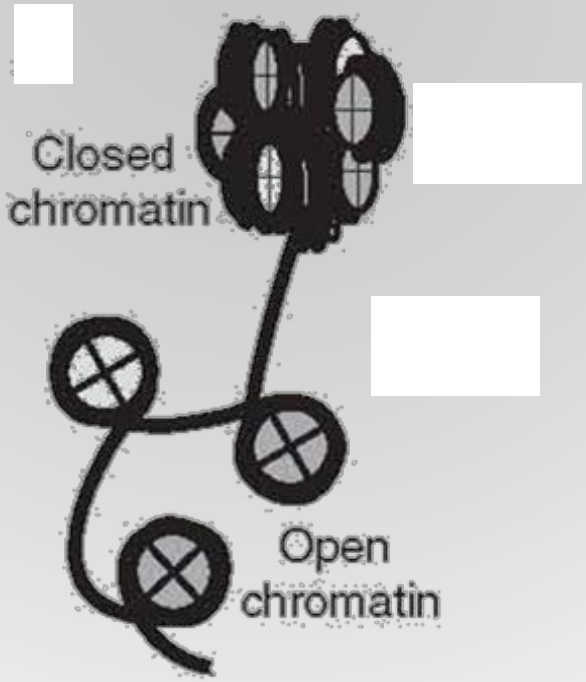
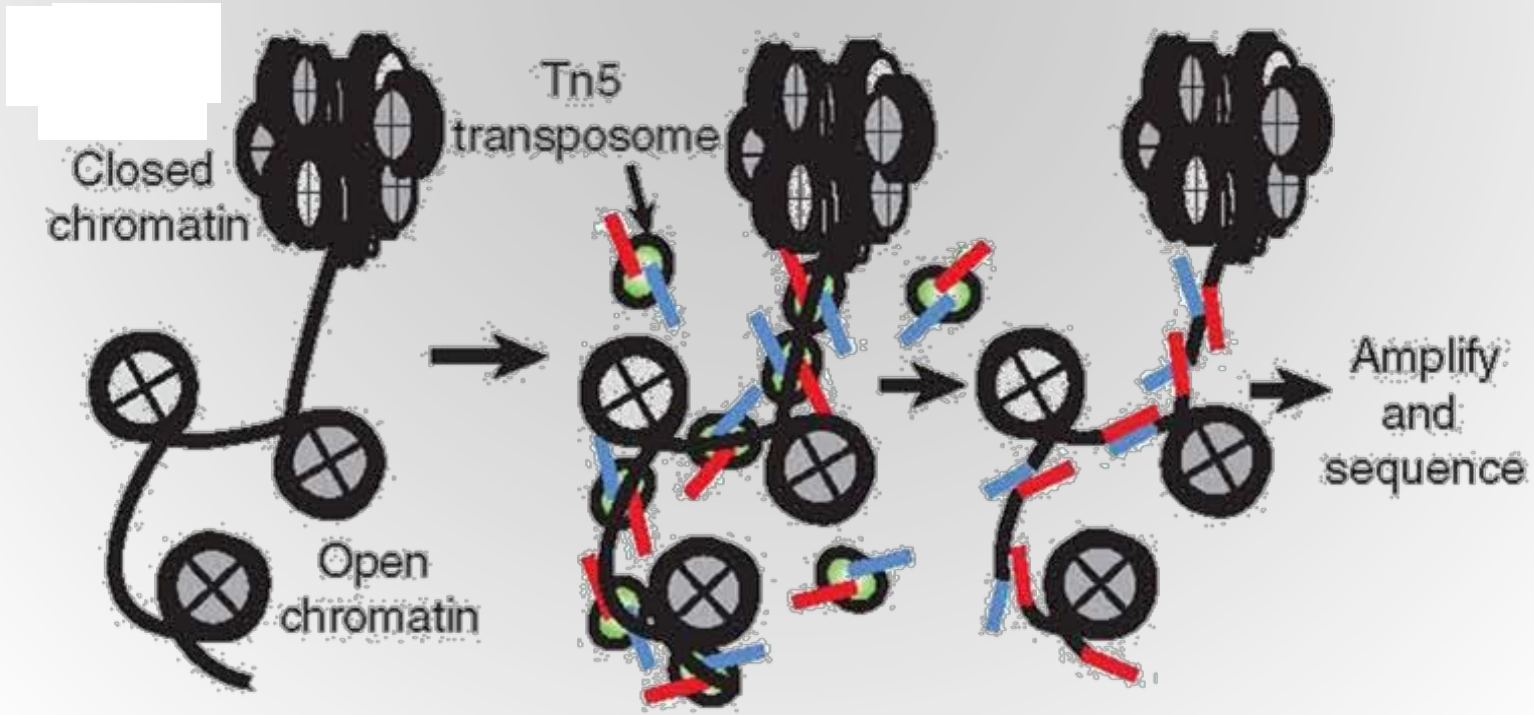
There are two states of chromatin



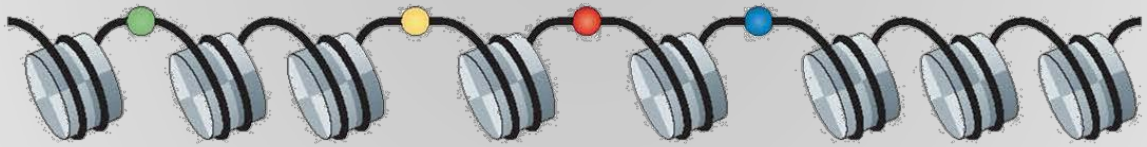
Buenrostro (2013)

ATAC-seq probes the conformation of chromatin



Buenrostro (2013)

