HARMONIZATION BENCHMARKING TOOL FOR NEUROIMAGING DATASETS

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ABSTRACT

A major data pre-processing step for large, multi-site studies is to handle site effects by harmonizing data, generating a dataset that enables more powerful analyses and more robust algorithms. There is a wide variety of data harmonization techniques, but there are few tools that streamline the process of harmonizing data, comparing across techniques, and benchmarking new techniques. In this paper, we introduce HArmonization BEnchmarking Tool (HABET), an open source tool for generating harmonized images and evaluating the performance of different harmonization algorithms. To demonstrate the capabilities of HABET, we harmonize diffusion MRI images from the Adolescent Brain and Cognitive Development (ABCD) study using two different approaches, and we compare their performance.

Index Terms— Harmonization, Open-source, ComBat, ABCD Study, Diffusion MRI

1. INTRODUCTION

With the increasing collaboration and pooling of data among neuroimaging research centers, the ability to reliably conduct mega-analyses is becoming more important. Traditionally, meta-analyses have often been the only option, being possible even when only aggregated data is available from each study. Mega-analysis, in which unaggregated data is pooled across studies, can be more powerful for analyzing structural neuroimaging data under typical conditions [1], and it is increasingly an option with multi-site neuroimaging studies becoming more common [2, 3, 4]. A major challenge when working with multi-site neuroimaging data is to deal with effects attributable to study site, such as scanner hardware, reconstruction algorithms, acquisition protocols, and image quality. These can all affect the final image [5] as well as downstream results [6, 7]. Data harmonization is the process of removing these effects. When working to discover biomarkers or construct predictive models out of multi-site medical image data, harmonization is a critical preprocessing step to ensure that results can be generalized and applied across a variety of clinical and research settings.

There is a wide variety of approaches to harmonization. A systematic review of harmonization literature was conducted in [8], where the authors classified existing techniques into four broad categories: distribution based techniques, image processing, synthesis, and invariant feature learning. Distribution based techniques such as ComBat [9] model the bias between different groups and subtract that bias out from the original data. Image processing based techniques such as resampling, image filtering, and normalization, employ image processing algorithms to harmonize the data. Synthesis and invariant feature learning methods typically involve deep learning. Synthesis techniques aim to generate samples from missing groups, similar to the task of style transfer. For example, this could transfer all of the images from different sites to match the image data distribution of a particular site. Lastly, invariant feature learning methods involve encoding image data in some site-invariant form, and using that encoding instead of the original images in downstream tasks.

A closely related task to harmonization is domain adaptation. This term is sometimes used to refer to the invariant feature learning [10, 11] or synthesis [12] categories described above, but it typically refers to the broader problem of transforming data to match a given data distribution, beyond the context of multi-center studies.

The Adolescent Brain and Cognitive Development (ABCD) Study [4] is a large, multi-site, longitudinal study monitoring the brain and cognitive development of a national cohort of children. Several studies have performed harmonization on the ABCD dataset. In [13], site effects in the ABCD fMRI images were examined by training a multinomial logistic classifier to predict scanner from the imaging data before and after ComBat harmonization [9]. In [14], ABCD 2.0 T1 and T2 weighted images were harmonized with a deep learning approach. In [15], ABCD DMRI images were harmonized with rotation invariant spherical harmonics (RISH).

Although many harmonization techniques have been developed, there is a need for tools that streamline the process of evaluating and comparing the various techniques on a given dataset. In this work, we introduce the open source HArmonization BEnchmarking Tool (HABET), and we apply it to investigate site effects in the ABCD Study dataset. This tool will be available to the research community as open source.
software; code can be found at https://github.com/KitwareMedical/habet. Currently HABET supports ComBat and global scaling out of the box, and it features a simple framework for adding new harmonization techniques. In principle, HABET could support techniques from any of the four aforementioned categories except for invariant feature learning, as these techniques skip the reconstruction step altogether. More techniques will be made available in the future. Report generation features allow researchers to quickly summarize and visualize the performance of different techniques. Unlike domain adaptation libraries such as [11], our goal is to provide evaluation metrics for the effectiveness of site effect removal. A similar work to ours is [12], where the extent of harmonization is evaluated by comparing features or images from a domain-adapted source dataset with those from a target dataset. HABET instead focuses its evaluation on statistical model based detection of site effects with different types of harmonization, and it accommodates harmonization models that operate on more than two sites. Our contributions are as follows:

1. Introduce the open source framework HABET for harmonization benchmarking.
2. Exemplify the capabilities of HABET by analyzing site effects in the ABCD data, before and after applying two different harmonization techniques.

