A polymer model explains the complexity of large-scale chromatin folding

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The underlying global organization of chromatin within the cell nucleus has been the focus of intense recent research. Hi-C methods have allowed for the detection of genome-wide chromatin interactions, revealing a complex large-scale organization where chromosomes tend to partition into megabase-sized “topological domains” of local chromatin interactions and intra-chromosomal contacts extends over much longer scales, in a cell-type and chromosome specific manner. Until recently, the distinct chromatin folding properties observed experimentally have been difficult to explain in a single conceptual framework. We reported that a simple polymer-physics model of chromatin, the strings and binders switch (SBS) model, succeeds in describing the full range of chromatin configurations observed in vivo. The SBS model simulates the interactions between randomly diffusing binding molecules and binding sites on a polymer chain. It explains how polymer architectural patterns can be established, how different stable conformations can be produced and how conformational changes can be reliably regulated by simple strategies, such as protein upregulation or epigenetic modifications, via fundamental thermodynamics mechanisms.

Introduction

The development of “chromosome conformation capture” (3C) methods and, in particular, of Hi-C technologies has given access to the complex three-dimensional organization of chromosomes at a great depth and at genome-scale.2–7 It has been proposed that chromatin tends to organize in arrays of megabase-scale domains (e.g., see ref. 3), termed “topological domains” (TDs),9 characterized by an enrichment of intra-chromosomal local contacts. Interactions within chromosomes extend, however, over much longer scales and contacts between different chromosomes have also been reported,1,10–13 highlighting a complex orchestration of genomes in time and space (see refs. 1–7 and references therein), which can be cell-type and chromosome specific, as found in FISH and more recent Hi-C mapping. Such discoveries have raised a number of fundamental conceptual questions on how the genome self-organizes in such a variety of complex patterns, how long-range contacts can be established reliably to have meaningful functions or how specific structures like TDs are assembled.

The properties of chromatin folding have been explored in Hi-C studies by analyzing, in particular, how the average frequency of intra-chromosomal pair interactions (i.e., the contact probability, \( P_c(s) \)) changes with the pair genomic distance (here named \( s \)).1,8–13 Intra-chromosomal contacts are more abundant locally, i.e., between neighboring chromatin regions, but extend with lower frequency up to scales of the order of tens of megabase pairs. The first Hi-C study, in a human lymphoblastoid cell line, reported that the average contact probability, \( P_c(s) \),

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across a genomic distances, $s$, is a power law, $P_c(s) \sim 1/s^\alpha$, in the 0.5–7 Mb range, having a specific exponent $\alpha = 1.08$.\(^1\) While in polymer models, $P_c(s)$ is often a power-law, such a value of $\alpha$ is not usually found in equilibrium (see 1, 14–17 and references therein). This result led to assume, thus, that chromosomes exist in a specific transient state found in ideal polymer chains models, named the fractal globule (FG), which is known to have an exponent $\alpha = 1$.\(^1\) However, a recent wave of additional Hi-C data\(^3,12,18\) made clear that the contact probability, $P_c(s)$, and its exponent $\alpha$ vary across different cell types, as well as across individual chromosomes within a given cell type (see Fig. 1). By analyzing Hi-C data from human cell lines,\(^1,8,11\) for instance, we showed that $\alpha$ ranges roughly from 0.9 to 1.7 (see Fig. 1 and 18). In other organisms, the $\alpha$ exponent is also different from 1.08, such as in Drosophila where, on a genome-wide scale, it is equal to 0.85, whereas in “closed” genomic regions it is equal to 0.7.\(^12\) Such a variety of behaviors is not compatible with the FG model which predicts a unique exponent $\alpha = 1.18$ And it raises additional questions: how are different structural conformations established in different systems and how can they be changed under different circumstances, for example during differentiation or in response to external signals?

### The Strings and Binders Switch Model

To try to rationalize such a range of experimental observations, we followed the idea that chromatin 3D conformations must be shaped by chromosome interactions with other nuclear elements, such as the nuclear envelope, nuclear bodies and DNA binding molecules.\(^16\) For instance, a variety of chromatin contacts mediated by DNA binding factors has been reported, between genomic sequences of the same as well as of different chromosomes. And chromatin contacts with other nuclear landmarks are also well documented. All these features will ultimately need to be considered,\(^16\) but for the sake of simplicity we started by exploring a scenario where chromatin interactions are established by diffusing molecules that bind to specific binding sites across the length of a DNA polymer.

