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# Survey of Dimensionality Reduction Techniques and their Applications for RNA-seq Data

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## Abstract

Biological data pose many challenges for applying machine learning methods, particularly low sample sizes and high dimensionality due to the large number of features being measured. Low sample sizes make the use of recent deep-learning and generative methods infeasible, and as such simpler models are still widely used. Here, we survey the impact of four dimensionality reduction techniques (*a priori* aggregation, principle component analysis, kernelized principle component analysis, and nonnegative matrix factorization) on improving the accuracy of five different simple classification algorithms (decision tree,  $k$ -nearest neighbors, naïve Bayes, random forest, and support vector machine) across nine different RNA sequencing datasets from the Gene Expression Omnibus. We find that the impact of dimensionality reduction is highly variable and likely depends on underlying biological context specifics of the dataset. We note that principle component analysis, kernelized principle component analysis, and nonnegative matrix factorization are nearly identical and that the number of reduced dimensions has a much greater impact than the choice of dimensionality reduction method.

## 1 Introduction

Machine learning techniques have been successfully applied to answer biological questions by analyzing a wide variety of biological data, such as analyzing sequence information to identify molecular interactions between RNA molecules [1], analyzing UV damage patterns to identify transcription factor binding sites [2], and, famously, analyzing structural data to predict protein folding [3]. Of particular interest is gene expression data, which reveals how cells are behaving at a molecular level. Within a cell, the information required to perform cellular activities, such as dividing, taking up nutrients, performing metabolic reactions, etc., is stored in the cell's DNA. The DNA is a molecule made from a series of repeating molecular units called nucleotides. There are four different nucleotides used in DNA: adenine (A), cytosine (C), guanine (G), and thymine (T). The information contained in the DNA is encoded in the sequence of nucleotides and is organized into units called genes. Genes are expressed when the cell creates a temporary copy of the gene's nucleotide sequence as a molecule of messenger RNA (mRNA) through a process known as transcription. The RNA molecule is structured similarly to the DNA, consisting of a sequence of the nucleotide bases A, C, G,

and U (where U represents uracil, which replaces thymine in RNA for evolutionary and chemical reasons). The mRNA transcript is then translated into a sequence of amino acids which folds into a protein, and the protein’s function ultimately confers traits to the organism. Cells very tightly regulate what genes they express and the degree to which they are expressed, and the exact complement of expressed genes determines the cell’s behavior, cell type, etc. Numerous diseases, notably cancers, ultimately result from aberrant gene expression. [4]

Perturbations to the cell (i.e. disease or infection) will alter its gene expression [4]. This begs the question of whether disease state can be inferred from the gene expression, which can be neatly phrased as a classification problem and naturally leads to an exciting application of machine learning techniques. The goal is to gather gene expression data on both diseased and healthy individuals, then train a machine learning model to classify the disease state of individuals. To measure what genes are being expressed by a population of cells, biologists can perform RNA sequencing (RNA-seq), where the RNA is isolated and the exact nucleotide sequences of the isolated RNA molecules are found. Each RNA molecule corresponds to a gene, the identity of which can be deduced from the sequence. The degree to which any given gene is being expressed can then be inferred from the relative abundance of isolated transcripts that correspond to that gene. [5] The National Institutes of Health has also encouraged researchers to deposit their RNA-seq data on the Gene Expression Omnibus (GEO), available at <https://www.ncbi.nlm.nih.gov/sites/GDSbrowser>.

However, like with any biological data, applying machine learning techniques to RNA-seq data poses many challenges. Particularly, the time and cost of conducting biological experiments leads to extremely low sample sizes, especially if the experiment involves human subjects. Additionally, RNA-seq requires the prescription of a set of genes to measure the expression of ahead of time. This results in a wide variety of slightly different methodologies and gene sets, which makes it difficult to meaningfully compare data between RNA-seq datasets or to sensibly combine data across multiple RNA-seq datasets. Often, the expression of tens of thousands of genes are measured, orders of magnitude more than the typical sample size. This results in data with a high dimensionality that far exceeds the number of data points. The advent of single-cell techniques, particularly single-cell RNA sequencing (scRNA-seq), has partially mitigated these problem. scRNA-seq differs from RNA-seq in that, instead of isolating RNA from a population of cells, the RNA is sequenced at the level of individual cells, meaning that every individual cell can act as a separate data point. [6] This allows for the collection of large sample sizes, and these data have been successfully used to create pretrained deep-learning models such as scGPT [7], Tahoe-x1 [8], and CellFM [9]. However, single-cell techniques are expensive, and traditional RNA-seq is still common [10]. While pretrained deep-learning models for RNA-seq data, namely BulkRNABert and DCNet [11, 12], these models are trained for specific applications in cancer utilizing data from the cancer genome atlas and expect a fixed set of genes as features for their inputs [11–13], making them unsuitable for applications to general RNA-seq datasets.