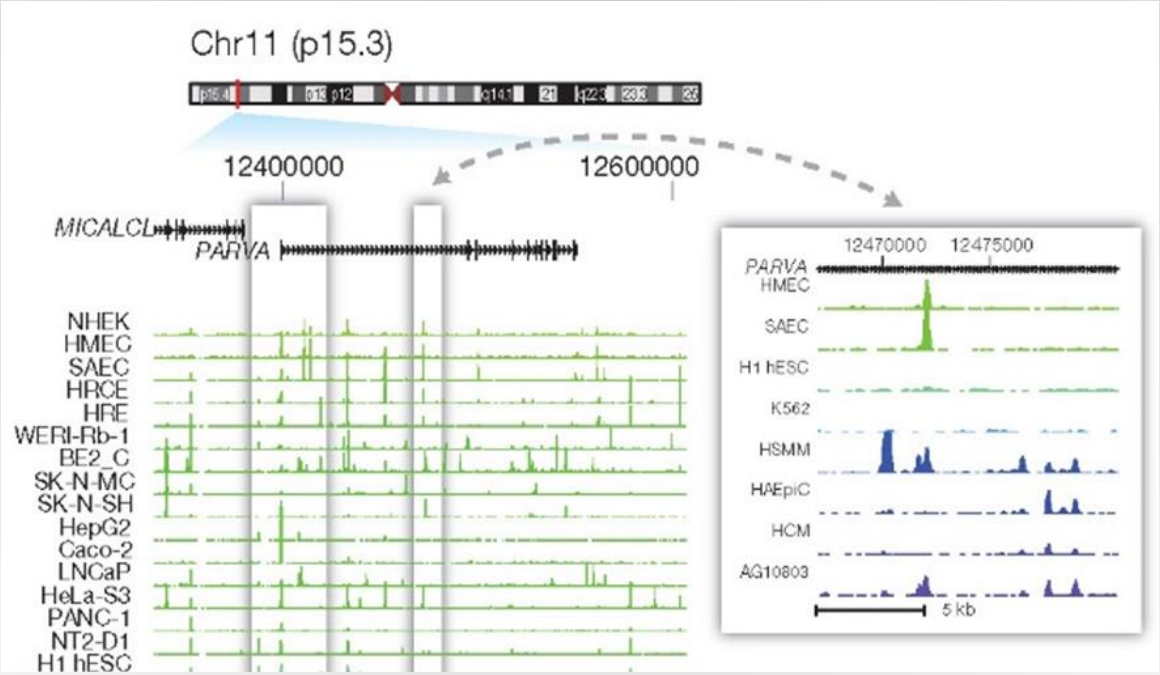
Open conformations create peaks



Fragmentation | Size selection | PCR | Sequencing | Mapping | Output

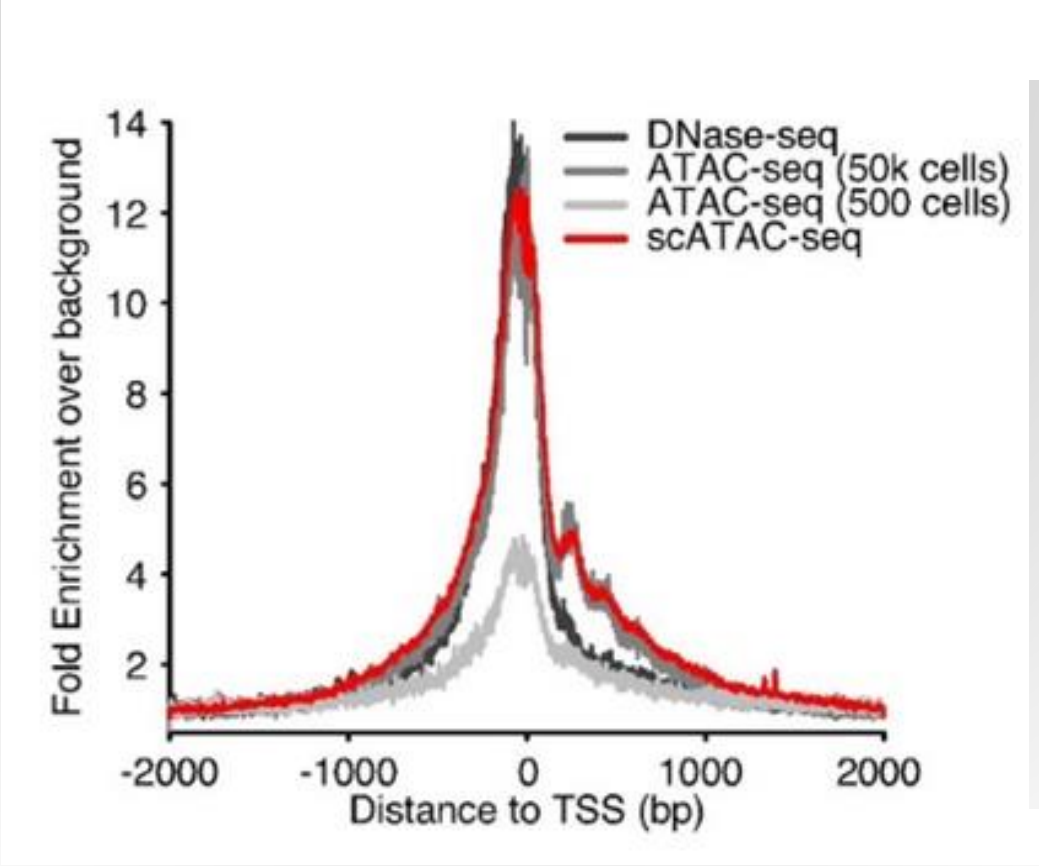
Meyer (2014)

Chromatin states vary between cell types



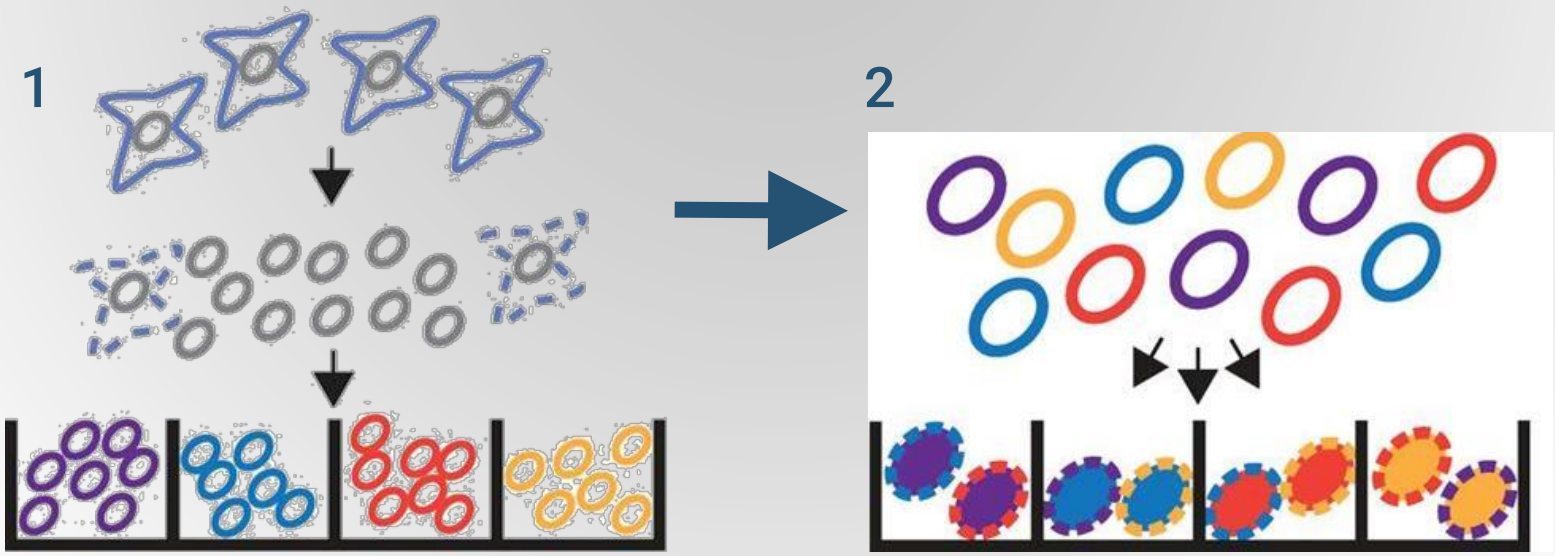
Thurman (2012)

The resolution of ATAC-seq is 500 cells



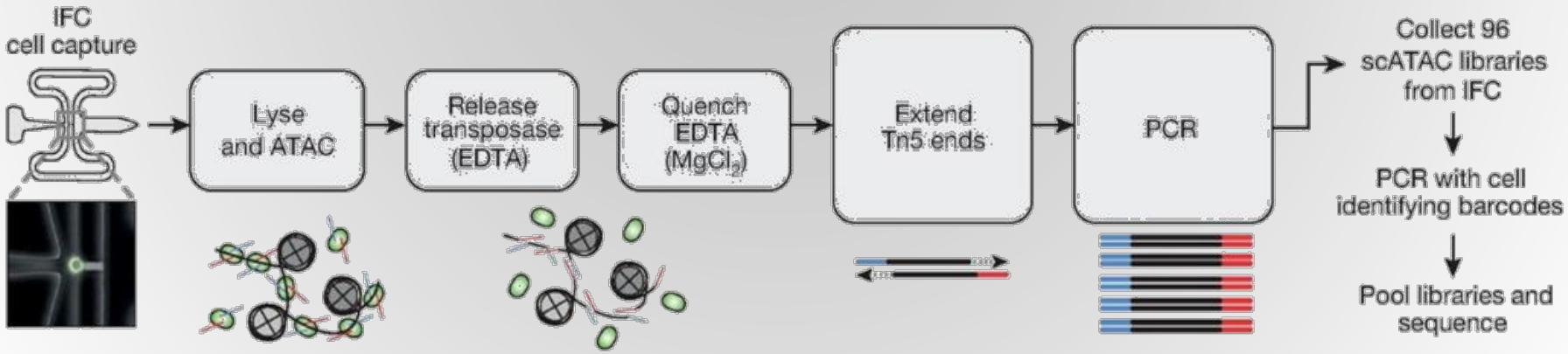
Buenrostro (2015)