2. METHOD

HABET provides a simple interface for both harmonizing imaging data and evaluating the performance of the harmonization technique used. HABET features two main components, harmonization and report generation; see an overview of the workflow in Figure 1. These two components are independent, so it is possible to use HABET only for the purpose of harmonizing images, or for comparing between different harmonization methods with already harmonized data.

Both components operate on a given set of images, a mask selecting which part of the image to process, and a table relating each image to some variables. This includes the categorical variables whose effect on the image is undesirable (e.g. site, scanner manufacturer), which we will refer to collectively as “site.” The table may also include covariates that are of interest for later analysis and that could be confounded with site. As previously stated, global scaling and ComBat are supported out of the box, with more harmonization methods to be added in the future. HABET also features a simple API for registering custom harmonization techniques, making it convenient for benchmarking newly developed approaches.

The report generation component aids in quantifying site effects for a given set of images. This can be executed on a set of images before and after harmonization, giving the user insight into the performance of a given set of harmonization methods. At any given voxel location, if there were no site effects then we would expect the within-site means of the voxel values to be roughly equal, with some variation due to sampling and other variables. This hypothesis can be tested via one-way ANOVA: we compute an $F$-statistic and an associated $p$-value at each voxel, with site as the independent variable and voxel intensity as the dependent variable. If, for a given voxel, the results of the ANOVA are found to be significant, then we conclude that there are site effects at that image location. We may wish to know, for those voxels that show significant $F$-scores, which sites cause the greatest discrepancy, and for this we run a $t$-test for each pair of sites. We report, as another measure of the extent of site effects, the fraction of site pairs that showed significant effects (similar to the approach in [16]). Bonferroni correction is applied to the $F$-test $p$-values to account for the number of voxels, and also to the $t$-test $p$-values to account for the number of voxels and site pairs. Finally, we want a measure of site effect magnitude when a location shows significant site effects. For this we report eta-squared values to indicate the proportion of the variance of each voxel value that can be attributed to site. Putting it together, each report consists of:

1. Site effect significance: a table of voxel-wise $F$-test results from the ANOVA and an image indicating the subset of the mask where site effects were detected.
2. Site effect size: a table and an image of eta-squared values at each voxel.
3. Pairwise site effect significance: a table of voxel-wise $t$-test results and an image depicting the fraction of significant $t$-tests at each location that showed significant site effects.
4. Pairwise site effect size: a table of Hedges’ $g$ values for voxels that showed significant site effects.
5. A summary table reporting the total numbers and fractions of $F$-tests and $t$-tests that were significant.

3. RESULTS

The ABCD study has 21 participating study sites across the country. A wide range of data are collected, including structural and functional neuroimaging. We focus on diffusion tensor imaging (DTI) – specifically fractional anisotropy (FA) images – both as an illustration of our tool and as a precursor for our future development of tools for white matter microstructure analysis. Ninety-six diffusion directions were used to acquire the DMRI images in the ABCD dataset, and the diffusion imaging protocols over the three different scanner manufacturers were chosen to be as similar as possible across sites [4]. For details on DMRI acquisition parameters and preprocessing, see [4]. To examine site effects in the ABCD dataset, we took a sample of 836 subjects from the baseline year. We ensured that the values of site, baseline age, sex, scanner hardware, and scanner software version that occur in the sample were representative of the full ABCD dataset. Deformable registration to align local structures was achieved with a deep learning approach based on inverse con-
The images were harmonized using two approaches: ComBat and global scaling. Reports were generated for each technique and the original images using HABET. A report was also generated for images (n = 58) from a single ABCD site with a fake site variable that randomly uniformly var-

![Workflow diagram](image)

**Fig. 1**: The workflow to evaluate a harmonization technique. The input data are an image dataset (a), an optional mask (b) selecting voxels for inclusion, and a table (c) associating images to groups (such as study site) over which to remove effects. Our tool provides two modules: harmonization (d) and report generation (e). A harmonization technique is configured (d) and an analysis of site effects is conducted (e), producing reports of the significance and magnitude of site effects before (f) and after (g) harmonization.

