No Party Like an ATAC-seq Party

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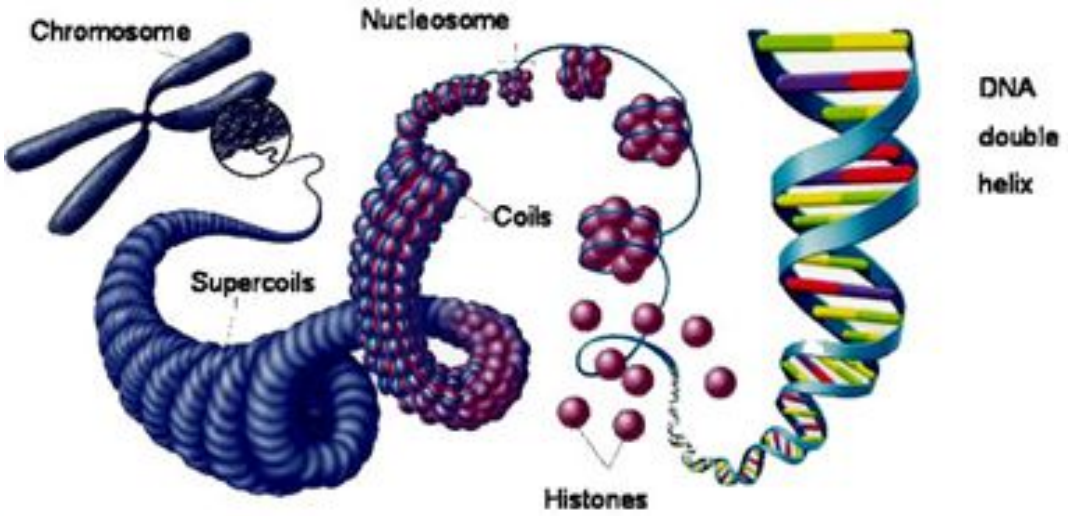
Introduction

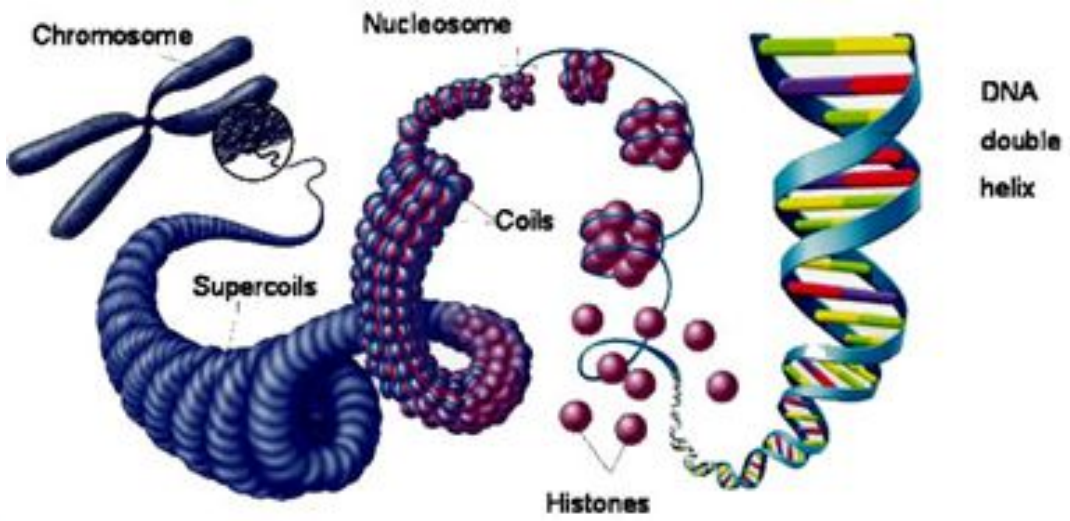
- DNA presents different levels of compaction.
- Basic level : nucleosomes -- basic units of DNA packaging in eukaryotes cells.
- Double helix wrapped around 8 histone protein chores.



