

A case study in reproducible applied statistics: Is tagging of therapist-patient interactions reliable?

K. Jarrod Millman (JM)
Division of Biostatistics
University of California, Berkeley

Kellie Ottoboni (KO)
Department of Statistics
University of California, Berkeley

Naomi A. P. Stark (NS)
Department of Philosophy
University of Pennsylvania

Philip B. Stark (PS)
Department of Statistics
University of California, Berkeley

1 Introduction

Parts of this text have been adapted from [Millman \(2015\)](#) and a shorter version was submitted to <https://github.com/BIDS/repro-case-studies>.

1) Who are you and what is your research field?

We are three applied statisticians (JM, KO, PS) at UC Berkeley working with a domain specialist (NS) at the University of Pennsylvania. Our case study involves assessing inter-rater reliability (IRR) of the assignment of “tags” applied by human raters to classify interactions during therapy sessions with children on the autistic spectrum.

2) Define what the term “reproducibility” means to you generally and/or in the particular context of your case study.

In this case study,¹ *reproducibility* means:

- *Computational reproducibility and transparency.* We have documented (and scripted) nearly every step of the analysis—from cleaning to coding to code execution—and made the code and documentation publicly available.
- *Scientific reproducibility and transparency.* We documented much of the discussion leading to our decisions to take each step in the analysis. We made the data publicly available in an open format, with an adequate data dictionary.
- *Computational correctness and evidence.* We tested our code thoroughly and in an automated fashion, to have justifiable confidence that the code does what it was intended to do. We made those tests publicly available, so that others can see how we validated our computations.

¹ This file along with the analysis script and results can be found here: <https://github.com/statlab/nsgk>

- *Statistical reproducibility.* We invested time to understand the fundamental problem and the results of our analysis so that we do *not* draw conclusions that are not justified by the data, the manner in which it was acquired, and our domain understanding. We avoided “p-hacking” and other potentially misleading selective reporting, and made all our analyses publicly available.

By keeping all code, text, and data in a public version-controlled repository, we have made our well-documented analysis available for anyone to examine, check, modify, or reuse. We published the data used in our study—both the original anonymized version as well as our cleaned version including the commands necessary to produce the cleaned version from the anonymized one. In addition to making what we did transparent to anyone who is interested, working in this way means that when errors are found we can identify how and when those errors were introduced. We have written tests for almost all our code, which means we have a high level of confidence that as we change our code we will catch any errors we might have introduced, and can correct them quickly and easily. And since we have automated the process of running our analysis, if errors are identified and corrected, it is easy to rerun the entire analysis from start to finish.

If you have standard tools (see § 5) on your computer and network access, you can run our complete analysis of the cleaned data by typing the following three commands from a Unix shell prompt:

```
$ git clone git@github.com:statlab/nsgk.git
$ cd nsgk/nsgk
$ make
```

The first command creates a directory `nsgk` in your current working directory with a copy of the project repository (i.e., a directory with our code, data, and text along with the provenance of these documents). This directory contains this document as well as everything needed to run our analysis. Inside `nsgk/nsgk` there is a `Makefile`, our analysis script `analysis.py`, and the output `results.csv` of that script.

When you enter the command `make`, the following commands will be run:

```
virtualenv -p /usr/bin/python2.7 venv
venv/bin/pip install --upgrade pip
venv/bin/pip install -r requirements.txt
venv/bin/python analysis.py
```

The first command creates a new virtual environment² (`venv`) for Python 2.7. Using this new virtual environment (`venv`) the subsequent commands respectively upgrade the Python package manager (`pip`) to the most recent version, install the necessary Python package dependencies (`numpy 1.11.0`, `scipy 0.17.0`, and `permute 0.1a2`), and run the analysis script `analysis.py`.

2 Workflow narrative

Our project arose from a pilot study NS was working on with Dr. Gilbert Kliman of the Children’s Psychological Health Center in San Francisco. To investigate therapeutic interventions with children

² Virtual environments are a way to create isolated Python environments. This allows you to keep the Python dependencies for different projects separate and, thus, allows you to install different version of the same software on your computer.

on the autistic spectrum, Dr. Kliman and NS collected some observational data (described below). NS approached PS about the data and the problem NS was studying. After investigating the problem further, PS emailed JM and KO a one-page proposal for a stratified permutation test to assess inter-rater reliability using stratified samples. We (JM, KO, PS) had recently begun developing a general purpose Python package for permutation tests, called `permute`,³ based on our collaborations. PS suggested this would be an interesting example to include.

