

PARALLEL SINGLE-CELL SEQUENCING LINKS TRANSCRIPTIONAL AND EPIGENETIC HETEROGENEITY

Angermueller et al., Nature Methods, January 11, 2016.
doi:10.1038/nmeth.3728.

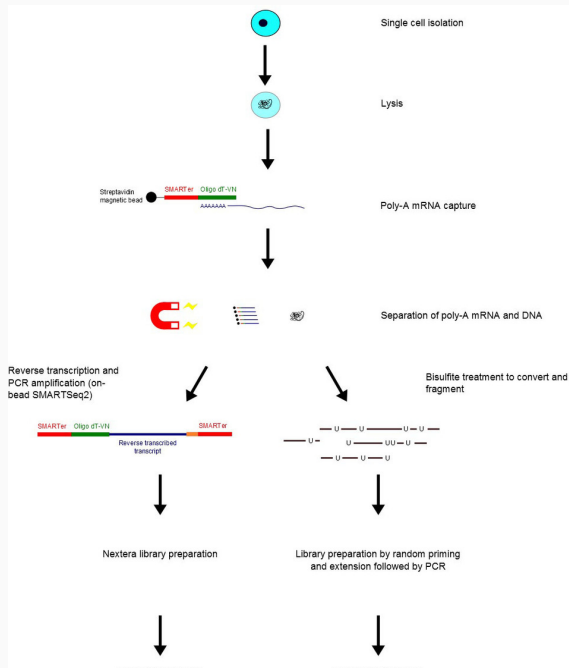
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February 11, 2016

BISC 542

scM&T-seq: Parallel single-cell genome-wide
methylation & transcriptome seq
⇒ Coupled/Uncoupled?

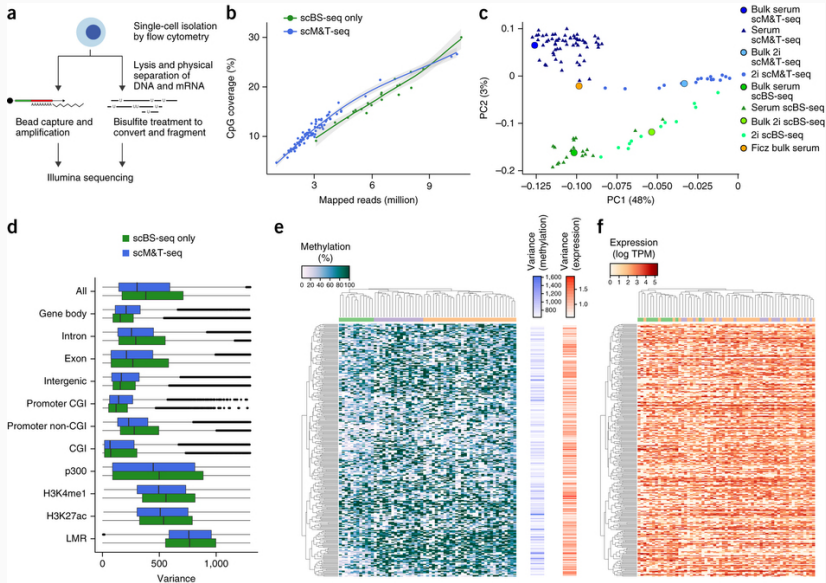
Protocol



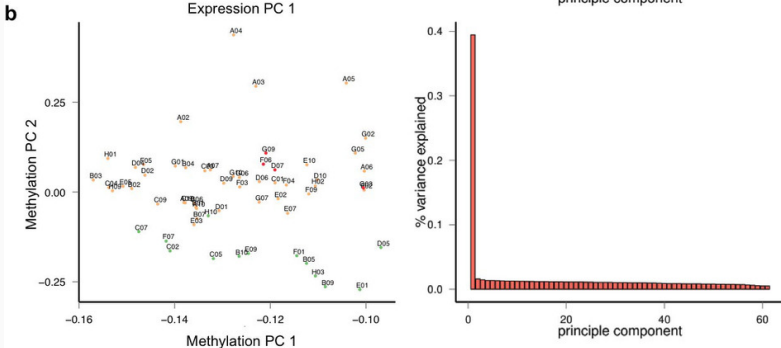
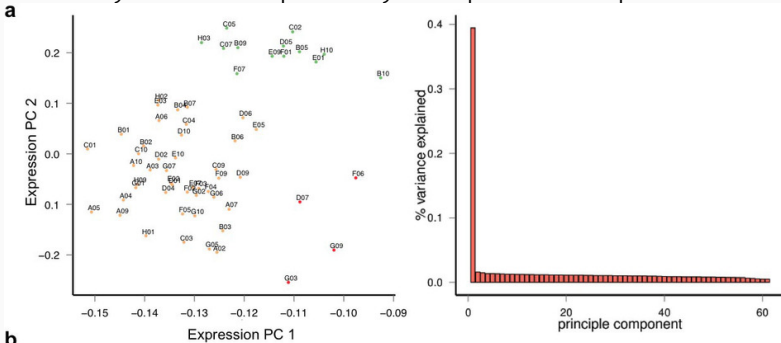
Data:

76 individual serum ESC + 16 ESCc in '2i'[induces hypomethylation]

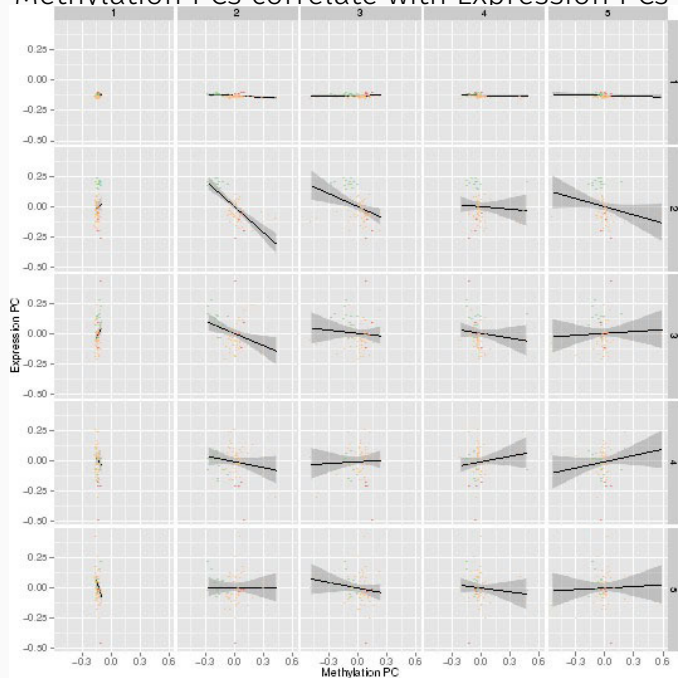
Variation in methylation levels are explained by cell type



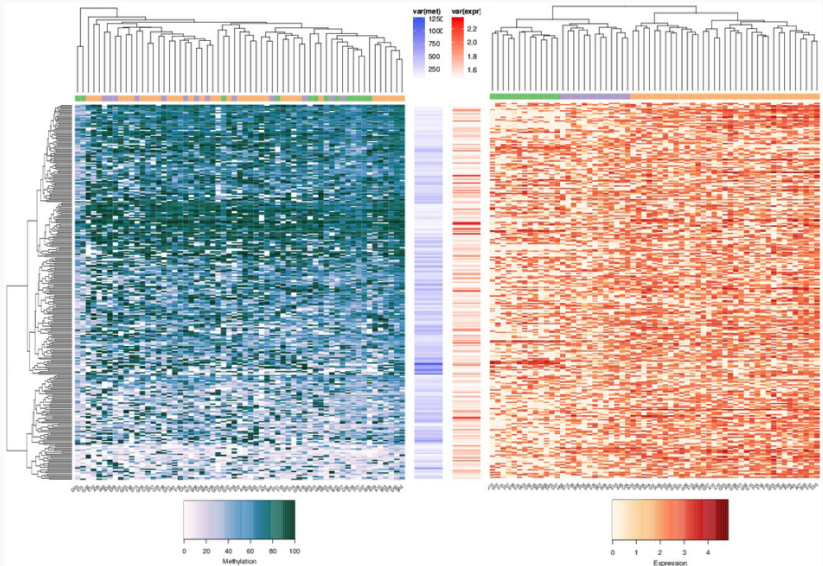
Methylation PCs partially recapitulate expression