One method of scATAC-seq uses **combinatorial indexing**



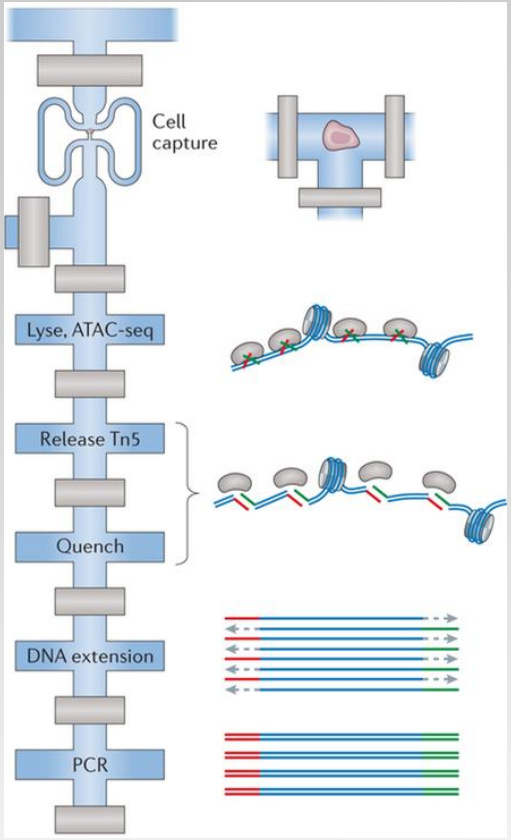
Cusanovich (2015)

A second method of scATAC-seq uses **microfluidics**



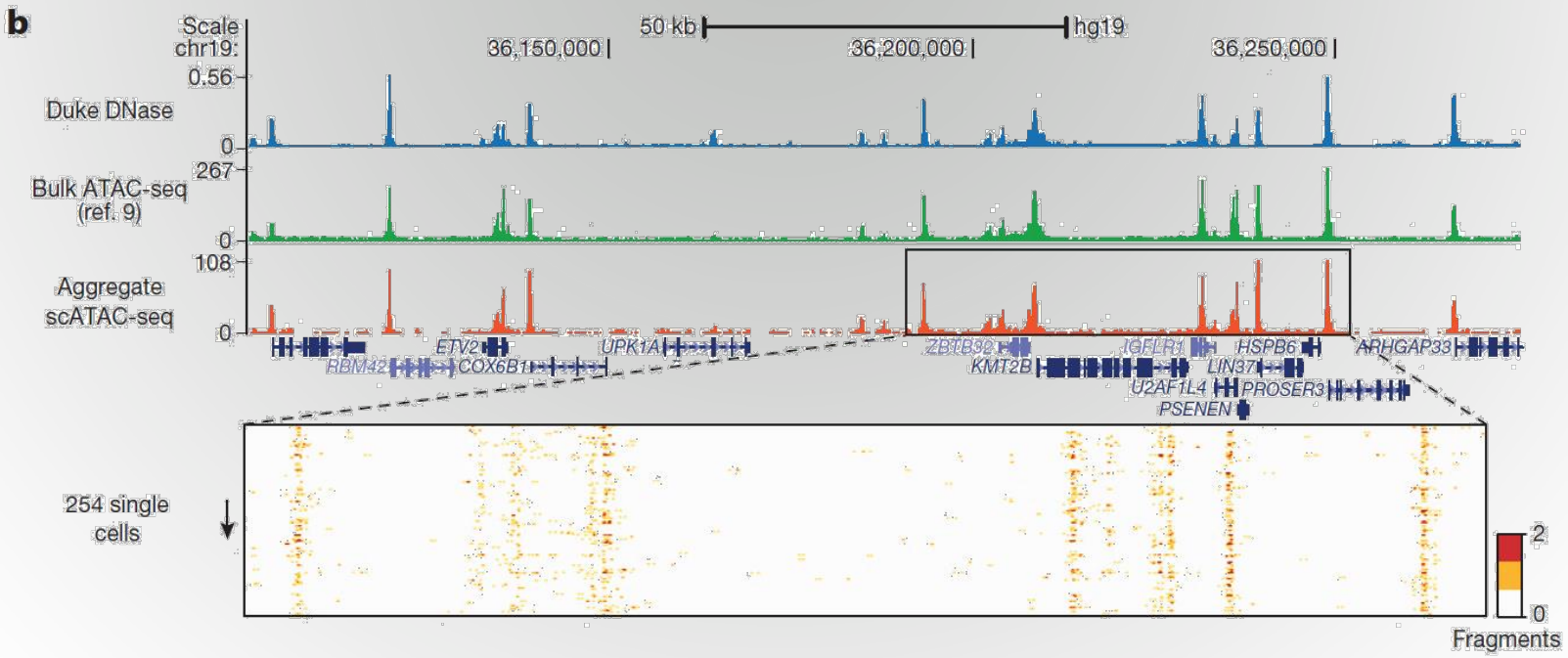
Buenrostro (2015)

The microfluidic device uses values to compartmentalize



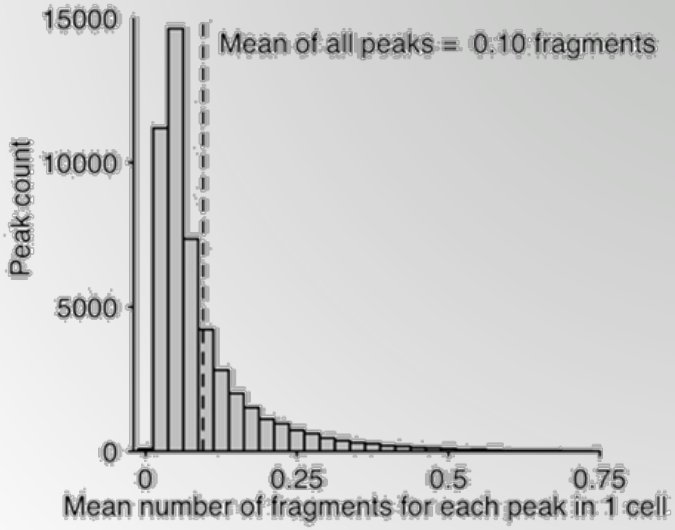
Prakadan (2017)

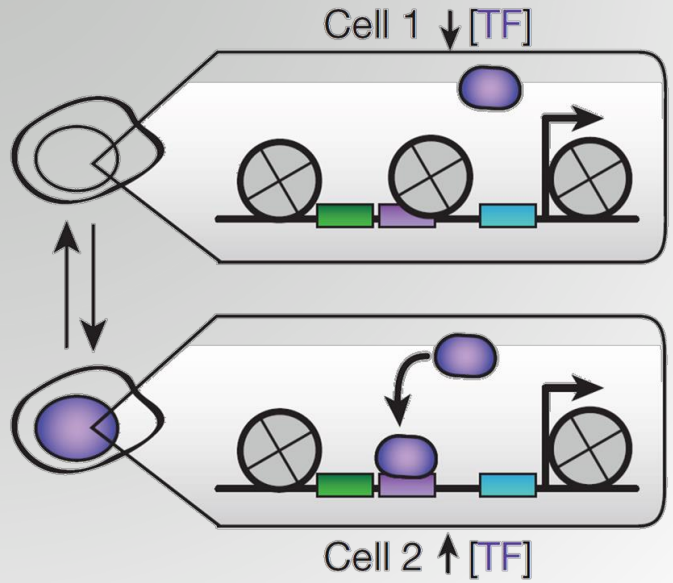
Aggregate single-cell accessibility profiles closely recapitulate profiles of DNase-seq and ATAC-seq



