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

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系统生物学课程报告

廖可琰
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Background

- Chromatin structure & chromatin accessibility

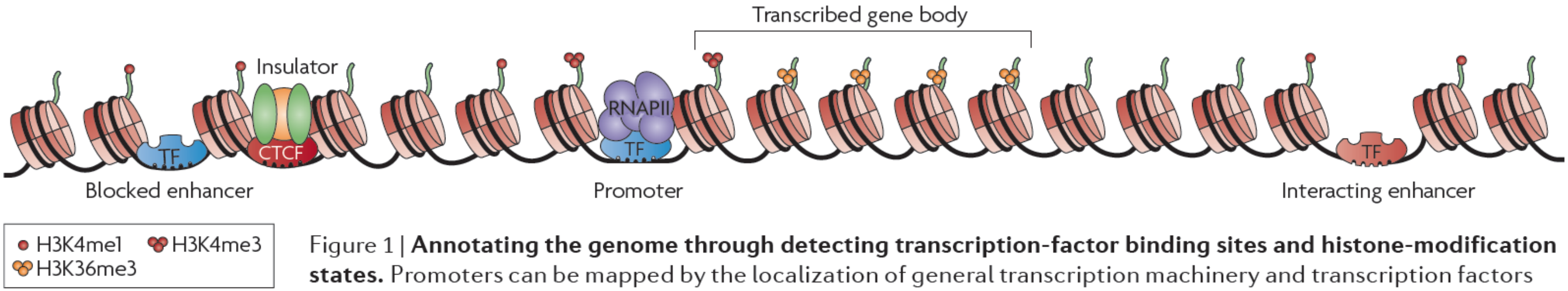
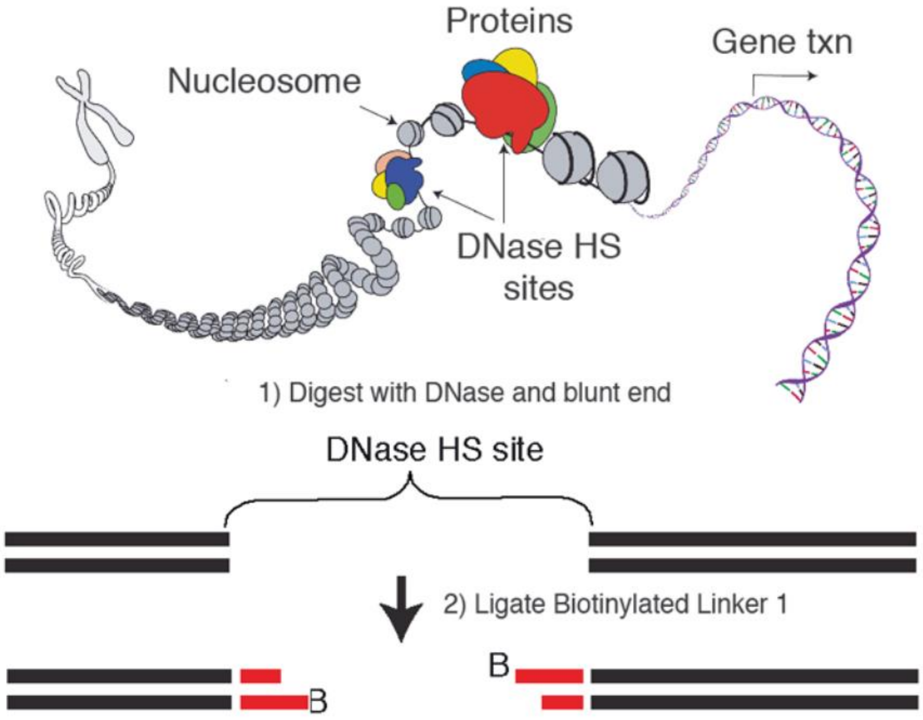