Introduction

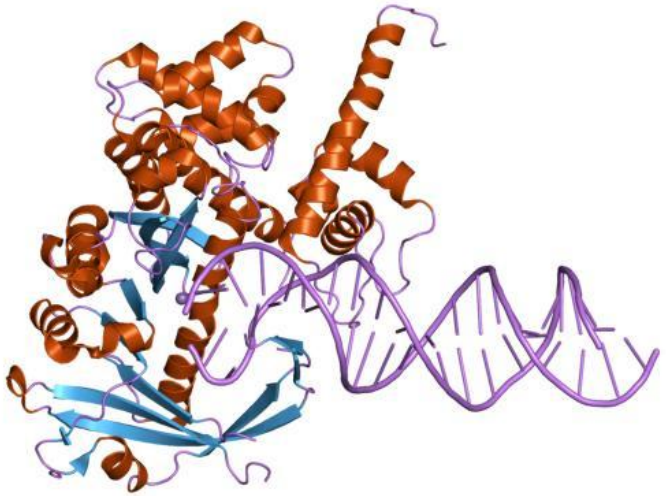
- Then folded through a series of successively higher order structures to eventually form a chromosome.

- Both compacts DNA and creates an additional layer of regulatory control, which ensures correct gene expression.



ATAC-seq

- Recent 2-step technique, Buenrostro et al. (2013), that aims at identifying accessible regions of the chromatin + nucleosomal position.
- Relies on the action of mutated Tn5 transposase.
- Enzyme that catalyzes the movement of transposons to other parts in the genome.



ATAC-seq

Buenrostro et al. used these method on B-cell lines to

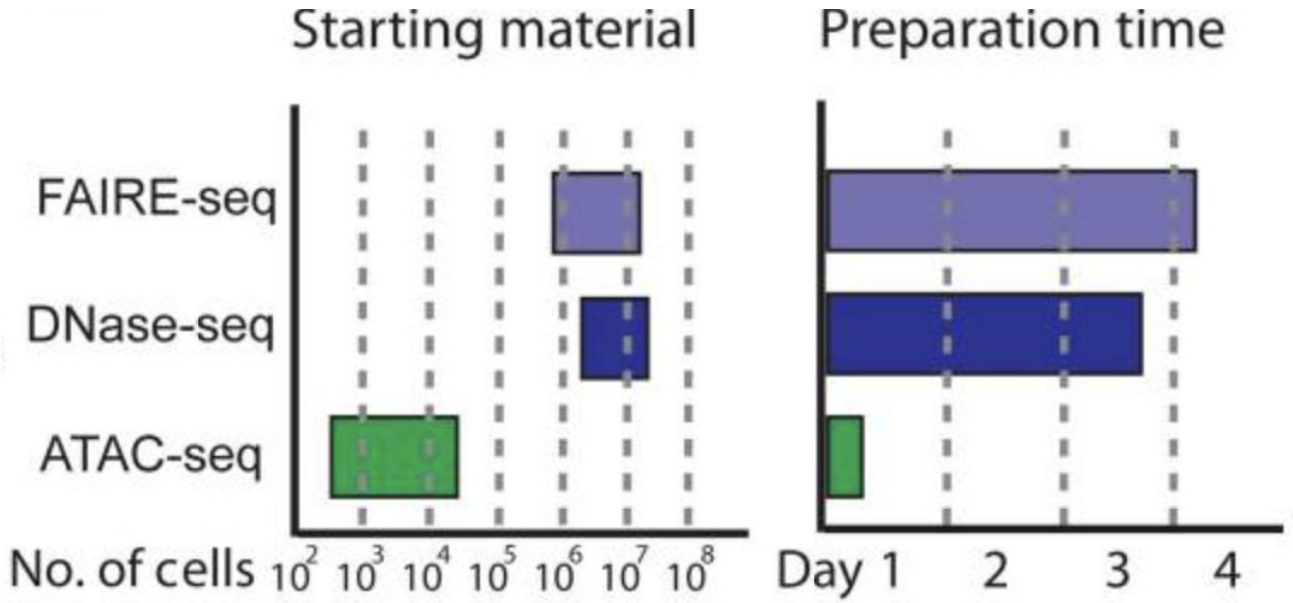
- identify regions of open chromatin;
- identify nucleosome-bound and nucleosome-free positions in regulatory regions;
- infer the positions of DNA binding proteins

Applied to assay personal T-cell epigenome of a healthy volunteer via standard serial blood draws

ATAC-seq

Proved to be more sensitive and more performant to measure and interpret the epigenome compared to FAIRE-seq and DNase-seq