The challenges posed by RNA-seq data, particularly the low sample sizes and the lack of a suitable pretrained model, make it infeasible to use modern generative or deep-learning models. As such, simpler machine learning models are still commonly used in biological contexts. However, the high dimensionality of the data still poses a challenge, motivating the application of dimensionality reduction. Here, we conduct a survey of four dimensionality reduction techniques—*a priori* aggregation, principle component analysis (PCA), kernelized principle component analysis (kPCA), and nonnegative matrix factorization (NMF)—and assess their impact on the accuracy of five simple machine learning models—the decision tree (DT),  $k$ -nearest neighbors ( $k$ -NN), the naïve Bayes classifier (NB), the random forest (RF), and the support vector machine (SVM)—in classifying disease state from RNA-seq data across nine different RNA-seq datasets (Tables 1, 2).

## 2 Methods

### 2.1 Datasets

Nine human datasets from the GEO (<https://www.ncbi.nlm.nih.gov/sites/GDSbrowser>) were surveyed to assess the generalizability of our findings across RNA-seq datasets (Tables 1, 2). The datasets were chosen to encompass a wide range of different sample sizes, number of class labels, and number of features. The most limiting case is the MDG dataset, which has only 36 data points in 12625 dimensions [22]. Additionally, the SCLC dataset has 130 data points with six classes that are

Table 1: Datasets utilized

Abbr.	GEO Accession	Title	Ref.
UCC	GDS1615	Ulcerative colitis and Crohn’s disease comparison: peripheral blood mononuclear cells	[14]
SCLC	GDS2373	Squamous cell lung carcinomas	[15]
SEC	GDS2771	Large airway epithelial cells from cigarette smokers with suspect lung cancer	[16]
MDS	GDS3795	Myelodysplastic syndrome: CD34+ hematopoietic stem cells	[17]
ALL	GDS4206	Pediatric acute leukemia patients with early relapse: white blood cells	[18]
HIV	GDS4228	HIV infection and Antiretroviral Therapy effects on mitochondria in various tissues	[19]
JIA	GDS4267	Systemic juvenile idiopathic arthritis and non-systemic JIA subtypes: peripheral blood mononuclear cells	[20]
GBM	GDS5205	Long-term adult survivors of glioblastoma: primary tumors	[21]
MDG	GDS963	Macular degeneration and dermal fibroblast response to sublethal oxidative stress	[22]

Table 2: Dataset parameters

Abbr.	Samples	Features	Classes	
			Num.	Description
UCC	127	22283	3	Normal, ulcerative colitis, Crohn’s disease
SCLC	130	22283	6	Type Ia, Ib, IIa, IIb, IIIa, IIIb
SEC	192	22283	3	No cancer, suspected cancer, cancer
MDS	200	54675	2	Healthy, myelodysplastic syndrome
ALL	197	54675	3	Early, late, no relapse
HIV	166	4825	2	HIV-negative, HIV-positive
JIA	154	54675	3	No JIA, systemic JIA, non-systemic JIA
GBM	70	54675	3	Short-term, intermediate, long-term overall survival
MDG	36	12625	2	Healthy, macular degeneration

all similar, each describing a different stage of lung cancer, and poses a challenging classification problem [15].

The datasets were downloaded as “full” SOFT files (text files) from the GEO. Gene expression values were extracted and stored in a tab-delimited tabular format. Features corresponding to sequencing platform controls were removed from consideration.

