ACROBAT - Automatic Registration of Breast Cancer Tissue

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Abstract. The ACROBAT challenge aims to advance the development of multimodal image registration algorithms for histopathological whole slide images (WSI). The objective is to align WSIs from routine pathology diagnostics with immunohistochemically (IHC) stained breast cancer tissue sections to corresponding sections stained with Haematoxylin-Eosine (H&E).

Keywords: Registration · WSI · Histopathology.

1 Introduction

Multimodal image registration enables information fusion for research and diagnostics. There is an increasing number of studies where histopathological information from one modality is used as a label to train weakly supervised models on the corresponding images in the other modalities. For example in [1, 2, 3, 4] immunohistochemical (IHC) slides are used as a local label to predict regions or objects of interest from Haematoxylin-Eosine (H&E) WSIs. In diagnostic settings, it may be interesting to overlay whole slide images (WSIs) of differently stained tissue to investigate patterns of correspondence and divergence between stains and to evaluate e.g. intra-tumor heterogeneity [5, 6, 7]. Data in digital pathology workflows is notoriously big, comparable to geographical and satellite data. Any WSI today can be of sizes exceeding 100,000 pixels wide (gigapixel), making their registration very challenging.

To enable the aforementioned research, automatic image registration is essential not only due to image sizes but also quantity, rendering a manual approach almost unfeasible. Therefore, in order to promote the development of registration methods for multi-stain WSI, we propose the ACROBAT challenge (AutomatiC

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Registration Of Breast cAncer Tissue) within the scope of the MICCAI conference (Medical Image Computing and Computer Assisted Intervention). The challenge data and description is found in the website https://acrobat.grand-challenge.org. Such a challenge will provide opportunity to develop novel algorithms and to comparably benchmark recent works.

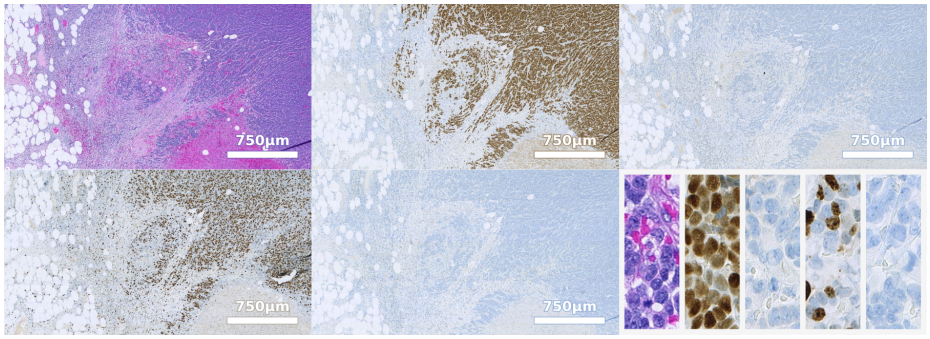

Fig. 1. Corresponding regions in each tissue section. HE is known for its pink and purple hues. IHC is known for its blue and brown hues. Brown colors mark the presence of a specific targeted protein. Each section is stained for different proteins. The targeted protein can appear in any part of a cell (nucleus, cytoplasm or membrane) and in different patterns (plain, spotted). All stains included in the challenge are routinely used in diagnosis.

Figure 1 shows an example of a corresponding region in each of the images one H&E and four IHC. The brown colored stain indicates the presence of a targeted protein, which serves as a label to look for interesting patterns and features in the corresponding areas in the H&E image. Additionally an example of the highest resolution for each image is displayed. WSI registration is particularly challenging not only due to the gigapixel scale but also to the variability in the tissue appearance for every stain. Furthermore, the micrometer-thin tissue sections can deform physically during sample preparation, some pieces can separate, move and deform independently or disappear (particularly if sections are not exactly consecutive). Routinely, sections stained with IHC may contain a control piece on the side of the slide to verify the staining, but they are completely different in each section and don't match (only the main piece of tissue matches). Figure 2 shows an example of what control pieces and deformations look like and a general overview of three IHC WSI.

Multi-stain WSI registration is therefore an active field of research and has previously been addressed in a way in the ANHIR [8] challenge, which has led to the publication of algorithms and code for several registration methods. However, it is unclear how the competing and other current WSI registration methods would perform on a real-world dataset from routine clinical workflows, where ar-

tifacts such as glass cracks, pen marks or air bubbles are common. Furthermore, the broad application of registration algorithms requires solutions that do not rely on a large number of manually generated paired landmarks for algorithm tuning but that can be optimized only with matched images. We therefore aim to release a dataset for the ACROBAT challenge that originates from routine diagnostics to assess real-world applicability. All WSIs in the challenge originate from surgical resection specimens of female primary breast cancer patients.

Some existing methods for WSI registration are summarized in [9]. Additionally frameworks are being created to wrap up existing tools like Elastix [10] to be used on WSI and histological data. More recently [11] presented a comprehensive summary of methods to use in WSIs ranging from affine to deformable, some extract and use landmarks or geometry alignment, others rely on pixel intensity information. Some search per patches, some use group registration. One thing is certain, whether existing or under development, methods have to be adjusted to work with the special needs of WSIs, which includes the performance evaluation methods. Even though artificial intelligence (AI) has been popularized in many fields, it has come somewhat later to the field of image registration, and there have been very few attempts to use AI registration methods in histological images. One of the first examples is presented in [12] further explained in [13].

