Can we better understand HOT regions based on 3D genome organization?

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6/20/2016

Motivation

- HOT regions are heavily clustered with transcription factor binding sites. The high accessibility should be related to the 3D structure of genome

- All analysis here were done in hES cell. We have slides to discuss how to explore the idea using similar data sets in worm and fly.

Chromosome conformation capture (3C) and Hi-C

Comprehensive Mapping of Long-Range Interactions Reveals Folding Principles of the Human Genome

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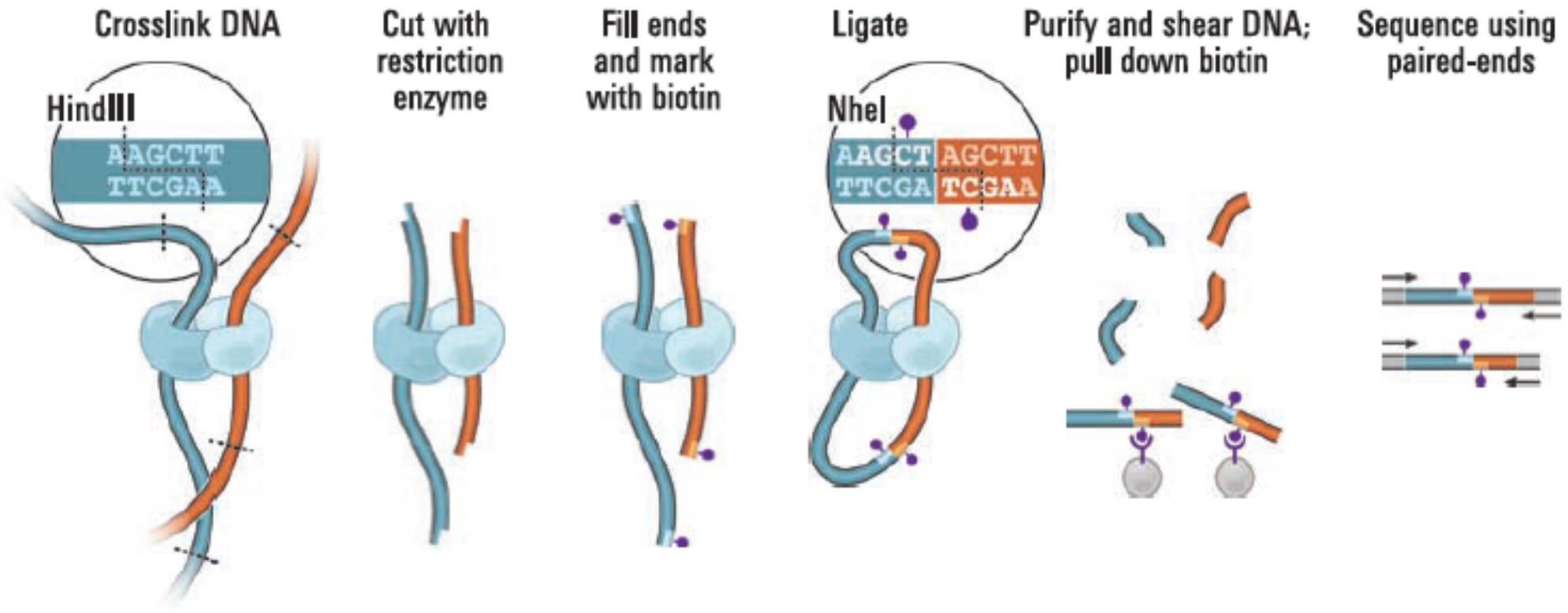
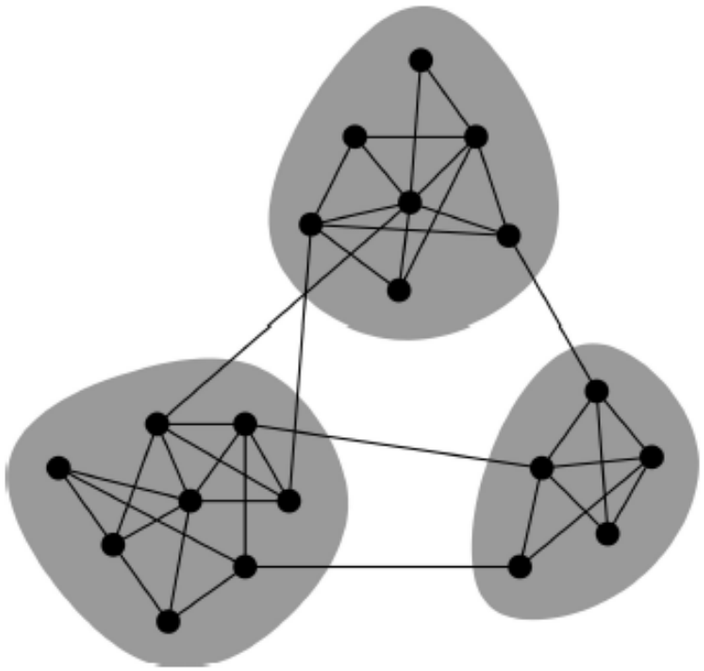
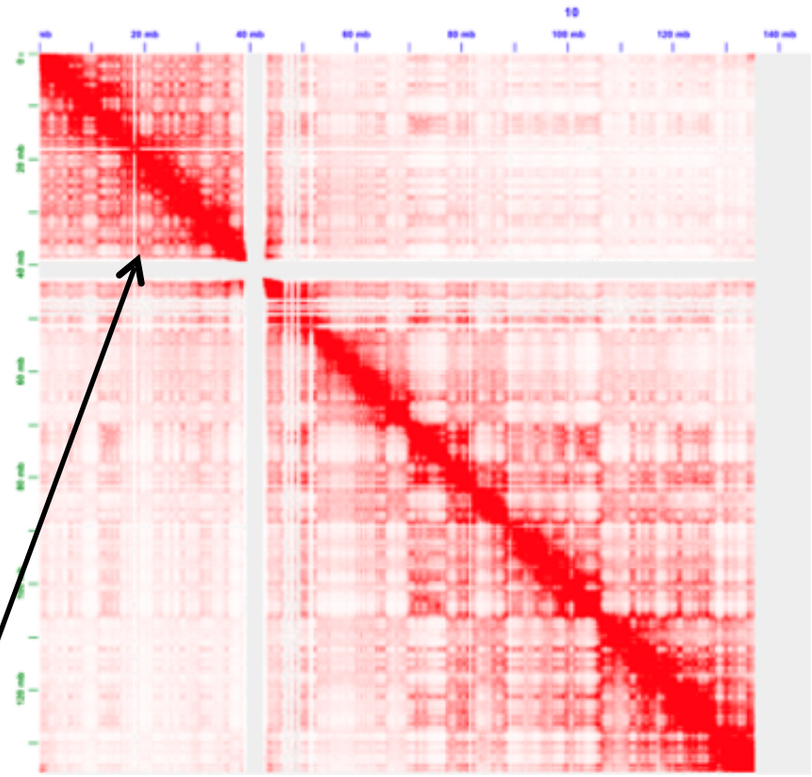


