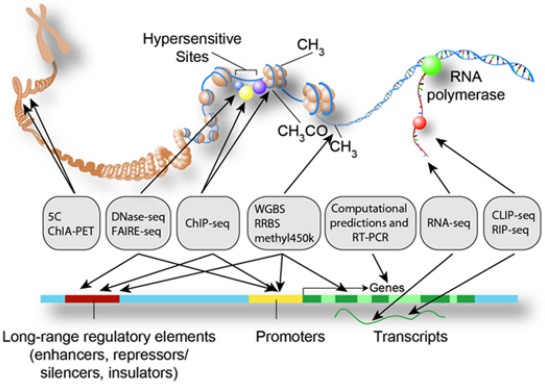
Visualizing Whole Genome Chromosome Structure

DNA carries genetic information as a series of 4 nucleotides (A, T, C, G) stored within a 2D double helix. The double helix of DNA then folds on itself to create higher order structures with increasing complexity until DNA is stored within chromatin, which form chromosomes.



Depicture of the increasing complexity of DNA from a double helix (right) to a chromosome (left). Methods used by the ENCODE project to analyze specific genomic regions are listed in grey boxes.

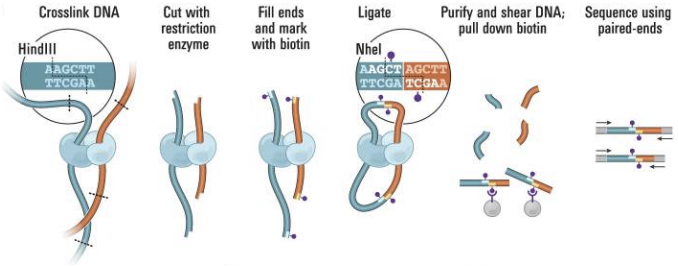
Why care about chromosome structure?

How genes are compartmentalized within chromatin determine their interactions with each other and their specific regulatory elements. Deciphering the 3D structure of the genome can allow genomic processes, such as transcription and replication, to be further understood (Van Berkum et al. 2010).

Methods to visualize chromosome structure

Chromosome Conformation Capture (3C) was developed to visualize physical interactions between genomic elements and revealed novel interactions between these elements within a spatial matrix (Dekker et al. 2002). 3C coupled with high throughput sequencing, called 4C and 5C (Epigenie), have allowed many loci within a genome to be mapped. The limitation of 3C and its derivatives is that only targeted loci can be mapped, making whole-genome mapping impossible (Van Berkum et al. 2010).

Hi-C attempts to probe the entire architecture of a genome by combining proximity-based ligation of the genome and high throughput sequencing. Below is an overview of Hi-C from Lieberman-Aiden et al. (2009), which first described the Hi-C protocol:



Regions of tightly coiled or relatively open chromatin can indicate whether a stretch of the genome is "on" or "off." Chromatin folding and looping are also regulatory mechanisms that can be revealed through chromosome visualization. Hi-C has revealed the connection between structure and function in the genome (Maze et al. 2014) as well as captured the interactome of chromatin within the genome (Jäger et al. 2015). Using Hi-C, researchers can explore genome functions, investigate the metagenome of an environment, and predict whole genome responses to variable conditions or stimuli.

Resources

Analogous to traditional genome browsers, 3D genome browser allow a user to peruse available genomes and their higher order structures.

3D Genome Browser
http://promoter.bx.psu.edu/hi-c/
Hi-C Data Browser and My5C portal
http://hic.umassmed.edu/welcome/welcome.php
Hi-C Genome-Wide Interaction Browser
http://homer.salk.edu/homer/interactions/

Further reading

- Dekker, Job, et al. "Capturing chromosome conformation." *Science* 295.5558 (2002): 1306-1311.
- Jäger, Roland, et al. "Capture Hi-C identifies the chromatin interactome of colorectal cancer risk loci." *Nature communications* 6 (2015).
- Lieberman-Aiden, Erez, et al. "Comprehensive mapping of long-range interactions reveals folding principles of the human genome." *science* 326.5950 (2009): 289-293.
- Maze, Ian, et al. "Analytical tools and current challenges in the modern era of neuroepigenomics." *Nature neuroscience* 17.11 (2014): 1476-1490.
- Van Berkum, Nynke L., et al. "Hi-C: a method to study the three-dimensional architecture of genomes." (2010).
- http://epigenie.com/epigenetics-research-methods-and-technology/chromatin-analysis/chromatin-conformation-analysis-3c-techniques/hi-c/