Paper: Canonical and single-cell Hi-C reveal distinct chromatin interaction sub-networks of mammalian transcription factors

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https://qdata.github.io/deep2Read/

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TF Co-Localization Dependencies

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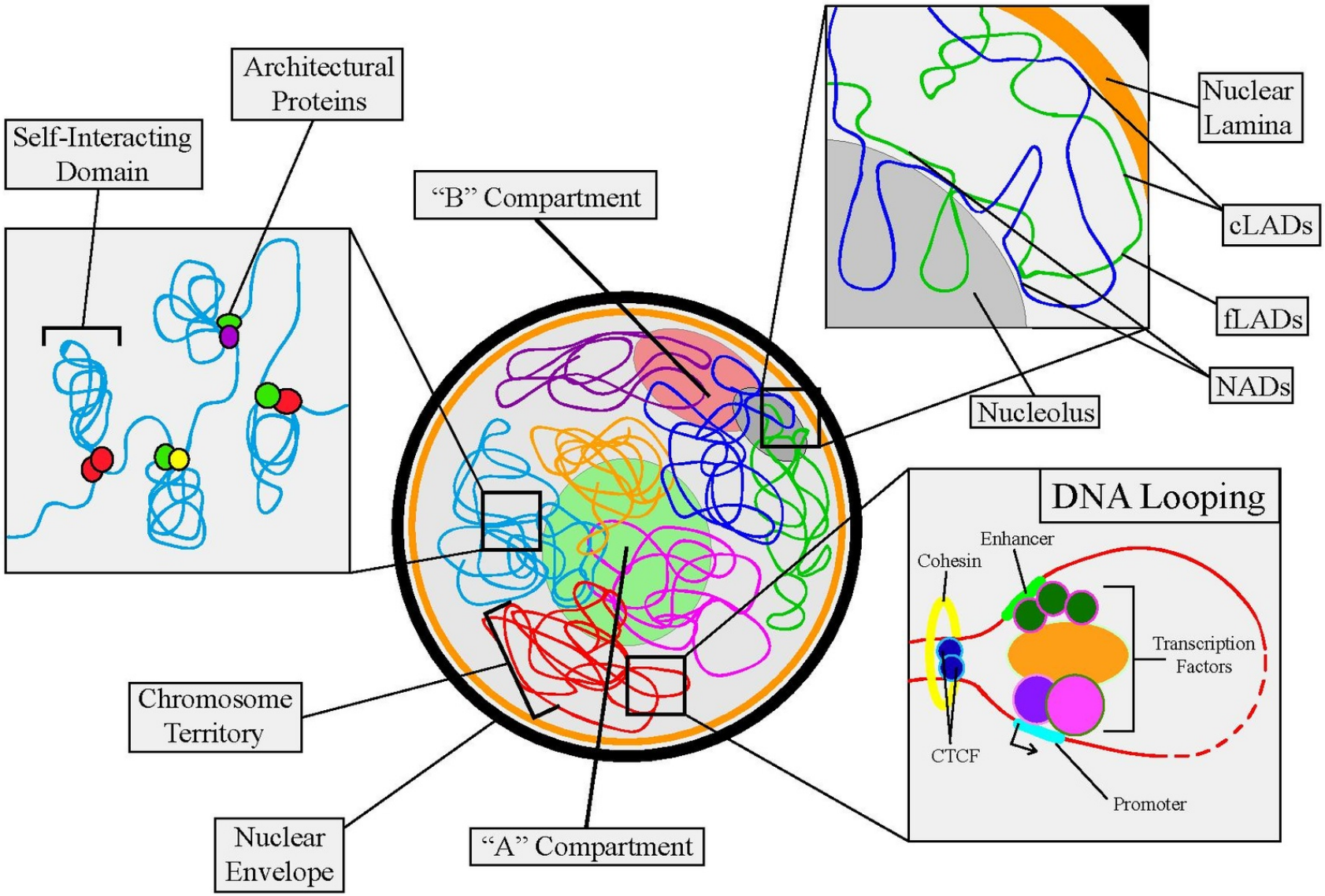
Canonical and single-cell Hi-C reveal distinct chromatin interaction sub-networks of mammalian transcription factors

Xiaoyan Ma[1], Daphne Ezer[2,3], Boris Adryan[4] and Tim J. Stevens[5*]

Nuclear Architecture (from Wikipedia)



Formulation

- Found all potential sites in the genome which match a PWM for any TF
- Sites which have a ChIP-Seq peak are labelled positive sites, and those without are labelled negative
- **Goal**: find out if co-localization (proximity of a potential site to all other potential sites) is correlated with positive TF binding

