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Experimenting with Reproducibility: a case study of Robustness in Bioinformatics

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Abstract:

Reproducibility has been shown to be limited in many scientific fields. This question is a fundamental tenet of the scientific activity, but the related issues of reusability of scientific data are poorly documented. Here, we present a case study of our difficulties to reproduce a bioinformatics method [1] although code and data were available. First, we tried to re-run the analysis with the code and data provided by the authors. Second, we reimplemented the whole method in a Python package to avoid dependency on a MATLAB license and ease the execution of the code on HPCC (High-Performance Computing Cluster). Third, we assessed reusability of our reimplementation and the quality of our documentation, testing how easy it would be to start from our implementation to reproduce the results. In a second section, we propose solutions from this case study and other observations to improve reproducibility and research efficiency at the individual and collective level.

While finalizing our code, we created case specific documentation and tutorials for the associated Python package StratiPy. Readers are thus invited to experiment our reproducibility case study by generating the two confusion matrices of Fig 3 (see more in 2.2.2).

Here we decided to propose two options: 1) a step-by-step process to follow in a Jupyter/IPython notebook; or 2) a Docker container ready to be built and run.

Availability: last version of StratiPy (Python) with two examples of reproducibility and dataset are available at GitHub [2] and Zenodo [3].

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If not, please give reasons for any omissions below. as follow-up to "**Experimental design and statistics** Full details of the experimental design and statistical methods used should be given in the Methods section, as detailed in our Minimum Standards Reporting Checklist. Information essential to interpreting the data presented should be made available in the figure legends. Have you included all the information requested in your manuscript? "	This review is especially based on the reproducibility issues. The illustrated method is directly based on the original paper by Hofree et al, 2013. We nevertheless described any specific variations.
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Availability of data and materials All datasets and code on which the conclusions of the paper rely must be either included in your submission or deposited in publicly available repositories (where available and ethically appropriate), referencing such data using a unique identifier in the references and in the “Availability of Data and Materials” section of your manuscript. Have you have met the above requirement as detailed in our Minimum Standards Reporting Checklist?	Yes

Experimenting with Reproducibility: a case study of Robustness in Bioinformatics

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Abstract

Reproducibility has been shown to be limited in many scientific fields. This question is a fundamental tenet of the scientific activity, but the related issues of reusability of scientific data are poorly documented. Here, we present a case study of our difficulties to reproduce a bioinformatics method [1] although code and data were available. First, we tried to re-run the analysis with the code and data provided by the authors. Second, we reimplemented the whole method in a Python package to avoid dependency on a MATLAB license and ease the execution of the code on HPCC (High-Performance Computing Cluster). Third, we assessed reusability of our reimplementation and the quality of our documentation, testing how easy it would be to start from our implementation to reproduce the results. In a second section, we propose solutions from this case study and other observations to improve reproducibility and research efficiency at the individual and collective level.

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Keywords

- Reproducibility
- Robustness
- Reusability
- Network Based Stratification (NBS)
- Standard consensus dataset
- Cancer

1 Background

The collective endeavor of science depends on researchers being able to replicate the work of others. In a recent survey of 1,576 researchers, 70% of them admitted having difficulty in reproducing experiments proposed by other scientists [4]. For 50%, this reproducibility issue even concerns their own experiments. Despite the growing attention on the replication crisis in science [5,6], this controversial subject is far from being new: already in the 17th century, scientists criticized the air pump invented by physicist Robert Boyle because it was too complicated and expensive to build [7].

Several concepts for reproducibility in computational science are closely associated [8,9]. Here we define them as mentioned by K. Whitaker [9]: obtaining the same results using same data and same code is ***Reproducibility***; if code is different, it is ***Robustness***. If we used different data but with the same code, it is ***Replicability***. Lastly, using different data and different code is referred as ***Generalizability***. Here we will primarily elaborate on ***Reproducibility*** and ***Robustness***, and acknowledge that new datasets or hardware environment introduce additional hurdles [10]. Reproducibility is a key first step, for instance, among the 400 algorithms published during the major artificial intelligence conferences, only 6% offered the code [11]. Even when authors provide data and code, the outcome can vary either marginally or fundamentally [12]. Tackling irreproducibility in bioinformatics thus requires considerable effort beyond code and data availability, an effort that is still poorly recognized in the current publication based research community. In most cases, there is a significant gap between apparent executable work (Fig 1 - i.e. above water portion of iceberg) and necessary effort in practice (Fig 1 - i.e. full iceberg). Such effort is nevertheless necessary to increase the consistency of the literature and *efficiency* of the scientific research process by making research products easily resuable.

