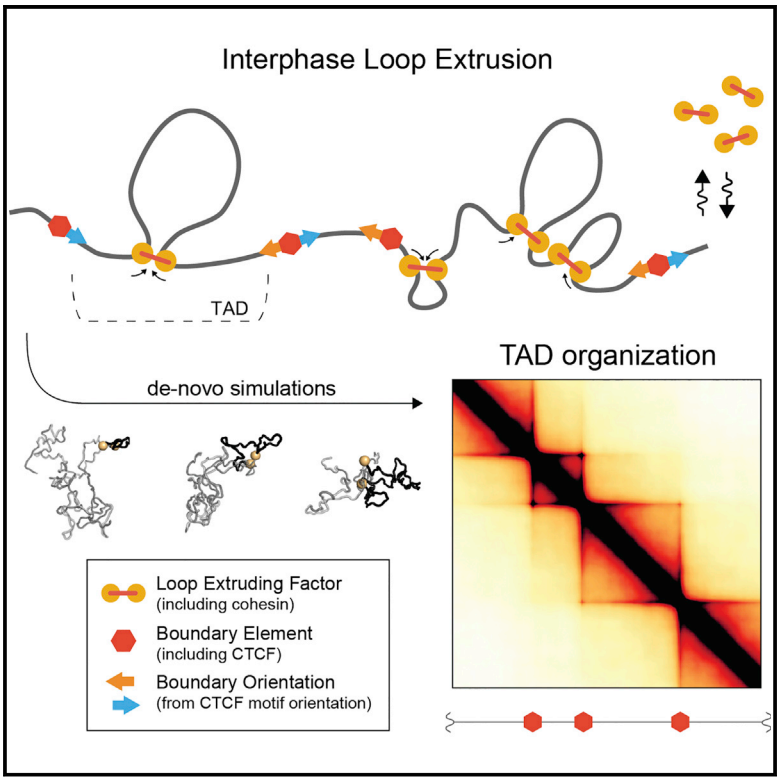
Article

Cell Reports

Formation of Chromosomal Domains by Loop Extrusion

Graphical Abstract



Authors

Geoffrey Fudenberg, Maxim Imakaev, Carolyn Lu, Anton Goloborodko, Nezar Abdennur, Leonid A. Mirny

Correspondence

leonid@mit.edu

In Brief

Topologically associating domains (TADs) are fundamental building blocks of human interphase chromosomes. Fudenberg et al. propose that TADs emerge as a consequence of loop extrusion limited by boundary elements. The authors use polymer simulations and genomic analyses to identify molecular roles for the architectural proteins cohesin and CTCF.

Highlights

- TADs can be formed by loop extrusion limited by boundary elements
- Polymer simulations and genomic analyses were jointly used to test this proposal
- Proposed roles of cohesin and CTCF reconcile diverse experimental observations

Fudenberg et al., 2016, Cell Reports *15*, 1–12
May 31, 2016
http://dx.doi.org/10.1016/j.celrep.2016.04.085

CellPress

Please cite this article in press as: Fudenberg et al., Formation of Chromosomal Domains by Loop Extrusion, Cell Reports (2016), http://dx.doi.org/10.1016/j.celrep.2016.04.085

Cell Reports
Article

Formation of Chromosomal Domains by Loop Extrusion

Geoffrey Fudenberg,[1,2,6] Maxim Imakaev,[3,6] Carolyn Lu,[4] Anton Goloborodko,[3] Nezar Abdennur,[5] and Leonid A. Mirny[1,2,3,*]
[1]Graduate Program in Biophysics, Harvard University, Cambridge, MA 01238, USA
[2]Institute for Medical Engineering and Science, Massachusetts Institute of Technology (MIT), Cambridge, MA 02139, USA
[3]Department of Physics, Massachusetts Institute of Technology (MIT), Cambridge, MA 02139, USA
[4]Program for Research in Mathematics, Engineering and Science for High School Students (PRIMES) and Undergraduate Research Opportunities Program (UROP), MIT, Cambridge, MA 02139, USA
[5]PhD Program in Computational and Systems Biology, MIT, Cambridge, MA 02139, USA
[6]Co-first author, listed alphabetically
*Correspondence: leonid@mit.edu
http://dx.doi.org/10.1016/j.celrep.2016.04.085