## 2.2 Models

Five simple machine learning strategies were surveyed: DT,  $k$ -NN, NB, RF, and SVM. Many combinations of different values for the model hyperparameters were tested. The DT was pruned to maximum depths of 2, 3, and 4, and features were chosen to split on by optimizing the entropy. The Minkowski distance was used with exponents of  $p = 1, 2, 3, 4$  for  $k$ -NN, and values of  $k$  were set to 3, 4, and 5. 100, 200, and 500 estimators were used for RF, and the individual estimators were pruned to maximum depths of 2, 3, and 4. The radial basis function (RBF), linear, quadratic, and cubic kernels were tested for the SVM, and values of  $C = 10^{-3}, 10^{-2}, 10^{-1}, 10^0, 10^1, 10^2, 10^3$  were chosen for the regularization parameter. All models were implemented via scikit-learn [23].

## 2.3 Dimensionality Reduction Strategies

As a baseline, no dimensionality reduction was applied, and the models were trained on the datasets “as-is.”

The first dimensionality reduction strategy we applied was aggregation of the data across features based on *a priori* biological knowledge. Genes do not function independently. For instance, some

genes encode transcription factors, which are proteins that alter the expression of other genes, and genes whose products all function as part of the same biological pathway or system are often coregulated. [4] The features of the datasets, which correspond to genes, can be therefore be grouped together based on their biological functionality. Genes are assigned a gene ontology (GO) category by the GO consortium [24, 25], and the dimensionality of the data is then reduced from  $n$ , the number of individual genes, to  $m$ , the number of GO categories. The value corresponding to each GO category is taken to be the mean of the values corresponding to each gene that belongs to that category. There are three different GO categorization schemes that were utilized: component, which corresponds to the subcellular compartment the gene product functions in (e.g. mitochondria, nucleus); function, which corresponds to what the gene product does (e.g. ATP binding, protein binding); and process, which corresponds to what biological pathway the gene product takes part in (e.g. MAPK cascade, inflammatory response).

The other three dimensionality reduction techniques we applied were: PCA, kPCA, and NMF, which are all commonly utilized in biological contexts. Briefly, PCA maintains only the components of the data that account for the highest variation kPCA exploits the fact that PCA can be calculated with only the inner product and utilizes the “kernel trick” to introduce nonlinearity, and NMF decomposes the data matrix into two lower-dimensional matrices whose products approximate the original data matrix in a way that, unlike PCA and kPCA, does not re-center the data but can only be approximated (up to 200 iterations were allowed for convergence during implementation). These three techniques were implemented via `scikit-learn`. [23] The dimension of the datasets were reduced to  $d = 2, 3, 4, 5, 6, 7, 8, 9$  with each of these methods to allow for visualization ( $d = 2$ ) and to encompass a range of dimensionalities whilst keeping the dimensionality ~one order of magnitude below the number of data points.

## 2.4 Assessment and Evaluation

Due to limited sample sizes, we utilized leave-one-out validation to assess the models. Models were assessed primarily based on their prediction accuracy because of the heterogeneity in the datasets (i.e. the variable number of classes).

## 3 Results

## 4 Discussion

## 5 Data and Code Availability

All the data and code used in this report, as well as supplementary figures and supporting information, are available at [https://github.com/nolan-middleton/CPT\\_S-Group-Project-Fall-2025](https://github.com/nolan-middleton/CPT_S-Group-Project-Fall-2025).

