

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

This manuscript ([permalink](#)) was automatically generated from [greenelab/czi-seed-rfa@4b24239](#) on November 13, 2018.

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

- **Thomas H. Hampton**

 [0000-0003-0543-402X](#) ·  [None](#) ·  [None](#)

Department of Microbiology and Immunology, Geisel School of Medicine at Dartmouth

Abstract

The HCA provides a reference atlas to human cell types, states, and the biological processes in which they engage. The utility of the reference therefore requires that one can easily compare references to each other, or a new sample to the compendium of reference samples. Because they compress the space, low-dimensional representations provide the building blocks for search approaches that can be practically applied across very large datasets such as the HCA. Our seed network proposes to compress HCA data into fewer dimensions that preserve the important attributes of the original high dimensional data and yield interpretable, searchable features. We hypothesize that using latent space methods to identify low dimensional representations of HCA data will accurately capture biological sources of variability and will be robust to measurement noise. We propose techniques that learn interpretable, biologically-aligned representations, improve techniques for fast and accurate quantification, and implement these base enabling technologies and methods for search, analysis, and latent space transformations as freely available, open source software tools. By using and extending our base enabling technologies, we will provide three principle tools and resources for the HCA: 1) software to enable fast and accurate search and annotation using low-dimensional representations of cellular features, 2) a versioned and annotated catalog of latent spaces corresponding to signatures of cell types, states, and biological attributes across the the HCA, and 3) short course and educational materials that will increase the use and impact of low-dimensional representations and the HCA in general.

Five Key References

1. Stephanie C Hicks, F William Townes, Mingxiang Teng, Rafael A Irizarry. Missing data and technical variability in single-cell RNA-sequencing experiments. *Biostatistics* (2017-11-06) <https://doi.org/gfb8g4> DOI: 10.1093/biostatistics/kxx053 · PMID: 29121214 · PMCID: PMC6215955
2. Genevieve L Stein-O'Brien, Brian S. Clark, Thomas Sherman, Christina Zibetti, Qiwen Hu, Rachel Sealfon, Sheng Liu, Jiang Qian, Carlo Colantuoni, Seth Blackshaw, Loyal A. Goff, Elana J. Fertig. Decomposing cell identity for transfer learning across cellular measurements, platforms, tissues, and species. *Cold Spring Harbor Laboratory* (2018-08-20) <https://doi.org/gd2xpn> DOI: 10.1101/395004
3. Avi Srivastava, Laraib Malik, Tom Sean Smith, Ian Sudbery, Rob Patro. Alevin efficiently estimates accurate gene abundances from dscRNA-seq data. *Cold Spring Harbor Laboratory* (2018-06-01) <https://doi.org/gffk42> DOI: 10.1101/335000

4. Brian Clark, Genevieve Stein-O'Brien, Fion Shiao, Gabrielle Cannon, Emily Davis, Thomas Sherman, Fatemeh Rajaii, Rebecca James-Esposito, Richard Gronostajski, Elana J. Fertig, Loyal A. Goff, Seth Blackshaw. Comprehensive analysis of retinal development at single cell resolution identifies NFI factors as essential for mitotic exit and specification of late-born cells. Cold Spring Harbor Laboratory (2018-07-27) <https://doi.org/gdwrrzh> DOI: 10.1101/378950
5. Rob Patro & Michael Love. tximeta. Bioconductor (2018) <https://doi.org/gfddxw> DOI: 10.18129/b9.bioc.tximeta