A network-based approach to find Topologically Associating Domains (TADs)



network	contact map
node	chromosome bin
edge	Hi-C contact
# of connections	coverage
module	domain



DNA picture adapted from Weinreb et al. Bioinformatics 2015

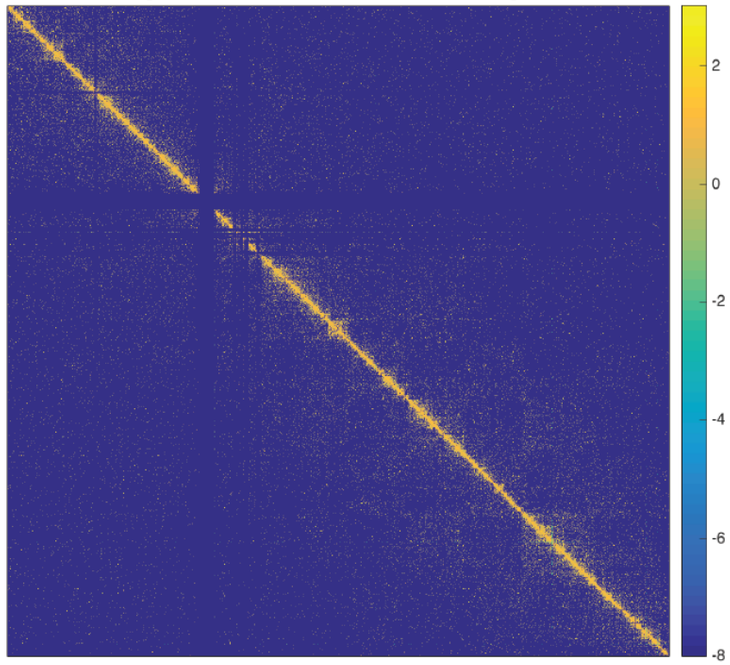
Modularity maximization

$$Q = \frac{1}{2m} \sum_{i,j} \left(W_{ij} - \frac{k_i k_j}{2m} \right) \delta_{\sigma_i \sigma_j}$$

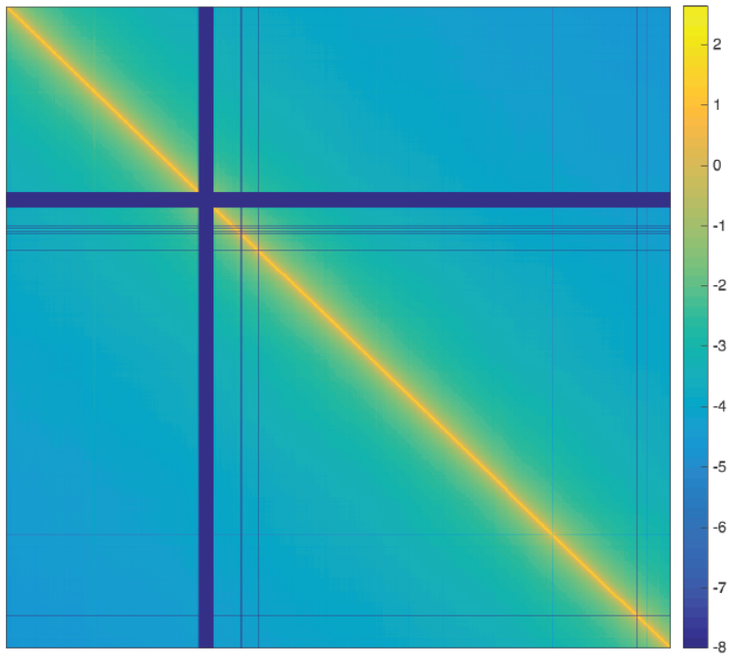
TADs have apparent Hierarchical organization

