Enhancing rigor and reproducibility by improving software availability, usability, and archival stability

Jaqueline J. Brito\textsuperscript{1,*}, Jun Li\textsuperscript{2}, Jason H. Moore\textsuperscript{5}, Casey S. Greene\textsuperscript{3,4}, Nicole A. Nogoy\textsuperscript{6}, Lana X. Garmire\textsuperscript{2$}, Serghei Mangul\textsuperscript{1,5*}

\textsuperscript{1} Department of Clinical Pharmacy, School of Pharmacy, University of Southern California, 1985 Zonal Avenue Los Angeles, CA 90089, USA
\textsuperscript{2} Department of Computational Medicine & Bioinformatics, Medical School, University of Michigan, 1301 Catherine St. Ann Arbor, MI 48109, USA
\textsuperscript{3} Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104, USA
\textsuperscript{4} Childhood Cancer Data Lab, Alex’s Lemonade Stand, Philadelphia, PA 19102, USA
\textsuperscript{5} Department of Biostatistics, Epidemiology, and Informatics, Institute for Biomedical Informatics, University of Pennsylvania, 3700 Hamilton Walk, Philadelphia, PA 19104, USA
\textsuperscript{6} GigaScience

$ -$ These authors contributed equally to the paper

*Correspondence: britoj@usc.edu; mangul@usc.edu
Abstract

Computational methods have reshaped the landscape of modern biology. While the biomedical community is increasingly dependent on computational tools, the mechanisms ensuring open data, open software, and reproducibility are variably enforced. Publications may describe the software for which source code is unavailable, documentation is incomplete or unmaintained, and analytical source code is missing. Publications that lack this information compromise the role of peer review in evaluating technical strength and scientific contribution. Such flaws also limit any subsequent work that intends to use the described software. We herein provide recommendations to improve reproducibility, transparency, and rigor in computational biology—precisely the values which should be emphasized in foundational life and medical science curricula. Our recommendations for improving software availability, usability, and archival stability aim to foster a sustainable data science ecosystem in biomedicine and life science research.

Keywords: Rigor, reproducible research, installability, archival stability, big data, open science

Main text

Biomedical informatics has the opportunity to be at the forefront of the biomedical community in practices around open data, open software, and reproducible research. The computational reproduction of previously published results is enabled by publicly releasing all research resources, from raw data to installable packages and source code, in a discoverable and
archivally stable manner. However, a lack of strict implementation or enforcement of journal policies for resource sharing has resulted in the loss of crucial research objects for many published studies. Publications lacking data or source code undermine scientific rigor, transparency, and reproducibility¹.

An astonishing number of bioinformatics software tools are designed each year to accommodate increasingly bigger, more complex, and more specialized biomedical datasets². Many of those software tools have limited installability and are hosted on Uniform Resource Locators (URLs) with undetermined archiving practices³. Closed-source software is another issue as researchers may not have access to the source code, which harms the transparency of research by avoiding others to audit methods and results. Here we discuss the pressing need for scientists to improving software availability, usability, and archival stability in computational biology. By following a set of best practices⁴, scientists can promote rigor and reproducibility, ultimately cultivating a sustainable, thriving research community.

1. Increase computational training opportunities targeted at reproducibility. Biomedical researchers who use computational tools must acquire specific computational skills in order to successfully apply the techniques to a large amount of data. Undergraduate students who lack formal computational training can be taught the skills required to promote reproducibility on specialized courses⁵. In addition to rigorous class training, advanced undergraduate and graduate students may benefit from short-term intensive workshops aimed at postdoctoral
scholars, clinical fellows, and faculty. Several institutions, including UCLA, have successfully hosted workshop-based programs for over five years and serve as valuable resources for pedagogy and curricula. Workshops for training researchers to use computational tools usually include hands-on training for implementing analysis tools, such as computational notebook technologies. In summary, comprehensive computational training programs are the way to prime future computational biologists towards reproducibility work in the data-driven fields of life science and biomedical research (Figure 1a).

2. Share open and discoverable data and metadata. Open source code depends on open and shareable data. Access to the data used to produce important research results is key for auditing the rigor of published studies. Many research laboratories and universities lack human and financial resources required to generate today's large, complex biomedical datasets. Open access to datasets is imperative to build a thriving and sustainable scientific community where all researchers can access and analyze existing data. However in practise, omics data of the patients often can not be shared publicly due to patient privacy and user agreement standards. While data are not freely publicly available, most studies provide controlled access, where researchers can access the raw data by providing a reason they would like to use the data. Also, cases where raw data are restricted from public use, usually summary data are publicly available.