Figure 1 | **Annotating the genome through detecting transcription-factor binding sites and histone-modification states.** Promoters can be mapped by the localization of general transcription machinery and transcription factors

Hawkins, NRG 2010

Background

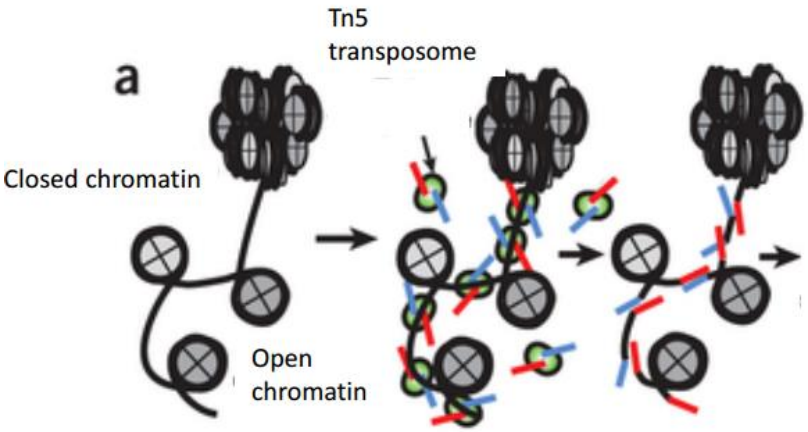
- DNase-seq

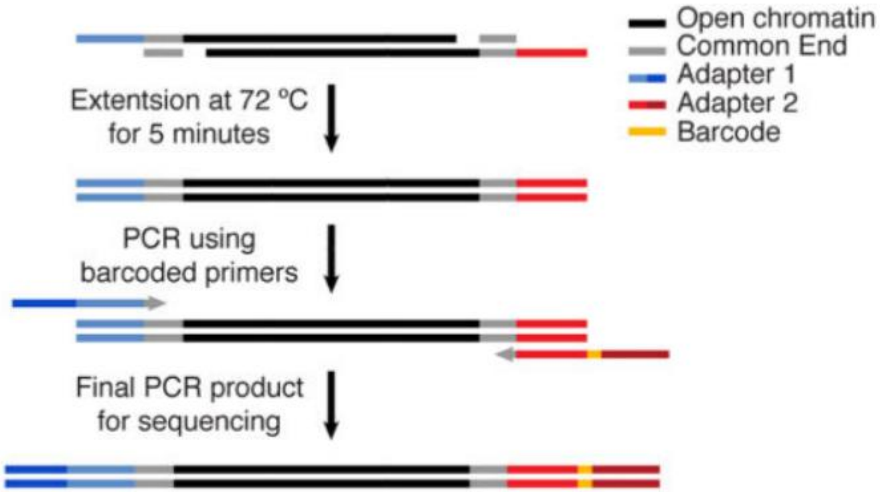


Song L, Crawford G E,Cold Spring Harbor Protocols, 2010

Background

- ATAC-seq





Buenrostro et al., Nature Methods, 2013

Materials

Mouse Cells：

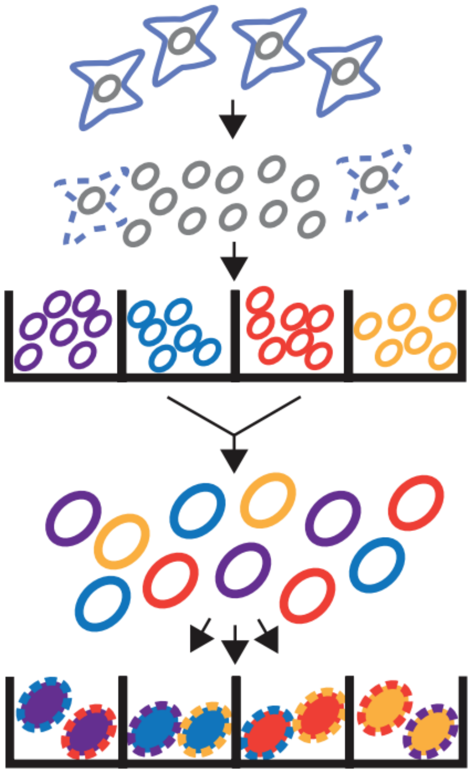
Patski embryonic kidney fibroblast
肾胚胎成纤维细胞