After coming to an initial understanding of NS’s underlying research question and experiment, including how she collected the data, we (JM, KO, PS) cleaned the data, developed a nonparametric approach to assessing IRR appropriate to the experiment, implemented the approach in Python, incorporated the resulting code into our evolving Python package of permutation tests, applied the approach to the cleaned data, documented the code and the analysis, and wrote up the results in L^AT_EX.

We distinguish the following aspects of our project, which are typical in applied statistics:

- understand problem
- get and clean data⁴
- design algorithm
- implement algorithm
- analyze data
- understand result

Figure 1 shows how each aspect of the project influenced the other aspects and gives estimates of the total person-hours we collectively spent on each aspect of the project. For example, if JM, KO, and PS spent an hour together discussing the problem in a meeting, then that meeting counts as 3 people hours.

We did not keep a detailed record of time spent, but our computational practices (§ 5) provide enough detail about who did what when that we believe our estimates provide an accurate qualitative account of the time demands for each aspect of the project. However, since these are only rough estimates, the reader should focus on the relative differences in the amount of time we spent on each aspect. We have found that researchers (ourselves included) often underestimate the time needed to understand the problem, acquire and clean the data, as well as understand the results, while overestimating the time needed for writing code. We have included our time estimates to give people an idea how “inexpensive” (or expensive) working more reproducibly is, to capture how our group understanding evolved, and in the hope that it might be instructive for students and collaborators.

Since we view computational reproducibility as a cross-cutting concern of all project aspects, we have adopted a set of computational practices, which we (JM, KO, PS) followed (almost) whenever we were working on the project.⁵ These computational practices, described in Millman and Pérez (2014), are used widely in the open source scientific Python community. While developed for managing software contributions, these practices are ideal for ensuring computational reproducibility

³ <http://statlab.github.io/permute/>

⁴ This step generally also requires obtaining a data dictionary, learning how to parse the data format, and so on.

⁵ Exceptions include that we did not record all of our in-person discussions or whiteboard work. However, we endeavored to record summaries of these activities.

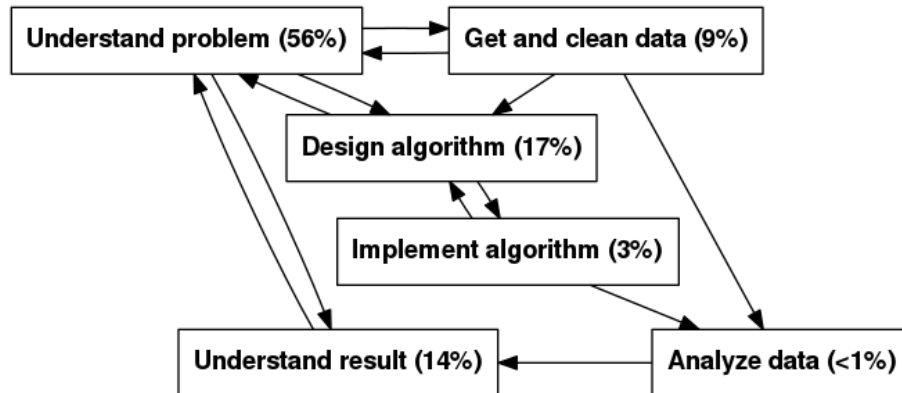


Figure 1: Each box corresponds to one aspect of the project. The percentages are estimates of the percent of our time spent on each aspect. Edges represent influence. **Understand problem** \rightarrow **Design algorithm**, for instance, corresponds to the fact that we had to understand the problem in order to design the correct statistical test.

in scientific and statistical research. We will illustrate how we leverage the software infrastructure and development practices of `permute` to conduct reproducible and collaborative applied statistics research with our colleagues. We discuss the software tools and practices briefly in § 5 below.