To quantify such a scenario, we introduced the strings and binders switch (SBS) polymer model (see Fig. 2, left) where chromatin is represented as a polymer chain having discrete binding sites for diffusing molecules. The molecules are present in molar concentrations, $c_m$, and have binding affinity $E_x$.\(^18,20\) The polymer has self-avoiding-walk (SAW) properties, and itself and its binders move in space by diffusion, simply under the constraint of no overlap. In contrast with other chromosome models, binders and polymers move in space and interact based only on the laws of physics, without ad hoc assumptions on their behavior and organization. In the SBS model, diffusing molecules have a binding multiplicity $\geq 2$ and can thus form “chromatin contacts” between distal binding sites along the polymer (see snapshots in Figs. 2 and 3). In its simplest version, the polymer binding sites are equally spaced. The model can be expanded and refined by considering different kinds of binding molecules and binding sites or by allowing co-binders that bind to binders but not directly to the polymer, as seen in biological systems. For the sake of simplicity, though, we focus first on the simplest cases. Up to 5120 beads have been considered in the polymer model, without finding major difference in the system overall properties upon changing the system size, as expected from the scaling properties of polymer physics.\(^23\)

### Self-Organization of Chromatin Folding and the Emerging Stable States of the SBS Model

To understand the mechanisms by which different polymer folding states can arise, we started by considering how diffusing factors produce contacts (i.e., bridges) between binding sites along the polymer in the SBS model.\(^19,20\)

At low concentrations of binding molecules, $c_m$, the formation of a chromatin loop between binding sites is statistically unlikely because it results from a sequence of two random events: a diffusing molecule must first find and bind to a site along the polymer, and then, before detaching, must encounter a second site by random diffusion. Thus, at low concentration, $c_m$, bridges exist only very transiently and the polymer will remain on average open. At high $c_m$, however, once a first bridge is established, the formation of a second bridge between other local binding sites is highly facilitated because they are kept in closer proximity by the first bridge and because of the increased probability of encountering a second binding molecule at higher concentrations. Once a second bridge is formed, it reinforces the first and helps the formation of a third and
so on, such that a positive feedback loop mechanism sets in to hold the polymer in a bridged, compact state. The polymer dynamically changes over time but retains a given stable average folded structure. The concentration value where such feedback loop mechanisms become overriding marks the transition point between the regime where the polymer is stably open to the regime where it spontaneously folds into a compact conformation. In fact, such a transition point corresponds to a thermodynamic phase transition (the polymer Θ-point) occurring in the system when the entropy loss due to the co-localization of different parts of the polymer is compensated by the energy gain associated with the formation of the bridging molecular bonds. The above pictorial description is illustrated in quantitative terms by the phase diagram of the SBS model (Fig. 2), which shows the state attained spontaneously by the system at different molar concentrations, $c_m$, and binder affinities, $E_x$. The two thermodynamic phases of the system correspond to two stable topological states. Below, at or above the phase transition line (see Fig. 2, right), the polymer folds in conformations belonging respectively to the class of: (1) the open folded state, (2) the Θ-point fractal state (i.e., the point where the polymer shrinks...
from an “expanded coil” state to a “collapsed globule”\(^{24}\) and (3) the compact state. Remarkably, the values of binder concentration and affinity at the transition state identified in the SBS model fall in the range of transcription factor concentrations and binding affinities found in biological systems, i.e., tens of nanomole/liter and in the weak energy range characteristic of non-covalent, H-bond biochemical interactions (few units in \(k_T\) at room temperature).

The thermodynamic mechanisms driving the phase transformations between open and looped chromatin states identified with the SBS model also explain how conformational changes in chromatin topology can be sharply and reliably regulated in a switch-like process. Increasing or decreasing \(c_m\) or \(E_X\) across the transition threshold between the different phases provides a robust and stable transition between open and looped chromatin states, with no need for fine tuning of the binder concentration or affinity.\(^{21,22}\) This can be accomplished via simple, well-known biological strategies such as up- or downregulation of the concentration of the polymer-binding molecules (i.e., acting on \(c_m\)) or by epigenetic modifications of the binding sites along the polymer (i.e., acting on \(E_X\)). The conversion between continuous, analogical parameters which are difficult to precisely control in vivo in single cells, into a digital open/looped chromatin state may be achieved either by changes in binding sites looping together change in biological systems, i.e., tens of nanomole/liter and in the weak energy range characteristic of non-covalent, H-bond biochemical interactions (few units in \(k_T\) at room temperature).

