

Professor Dr Sara Zandomeneghi
Editor-in-Chief
BMC Bioinformatics

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Dear Editor-in-Chief:

Thank you very much for managing our manuscript entitled “Toward reliable false discovery rate control in classification problems under distribution shift”. We were requested to resubmit our manuscript, because the data availability section was filled incorrectly on the website during submission. Hence, we are resubmitting again our manuscript, hopefully correctly this time.

For your convenience, we keep the previous cover letters below. Before the first peer review, we were asked for a minor revision to include direct web links to the datasets we analyzed in your study. The editor’s comment is quoted below in blue color:

“1. Please include the accession numbers or direct web links and the full names of the data banks/repositories corresponding to any datasets obtained from web-based sources and subsequently analysed in your study in the ‘Data availability’ Declaration on the manuscript submission system, including any reference datasets. If accession numbers or web links are listed in a table or additional file, please include an in-text reference to the file or table and the database/repository the accession numbers correspond to in the ‘Data Availability’ declaration on the manuscript submission system as well as in the main body of text in your manuscript.

At this stage, we ask that you submit a clean version of your manuscript and do not include any track changes or highlights.”

We made the changes accordingly. In particular, we

1. included direct web links and the full names of the data repositories, analyzed in our study, to the ‘Data availability’ Declaration in a table. This table is, now, Table 2.
2. We included direct text references to this Table 2 in the main text and in the ‘Data availability’ Declaration.

For your convenience, we include below the original cover letter.

Affiliations:

1. The corresponding author is: Prof. Attila Kertesz-Farkas, akerteszfarkas@hse.ru,
2. Co-author, first author: Andrey Borevskiy.

We are both part of the same laboratory: Laboratory on AI for Computational Biology, Faculty of Computer Science, HSE University, Moscow Russian Federation

We note that our institution is not under sanctions and we are not involved in any research related to the Russian military, etc.

An explanation of why your manuscript should be published in BMC Bioinformatics:

We present our study on controlling false discovery rates (FDR) under data distribution shift in classification problems in the biomedical domain. In this study, we draw attention to a very important but

often neglected problem; namely, the performance of deep-learning based classifiers is assumed to be the same in application. However, it often can be much worse than thought due to data distribution shift (a.k.a. covariate shift), data label distribution shift, batch effects caused by some confounding factors, and overfitting. This performance drop of a machine learning system often remains undetected, resulting in risk for people in health care and clinical applications.

In this manuscript, we present a simple, fast and robust method to adjust the test prediction scores so that the latent test null distribution will be more similar to the train null distribution. This will result in more accurate FDR control.

Our method operates in the 1-dimensional prediction score space. Therefore, it is not hindered by high-dimensional space, data sparsity (i.e. curse-of-dimensionality), and correlated features. In addition, our method does not rely on data clustering or graphical causal models.

We tested our method with four public benchmark datasets commonly used in biomedical image analysis: PatchCamelyon (PCam), Chest x-ray (CheXpert), TissueNet, and Breast Cancer Semantic Segmentation (BCSS). With our method, we obtained much more accurate FDR control under data distribution shifts in the test data compared to a recent algorithm, called Learn-then-test, developed by Michael Jordan's lab from Stanford University.

A declaration of any potential competing interests:

None.

Confirmation that all authors have approved the manuscript for submission:

This manuscript has been approved by both authors.

Confirmation that the content of the manuscript has not been published:

This manuscript has never been submitted to any other journals. The manuscript will be properly formatted for the journal if it is needed for the reviewing stage or once it is accepted. We did not use AI chat bots in manuscript preparation or in this study in general.

Suggested reviewers:

1. Nikita Moshkov, PhD, Institute of Biochemistry, Biological Research Center. Szeged, Hungary, Deep Learning specialist in biological image analysis, cell segmentation, etc. nikita.moshkov@brc.hu
2. Peter Horvath, PI at AI for Health, Helmholtz Munich, Germany; PI at Biological Research Center, Szeged, Hungary horvath.peter@brc.hu
3. Pavel Sulimov, PhD, ZHAW School of Engineering, Switzerland, pavel.sulimov@zhaw.ch
4. Yang Lu, PhD, Assistant Professor, University of Waterloo, Canada, yanglu@uwaterloo.ca

We hope that this manuscript provides a useful and interesting study for the readers of *BMC Bioinformatics*.

Best regards,

Attila Kertesz-Farkas,
Professor
Head of the Laboratory on AI for Computational Biology, Faculty of Computer Science
HSE University, Moscow, Russia