Buenrostro (2015)

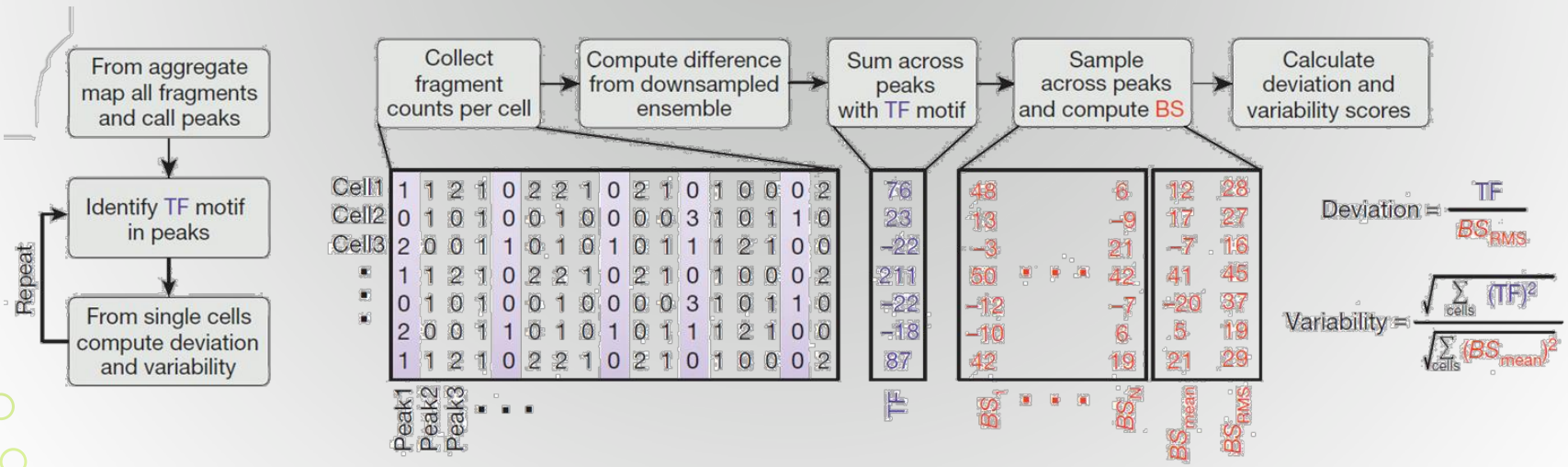
Differences in cellular states leads to differential chromatin accessibility





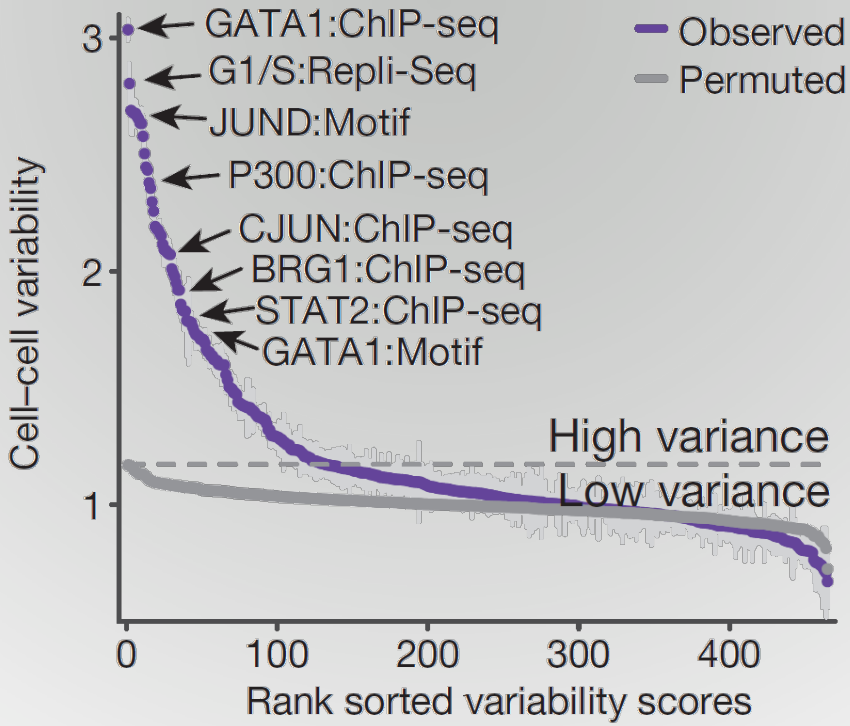
Buenrostro (2015)

Analysis infrastructure to calculate TF deviations and variability from scATAC-seq data



Buenrostro (2015)

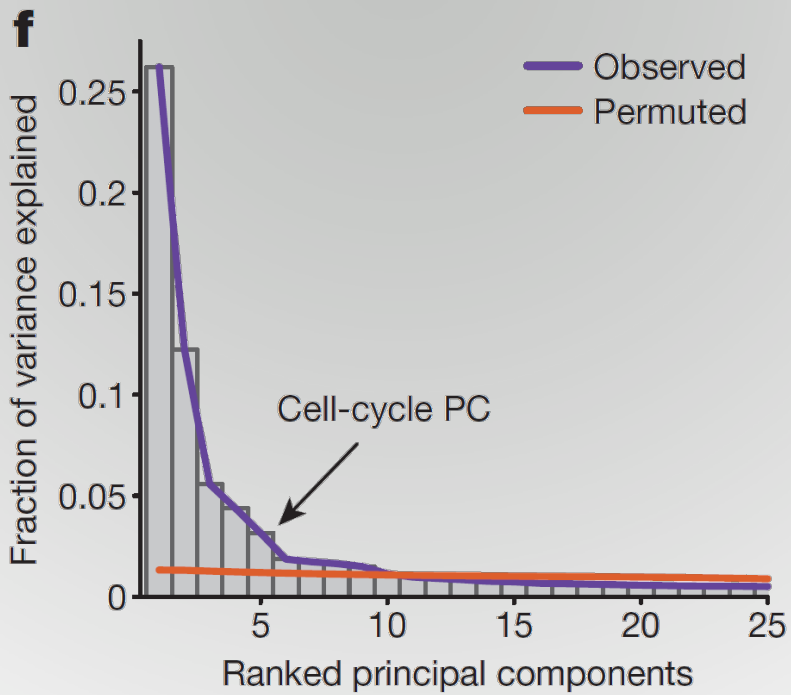
Observed cell-to-cell variability within sets of genomic features



Discovery of set of *trans*-factors associated with high variability.