Contact Probabilities in the SBS Model and in Hi-C Data

The SBS model provides a mechanistic framework to explore how polymer folding states depend on the concentration and affinity of chromatin binders and identifies three architectural classes that correspond to stable emergent states: open polymer, closed polymer and an intermediate (\(\Theta\)-point) fractal state. To relate the polymer folding properties identified by the SBS model with chromatin contact frequencies measured by Hi-C, we calculated the contact probability, \(P_c(s)\), in our polymers modeled with a range of parameter values.\(^{18}\) In the SBS model, at large genomic separations, \(s\), the shape of \(P_c(s)\) is also a power law, \(P_c(s) \propto 1/s^{\alpha}\). The value of the exponent \(\alpha\) is not unique, but depends on the thermodynamic phase the system is into (either open, closed or in the transition state). Thus, the exponent \(\alpha\) has a switch-like behavior as a function of binder concentration or affinity, with a higher plateau at \(\alpha = 2.1\) at low \(c_m\) or \(E_X\) (i.e., in the open phase), a lower plateau at \(\alpha = 0\) at high \(c_m\) or \(E_X\) (in the compact phase) and a narrow inflection point corresponding to the phase transition line at the threshold values for concentration and affinity, where \(\alpha\) ranges between 0 and 2.1 (at the \(\Theta\)-point \(\alpha = 1.5\)).

The different values of the exponent \(\alpha\) recorded experimentally can be thus, interpreted in a very simple way, as averages in different systems across a number of differently folded chromatin pieces, for all genomic regions in the same cell and for each genomic region in a population of cells. Within a given sample there can be many different kinds of folding structures mixed together in different proportions, such as hetero- and euchromatin, as shown by Hi-C and FISH (see ref. 18 and references therein). To illustrate that concept, we considered mixtures of open and closed SBS polymers, and measured their contact probability distribution, \(P_c(s)\), and the corresponding effective value of its exponent \(\alpha\). More specifically, we modeled a mixture of polymers\(^{18}\) containing a fraction, \(f\), of polymers in the open conformation (where \(\alpha = 2.1\), see Fig. 3) and a fraction, \(1-f\), of polymers in the compact conformation (where \(\alpha = 0.0\)). We found that the effective \(\alpha\) depends on the fraction \(f\) (see Fig. 3, left). For instance, a value \(\alpha = 1.08\) is found for \(f = 60\%\), in a range of \(s\) spanning one order of magnitude, as observed in the original Hi-C data from the human GM06990 cell line.\(^{1}\) If \(f\) is decreased down to 45%, the mixture has \(\alpha = 0.93\) in the same range, a value close to the one found, for instance, for chromosome X in the human female cell lines GM06990 and IMR90.\(^{8,18}\) Analogously, in a system where \(f = 80\%\), i.e., enriched for open regions, we identify \(\alpha = 1.3\), as found for chromosome 19 in the above cell lines,\(^{8,18}\) or the genome-wide average in the GM12878 cell line\(^{1,18}\) (see Fig. 1).

In summary, our analyses\(^{18}\) of the Hi-C data (see Fig. 1) shows that different cell systems, and even different chromosomes of a given system, have different contact probabilities, \(P_c(s)\). All \(\alpha\) exponents measured experimentally across different species and cell types so far fall in the range of exponents predicted by the SBS model (0 to 2.1). Furthermore, these differences can be explained either by changes in local intra-chromosomal interactions that increase with greater binder concentration or affinity or definitely by the presence of varying mixtures of open, closed and, in principle, of \(\Theta\)-point fractal state chromatin regions.

Formation of Topological Domains in the SBS Model

High resolution Hi-C and 5C analysis highlighted the existence of TDs consisting of ~1 Mb size domains enriched in intra-chromosomal interactions,\(^{8,9}\) which had previously been observed while studying chromatin folding in nuclei by microscopy (e.g., see refs. 2, 14, and refs. therein). The looping out of chromatin fibers from whole chromosome territories has also been observed following gene activation in single cell FISH analyses.\(^{37,39}\)

The formation of TDs and the looping out of specific loci can be rationalized elegantly within the SBS model by specialization of polymer binding sites and binding molecules.\(^{18}\) In Figure 4, we show the folded state achieved spontaneously by an SBS polymer system containing two kinds of binding sites, located in two separate halves of the polymer length. When each type of site has a specific affinity to only one kind of binder, separate domains naturally appear within the polymer’s organization. They are characterized by a contact matrix similar to the ones
Discussion

In summary, the SBS model provides a key to understand: (1) how three-dimensional polymer organization can be established using randomly diffusing binding molecules and a freely moving polymer; (2) how different stable polymer conformations are produced; (3) how architectural changes are reliably regulated; and (4) how the variety of biological behaviors identified experimentally can be rationalized in a single mechanistic framework. In fact, the SBS model has the power to explain all currently available Hi-C and FISH data, ranging from the average contact probability and mean square distance between loci, the moment ratio of locus distances (K) and finally the contact matrices of TD, all in a simple unifying scenario. The SBS model also highlights the key physical concepts and basic required ingredients to explain chromatin folding. Folding classes correspond to stable emergent phases and conformational changes can be sharply controlled by simple strategies, such as protein upregulation or epigenetic chromatin modifications, via fundamental thermodynamics mechanisms. And a variety of transient conformations can exist in the SBS model, including structures such as the "fractal globule."