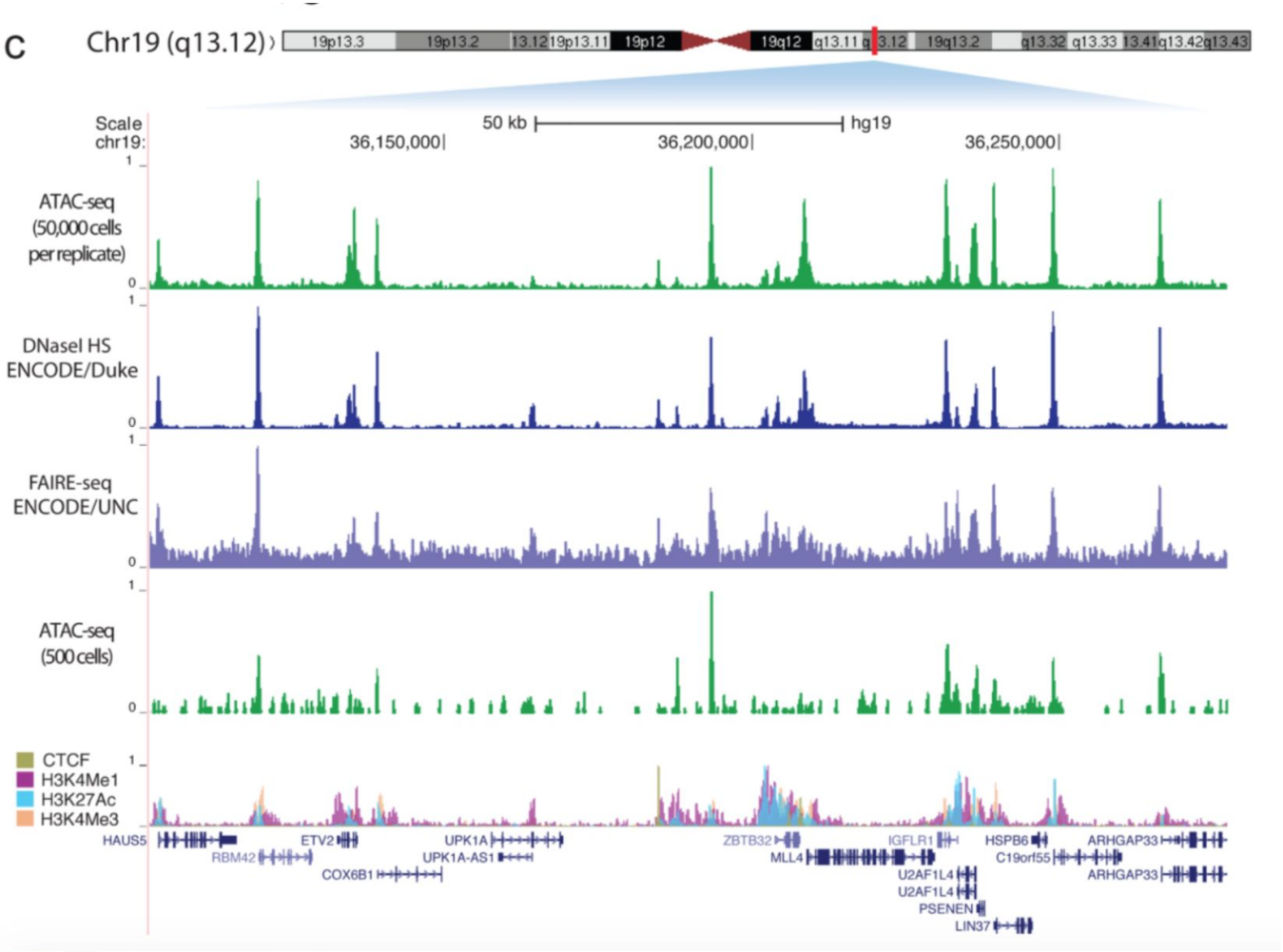
- Faster;
- Requires fewer cells (500 to 50,000).



ATAC-seq probes chromatin accessibility with transposons

- Uses Tn5 transposase to integrate adapter into accessible chromatin regions
- Steric hindrance makes transposition of less accessible chromatin less probable
- Amplifiable DNA fragments suitable for high-throughput sequencing are generated at open chromatin locations
- Simple two-step process involving Tn5 transposase insertion and PCR for amplification

ATAC-seq probes chromatin accessibility with transposons



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ATAC-seq probes chromatin accessibility with transposons

- Accurate, sensitive measure of chromatin accessibility
- ATAC-seq has similar signal-to-noise as DNase-seq, even when the latter is prepared with many more cells
- ROC curves display similar sensitivity and specificity for both ATAC-seq and DNase-seq
- Correlate well with active chromatin, not just regions of transposase preference
- Peak intensities highly correlated between ATAC-seq, DNase-seq

ATAC-seq insert sizes disclose nucleosome positions

- Paired-end reads provide a wealth of information about nucleosome packing and positioning