Buenrostro (2015)

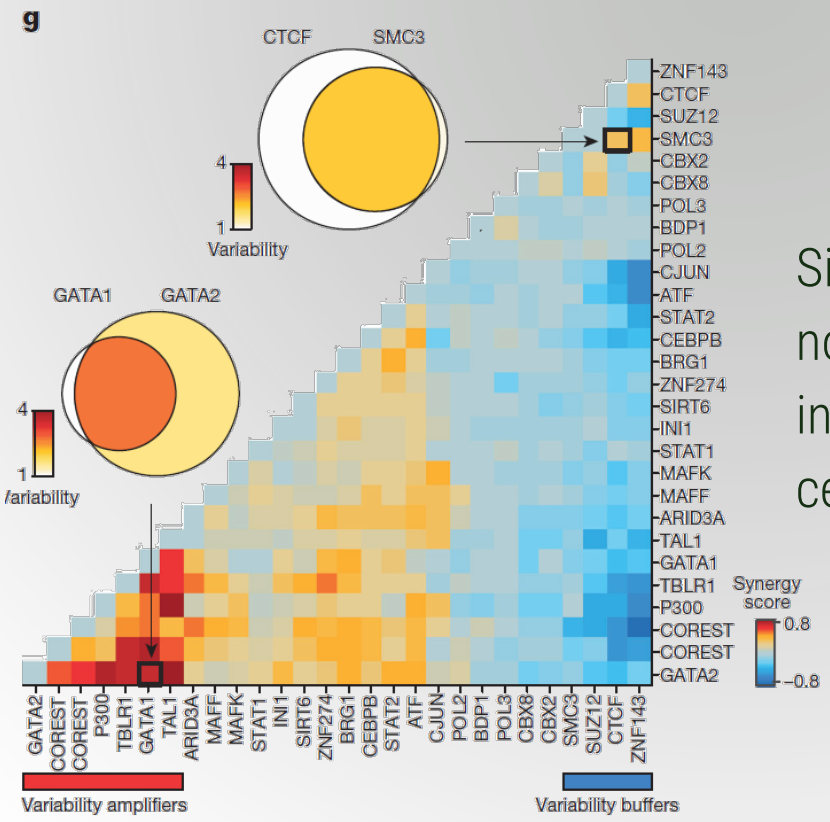
Principal components ranked by fraction of variance explained from observed deviation data and permuted data



High-variance *trans*-factors are variable independent of the cell cycle.

Buenrostro (2015)

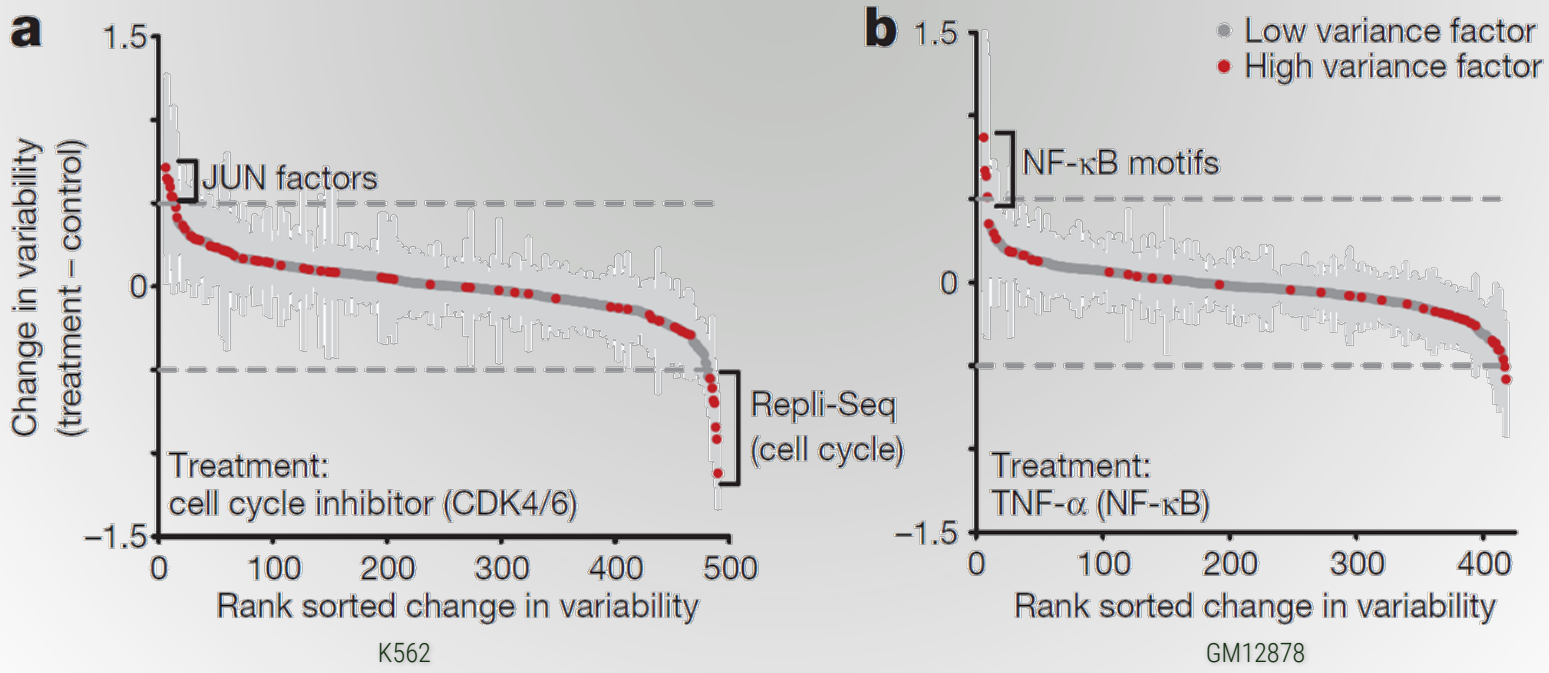
Calculated changes in associated variability of factors when present together versus independently



Single cell accessibility profiles nominate distinct *trans*-factors that, in combination, induce or suppress cell-to-cell regulatory variation.

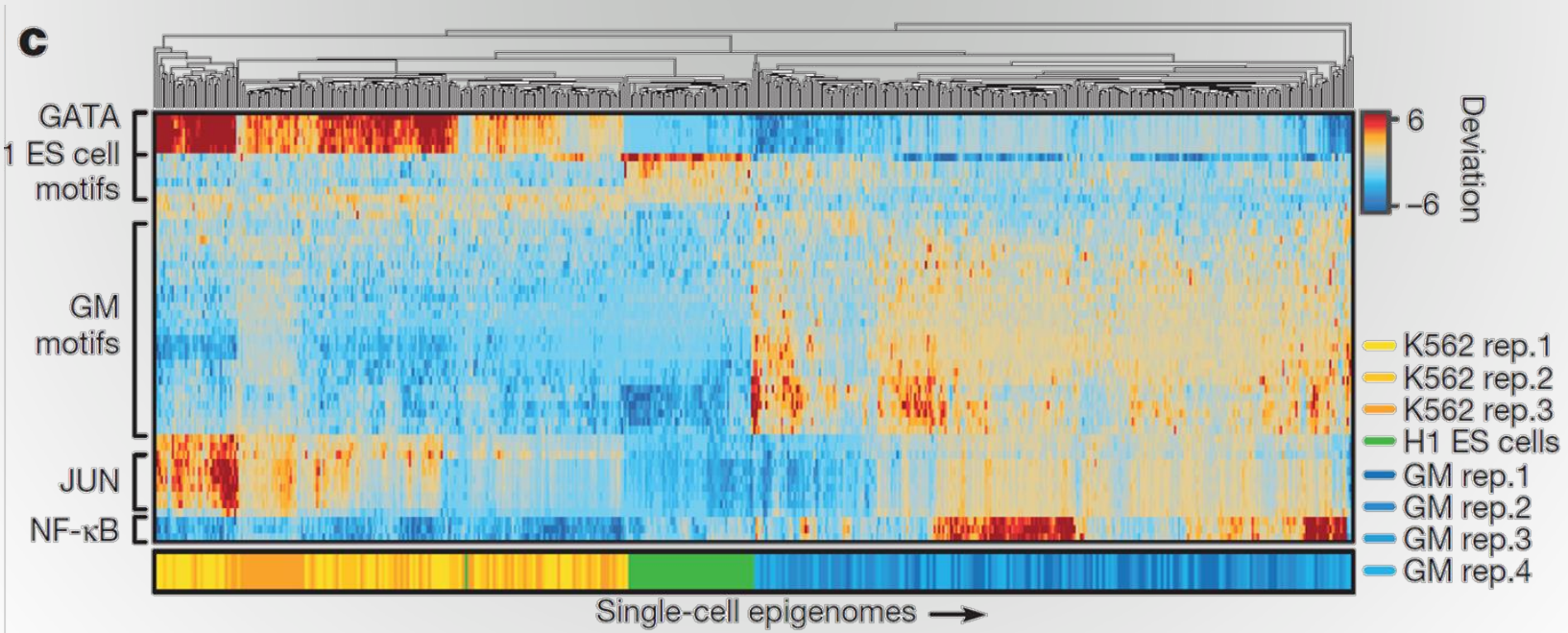
Buenrostro (2015)