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. Thomas 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 A. Goff is an Assistant Professor of Neuroscience at Johns Hopkins University. He is an expert in high-throughput gene expression analysis with a focus on neural development, cell fate specification, and neurodegeneration. He has extensive experience in experimental molecular biology, technology development, and computational analysis and software development for RNA-Seq. In collaboration with Dr. Fertig, he has developed the transfer learning tool ProjectR [1], and helped adapt scCoGAPs for scRNA-Seq data. Dr. Goff will serve as coordinating PI and in collaboration with co-PIs, will develop a catalog of low-dimensional representations of HCA data (Aim 1) and contribute to the development and implementation of the educational materials (Aim 3).
2. Stephanie C. Hicks is an Assistant Professor of Biostatistics at the Johns Hopkins 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 [2]. 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 2).
3. Elana Fertig is an Associate Professor of Oncology and Applied Mathematics and Statistics at Johns Hopkins University. She developed the Bayesian non-negative matrix factorization

algorithm CoGAPS [3] 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 [1]. Dr. Fertig will incorporate error models from Aim 1 into latent space representations, dimensionality estimation, and biological assessment metrics in Aim 2. She is developing standardized language for latent space representation in collaboration with other co-PIs[4] that will provide a strong foundation for standardization of these approaches across different unsupervised learning tools.

4. Casey Greene is an Assistant Professor of Systems Pharmacology and Translational Therapeutics at the University of Pennsylvania's Perelman School of Medicine. He is an expert in deep learning techniques that learn low-dimensional representations of gene expression data[5]. He will work with the co-PIs to implement and evaluate techniques that learn shared low-dimensional representations for scRNA-seq data and methods to search over them (Aim 1). He has experience teaching machine learning to non-computational biologists, including at a course with co-PI Tom Hampton. He will enhance and extend this curriculum to support machine learning methods over the HCA (Aim 3).
5. Tom Hampton is Director of Bioinformatic Training for two program projects at the Geisel School of Medicine at Dartmouth. In that role, he has a long collaboration with co-PI Casey Greene, including the development of short courses taught at Mount Desert Island Biological Laboratory and at Dartmouth. Dr Hampton's research is focused on using data from multiple independent studies to identify concordant patterns of gene express in response to stressors such as infection and environmental stress.
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 [9] and tximport [10] 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 [11]. 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 is an Assistant Professor of Computer Science at Stony Brook University. He leads the COMBINE-lab, that [develops and maintains open-source genomics tools](#). He is the primary developer of the popular transcript quantification tools Sailfish [12] and Salmon [11]. Dr. Love and he are actively collaborating on improved methods for transcript quantification, differential testing, and reproducible analysis via [tximeta](#) [13]. He is focused on developing improved methods for gene-level quantification from tagged-end scRNA-Seq data, as implemented in the tool alevin [14]. He will work with co-PIs to develop improved single-cell quantification tools that account for gene-ambiguous reads and provide quantification uncertainty estimates — which is important for accurate and robust creation of reduced-dimensionality representations. He will additionally develop algorithms and data structures to enable efficient expression and sample search over low-dimensional representations of HCA data (Aim 1).

Proposal Body

The Human Cell Atlas (HCA) provides unprecedented characterization of molecular phenotypes across individuals, tissues and disease states – resolving differences to the level of individual cells. This dataset provides an extraordinary opportunity for scientific advancement, enabled by new tools to rapidly query, characterize, and analyze these intrinsically high-dimensional data. To facilitate this, our seed network proposes to compress HCA data into fewer dimensions that preserve the important attributes of the original high dimensional data and yield interpretable, searchable 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. We hypothesize that using latent space methods to identify low dimensional representations of HCA data will accurately capture biological sources of variability and will be robust to measurement noise. Our seed network incorporates biologists, computer scientists, statisticians, and data scientists from five leading academic institutions who will work collaboratively together to create foundational technologies and educational opportunities that promote effective interpretation of low dimensional representations of HCA data. We will continue our active collaborations with other members of the broader HCA network to integrate state of the art latent space tools, portals, and annotations to enable biological utilization of HCA data through latent spaces.

Scientific Goals

We will create low-dimensional representations that provide search and catalog capabilities for the HCA. Given both the scale of data, and the inherent complexity of biological systems, we believe these approaches are crucial to the long term success of the HCA. 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.

