Quick Annotator: an open-source digital pathology based rapid image annotation tool

Runtian Miao1, Robert Toth2, Yu Zhou1, Anant Madabhushi1,3 and Andrew Janowczyk1,4*

1Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA
2Toth Technology LLC, Dover, NJ, USA
3Louis Stokes Veterans Administration Medical Center, Cleveland, OH, USA
4Precision Oncology Center, Lausanne University Hospital, Lausanne, Switzerland

*Correspondence to: Andrew Janowczyk, Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA. E-mail: andrew.janowczyk@case.edu

Abstract

Image-based biomarker discovery typically requires accurate segmentation of histologic structures (e.g. cell nuclei, tubules, and epithelial regions) in digital pathology whole slide images (WSIs). Unfortunately, annotating each structure of interest is laborious and often intractable even in moderately sized cohorts. Here, we present an open-source tool, Quick Annotator (QA), designed to improve annotation efficiency of histologic structures by orders of magnitude. While the user annotates regions of interest (ROIs) via an intuitive web interface, a deep learning (DL) model is concurrently optimized using these annotations and applied to the ROI. The user iteratively reviews DL results to either (1) accept accurately annotated regions or (2) correct erroneously segmented structures to improve subsequent model suggestions, before transitioning to other ROIs. We demonstrate the effectiveness of QA over comparable manual efforts via three use cases. These include annotating (1) 337,386 nuclei in 5 pancreatic WSIs, (2) 5,692 tubules in 10 colorectal WSIs, and (3) 14,187 regions of epithelium in 10 breast WSIs. Efficiency gains in terms of annotations per second of 102, 9, and 39 were, respectively, witnessed while retaining f-scores >0.95, suggesting that QA may be a valuable tool for efficiently fully annotating WSIs employed in downstream biomarker studies.

Keywords: digital pathology; computational pathology; deep learning; active learning; annotations; open-source tool; nuclei; epithelium; tubules; efficiency

Introduction

The discovery of biomarkers associated with diagnosis, prognosis, and therapy response from digital pathology whole slide images (WSIs) often requires extracting features from precise segmentations of the histologic structures contained within them (e.g. cell nuclei boundaries, tubule shapes, and regions of epithelium) [1–4]. Manually annotating each instance of these histologic structures rapidly becomes intractable, even in small cohorts. For example, the number of nuclei in a single WSI can order into the hundreds of thousands, making accurately individually annotating each cell unfeasible. While a number of image analysis based algorithms have been proposed to help reduce annotation effort, they are not yet integrated into tools with user interfaces enabling their employment [5–8]. Other efforts have resulted in proprietary closed-source tools [9,10] which can be too costly to purchase in academic settings, or do not provide an open environment for facile testing and integration of new algorithms. Other approaches provide command line scripts [11] which...
are not readily employable by lay users, while additionally requiring the colocation of the user, data, and compute-infrastructure. It is thus clear that an all-inclusive computational tool designed for remote access by pathologists to aid in this annotation process at scale is needed.

Recognizing the need for a modular, user-friendly, annotation tool which significantly accelerates annotation tasks, we present here an open-source image annotation application, Quick Annotator (QA). QA is able to provide significant improvements in annotation efficiency by intelligent usage of deep learning (DL), a form of supervised machine learning which involves multiple neural network layers. QA involves integrating DL [12] with active learning [13], an interactive supervised approach for training machine learning approaches based off selective user feedback. As the user annotates structures in the web-browser based frontend, a popular DL model (u-net [14]) is trained in the backend. This DL model then makes predictions highlighting the structure, allowing the user to either accept or refine pixel-level boundaries in a rapid fashion. This approach allows the DL model to provide feedback to the user, accentuating regions in the image which require additional user input to maximally improve the performance of the next iteration of the supervised classifier. Through this iterative active learning-based process, QA empowers the end user to spend more time efficiently verifying, as opposed to painstakingly annotating histologic structures.