2 Reproducibility and Robustness in bioinformatics: a case study

2.1 Reproducibility: from MATLAB to MATLAB, OS and environment

Our team studies Autism Spectrum Disorders (ASD), a group of neurodevelopmental disorders well known for its heterogeneity. One of the current challenges of our research is to uncover homogeneous subgroups of patients (i.e. stratification) with more precise clinical outcomes, improving their prognosis and treatment [13,14]. An interesting stratification method was recently proposed in the field of cancer research [1], where the authors proposed to combine genetic profiles of patients' tumors with protein-protein interaction networks to uncover meaningful homogeneous subgroups, a method called Network Based Stratification (NBS).

Before using NBS method on our data, we studied the method by reproducing results from the original study. We are very grateful to the main authors who kindly provided online all the related data and code, and gave us invaluable input upon request. The authors of this study did much more to help reproduce their results than is generally done. Despite their help we experienced a number of difficulties that we document here, hoping that this report will help future researchers to improve the reproducibility of results and reusability of research products.

The first step of our project was to execute the original method code with the given data: reproducibility (Table 1). To improve execution speed, the original authors used a library for MATLAB on a Linux platform, using executable compiled code MEX file [15]: MTIMESX [16], a library allowing acceleration of large matrix multiplication. MEX files however are specific to the architecture and have to be recompiled for each Operating System (OS). Since our lab was using Mac OS X Sierra, the compilation of this MEX file into a mac64 binary required a new version of MTIMESX. It was also necessary to install and to configure properly OpenMP [17], a development library for parallel computing. After this, the original MATLAB code was successfully run in our environment.

	Code	Data	Technical issues	Other issues
Reproducibility	Same: MATLAB	Same	**OS**: MEX file specificity linked to OS (e.g. Linux → OSX)	
Robustness	MATLAB → Python	Same	**File format**: we can load sparse matrices from *.mat* file but cannot save them into HDF5 using h5py package **Default parameters**: linkage method use for the hierarchical clustering • MATLAB (MathWorks): UPGMA (average) • Python (SciPy): single	• Metadata structure • Important parameter value not explained in the original paper • Remaining discarded work ('code ruins') and traces of debugging
Reproducibility of Robustness	Same: Python	Same	**OS:** Numpy package and BLAS library compiled for specific OS (e.g. OSX → Linux)	Documentation

Table 1: Technical problems encountered during our reproducibility and robustness case study.

These issues are classic but may not be overcome by researchers with little experience in compilation or installation issues. For these reasons alone, many individuals may turn down the opportunity of reusing code.

The next part will focus on code re-implementation, a procedure, which can help understanding the method, but is even more time consuming.

2.2 Robustness: from MATLAB to Python, language and organization

To fully master the method, we developed a complete open source toolkit of genomic stratification in Python [2]. Python is also an interpreted programming language, but contrary to MATLAB is free of use and has a GPL-compatible license [18], which fosters both robustness and generalizability. Recoding in another language in a different environment will lead to be some unavoidable problems such as variation in low level libraries (e.g. glibc): it is likely that the outcomes will vary even if the same algorithm is implemented [19]. In addition, we rely on Python packages to perform visualization or linear algebra computations (e.g. Matplotlib, SciPy, NumPy [20–22]), and results may depend on these packages versions. Python is currently in a transitional period between two major versions 2 and 3. We chose to write the code in Python 3, which is the current recommendation.

2.2.1 Metadata and File formats

Even if the original code could be run, we had to handle several file formats to check and understand the structure of the original data. For instance the data was provided by The Cancer Genome (TCGA) [23] and made available in a MATLAB *.mat* file format as compressed data (sparse matrices). Thanks to SciPy, Python can load all versions through v7.2 MATLAB files, but to read v7.3 *.mat* files, we needed an HDF5 Python library. We decided to continue using Python's h5py package but Scipy's sparse matrices could not be stored in HDF5 format (Table 1). Moreover, the original authors had denoted download dates of patients' data of TCGA, thereby clarifying source of data. But in the absence of structural metadata, it was not always obvious how to interpret dataset variables (e.g. patient ID, gene ID, phenotype). Fig 2 shows an analogy between robustness issues and road transport: driving in a different environment (e.g. OS), we attempt to obtain identical results (i.e. to reach the same location) using the same input data (i.e. gasoline), but with different computational environment (i.e. cars), different implementation of the method (i.e. engine) and different programming languages (i.e. MATLAB and Python roads).