First, we will identify techniques that learn interpretable, biologically-aligned representations. We will consider both linear and non-linear techniques as each may identify distinct components of biological systems. For linear techniques, we rely on our Bayesian, non-negative matrix factorization method scCoGAPS [15] (PIs Fertig & Goff). This technique learns biologically relevant features across contexts and data modalities [16], including notably the HPN DREAM8 challenge [20]. This technique is specifically selected as a base enabling technology because its error distribution can naturally account for measurement-specific technical variation [21] 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 [8] (PI Greene) that model these diverse features of HCA data. We will make use of substantial progress that has already been made in both linear and non-linear techniques (e.g., [22]). and rigorously evaluate emerging methods into our search and catalog tools. We will extend transfer

learning methods, including ProjectR [1] (PIs Goff & Fertig) to enable rapid integration, interpretation, and annotation of learned latent spaces. 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.

Second, we will improve techniques for fast and accurate quantification. Existing approaches for scRNA-seq data using tagged-end protocols (e.g. 10x Chromium, drop-Seq, inDrop, etc.) do not account for reads mapping between multiple genes. This affects approximately 15-25% of the reads generated in a typical experiment, reducing quantification accuracy, and leading to systematic biases in gene expression estimates [14]. To address this, we will build on our recently developed quantification method for tagged-end data that accounts for reads mapping to multiple genomic loci in a principled and consistent way [14] (PI Patro), and extend this into a production quality tool for scRNA-seq preprocessing. Our tool will support: 1. Exploration of alternative models for Unique Molecular Identifier (UMI) resolution. 2. Development of new approaches for quality control and filtering using the UMI-resolution graph. 3. Creation of a compressed and indexable data structure for the UMI-resolution graph to enable direct access, query, and fast search prior to secondary analysis.

We will implement these base enabling technologies and methods for search, analysis, and latent space transformations as freely available, open source software tools. We will additionally develop platform-agnostic input and output data formats and standards for latent space representations of the HCA data to maximize interoperability. The software tools produced will be fast, scalable, and memory-efficient by leveraging the available assets and expertise of the R/Bioconductor project (PIs Hicks & Love) as well as the broader HCA community.

By using and extending our base enabling technologies, we will provide three principle tools and resources for the HCA. These include 1) software to enable fast and accurate search and annotation using low-dimensional representations of cellular features, 2) a versioned and annotated catalog of latent spaces corresponding to signatures of cell types, states, and biological attributes across the the HCA, and 3) short course and educational materials that will increase the use and impact of low-dimensional representations and the HCA in general.

Aim 1

Rationale: The HCA provides a reference atlas to human cell types, states, and the biological processes in which they engage. The utility of the reference therefore requires that one can easily compare references to each other, or a new sample to the compendium of reference samples. 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 distance functions that enable biologically meaningful comparisons. Ideal low-dimensional representations are predicted to be much faster to search, and potentially more biologically relevant, as noise can be removed. In this aim, we will evaluate novel, low-dimensional representations to identify those with optimal qualities of compression, noise reduction, and retention of biologically meaningful features. Current scRNA-seq approaches require investigators to perform gene-level quantification on the entirety of a new sample. We aim to search during sample preprocessing, prior to gene-level quantification. This will enable in-line annotation of cell types and states and identification of novel features as samples are being processed. We will implement and evaluate techniques to learn and transfer shared low-dimensional representations between raw or lightly processed data (e.g., kmer representations or UMI-graphs) and quantified samples, so that samples where either quantified or raw data are available can be used for search and annotation [30].

Similar to the approach by which comparisons to a reference genomes can identify specific differences in a genome of interest, we will use low-dimensional representations from latent spaces to define a reference transcriptome map (the HCA), and use this to quantify differences 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, which 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 [31], 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 be scalable to billions of cells using low-dimensional representations.

