Practical search and analysis with low-dimensional representations of the HCA

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Authors

- **Loyal A. Goff**
  0000-0003-2875-451X · loyale · loyalgoff
  Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine; Kavli Neurodiscovery Institute, Johns Hopkins University; McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine

- **Casey S. Greene**
  0000-0001-8713-9213 · cgreene · greenescientist
  Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania

- **Stephanie C. Hicks**
  0000-0002-7858-0231 · stephaniehicks · stephaniechicks
  Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health

- **Rob Patro**
  0000-0001-8463-1675 · rob-p
  Department of Computer Science, Stony Brook University

- **Elana J. Fertig**
  0000-0003-3204-342X · ejfertig · FertigLab
  Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, School of Medicine, Johns Hopkins University; Department of Applied Mathematics and Statistics, Whiting School of Engineering, Johns Hopkins University

- **Michael I. Love**
  0000-0001-8401-0545 · mikelove · mikelove
  Department of Biostatistics, University of North Carolina at Chapel Hill; Department of Genetics, University of North Carolina at Chapel Hill

Abstract

Instructions: Describe your collaborative project, highlighting key achievements of the project; limited to 250 words.

Five Key References

- Hicks refs: [1]
- ProjectR & scCoGAPS: [2]
- Alevin: [3]

Project Team

PI information

1. Loyal Goff (Submitter)
    - Title: Assistant Professor
    - Degrees: PhD
    - Type of organization: Academic
    - Tax ID: 52-0595110 (JHU)
    - Email: loyalgoff@jhmi.edu
2. Stephanie Hicks
    - Title: Assistant Professor
    - Degrees: PhD
    - Type of organization: Academic
    - Tax ID: 52-0595110 (JHU)
    - Email: shicks19@jhu.edu
3. Elana Fertig
    - Title: Associate Professor
    - Degrees: PhD
    - Type of organization: Academic
    - Tax ID: 52-0595110 (JHU)
    - Email: ejfertig@jhmi.edu
4. Casey Greene
    - Title: Assistant Professor
    - Degrees: PhD

- Type of organization: Academic
- Tax ID: 23-1352685 (UPenn)
- Email: greenescientist@gmail.com

5. Tom Hampton
    - Title: Senior Bioinformatics Analyst
    - Degrees: PhD
    - Type of organization: Academic
    - Tax ID: 02-0222111 (Dartmouth)
    - Email: Thomas.H.Hampton@dartmouth.edu
6. Michael Love
    - Title: Assistant Professor
    - Degrees: Dr. rer. nat.
    - Type of organization: Academic
    - Tax ID: 56-6001393 (UNC)
    - Email: milove@email.unc.edu
7. Rob Patro
    - Title: Assistant Professor
    - Degrees: PhD
    - Type of Organization: Academic
    - Tax ID: 16-1514621 (Stony Brook)
    - Email: rob.patro@cs.stonybrook.edu

Description (750 words TOTAL)

1. Loyal Goff
2. Stephanie C. Hicks is an Assistant Professor of Biostatistics at the Johns Hopkins Bloomberg School of Public Health. She is an expert in statistical methodology with a strong track record in processing and analyzing single-cell genomics data, including extensive experience developing fast, memory-efficient R/Bioconductor software to remove systematic and technical biases from scRNA-seq data [1]. Dr. Hicks will work together with Co-PIs to implement fast search algorithms in latent spaces (Aim 1) and to implement the methods developed into fast, scalable, and memory-efficient R/Bioconductor software packages (Aim 3).
3. Elana Fertig is an Associate Professor of Oncology and Applied Mathematics and Statistics at Johns Hopkins University. She developed of the Bayesian non-negative matrix factorization algorithm CoGAPS [4] for latent space analysis. In collaboration with co-PI Goff, she adapted this tool to scRNA-seq data and developed a new transfer learning framework to relate the low-dimensional features in scRNA-seq data across data modalities, biological conditions, and organisms [2]. Dr. Fertig will work with the co-PIs to incorporate the error models from Aim 1 into the latent space representations, dimensionality estimation, and biological assessment

metrics in Aim 2. She is developing standardized language for latent space representation in collaboration with co-PIs Goff and Greene [5] that will provide a strong foundation for standardization of these approaches across different unsupervised learning tools.

4. Casey Greene
5. Tom Hampton
6. Michael Love is an Assistant Professor of Biostatistics and Genetics at the University of North Carolina at Chapel Hill. He is a leading developer of statistical software for RNA-seq analysis in the Bioconductor Project, maintaining the widely used DESeq2 [6] and tximport [7] packages. He is a close collaborator with Dr. Rob Patro on bias-aware estimation of transcript abundance from RNA-seq and estimation of uncertainty during transcript quantification [8]. Dr. Love will work with co-PIs to disseminate versioned reference cell type catalogs through widely used frameworks for genomic data analysis including R/Bioconductor and Python.
7. Rob Patro

Proposal Body (2000 words)

The Human Cell Atlas (HCA) provides unprecedented characterization of the molecular phenotypes of each cell across tissues, organisms, and individuals. Computational techniques that provide the ability to rapidly query, characterize, and analyze this atlas will accelerate the pace of discovery in biomedicine. HCA data are high dimensional, but they can often be compressed into fewer dimensions without a substantial loss of information while yielding interpretable features. For transcriptomic data, compressing on the gene dimension is most attractive: it can be applied to single samples, and genes often provide information about other co-regulated genes or cellular attributes. In the best case, the reduced dimensional space captures biological sources of variability while ignoring noise and each dimension aligns to interpretable biological processes.