2.2.2 Codes and parameters

Once the environment, file format and data issues were resolved, the code was finally executed. Unfortunately, "unexpected" results were obtained. One cause was the application of the hierarchical clustering step for which we used the clustering tools of

SciPy. Both SciPy and MATLAB (MathWorks) functions offer seven linkage methods, however, SciPy's default option (single method) [24] differs from MATLAB's default option (UPGMA or average method) [25], which was used in the original study (Table 1). Another cause for the variation in results is the value of one of the most important parameters of the method, the graph regulator factor, which was not clarified in the original paper. From the article, we believed that this factor had a constant value of 1.0 until we found in the original code that its value varies across iterations and converges to an optimal value around 1800. Therefore, we initially obtained very different results from the original NBS (Fig 3 a) with heterogeneous subgroups. Once the optimal value was set up, we finally observed homogenous clusters (Fig 3 b). Moreover, during our attempts to run the original code to understand the causes of the errors, we realized that some parts of the code were not run anymore (e.g. discarded work, remaining traces of debugging) which made understanding the implementation harder.

To allow others to reproduce our results, we wrote some documentation and tutorials for the Python package *StratiPy* [2]. Readers are thus invited to experiment with reproducibility too by generating the two confusion matrices of Fig 3. They will use the different tools described in the following: GitHub, Docker, and Jupyter/IPython notebook.

2.2.3 Jupyter/IPython

During the re-coding process, we used an enhanced Python interpreter to debug: IPython, an interactive shell supporting both Python 2 and 3. Since the dataset is large and the execution takes a significant amount of time, we used IPython to re-run interactively some sub-sections of the script, which is one of the most helpful features. IPython can be integrated in the web interface Jupyter Notebook, offering an advanced structure for mixing code and documentation. While the Jupyter/IPython notebook was therefore initially convenient, it does not scale well to large programs and is not well adapted to versioning. However, ability of mixing code with document text is very useful for tutorials: a user of the code can read documentation (docstring), text explanations, and see how to run the code, explore parameters and visualize results in the browser. Our work on NBS, as related here, can be reproduced with a Jupyter/IPython notebook available on our GitHub [2]. One can find more examples and several helpful links on this "gallery of interesting Jupyter Notebooks" [26], which contains a section about "Reproducible academic publications".

2.3 Reproducibility of Robustness: from Python to Python

Besides Jupyter/IPython notebooks, we used versioning tools like the Git code version control system (VCS) to document the development of our Python code. Git is arguably one of the most powerful VCS, allowing easy development of branches and helping us to work together as a distributed team (Paris, Berkeley, Montreal) on the same project. This project, *StratiPy*, is hosted on GitHub, a web-based Git repository hosting service [2]. While the original code was not available on GitHub, the main authors shared their code on a website. This should be sufficient for our purpose but makes it less easy to collaborate on code. While working on our GitHub repository, researchers from USA, India, China, and Europe contacted us about our robustness

experiment. Not only GitHub supports a better organization of projects, it also facilitates the collaboration of open-source software projects, thanks to its social network functions [27]. We adopted open source coding standards and learnt how to efficiently use Git and GitHub. Both required considerable training efforts on the short-term but brought clear benefits on the long-term, especially regarding collaboration and debugging.

We then attempted to re-run and reproduce the results we obtained on another platform. While the Python code was developed under Mac OS X Sierra (10.12), we used an Ubuntu 16.04.1 (Xenial) computer to test the Python implementation. Some additional issues emerged (Table 1). First, our initial documentation did not include the list of the required packages and instructions to launch the code. Second, the code was very slow to the extent that it was impractical to run it on a laptop because the Numpy package had not been compiled with BLAS (Basic Linear Algebra Subprograms) that speeds up low-level routines performing basic vector and matrix operations. Last, there was (initially) no easy way to check whether the results obtained on a different architecture were the expected ones. We added documentation and tests on the results files md5sum to solve this. To summarize, although the reuse and reproducibility of the results of the developed package were improved, these were far from being optimal.

3 Potential solutions: from local to global

3.1 Act locally: simple practices and available tools

Given the observed difficulties, in this section we draw some conclusions on this reproducibility case study experiment and suggest some tools and best practices. In addition, we suggest to follow the programing best practices of Wilson et al. such as modularizing and re-using code, unit testing, document design, data management, and project organization [5,28]. Sandve and colleagues [29] also suggest to keep the data provenance with recording all intermediate results.