Aim 2

Rationale: Biological systems are comprised of diverse cell types and states with overlapping molecular phenotypes. Furthermore, biological processes are often reused with modifications across cell types. Low-dimensional representations can identify these shared features, independent of total distance between cells in gene expression space, across large collections of data including the HCA. We will evaluate and select methods that define latent spaces that reflect discrete biological processes or cellular features. These latent spaces can be shared across different biological systems and can reveal context-specific divergence such as pathogenic differences in disease. *We propose to establish a versioned catalog of cell types, states, and biological processes derived from low-dimensional representations of the HCA.*

Establishing a reference catalog of cellular features using low-dimensional representations can help to 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 biological 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 [1] (PIs Greene, Goff & Fertig). These provide a foundation to compare different low-dimensional representations through cross-validation techniques by learning representations in source datasets and testing their ability to transfer into a target dataset. Generalizable representations should also be robust in cross-study validation, transferring across datasets of related biological contexts, while representations of noise will not. In addition, we have found that combining multiple representations can better capture biological processes across scales [6], and that representations across scales capture distinct, valid biological signatures [21]. Therefore, we will establish a catalog consisting of low-dimensional features learned across both linear and non-linear methods from our base enabling technologies and proposed extensions in Aim 1.

We will package and version low-dimensional representations of the HCA and annotate these latent spaces via their corresponding cellular features. We will deliver these as structured data objects in Bioconductor as well as platform-agnostic data formats. Where applicable, we will leverage the computational tools previously developed by Bioconductor for single-cell data access to the HCA, data representation (`SingleCellExperiment` , `beachmat` , `LinearEmbeddingMatrix` , `DelayedArray` , `HDF5Array` and `rhdf5`) and data assessment and amelioration of data quality (`scater` , `scraper` , `DropletUtils`). 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 catalog by the gene weights and transcript nucleotide sequences using a hash function. We (PIs Love and Patro) previously developed hash-based versioning and provenance detection framework for bulk RNA-seq that supports reproducible computational analyses and has proven to be successful [13]. Our versioning and dissemination of reference latent space catalogs 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 and state, or individual-specific differences with the linear models proposed in Aim 1.

Aim 3

Rationale: Low-dimensional representations of scRNA-seq and HCA data make tasks faster and provide interpretable summaries of complex high-dimensional cellular features. The HCA data-associated methods and workflows will be valuable to many biomedical fields, but their use will

require an understanding of basic bioinformatics, scRNA-seq, and how the tools being developed work. Furthermore, researchers will need exposure to the conceptual basis of low-dimensional interpretations of biological systems. This aim addresses these needs in three ways.

First, we will develop a bioinformatic training program for biologists at all levels, including those with no experience in bioinformatics. Lecture materials will be extended from existing materials from previous bioinformatic courses we (PI Hampton) have run at Mount Desert Island Biological Laboratory, the University of Birmingham, UK, and Geisel School of Medicine at Dartmouth since 2009. These courses have trained over 400 scientists in basic bioinformatics and always achieve approval ratings of over 90%. We believe part of the success of these learning experiences has to do with our instructional paradigm, which includes a very challenging course project coupled with one-on-one support from instructors. We will develop a new curriculum specifically tailored to HCA that incorporates: 1) didactic course material on single cell gene expression profiling (PI Goff), 2) machine learning methods (PI Greene), 4) statistics for genomics (PIs Fertig and Hicks), 4) search and analysis in low-dimensional representations, and 5) tools developed by our group in response to this RFA.

Second, the short course will train not only students, but also instructors. Our one-on-one approach to course projects will require a high instructor-to-student ratio. We will therefore recruit former participants of this class to return in subsequent years, first as teaching assistants, and later as module presenters. We have found that course alumni are eager to improve their teaching resumes, that they learn the material in a new way as they begin to teach it, and that they are an invaluable resource in understanding how to improve the course over time. Part of our strategy is to support this community, which includes many people who will drive the next wave of innovation. All of our course materials will be freely available, enabling course participants to bring what they learned home with them. A capstone session will be included in which we will provide suggestions about how the materials presented in the course can be incorporated into existing course curricula. Course faculty will be available to assist with integration effort after the course. Finally, the short course will facilitate scientific collaborations by engaging participants in utilizing these tools for collaborative research efforts.