- High-resolution readout of nucleosome-associated and nucleosome-free regions in regulatory elements genome-wide

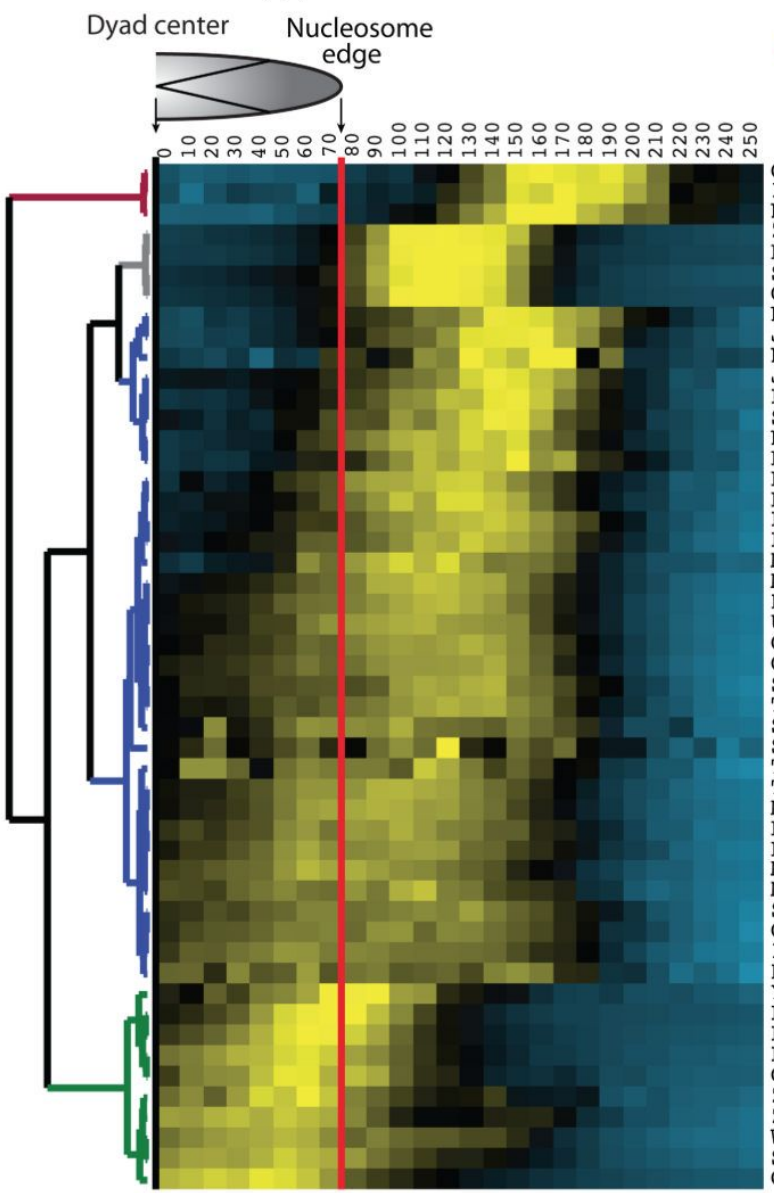
ATAC-seq insert sizes disclose nucleosome positions

- Different functional states of chromatin have differing accessibility “fingerprints” -- may be read with ATAC-seq

