# Recommendations to enhance rigor and reproducibility in biomedical research

Jaqueline J. Brito, PhD
Mangul Lab - USC

February 27, 2020

Quantitative Biology > Other Quantitative Biology

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

Jaqueline J. Brito, Jun Li, Jason H. Moore, Casey S. Greene, Nicole A. Nogoy, Lana X. Garmire, Serghei Mangul

*(Submitted on 15 Jan 2020)*

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.

Subjects: **Other Quantitative Biology (q-bio.OT)**
Cite as: arXiv:2001.05127 [q-bio.OT]
(or arXiv:2001.05127v1 [q-bio.OT] for this version)

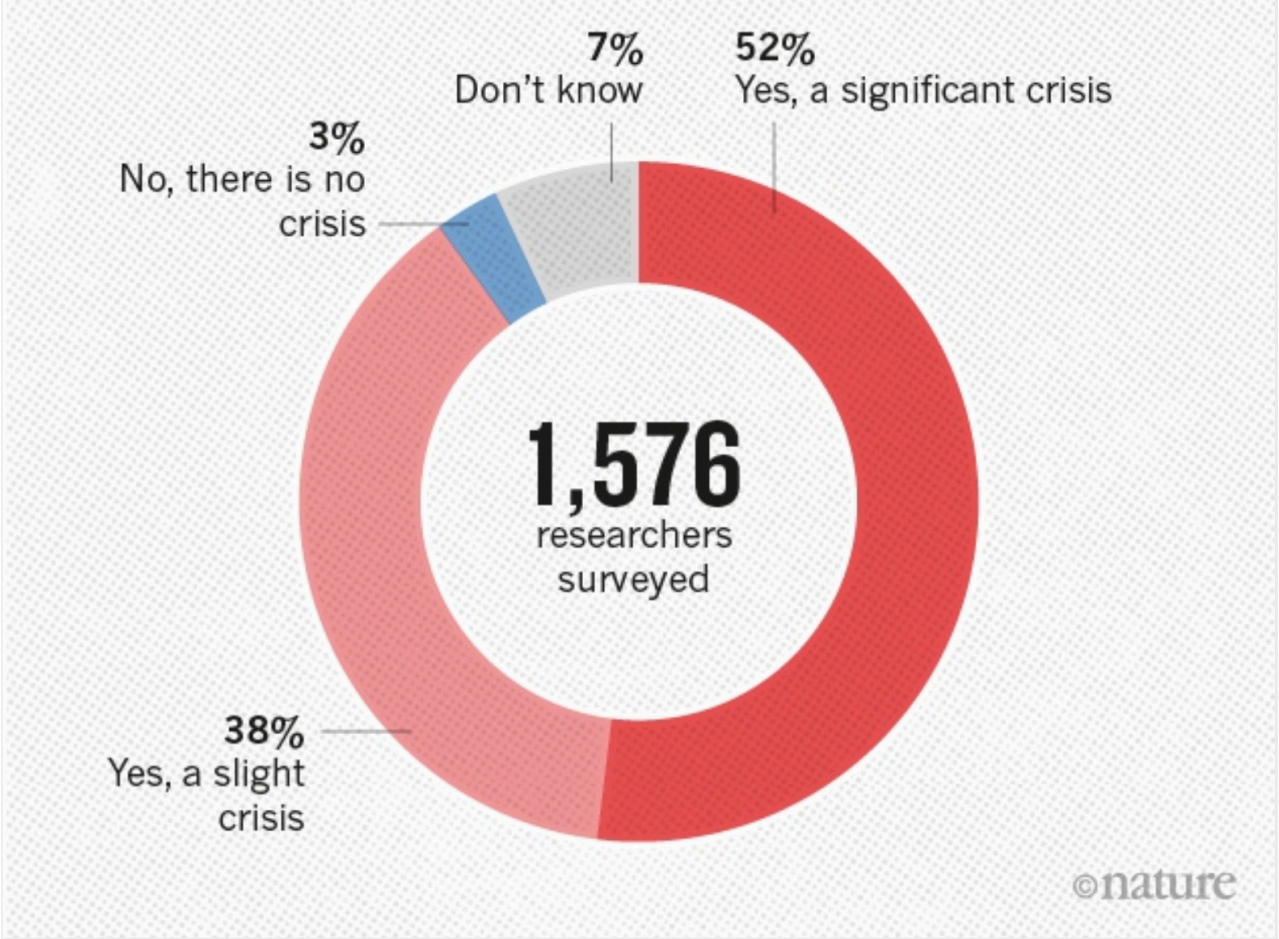
## Bibliographic data

[Enable Bibex (What is Bibex?)]

## Submission history

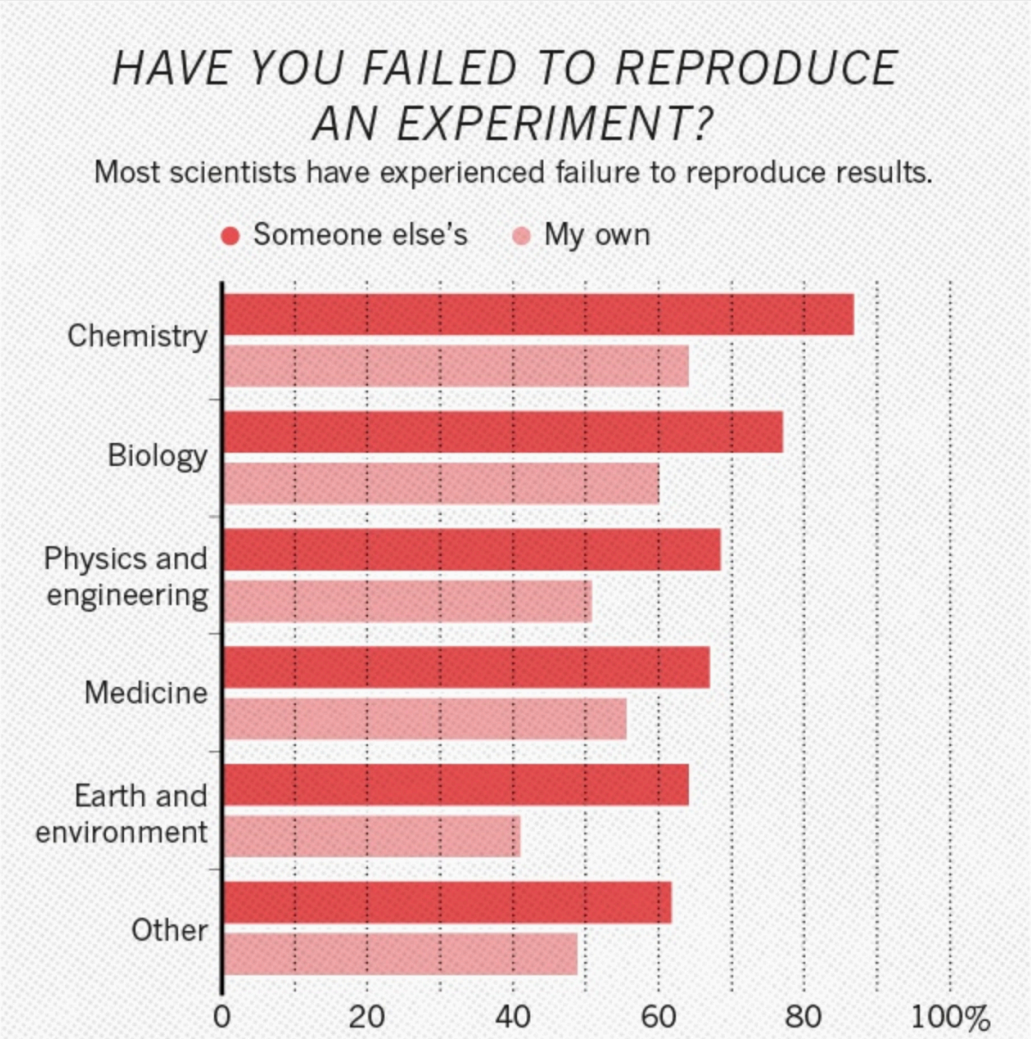
From: Jaqueline Brito [view email]
**[v1]** Wed, 15 Jan 2020 04:22:15 UTC (241 KB)

# Reproducibility crisis?




Source: https://www.nature.com/news/1-500-scientists-lift-the-lid-on-reproducibility-1.19970

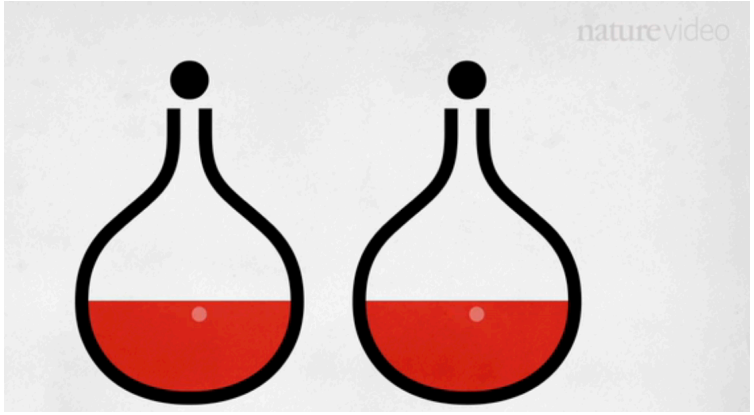
# Reproducibility crisis?




Source: https://www.nature.com/news/1-500-scientists-lift-the-lid-on-reproducibility-1.19970

# Ideal scenario with all information

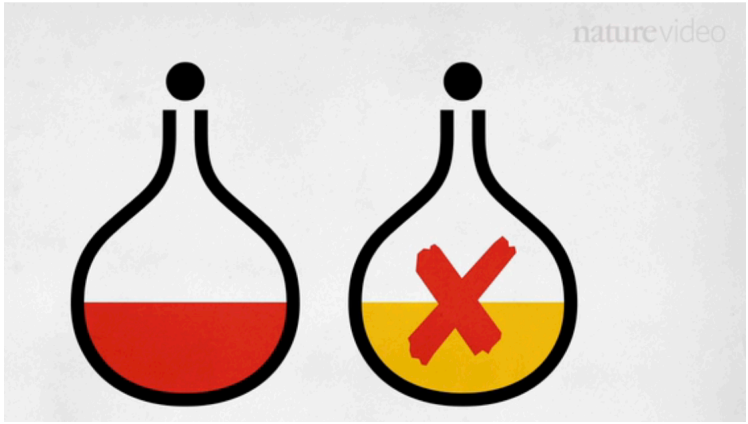
Researchers obtain different results even when they follow detailed procedures




No guarantee of same results

Several factors can affect results

- Human factor
- Environment settings






Source: https://www.nature.com/news/1-500-scientists-lift-the-lid-on-reproducibility-1.19970

# The reality is even worse

Many researchers do not share the information necessary to reproduce their results