## References

- [1] Tingpeng Yang, Yonghong He, and Yu Wang. Introducing tec-Incmir for prediction of lncrna-mirna interactions through deep learning of rna sequences. *Brief Bioinform*, 26(1):bbaf046, 02 2025. ISSN 1477-4054. doi: 10.1093/bib/bbaf046. URL <https://doi.org/10.1093/bib/bbaf046>.
- [2] Hannah E Wilson, Scott Stevison, Levi Lamprey, and John J Wyrick. Mapping transcription factor binding sites by learning uv damage fingerprints. *Nucleic Acids Res*, 53(19):gkaf1014, 10 2025. ISSN 1362-4962. doi: 10.1093/nar/gkaf1014. URL <https://doi.org/10.1093/nar/gkaf1014>.
- [3] John Jumper, Richard Evans, Alexander Pritzel, Tim Green, Michael Figurnov, Olaf Ronneberger, Kathryn Tunyasuvunakool, Russ Bates, Augustin Žídek, Anna Potapenko, Alex Bridgeland, Clemens Meyer, Simon A A Kohl, Andrew J Ballard, Andrew Cowie, Bernardino Romera-Paredes, Stanislav Nikolov, Rishabh Jain, Jonas Adler, Trevor Back, Stig Petersen, David Reiman, Ellen Clancy, Michal Zielinski, Martin Steinegger, Michalina Pacholska, Tamas Berghammer, Sebastian Bodenstein, David Silver, Oriol Vinyals, Andrew W Senior, Koray Kavukcuoglu, Pushmeet Kohli, and Demis Hassabis. Highly accurate protein structure prediction with AlphaFold. *Nature*, 596(7873):583–589, August 2021. doi: 10.1038/s41586-021-03819-2. URL <https://doi.org/10.1038/s41586-021-03819-2>.
- [4] Jocelyn Krebs, Elliott Goldstein, and Stephen Kilpatrick. *Lewin’s Genes XII*. Jones & Bartlett Learning, 5 Wall Street, Burlington, MA 01803, 12 edition, 2018. ISBN 9781284104493.
- [5] Zhong Wang, Mark Gerstein, and Michael Snyder. RNA-Seq: a revolutionary tool for transcriptomics. *Nat Rev Genet*, 10(1):57–63, January 2009. doi: 10.1038/nrg2484. URL <https://doi.org/10.1038/nrg2484>.
- [6] Fuchou Tang, Catalin Barbacioru, Yangzhou Wang, Ellen Nordman, Clarence Lee, Nanlan Xu, Xiaohui Wang, John Bodeau, Brian B Tuch, Asim Siddiqui, Kaiqin Lao, and M Azim Surani. mRNA-Seq whole-transcriptome analysis of a single cell. *Nat Methods*, 6(5):377–382, May 2009.
- [7] Haotian Cui, Chloe Wang, Hassan Maan, Kuan Pang, Fengning Luo, Nan Duan, and Bo Wang. scGPT: toward building a foundation model for single-cell multi-omics using generative AI. *Nat Methods*, 21(8):1470–1480, August 2024. doi: 10.1038/s41592-024-02201-0. URL <https://doi.org/10.1038/s41592-024-02201-0>.
- [8] Shreshth Gandhi, Farnoosh Javadi, Valentine Svensson, Umair Khan, Matthew G. Jones, Johnny Yu, Daniele Merico, Hani Goodarzi, and Nima Alidoust. Tahoe-x1: Scaling perturbation-trained single-cell foundation models to 3 billion parameters. *bioRxiv*, 2025. doi: 10.1101/2025.10.23.683759. URL <https://www.biorxiv.org/content/10.1101/2025.10.23.683759v1>.
- [9] Zhuoyi Wei, Yun Su, Ningyuan Shangguan, Shuangyu Yang, Chengyang Zhang, Wenbing Li, Jinbo Zhang, Nan Fang, Hongyu Zhang, Huiying Zhao, Yutong Lu, Jue Fan, Weijiang Yu, Yuansong Zeng, Jiancong Xie, and Yuedong Yang. Cellfm: a large-scale foundation model pre-trained on transcriptomics of 100 million human cells. *Nat Commun*, 16(4679), May 2025. doi: 10.1038/s41467-025-59926-5. URL <https://doi.org/10.1038/s41467-025-59926-5>.
- [10] Tracy Boakye Serebour, Adam P. Cribbs, Mathew J. Baldwin, Collen Masimirembwa, Zedias Chikwambi, Angeliki Kerasidou, and Sarah J. B. Snelling. Overcoming barriers to single-cell rna sequencing adoption in low- and middle-income countries. *Eur J Hum Genet*, 32(10):1206–1213, October 2024. doi: 10.1038/s41431-024-01564-4. URL <https://doi.org/10.1038/s41431-024-01564-4>.
- [11] Maxence Gélard, Guillaume Richard, Thomas Pierrot, and Paul-Henry Cournède. Bulkrnabert: Cancer prognosis from bulk rna-seq based language models. In Stefan Hegselmann, Helen Zhou, Elizabeth Healey, Trenton Chang, Caleb Ellington, Vishwali Mhasawade, Sana Tonekaboni, Peniel Argaw, and Haoran Zhang, editors, *Proceedings of the 4th Machine Learning for Health Symposium*, volume 259 of *Proceedings of Machine Learning Research*, pages 384–400. PMLR, 15–16 Dec 2025. URL <https://proceedings.mlr.press/v259/gelard25a.html>.