To aid in the annotation process, a number of common image annotation tools are provided, such as brushes and erasers of various sizes, along with polygon style annotation tools. More interestingly, QA also provides the option of highlighting image regions via the selection of DL-derived superpixels [15], which are incrementally improved as the DL model improves, facilitating high-fidelity pixel-level boundary selection (see supplementary material, Figure S1 and Section SM1). Importantly, QA is designed in an especially modular way such that, as improvements in both DL technology and architectures are discovered, they can rapidly be integrated into QA with minimal modifications to the base application. The main output from QA consists of the binary masks produced by the user in concert with QA. These masks can immediately be used for the computation of statistics or in downstream applications such as feature extraction or training a larger more sophisticated DL segmentation model. Image-level and project-level statistics related to the number of annotated objects and regions are also available for review and download. In this work, we demonstrate the utility of QA for segmentation at three scale lengths typical in computational pathology (Table 1 and supplementary material, Figure S2). At the lowest length scale, from five WSIs corresponding to pancreatic cancer, 337,386 nuclei were segmented. For the intermediate scale, from 10 WSIs containing colorectal cancer, 5,692 tubules were segmented. Lastly, for the largest scale, 14,187 regions of epithelium, totaling an area of 35,844,637 pixels, were segmented in 10 WSIs.

### Materials and methods

In accordance with the QA workflow (see supplementary material, Section SM2), each WSI was broken into tiles and processed individually. To begin, tiles originating from the same WSI were uploaded into QA, which divided these tiles into smaller 256 × 256 patches. A u-net consisting of a block depth of five layers and 113,306 parameters was trained on these image patches in an autoencoding fashion to produce a baseline model, a process shown to learn features associated with tissue presentation [16]. This base model is subsequently fine-tuned in a supervised fashion to segment the structure of interest, a common approach to help reduce annotated data requirements [17]. Next, the user viewed all patches processed by this model in a uniform manifold approximation and projection

| Tissue scale | Histologic structure | Number of slides | Number of ROIs | Number of histologic structures | QA total time (min) | QA human time (QA, min) | Manual time (M, min) | Speed up (f) | f-score |
|--------------|----------------------|-----------------|----------------|---------------------------------|-------------------|------------------------|-------------------|-------------|--------|
| Small        | Cell nuclei          | 5               | 400            | 337,386                         | 473               | 391                    | 40,165            | 102×        | 0.97   |
| Medium       | Tubules              | 10              | 100            | 5,692                           | 121               | 101                    | 923               | 9×          | 0.95   |
| Large        | Epithelium           | 10              | 100            | 14,187                          | 167               | 113                    | 4,433             | 39×         | 0.89   |

As mentioned above, the difference between QA total time and QA human time is that human time removes DL training time, as the human annotator was dismissed to perform other non-related annotation tasks. On the other hand, QA total time includes model training time under the assumption that the user kept annotating during backend training. Manual time is derived by extrapolating the measured annotations per minute from a subset of the annotations.
Figure 1. The user interface consists of (A) an embedding plot page, and (B & C) an annotation page. The embedding page is a two-dimensional representation of all patches in the system, where patches perceived to be similar by the model are plotted closely together, and updates as the model trains. By actively annotating patches across the space, the user provides more diverse training exemplars to the DL model, thus facilitating the creation of a more robust model sooner. When hovering over a dot, a preview of the patch is shown (red arrow), and subsequently clicking on the dot takes the user to the (B) annotation page centered around that patch. There, the user selects (yellow arrow) a square region which is then loaded into the high-magnification annotation window (green arrow). The user annotates positive regions in turquoise and nontarget areas in fuchsia using common image markup tools. After annotating at least three patches, the user can train a DL classifier to generate annotation suggestions in (C) white overlay. The user may then import the classifier’s suggestions into an annotation window (blue arrow) and edit, if needed, before accepting.

(UMAP [18]) plot (Figure 1A). This plot maps the high-dimensional space learned by the DL model into a two-dimensional representation such that patches perceived to be similar by the model are plotted proximally. The user selects dispersed patches for annotation (see supplementary material, Figure S3) to improve training set diversity. As the user annotates these patches (Figure 1B), the DL model begins to make suggestions which can be accepted or modified (Figure 1C).

The time to annotate the tiles is recorded to estimate a metric of structures per second, which is reported in both total time and human time. The difference between these metrics is that human time removes the DL model training time, as the human annotator can be dismissed to perform other unrelated tasks.
To form a manual baseline for comparison, an open-source digital pathology tool, QuPath [19], was employed. QuPath is one of the most widely used open-source image analysis toolkits used by researchers and pathologists, owing to its highly polished and intuitive interface, cross platform support, and ease of execution of common analytical workflows. In each use case, QuPath was used to annotate a subset of the data, forming the ground truth for comparison. In addition, the manual time needed to annotate this subset was recorded and used to compute an approximate total annotation time ($M_t$) needed for completion of the entire task. Quantitatively, efficiency improvement was defined as the ratio ($\theta_t$) between $M_t$ and QA time ($QAt$). Pixel-level $f$-scores were reported comparing the masks created in the manually annotated subset of data with that of QA-aided annotations to ensure comparable annotations were produced.