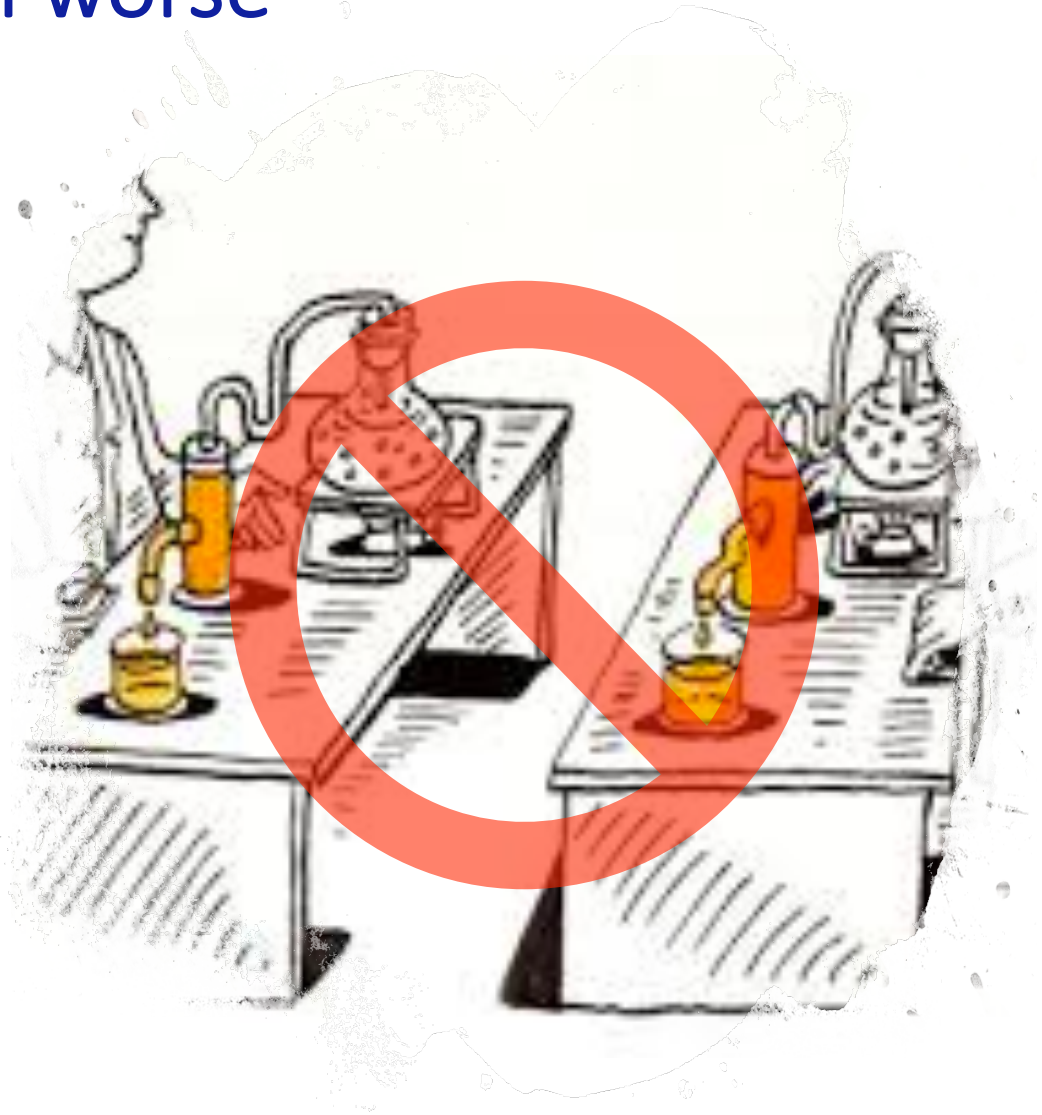


Image source: https://www.displayr.com/what-is-reproducible-research/

# Will it ever be possible to reproduce biomedical research routinely?

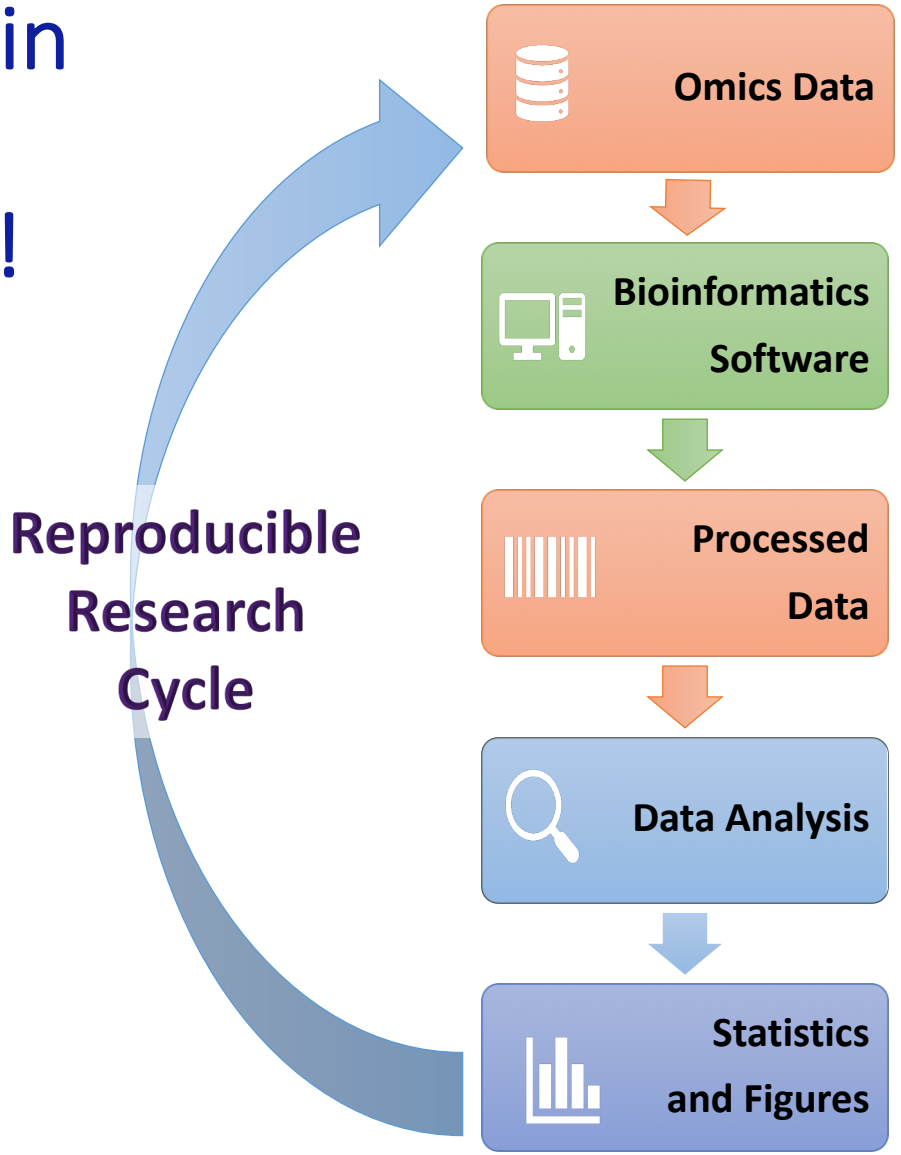
Many aspects are involved

- What is the level of details necessary to be provided to ensure reproducibility?
- Can the human factors be leveraged?

Is it feasible to develop procedures to ensure reproducibility?

