single chromosome conformation is hierarchically folded with distinct contact maps similar to hierarchical Parisi matrix shown in the Fig.2C. Since many such conformations may have similar energies, in the resulting averaged structure of contacts the hierarchical behavior could be smeared out. Besides, the largest compartments get smeared the least, because the shift in the position of largest fold corresponds to the largest energy change. We believe that the hierarchical compartmentalization of chromosomes into large domains, widely observed in experiments is facilitated by a collective effect of many similar microscopic monomer-monomer interactions of heteropolymer primary structure folded as a fractal globule.
The authors are grateful to M. Imakaev, L. Mirny, A. Mironov and J. Mozziconacci for stimulating discussions. This work was partially done during the visit of M.T. and L.N. to LPTMS, Universite Paris 6, the authors appreciate the hospitality of their hosts as well as financial support from the IRSES project FP7-PEOPLE-2010-IRSES 269139 DCP-PhysBio, which payed for this visit. M.T. and V.A. acknowledge the financial support of the Higher School of Economics program for Basic Research.

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