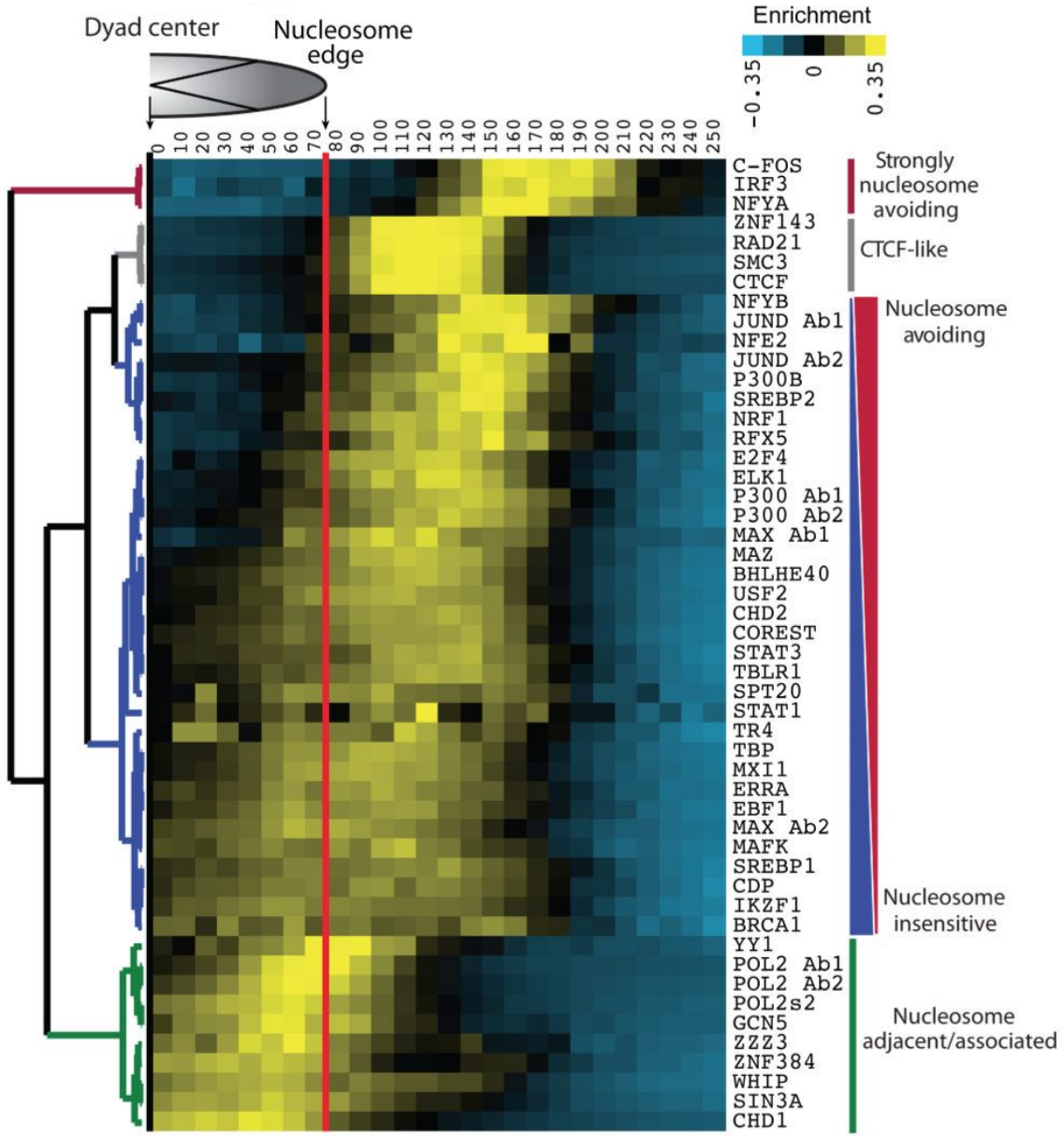
- Reveals differentially accessible forms of chromatin, hypothesized to exist *in vivo* but difficult to confirm

ATAC-seq reveals patterns of nucleosome - Transcriptome factor (TF) spacing

- Use CHIP-Seq to find where TF binds
- Compare nucleosome position to TF position
- Use unsupervised hierarchical clustering



ATAC-seq reveals patterns of nucleosome - Transcriptom e factor (TF) spacing



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ATAC-seq reveals patterns of nucleosome - Transcriptome factor (TF) spacing

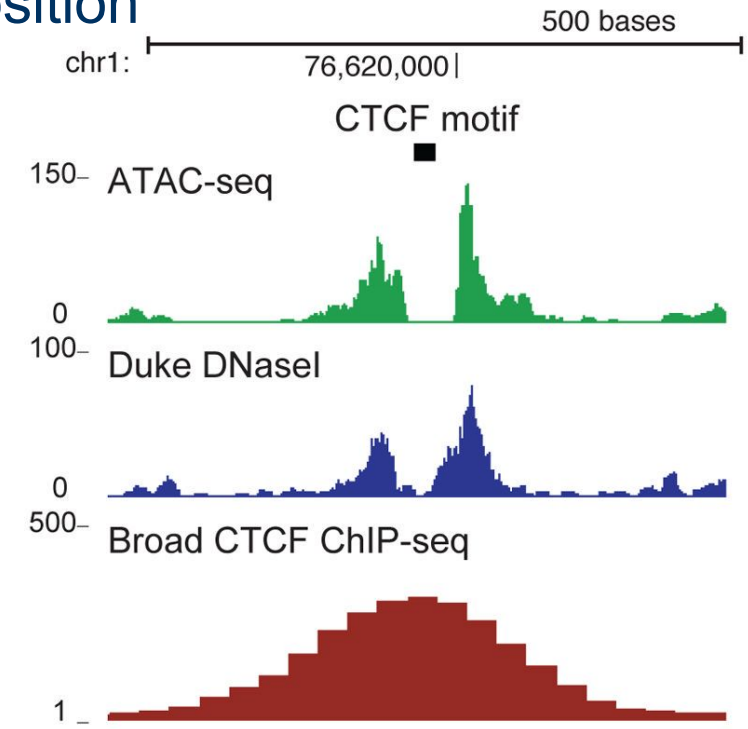
“The interplay between precise nucleosome positioning and locations of DNA binding factor immediately suggests specific hypotheses for mechanistic studies, a potential advantage of ATAC-seq.”