# Unique opportunity in computational biomedical research!

Research cycle of automatic processes that can be shared



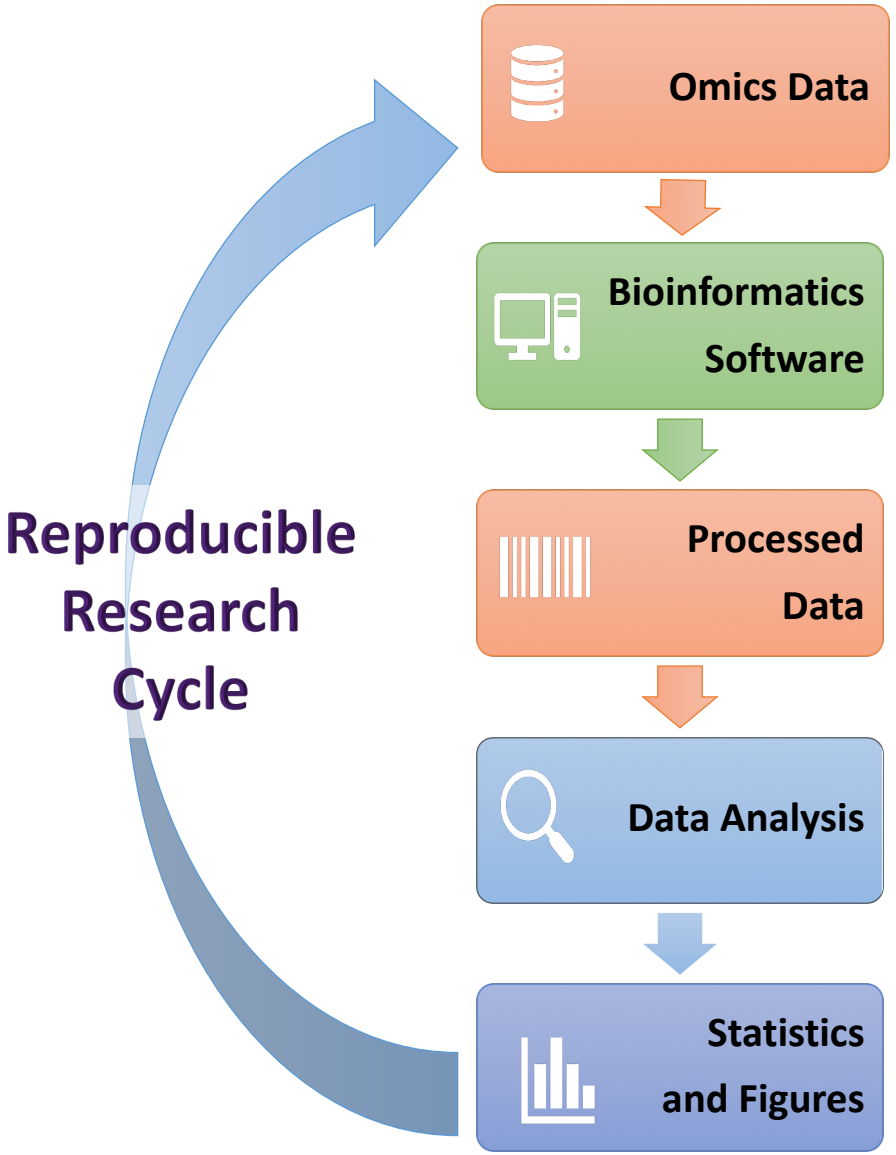

Still many studies are still not reproducible

- No data
- No source code

# How do we enable reproducible results?

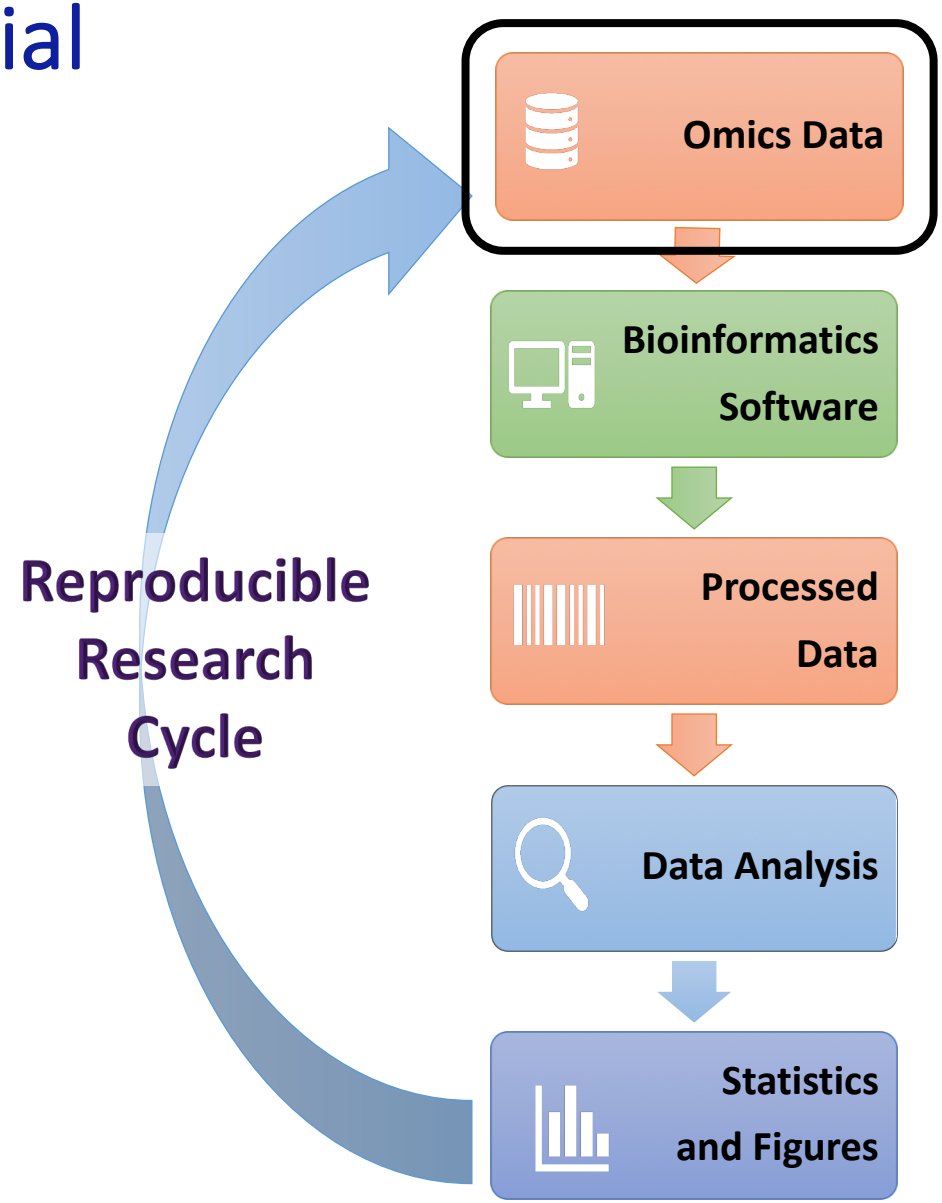
The problem can be solved by sharing all data and code across the entire cycle

We need to follow certain practices to enable and facilitate reproducibility



# Data access is essential

Data is essential for replicating and auditing results

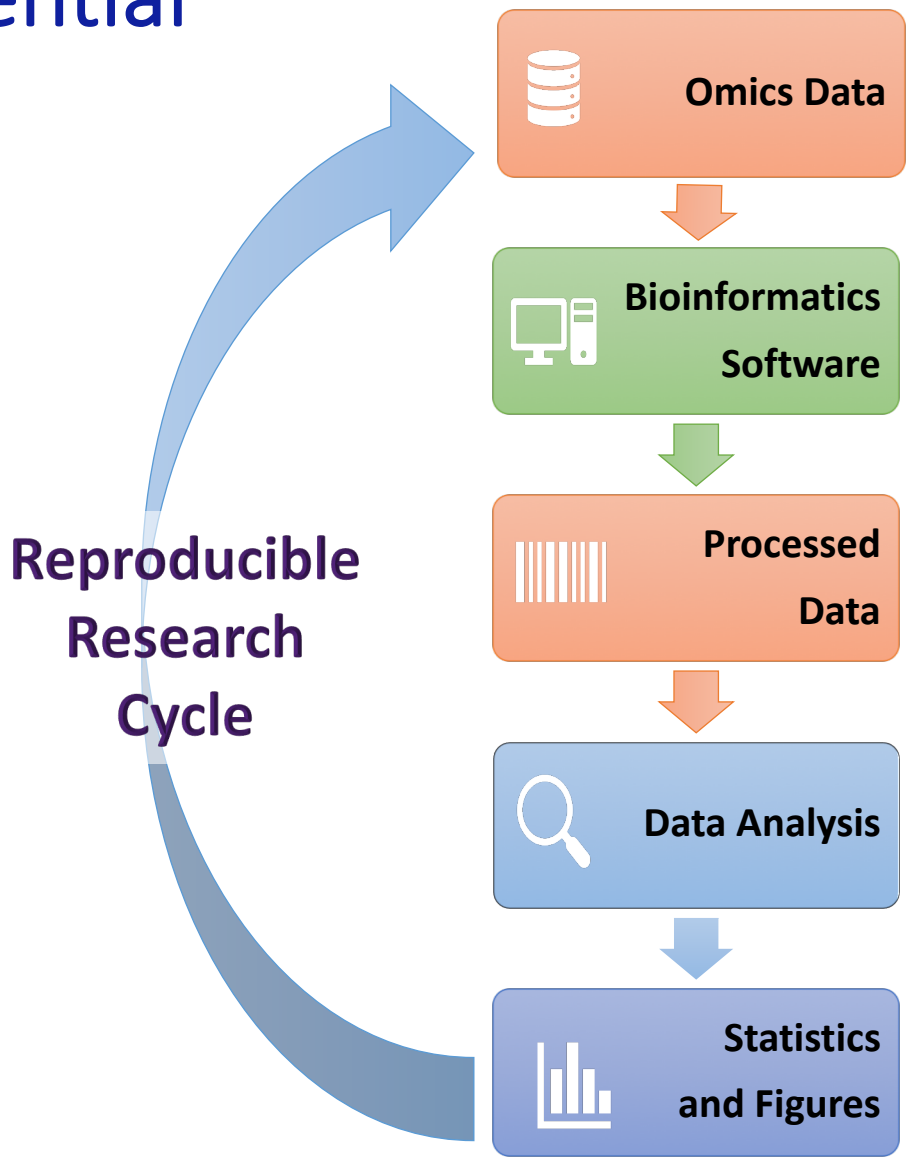


# Metadata is also essential

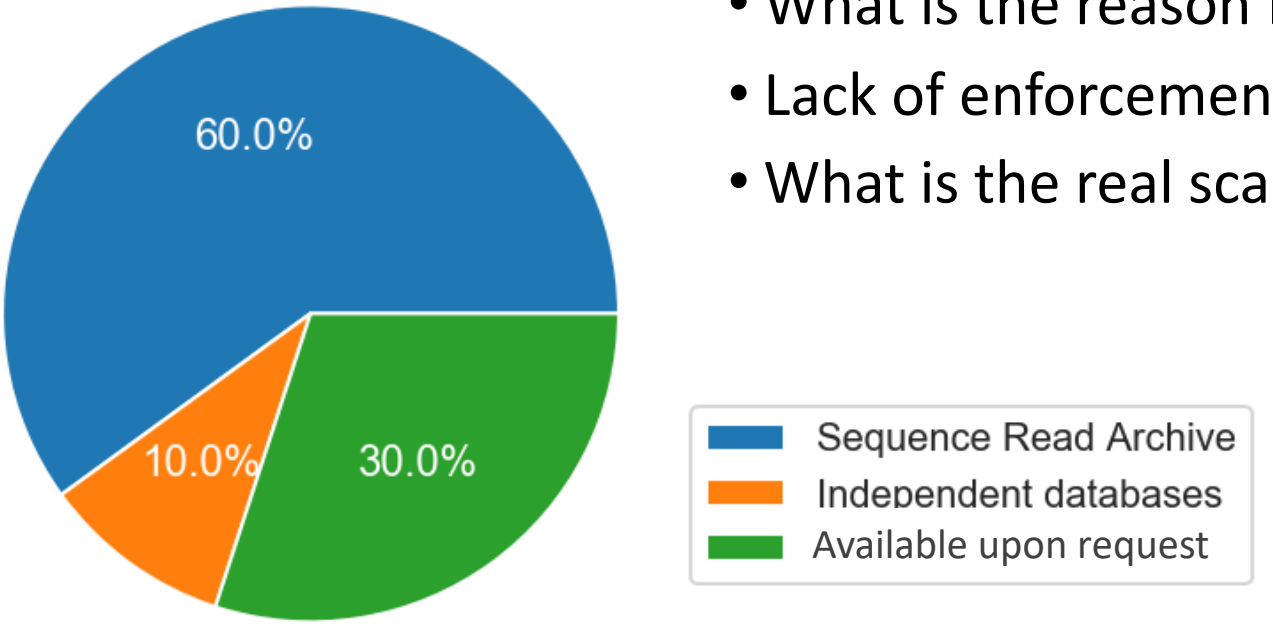
Omics raw data is mostly shared, but metadata is usually not properly formatted and shared

- Often incomplete
- Lack of agreement on the standards

Prohibits or makes it extremely challenging to search for specific phenotypes



# Many researchers still don’t share data




- What is the reason for not sharing?
- Lack of enforcement from editors?
- What is the real scale of the problem?

Data sharing of clinical metagenomics studies between 2015-2019

Source: Loeffler, Caitlin, et al. "Unlocking the diagnostic and therapeutic potential of metagenomics." *arXiv preprint arXiv:1911.11304* (2019).

# The “Upon request model” is not sustainable

## An empirical analysis of journal policy effectiveness for computational reproducibility

Victoria Stodden, Jennifer Seiler, and Zhaokun Ma

PNAS March 13, 2018 115 (11) 2584-2589; first published March 12, 2018 https://doi.org/10.1073/pnas.1708290115

Edited by David B. Allison, Indiana University Bloomington, Bloomington, IN, and accepted by Editorial Board Member Susan T. Fiske January 9, 2018 (received for review July 11, 2017)

Authors response to data access requests

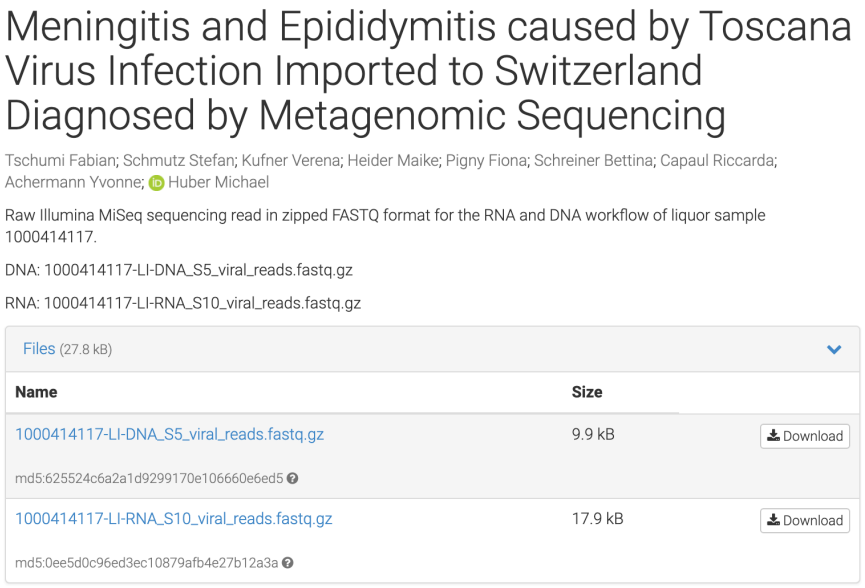
When you approach a PI for the source codes and raw data, you better explain who you are, whom you work for, why you need the data and what you are going to do with it.

I have to say that this is a very unusual request without any explanation! Please ask your supervisor to send me an email with a detailed, and I mean detailed, explanation.