3.1.1 Environment

In 1995, Buckheit and Donoho were already thinking about reproducible research in computer science. Their motto was "When we publish articles containing figures which were generated by computer, we also publish the complete software environment which generates the figures" by offering a complete and free package (WaveLab) to reproduce the published output [30]. Container and virtual machines technologies such as Docker [31], Vagrant [32], Singularity [33,34] (easily works in cluster environments) are becoming a standard solution to installation issues. These rely however on competencies that we think too few biologists possess today. While a container might encapsulate everything needed for a software execution, it could be hard to develop in a container. For instance, running Jupyter/IPython notebooks in Docker's container requires knowledge on advanced port forwarding , which can be discouraging for some biologists. Therefore, we decided to propose two options in our example implementation of reproducibility: 1) a step-by-step process to follow in a Jupyter/IPython notebook; or 2) a Docker container

ready to be built and run. Nevertheless, mastering Docker –or other container tools– will become an important skill for computational reproducible researchers.

3.1.2 Metadata

Standard metadata are vital for an efficient documentation of both data and software. In our example, we still lack the standard lexicon to document the data as well as documenting the software. We however aim to follow the recommendations by Stodden *et al.* [35]: *"Software metadata should include, at a minimum, the title, authors, version, language, license, Uniform Resource Identifier/DOI, software description (including purpose, inputs, outputs, dependencies), and execution requirements".* The more comprehensive is the metadata description, the more likely the reuse will be both efficient and appropriate [36].

3.1.3 Write readable code

Anyone who has spent time to understand someone else's code would advise some simple basic rules to help make the code readable and understandable.

First, the structure of the program should be clear and easily accessible. Second, good concise code documentation and naming convention will help readability. Third, the code should not contain left-overs of previously tested solutions. When a solution takes a long time to compute, an option to store it locally can be proposed. Using standard coding and documentation conventions (e.g. PEP 8 and PEP 257 in Python [37,38]) with detailed comments and references of papers makes the code more accessible. When an algorithm is used, any modification from the original reference should be explained and discussed in the article as well as in the code. We advocate for researchers to write code "for their colleagues", hence, ask for the opinion and review of co-working or partner laboratories. Furthermore, the collaboration between researchers working on different environments can more easily isolate reproducibility problems. In the future, journals may consider review of code as part of the standard review process [39].

3.1.4 Test the code

To check if the code is yielding a correct answer, software developers associate test suites (unit tests or integration tests) with their software. While we developed only a few tests in this project, we realize that this has a number of advantages, such as checking if the software installation seems correct, check if updates in the code or in the operating system impact the results, etc. In our case, we propose to check for the integrity of the data and for the results of some key processing.

3.2 Think globally: from education to community standards

3.2.1 Training the new generation of scientists to digital tools and practices

The training in coding is still too limited for biologists. Often, it is self-training, from searching answers on Stack Overflow or equivalent. Despite efforts by organizations such as Software [40] or Data Carpentry [41] and the growing demand for 'data scientists' in life science, university training on coding practices is still not enough generalized. The difficulty to access and understand code may lead to applying code blindly without checking the validity of the results: often, scientists may prefer to believe that the results are correct because of the time that would be needed to check the validity of the results. Mastering a package such that results are truly understood can take a long time, as it was the case in our experiment.

Academia could instruct young scientists best practices for reproducibility. For instance, Hothorn and Leisch organized a reproducibility workshop gathering mostly PhD students and young postdocs specialized in bioinformatics and biostatistics. Then they evaluated 100 random sample papers from *Bioinformatics* [6]. Their study revealed how such a workshop can raise young scientists awareness about *"what makes reproduction easy or hard at first hand"*. Indeed, they found out that only a third of the original papers and two-thirds for applications notes had given access to the source code of software used.

3.2.2 Standard consensus dataset and testing ecosystem

We propose here that bioinformatics methods publications are systematically accompanied with a test dataset, code source and some basic tests. As the method is tested on new datasets, the number of tests of the method would increase in number and cover a wider range of applications. We give a first example with our NBS re-implementation. We develop below how this could generalize and what would be the benefit for the scientific community.

A schematic overview of a possible testing ecosystem is shown in Fig 4. The core of this system would be a set of standard consensus datasets used to validate methods. For instance in the field of machine learning, standard image databases are widely used for training and testing (e.g. MNIST for handwritten digits [42]). In the case of our proposal, data could be from different categories such as binary, text, image (shown as folders in different colors, Fig 4 b), and sub-categories to introduce criteria such as size, quantitative/qualitative, discrete/continuous using a tagging system. Datasets could be issued from simulations or from acquisition, and would validate a method on a particular component. This testing ecosystem will help scientists that cannot release their data because of privacy issues (Fig 4 a.1) (although these can often be overcome) but also give access to data and tests to a wide community including establishments with weak financial means.