**Results and discussion**

Our results (Table 1) indicate that (1) the speed efficiency improvement afforded by QA is significant and (2) QA annotations remained highly concordant with those produced manually. It is important to note that the user is the final arbiter of what is an acceptable annotation, and always has the ability to manually adjust any pixel that they are in disagreement with. Interestingly, differences still remain in the reported $f$-scores between manual and QA produced masks. This can be attributed to the higher level of precision afforded by computational tools (Figure 2 and supplementary material, Figure S4), a phenomenon that others have reported [12,20], and which further represents an interesting opportunity for such tools to significantly improve the quality of annotated datasets. Although QA has been validated here using H&E images, given the DL-based back end, QA is agnostic to stain type and can thus be used with any stain or type of image. The small modifications needed are laid out in the supporting documentation.

Usage of QA appears to proceed in two distinct workflows. At the beginning, the user is required to provide individual manual annotations, as the model itself is not sufficiently exposed to a representative set of training exemplars. In this workflow, QA and manual annotation efficiency are comparable. This workflow quickly transitions (Figure 3) to one wherein the user effort is more focused on reviewing and accepting predictions from the DL model. Here, the efficiency gains appear to greatly improve, as with a singular click the user can accept large regions containing many structures, as opposed to manually interacting with each of them. This behavior is seen in all use cases, and interestingly creates a point of discussion on the suitability of tasks for QA. In those cases where very few structures of interest are present, such as delineating a single large tumoral region, there is likely minimal value in employing QA, and instead the slides should be annotated manually. On the other hand, when the number of individual annotations required rises, it becomes evident that employing QA may result in significant efficiency gains (see supplementary material, Section SM3).

Worth noting is that, post-installation of QA, no internet connection is required, thus making it suitable...
for non-anonymized clinical data. In fact, given the modestly sized DL networks employed, and its operating system agnostic design, recently purchased laptops are sufficiently powerful to use QA. In spite of this, one can easily host QA on a server with a powerful graphics processing unit (GPU), thus enabling remote access for, e.g., clinical pathologists to collect annotations (i.e. bringing the expert to the data) without the need for the local download and manipulation of large amounts of data (i.e. bringing the data to the expert), an often burdensome paradigm. A helpful consequence of this approach is that no software needs to be installed locally, which is often heavily restricted in clinical environments.

In conclusion, QA is a high-throughput image annotation tool being publicly released for community review, comment, and usage. QA has demonstrated significant improvements in annotation efficiency, without sacrificing annotation fidelity, and in fact often improves upon what may be possible for humans to complete without computer-aided tools. Future versions of QA are aimed at incorporating support for directly annotating WSI, as well as further hiding the latency of DL training from the user perspective. The source code of QA is freely available for use, modification, and contribution (https://github.com/choosehappy/QuickAnnotator).

Acknowledgements

Research reported in this publication was supported by the National Cancer Institute under award numbers 1U24CA199374-01, R01CA202752-01A1, R01CA208236-01A1, R01 CA216579-01A1, R01 CA220581-01A1, 1U01 CA239055-01, 1U01CA248226-01, and 1U54CA254566-01; the Ohio Third Frontier Technology Validation Fund; the National Heart, Lung and Blood Institute (1R01HL15127701A1); the National Institute for Biomedical Imaging and Bioengineering 1R43EB028736-01; the National Center for Research Resources under award number 1C06 RR12463-01; VA Merit Review Award IBX004121A from the United States Department of Veterans Affairs Biomedical Laboratory Research and Development Service; the Office of the Assistant Secretary of Defense for Health Affairs, through the Breast Cancer Research Program (W81XWH-19-1-0668), the Prostate Cancer Research Program (W81XWH-15-1-0558, W81XWH-20-1-0851), the Lung Cancer Research Program (W81XWH-18-1-0440, W81XWH-20-1-0595), and the Peer Reviewed Cancer Research Program (W81XWH-18-1-0404); the Kidney Precision Medicine Project (KPMP) Glue Grant; the Clinical and Translational Science Collaborative of Cleveland (UL1TR0002548) from the National Center for Advancing Translational Sciences (NCATS) component of the National Institutes of Health and NIH roadmap for Medical Research; and the Wallace H. Coulter Foundation Program in the Department of Biomedical Engineering at Case Western Reserve University.

The authors also thank the NVIDIA Corporation for the gift of two Titan-X GPUs. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the United States Department of Veterans Affairs, the Department of Defense, or the United States Government.