Workflow

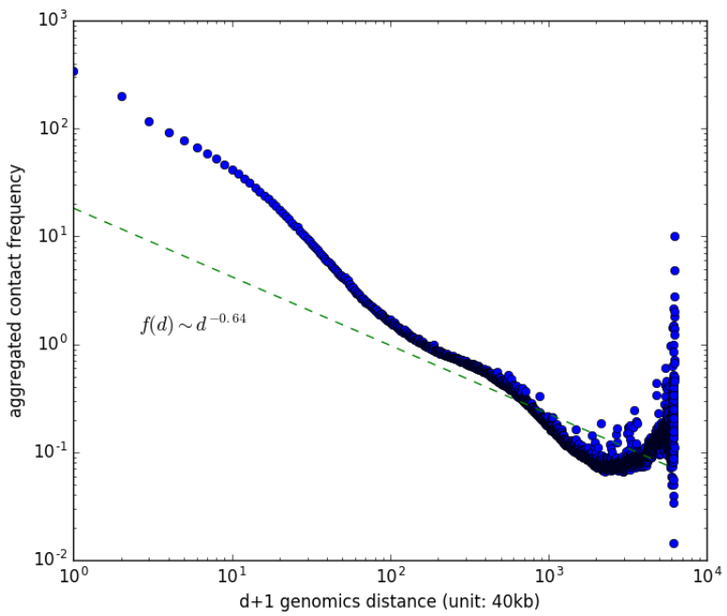
input: contact map W



null model E



$$E_{ij} = c_i^* c_j^* f(|i-j|)$$



Choose a particular resolution γ
Optimize Q over all possible partitions

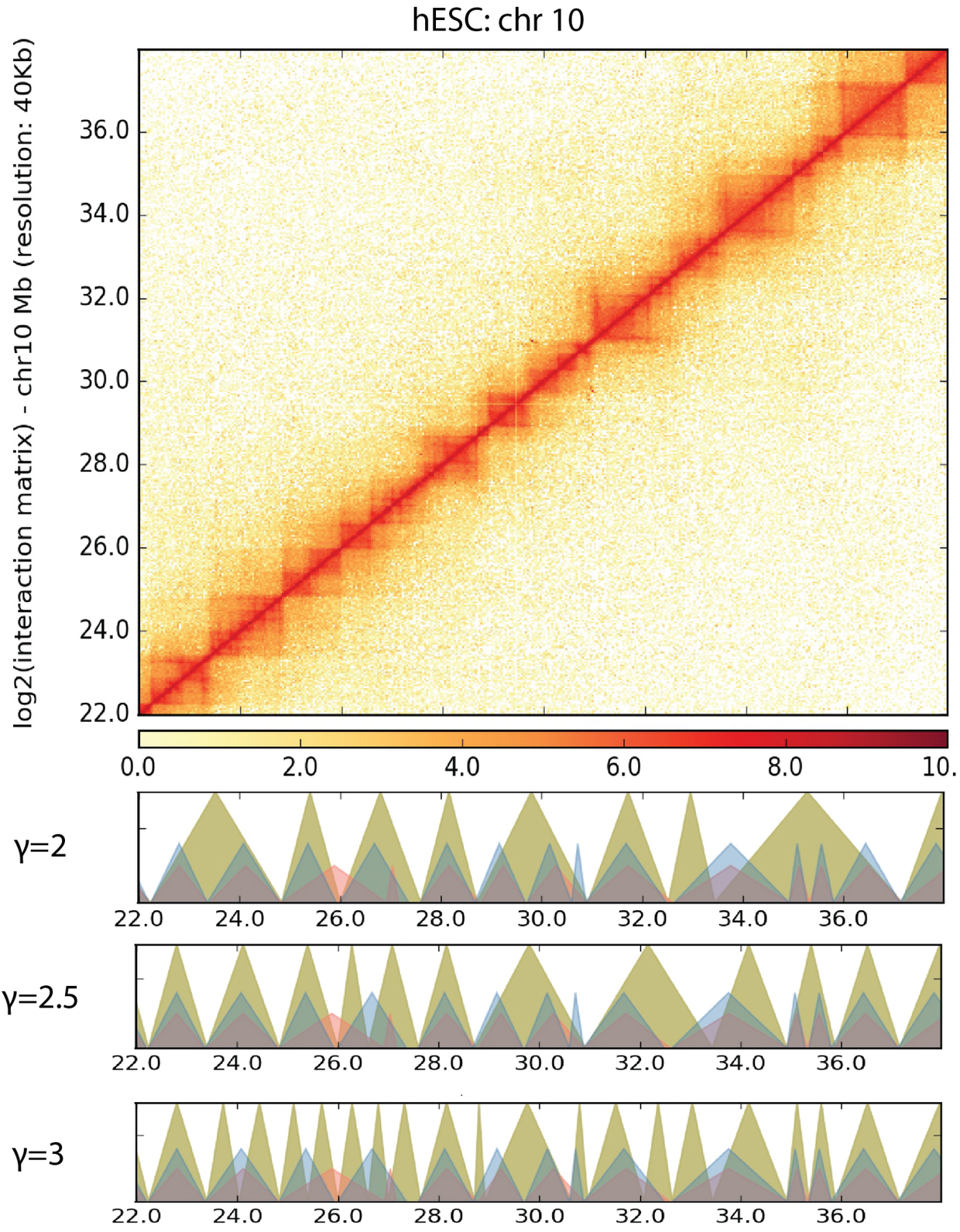
$$Q = \frac{1}{2N} \sum_{ij} (W_{ij} - \gamma E_{ij}) \delta_{\sigma_i \sigma_j}$$