We divide those who interact with scientific software or analysis code in two broad categories. First, the authors ("A") who propose a method and need to verify its validity and usefulness with open and/or private – data. Second, the users ("U", e.g. developers, engineers, bioinformaticians) who need to test and evaluate the proposed methods with other data.

When authors propose a new method, this method could have a reproducibility profile, which will progressively be built by authors and users (Fig 4 b.3, b.4). The information of which method does or does not work with well identified data is crucial for future work. During the optimization of a project, the software code and associated documentation should be accessible to foster collaboration on additional use cases and data. When the work achieve some level of maturity, a full fledge article can be posted on a preprint servers such as bioRxiv [43,44] and be associated with a GitHub repository by digital object identifiers (DOI). With considerable effort, Stodden *et al.* conducted a reproducibility study on 204 random articles of Science: despite some availability of the code, it had often been changed after publication, causing difficulties in replication [45]. In our proposed testing ecosystem, users will be able to launch reproducibility projects more easily thanks to code and article versioning.

Users who test and approve reproducibility on original or new data could be credited and recognized by the scientific and developer communities (i.e. Stack Overflow, GitHub). This testing ecosystem could thus facilitate collaborations between methodology development and biological research communities.

4 Conclusion and perspective

In the 19th century, Pasteur introduced a detailed "Methods" section in his report: this advanced approach was necessary to reproduce his experiments and became new norms in the philosophy of science [46]. Today with the advent of computational science, the reproducibility issue is seen as a growing concern. Before reusing a published method, we attempted to reproduce the initial results and recoded the method to have a deep understanding of it. The investment in time to verify a previously published method can be as or even more important than the work needed to publish a new paper. Despite the willingness of the authors to share their tool and help us in our work, we have faced computational reproducibility and robustness problems due to compatibility between environments, programming languages and software versions, choice of parameters, data identification, etc. In addition to individual effort to write well documented and readable code, we recommend to use online repositories and tools to help other scientists in their exploration of the method: Docker for environment standardization, GitHub for code version management, and Jupyter notebooks for demonstration and tutorial [26,27,31]. We suggest to adopt such practices, not only for writing code but also manuscripts [5]. At the community level, we should enhance the cooperation between academic education and industry to foster a new generation of well-trained scientists in software development. For instance, Academia-Industry Software Quality & Testing summit (AISTQ) organizes conference in order to encourage collaboration between Academia and Industry [47]. This is also in line with the work of the Software or Data carpentry organizations [40,41]. Here, we propose a testing ecosystem where the community uses standard, well-identified datasets to validate tools and their versions. The scope of a proposed method could be continuously evaluated on new datasets. Eventually, data and software can be versioned and cited to give credit to the individuals who have contributed to these building blocks of Science. This testing ecosystem is not only a reproducibility validation tool; it is an attempt to make research product more reusable using online platforms and open source tools, beyond the publication of a PDF file. Such system could be seen as a generalization of already existing workflow systems

such as Galaxy or GATK, integrating data and software provenance [48,49]. Some top-down initiatives already provide some incentives for such a process i.e. Horizon 2020 (H2020) [50] project of the European Commission (EC) mandates open access of research data, while respecting security and liability. H2020 supports OpenAIRE [51] a technical infrastructure of the open access, which allows the interconnection between projects, publications, datasets, and author information across Europe. Thanks to common guidelines, OpenAIRE interoperates with other web-based *generalist* scientific data repositories such as Zenodo, hosted by CERN, which allows combining data and GitHub repository using DOI. The Open Science Framework also hosts data and software for a given project [52]. Respecting standard guidelines to transparently communicate the scientific work is a key step towards tackling irreproducibility and insures a robust scientific endeavor.

Key points

- Main barrier for reproducibility is in the lack of compatibility between environments, programming languages, software versions, etc.
- At the individual level, the key is in research practices such as well written, tested and documented code, and well curated data and the use of online repositories and collaborative tools.
- At the community level, we propose a testing ecosystem where standard consensus datasets are used to validate new methods and foster their generalizability.

Declarations

Ethics approval and consent to participate

We used the uterine endometrial carcinoma data as they were downloaded on January 1st, 2013 from the The Cancer Genome Atlas (TCGA) portal by Hofree and colleagues [1].

Consent for publication

Not applicable

Availability of data and material

Last version of StratiPy (Python) with two examples of reproducibility and dataset are available at GitHub [2].

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Y-M. K., J-B. P., and G.D. wrote the manuscript, Y-M. K. and G.D. developed the StratiPy module.

All authors read and approved the final manuscript.

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Keywords: Autism Spectrum Disorder; Network; Protein-Protein Interaction; Personalize Medicine; Network-Based Stratification; Computational Biology.