Table 1: The values of $n_F$, $f_F$, and $n_t$ reported for the ABCD sample before and after harmonization with global scaling and ComBat. Note that after harmonization with ComBat, we can no longer detect any site effects. N/A is reported for the value of $n_t$ for ComBat because no t-tests were run.

| Harmonization Method | $n_F$ | $f_F$ | $n_t$ |
|----------------------|-------|-------|-------|
| None (Original Data) | 5123  | 0.43  | 24216 |
| Global Scaling       | 3266  | 0.27  | 4887  |
| ComBat               | 0     | 0     | N/A   |

where $\epsilon_{iv}$ $\sim$ $N(0, \sigma^2)$. After fitting the data to obtain the parameters $\theta_{i}^{loc}$, $\theta_{i}^{reg}$, and $\sigma^2$ at each voxel, harmonization proceeds by applying the transformation $y_i^v$ to the values of each image from site $i$. In the terminology of [5], this is a global as opposed to voxel-wise approach to harmonization. We use global scaling as a baseline global method to compare with voxel-wise methods like ComBat.

ComBat, introduced for genomics in [9] and used for imaging data in [21], is based on the model

$$y_{ijv} = \alpha_v + X_{ij}\beta_v + \gamma_{iv} + \delta_{iv}\epsilon_{ijv},$$

where $j$ indexes the subject images. Here the site effects are modeled by the parameters $\gamma_{iv}$ and $\delta_{iv}$; see [21] for details.

When applying ComBat to the ABCD data, we included age and sex as covariates in the model (i.e. the matrix $X_{ij}$ in (1)), protecting these variables from having their effects washed out by the harmonization. We used a significance level of $\alpha = 0.05$ for the ANOVA and t-tests.

Table 1 shows summary results for harmonized and unharmonized data: the number $n_F$ and fraction $f_F$ of significant ANOVA tests and the number $n_t$ of significant t-tests. Figure 2 shows a slice of each output image from the generated reports. For the unharmonized and global scaling images, all of the $\eta^2$ values from the significant ANOVA tests were found to be above 0.06. Figure 3 shows the full distribution of $\eta^2$ values, regardless of significance, for each harmonization method and for the unharmonized data.
4. DISCUSSION

We have demonstrated how HABET can be used to measure site effects in the ABCD diffusion MRI data and to compare the performance of different harmonization techniques.

In the unharmonized images, site effects were detected in nearly half (43%) of the voxels chosen for analysis. All of the corresponding effect-sizes were above 0.06, which is typically considered to be a medium effect size. In short, site effects appear to be common and of considerable magnitude in the unharmonized images.

Global scaling decreased the percentage of voxels at which site effects were detected to 27%. This is an improvement from the unharmonized images, but it is still high. Again, all of the corresponding effect-sizes were above 0.06. With ComBat, no site effects were detected. In [21], a similar vanishing of detected site effects was observed with ComBat harmonization, this could be a statement about the specificity of our site effect detector as much as it could be a statement about the effectiveness of ComBat. We can get around this limitation by incorporating spatially informed techniques for multiple testing correction.

Fig. 3: The estimated distributions of $\eta^2$ values for the unharmonized images and the images harmonized with global scaling and ComBat. Each density function was estimated from $\eta^2$ observations at each of the 11880 voxel locations under consideration. Note that all voxels are included, rather than only the ones that had a significant ANOVA.

Second, our one-way ANOVA relies on the assumption that the intensity distribution at a given voxel is normally distributed within each site, with the same variance across sites. The departure of the data from these assumptions is currently not reported.

5. CONCLUSION

In this paper, we presented a new harmonization benchmarking tool, HABET, which can be used to harmonize a multi-site dataset, compare different harmonization techniques, and evaluate new harmonization techniques. We demonstrated the use of HABET by investigating site effects in DMRI images from the ABCD study dataset and analyzing the effectiveness of ComBat compared to a simpler harmonization approach.

6. COMPLIANCE WITH ETHICAL STANDARDS

This research study was conducted retrospectively using data made available by the NIMH Data Archive. Ethical approval was not required because analyses using de-identified ABCD Study data are not considered human subjects research by NIH criteria.
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