consensus boundaries based on the boundary scores

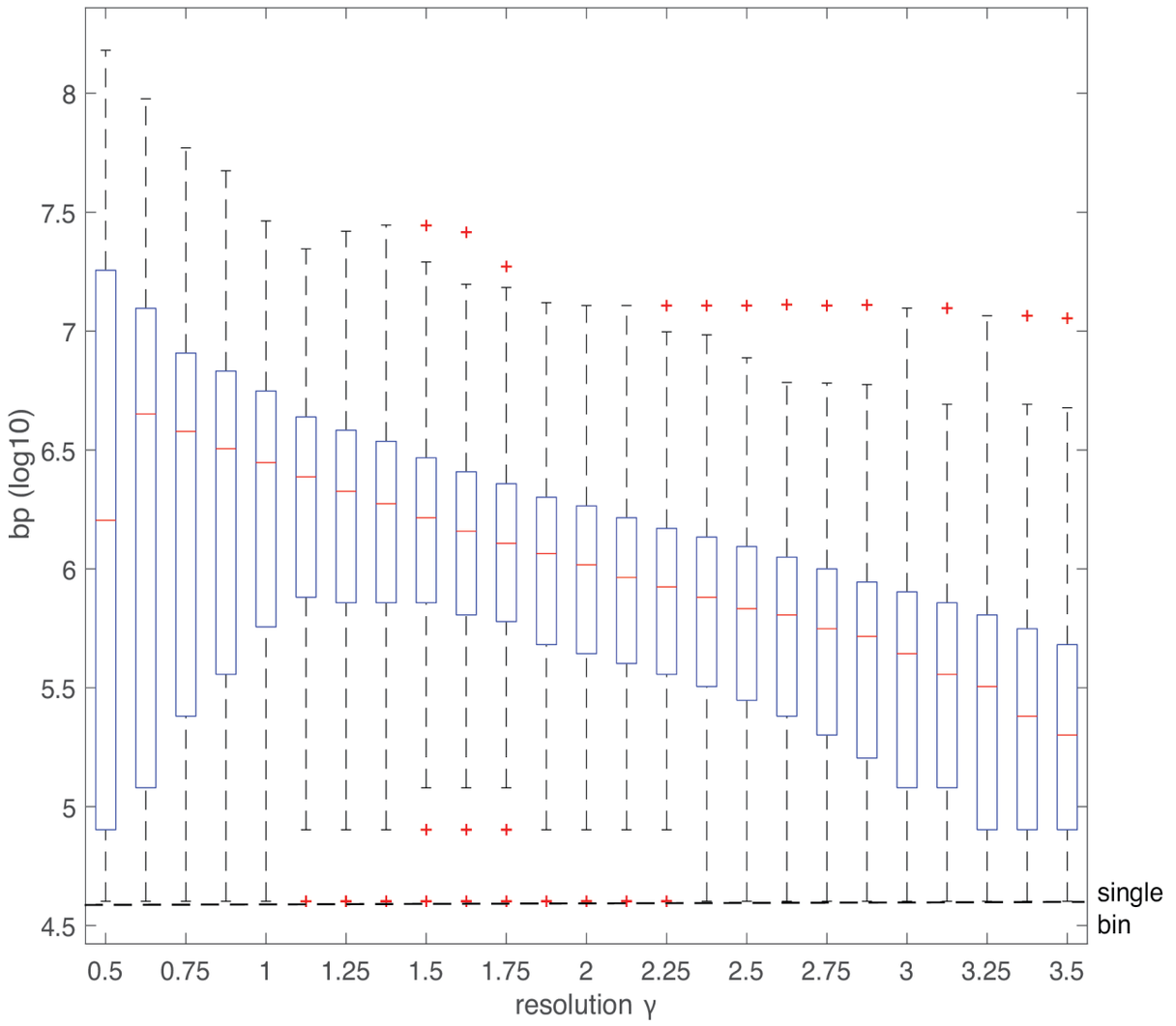
consensus domains

multiple trials to define boundary scores for all adjacent bins

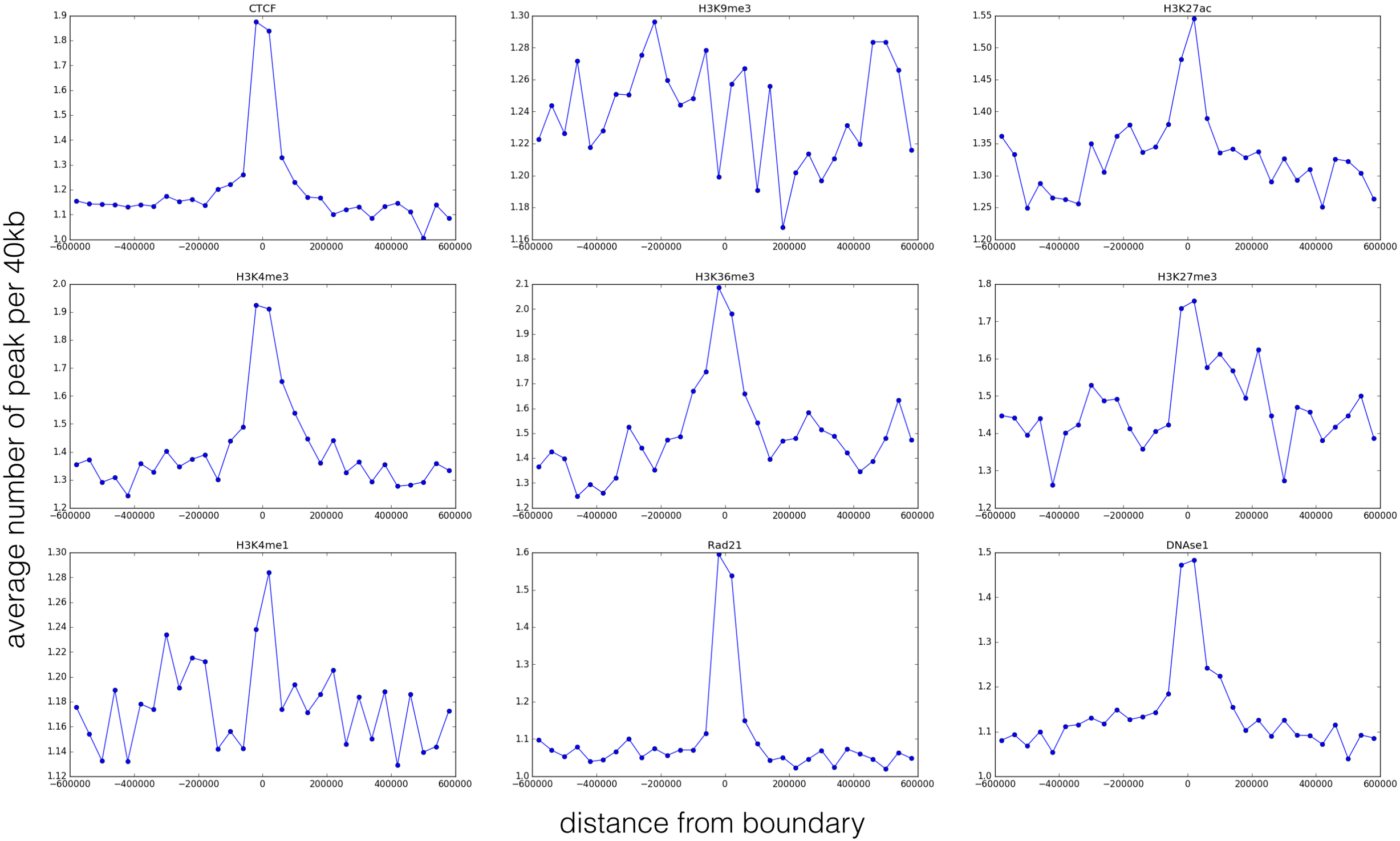
TADs in different resolutions



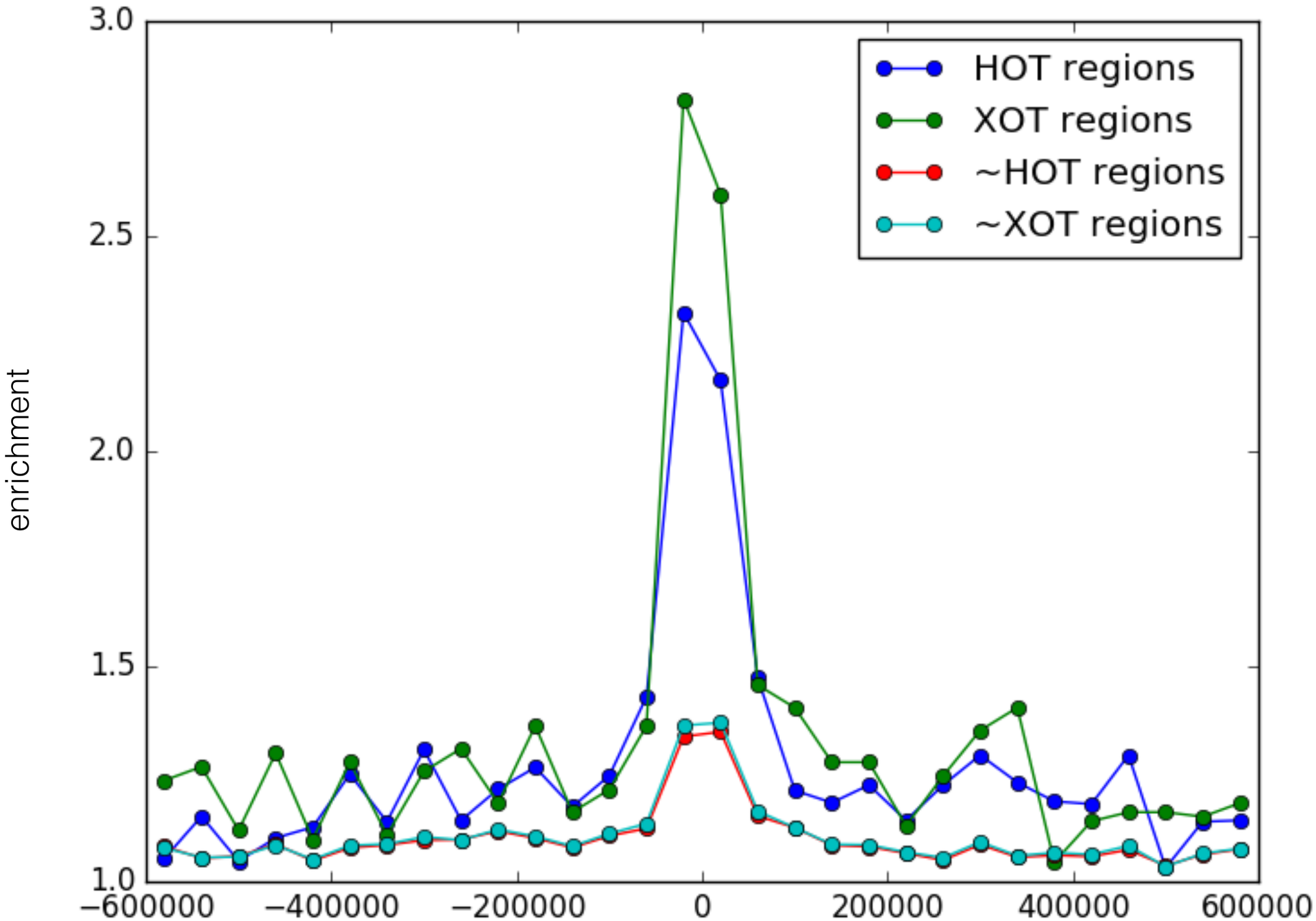
smaller TADs but are detected
as the resolution increases