Hi-C Map Details

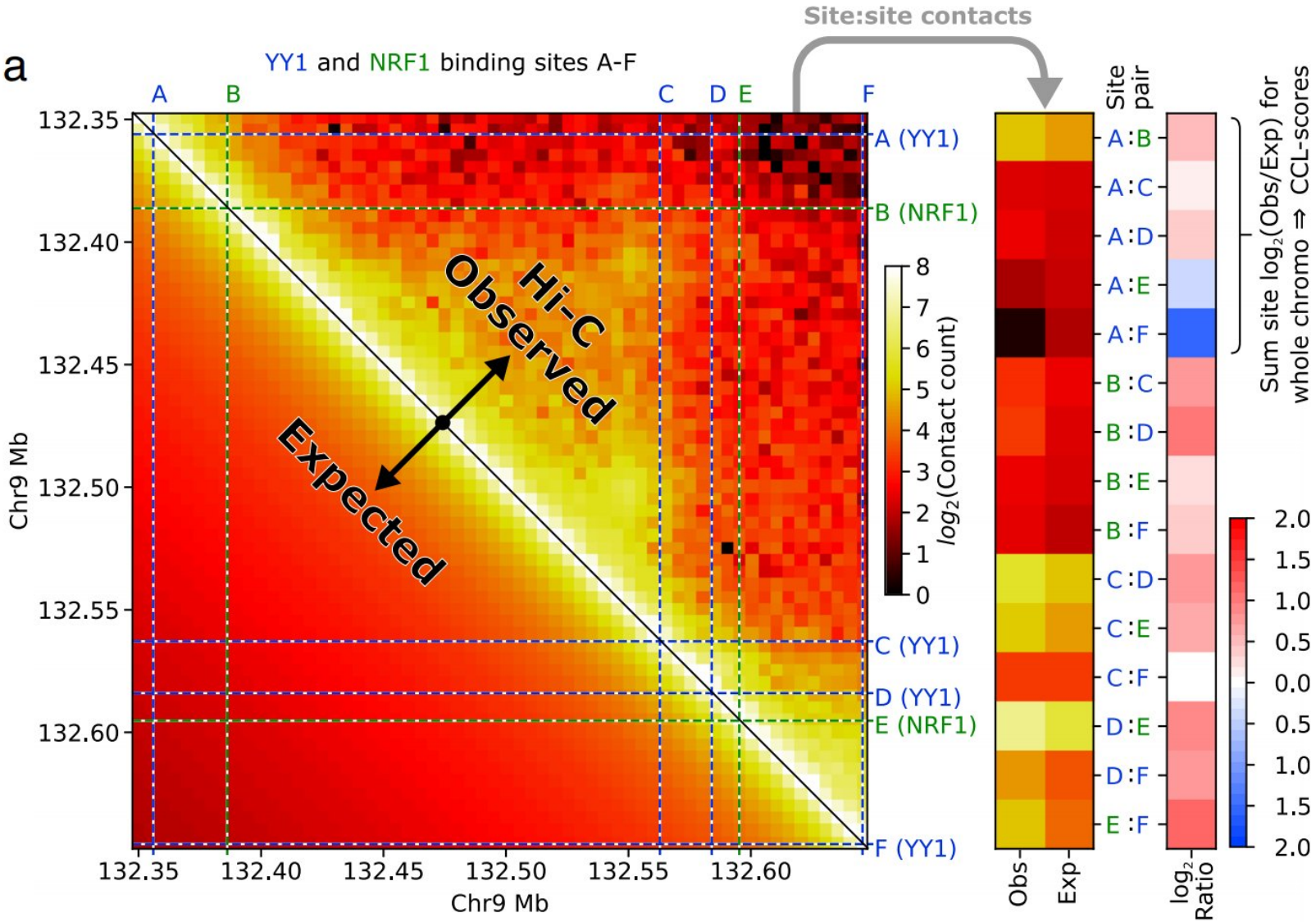
- Used 5k resolution Hi-C Mpas
- Diagonal elements of the Hi-C contact map as well as the adjacent 25k regions (i.e. 5 bins) either side were excluded to:

    1. Avoid potentially large variations in near-diagonal regions of the contact map
    2. Focus our analysis on the contacts between sequentially distal sites more than 25 kb away

