Signature Analyzer: scaling Bayesian NMF to millions of individuals with GPUs

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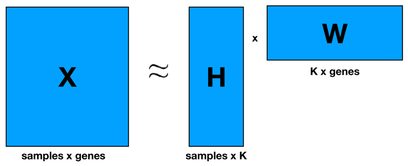
Introduction

- Current methodologies for analyzing genomic data, **notably non-negative matrix factorization,** were designed for tens to thousands of samples.
- Dataset sizes are reaching millions of samples or individual cells.
- CPU implementations use thousands of cores, costing money and time.
- GPUs reduce **run time** and **lower costs** by offering more compute power.

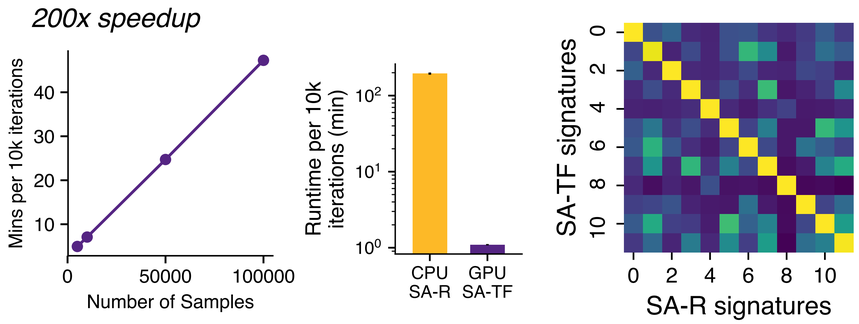


Non-negative Matrix Factorization

*We aim to implement a Bayesian variant of non-negative matrix factorization at **scale**.*

Transitioning to GPUs

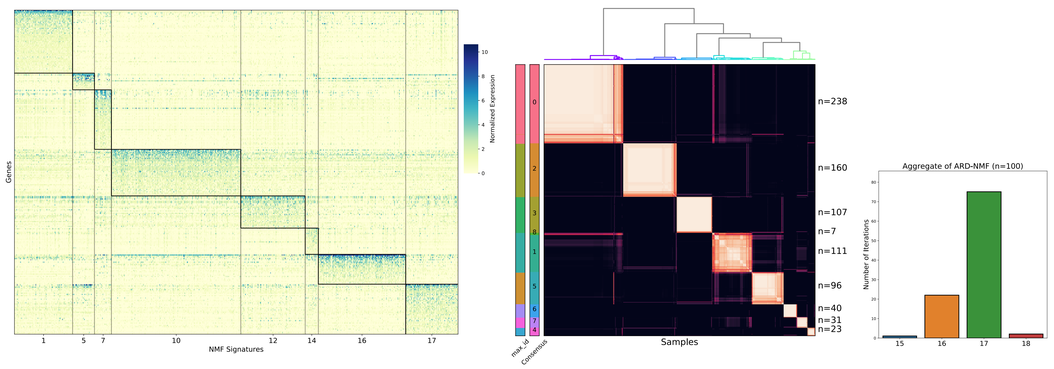
- Open source libraries, such as PyTorch and TensorFlow, make method optimization easy.
- Native execution on GPU and CPU enables cheap development and simple transition to GPU without specialized environments. (*see Links)*



(**Left**) *Running **S**ignature **A**nalyzer scales linearly as a function of number of samples.* (**Center**) *Average run time to compute 10,000 iterations of ARD NMF using **S**ignature **A**nalyzer in R (yellow) and **S**ignature **A**nalyzer-**GPU** (purple).* (**Right**) *Correlation heat map of signatures derived from both methods using the same input mutation counts matrix.*