Enrichment of chromatin marks near TAD boundaries

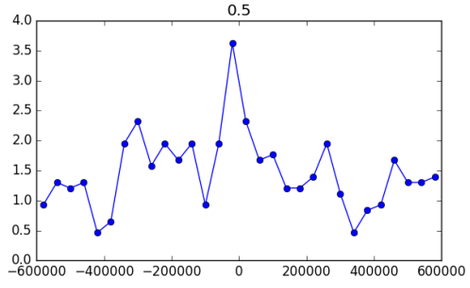


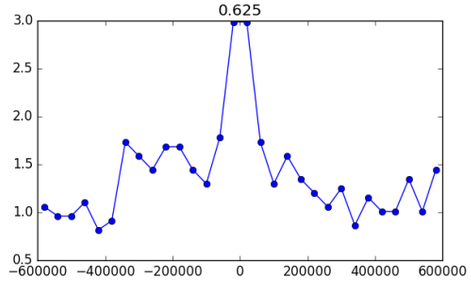
Enrichment of HOT regions near TAD boundaries

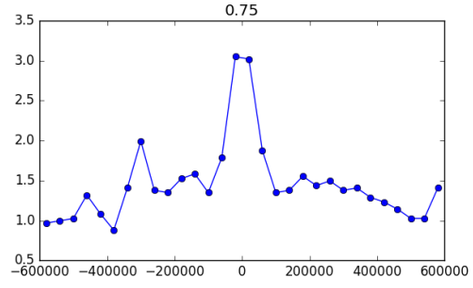


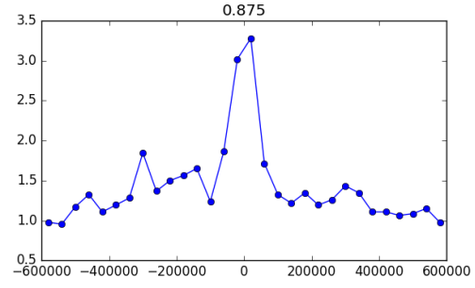
HOT regions:
http://www.stanford.edu/~claraya/metrn/data/hot/