In general, the data should also be discoverable via centralized repositories like SRA and GEO and annotated with descriptive metadata (Figure 1c). When data is shared on centralized
repositories in easy-to-use formats, other researchers can examine and re-analyze the data, challenge existing interpretations, and test new theories. In general, data sharing corresponds to a true spirit of science where each new discovery is based on previous work. Discoveries in multiple fields were solely based on shared data (e.g., economics and meteorology). Sharing data can enable the reproducibility and robustness of science because of the ability to utilize data generated from individual studies to a larger scale. Additionally, secondary analysis is economically sustainable and can be used in countries with limited resources\textsuperscript{17,18,19}. In general, reusing the data speaks about the quality and importance of generated data and contributed to the impact of the original work.

3. **Build open-source software.** The software provides a foundation for the reproducibility of published biomedical research, defined as the ability to replicate published findings by running the same computational tool on data generated by the study\textsuperscript{4,5}. For this reason, closed-source software restricts the reproducibility of biomedical research. First, researchers may not have access to the source code, which limits their ability to audit the results of published studies. Second, license restrictions may prohibit the creation of new functionalities that would be released on modified versions of existing tools. For proprietary software, generally, there is also the cost of acquisition and maintenance of licenses, which is not affordable for every laboratory. Therefore, the adoption of standard open licenses for data and software tools can enhance the rigor and impact of research by allowing others to reproduce published studies.
However, just publicly releasing the code does not guarantee the computational reproducibility of biomedical research. The released code should be well documented with user manuals, and installable in a user-friendly manner. The code used in a published analysis should be hosted on an archivally stable platform such as GitHub (Figure 1b). Currently, over a quarter of computational software resources cannot be accessed through the URLs provided in the original publication, suggesting that the repositories are poorly maintained\(^3\). Additionally, many bioinformatics tools are too difficult, and some impossible, for a new user to install\(^3\). Use of Open Source Initiative license models (https://opensource.org/licenses) allows users to easily use and adapt tools, increasing the sustainability of the biomedical research community. New platforms are also being proposed, such as CODE CHECK (https://sje30.github.io/codecheck/), where researchers can, input of their code and data, check that their analysis is reproducible. CODE CHECK issues for verified analyses a time-stamped “certificate of reproducible computation” which can inform the peer review of a paper.

4. **Use platforms to archive and share data and software.** In addition to software and datasets, computational biology researchers commonly produce resources such as experiment protocols, workflows, and annotations. Storing and sharing these resources allows other researchers to cite them within a publication, which would increase the reproducibility of a paper and increase the visibility of previously developed methods. The inclusion of citable digital object identifiers (DOIs) also facilitates the discover of reusable resources as they provide long-term access to
published resources. Several innovative platforms designed to promote reproducibility have recently emerged (Figure 1d).

**a) Platforms to archive and share data.** Protocols.io is an open-source protocol repository, where researchers can manage, share, tweak, optimize and adopt existing methods even after a scientist has left a lab. Scicrunch.org is a platform for curating research resources that enables the user to discover, access, view, and use research objects. Scicrunch.org encourages researchers to register any research object, from antibodies, animal models, and tools, after which they are assigned a specific research resource identifier (RRID) to be cited in manuscripts. The RRID allows other users to easily locate and access the resources. Hypothes.is ([https://web.hypothes.is/](https://web.hypothes.is/)) is an open-source annotation tool that allows any researcher to annotate any resource on the web, including to create annotations for personal use or as part of conversations with private groups or the general public.

**b) Platforms to archive and share software.** Virtual machines (VMs) and containers are also useful tools to facilitate the reproducibility of a work. VMs are software pieces that are capable of encapsulating entire operating systems, libraries, codes, and data. Containers (e.g., Docker ([www.docker.com](http://www.docker.com)) and Singularity ([singularity.lbl.gov](http://singularity.lbl.gov))) are lightweight solutions when compared to VMs as they do not encapsulate the operating system; rather, they rely on the host kernel to run required functions. Both VMs and
containers are shared via image files and can be included as supplementary material at certain journals or stored in zenodo (https://zenodo.org/), figshare (https://figshare.com/), or other general-purpose archival repositories. Stencila (https://stenci.la/) is an open-source framework for executable documents that enable open access to data and reproducibility of results. Stencila supports commonly used environments and tools, such as Jupyter Notebook, RMarkdown, Python, and SQL. Given the many different tools available that can promote reproducibility, a research lab should define their own standards on a suite of tools and platforms that support their research practices.