2.1 Understand problem (80 hours)

The Kliman-Stark research project sought to identify characteristics of effective clinical interactions with children on the autistic spectrum. The project first required developing a set of characteristics that observers could use to “tag” what was happening in each 30-second interval of a therapy session. After they developed a taxonomy of clinical interactions, Kliman and NS had a number of trained raters watch videos of therapy sessions and label each 30-second interval using the collection of tags. For the classification system to be meaningful and useful, different raters must generally agree on whether a given tag applies to a given video segment: there must be inter-rater reliability. Of course, if a tag is never used or is always used, inter-rater reliability will be perfect, but the tag is useless for distinguishing clinical interactions.

That led to a statistical question: how to assess the evidence in the tagged videos that different raters tag interactions the same way? After numerous conversations, it made sense to consider the null hypothesis to be that, conditional on the number of times a given rater applied a given label to a given video, all assignments of that label to time stamps in the video by that rater are equally likely, and the ratings given by different raters are exchangeable (essentially, that raters are independent).

Once PS had an initial understanding of NS’s problem, we (JM, KO, PS) met regularly (approximately weekly, sometimes more) as a team to discuss the project. Initially these discussions involved a lot of work on whiteboards and asking a lot of probing questions. This helped us develop a shared understanding of the problem, understanding that improved by explaining things to one another and by asking hard questions about our planned approach and whether it could address the question of interest. As our understanding of the problem progressed, our work transitioned from

working on whiteboards to testing our ideas out on a computer. We often used pair programming at this stage and sometimes we all sat in front of one computer, while one of us typed code in an interactive IPython session. This helped ensure that we all understood the problem well and it also helped us catch errors (typos as well as conceptual misunderstandings).

2.2 Get and clean data (13 hours)

The tag data were collected by NS and raters working at her direction. The data comprise ratings of segments of 8 videos by 10 trained raters. Each video is divided into approximately 40 time segments. In each time segment, none, any, or all of 183 types of activity might be taking place. The raters indicated which of those activities was taking place during each segment of each video.

PS received the data from NS as an Excel spreadsheet that had been entered by hand by NS and an assistant. Understanding the “data dictionary” and vetting for obvious errors entailed several rounds of email between PS and NS before PS had a version of the data that did not have obvious errors. PS then exported the Excel data to comma-separated value (CSV) format. The original data contained personally identifying information. Using regular expressions in an interactive text editor, PS substituted unique numerical identifiers for raters’ names in the CSV file. While this step was not performed reproducibly (i.e., not scripted), it can be checked readily.

After PS generated the original anonymized data, JM committed it to our repository and added a data loader with tests to ensure that if the data changed we would know. At this point, we (JM, PS) screened the anonymized data for transcription errors (e.g., duplicate rows). This involved writing a number of quality assurance tools (e.g., to find duplicate consecutive rows), which are now included in `permute`. Once we identified entries incompatible with our understanding of what should be in the data, JM wrote a `sed` script to “correct” the inferred typos. The exact commands used to clean the data are included in the commit corresponding to that cleaning step. After carefully examining the data for potential errors and documenting every change we made and why, we sent the cleaned data and an explanation of what we did to NS to verify that the corrections were appropriate. As a result, we provide the cleaned data in our project repository as well as a careful account of its provenance.

2.3 Design algorithm (25 hours)

Although the test we eventually implemented was very similar to the original test proposed by PS at the start of the project, we (JM, KO, PS) spent significant time focused on “problem appreciation,” some of which resulted in considerable simplification of the algorithm used to implement the test. We also developed a more general terminology (see Table 1).

NSGK	IRR
183 types of activity	T tags
8 videos	S strata
40 segments/videos	N_s items/strata
10 raters	R raters

Table 1: Mapping between terms from our motivating problem (NSGK) and the terms used in our general algorithm (IRR).