Methylation PCs correlate with Expression PCs

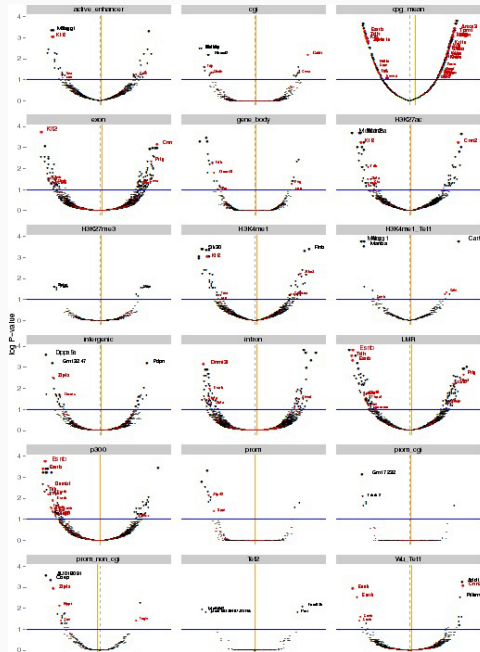


Global methylome and transcriptome profiles are complementary

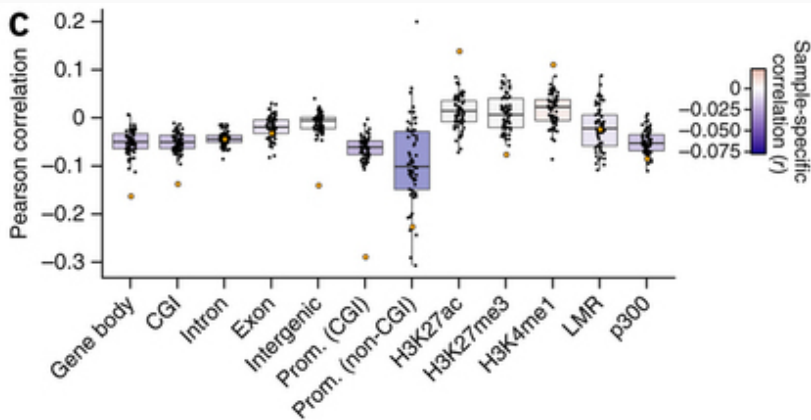


Association between expression
levels and methylation : BOTH
negative and positive \Rightarrow
Interactions are Complex!

Correlation coefficients in alternative genomic context:



Validates with bulk RNA-seq and
BS-seq[Oranges]



Insights

Transcriptome and Methylome can be
uncoupled

Insights

Association with transcription:

- v/s methylation at non-CpG island promoters :
negative (known)
- v/s methylation at distal regulatory elements :
both

Summary

- Parallel methylome & transcriptome profiling: feasible
- Associations can be quantified at single-cell level
- Fluctuating pluripotency in serum ESC \cong Epigenetic heterogeneity

Ideas/Issues

- Spearman Correlation? for individual CpGs or regions to observe trend
- Infer cell state from data?[Complementary]
- CA instead of PCA to reveal transcriptome-methylome clusters. See Fellenberg et al.
- $(-)\log_{10}(q - val)$ and Pearson (r^2)?

Academic Valentine

<http://tinyurl.com/acadvalentines>

References

- Seisenberger, Stefanie, et al. "The dynamics of genome-wide DNA methylation reprogramming in mouse primordial germ cells." *Molecular cell* 48.6 (2012): 849-862.
- Han, Han, et al. "DNA methylation directly silences genes with non-CpG island promoters and establishes a nucleosome occupied promoter." *Human molecular genetics* (2011): ddr356.
- Ficiz, Gabriella, et al. "Dynamic regulation of 5-hydroxymethylcytosine in mouse ES cells and during differentiation." *Nature* 473.7347 (2011): 398-402.
- Macaulay, Iain C., et al. "G&T-seq: parallel sequencing of single-cell genomes and transcriptomes." *Nature methods* 12.6 (2015): 519-522.
- Smallwood, Sébastien A., et al. "Single-cell genome-wide bisulfite sequencing for assessing epigenetic heterogeneity." *Nature methods* 11.8 (2014): 817-820.
- Yang, Xiaojing, et al. "Gene body methylation can alter gene expression and is a therapeutic target in cancer." *Cancer cell* 26.4 (2014): 577-590.
- Bogdanović, Ozren, et al. "Temporal uncoupling of the DNA methylome and transcriptional repression during embryogenesis." *Genome research* 21.8 (2011): 1313-1327.
- Fellenberg, Kurt, et al. "Correspondence analysis applied to microarray data." *Proceedings of the National Academy of Sciences* 98.19 (2001): 10781-10786.