5. Publish with journals that promote reproducibility. Journals have various publishing standards. Researchers may elect to publish in journals that encourage best practices (e.g., adopting the FAIR principles) that aim to increase the impact of their work (Figure 1e). In 2014, a consortium from academia and industry defined a set of principles stating that research data should be Findable, Accessible, Interoperable, and Reusable (FAIR). To ensure reproducibility, many journals now require that biomedical data generated by a published study be shared when the paper is released. For instance, GigaScience has been promoting reproducibility of analyses since 2012 by mandating open data that follow the FAIR principles and it requires that any source code have an OSI (Open Source Initiative) approved license. Other journals, such as Biostatistics, have implemented badges for articles with data and code
sharing. eLife suggests a code-based publication, which enables data and analysis to be fully reproducible by the reader, challenging the traditional static representation of results using PDF or HTML formats.

6. Support reusable resources. Successfully implementing and widely distributing software tools developed in academia involves unique challenges when compared to the industry. In academia, software tools are developed by small groups comprised of graduate or postdoctoral scholars, who have fairly fast turn-over rates of 2-5 years. These groups are less professionally trained when compared to software development groups in the industry, where holistic teams of specialists support the long-term maintenance of projects. In order to enhance the quality and reuse of open software, professionally trained software engineers should be hired to partner with the students and postdocs. To make this happen, funding agencies need better mechanisms of acknowledging and incentivizing funding earmarked for critical bioinformatics infrastructure. In addition, funders should recognize the rigor of software development, rather than just considering 'novelty'-based conventional criteria of research. The availability of well-resourced grant mechanisms to convert minimum viable products produced by trainees into reliable software could enhance the impact of research-grade software on the community.
Conclusions

We outlined key elements to improve the rigor of biomedical studies and foster reproducibility in computational biology. The infrastructure required to systematically adopt best practices for reproducibility of biomedical research is largely in place. The remaining challenge to the systemic promotion of reproducibility is that incentives are not currently aligned to support good practices. Instead, current efforts rely on individual researchers electing to follow best practices, often at their own time and expense. We believe it is time for a fundamental cultural shift in the scientific community: rigor and reproducibility should become primary concerns in the criteria and decision-making process of designing studies, funding research, and writing and publishing results. Successful systematic adoption of best practices will require the buy-in of multiple stakeholders in the scientific communities, from publishers, academic institutions, funding agencies, and stakeholders. This increases the lifetime and value of published research as resources naturally become reusable, testable, and discoverable. Community-wide adoption of best practices for reproducibility is critical to realizing the full potential of fast-paced, collaborative analyses of large datasets in the biomedical and life sciences.

Abbreviations

DOI, Digital Object identifier; FAIR, Findable, Accessible, Interoperable, and Reusable; OSI, Open Source Initiative; VM, Virtual Machine.
Competing interests

The authors declare that they have no competing interests.

Funding

CSG was supported by grants from the NIH (R01HG010067 and R01CA237170), the Gordon and Betty Moore Foundation (GBMF4552), the Chan Zuckerberg Initiative Donor Advised Fund of the Silicon Valley Community Foundation (2018-182718), and Alex’s Lemonade Stand Foundation (CCDL). LXG is supported by grants K01ES025434 awarded by NIEHS through funds provided by the trans-NIH Big Data to Knowledge (BD2K) initiative (http://datascience.nih.gov/bd2k), R01 LM012373 and R01 LM012907 awarded by NLM, and R01 HD084633 awarded by NICHD. The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors’ contributions

| Author | Contribution |
|--------|--------------|
| JJB    | Writing - Original Draft Preparation, review and editing. |
| JL     | Writing - review and editing. |
| CSG    | Writing - review and editing. |
| JM     | Writing - review and editing. |
| NN     | Conceptualization and structure of the manuscript; Writing - review and editing; Visualization - creation of Figures. |
| LG       | Conceptualizing the project; Writing - review and editing. |
|---------|----------------------------------------------------------|
| SM      | Conceptualization and structure of the manuscript; Writing - review and editing. |

**Acknowledgments**

We thank Dr. Lana Martin for discussions and helpful comments on the manuscript.