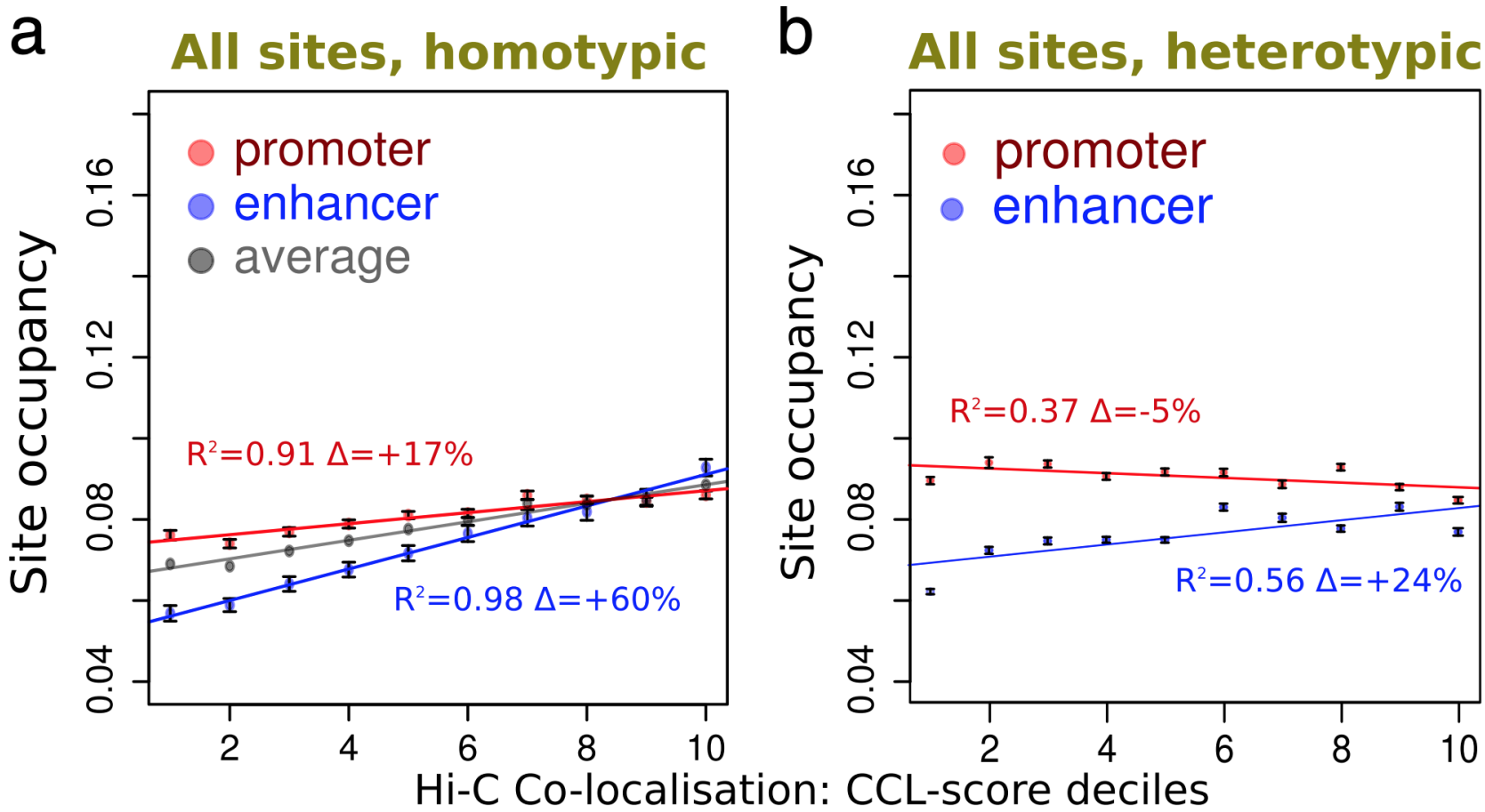
Chromatin Co-localization score (CCL)

- CCL-score: value for each TF binding site proportional to the contact enrichment of the site with other sites
  - Homotypic case, where the sites relate to the same TF
  - Heterotypic case, where the sites relate to two different TFs
- Given a CCL-score for all TF sites (the degree of co-localization to other sites), different sites were ranked for each TF and then combined to study all TFs collectively