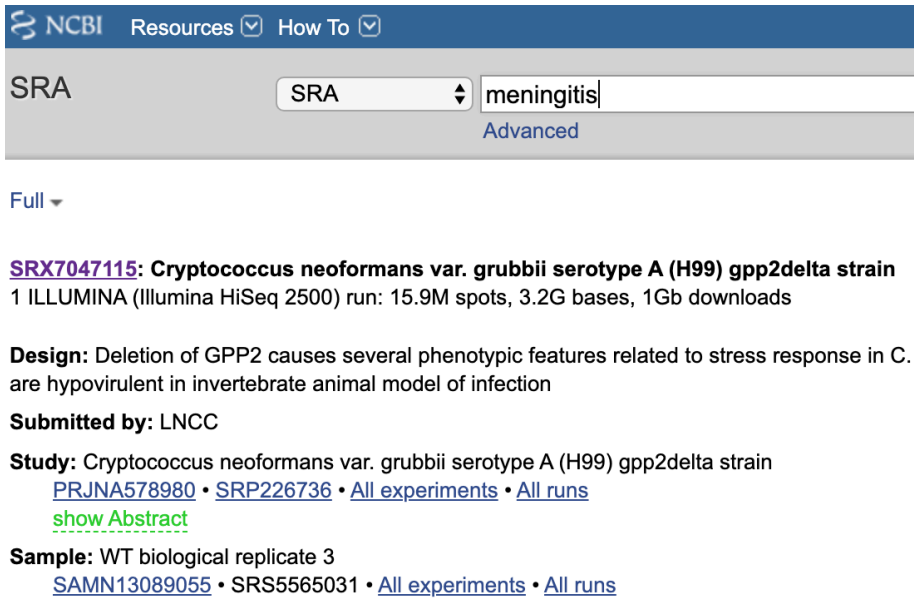
# Shared does not mean discoverable

**Archival:** via random pages that may never be found

**Discovery:** via centralized repositories with complete metadata allowing discovery via search tools




Archived

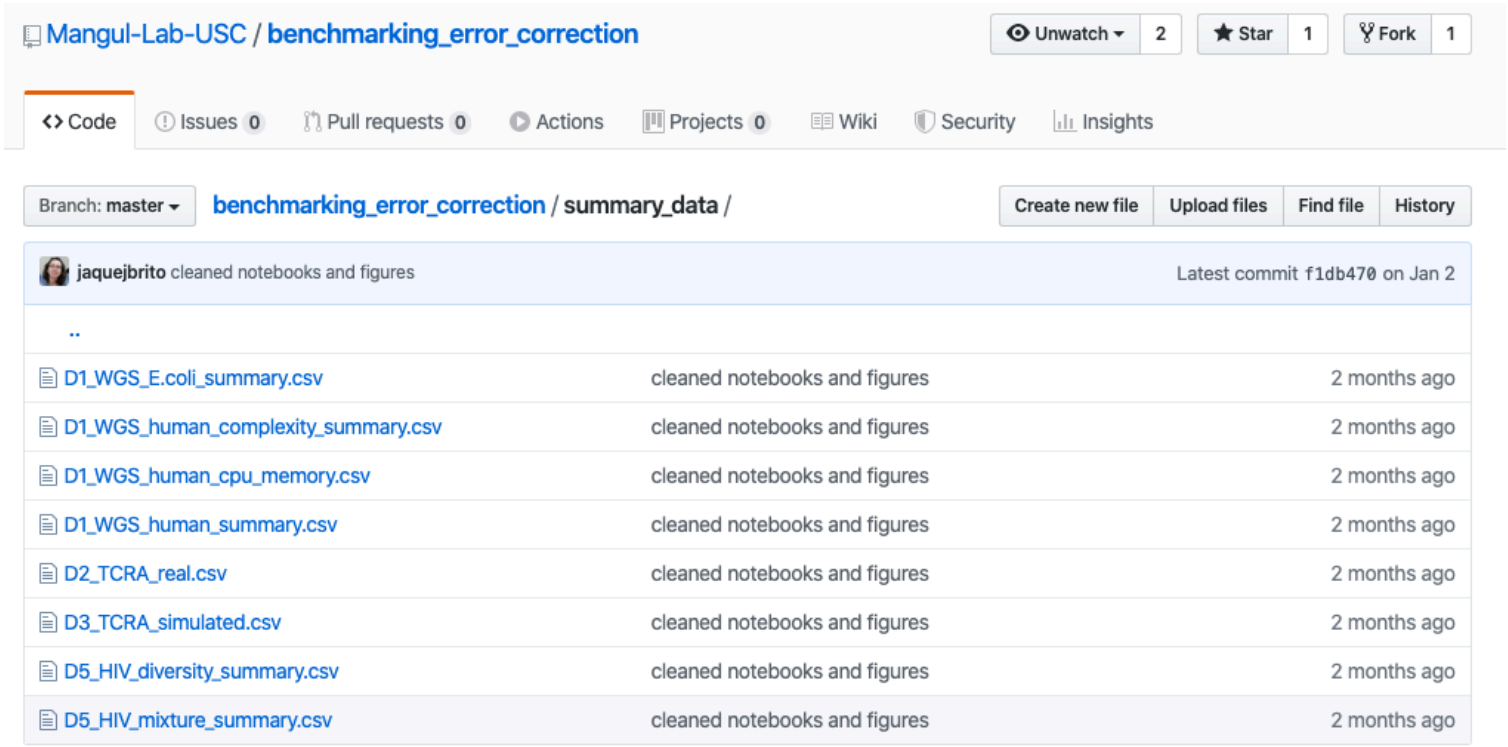



Discoverable

# Sharing processed data (summary statistics)

## Usually small files

### Example: GitHub



# Sharing processed data (summary statistics)

Branch: master ▾ benchmarking_error_correction / summary_data / D1_WGS_E.coli_summary.csv  Find file  Copy path

jaquejbrito cleaned notebooks and figures  f1db470 on Jan 2

1 contributor

301 lines (301 sloc) | 62.9 KB  Raw  Blame  History

Search this file...

| | | EC Filename | Wrapper Name | Kmer Size | Read - TP | Read - TN | Read - FN | Read - FN WRONG | Read - FP | Read - FP IN |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 0 | bfc_wgsim_rl_100_cov_1_20.corrected.fastq | bfc | 20 | 265 | 28574 | 18139 | 3 | 209 | 0 |
| 3 | 1 | bfc_wgsim_rl_100_cov_1_22.corrected.fastq | bfc | 22 | 249 | 28596 | 18180 | 3 | 162 | 0 |
| 4 | 2 | bfc_wgsim_rl_100_cov_1_24.corrected.fastq | bfc | 24 | 236 | 28605 | 18186 | 3 | 160 | 0 |
| 5 | 3 | bfc_wgsim_rl_100_cov_1_26.corrected.fastq | bfc | 26 | 245 | 28630 | 18192 | 2 | 121 | 0 |
| 6 | 4 | bfc_wgsim_rl_100_cov_1_28.corrected.fastq | bfc | 28 | 223 | 28631 | 18219 | 2 | 115 | 0 |
| 7 | 5 | bfc_wgsim_rl_100_cov_1_30.corrected.fastq | bfc | 30 | 225 | 28634 | 18220 | 1 | 110 | 0 |
| 8 | 6 | bfc_wgsim_rl_100_cov_16_20.corrected.fastq | bfc | 20 | 265904 | 453943 | 27986 | 123 | 7086 | 0 |
| 9 | 7 | bfc_wgsim_rl_100_cov_16_22.corrected.fastq | bfc | 22 | 262422 | 453846 | 31428 | 113 | 7233 | 0 |
| 10 | 8 | bfc_wgsim_rl_100_cov_16_24.corrected.fastq | bfc | 24 | 258535 | 453754 | 35259 | 106 | 7388 | 0 |

# Sharing raw omics data

Sharing real data

- SRA (Short Sequence Archive)
- GEO (Gene Expression Omnibus)

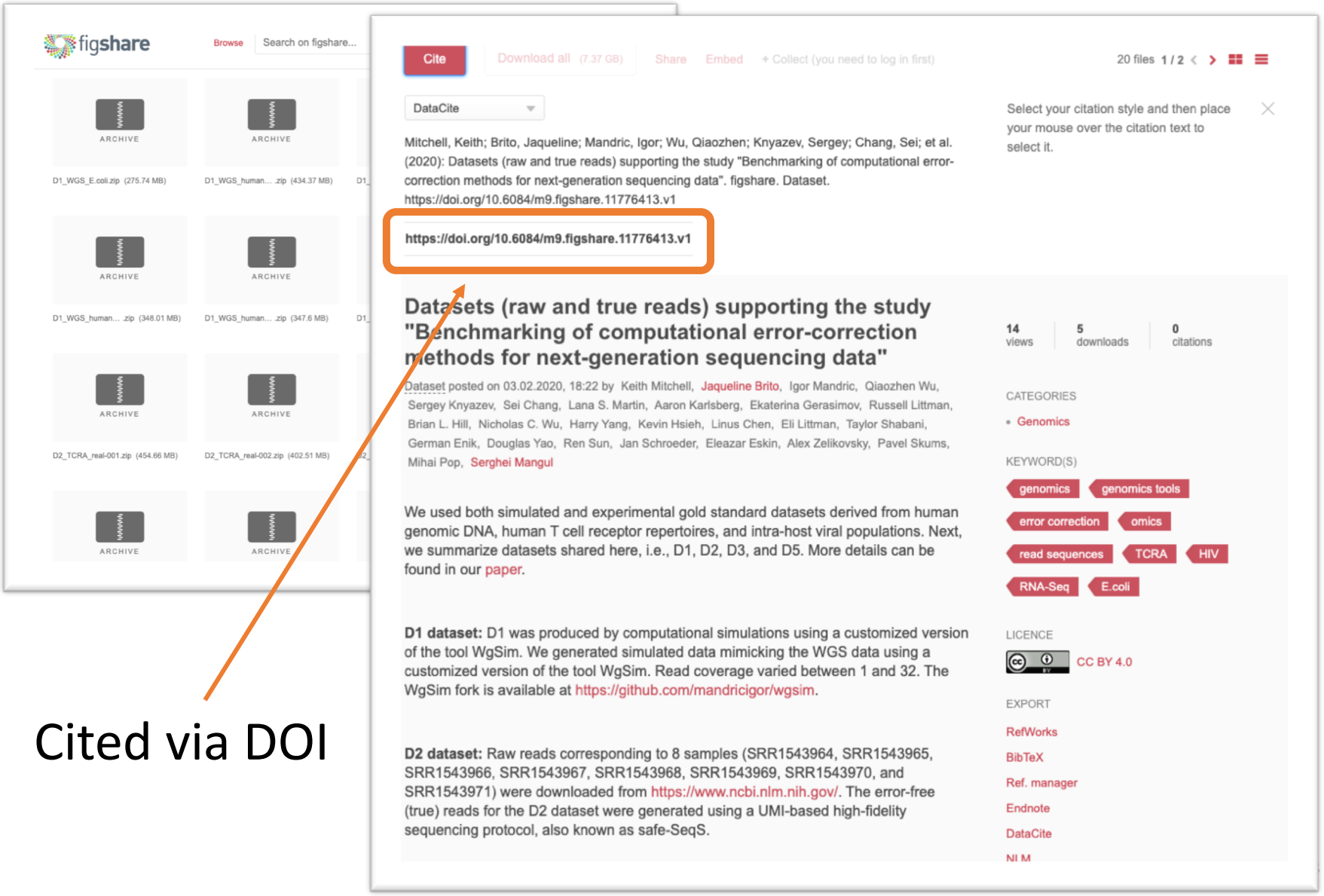
How do we share simulated/manipulated data?