[I feel like we are missing a concluding summary of broader impacts to pull this together - could be a brief bulleted summary of tools required by app as Andrew suggested - EJF]

References

1. Decomposing cell identity for transfer learning across cellular measurements, platforms, tissues, and species.

Genevieve L Stein-O'Brien, Brian S. Clark, Thomas Sherman, Christina Zibetti, Qiwen Hu, Rachel Sealfon, Sheng Liu, Jiang Qian, Carlo Colantuoni, Seth Blackshaw, ... Elana J. Fertig
Cold Spring Harbor Laboratory (2018-08-20) <https://doi.org/gd2xpn>
DOI: [10.1101/395004](https://doi.org/10.1101/395004)

2. Missing data and technical variability in single-cell RNA-sequencing experiments

Stephanie C Hicks, F William Townes, Mingxiang Teng, Rafael A Irizarry
Biostatistics (2017-11-06) <https://doi.org/gfb8g4>
DOI: [10.1093/biostatistics/kxx053](https://doi.org/10.1093/biostatistics/kxx053) · PMID: [29121214](https://pubmed.ncbi.nlm.nih.gov/29121214/) · PMCID: [PMC6215955](https://pubmed.ncbi.nlm.nih.gov/PMC6215955/)

3. CoGAPS: an R/C++ package to identify patterns and biological process activity in transcriptomic data

Elana J. Fertig, Jie Ding, Alexander V. Favorov, Giovanni Parmigiani, Michael F. Ochs
Bioinformatics (2010-09-01) <https://doi.org/cwqsv4>
DOI: [10.1093/bioinformatics/btq503](https://doi.org/10.1093/bioinformatics/btq503) · PMID: [20810601](https://pubmed.ncbi.nlm.nih.gov/20810601/) · PMCID: [PMC3025742](https://pubmed.ncbi.nlm.nih.gov/PMC3025742/)

4. Enter the Matrix: Factorization Uncovers Knowledge from Omics

Genevieve L. Stein-O'Brien, Raman Arora, Aedin C. Culhane, Alexander V. Favorov, Lana X. Garmire, Casey S. Greene, Loyal A. Goff, Yifeng Li, Aloune Ngom, Michael F. Ochs, ... Elana J. Fertig
Trends in Genetics (2018-10) <https://doi.org/gd93tk>
DOI: [10.1016/j.tig.2018.07.003](https://doi.org/10.1016/j.tig.2018.07.003) · PMID: [30143323](https://pubmed.ncbi.nlm.nih.gov/30143323/)

5. ADAGE-Based Integration of Publicly Available Pseudomonas aeruginosa Gene Expression Data with Denoising Autoencoders Illuminates Microbe-Host Interactions

Jie Tan, John H. Hammond, Deborah A. Hogan, Casey S. Greene
mSystems (2016-01-19) <https://doi.org/gcgmbq>
DOI: [10.1128/msystems.00025-15](https://doi.org/10.1128/msystems.00025-15) · PMID: [27822512](https://pubmed.ncbi.nlm.nih.gov/27822512/) · PMCID: [PMC5069748](https://pubmed.ncbi.nlm.nih.gov/PMC5069748/)

6. Unsupervised Extraction of Stable Expression Signatures from Public Compendia with an Ensemble of Neural Networks

Jie Tan, Georgia Doing, Kimberley A. Lewis, Courtney E. Price, Kathleen M. Chen, Kyle C. Cady, Barret Perchuk, Michael T. Laub, Deborah A. Hogan, Casey S. Greene
Cell Systems (2017-07) <https://doi.org/gcw9f4>
DOI: [10.1016/j.cels.2017.06.003](https://doi.org/10.1016/j.cels.2017.06.003) · PMID: [28711280](https://pubmed.ncbi.nlm.nih.gov/28711280/) · PMCID: [PMC5532071](https://pubmed.ncbi.nlm.nih.gov/PMC5532071/)