Many structural and functional constraints arise in real nuclei. For instance, a variety of specific binding factors exist, and different regions can spontaneously fold into different states dependent on the location and type of the binding sites, the concentration of the binder and their affinity for one another. Importantly, however, polymer scaling theory ensures that the general structural behavior of folding is independent of the minute details of the system considered and reflect universal properties, as those captured by the SBS model. Thus, the different regions have to fold into one of the states discussed here (closed, Θ-point fractal or open). Crowding and entanglement effects can be also included in the model as they can have important roles on the

Insights from Single Cell FISH Data

Studying chromatin folding on single cells by imaging techniques, such as FISH, has revealed fascinating properties of chromosome biology over the years. Chromosomes are not fully entangled, but are organized in territories, which are constrained by their own inherent cis-interactions, by the presence of other chromosomes, the nuclear membrane and by attachments to the nuclear lamina. Importantly, the nuclear membrane and by attachments the presence of other chromosomes, the their own inherent cis-interactions, by

systems and, since it is dimensionless, it can be used to compare directly polymer models and experimental data. Comparison of the range of values of the kurtosis found with the SBS model and observed in FISH experiments (see Figure 5) reveals one of the most fascinating features of the SBS model. In the currently available single-cell FISH data, the kurtosis varies between 1.5 and 5. And, interestingly, as we change concentration or affinity of binders in the SBS model and the polymer folding evolves from open to compact, the kurtosis spans the same range of values from 1.5 to 5. In particular, the value 1.5 corresponds to the open and compact state, whereas around the transition point the values peak up to 5. In the light of the SBS model, the observation that many pairs of studied loci have K higher than 1.5 (the value predicted for the ideal Gaussian polymer chain) suggests that chromatin folding in real nuclei is better explained by considering also transition fractal states.

Figure 4. Specialization can spontaneously induces the formation of distinct domains in the SBS model. Binding site specialization is illustrated here as red and green polymer sites bound respectively by red and green diffusing molecules (left). Chromatin domains can form when binders are in sufficiently high cm or E (center). Looping out of a specific loci from one of the domains can also result from specialization, in this case the loss of affinity for the binding molecules represented by the blue polymer sites. The corresponding SBS contact matrix (right) closely resembles those observed for chromatin TDs from Hi-C or 5C experiments.
system dynamics, as found by ours and other groups in the study of other complex fluids. 26-30 The SBS model could be employed to describe the folding behaviors of specific chromosomal loci, such as the Xir locus. 31,33 It can also help describe other specific cases of chromatin organization, like for example chromosome conformation at meiosis. 34,35

Overall, the available experimental data and the insights from the SBS model point toward a scenario where chromatin is a complex and dynamic mixture of differentially folded regions. Yet, with simple models that consider the most basic biochemical features of chromatin and its regulatory binding factors, we can begin to comprehend the nature of the folding states of chromatin, as well as the fundamental physical mechanisms through which it self-organizes across spatial scales in such complex patterns.

Disclosure of Potential Conflicts of Interest
No potential conflict of interest was disclosed.

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Figure 5. (Left) Experimental FISH data, from a number of chromosomal loci and genomic separations, are shown of the moment ratio, <r^4>/<r^2>, i.e., the dimensionless ratio of the average of the fourth power of the physical distance between two loci, r, and the square of the average of R^2. For comparison, the horizontal dashed line highlights the value, 1.5, known for the ideal Gaussian polymer chain model. (Right) The value of <r^4>/<r^2> in the SBS model depends on which phase the system is into (i.e., on the binder concentration c_b). In both the open and compact states, <r^4>/<r^2> is 1.5, but at the transition region it has a sharp peak spanning the same range found experimentally. The comparison of experiments and model predictions points out a scenario where chromosomal loci exist not only in the open and compact state (where <r^4>/<r^2> > 1.5), but also close to the 0-point transition state (where <r^4>/<r^2> > 1.5 peaks up to around 5).
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