- Platforms such as GitHub do not accept large files

Examples of platforms to store large data files

- Zenodo
- Figshare

# Sharing raw omics data

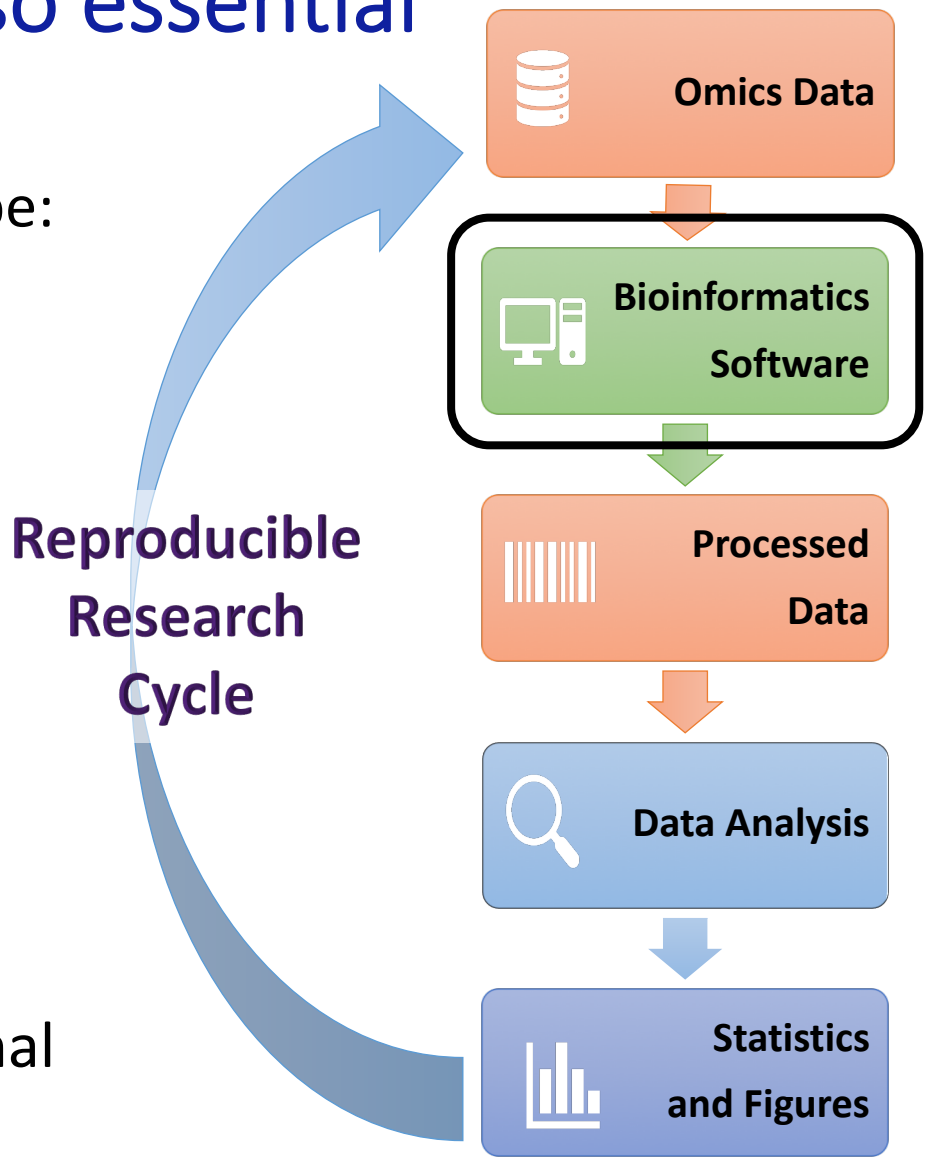



Cited via DOI

# Software access is also essential

Ideally, software sharing should be:

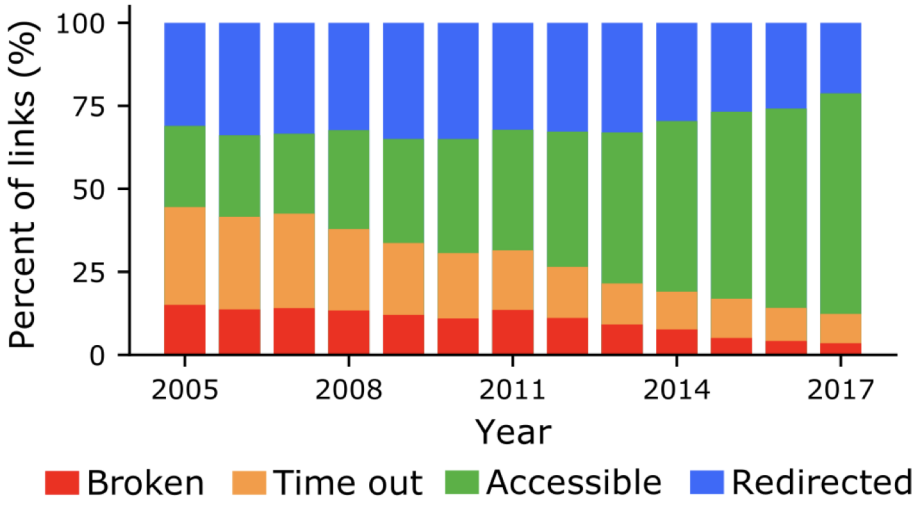
- Open-source
- Well documented
- Easy to install
- Maintained via centralized repositories
- Stored on archivally stable resources

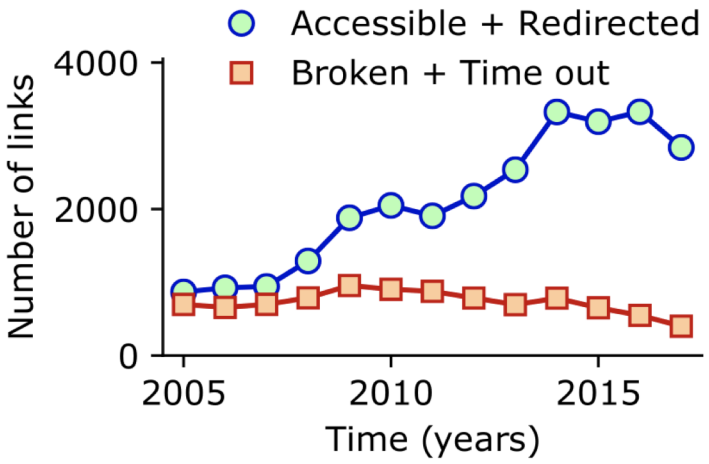



Limited software usability and archival stability of computational tools leads to computational reproducibility crisis

# Limited archival stability

Archival stability of 36,702 published URLs across 10 systems and computational biology journals over the span of 13 years

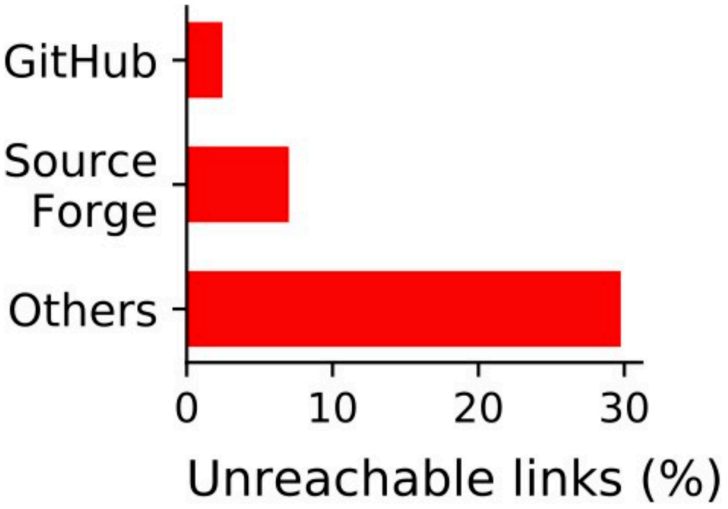


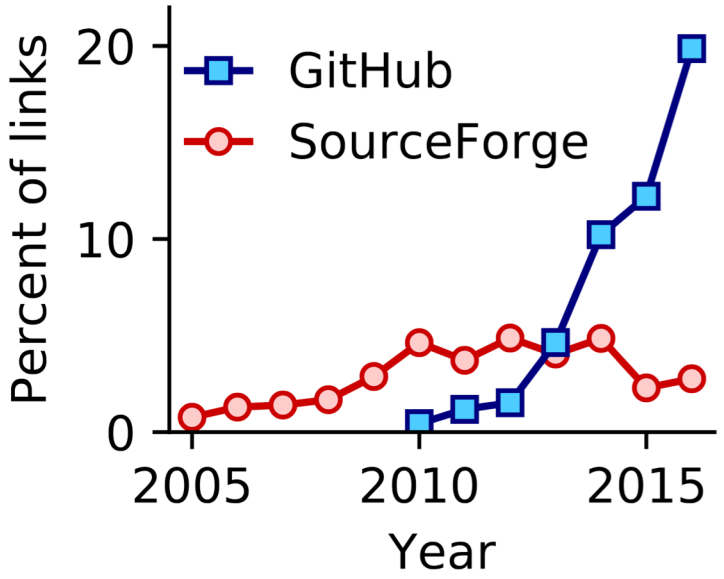




Source: Mangul, Serghei, et al. "Challenges and recommendations to improve the installability and archival stability of omics computational tools." *PLoS biology* 17.6 (2019): e3000333.

# Limited archival stability

Vast majority of URLs hosted on GitHub or SourceForge are archivally stable

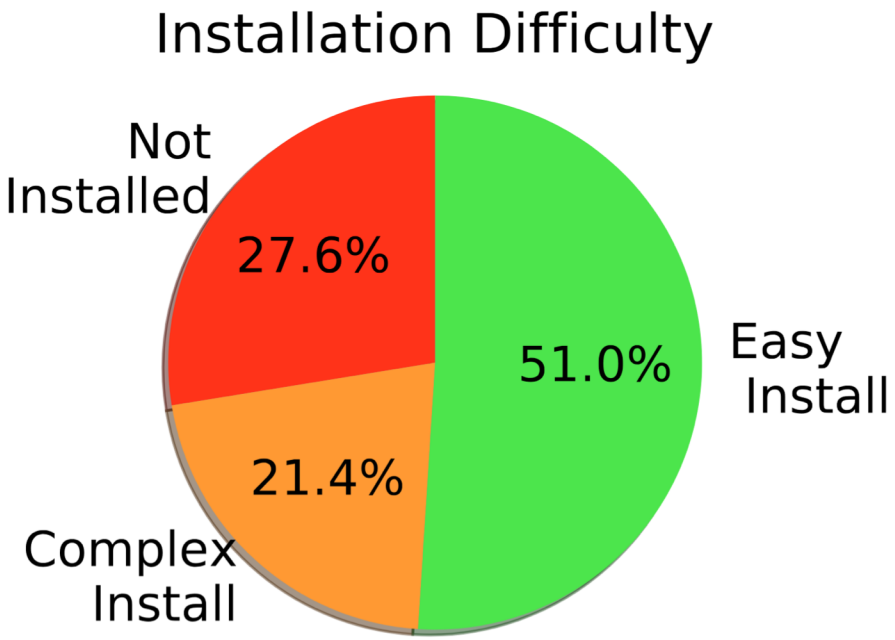



Source: Mangul, Serghei, et al. "Challenges and recommendations to improve the installability and archival stability of omics computational tools." *PLoS biology* 17.6 (2019): e3000333.