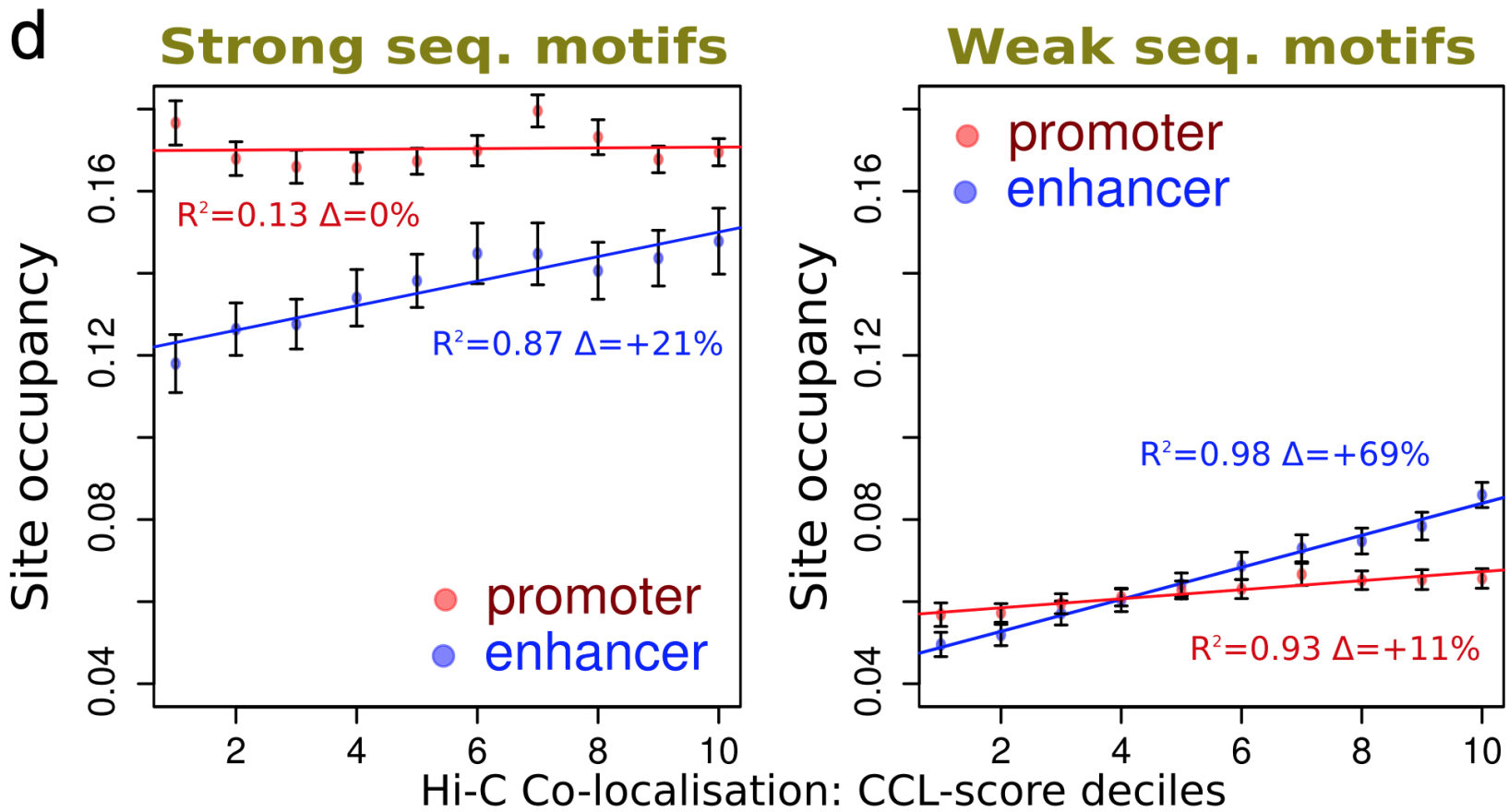
Chromatin Co-localization score (CCL)