We decided to assess rater reliability in identifying (i.e., tagging) each of the 183 types of activity separately, because they are of separate interest. This introduces questions about whether inferences are to be made about each tag separately (per-comparison error rate, PCER) or simultaneously (familywise error rate, FWER), or whether we are concerned with the fraction of tags we conclude are reliable that in fact are not reliable (false discovery rate, FDR). Ultimately, we decided that the PCER was the most relevant error criterion, since the tags are individually interesting. As a “first cut” through the rating scheme, eliminating tags that are clearly not reliable across raters simplifies the scheme and reduces the cognitive burden on raters, because they do not have to keep so many categories of activity in mind. We imagined that if we could eliminate a substantial number of the tags as unreliable, there would be a repeat of the tagging using a different set of raters to validate or refine the results, reducing the rate of “false positives.” On the other hand, incorrectly rejecting tags as unreliable could eliminate a potentially useful predictor of successful therapeutic outcomes, so the FWER seemed far too stringent a criterion. See § 2.6 for more discussion.

Since each of the videos contained different sessions of therapist-patient interactions, in general rated by different people, we stratified the test by video. A literature search for approaches to assessing IRR led us to conclude that there was no existing suitable method for several reasons: the experiment was stratified; there were multiple raters but not the same set for all videos; and standard methods required indefensible parametric assumptions or population models, which we hoped to avoid.

After deciding to use permutation tests, we (JM, KO, PS) then determined that permuting each rater’s ratings within a video, independently across raters and across videos, made sense as the appropriate invariant under the null hypothesis. We chose to use concordance of ratings as our partial test statistic within each stratum. We (JM, PS) derived a simple expression for efficiently computing the concordance. To combine tests across strata, we (JM, KO, PS) used the nonparametric combination (NPC) of tests (Pesarin and Salmaso, 2010) with Fisher’s combining function. Finally, we developed a computationally efficient approach to finding the overall p -value for the NPC test.

2.4 Implement algorithm (5 hours)

Once we had a blueprint of the algorithm, KO led the implementation effort. She did most of the coding; JM and PS reviewed the code and discussed the implementation. Following our software development practices (§ 5), KO also wrote tests for every function she implemented. After a few iterations of coding, testing, and review, KO finalized our implementation and we merged it into `permute`.

KO wrote three functions to implement our general IRR algorithm:

1. a function to compute the IRR partial test statistic from a binary matrix with one row per rater and one column per item;
2. a function to simulate the permutation distribution of the IRR partial test statistic for a matrix of ratings of a single stratum;
3. a function to simulate the permutation distribution of the NPC test statistic by combining the S distributions of the IRR partial test statistic for each of the S strata.

2.5 Analyze data (1 hour)

Once we merged KO’s implementation of the general algorithm (including tests) into `permute`, KO wrote a short script (about 50 lines of Python) to analyze the cleaned data from NS.

Since we included the main workhorse functions in `permute`, the analysis script contained only high-level commands:

1. Load the cleaned data
2. For each of the 183 categories of activity:
 - (a) For each of the 8 videos:
 - i. Compute the mean and standard deviation of the number of times the tag was applied
 - ii. Compute the IRR partial test statistic
 - (b) Simulate the permutation distribution of the NPC test statistic for each tag combined over the 8 videos, and report a single p -value
3. Save the results to a CSV file

2.6 Understand result (20 hours)

At a high level, even the summary statistics we computed were useful: some tags were never applied by any rater to any video. Presumably, the tag taxonomy could be simplified by eliminating those tags from the universe of labels, reducing the cognitive burden on the human raters. There were also tags that were used so frequently that high concordance was virtually guaranteed—and therefore high inter-rater concordance was not evidence of inter-rater reliability. This may also imply that any differences in efficacy of therapy are not attributable to whether the corresponding activity is taking place, since it is often taking place, at least in these sessions. Whether it makes sense to keep such tags in the taxonomy depends in part on subject matter knowledge: are those interactions typical only in the videos in these evaluation data, or are they typical of all therapeutic interventions with children on the autistic spectrum?

At the other extreme, there were tags for which the concordance of use was quite low, but still highly significant. This raises the scientific question of what threshold level of agreement among raters makes a tag interesting or useful, separate from whether the agreement is statistically significant. That is a matter we need to discuss at greater length with the domain specialists. It also points to a frequent situation in statistics: practical significance and statistical significance are not the same thing, and one must consider “fitness for use” when devising summary statistics.