# Limited Usability

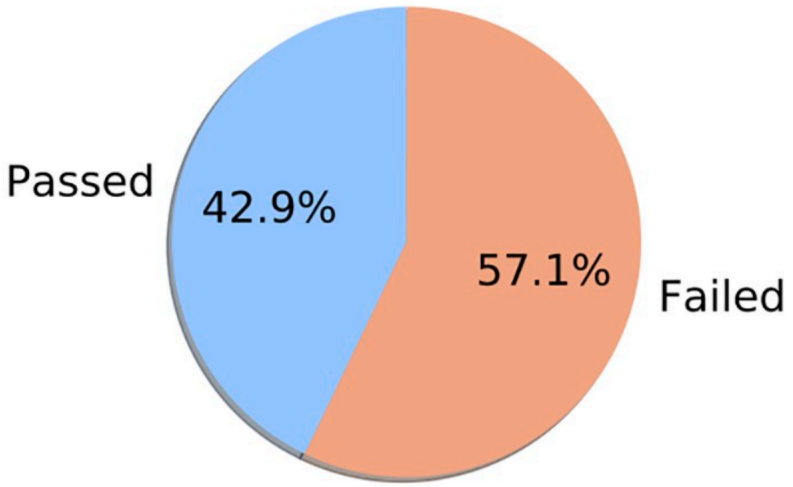
Many tools are hard or impossible to install

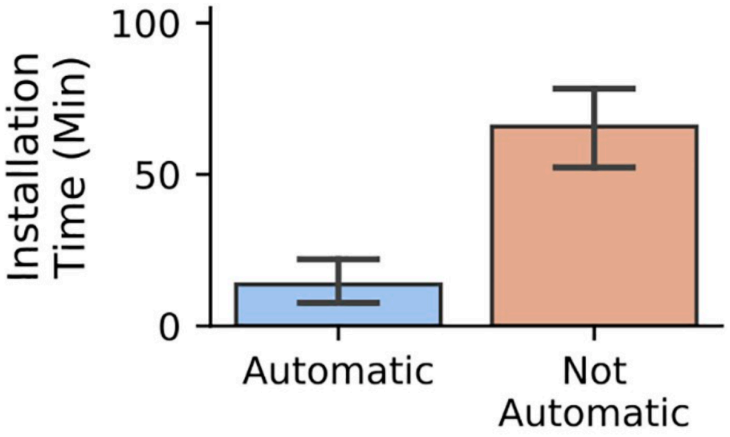



Source: Mangul, Serghei, et al. "Challenges and recommendations to improve the installability and archival stability of omics computational tools." *PLoS biology* 17.6 (2019): e3000333.

# Limited Usability

## Automatic installation test

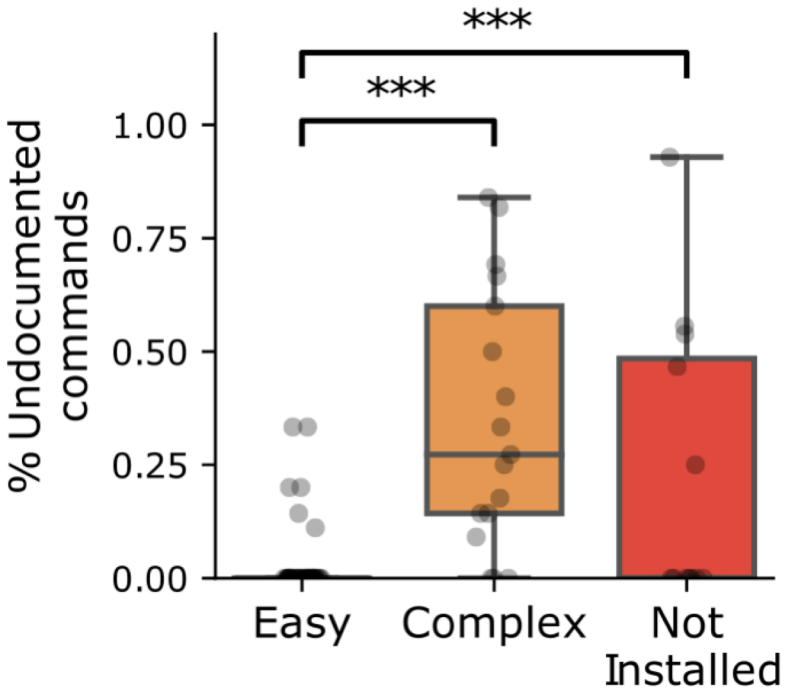



Source: Mangul, Serghei, et al. "Challenges and recommendations to improve the installability and archival stability of omics computational tools." *PLoS biology* 17.6 (2019): e3000333.

# Limited Usability

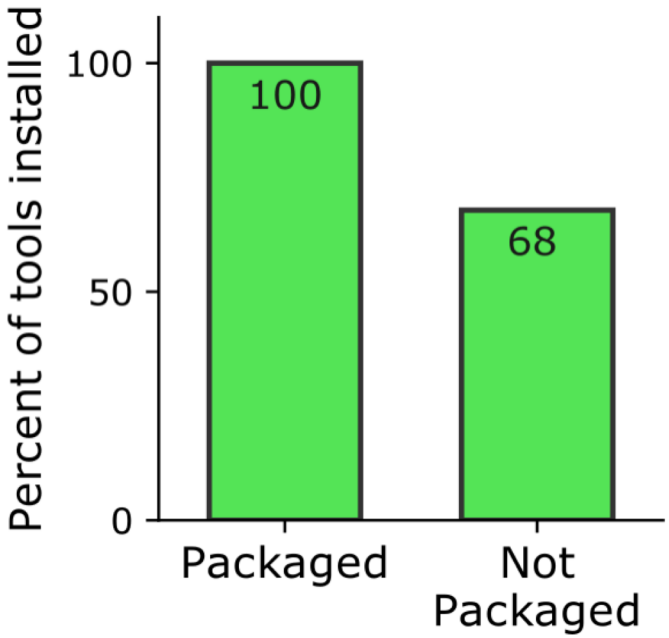
Tools easy to install have few undocumented commands




Source: Mangul, Serghei, et al. "Challenges and recommendations to improve the installability and archival stability of omics computational tools." *PLoS biology* 17.6 (2019): e3000333.

# Limited Usability

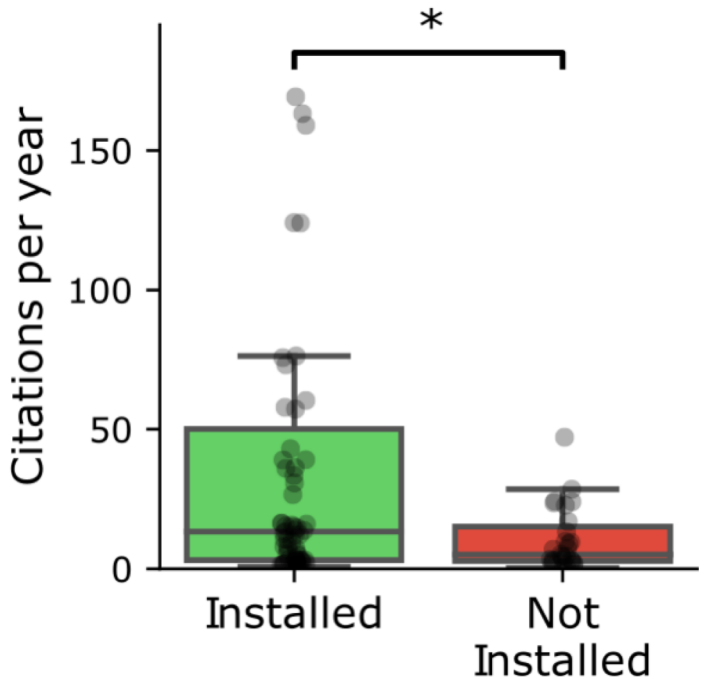
Bioconda tools were always installable




Source: Mangul, Serghei, et al. "Challenges and recommendations to improve the installability and archival stability of omics computational tools." *PLoS biology* 17.6 (2019): e3000333.

# Limited Usability

Installable tools are more cited and probably more likely to be reused

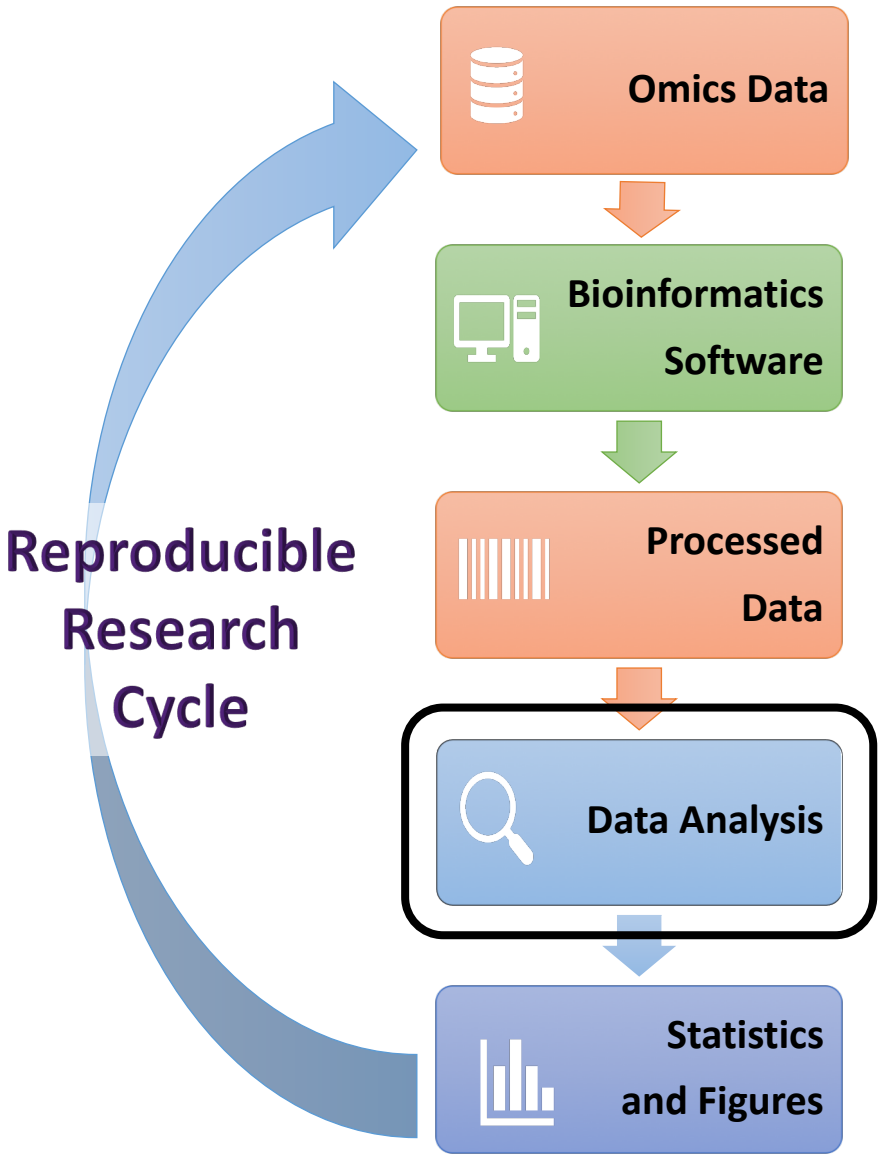



Source: Mangul, Serghei, et al. "Challenges and recommendations to improve the installability and archival stability of omics computational tools." *PLoS biology* 17.6 (2019): e3000333.