Co-localization vs Site Occupancy

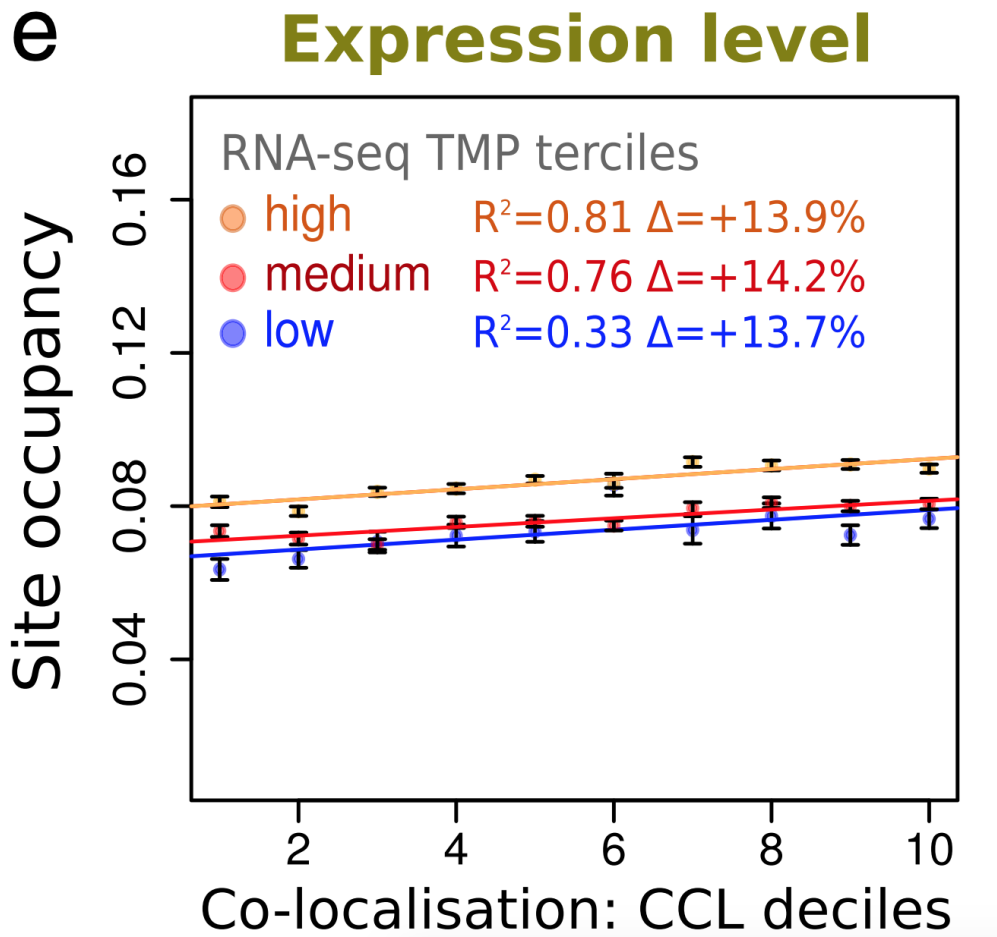


Homotypic co-localization with Motifs

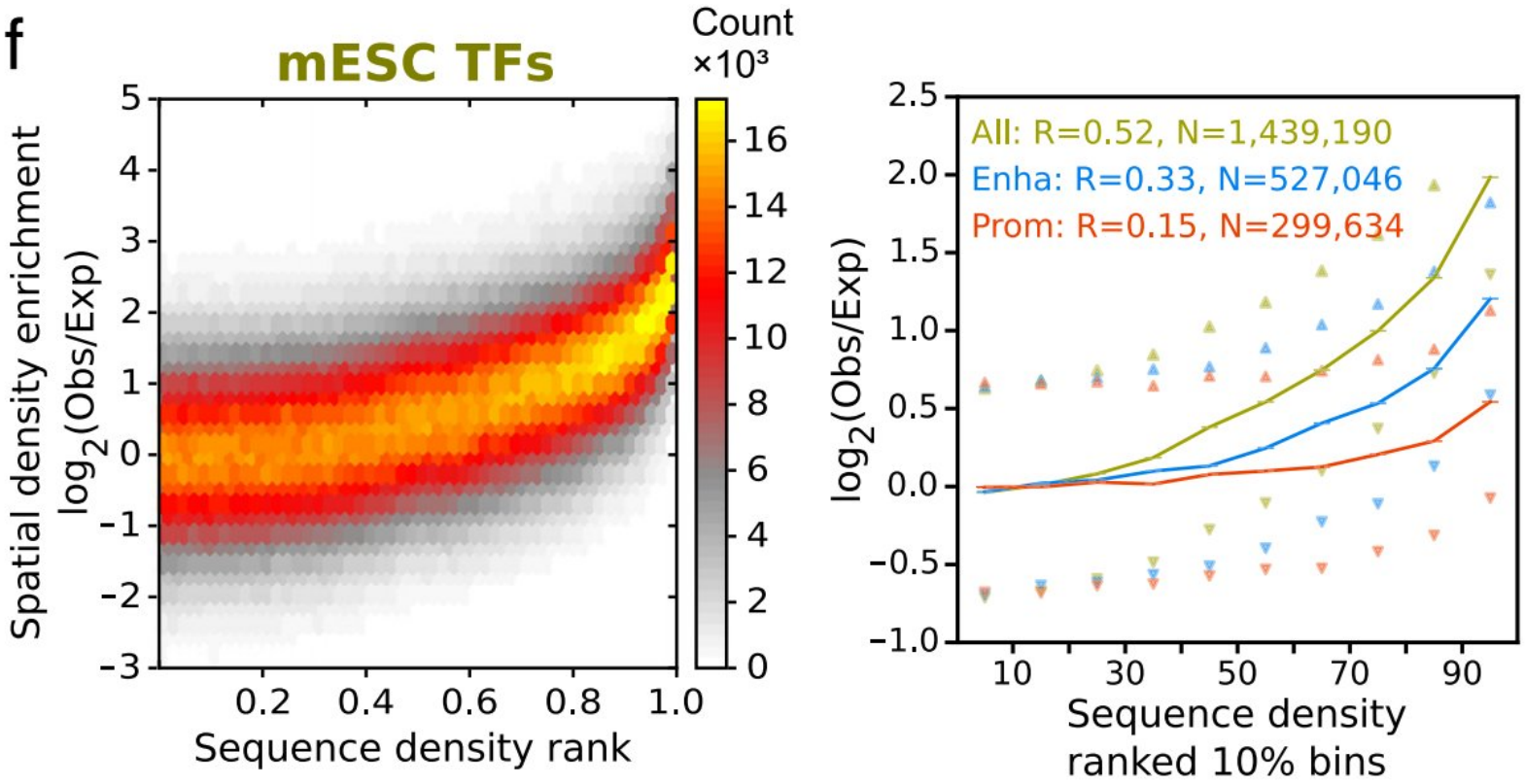