We hope that the concrete findings will lead to a refinement of the taxonomy and additional tests of reliability. We hope that those tests will involve greater automation of data collection and transcription, to eliminate some of the sources of error in the data. Regardless, this work has led to a new nonparametric test for inter-rater reliability, now available publicly in the `permute` package.

3 Pain points

Given our different backgrounds and experiences we (JM, KO, PS) each found different points in the process challenging. However, for all of us the most challenging aspect—and the most time-

consuming—was the necessary struggle to understand the scientific question and the experiment well enough to devise an approach to answering the question.

For KO and PS there was a learning curve to master the tools and practices. This involved understanding the data model used by Git, acquiring habits such as writing tests for all functions and following a common style guide, and learning to contribute to the project repository indirectly through GitHub’s pull request mechanism. JM was already familiar with the tools and practices, and devoted significant time to teaching KO and PS the workflow. Once mastered, the benefits of these tools and habits outweigh the time and effort spent learning them.

For JM the most painful part of the project was vetting hand-entered data to look for errors and inconsistencies. Not only was this laborious, but it involved inferring what the data should have been without any direct way to ensure that these inferences were correct: the original raters and videos were not available to us. The solution to this pain point is to automate data collection as much as possible. However, when data have already been entered by hand, there is not much that can be done other than being cautious when “fixing” data entry errors and recording every aspect of the data cleaning process.

4 Key benefits

Since [Buckheit and Donoho \(1995\)](#) popularized the idea of computational reproducibility, applied statisticians have increasingly embraced version control and process automation. Many of our colleagues have made the idea of computational reproducibility central in both the classroom and the lab. Some ask anyone working with them to follow a set of computational practices including version control.⁶

However, the computational practices described in this study (see § 5) go beyond the standard work habits of our colleagues. Our computational practices provide the following benefits:

1. it reduces the number of errors introduced by new code and changes to existing code
2. it makes it easy to modify the analysis when errors are found, to apply the analysis to new data sets, and so on
3. the process is self-documenting, making it easier to draft a paper about the results or to pick up where we left off after working on something else
4. the methods are abstracted from the analysis and incorporated into a package so that others can discover, check, use, and extend our methods.

5 Key tools and practices

As part of the development of our software package `permute`, we invested significant effort in setting up a development infrastructure to ensure our work is tracked, thoroughly and continually tested, and incrementally improved and documented. To this end, we have adopted best practices for software development used by successful open source projects ([Millman and Pérez, 2014](#)).

⁶ For example, see <http://www.stat.berkeley.edu/~epurdum/studentResources.html>.

5.1 Version control and code review

We (JM, KO, PS) use Git⁷ as our version control system (VCS) and GitHub⁸ as the public hosting service for our official **upstream** repository (<https://github.com/statlab/permute>). Each of us has our own copy, or fork, of the **upstream** repository. We each work on our own repositories and use the **upstream** repository as our coordination or integration repository.

This allows us to track and manage how our code changes over time and to review new functionality before merging it into the **upstream** repository. To get new code or text integrated in the **upstream** repository, we use GitHub's *pull request* mechanism. This enables us to review code and text before integrating it. Below, we describe how we automate testing our code to generate reports for all pull requests. This way we can reduce the risk that changes to our code break existing functionality. Once a pull request is reviewed and accepted, it is merged into the **upstream** repository.

Requiring all new code to undergo review provides several benefits. Code review increases the quality and consistency of our code. It helps maintain a high level of test coverage (see below). Moreover, it also helps keep the development team aware of the work other team members are doing. While we are currently a small team and we meet regularly, having the code review system in place will make it easier for new people to contribute as well as capturing our design discussions and decisions for future reference.

5.2 Testing and continuous integration

We used the **nose** testing framework for automating our testing procedures.⁹ This is the standard testing framework¹⁰ used by the core packages in the scientific Python ecosystem. Automating testing allows us to monitor a proxy for code correctness when making changes as well as simplifying the code review process for new code. Without automated testing, we would have to manually test all the code every time a change is proposed. The **nose** testing framework simplifies test creation, discovery, and execution. It has an extensive set of plugins to add functionality for coverage reporting, test annotation, profiling, as well as inspecting and testing documentation.