- [12] Liu D Wang N He D Wu Z Zhu X Wen X Li X Li J Wang Z Wang X, Wang H. Deep learning using bulk rna-seq data expands cell landscape identification in tumor microenvironment. *Oncotarget*, 25(11), February 2022. doi: 10.1080/2162402X.2022.2043662.
- [13] Allison P. Heath, Vincent Ferretti, Stuti Agrawal, Maksim An, James C. Angelakos, Renuka Arya, Rosita Bajari, Bilal Baqar, Justin H. B. Barnowski, Jeffrey Burt, Ann Catton, Brandon F. Chan, Fay Chu, Kim Cullion, Tanja Davidsen, Phuong-My Do, Christian Dompierre, Martin L. Ferguson, Michael S. Fitzsimons, Michael Ford, Miyuki Fukuma, Sharon Gaheen, Gajanan L. Ganji, Tzintzuni I. Garcia, Sameera S. George, Daniela S. Gerhard, Francois Gerthoffert, Fauzi Gomez, Kang Han, Kyle M. Hernandez, Biju Issac, Richard Jackson, Mark A. Jensen, Sid Joshi, Ajinkya Kadam, Aishmit Khurana, Kyle M. J. Kim, Victoria E. Kraft, Shenglai Li, Tara M. Lichtenberg, Janice Lodato, Laxmi Lolla, Plamen Martinov, Jeffrey A. Mazzone, Daniel P. Miller, Ian Miller, Joshua S. Miller, Koji Miyauchi, Mark W. Murphy, Thomas Nullet, Rowland O. Ogwara, Francisco M. Ortuño, Jesús Pedrosa, Phuong L. Pham, Maxim Y. Popov, James J. Porter, Raymond Powell, Karl Rademacher, Colin P. Reid, Samantha Rich, Bessie Rogel, Himanso Sahni, Jeremiah H. Savage, Kyle A. Schmitt, Trevor J. Simmons, Joseph Sislow, Jonathan Spring, Lincoln Stein, Sean Sullivan, Yajing Tang, Mathangi Thiagarajan, Heather D. Troyer, Chang Wang, Zhining Wang, Bedford L. West, Alex Wilmer, Shane Wilson, Kaman Wu, William P. Wysocki, Linda Xiang, Joseph T. Yamada, Liming Yang, Christine Yu, Christina K. Yung, Jean Claude Zenklusen, Junjun Zhang, Zhenyu Zhang, Yuanheng Zhao, Ariz Zubair, Louis M. Staudt, and Robert L. Grossman. The nci genomic data commons. *Nat Genet*, 53(3):257–262, March 2021. doi: 10.1038/s41588-021-00791-5. URL <https://doi.org/10.1038/s41588-021-00791-5>.
- [14] Michael E Burczynski, Ron L Peterson, Natalie C Twine, Krystyna A Zuberek, Brendan J Brodeur, Lori Casciotti, Vasu Maganti, Padma S Reddy, Andrew Strahs, Fred Immermann, Walter Spinelli, Ulrich Schwertschlag, Anna M Slager, Monette M Cotreau, and Andrew J Dorner. Molecular classification of crohn's disease and ulcerative colitis patients using transcriptional profiles in peripheral blood mononuclear cells. *J Mol Diagn*, 8(1):51–61, February 2006.
- [15] Mitch Raponi, Yi Zhang, Jack Yu, Guoan Chen, Grace Lee, Jeremy M G Taylor, James Macdonald, Dafydd Thomas, Christopher Moskaluk, Yixin Wang, and David G Beer. Gene expression signatures for predicting prognosis of squamous cell and adenocarcinomas of the lung. *Cancer Res*, 66(15):7466–7472, August 2006.
- [16] Adam M Gustafson, Raffaella Soldi, Christina Anderlind, Mary Beth Scholand, Jun Qian, Xiaohui Zhang, Kendal Cooper, Darren Walker, Annette McWilliams, Gang Liu, Eva Szabo, Jerome Brody, Pierre P Masson, Marc E Lenburg, Stephen Lam, Andrea H Bild, and Avrum Spira. Airway PI3K pathway activation is an early and reversible event in lung cancer development. *Sci Transl Med*, 2(26):26ra25, April 2010.
- [17] Petra Gorombei, Fabien Guidez, Saravanan Ganesan, Mathieu Chiquet, Andrea Pellagatti, Laure Goursaud, Nilgun Tekin, Stephanie Beurlet, Satyananda Patel, Laura Guerenne, Carole Le Pogam, Niclas Setterblad, Pierre de la Grange, Christophe LeBoeuf, Anne Janin, Maria-Elena Noguera, Laure Sarda-Mantel, Pascale Merlet, Jacqueline Boultwood, Marina Konopleva, Michael Andreeff, Robert West, Marika Pla, Lionel Adès, Pierre Fenaux, Patricia Krief, Christine Chomienne, Nader Omidvar, and Rose Ann Padua. BCL-2 inhibitor ABT-737 effectively targets leukemia-initiating cells with differential regulation of relevant genes leading to extended survival in a NRAS/BCL-2 mouse model of high risk-myelodysplastic syndrome. *Int J Mol Sci*, 22(19):10658, September 2021.
- [18] Lüder Hinrich Meyer, Sarah Mirjam Eckhoff, Manon Queudeville, Johann Michael Kraus, Marco Giordan, Jana Stursberg, Andrea Zangrando, Elena Vendramini, Anja Möricke, Martin Zimmermann, Andre Schrauder, Georgia Lahr, Karlheinz Holzmann, Martin Schrappe, Giuseppe Basso, Karsten Stahnke, Hans Armin Kestler, Geertruy Te Kronnie, and Klaus-Michael Debatin. Early relapse in ALL is identified by time to leukemia in NOD/SCID mice and is characterized by a gene signature involving survival pathways. *Cancer Cell*, 19(2):206–217, February 2011.
- [19] Caryn G Morse, Joachim G Voss, Goran Rakocevic, Mary McLaughlin, Carol L Vinton, Charles Huber, Xiaojun Hu, Jun Yang, Da Wei Huang, Carolea Logun, Robert L Danner, Zoila G

