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Published in final edited form as:
Pombo A, Nicodemi M. Physical mechanisms behind the large scale features of chromatin organization. *Transcription*. 2014 Apr-Jun ; 5(2): e28447. | doi: <http://dx.doi.org/10.4161/trns.28447>
Landes Bioscience (U.S.A.) ►

Commentary paper

Physical mechanisms behind the large scale features of chromatin organization

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Abstract

We review the picture emerging from recently published models of classical polymer physics of the general features of chromatin large scale spatial organization, as revealed by microscopy and Hi-C data.

In the nucleus of eukaryotic cells chromosomes are arranged in a complex three-dimensional (3D) architecture. Microscopy, for instance, has shown they occupy discrete nuclear regions, called chromosomal territories [1,2]. More recently, 3C-based technologies, such as Hi-C [3], have allowed to derive detailed genome-wide contact matrices of the frequency of physical contacts between all genomic regions. An intricate network of interactions emerges with fascinating properties. A striking feature is the discovery that each chromosome is subdivided in Mb-sized domains, named TADs, characterized by enriched levels of interactions [4,5]. Nevertheless, the origin of TADs and their underlying mechanisms remain unknown. More generally, one of the key open challenges in the field concerns the understanding of the structure of the nucleus, the origin of the observed patterns, the factors that shape them and how they are regulated by the cell for functional purposes. All these issues have conceptual and practical implications as, for example many cancers are related to chromosome incorrect folding [6].

Hi-C contact matrices have shown, in particular, that the average interaction probability between pairs of loci decreases with the genomic separation of the loci considered, with a power law decay at least within the 0.5-7Mb range [3]. It has become clear, though, that the exponent, α , of the power law is different in

different systems (Fig. 1; [7]). For instance, human embryonic stem cells (ESCs) have on average $\alpha \sim 1.6$ [7], while human chromatin from lymphoblastoid cells at interphase has $\alpha \sim 1.1$ [3]. Human chromosomes in metaphase from a cancer (HeLa) cell line have $\alpha \sim 0.5$ [8]. The exponent α also varies widely in different species. In mouse ESCs it is $\alpha \sim 0.7-0.9$ [5], in *Drosophila* $\alpha \sim 0.7-0.8$ [9], in Yeast $\alpha \sim 1.5$ [10]. In fact, even in a given cell system different chromosomes can have different exponents [7,11]. These observations have contradicted the initial hope that a single universal architecture, originally envisaged in the Fractal Globule model [3], where $\alpha=1$, might describe chromosome folding.

A different approach has emerged from polymer physics to try to understand chromosome conformations, based on the idea that folding is shaped by chromatin interactions with other nuclear elements, such as DNA-binding molecules. Such a scenario has been explored for instance within the Strings & Binders Switch (SBS) model [7,12] and later in the Dynamic Loop (DL) model [13,14].

In the SBS model, chromosomes are represented as self-avoiding walk (SAW) polymer chains with binding sites for diffusing molecules. In this system, chromatin folding classes correspond to stable emergent thermodynamic phases, while the switch between conformations can be shown to be controlled by standard biochemical strategies, such as protein up-regulation or chromatin modification. The simplest version of the model discussed here helps illustrating the origin of its general emerging behaviours, yet the SBS can take into account additional complications, such as crowding and off-equilibrium effects as encountered in real complex fluids [15-19], which need to be considered and further explored. Importantly, a variety of transient conformations can be observed in the SBS model, including, under special conditions, the Fractal Globule.

An interesting property of the SBS models, predicted by polymer physics, is the existence of three major folding classes, independently of the minute biochemical details (which set the class a polymer folds into): the randomly folded open polymer state, the compact globule state and the Θ -point state at the transition between the open and compact states. The exponent is $\alpha \sim 2.1$ in the open state, where the polymer is randomly folded, $\alpha \sim 1.5$ in the Θ -point state, and $\alpha \sim 0$ in the compact state. In fact, mixture systems including different fractions of open and compact (and Θ -point) conformations can easily explain the range of effective exponents found experimentally in different chromosomes, cell cycle stages, and cell types [7], as seen in Fig.1.