Our goal is to test every line of code. For example, not only do we want to test every function in our package, but if a specific function has a conditional branching structure we test each possible execution path through that function. Having tested each line of code increases our confidence in our code and provides some assurance that changes we make do not break existing code. It also increases our confidence that new code works, which reduces the friction of accepting contributions. Currently over 98% of the lines of code in **permute** get executed at least once by our test system.

We often work on several pull requests simultaneously. These pull requests may take several weeks or months before they are reviewed, improved, and accepted in our **upstream** repository. While we are working on one pull request, we may merge several others. Since the underlying code base is changing, each pull request may potentially introduce integration conflicts when we attempt to merge it back into the main line. To mitigate the difficulty in managing these conflicts we employ continuous integration and track our test coverage.

⁷ <http://git-scm.com>

⁸ <https://github.com>

⁹ <https://nose.readthedocs.org>

¹⁰ As **nose** has been in maintenance mode for the last few years, projects are starting to look into newer testing frameworks. We are migrating to **pytest** (<http://pytest.org>). While we may transition to a new testing framework, any system we migrate to will have the same basic features and benefits as **nose**.

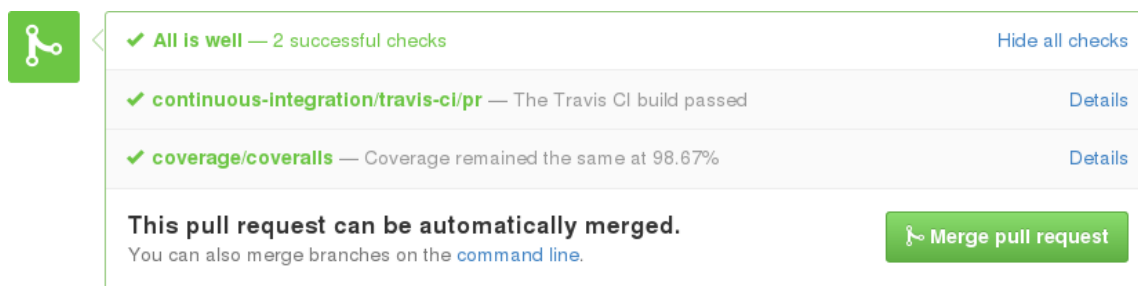


Figure 2: The above report indicates that the associated pull request does not break existing code and does not change our test coverage.

Continuous integration works as follows: Each pull request (as well as a new commit to an existing pull request) triggers an automated system¹¹ to run the full test suite on the updated code. The automated system checks whether any of our automated tests fail as well as tracks the percentage of our code that is covered by our automated tests. This means that when you review a pull request, you can immediately see whether the proposed changes break any tests and whether the new code decreases the overall test coverage (see Figure 2).

5.3 Documentation

We use Sphinx¹² as our documentation system and have extensive developer documentation and the foundation for high-quality user documentation. Sphinx is the standard documentation system for Python and is used by the core scientific Python packages. We use Python docstrings and follow the NumPy docstring standard¹³ to document all the modules and functions in `permute`. Using Sphinx and some NumPy extensions, we have a system for autogenerating the project documentation (as HTML or PDF) using the docstrings as well as stand-alone text written in a light-weight markdown-like language, called reStructuredText.¹⁴ This system enables us to easily embed references, figures, code that is auto-run during documentation generation, as well as mathematics using \LaTeX .

5.4 Release management

Our development workflow ensures that the official `upstream` repository is always stable and ready for use. This means anyone can install our official upstream master at any time and start using it. We also make official releases available as source tarballs and as Python built-packages¹⁵ uploaded to the Python Package Index, or PyPI,¹⁶ with release announcements posted to our mailing list.

¹¹ We have configured Travis CI (<https://travis-ci.org>) and `coveralls` (<https://coveralls.io>) to be automatically triggered whenever a commit is made to a pull request or the `upstream` master. These systems run the full test suite using different versions of our dependencies (e.g., Python 2.7 and 3.4) every time a new commit is made to a repository or a pull is requested. Travis CI checks that all the tests pass, while `coveralls` generates a test coverage report so that we can monitor what parts of our code are checked by a test and which are not.