Chemical perturbations affect variability on a per-cell basis



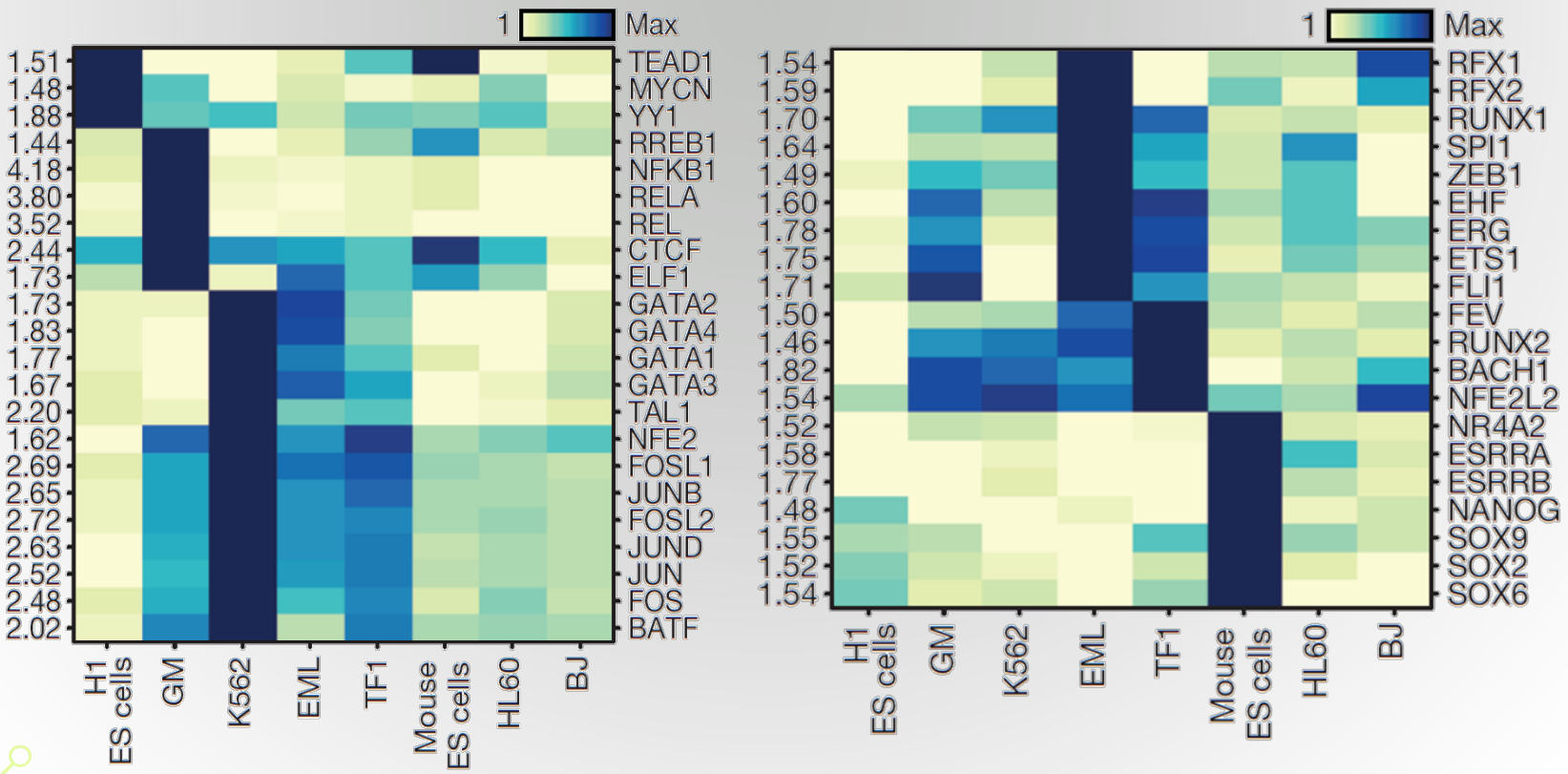
Buenrostro (2015)

Mixtures of cells can be deconvolved by *trans*-factor variability



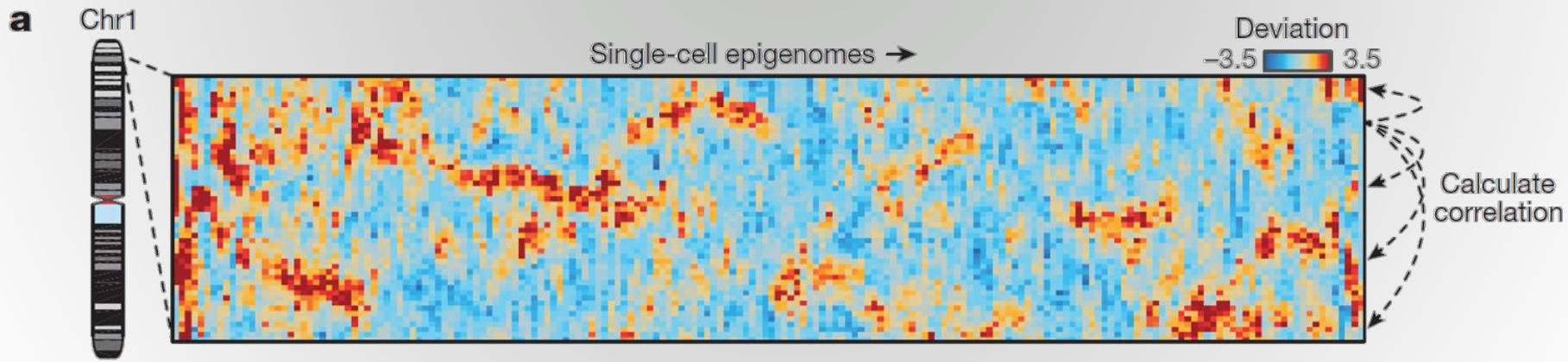
Buenrostro (2015)