ATAC-seq footprints infer factor occupancy genome-wide

Assumption: DNA-sequences occupied by DNA-binding proteins are protected for transposition

Results

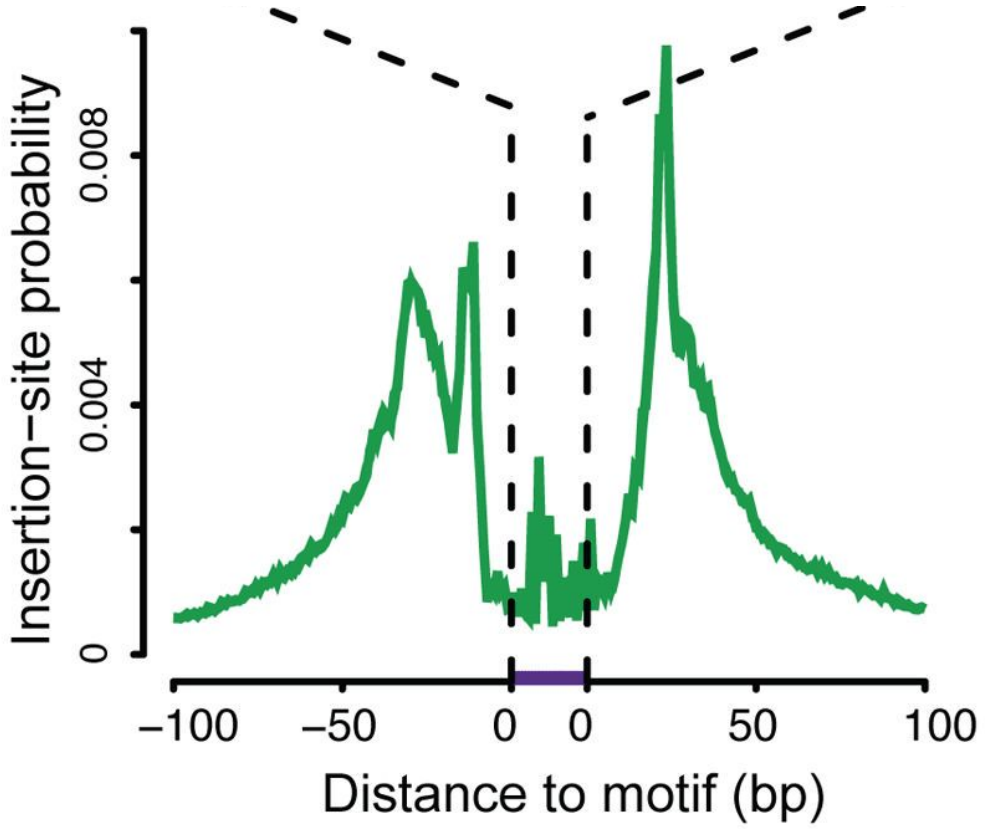
One locus



ATAC-seq footprints infer factor occupancy genome-wide