SUMMARY

Topologically associating domains (TADs) are fundamental structural and functional building blocks of human interphase chromosomes, yet the mechanisms of TAD formation remain unclear. Here, we propose that loop extrusion underlies TAD formation. In this process, *cis*-acting loop-extruding factors, likely cohesins, form progressively larger loops but stall at TAD boundaries due to interactions with boundary proteins, including CTCF. Using polymer simulations, we show that this model produces TADs and finer-scale features of Hi-C data. Each TAD emerges from multiple loops dynamically formed through extrusion, contrary to typical illustrations of single static loops. Loop extrusion both explains diverse experimental observations—including the preferential orientation of CTCF motifs, enrichments of architectural proteins at TAD boundaries, and boundary deletion experiments—and makes specific predictions for the depletion of CTCF versus cohesin. Finally, loop extrusion has potentially far-ranging consequences for processes such as enhancer-promoter interactions, orientation-specific chromosomal looping, and compaction of mitotic chromosomes.

INTRODUCTION

Interphase chromosome organization in three dimensions underlies critical cellular processes, including gene regulation via enhancer-promoter interactions. Mapping chromosomal interactions genome-wide has revealed that interphase chromosomes of higher eukaryotes are partitioned at a sub-megabase scale into a sequence of self-interacting regions, termed topologically associating domains (TADs; Dixon et al., 2012; Nora et al., 2012), or domains (Rao et al., 2014; Sexton et al., 2012). An increasing number of studies have found important functional roles for TADs in the control of gene expression and development (Andrey et al., 2013; Lupiáñez et al., 2015; Symmons et al., 2014).

TADs are contiguous regions of enriched contact frequency that appear as squares in a Hi-C map (Figure 1A), which are relatively insulated from neighboring regions. Many TADs have homogeneous interiors, while others have particularly enriched boundaries, or even more complex features. More recently, high-resolution maps revealed peaks of interactions between loci at the boundaries of TADs (“peak loci”; Rao et al., 2014). TADs differ from larger scale A/B compartments in that they do not necessarily form an alternating “checkerboard” pattern of enriched contact frequencies (Lajoie et al., 2015), and several TADs often reside within a single contiguous compartment (Gibcus and Dekker, 2013; Gorkin et al., 2014) (Supplemental Notes).

Although often illustrated as such, several lines of evidence indicate that TADs are not simply stable loops formed between pairs of boundary loci. First, only 50% of TADs have corner-peaks (Rao et al., 2014). Second, boundary loci do not appear to be in permanent contact either by fluorescence in situ hybridization (FISH) (Rao et al., 2014) or by their relative contact frequency (see Results). Third, while TADs are enriched in contact probability throughout the domain, polymer simulations show that simple loops display enrichment only at the loop bases, unless the loop is very short (Benedetti et al., 2014; Doyle et al., 2014). For these reasons, identifying mechanisms of how TADs are formed remains an important open question.

While polymer models have provided insight into multiple levels of chromosome organization (Baù et al., 2011; Lieberman-Aiden et al., 2009; Marko and Siggia, 1997; Naumova et al., 2013; Rosa and Everaers, 2008), relatively few have focused on TADs. Of those that have considered TADs, some have focused primarily on characterizing chromosome structure rather than the mechanisms of folding (Giorgetti et al., 2014; Hofmann and Heermann, 2015). Others (Barbieri et al., 2012; Jost et al., 2014) have considered models where monomers of the same type experience preferential pairwise attractions to produce TADs; such models, however, when generalized to the genome-wide scale, would require a separate factor to recognize and compact each TAD. With only several types of monomers, this would produce checkerboard patterns for each type, which is characteristic of compartments rather than