The SBS model also explains the behavior of the mean square distance, R^2 , with the genomic separation between loci in the same chromosome and, in particular,

its plateauing at large genomic distances [7]. An important additional quantity is the distance moment ratio, $\langle R^4 \rangle / \langle R^2 \rangle^2$. It is a dimensionless, pure number that can be used to compare directly data and models. In particular, it can help distinguishing the different chromatin folding states. In the SBS model, $\langle R^4 \rangle / \langle R^2 \rangle^2$ is ~ 1.5 in the open and compact state, but it has a sharp peak, up to ~ 5 , in the transition region around the Θ -point. Interestingly, the very same dynamic range is seen in microscopy FISH data, suggesting that chromatin states in cells contain a mixture of not only open and compact regions (envisaged as eu- and heterochromatin), but also a third, previously overseen type of conformation, close to the Θ -point state [7].

Finally, in the SBS model, chromatin 'topological domains' (TADs) can emerge naturally, e.g., by specialization of binding sites (Fig. 2). Furthermore, changes in binding site specialization, upon domain formation, lead to chromatin looping events, a feature observed experimentally across short time scales [7]. Specificity of binding at different loci or domains can be achieved, e.g., by a combination of single molecular factors. In fact, more complex architectures, with different, nested layers of organization could be easily obtained. Other mechanisms could play a role in folding chromatin in compact states, such as supercoiling [20] and plectoneme formation [21]. The above results, illustrated within the SBS model, are supported by similar findings in the DL model. In particular, the DL model has been used to frame the effects of entropy in mixtures of long, looped polymers, which may result in effective repulsive forces [13,14].

A new picture of chromatin emerges [7] as a complex mixture of differently folded regions controlled by basic mechanisms of polymer physics, through regulation of chromatin binding and modifications. In that picture folding classes correspond to stable emergent phases. As a specific locus can be folded in different conformations across a population of cells, as much as different loci can be folded in different conformations inside a single cell, the contact probability and its exponent from Hi-C is an average. Additional quantities, e.g. $\langle R^4 \rangle / \langle R^2 \rangle^2$, can help better dissecting chromatin folding states. The SBS model describes some of the basic physical mechanisms of self-organization and, with simple elements, can explain the range of available data from FISH and Hi-C, including the contact probability, the mean square distance, moment ratios, TAD formation, and more.

Models such as the SBS, informed with biological details, can be also employed to predict the folding of specific loci. We, and others, currently use high-resolution single-cell mapping of interactions across single loci, combined with SBS modeling of epigenetics features to unveiled some of the determinants of folding. Our ongoing work supports a scenario where a deep connection exists between architecture and transcription. A variant of the SBS has also been used to

describe and make predictions about the folding of the *Xist* locus [22], and meiotic chromosome recognition [23]. SBS models can be also employed for ‘inverting’ Hi-C matrices, i.e., to establish from Hi-C data the corresponding chromatin spatial conformation and the involved key interaction regions. As recent technological advances are exposing the complexity and extent of genomic organization [24], the combination of experimental and modeling approaches promises to convey a deeper understanding of the principles of genome function and, in the future, of related diseases.