Cell lines have corresponding highly variable *trans*-factors



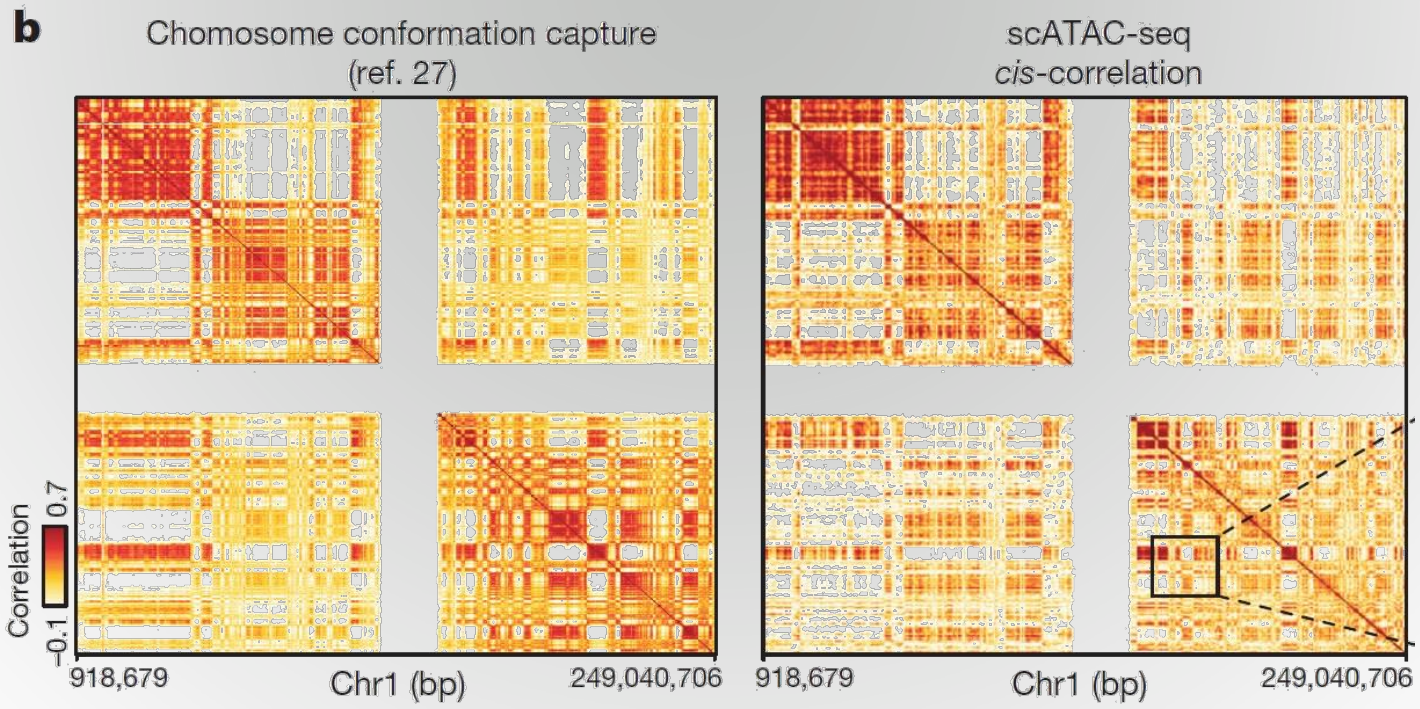
Buenrostro (2015)

Covariability across *cis*-elements, sliding windows per-cell



Buenrostro (2015)

scATAC-seq used to assess chromosome conformation



Buenrostro (2015)

In summary...

- Single cell data recapitulates bulk
- Variability in accessibility is associated with
  - *Trans*-factors: traced by cell type
  - *Cis*-elements: traced by chromosome conformation

Single cell ATAC-seq by cellular indexing

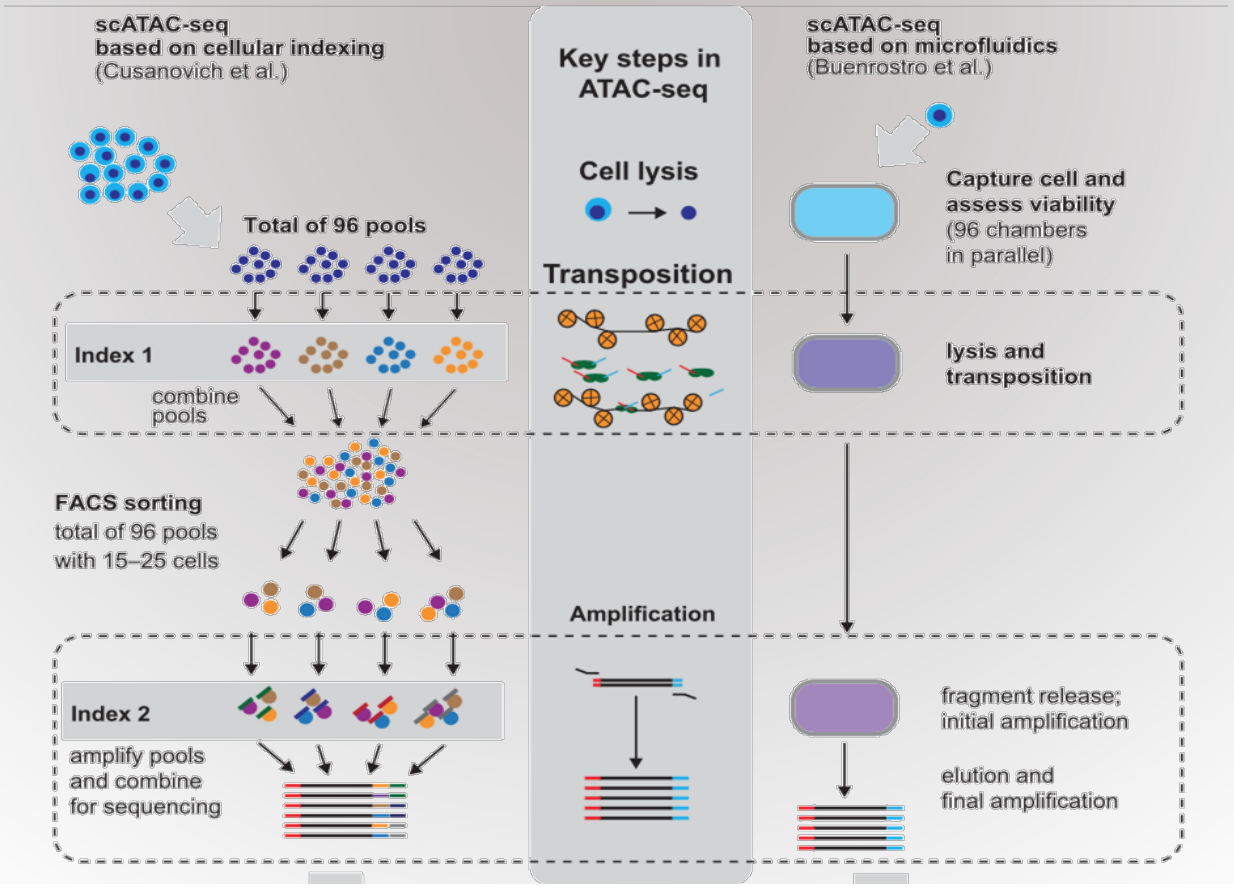
EPIGENETICS

Multiplex single-cell profiling of chromatin accessibility by combinatorial cellular indexing

Darren A. Cusanovich,[1] Riza Daza,[1] Andrew Adey,[2] Hannah A. Pliner,[1] Lena Christiansen,[3] Kevin L. Gunderson,[3] Frank J. Steemers,[3] Cole Trapnell,[1] Jay Shendure[1]*