Human Cells：

GM12878	HEK293T	HL-60
B淋巴细胞	肾胚胎细胞衍生株	早幼粒白血病细胞

Methods

- Schematic of combinatorial cellular indexing



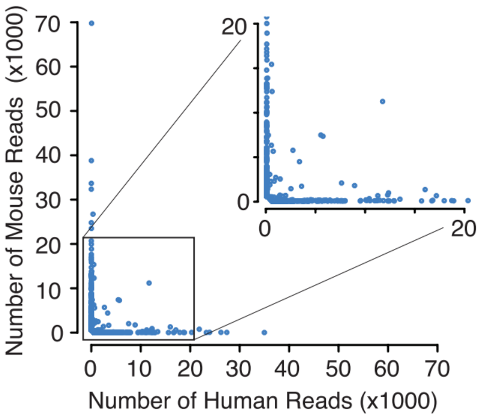
Nuclei are isolated and molecularly tagged in bulk with barcoded Tn5 transposases in wells (different barcodes are represented by the different colors outlining the nuclei).

Nuclei are then pooled and a limited number redistributed in to a second set of wells. A second barcode (represented by the color filling each nucleus) is introduced during PCR .

Result

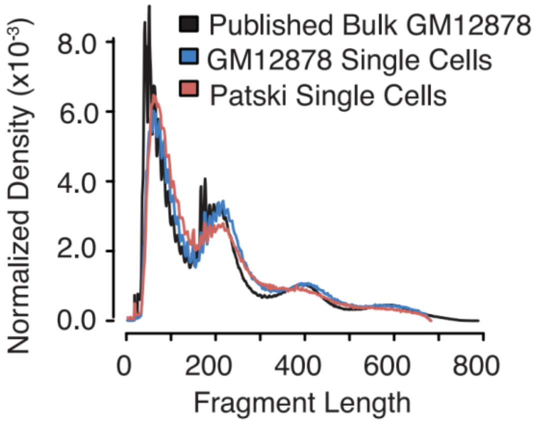
- validation for measuring single-cell chromatin accessibility

A



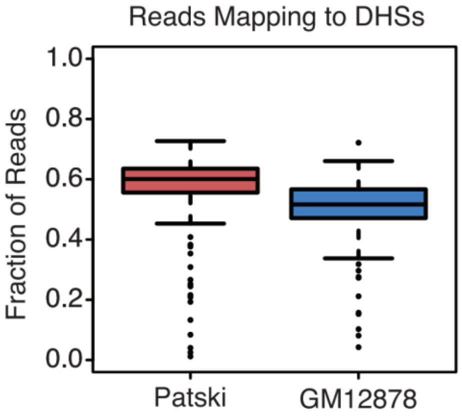
Scatterplot of number of reads mapping uniquely to human or mouse genome for individual barcode combinations.

B



Fragment size distribution for single-cell ATAC-seq versus published bulk ATAC-seq .