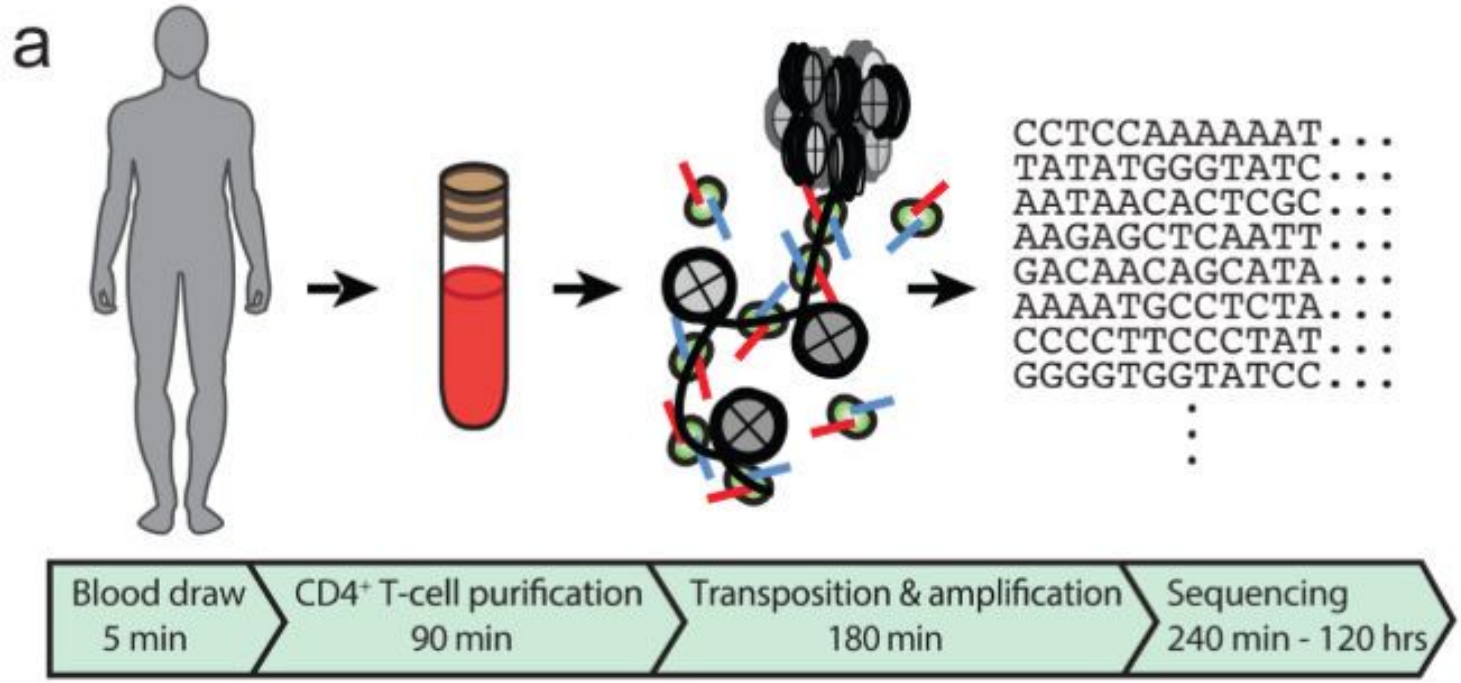
Results

Average over all loci



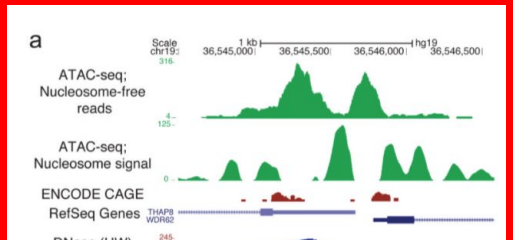
Possible Personal Epigenomics?

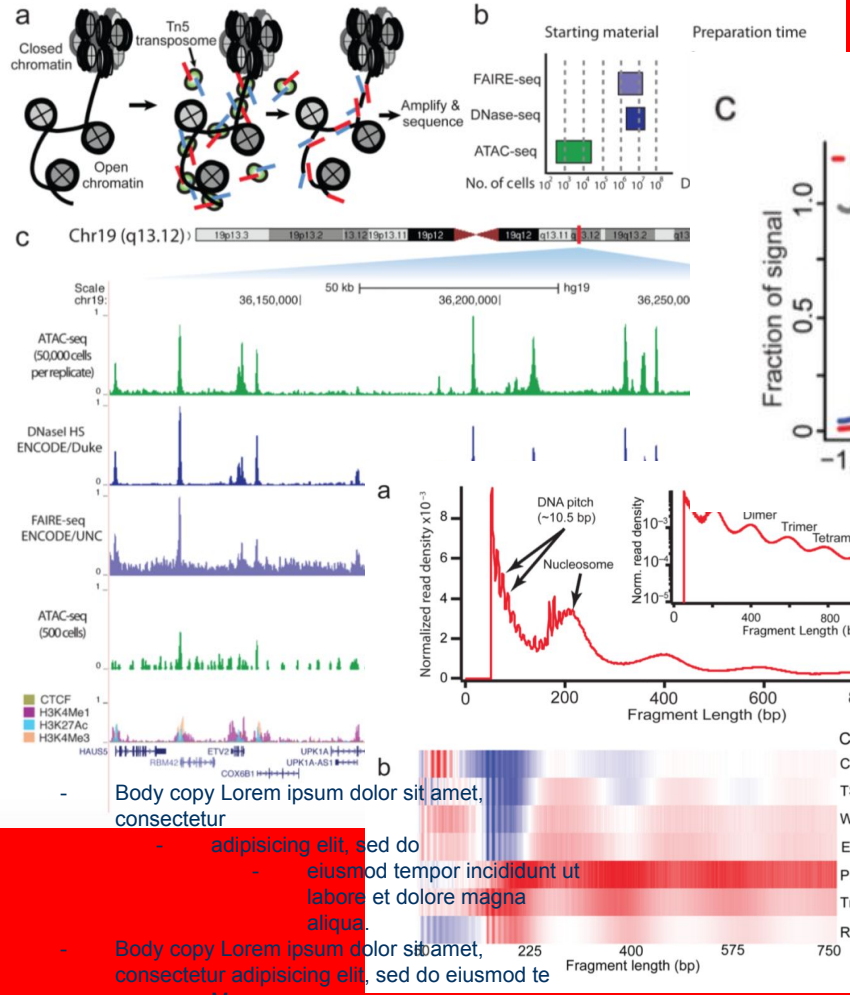
ATAC-Seq enables epigenomic analysis on clinical timescales

