

Network aspects of chromosome interactomes

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Epigenetics

- Reversible The epigenome can activate, inactivate and modify different cells.
- Heritable Information collected during an individual's life may can be used in future generations
- It is not directly coded in DNA
- Uses additional physical properties of the chromatin molecule
 - Methylation
 - Histone Modifications





Epigenetics: Chromatin Structure

Stained Chromatin



Higher order folding

Inactive Chromatin









Nature Reviews | Genetics



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Observing Chromatin Structure

- Fluorescent in Situ Hybridization
 - One to One interactions (slow)
 - Cannot discover new
 - Low resolution 0.1 Microns



- Hi-C All to All but bad resolution, reproducibility?
- 4C One to Many, 100bp resolution, highly reproducible, but requires a known starting point, the bait





The Ohlsson group bait: H19ICR

- Sits on the end of the long arm of Chromosome 11, high mobility area
- Contains the Imprinted Control Region (ICR) which regulates the genes H19 and Igf2
- Modifying this non-coding region pre-disposes for cancer and enables parthenogenesis



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High throughput sequencing



- Run 4C and amplify using primers on bait
- Sequencing so far through 454 sequencing
- Sequencing generates 500k digitalized "reads"
- The reads have the following characteristics:
 - 30 to 400bp long
 - Homopolymer error
 - High quality
 - The most interesting 4C reads are chimeric
 - Chimeric means: they contain snippets from more than one genomic position, indicating that the H19ICR bait interacted simultaneously with two (or more) target ´sequences





Network structure of chromatin interactions

Three-way interactions in human embryoid bodies seen from the H19 ICR perspective.

Layers of different connectivities (K-shells) are color-coded red, green, blue.



Size proportional to node degree.



Degree distribution of nodes and relation between read counts and centrality (K-shell index) of nodes





Conclusions

- Chromosome interactomes constitute a new kind of biological network, presumably involved in high-order gene regulation;
- These interactomes have some "scale-free" properties (probably not the most interesting thing about them);
- They have already been used to give evidence that chromosomes follow the "fractal globule" model of non-equilibrium polymer shapes (Lieberman-Aiden *et al*, Science (2009));
- The physical properties and physical organization of the nucleus is not random, and these non-random shapes presumably have functions.



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