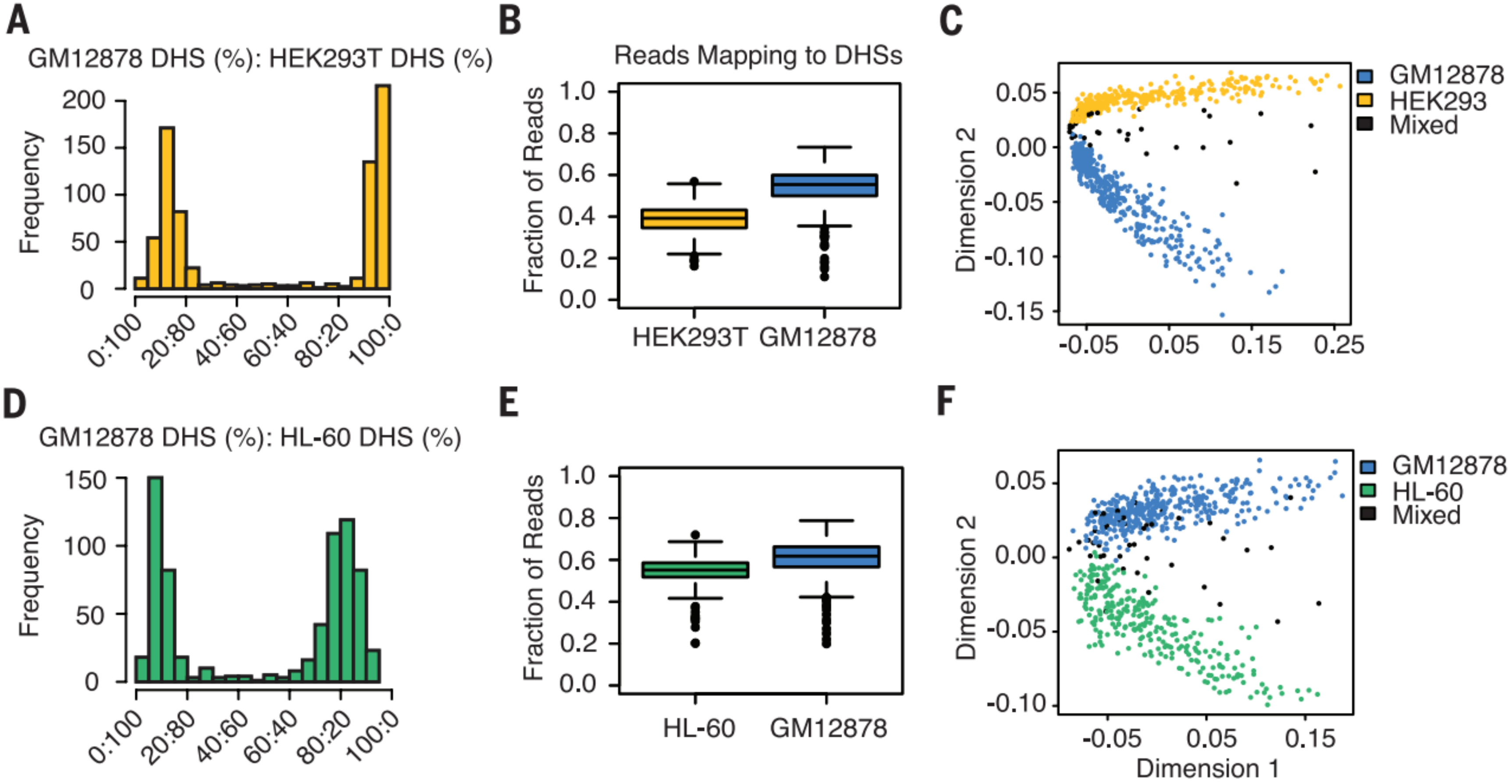
C



Box plot of the fraction of reads mapping to ENCODE -defined DHSs for individual Patski and GM12878 cells.