¹² <http://sphinx-doc.org>

¹³ https://github.com/numpy/numpy/blob/master/doc/HOWTO_DOCUMENT.rst.txt

¹⁴ <http://docutils.sourceforge.net/rst.html>

¹⁵ Currently our code is pure Python, but we release Python wheels. Wheels are the standard built-package format for Python.

¹⁶ PyPI is the Python equivalent of *The Comprehensive R Archive Network* (CRAN).

By making official releases whenever we reach an important stage of an applied project, we are able to easily recover the exact version of our analysis at a later date. To install the exact version of `permute` used in this case study, type the following command from a shell prompt (assuming you have Python and a recent version of `pip`):

```
$ pip install permute==0.1a2
```

References

- Jonathan B. Buckheit and David L. Donoho. Wavelab and reproducible research. In Anestis Antoniadis and Georges Oppenheim, editors, *Wavelets and Statistics*. Springer, 1995.
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- Fortunato Pesarin and Luigi Salmaso. *Permutation tests for complex data: theory, applications and software*. John Wiley & Sons, 2010.

Appendix

A stratified permutation test for multi-rater inter-rater reliability.

There are S strata. There are N_s items in stratum s . There are $N = \sum_{s=1}^S N_s$ items in all.

Each item might belong to none, some, or all of C non-exclusive categories. That is, each item might be “tagged” with any of the 2^C subsets of the C labels, including the empty set.

There are R “raters,” each of whom tags each of the N items with zero or more elements of C .

Define $L_{s,i,c,r} = 1$, if rater r assigns label c to item i in stratum s and $L_{s,i,c,r} = 0$ if not.

We observe $\{L_{s,i,c,r}\}$ for $s = 1, \dots, S$; $i = 1, \dots, N_s$; $c = 1, \dots, C$; and $r = 1, \dots, R$.

We want to know whether the categorizations are “reliable,” in the sense that agreement among the raters is higher than would be expected “by chance.”¹⁷ The reliability of each category c is of interest, rather than an overall rating for all C categories.

Fix c , since we are considering only one category at a time.

The null hypothesis for category c is that, given the number of times each rater assigns category c to each video, all assignments are equally likely, the assignments are independent across strata, and raters’ ratings are exchangeable with respect to each other.

Our test conditions on the number of times each rater assigns each label within each stratum, but not on the items to which those labels are assigned. The null distribution arises from permuting the assignments each given rater makes of category c to items within each stratum s , permuting independently across raters and across strata.

Let $y_{si} = \sum_{r=1}^R L_{s,i,r}$ be the number of raters who tagged item i in stratum s . The test statistic within stratum s is

$$\begin{aligned} \rho_s &\equiv \frac{1}{N_s \binom{R}{2}} \sum_{i=1}^{N_s} \sum_{r=1}^{R-1} \sum_{v=r+1}^R \mathbf{1}(L_{s,i,r} = L_{s,i,v}) \\ &= \frac{1}{N_s R(R-1)} \sum_{i=1}^{N_s} (y_{si}(y_{si} - 1) + (R - y_{si})(R - y_{si} - 1)). \end{aligned}$$

That is, within each stratum, we count the number of concordant pairs of assignments. The statistic simplifies to the second line, which counts the pairs of raters who tag the item plus the pairs of raters who do not tag the item. If all R raters agree whether item i in stratum s belongs to category c , that contributes a term $\binom{R}{2}$ to the sum. If only half agree, the term for item i contributes $2\binom{N/2}{2}$ to the sum. The normalization makes perfect agreement within stratum s correspond to $\rho_s = 1$.

To combine the results across strata to get an overall p -value, we used the NPC (nonparametric combination of test) methods described in Pesarin and Salmaso, based on the p -values in different strata. NPC can use variety of combining functions for the p -values; the tests reported above used Fisher’s combining function:

$$\lambda = -2 \sum_{s=1}^S \log \hat{p}_s.$$

¹⁷ Specifying the chance model amounts to specifying the null hypothesis. See the discussion above.