# Data Analysis

To reproduce the results one need to use the same data analysis procedures from the original publication

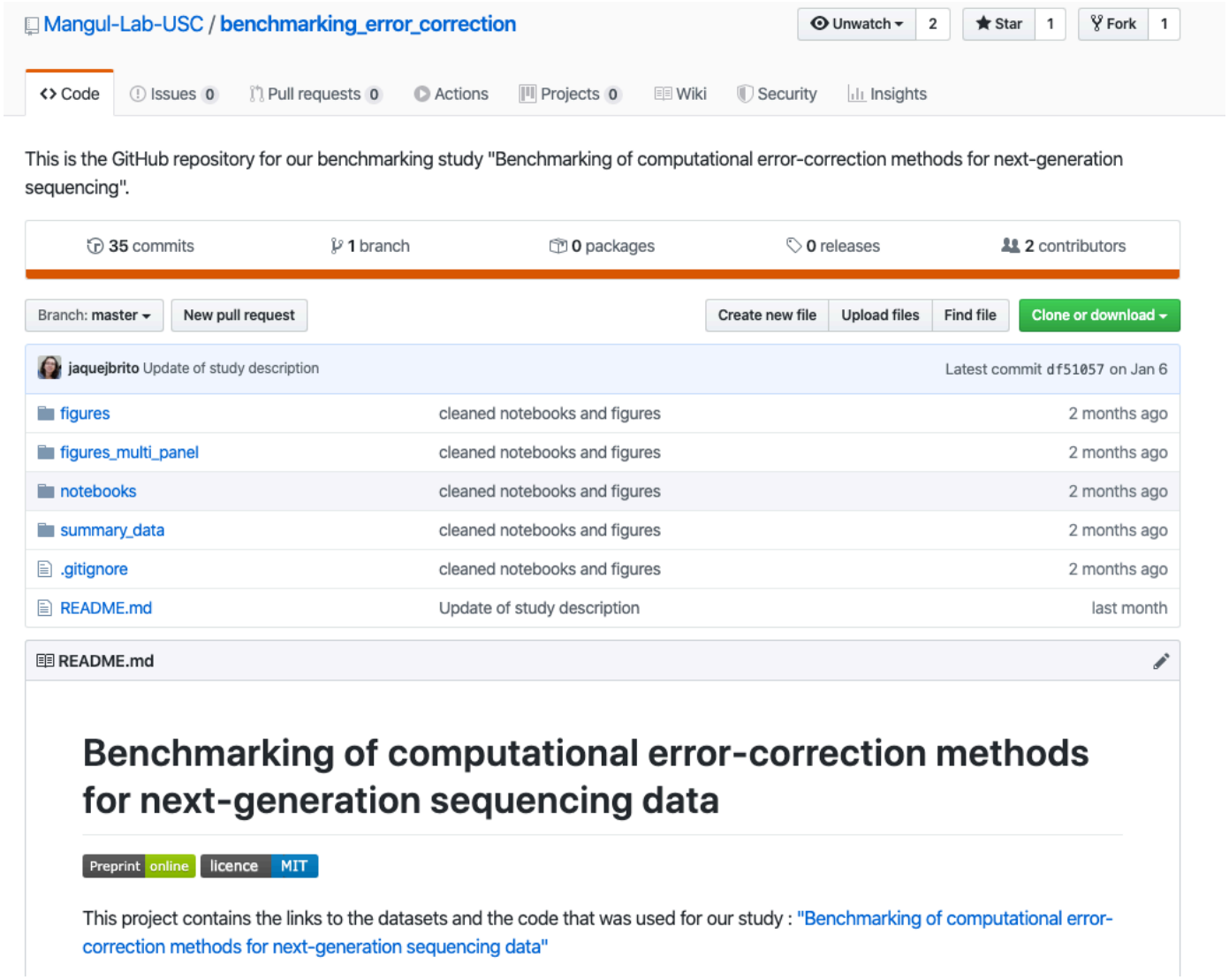
Interactive notebooks (e.g., Jupyter) allows straightforward way to reproduce the results



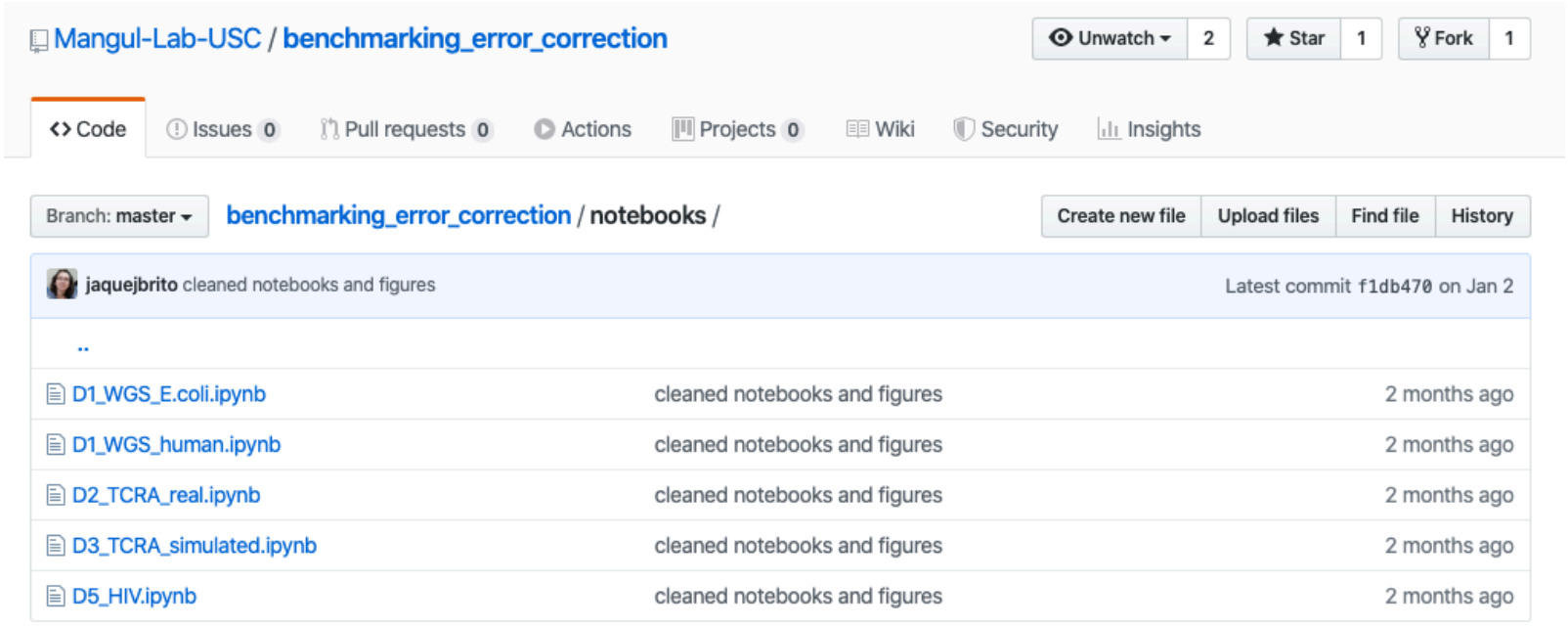
# Interactive notebooks allow us to go beyond reproducibility

- Easy change of parameters
- Check results' robustness
- Majority provide support to R and Python

# Jupyter Notebooks



# Jupyter Notebooks



# Jupyter Notebooks

422 lines (422 sloc) | 341 KB — Raw | Blame | History

## Dataset D1 - WGS E.coli

### Importing libraries

In [1]:
```
from __future__ import division
import pylab as pl
import numpy as np
import pandas as pd
import matplotlib.pyplot as plt
from scipy import stats
import math
import seaborn as sns
import os
```

### Data reading and cleaning

In [2]:
```
data = pd.read_csv('../summary_data/D1_WGS_E.coli_summary.csv')
data["Trim Effeciency"] = data["Base - TP TRIM"]/(data["Base - TP TRIM"] + data["Base - FP TRIM"])
data['total_corrections'] = data['Base - TP']+ data['Base - FP']
```

### Defining color dictionary

In [3]:
```
color_dict=dict({'Bfc':'purple','Bless':'orange','Coral':'brown','Fiona':'gray','Lighter':'pin
k','Musket':'blue','Pollux':'yellow','Racer':'green','Reckoner':'red','Sga':'black'})
```

### Selecting best kmer for each tool

In [4]:
```
data_best = data.loc[data.groupby(["Tool","Coverage"])["Base Gain"].idxmax()]
data_best = data_best.fillna(0)
```

# Jupyter Notebooks

## Figure 2g

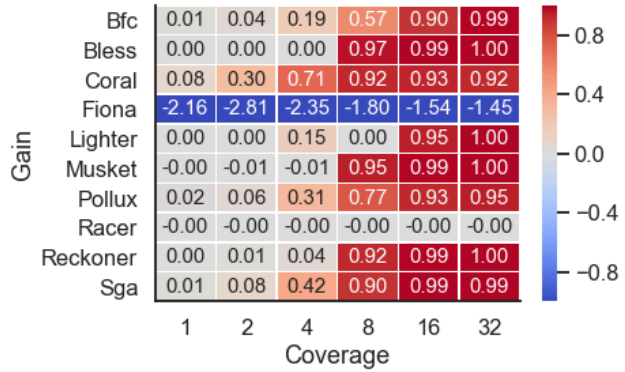
Heatmap depicting the gain across various coverage settings.
Each row corresponds to an error correction tool, and each column corresponds to a dataset with a given coverage.
For each tool, the best k-mer size was selected.

In [5]:
```
result = data_best.pivot(index='Tool', columns='Coverage', values='Base Gain') \
    .sort_values(by="Tool", ascending=False)

import matplotlib.pyplot as plt
import seaborn as sns
g=sns.set_style("white")
g=sns.set_context("talk")
g=sns.heatmap(result,
              annot=True,
              cmap='coolwarm',
              center=0,
              linewidths=.5,
              annot_kws={'size':15},
              fmt=".2f",
              vmin=-1,
              vmax=1)


g.set(xlabel='Coverage', ylabel='Gain')
g.set_ylim(0, 10)
g=sns.despine()

plt.savefig("../figures/D1_WGS_E.coli/Fig2g_heatmap_ecoli_gain.png", bbox_inches="tight")
plt.savefig("../figures/D1_WGS_E.coli/Fig2g_heatmap_ecoli_gain.pdf",bbox_inches="tight")
```



# What if we do reproducible research properly?

Enable secondary analysis

Potential for powerful discoveries in science in the dry lab settings

Accessible for labs in countries with limited resources

nature biotechnology

Career Feature | Published: 04 March 2019

CAREER FEATURE

**How bioinformatics and open data can boost basic science in countries and universities with limited resources**

Serghei Mangul, Lana S. Martin, Ben Langmead, Javier E. Sanchez-Galan, Ian Toma, Fereydoun Hormozdiari, Pavel Pevzner & Eleazar Eskin

*Nature Biotechnology* **37**, 324–326(2019) | Cite this article

**2160** Accesses | **4** Citations | **107** Altmetric | Metrics

**Providing training and access to standard computing hardware and cloud-based resources can enable scientists in lower-resource institutions and countries to reanalyze published '-omics' data and produce career-enhancing STEM research.**

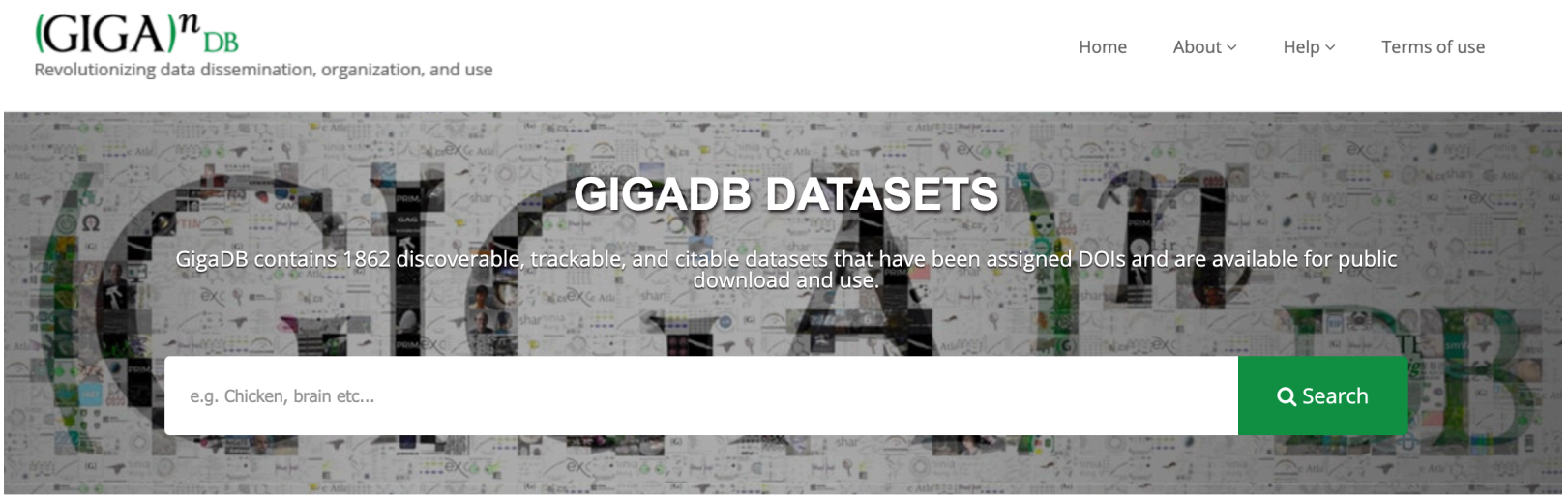
# Journal policies for ensuring and promoting reproducibility