References

1. Whitney J, Corredor G, Janowczyk A, et al. Quantitative nuclear histomorphometry predicts oncopetotype DX risk categories for early stage ER+ breast cancer. *BMC Cancer* 2018; 18: 610.
2. Lu C, Koyuncu C, Corredor G, et al. Feature-driven local cell graph (FlockK): new computational pathology-based descriptors for...
prognosis of lung cancer and HPV status of oropharyngeal cancers. Med Image Anal 2020; 68: 101903.
3. Javed S, Mahmood A, Fraz MM, et al. Cellular community detection for tissue phenotyping in colorectal cancer histology images. Med Image Anal 2020; 63: 101696.
4. Fajlmezger H, Muralidhar S, Rullan A, et al. Topological tumor graphs: a graph-based spatial model to infer stromal recruitment for immunosuppression in melanoma histology. Cancer Res 2020; 80: 1199–1209.
5. Carse J, McKenna S. Active learning for patch-based digital pathology using convolutional neural networks to reduce annotation costs. In: Digital Pathology. Lecture Notes in Computer Science, Reyes-Aldasoro CC, Janowczyk A, Veta M, et al. (Eds). Springer International Publishing: Cham, 2019; 20–27.
6. Das A, Nair MS, Peter DS. Batch mode active learning on the Riemannian manifold for automated scoring of nuclear pleomorphism in breast cancer. Artif Intell Med 2020; 103: 101805.
7. Pati P, Foncubierta-Rodriguez A, Goksel O, et al. Reducing annotation effort in digital pathology: a co-representation learning framework for classification tasks. Med Image Anal 2021; 67: 101859.
8. Van Eycke Y-R, Foucart A, Decaestecker C. Strategies to reduce the expert supervision required for deep learning-based segmentation of histopathological images. Front Med (Lausanne) 2019; 6: 222.
9. Lindvall M, Sanner A, Petré F, et al. TissueWand, a rapid histopathology annotation tool. J Pathol Inform 2020; 11: 27.
10. Martel AL, Hosseinzadeh D, Senaras C, et al. An image analysis resource for cancer research: PIIP – pathology image informatics platform for visualization, analysis and management. Cancer Res 2017; 77: e83–e86.
11. Lutnick B, Ginley B, Govind D, et al. An integrated iterative annotation technique for easing neural network training in medical image analysis. Nat Mach Intell 2019; 1: 112–119.
12. Janowczyk A, Madabhushi A. Deep learning for digital pathology image analysis: a comprehensive tutorial with selected use cases. J Pathol Inform 2016; 7: 29.
13. Doyle S, Monaco J, Feldman M, et al. An active learning based classification strategy for the minority class problem: application to histopathology annotation. BMC Bioinformatics 2011; 12: 424.
14. Ronneberger O, Fischer P, Brox T. U-Net: convolutional networks for biomedical image segmentation. In: Medical Image Computing and Computer-Assisted Intervention – MICCAI 2015. Lecture Notes in Computer Science, Navab N, Hornegger J, Wells WM, et al. (Eds). Springer International Publishing: Cham, 2015; 234–241.
15. Achanta R, Shaji A, Smith K, et al. SLIC superpixels compared to state-of-the-art superpixel methods. IEEE Trans Pattern Anal Mach Intell 2012; 34: 2274–2282.
16. Janowczyk A, Basavanahally A, Madabhushi A. Stain Normalization using Sparse AutoEncoders (StaNoSA): application to digital pathology. Comput Med Imaging Graph 2017; 57: 50–61.
17. Kandel I, Castelli M. How deeply to fine-tune a convolutional neural network: a case study using a histopathology dataset. Appl Sci 2020; 10: 3359.
18. McInnes L, Healy J, Saul N, et al. UMAP: uniform manifold approximation and projection. J Open Source Softw 2018; 3: 861.
19. Bankhead P, Loughrey MB, Fernández JA, et al. QuPath: open source software for digital pathology image analysis. Sci Rep 2017; 7: 16878.
20. Doyle S, Feldman M, Tomaszewski J, et al. A boosted Bayesian multisolution classifier for prostate cancer detection from digitized needle biopsies. IEEE Trans Biomed Eng 2012; 59: 1205–1218.
21. Hou L, Gupta R, Van Arnam JS, et al. Dataset of segmented nuclei in hematoxylin and eosin stained histopathology images of ten cancer types. Sci Data 2020; 7: 185.

Reference 21 is cited only in the supplementary material.