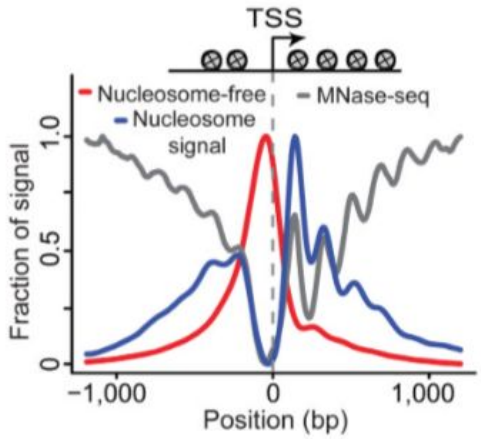


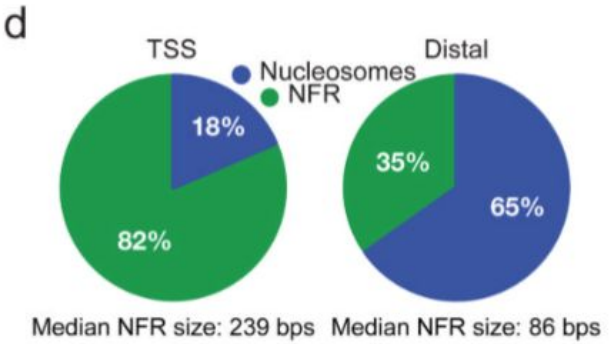
Total time

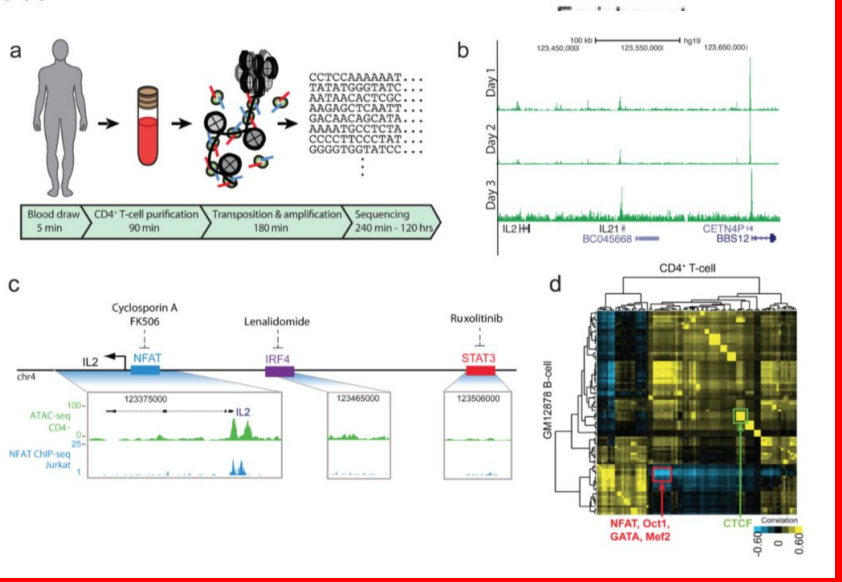
Thank you! Questions?











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