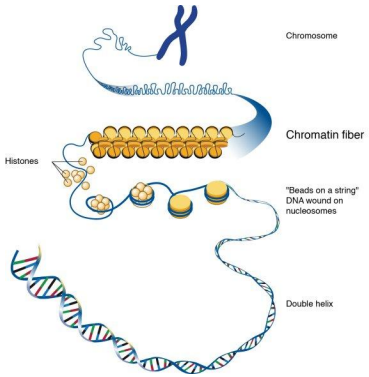
Exploring the three-dimensional organization of genomes



How DNA is organized in three dimensions (3D)? And how does it affect the ways in which cells access, read and interpret genetic information?

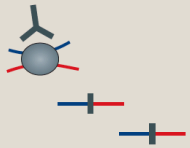
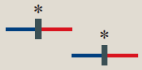
All **chromosome conformation capture (3C)** based methods allow the determination of **the frequency** with which any pair of loci in the genome is in close enough physical proximity (probably in the range of 10–100 nm) to become cross-linked.

Rationale: when a sufficient number of pairwise interaction frequencies are determined for a genomic region, chromosome or whole genome, its 3D arrangement can be inferred.

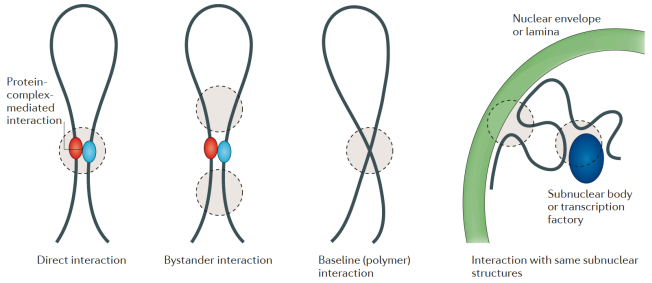
1. 3C-based methods to study three dimensional chromosome folding

a 3C: converting chromatin interactions into ligation products

b Ligation product detection methods

3C	4C	5C	ChIA–PET	Hi-C
One-by-one All-by-all	One-by-all	Many-by-many	Many-by-many	All-by-all
			• DNA shearing • Immunoprecipitation 	• Biotin labelling of ends • DNA shearing 
PCR or sequencing	Inverse PCR sequencing	Multiplexed LMA sequencing	Sequencing	Sequencing

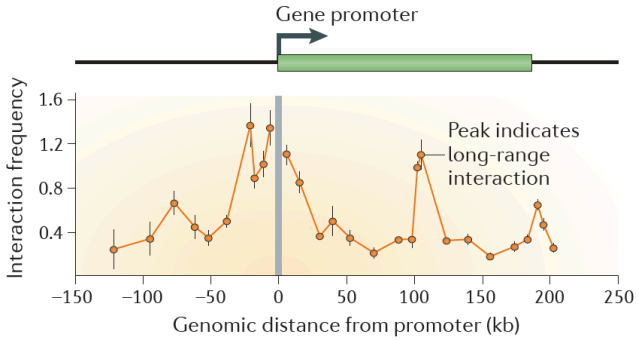
2. Processes leading to close spatial proximity of loci



(1) These methods do not distinguish functional from non-functional associations nor do they reveal the mechanisms that led to their co-localization.

(2) 3C interaction frequency data represent the sum of interactions across a large cell population, and in each cell chromosome conformation is determined by many different constraints that act on the chromatin fiber.

3. 3C data for the *CFTR* gene in Caco-2 cells



Dekker et al., 2013, *Nat Rev Genet*
Gheldof et al., 2010, *Nucleic Acids Research*