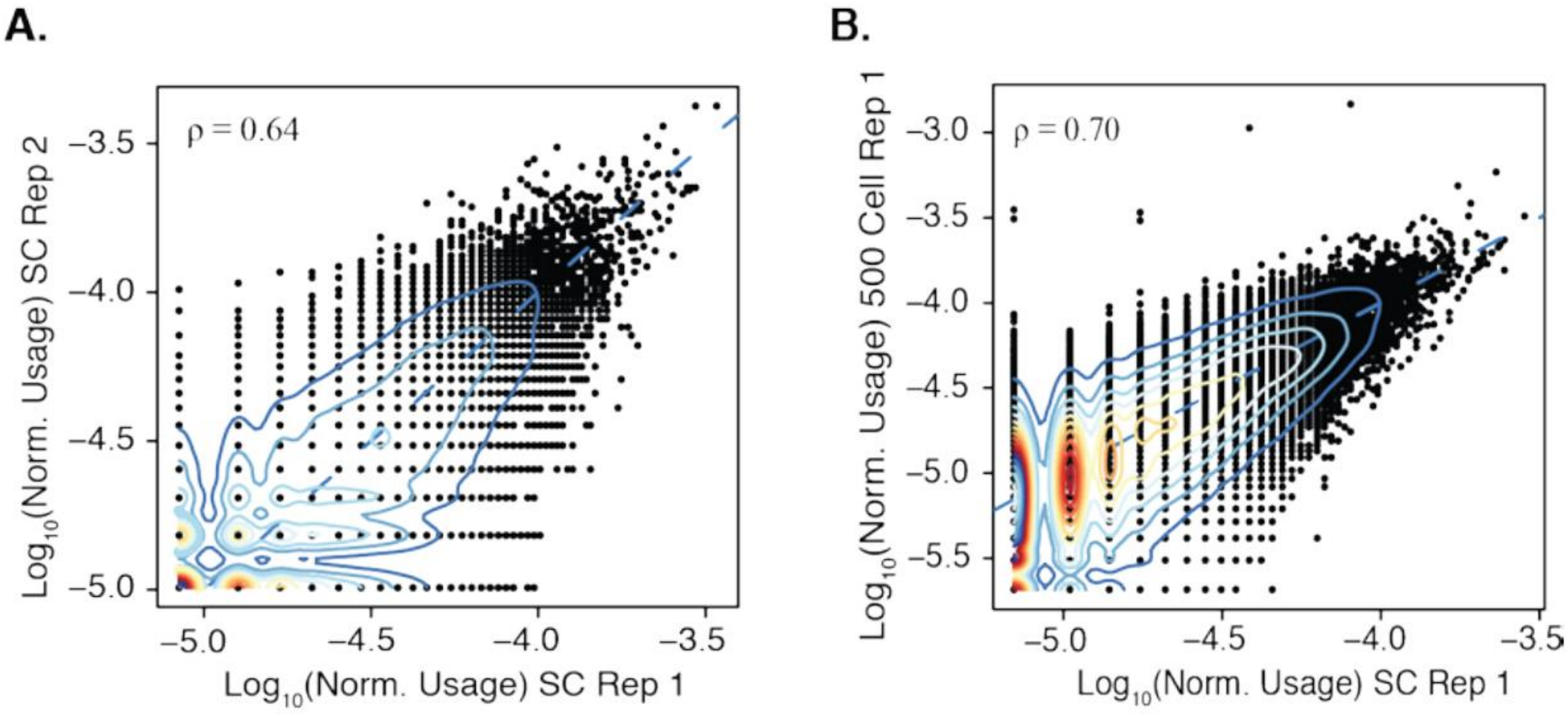
Result

➢ Single-cell ATAC-seq deconvolutes human celltype mixtures



Result

- Reproducibility of hypersensitive site usage for individual cells.