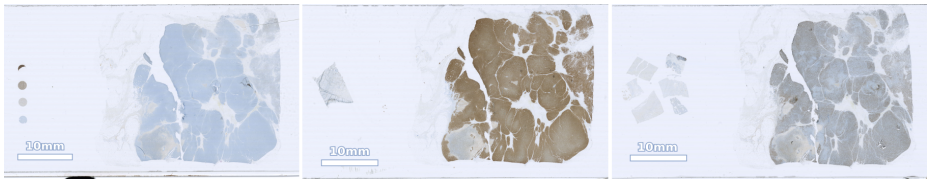

Fig. 2. Example of three IHC WSI showing control pieces that don't match and should not be included when computing alignment

We hope that the ACROBAT challenge can contribute to the development and publication of robust registration tools that can be an enabling technology for future research and diagnostics in histopathology.

2 Materials & Methods

2.1 Data

All images in this challenge are WSIs generated by Hamamatsu scanners at approximately 0.23 µm per pixel (40X). Images are provided at several lower resolutions, starting at 10X and decreasing. For each image, an anonymous case id will be provided, along with information on whether the tissue in the image was stained with H&E or immunohistochemistry and if so, which IHC stain. All images originate from FFPE fixated surgical resection specimen from female

primary breast cancer patients that were diagnosed in Sweden. Tumor resections, fixations, stainings and scanning were all performed by trained experts in the respective discipline.

The training data set will consist of 750 cases. For each case, one H&E WSIs and up to four IHC WSIs will be provided. Four routine diagnostic IHC stains will be included: ER, PGR, HER2 and KI67. The validation and test data set will consist of 100 and 300 cases respectively. Validation and test cases will only have one H&E WSI and one randomly selected IHC WSI available. Cases in the validation and test set are split off using random stratification based on clinical characteristics that pertain to the IHC stains. For test cases, we have region-level pathologist annotations for invasive cancer, carcinoma in situ, non-malignant changes, lymphovascular invasion and artefacts, which will provide us further insights on the performance of submitted solutions in different tissue types.

2.2 Landmark Annotation

Annotations will be generated by members of the ABCAP research consortium [14] using a specially designed version of TissUUmaps [15]. A version of the annotation manual with sensitive information e.g. regarding remote access removed is available on Github (https://github.com/rantalainenGroup/ACROBAT). Figure 3 shows an example of a paired landmark. First annotator annotates image pair, starting by placing landmarks in the moving image (IHC) and adjusting the location of the corresponding landmark in the target image (H&E). Once 50 landmarks have been placed, the annotations will be saved. Then, noise is added to the target image annotations. A second annotator (or further annotators) loads these annotations and moves the target image annotations to the correct locations and this way evaluate inter-observer variability.

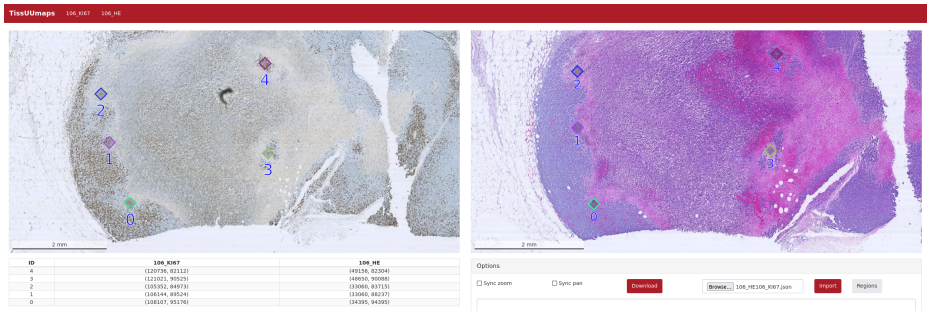

Fig. 3. Example of numbered corresponding landmarks selected and placed in the annotation tool based on TissUUmaps

2.3 Challenge Evaluation

Registered landmarks need to be submitted in metric coordinates. For each landmark, a metric distance to the human-annotated coordinates of this point will be computed. Each missing landmark in the submissions is assigned a default value that is based on the unregistered transferal of the moving image point to the target image point through padding both images to equal size. Then, for each case, we will compute the 90th percentile of the distances as the score for this image. Participants will be ranked on the mean score across all images. The code for evaluation will be shared through Github along with the annotation manual.

2.4 Leader board & Prizes

Participants will be able to submit registered landmarks and be ranked in a leader board based on the validation data starting towards the end of May 2022. The deadline for the submission of registered test set landmarks is the 19th of August 2022. The test set leader board will be revealed at the associated MICCAI workshop. Only teams that in addition to the test set landmarks also submit a brief description of their algorithm are eligible to appear in the test set leader board. After the challenge, this ranking will also be made public through the challenge website. There will be two sets of prize money in this competition. The first set will be distributed to the three highest ranked entries in the leader board. The second set will be distributed to the three top-performing methods which publish their code. Teams are eligible to receive prize money twice if applicable.

3 Discussion & Outlook

So far, 185 participants from at least 28 countries have signed up for participation. We hope that at least 25 teams will actively participate and submit an algorithm. The challenge will take place on the 22nd of September 2022 as a MICCAI workshop. We hope that it will provide a platform that enables lively discussions on the state of WSI registration.

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