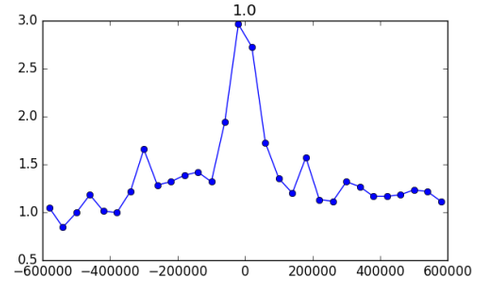
HOT regions in different resolutions

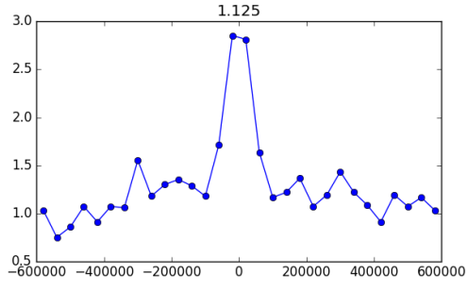


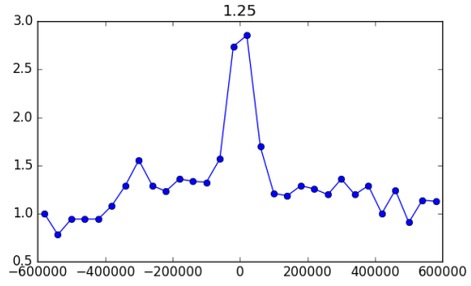


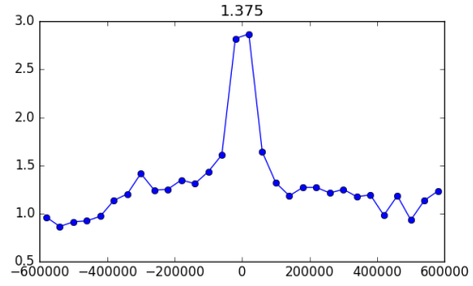


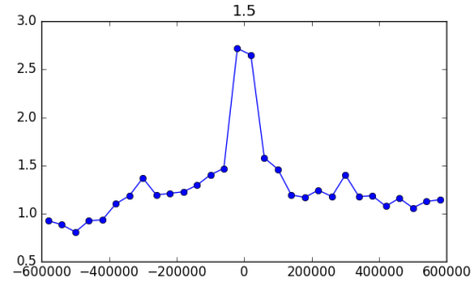


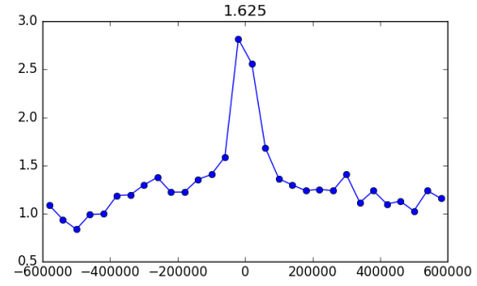


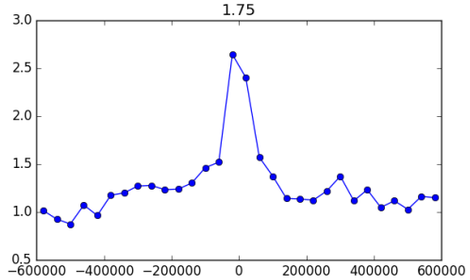


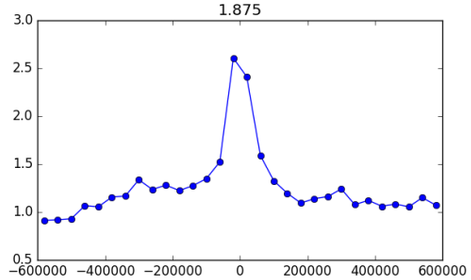


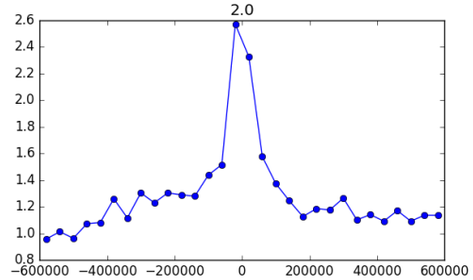


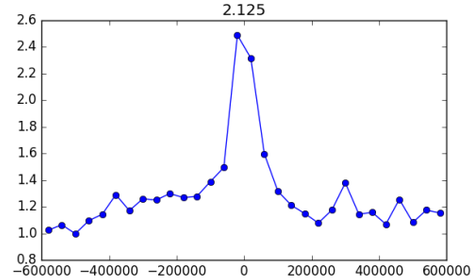


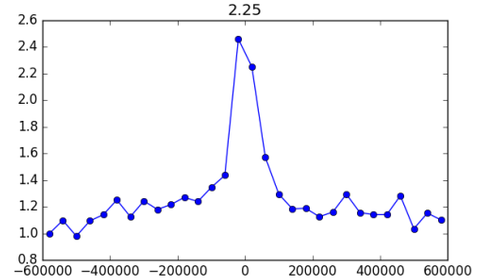


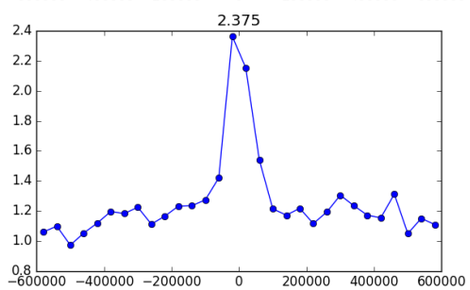


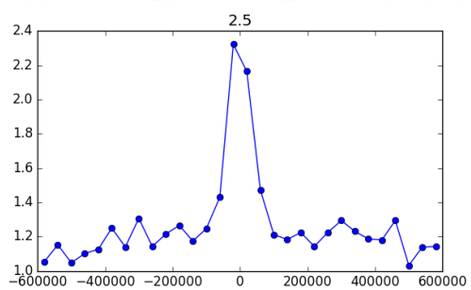


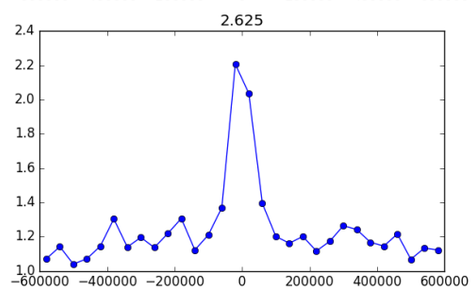


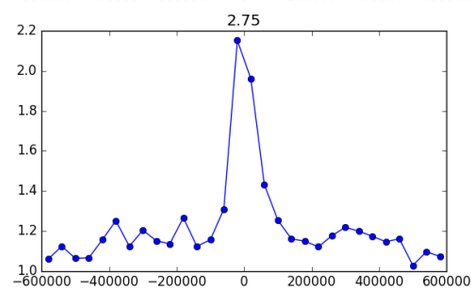


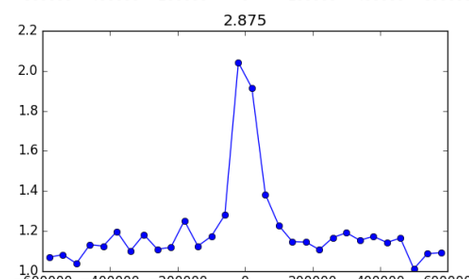


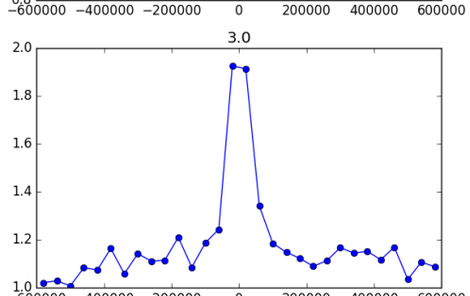


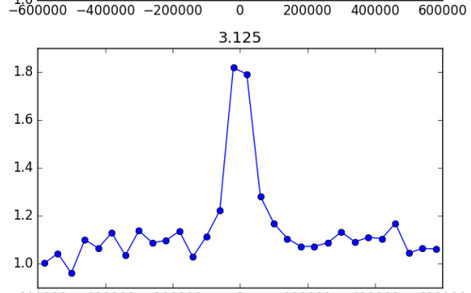


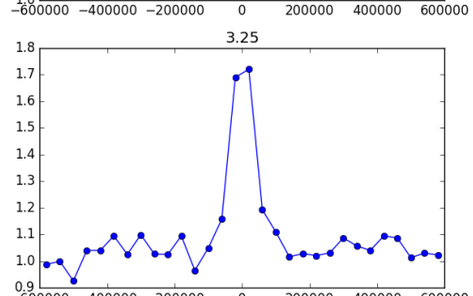


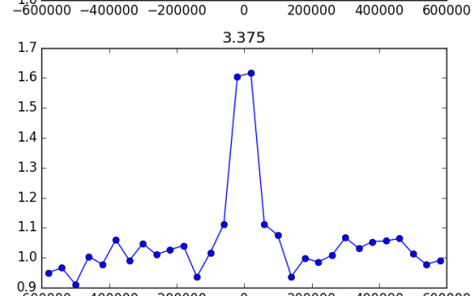


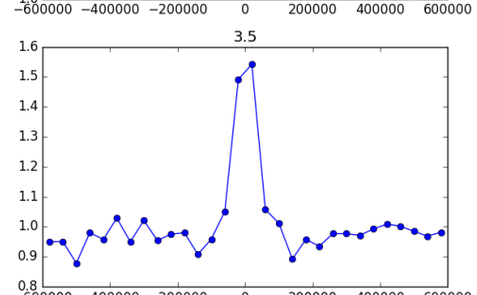