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Figures

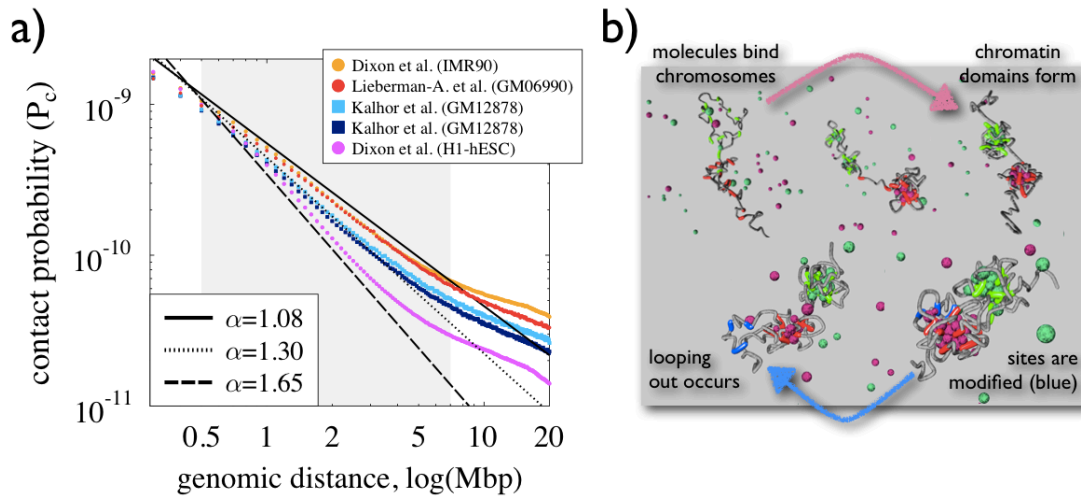


Fig. 1 Chromosome contact probability and the SBS model

a) The average contact probability, $P_c(s)$, from Hi-C data highlights a pattern of chromatin interactions extending across genomic scales. In the 0.5-7Mb range, $P_c(s)$ can be fitted by power-laws with an exponent α . Data from independent experiments across different human cell lines yield varying exponents reflecting distinct chromatin behaviours in different system. **b)** In the SBS model, here in a pictorial view, chromatin is represented as a polymer chain having binding sites for diffusing molecules. In a mixture of open and compact SBS polymers, the contact probability, $P_c(s)$ and its exponent α , depend on the mixture composition. In particular, the entire range of Hi-C data exponents can be recovered (superimposed lines in Fig.1a).

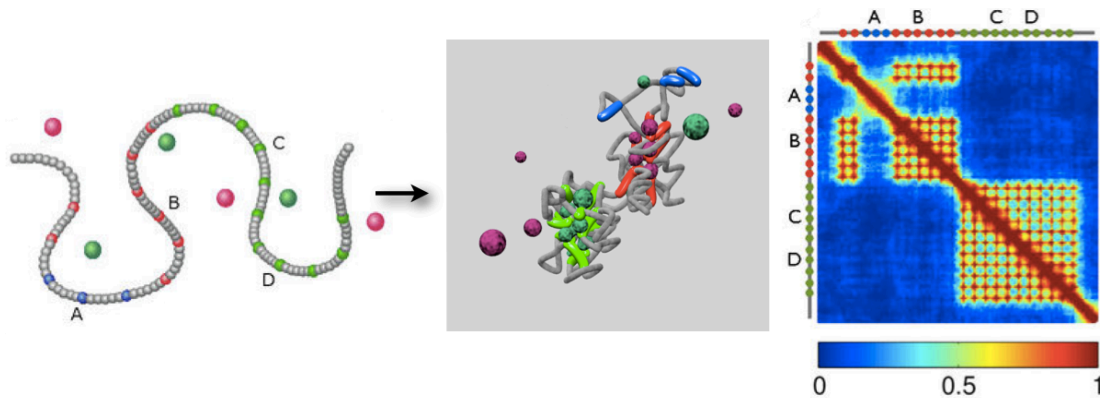


Fig. 2 Topological Domains and the SBS model

In the SBS model, as different types of binding sites are considered, here shown as red and green polymer sites (**left**), different domains naturally form (**center**, see also Fig1b). Looping out of a given locus from one of the domains can result from binding site specialization, in this case, through the loss of affinity for the red binding molecules represented by a change in polymer sites from red to blue. The corresponding SBS contact matrix (**right**) closely resembles those observed for chromatin Topological Domains from experiments.