Reproducibility can be assured upon publication


Various journals require sharing of materials

- Guidelines based on FAIR principles
- Badges to acknowledge reproducible studies

# Journal policies for ensuring and promoting reproducibility



# Supporting data for "Telescope: an interactive tool for managing large scale analysis from mobile devices"

Dataset type: Software
Data released on December 19, 2019

Brito JJ; Mosqueiro T; Rotman J; Xue V; Chapski DJ; la Hoz JD; Matias P; Martin LS; Zelikovsky A; Pellegrini M; Mangul S (2019):
Supporting data for "Telescope: an interactive tool for managing large scale analysis from mobile devices" GigaScience Database.
http://dx.doi.org/10.5524/100686

DOI 10.5524/100686

In today's world of big data, computational analysis has become a key driver of biomedical research. High-performance computational facilities are capable of processing considerable volumes of data, yet often lack an easy-to-use interface to guide the user in supervising and adjusting bioinformatics analysis via a tablet or smartphone. Telescope is a novel tool that interfaces with high-performance computational clusters to deliver an intuitive user interface for controlling and monitoring bioinformatics analyses in real-time. Telescope provides a user-friendly method for integrating computational analyses with experimental biomedical research.

Keywords:
bioinformatics job scheduler high throughput computing bioinformatics analysis

## Additional details

**Read the peer-reviewed publication(s):**

Brito, J. J., Mosqueiro, T., Rotman, J., Xue, V., Chapski, D. J., la Hoz, J. D., ... Mangul, S. (2020). Telescope: an interactive tool for managing large-scale analysis from mobile devices. GigaScience, 9(1). doi:10.1093/gigascience/giz163

**Additional information:**

https://scicrunch.org/resolver/RRID:SCR_017626

https://bio.tools/Telescope

**Github links:**

https://github.com/Mangul-Lab-USC/telescope

https://github.com/QCB-Collaboratory/telescope

Files Funding History

(FTP site) Table Settings

| File Name | Sample ID | Data Type | File Format | Size | Release Date | |
|---|---|---|---|---|---|---|
| readme_100686.txt | | readme.txt | TEXT | 1.76 KB | 2019-12-19 | |
| telescope-master.zip | | GitHub archive | archive | 1.27 MB | 2019-12-12 | |

# Improve support and acknowledgement

Producing reproducible research requires a lot of effort from researchers

Reality of most research groups

- Lack of experience on software development
- No knowledge of better practices for long-term maintenance

# Improve support and acknowledgement

There is a need of better mechanisms to support reproducibility

- Funding for building proper infrastructure
- Acknowledgement for producing reproducible research

Example: Research Parasite and Symbiotic Awards

- Recognizes rigorous secondary data analyses
- https://researchparasite.com/

Source: Greene, Casey S., et al. "Celebrating parasites." *Nature genetics* 49.4 (2017): 483-484.

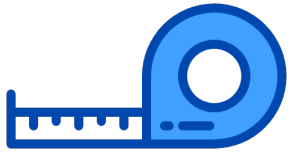
# Mechanisms for ensuring reproducibility

Variably enforced by academic institutions, funders and publishers

- Published software source code is unavailable
- Documentation is incomplete or unmaintained
- Analytical source code is missing

Who is responsible?

How can we measure reproducibility?



# Mechanisms for sustaining reproducibility

Where do you store the data and code from the studies?

- GitHub? SourceForge?

Is it sustainable to rely on commercial solutions?

Are these solutions sustainable in the long run?

What are the alternatives solutions?

# Beyond reproducibility

README.md

## Automated scholarly manuscripts on GitHub

manuscript HTML manuscript PDF

### Manuscript description

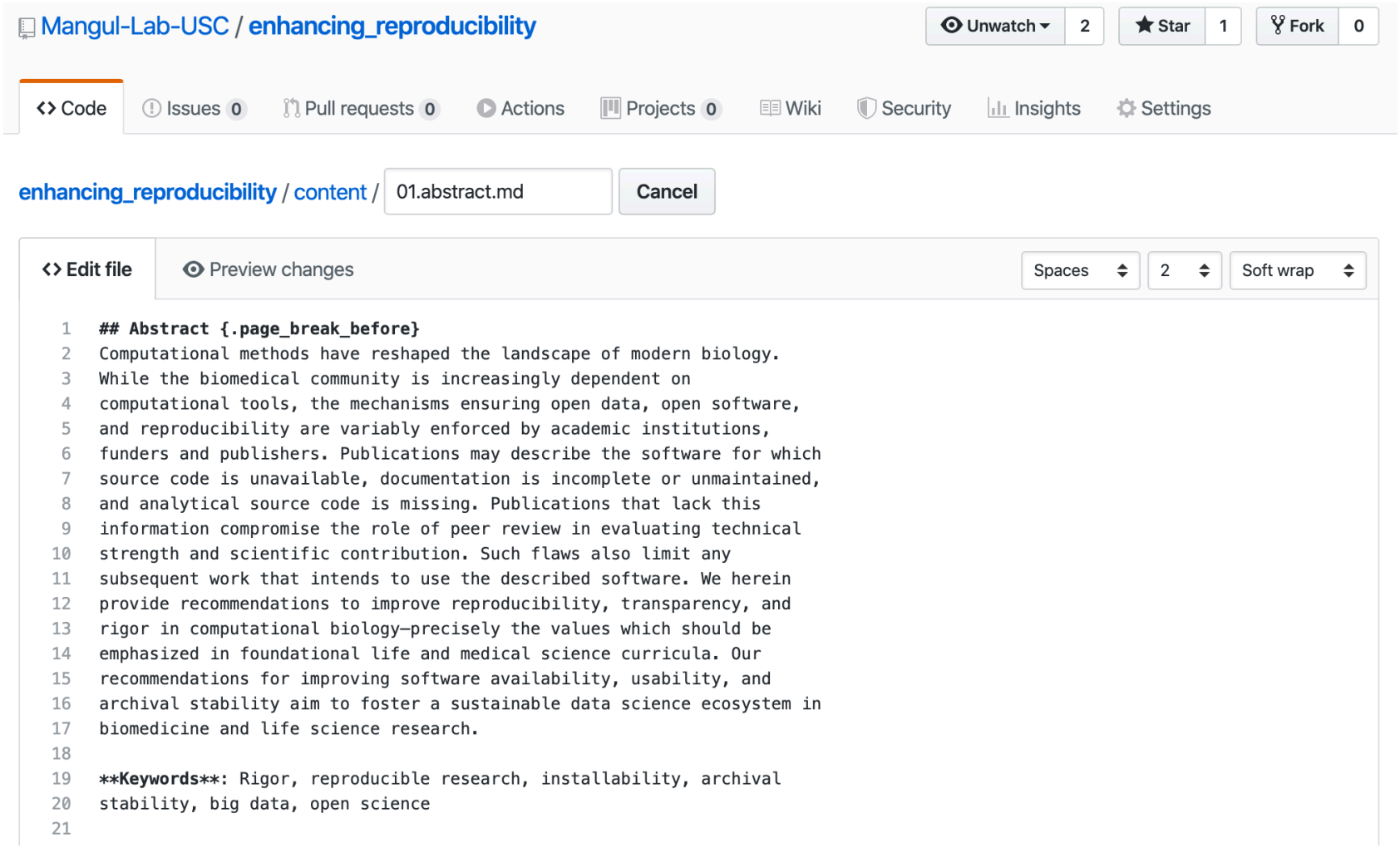
This repository is a dynamic version of the paper "Recommendations to enhance rigor and reproducibility in biomedical research" with an extended list of references.

### Manubot

Manubot is a system for writing scholarly manuscripts via GitHub. Manubot automates citations and references, versions manuscripts using git, and enables collaborative writing via GitHub. An overview manuscript presents the benefits of collaborative writing with Manubot and its unique features. The rootstock repository is a general purpose template for creating new Manubot instances, as detailed in `SETUP.md`. See `USAGE.md` for documentation how to write a manuscript.

Please open an issue for questions related to Manubot usage, bug reports, or general inquiries.

# Beyond reproducibility



# Beyond reproducibility

## Recommendations to enhance rigor and reproducibility in biomedical research

*This manuscript was automatically generated on February 23, 2020.*

### Authors

### 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 by academic institutions, funders and publishers. 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

# Our recommendations

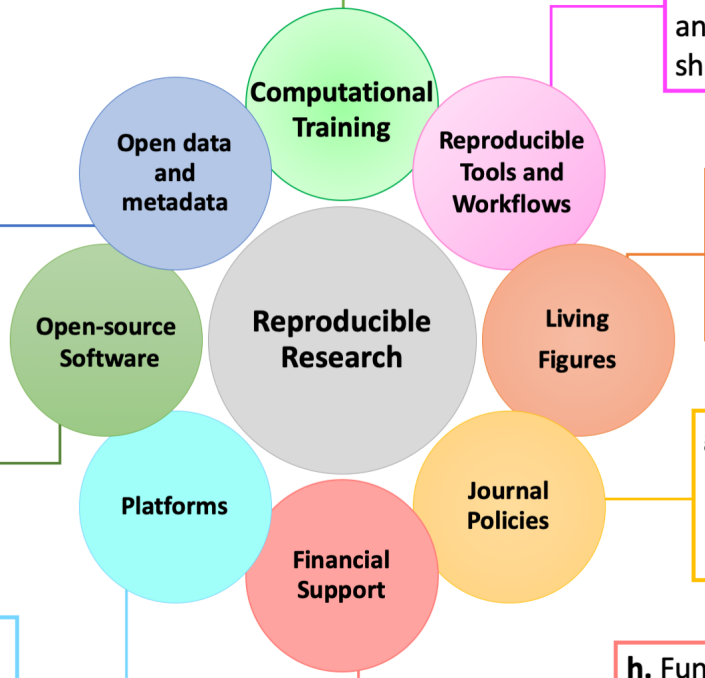
Main components we believe to be necessary for enhancing reproducibility

**a.** Researchers should acquire computational skills required to promote reproducibility on specialized training courses.

**b.** Data and metadata should be shared in an openly and discoverable manner via centralized repositories.

**c.** Software should be well documented and shared on an archivally stable platforms, under open source licenses.

**d.** Reusable resources should be shared on online platforms for long-term access and easy discover via digital identifiers.




**e.** Reproducibility can be facilitated with the use of virtual machines (VMs) and containers and platforms for sharing tools and workflows.

**f.** Presentation of results should be dynamic in the form of living figures where readers can alter code and parameters on the fly.

**g.** Researchers should publish with open access, and with journals that promote reproducibility aiming to increase the impact of their work.

**h.** Funding agencies need better mechanisms of acknowledging and incentivizing funding earmarked for critical bioinformatics infrastructure.

# Conclusions

Our recommendations aim 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, but incentives are not currently aligned to support good practices

Current efforts rely on effort of individual researchers

Successful systematic adoption of best practices will require the buy-in of multiple stakeholders from publishers, academic institutions, funding agencies

Community-wide adoption of best practices is essential to produce reproducible research

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