7. Extracting a biologically relevant latent space from cancer transcriptomes with variational autoencoders.

Gregory P Way, Casey S Greene

Pacific Symposium on Biocomputing. Pacific Symposium on Biocomputing (2018) <https://www.ncbi.nlm.nih.gov/pubmed/29218871>

PMID: [29218871](#) · PMCID: [PMC5728678](#)

8. Parameter tuning is a key part of dimensionality reduction via deep variational autoencoders for single cell RNA transcriptomics

Qiwen Hu, Casey S Greene

Cold Spring Harbor Laboratory (2018-08-05) <https://doi.org/gdxxjf>

DOI: [10.1101/385534](#)

9. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2

Michael I Love, Wolfgang Huber, Simon Anders

Genome Biology (2014-12) <https://doi.org/gd3zvn>

DOI: [10.1186/s13059-014-0550-8](#) · PMID: [25516281](#) · PMCID: [PMC4302049](#)

10. Differential analyses for RNA-seq: transcript-level estimates improve gene-level inferences

Charlotte Soneson, Michael I. Love, Mark D. Robinson

F1000Research (2015-12-30) <https://doi.org/gdtgw8>

DOI: [10.12688/f1000research.7563.1](#) · PMID: [26925227](#) · PMCID: [PMC4712774](#)

11. Salmon provides fast and bias-aware quantification of transcript expression

Rob Patro, Geet Duggal, Michael I Love, Rafael A Irizarry, Carl Kingsford

Nature Methods (2017-03-06) <https://doi.org/gcw9f5>

DOI: [10.1038/nmeth.4197](#) · PMID: [28263959](#) · PMCID: [PMC5600148](#)

12. Sailfish enables alignment-free isoform quantification from RNA-seq reads using lightweight algorithms

Rob Patro, Stephen M Mount, Carl Kingsford

Nature Biotechnology (2014-04-20) <https://doi.org/gfghc2>

DOI: [10.1038/nbt.2862](#) · PMID: [24752080](#) · PMCID: [PMC4077321](#)

13. tximeta

Rob Patro Michael Love

Bioconductor (2018) <https://doi.org/gfddxw>

DOI: [10.18129/b9.bioc.tximeta](#)

14. Alevin efficiently estimates accurate gene abundances from dscRNA-seq data

Avi Srivastava, Laraib Malik, Tom Sean Smith, Ian Sudbery, Rob Patro

Cold Spring Harbor Laboratory (2018-06-01) <https://doi.org/gffk42>

DOI: [10.1101/335000](https://doi.org/10.1101/335000)

15. Comprehensive analysis of retinal development at single cell resolution identifies NFI factors as essential for mitotic exit and specification of late-born cells

Brian Clark, Genevieve Stein-O'Brien, Fion Shiau, Gabrielle Cannon, Emily Davis, Thomas Sherman, Fatemeh Rajaii, Rebecca James-Esposito, Richard Gronostajski, Elana Fertig, ... Seth Blackshaw

Cold Spring Harbor Laboratory (2018-07-27) <https://doi.org/gdwrzh>

DOI: [10.1101/378950](https://doi.org/10.1101/378950)

16. Gene expression signatures modulated by epidermal growth factor receptor activation and their relationship to cetuximab resistance in head and neck squamous cell carcinoma

Elana J Fertig, Qing Ren, Haixia Cheng, Hiromitsu Hatakeyama, Adam P Dicker, Ulrich Rodeck, Michael Considine, Michael F Ochs, Christine H Chung

BMC Genomics (2012) <https://doi.org/gb3fgp>

DOI: [10.1186/1471-2164-13-160](https://doi.org/10.1186/1471-2164-13-160) · PMID: [22549044](https://pubmed.ncbi.nlm.nih.gov/22549044/) · PMCID: [PMC3460736](https://pubmed.ncbi.nlm.nih.gov/PMC3460736/)

17. CoGAPS matrix factorization algorithm identifies transcriptional changes in AP-2alpha target genes in feedback from therapeutic inhibition of the EGFR network