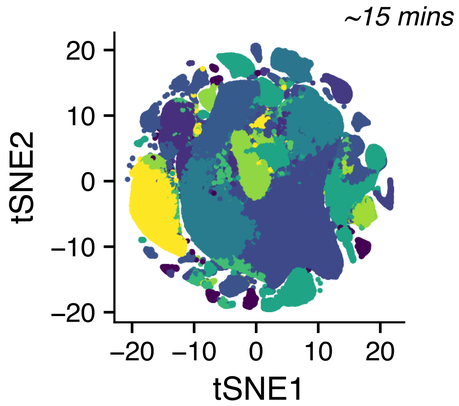
Clustering Large RNA-Seq Cohorts

~ 1000 Bulk RNA-Seq



(**Left**) *Best ARD-NMF solution for Bulk RNA-Seq decomposition of tumor dataset. We identify 8 de novo transcriptional programs.* (**Center**) *Consensus solution of 100 runs. At scale, we can generate consensus statistics for large transcriptional datasets.* (**Right**) *Distribution of latent dimensions over 100 runs (~ 40 mins).*

~ 1 mil single-cell RNA-Seq



(**Above**) *t-Distributed Stochastic Neighbor Embedding (t-SNE) of 1e6 embryonic mouse brain cells. Colors indicate transcriptional programs identified using SA-GPU.*

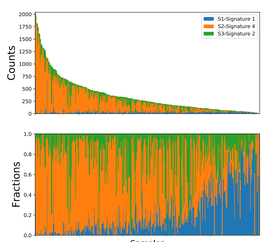
Mapping Mutational Signatures

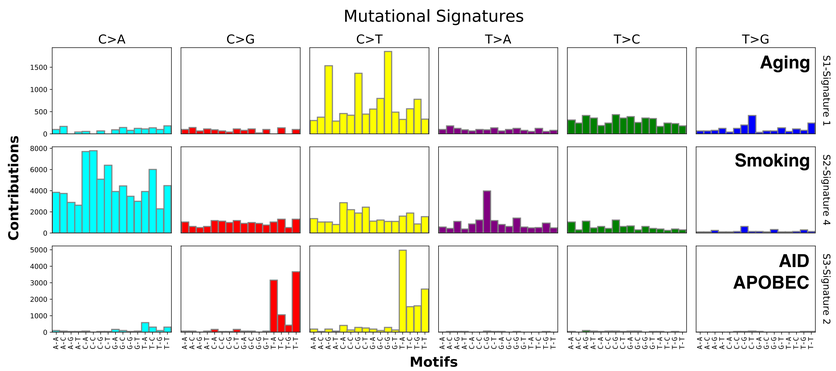
We support mapping & plotting API for:

- COSMIC2 Single-Base Substitutions
- COSMIC3 Single-Base Substitutions (WGS/WES)
- COSMIC3 Doublet-Base Substitutions
- COSMIC3 Indels

LUAD MC3 I ARD-NMF decomposition of mapped, 96-base context vector encoding for single-base substitutions. (**Right**) Patient-level signature contributions extracted. (**Far-Right**) Bar-plot of 96 single-base substitution contributions labeled by canonical phenotypes.

~ 500 patients





Links

Paper (*Genome Biology*)

Taylor-Weiner, A., Aguet, F., Haradhvala, N.J. *et al.* Scaling computational genomics to millions of individuals with GPUs. *Genome Biol* **20,** 228 (2019) doi:10.1186/s13059-019-1836-7

Signature Analyzer (Github)

A GPU-enabled implementation of a Automatic Relevance Determination (ARD) non-negative matrix factorization; mapping for mutational signatures and use with expression matrices

Discussion

- Simply re-implementing current methods using open source GPU compatible libraries results in orders of magnitude increase in speed. (*see Links*)
- Scaling methods in this way made possible hypotheses involving more complex models, larger datasets, with more accurate empirical measurements.
- We demonstrate extraction of **transcriptional programs** across millions of single-cells and fast decomposition & mapping of **somatic mutational signatures**
- Aggregating across multiple runs of stochastic methods allows for robust statistics
- We anticipate a transition to GPU-based computing for computational genomics methods.

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