Homotypic Co-localization with Expression

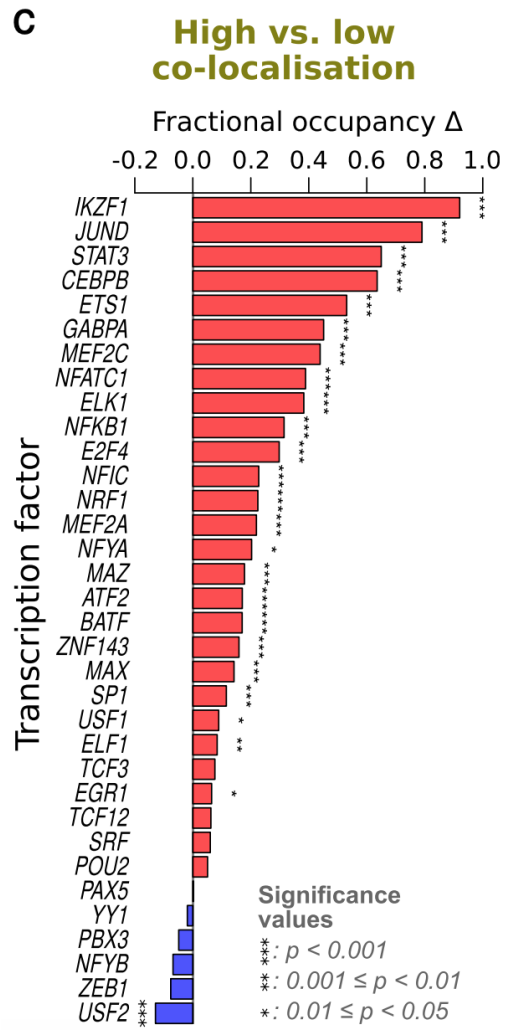
Only promoter regions where expression level is experimentally measured