Elana J. Fertig, Hiroyuki Ozawa, Manjusha Thakar, Jason D. Howard, Luciane T. Kagohara, Gabriel Krigsfeld, Ruchira S. Ranaweera, Robert M. Hughes, Jimena Perez, Siân Jones, ... Christine H. Chung

Oncotarget (2016-09-16) <https://doi.org/f9k8d8>

DOI: [10.18632/oncotarget.12075](https://doi.org/10.18632/oncotarget.12075) · PMID: [27650546](https://pubmed.ncbi.nlm.nih.gov/27650546/) · PMCID: [PMC5342018](https://pubmed.ncbi.nlm.nih.gov/PMC5342018/)

18. Pattern Identification in Time-Course Gene Expression Data with the CoGAPS Matrix Factorization

Elana J. Fertig, Genevieve Stein-O'Brien, Andrew Jaffe, Carlo Colantuoni

Gene Function Analysis (2013-10-24) <https://doi.org/f5j7xj>

DOI: [10.1007/978-1-62703-721-1_6](https://doi.org/10.1007/978-1-62703-721-1_6) · PMID: [24233779](https://pubmed.ncbi.nlm.nih.gov/24233779/)

19. Integrated time course omics analysis distinguishes immediate therapeutic response from acquired resistance

Genevieve Stein-O'Brien, Luciane T. Kagohara, Sijia Li, Manjusha Thakar, Ruchira Ranaweera, Hiroyuki Ozawa, Haixia Cheng, Michael Considine, Sandra Schmitz, Alexander V. Favorov, ... Elana J. Fertig

Genome Medicine (2018-05-23) <https://doi.org/gfc4dq>

DOI: [10.1186/s13073-018-0545-2](https://doi.org/10.1186/s13073-018-0545-2) · PMID: [29792227](https://pubmed.ncbi.nlm.nih.gov/29792227/) · PMCID: [PMC5966898](https://pubmed.ncbi.nlm.nih.gov/PMC5966898/)

20. Inferring causal molecular networks: empirical assessment through a community-based effort

Steven M Hill, Laura M Heiser, Thomas Cokelaer, Michael Unger, Nicole K Nesser, Daniel E Carlin,

Yang Zhang, Artem Sokolov, Evan O Paull, ... Sach Mukherjee

Nature Methods (2016-02-22) <https://doi.org/f3t7t4>

DOI: [10.1038/nmeth.3773](https://doi.org/10.1038/nmeth.3773) · PMID: [26901648](https://pubmed.ncbi.nlm.nih.gov/26901648/) · PMCID: [PMC4854847](https://pubmed.ncbi.nlm.nih.gov/PMC4854847/)

21. Preferential Activation of the Hedgehog Pathway by Epigenetic Modulations in HPV Negative HNSCC Identified with Meta-Pathway Analysis

Elana J. Fertig, Ana Markovic, Ludmila V. Danilova, Daria A. Gaykalova, Leslie Cope, Christine H. Chung, Michael F. Ochs, Joseph A. Califano

PLoS ONE (2013-11-04) <https://doi.org/gcpqgc6>

DOI: [10.1371/journal.pone.0078127](https://doi.org/10.1371/journal.pone.0078127) · PMID: [24223768](https://pubmed.ncbi.nlm.nih.gov/24223768/) · PMCID: [PMC3817178](https://pubmed.ncbi.nlm.nih.gov/PMC3817178/)

22. Single cell RNA-seq denoising using a deep count autoencoder

Gökçen Eraslan, Lukas M. Simon, Maria Mircea, Nikola S. Mueller, Fabian J. Theis

Cold Spring Harbor Laboratory (2018-04-13) <https://doi.org/gdjcb3>

DOI: [10.1101/300681](https://doi.org/10.1101/300681)

23. Bayesian Inference for a Generative Model of Transcriptome Profiles from Single-cell RNA Sequencing

Romain Lopez, Jeffrey Regier, Michael B Cole, Michael I Jordan, Nir Yosef

Cold Spring Harbor Laboratory (2018-03-30) <https://doi.org/gdm9jf>

DOI: [10.1101/292037](https://doi.org/10.1101/292037)