Our seed network aims to create low-dimensional representations that provide search and catalog capabilities for the HCA. The benefit of these approaches will become particularly pronounced as the number of cells and tissues becomes large. Our **central hypothesis** is that these approaches will enable faster algorithms while reducing the influence of technical noise. We propose to advance **base enabling technologies** for low-dimensional representations. We also propose three aims: 1) fast and accurate search for cells, samples, and pathways; 2) a catalog of cell type, state, and biological process representations in low-dimensional spaces; and 3) educational materials to increase the impact of low-dimensional representations and the HCA in general.

The first goal of our base enabling technology work is to identify techniques that learn interpretable, biologically-aligned representations. We consider both linear and non-linear techniques. For linear techniques, we rely on our Bayesian, non-negative matrix factorization method scCoGAPS [9] (PI Fertig). This technique learns biologically relevant features across contexts and data modalities [10], including notably the HPN DREAM8 challenge [14]. This technique is specifically selected as a base enabling technnology because its error distribution can

naturally account for measurement-specific technical variation [15] and its prior distributions for different feature quantifications or spatial information. For non-linear needs, neural networks with multiple layers, provide a complementary path to low-dimensional representations [16] (PI Greene) that model these diverse features of HCA data. We note that many groups are working in this area for both linear and non-linear techniques (e.g., [17]). Because of the substantial number of groups developing neural network based methods, we do not currently plan additional efforts on methods development beyond scCoGAPS. However, we will continue to use and rigorously evaluate these methods and incorporate the best performing methods into our search and catalog tools. The latent space team from the HCA collaborative networks RFA (including PIs Fertig, Goff, Greene, and Patro) is establishing common definitions and requirements for latent spaces for the HCA, as well as standardized output formats for low-dimensional representations from distinct classes of methods.

The *second part of our work on base enabling technologies* is the improvement of techniques for fast and accurate quantification. Existing approaches for quantification from scRNA-seq data using tagged-end end protocols (e.g. 10x Chromium, drop-Seq, inDrop, etc.) have no mechanism for accounting for reads mapping between multiple genes in the resulting quantification estimates. This affects approximately 15-25% of the reads generated in a typical experiment. This reduces quantification accuracy, and leads to systematic biases in gene expression estimates that correlate with the size of gene families and gene function[3]. We recently developed a quantification method for tagged-end data that accounts for reads mapping to multiple genomic loci in a principled and consistent way [**CITE?**]. We will expand on this work by, building these capabilities into a production quality tool for the processing of scRNA-seq data. The tool will support: 1. Exploring alternative models for UMI resolution. 2. Developing new approaches for quality control and filtering using the UMI-resolution graph. 3. Creating a compressed and indexible data structure for the UMI-resolution graph to enable direct access, query, and fast search.

We will implement the base enabling technologies and methods for search, analysis, and transformation into R/Bioconductor and Python frameworks. The python and R software will use common input and output formats. The software will be fast, scalable, and memory-efficient because will leverage the computational tools previously developed by Bioconductor for single-cell data access to the HCA, data representation (`SingleCellExperiment`, `beachmat`, `DelayedArray`, `HDF5Array` and `rhdf5`) and data assessment and amelioration of data quality (`scater`, `scran`, `DropletUtils`).

Aim 1

Rationale: The HCA provides a reference atlas to human cells, cell types, and the pathways that they express. Scientists will benefit most from the HCA when they can quickly identify find cells and cell types and compare references to find differences. Low-dimensional representations, because they compress the space, provide the building blocks for search approaches that can be practically

applied across very large datasets such as the HCA. *We propose to develop algorithms and software for efficient search over the HCA using low-dimensional representations.*

The primary approach to search in low-dimensional spaces is straightforward: one must create an appropriate low-dimensional representation and identify a distance function or functions that match what biologists seek. Using the low-dimensional representation improves speed and can also reduce noise. We will evaluate representations for their ability to support search and implement the best performing approach. However, the most obvious approaches require investigators to perform quantification on the entirety of a new sample and select cells or cell types that they wish to search for. We also aim to enable search even before investigators complete quantification. This will allow software to identify similar tissues or identify cells that are unusual as data are being collected. We will implement and evaluate techniques to learn shared low-dimensional representations between the UMI-resolution graph and quantified samples, so that samples where either component is available can be used for search **[CASEY ADD SHARED LATENT SPACE REF]**. These UMI-graphs will be embedded in the prior of scCoGAPS and architecture of non-linear latent space techniques.