- Rangel, Peter J Munson, Jan M Orenstein, Elisabeth J Rushing, Richard A Lempicki, Marinos C Dalakas, and Joseph A Kovacs. HIV infection and antiretroviral therapy have divergent effects on mitochondria in adipose tissue. *J Infect Dis*, 205(12):1778–1787, June 2012.
- [20] Claas H Hinze, Ndate Fall, Sherry Thornton, Jun Q Mo, Bruce J Aronow, Gerlinde Layh-Schmitt, Thomas A Griffin, Susan D Thompson, Robert A Colbert, David N Glass, Michael G Barnes, and Alexei A Grom. Immature cell populations and an erythropoiesis gene-expression signature in systemic juvenile idiopathic arthritis: implications for pathogenesis. *Arthritis Res Ther*, 12(3):R123, June 2010.
- [21] Guido Reifenberger, Ruthild G Weber, Vera Riehmer, Kerstin Kaulich, Edith Willscher, Henry Wirth, Jens Gietzelt, Bettina Hentschel, Manfred Westphal, Matthias Simon, Gabriele Schackert, Johannes Schramm, Jakob Matschke, Michael C Sabel, Dorothee Gramatzki, Jörg Felsberg, Christian Hartmann, Joachim P Steinbach, Uwe Schlegel, Wolfgang Wick, Bernhard Radlwimmer, Torsten Pietsch, Jörg C Tonn, Andreas von Deimling, Hans Binder, Michael Weller, Markus Loeffler, and German Glioma Network. Molecular characterization of long-term survivors of glioblastoma using genome- and transcriptome-wide profiling. *Int J Cancer*, 135(8):1822–1831, October 2014.
- [22] Nataly Strunnikova, Sara Hilmer, Jessica Flippin, Michael Robinson, Eric Hoffman, and Karl G Csaky. Differences in gene expression profiles in dermal fibroblasts from control and patients with age-related macular degeneration elicited by oxidative injury. *Free Radic Biol Med*, 39(6):781–796, September 2005.
- [23] F. Pedregosa, G. Varoquaux, A. Gramfort, V. Michel, B. Thirion, O. Grisel, M. Blondel, P. Prettenhofer, R. Weiss, V. Dubourg, J. Vanderplas, A. Passos, D. Cournapeau, M. Brucher, M. Perrot, and E. Duchesnay. Scikit-learn: Machine learning in Python. *Journal of Machine Learning Research*, 12:2825–2830, 2011.
- [24] M Ashburner, C A Ball, J A Blake, D Botstein, H Butler, J M Cherry, A P Davis, K Dolinski, S S Dwight, J T Eppig, M A Harris, D P Hill, L Issel-Tarver, A Kasarskis, S Lewis, J C Matese, J E Richardson, M Ringwald, G M Rubin, and G Sherlock. Gene ontology: tool for the unification of biology. the gene ontology consortium. *Nat Genet*, 25(1):25–29, May 2000.