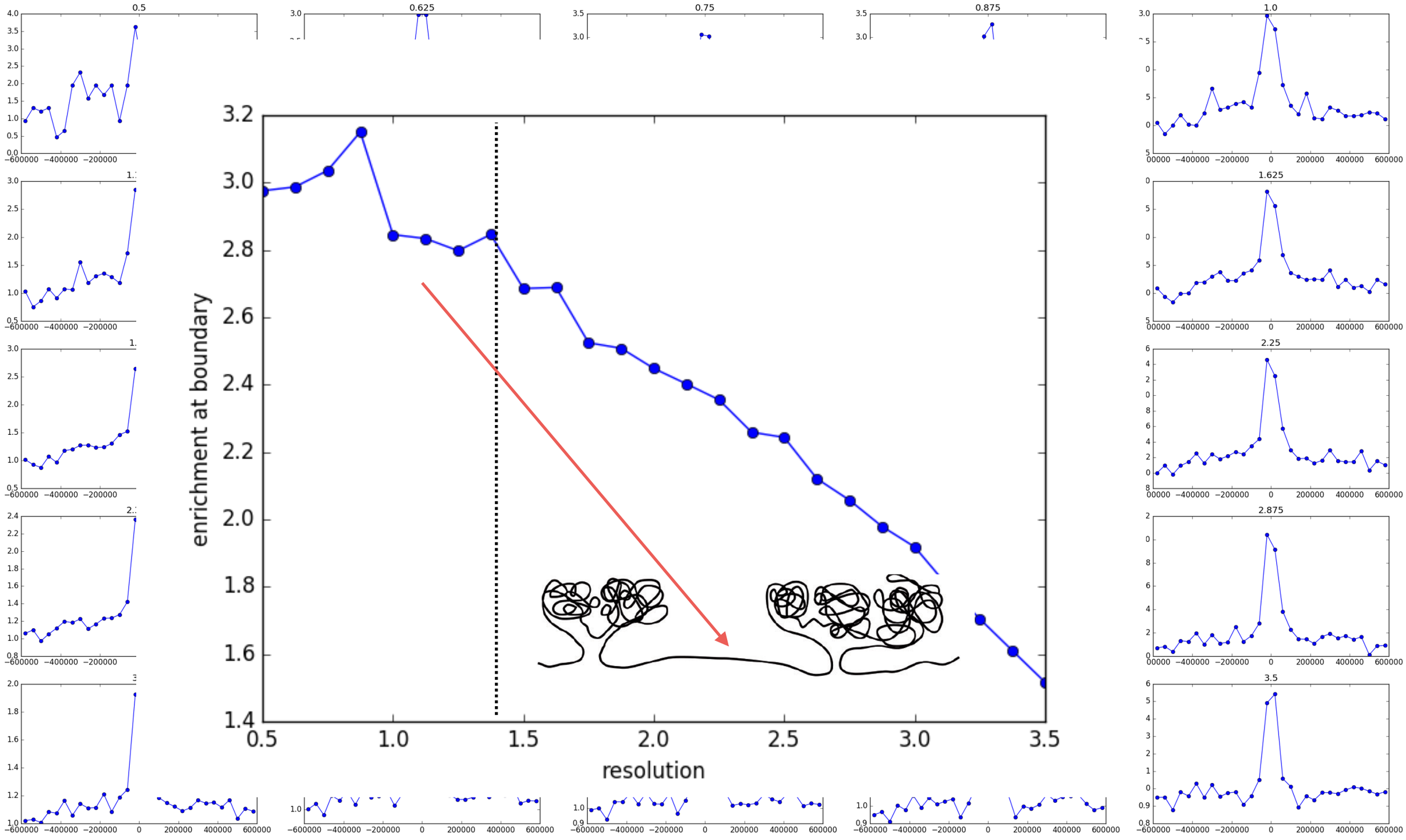




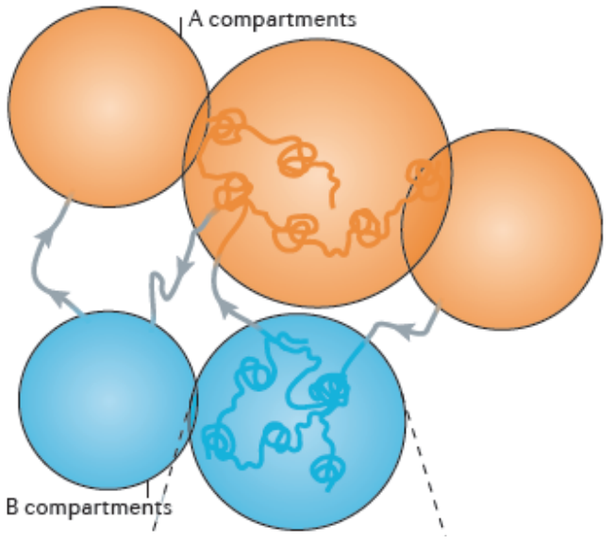




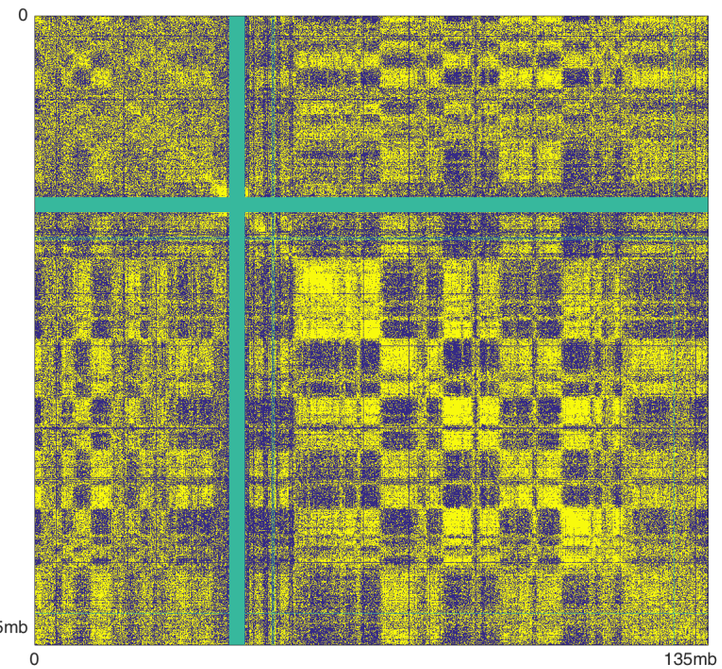
HOT regions in different resolutions

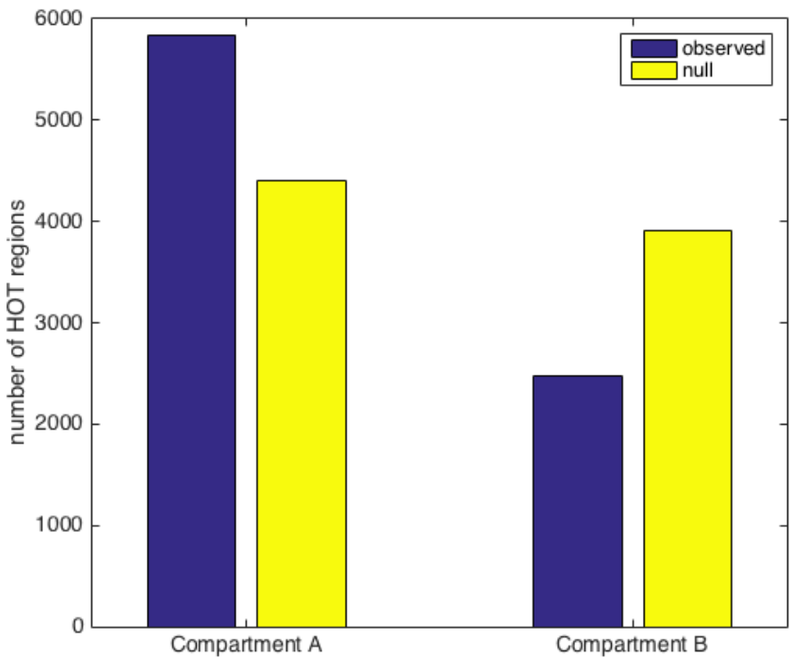


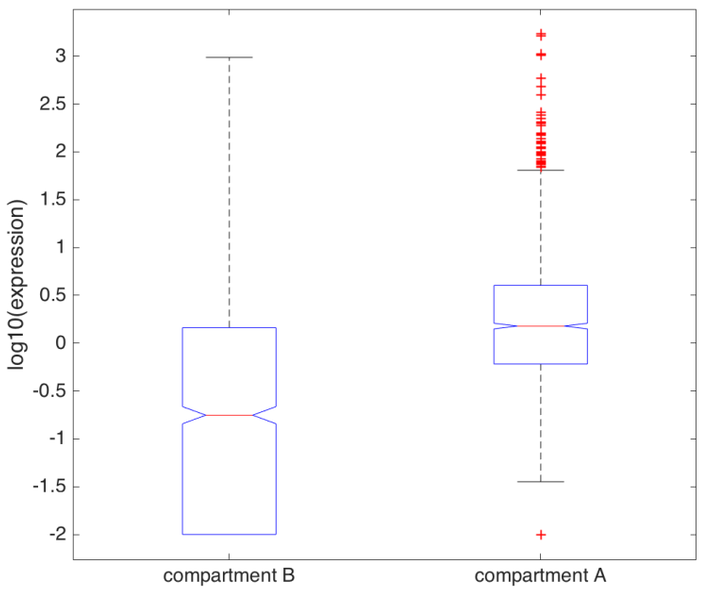
HOT regions are enriched in the Compartment A

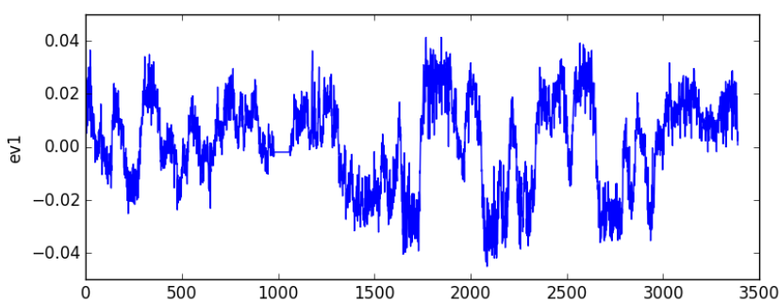


$$C_{ij} = cor(W_{ij}/E_{ij})$$









Hi-C data in worm and fly

LETTER

doi:10.1038/nature14450

Condensin-driven remodelling of X chromosome topology during dosage compensation

worm embryo

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Cell

fly cell lines: s2, Kc167, DmBG3-c2, OSC

Molecular Cell
Resource

Kc167

Three-Dimensional Folding and Functional Organization Principles of the *Drosophila* Genome

Tom Sexton,[1,4] Eitan Yaffe,[2,4] Ephraim Kenigsberg,[2] Frédéric Bantignies,[1] Benjamin Leblanc,[1] Michael Hoichman,[2] Hugues Parrinello,[3] Amos Tanay,[2,*] and Giacomo Cavalli[1,*]
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Gene Density, Transcription, and Insulators Contribute to the Partition of the *Drosophila* Genome into Physical Domains

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Research

Active chromatin and transcription play a key role in chromosome partitioning into topologically associating domains

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fly embryo

Summary and Possible threads

- The location of HOT regions is related to 3D genome organization, as shown in hES cells.
- Possible threads to follow:
  - Identify TADs in worm and fly; we expect similar observations.
  - Make further use of our ChIP-Seq data:
    - architectural proteins for domain formation:
      - CTCF, YY1, Rad21 in human
      - fly: Zw5, dCTCF, Su(Hw)… worm?
    - use the binding of specific TFs to predict domains/ boundaries formation