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Figure legends

Figure 1: Hidden reproducibility issues like underwater iceberg. Scientific journals readers have the impression that they can almost see the full work of method. But in reality, articles do not take into account adjustment and configuration for significant replication in most cases. Therefore, there is a significant gap between apparent executable work (i.e. above water portion of iceberg) and necessary effort in practice (i.e. full iceberg).

Figure 2: Analogy between robustness issues and road transport. The aim is to achieve same output (i.e. to reach the same location) using published methods (i.e. engine). Despite the same input data (i.e. gasoline), we obtained different results due to different programming languages —e.g. MATLAB and Python— (i.e. different roadways) and environments (i.e. different vehicles).

Figure 3: Normalized confusion matrices between original and replicated results. Before (a) and after (b) applying appropriate value of graph regularization factor on NBS method. Each row or column corresponds to a subgroup of patients (here three subgroups). The diagonal elements show the frequency of correct classifications for each subgroup: a high value indicates a correct prediction.

Figure 4: Working principles of testing ecosystem with private data. Figure 4a shows a classical case: (a.1) Authors take private data (e.g. blue data) then publish their method and corresponding results; (a.2) Users having their own data (e.g. orange data) find a relevant paper but will be lost in the labyrinth of reproducibility. Figure 4b shows testing ecosystem with standard consensus dataset: (b.1) If authors work with their own data, they must identify corresponding standard data tag(s) (e.g. blue data); (b.2) Authors initiate to develop their method with corresponding standard data and reproducibility profile will be progressively built. Bar length on iceberg corresponds to progression of replication test; (b.3) Users can test proposed method with other standard data (e.g. orange and green data) and thus participate to enhancement of the reproducibility profile; (b.4) Thanks to the collective work on testing, the method could be optimized and authors can upgrade their initial paper (versioning).