- [25] The Gene Ontology Consortium, Suzi A Aleksander, James Balhoff, Seth Carbon, J Michael Cherry, Harold J Drabkin, Dustin Ebert, Marc Feuermann, Pascale Gaudet, Nomi L Harris, David P Hill, Raymond Lee, Huaiyu Mi, Sierra Moxon, Christopher J Mungall, Anushya Muruganugan, Tremayne Mushayahama, Paul W Sternberg, Paul D Thomas, Kimberly Van Auken, Jolene Ramsey, Deborah A Siegele, Rex L Chisholm, Petra Fey, Maria Cristina Aspromonte, Maria Victoria Nugnes, Federica Quaglia, Silvio Tosatto, Michelle Giglio, Suvarna Nadendla, Giulia Antonazzo, Helen Attrill, Gil dos Santos, Steven Marygold, Victor Strelets, Christopher J Tabone, Jim Thurmond, Pinglei Zhou, Saadullah H Ahmed, Praoparn Asanithong, Diana Luna Buitrago, Meltem N Erdol, Matthew C Gage, Mohamed Ali Kadhum, Kan Yan Chloe Li, Miao Long, Aleksandra Michalak, Angeline Pesala, Armalya Pritazahra, Shirin C C Saverimuttu, Renzhi Su, Kate E Thurlow, Ruth C Lovering, Colin Logie, Snezhana Oliferenko, Judith Blake, Karen Christie, Lori Corbani, Mary E Dolan, Harold J Drabkin, David P Hill, Li Ni, Dmitry Sitnikov, Cynthia Smith, Alayne Cuzick, James Seager, Laurel Cooper, Justin Elser, Pankaj Jaiswal, Parul Gupta, Pankaj Jaiswal, Sushma Naithani, Manuel Lera-Ramirez, Kim Rutherford, Valerie Wood, Jeffrey L De Pons, Melinda R Dwinell, G Thomas Hayman, Mary L Kaldunski, Anne E Kwitek, Stanley J F Laulederkind, Marek A Tutaj, Mahima Vedi, Shur-Jen Wang, Peter D'Eustachio, Lucila Aimo, Kristian Axelsen, Alan Bridge, Nevila Hyka-Nouspikel, Anne Morgat, Suzi A Aleksander, J Michael Cherry, Stacia R Engel, Kalpana Karra, Stuart R Miyasato, Robert S Nash, Marek S Skrzypek, Shuai Weng, Edith D Wong, Erika Bakker, Tanya Z Berardini, Leonore Reiser, Andrea Auchincloss, Kristian Axelsen, Ghislaine Argoud-Puy, Marie-Claude Blatter, Emmanuel Boutet, Lionel Breuza, Alan Bridge, Cristina Casals-Casas, Elisabeth Coudert, Anne Estreicher, Maria Livia Famiglietti, Marc Feuermann, Arnaud Gos, Nadine Gruaz-Gumowski, Chantal Hulo, Nevila Hyka-Nouspikel, Florence Jungo, Philippe Le Mercier, Damien Lieberherr, Patrick Masson, Anne Morgat, Ivo Pedruzzi, Lucille Pourcel, Sylvain Poux, Catherine Rivoire, Shyamala Sundaram, Alex Bate-man, Emily Bowler-Barnett, Hema Bye-A-Jee, Paul Denny, Alexandr Ignatchenko, Rizwan Ishtiaq, Antonia Lock, Yvonne Lussi, Michele Magrane, Maria J Martin, Sandra Orchard,

Pedro Raposo, Elena Speretta, Nidhi Tyagi, Kate Warner, Rossana Zaru, Alexander D Diehl, Raymond Lee, Juancarlos Chan, Stavros Diamantakis, Daniela Raciti, Magdalena Zarowiecki, Malcolm Fisher, Christina James-Zorn, Virgilio Ponferrada, Aaron Zorn, Sridhar Ramachandran, Leyla Ruzicka, and Monte Westerfield. The gene ontology knowledgebase in 2023. *Genetics*, 224(1):iyad031, 03 2023. ISSN 1943-2631. doi: 10.1093/genetics/iyad031. URL <https://doi.org/10.1093/genetics/iyad031>.