**Authors’ Information**

NAN is an Editor at *GigaScience* and is an open science advocate with over 7 years experience in publishing reproducible research.

**References**

1. Stodden, V., Seiler, J. & Ma, Z. An empirical analysis of journal policy effectiveness for computational reproducibility. *Proc. Natl. Acad. Sci. U. S. A.* 115, 2584–2589 (2018).
2. Wren, J. D. Bioinformatics programs are 31-fold over-represented among the highest impact scientific papers of the past two decades. *Bioinformatics* 32, 2686–2691 (2016).
3. Mangul, S., Martin, L. S., Eskin, E. & Blekhman, R. Improving the usability and archival stability of bioinformatics software. *Genome Biology* vol. 20 (2019).
4. Piccolo, S. R. & Frampton, M. B. Tools and techniques for computational reproducibility. *GigaScience* vol. 5 (2016).
5. Shade, A., Dunivin, T. K., Choi, J., Teal, T. K. & Howe, A. C. Strategies for Building Computing
Skills To Support Microbiome Analysis: a Five-Year Perspective from the EDAMAME Workshop. *mSystems* **4**, (2019).

6. Taroni, J. N. Making Workshops Work: Insights from EDAMAME. *mSystems* **4**, (2019).

7. Mangul, S., Martin, L. S., Hoffmann, A., Pellegrini, M. & Eskin, E. Addressing the Digital Divide in Contemporary Biology: Lessons from Teaching UNIX. *Trends Biotechnol.* **35**, 901–903 (2017).

8. Greene’s Lab GitHub. Materials for GCB535 taught at the University of Pennsylvania. https://github.com/greenelab/GCB535. Accessed 14 January 2020.

9. Data Access in Genomics. https://www.nature.com/collections/diadgjciaj (2019).

10. Gewin, V. *et al.* Data sharing and the future of science. *Nat. Commun.* **9**, 1–2 (2018).

11. No impact without data access. *Nat. Genet.* **47**, 691–691 (2015).

12. Brody, J. A. *et al.* Analysis commons, a team approach to discovery in a big-data environment for genetic epidemiology. *Nat. Genet.* **49**, 1560–1563 (2017).

13. M Shabani B M Knoppers, Y. Joly, ES. Dove, BM. Knoppers, M. Bobrow, D. Chalmers & J. Kaye, N. H. Analysis of five years of controlled access and data sharing compliance at the International Cancer Genome Consortium. *Nat. Genet.* **48**, 224–225 (2016).

14. Yuan, J. *et al.* DNA.Land is a framework to collect genomes and phenomes in the era of abundant genetic information. *Nat. Genet.* **50**, 160–165 (2018).

15. Manolio, T. A. UK Biobank debuts as a powerful resource for genomic research. *Nat. Med.* **24**, 1792–1794 (2018).

16. Sampson, Matthew G., and Hyun Min Kang. Using and producing publicly available genomic data to accelerate discovery in nephrology. Nature Reviews Nephrology (2019): 1.
17. Greene, C. S., Garmire, L. X., Gilbert, J. A., Ritchie, M. D. & Hunter, L. E. Celebrating parasites. *Nature genetics* vol. 49 483–484 (2017).

18. Mangul, S. *et al.* Using bioinformatics training to boost research capacities in resource-limited regions. *PeerJ Preprints* 6:e27415v1 doi:10.7287/peerj.preprints.27415.

19. Mangul, S. *et al.* How bioinformatics and open data can boost basic science in countries and universities with limited resources. *Nat. Biotechnol.* 37, 324–326 (2019).

20. Wilkinson, M. D. *et al.* The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 3, 160018 (2016).

21. GigaScience | Oxford Academic. *OUP Academic* https://academic.oup.com/gigascience (1753).

22. News | Open Source Initiative. https://opensource.org/.

23. Michelle Lewis, L. *et al.* Replication Study: Transcriptional amplification in tumor cells with elevated c-Myc. (2018) doi:10.7554/eLife.30274.

24. Altschul, S. *et al.* The anatomy of successful computational biology software. *Nat. Biotechnol.* 31, 894–897 (2013).
Figure 1. Recommendations to improve reproducibility and rigor of research.

- Increase computational training opportunities targeted at reproducibility
- Share open and discoverable data and metadata
- Build open-source software
- Use platforms to archive and share data and software
- Publish with journals that promote reproducibility
- Support reusable resources.