Sequence vs Spatial Density

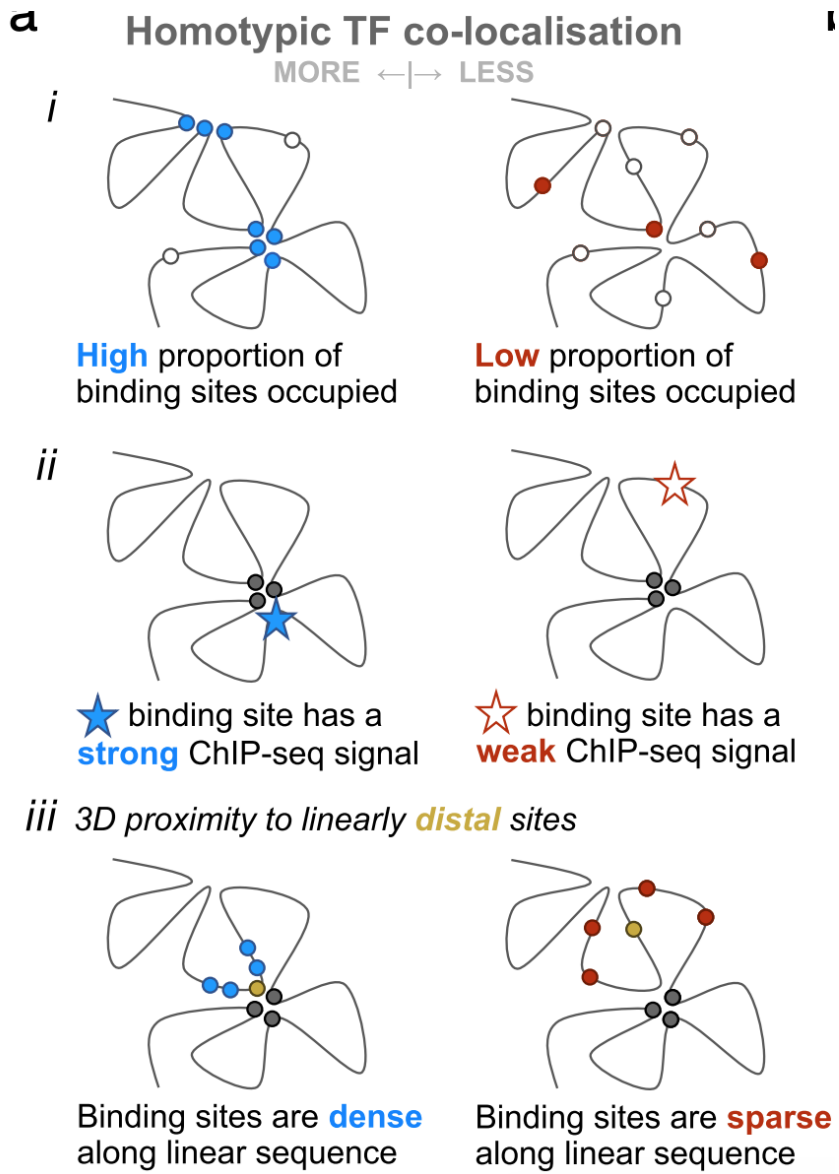


Homotypic co-localization with Expression



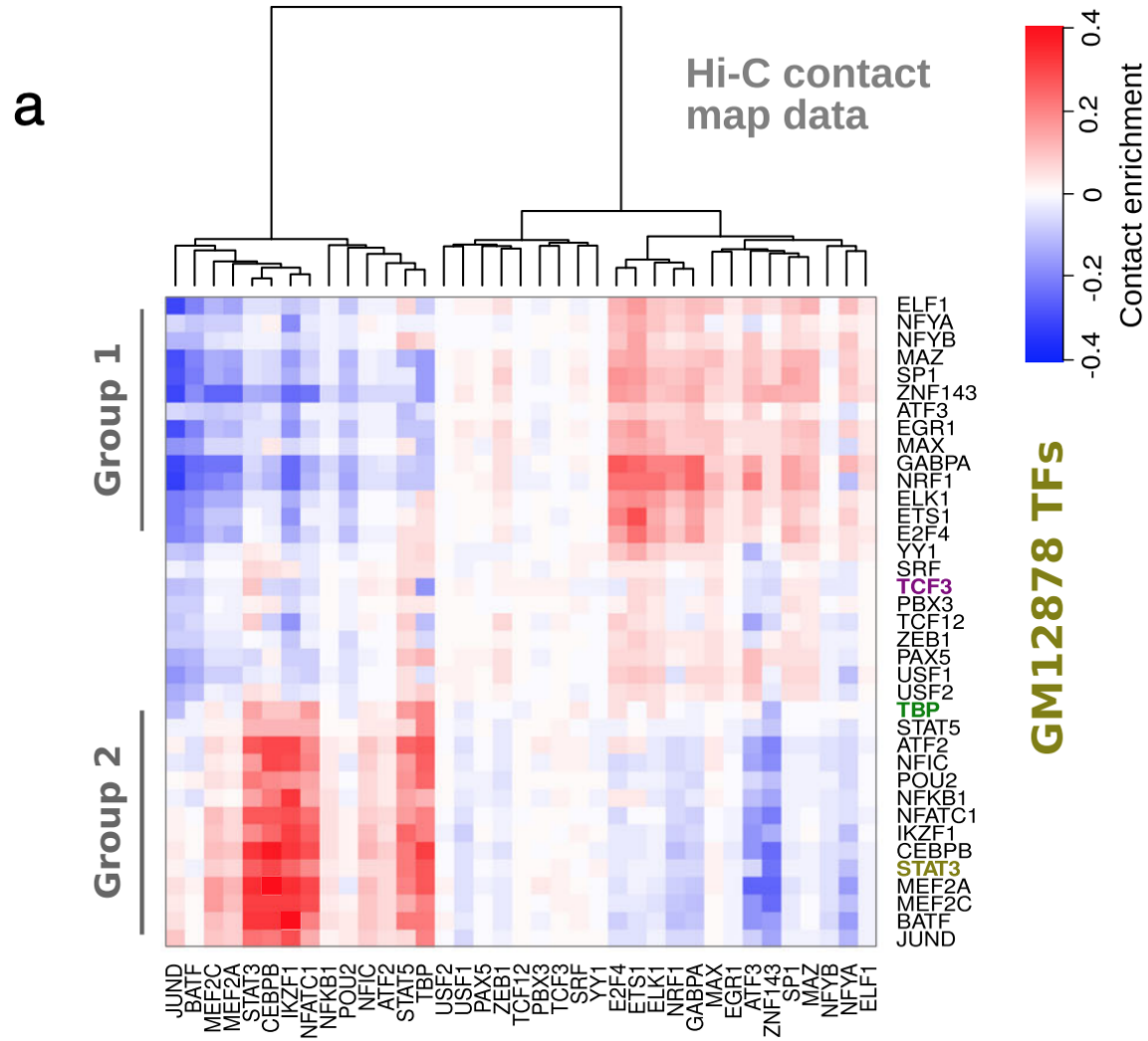
For each TF, bar shows the fractional increase in binding site occupancy when comparing the top and bottom 1/3 of CCL-scores