24. Exploring Single-Cell Data with Deep Multitasking Neural Networks

Matthew Amodio, David van Dijk, Krishnan Srinivasan, William S Chen, Hussein Mohsen, Kevin R Moon, Allison Campbell, Yujiao Zhao, Xiaomei Wang, Manjunatha Venkataswamy, ... Smita Krishnaswamy

Cold Spring Harbor Laboratory (2017-12-19) <https://doi.org/gfgrpk>

DOI: [10.1101/237065](https://doi.org/10.1101/237065)

25. Massive single-cell RNA-seq analysis and imputation via deep learning

Yue Deng, Feng Bao, Qionghai Dai, Lani Wu, Steven Altschuler

Cold Spring Harbor Laboratory (2018-05-06) <https://doi.org/gfgrpm>

DOI: [10.1101/315556](https://doi.org/10.1101/315556)

26. Transfer learning in single-cell transcriptomics improves data denoising and pattern discovery

Jingshu Wang, Divyansh Agarwal, Mo Huang, Gang Hu, Zilu Zhou, Vincent B. Conley, Hugh MacMullan, Nancy R. Zhang

Cold Spring Harbor Laboratory (2018-10-31) <https://doi.org/gfgrpn>

DOI: [10.1101/457879](https://doi.org/10.1101/457879)

27. Efficient Generation of Transcriptomic Profiles by Random Composite Measurements

Brian Cleary, Le Cong, Anthea Cheung, Eric S. Lander, Aviv Regev

Cell (2017-11) <https://doi.org/gcrjhc>

DOI: [10.1016/j.cell.2017.10.023](https://doi.org/10.1016/j.cell.2017.10.023) · PMID: [29153835](https://pubmed.ncbi.nlm.nih.gov/29153835/) · PMCID: [PMC5726792](https://pubmed.ncbi.nlm.nih.gov/PMC5726792/)

28. Detecting heterogeneity in single-cell RNA-Seq data by non-negative matrix factorization

Xun Zhu, Travers Ching, Xinghua Pan, Sherman M. Weissman, Lana Garmire

PeerJ (2017-01-19) <https://doi.org/gfgr7c>

DOI: [10.7717/peerj.2888](https://doi.org/10.7717/peerj.2888) · PMID: [28133571](https://pubmed.ncbi.nlm.nih.gov/28133571/) · PMCID: [PMC5251935](https://pubmed.ncbi.nlm.nih.gov/PMC5251935/)

29. Integrative inference of brain cell similarities and differences from single-cell genomics

Joshua Welch, Velina Kozareva, Ashley Ferreira, Charles Vanderburg, Carly Martin, Evan Macosko

Cold Spring Harbor Laboratory (2018-11-02) <https://doi.org/gfgr7b>

DOI: [10.1101/459891](https://doi.org/10.1101/459891)

30. greenelab/shared-latent-space

chrsunwil

GitHub <https://github.com/greenelab/shared-latent-space>

31. quantro: a data-driven approach to guide the choice of an appropriate normalization method.

Stephanie C Hicks, Rafael A Irizarry

Genome biology (2015-06-04) <https://www.ncbi.nlm.nih.gov/pubmed/26040460>

DOI: [10.1186/s13059-015-0679-0](https://doi.org/10.1186/s13059-015-0679-0) · PMID: [26040460](https://pubmed.ncbi.nlm.nih.gov/26040460/) · PMCID: [PMC4495646](https://pubmed.ncbi.nlm.nih.gov/PMC4495646/)

32. MultiPLIER: a transfer learning framework reveals systemic features of rare autoimmune disease

Jaclyn N Taroni, Peter C Grayson, Qiwen Hu, Sean Eddy, Matthias Kretzler, Peter A Merkel, Casey S Greene

Cold Spring Harbor Laboratory (2018-08-20) <https://doi.org/gfc9bb>

DOI: [10.1101/395947](https://doi.org/10.1101/395947)