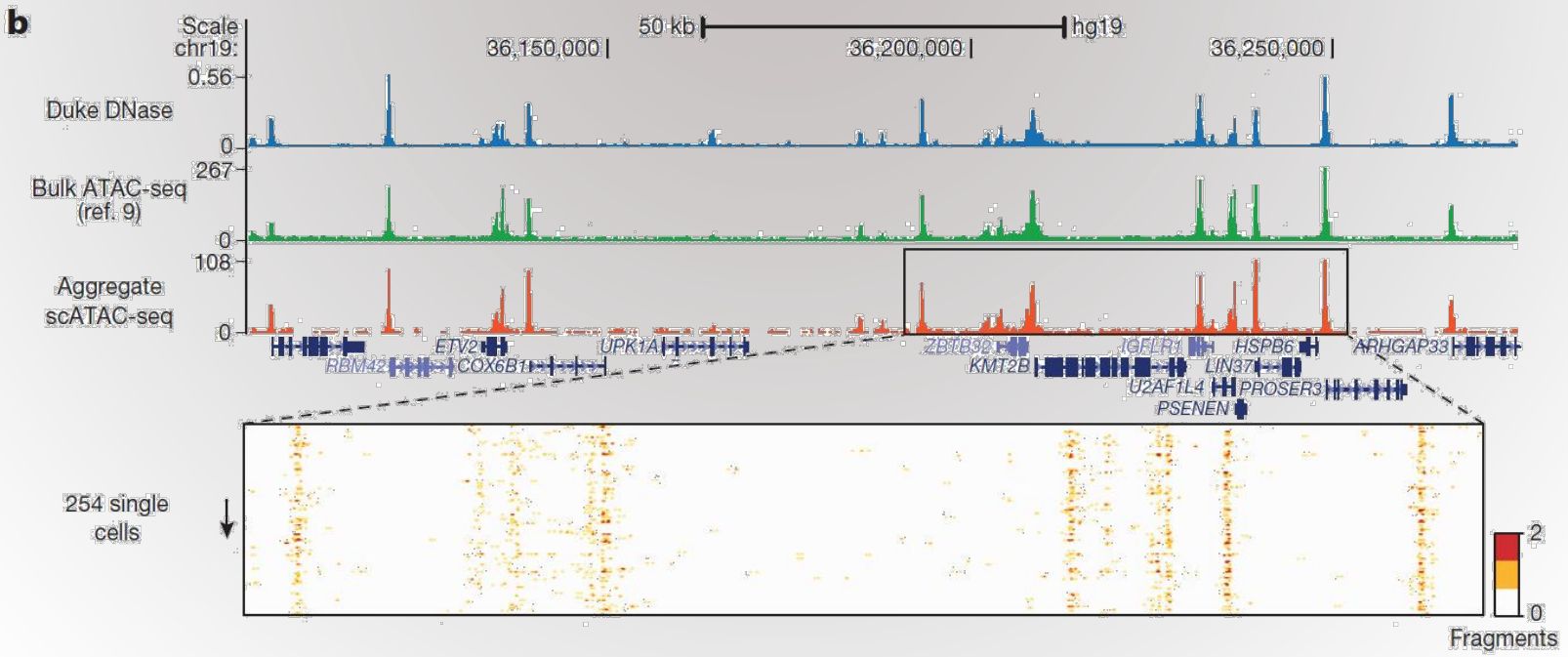
Technical advances have enabled the collection of genome and transcriptome data sets with single-cell resolution. However, single-cell characterization of the epigenome has remained challenging. Furthermore, because cells must be physically separated before biochemical processing, conventional single-cell preparatory methods scale linearly. We applied combinatorial cellular indexing to measure chromatin accessibility in thousands of single cells per assay, circumventing the need for compartmentalization of individual cells. We report chromatin accessibility profiles from more than 15,000 single cells and use these data to cluster cells on the basis of chromatin accessibility landscapes. We identify modules of coordinately regulated chromatin accessibility at the level of single cells both between and within cell types, with a scalable method that may accelerate progress toward a human cell atlas.

Cellular Indexing vs. Microfluidics



Pott (2015)

Significance of Single Cell ATAC-sequencing



Buenrostro (2015)

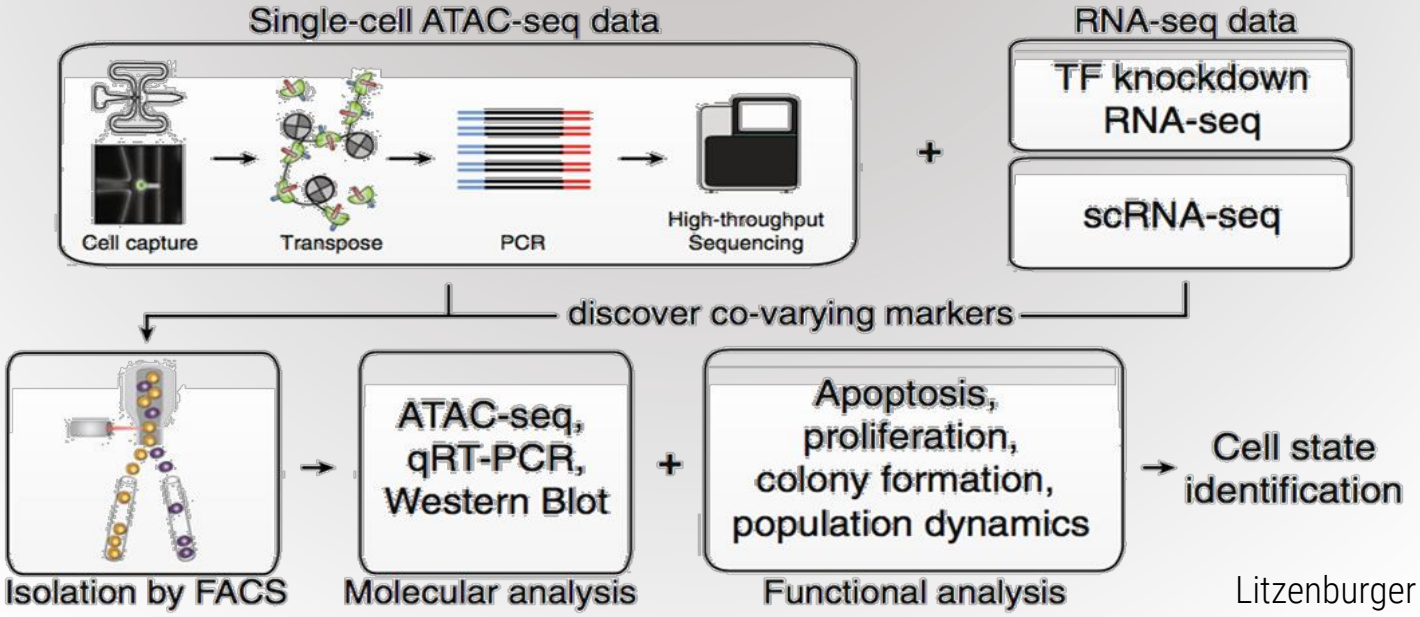

25¢


25¢

The future of scATAC-seq

RESEARCH Open Access

Single-cell epigenomic variability reveals functional cancer heterogeneity



Litzenburger (2017)

Questions?

References

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3. Thurman RE, Rynes E, Stamatoyannopoulos JA, et al. 2012. The accessible chromatin landscape of the human genome. *Nature* **489**: 75-82.
4. **Buenrostro JD, Wu B, Litzenburger UM, Ruff D, Gonzalez ML, Snyder MP, Chang HY, Greenleaf WJ. 2015. Single-cell chromatin accessibility reveals principles of regulatory variation. *Nature* 523: 486-490.**
5. Cusanovich DA, Daza R, Adey A, Pliner HA, Christiansen L, Gunderson KL, Steemers FJ, Trapnell C, Shendure J. 2015. Multiplex single-cell profiling of chromatin accessibility by combinatorial cellular indexing. *Science* **348**: 910-914.
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7. Pott S, Lieb JD. 2015. Single-cell ATAC-seq: strength in numbers. *Genome Biology* **16**:1-4.
8. Litzenburger UM, Buenrostro JD, Wu B, Shen Y, Sheffield NC, Kathiria A, Greenleaf WJ, Chang HY. 2017. Single-cell epigenomic variability reveals functional cancer heterogeneity. *Genome Biology* **18**:1-12.