In the case of mutations, reference genomes allow scientists to identify specific differences between the reference and genomes of interest. We will use low dimensional representations from latent spaces to define a reference transcriptome map (the HCA) and differences from that reference in target transcriptome maps from new samples of interest. We will leverage common low-dimensional representations and cell-to-cell correlation structure both within and across transcriptome maps from Aim 2 to define this reference. Quantifying the differences between samples characterized at the single-cell level reveals population or individual level differences. Comparison of scRNA-seq maps from individuals with a particular phenotype to the HCA reference that is computationally infeasible from the large scale of HCA data becomes tractable in these low dimensional spaces. We (PI Hicks) have extensive experience dealing with the distributions of cell expression within and between individuals [25], which will be critical for defining an appropriate metric to compare references in latent spaces. We plan to implement and evaluate linear mixed models to account for the correlation structure within and between transcriptome maps. This statistical method will be fast, memory-efficient and will scale to billions of cells because we will use low-dimensional representations.

Aim 2

Rationale: Biological systems are comprised of diverse cell types with overlapping molecular phenotypes and biological processes are often reused with modifications across cell types. Low-dimensional representations can reveal these fundamental mechanisms across large collections of data including the HCA. We are evaluating and selecting methods that define basis vectors that reflect discrete biological processes or features. These basis vectors can be shared across different biological systems and can reveal context-specific perturbations such as pathogenic

differences in disease. *We propose a central catalog of cell types and biological processes derived from low-dimensional representations of the HCA.*

Basing a catalog of cell types and their corresponding processes off of multiple low-dimensional representations can reduce noise and aid in biological interpretability. However, there are currently no standardized, quantitative metrics to determine the extent to which low-dimensional representations capture generalizable biolobical features. We have developed new transfer learning methods to quantify the extent to which latent space representations from one set of training data are represented in another [2]. These provide a strong foundation to compare low-dimensional representations across different low dimensional data representation techniques. Generalizable representations should transfer across datasets of related biological contexts. In addition, we have found that combining multiple representations can better capture biological processes across scales [27], and that representations across scales capture distinct, valid signatures [15]. Therefore, we will form a catalogue from the set of low dimensional features learned across linear and non-linear methods from our base enabling technologies and proposed extensions in Aim 1.

We will package and version reference cell types and their corresponding low-dimensional representations and deliver these as structured data objects in Bioconductor and Python. Such summaries and annotations have proven widely successful for the ENCODE, Roadmap Epigenome Mapping, and GTEx projects. We are core package developers and power users of Bioconductor (PIs Hicks and Love) and will support on-the-fly downloading of these materials via the *AnnotationHub* framework. To enable reproducible research leveraging HCA, we will implement a content-based versioning system, which identifies versions of the reference cell type catalog by the gene weights and transcript nucleotide sequences using a hash function. We (PI Love) developed hash-based versioning and provenance identification and detection framework for bulk RNA-seq that supports reproducible computational analyses and has proven to be successful [28]. This will help to avoid scenarios where researchers report on matches to a certain cell type in HCA without precisely defining which definition of that cell type. We will develop *F1000Research* workflows demonstrating how HCA-defined reference cell types and tools developed in this RFA can be used within a typical genomic data analysis. This catalogue will be used as the basis of defining the references for cell-type or individual-specific differences with the linear models proposed in Aim 1.

Aim 3

Rationale: Low-dimensional representations for scRNA-seq and HCA data make tasks faster and provide interpretable summaries of complex high-dimensional data. The HCA data associated methods, will be valuable to many biomedical fields, but their use will require experience with this new toolkit. A scalable education effort that reaches students at and beyond undergraduate level will be needed to prepare students and maximize impact. *We propose short-course training for the*

HCA, single cell profiling, machine learning methods, low-dimensional representations, and tools developed by our group in response to this RFA.

Our educational program is based on a one-week short course that we (PI Hampton) have run annually at Mount Desert Island Biological Lab over the last **X TOM FILL IN** years. The course covers R, gene expression analysis, statistical interpretation, and introduces machine learning (PI Greene). Attendees rate the course well and report that they incorporate new knowledge into their research and teaching. For this grant we will add topics centered on the HCA and increase the frequency of the course. We will run the course at locations distributed throughout the US and provide open course materials on GitHub to allow others to replicate the course. New topics will include:

- Comparison of Bulk and Single-cell Assays and Data
- The Human Cell Atlas Project
- scRNA-seq: Expression Quantification and Cell Type Discovery
- scRNA-seq: Low-dimensional Representations
- scRNA-seq: Search and Analysis in Low-dimensional Representations

We aim to provide a force-multiplier for the HCA and low-dimensional methods as course attendees transmit what they learn to tens of students each year at their own institutions. We will run this course on a cost recovery model, but to maximize the multiplier effect we budget at least *ten scholarships* per offering to cover the room, board, and tuition of faculty who are primarily engaged in undergraduate instruction. This will allow faculty who will disseminate these materials in their own reaching to attend at very low cost. We will develop a one-week module that can be added in to an undergraduate class on single-cell profiling and the HCA, which we will distribute via GitHub. Materials will include recorded videos (intended for a refresher for instructors), slides, and exercises. We expect that this module will support faculty who attend with an easy enhancement to any bioinformatics or computational biology instruction that they are already providing at their institution.

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