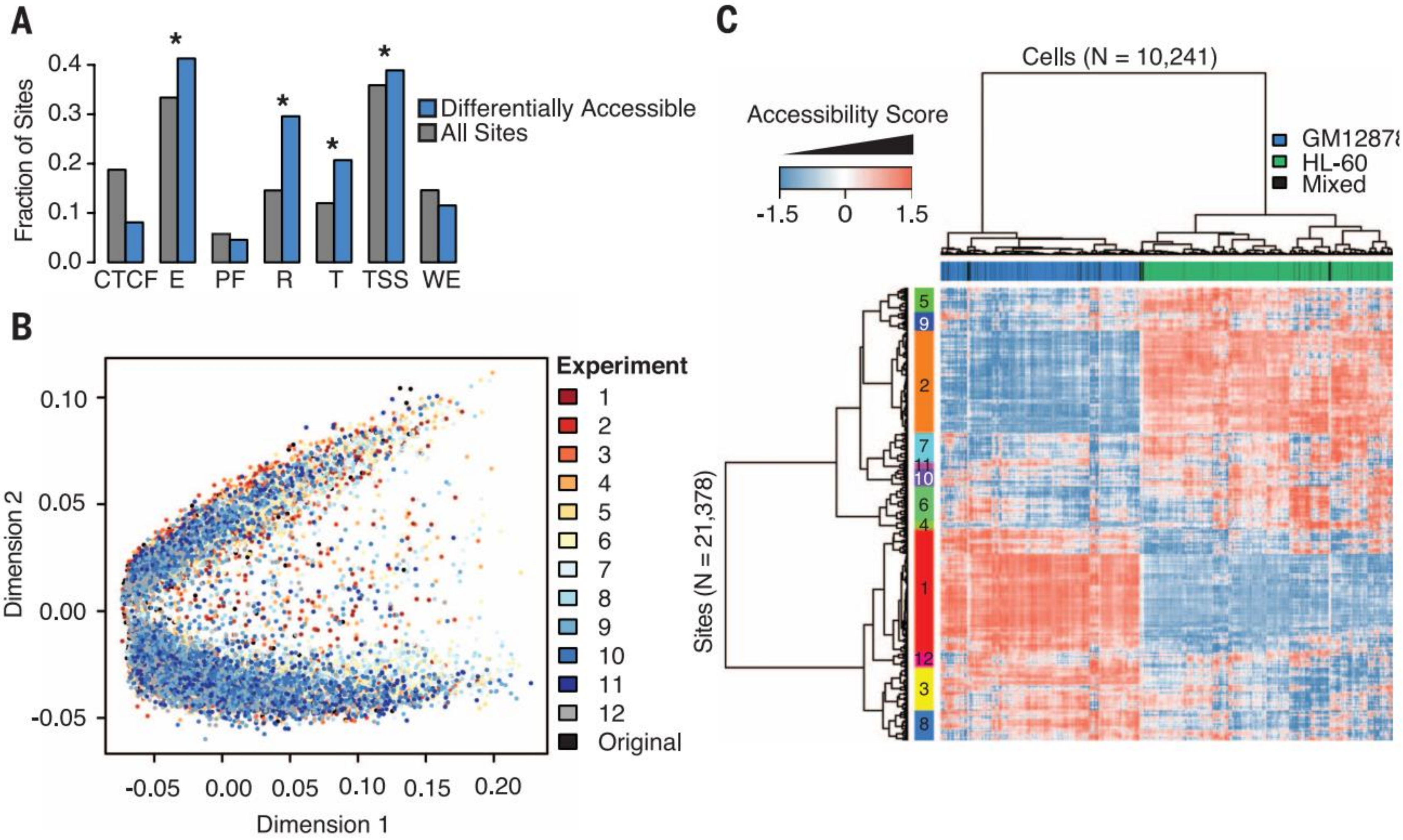


GM12878 /Patski & GM12878/HL-60

Bluk ATAC-seq & GM12878/Patski

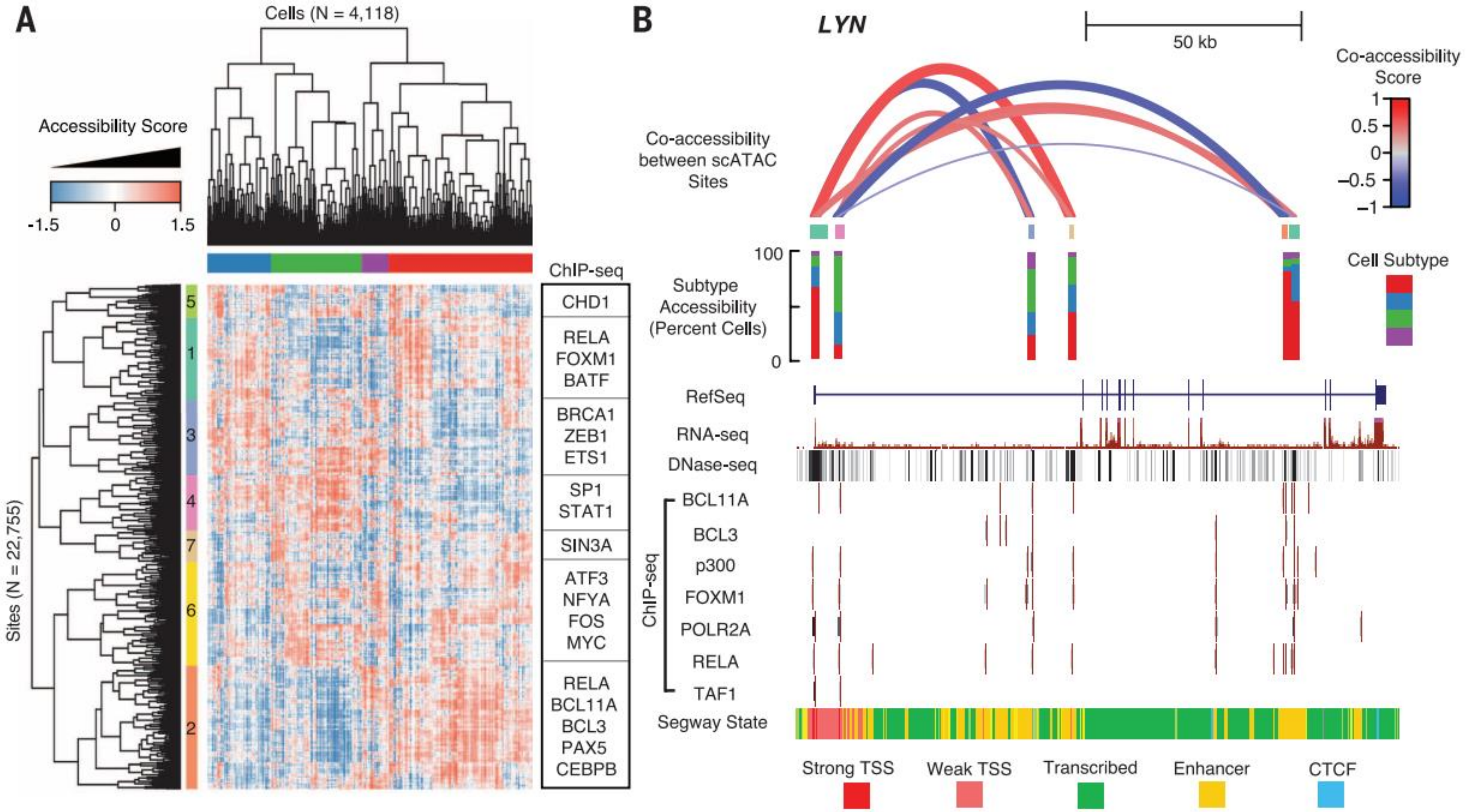
Result

- ➢ Single-cell ATAC-seq identifies functionally relevant differences in accessibility between cell types



Result

- ➢ Single-cell ATAC-seq identifies GM12878 subtypes



Conclusion

创新：第一次将ATAC-seq和combinatorial indexing的方式相结合，避免了物理方法分隔细胞，在single cell 的水平上观察染色质的概况

启发：研究染色质在基因组上的整体概况，可以看出不同细胞系或者单细胞之间的整体性的差异，与ChIP-seq或者其他数据相结合，能够加深对于染色质结构与基因调控之间的关系的印象。

不足：虽然相对于细胞来说输入量降低了，但却不可避免实验的特异性以及准确性所带来的误差

THANKS