Measures relating TF presence at binding sites to spatial co-localization

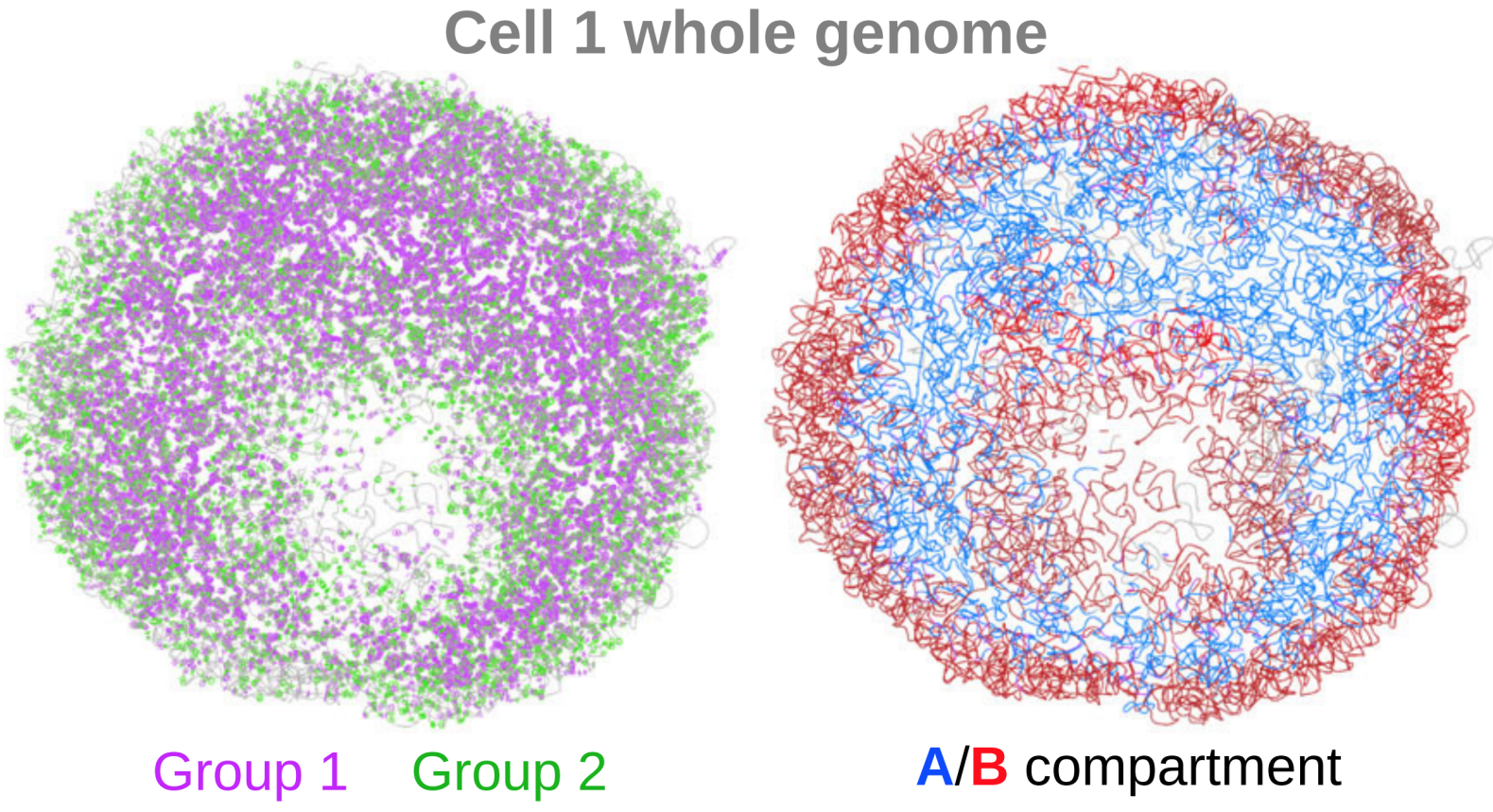


Heterotopic Co-localization

Localization between different TFs



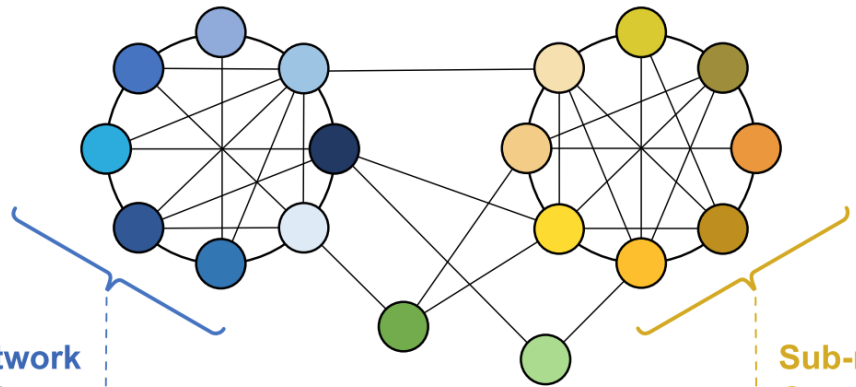
Heterotopic Co-localization vs 3D Structure and Accesibility



Grouping of TFs into proximity sub-networks

Heterotypic TF-TF co-localisation

i *TF-TF spatial proximity sub-networks among TFs with ChIP-seq data.*
Two main groups distinguished by relationship to TSS (not TF members).
Present in lymphoblastoid Hi-C and single-cell ESC genome structures.



Sub-network Group 1

Some TFs are in neither sub-network

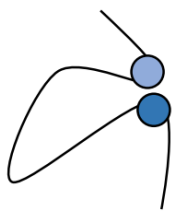
Sub-network Group 2

- More constitutive
- Close to TSS and CTCF sites
- Compartment A1 (lymphoblastoid) or A (embyonic stem cell) enriched

- More lineage-specific
- Separated from TSS and CTCF sites
- Compartment A2 (lymphoblastoid) or B (embyonic stem cell) enriched

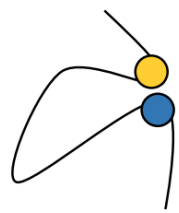
ii

Intra-group interaction:



Increase in TF occupancy

Inter-group interaction:



Usually a decrease in TF occupancy

Conclusions

- Measures of a TF's presence correlate with its spatial co-localization and hence indicate that TF binding is linked to, and reflected by, the 3D organization of TF sites within the chromosomes
  - Suggests a role for the 3D chromosome conformation to allow, and perhaps promote, TF function
- We also show that analyzing the spatial co-localization of sites for different TFs provides a way to predict biologically relevant interacting TF-TF pairs