Figure 2

Click here to download Figure fig2_cars_lzw.tif

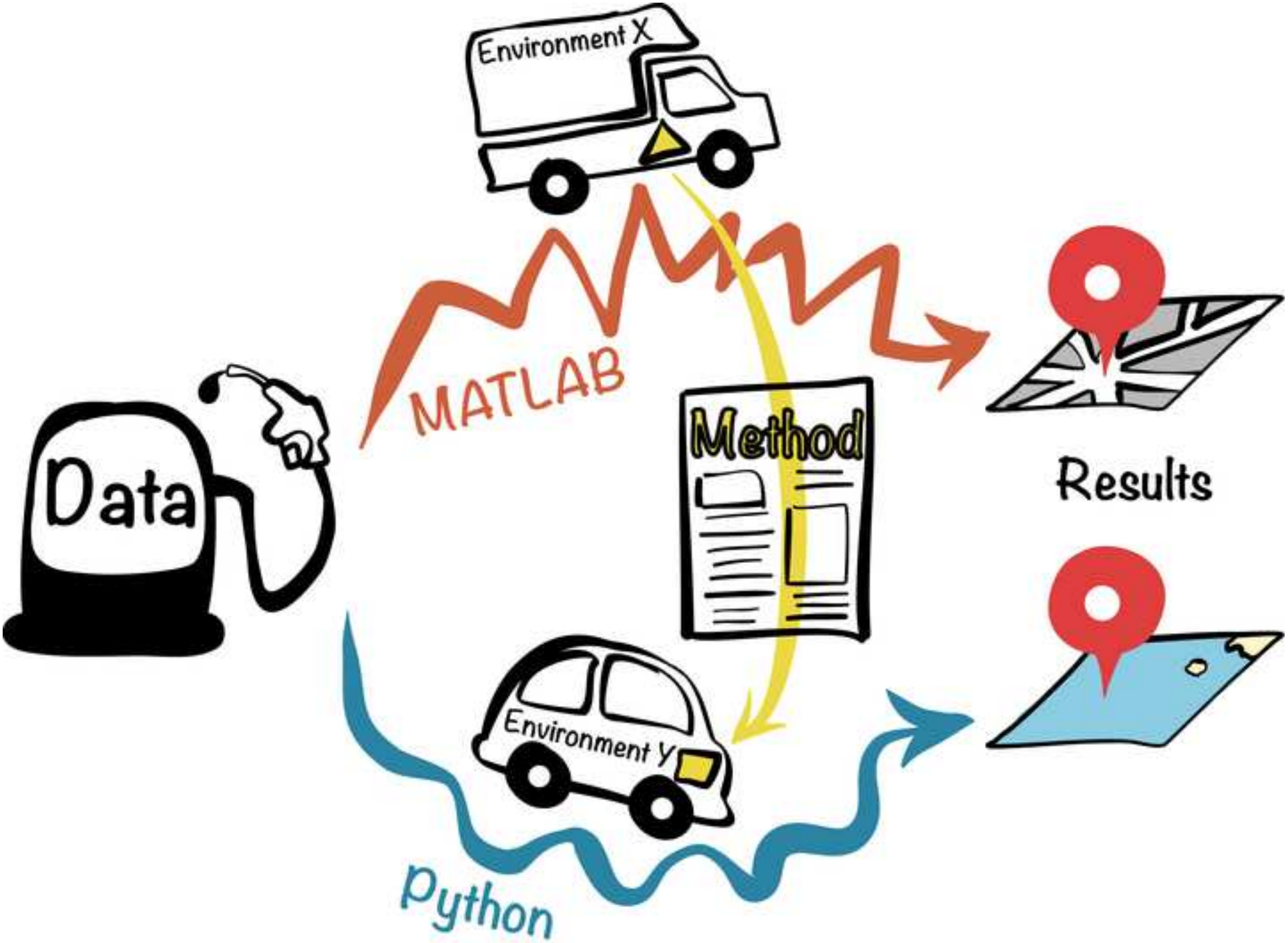

Figure 3

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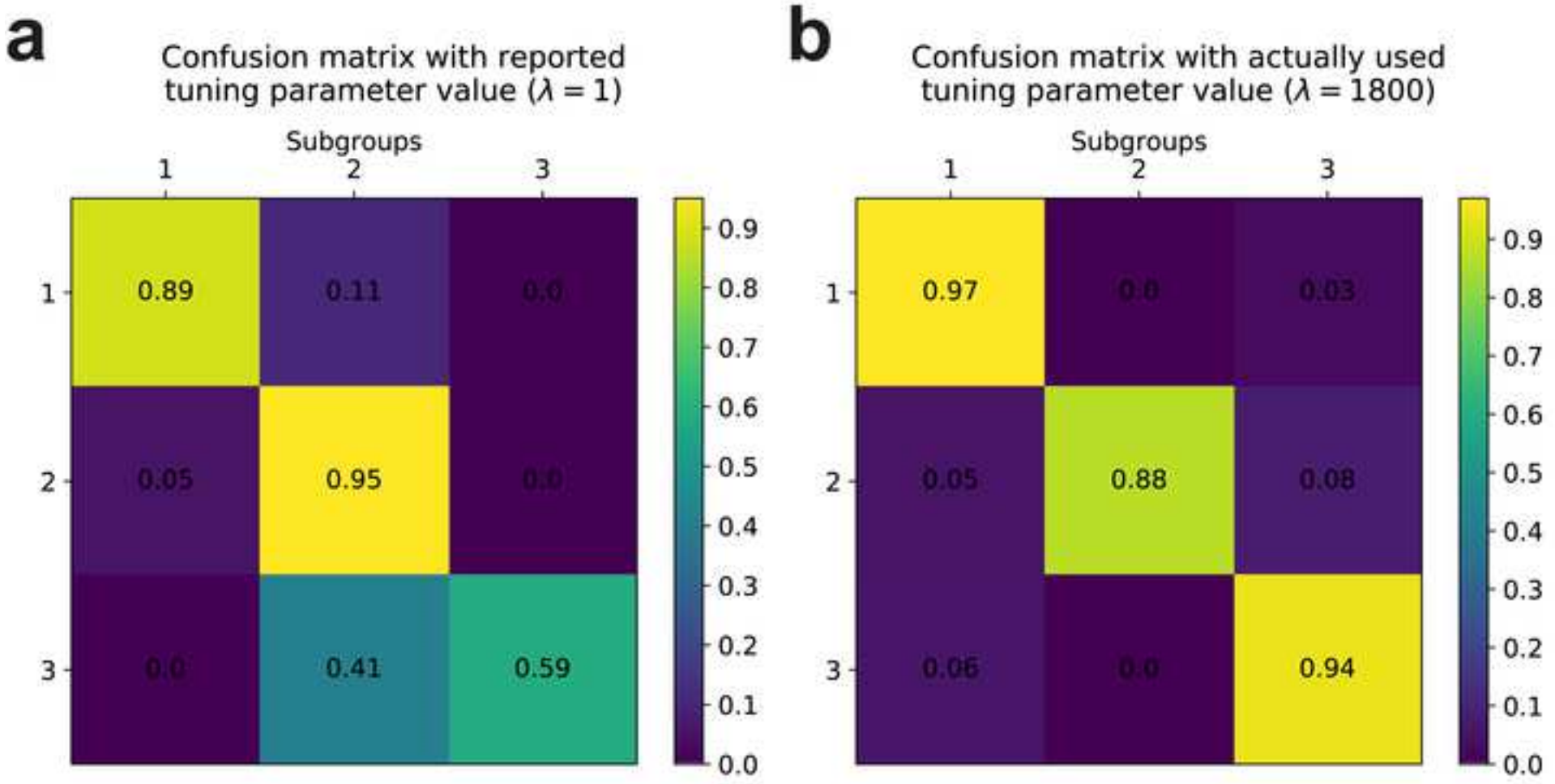

Figure 1

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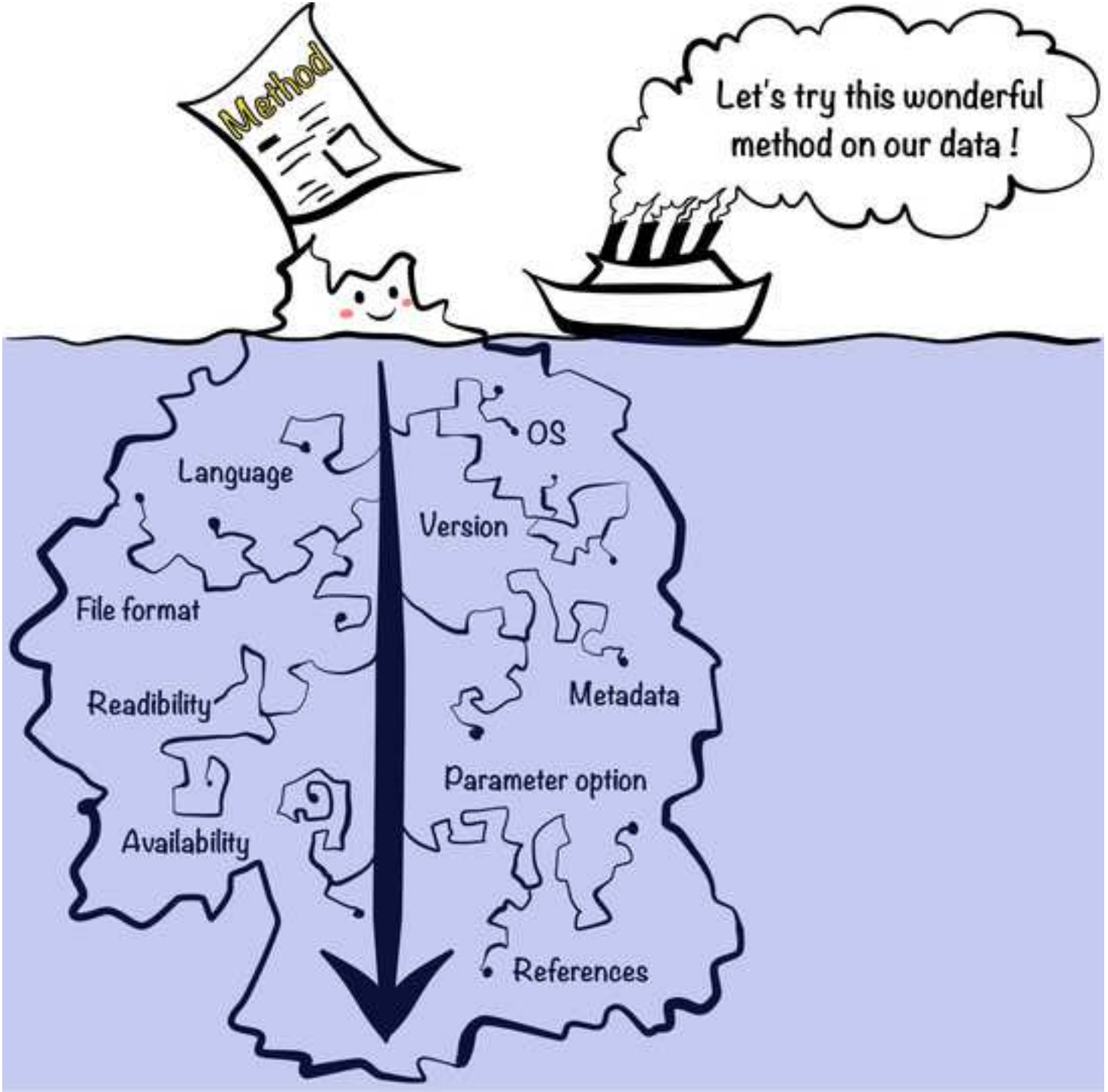

Figure 4

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