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A Review of Current Cell Annotation Systems for Histopathology Images

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ABSTRACT

Histopathology techniques offer a unique way to study the structural and functional characteristics of biological model systems such as cultured cells, tissues and organoids. As the field of histopathology advances and more complex properties of living organisms are revealed through novel assays, there is a growing need for image analysis methods that are robust and easy to use. In many histopathology image analysis workflows, the first step is to segment cell nuclei, as they serve as the fundamental block for identifying individual cells in histopathology images. Such methods are crucial in a range of research studies, from counting cells and tracking moving populations to localizing proteins, classifying phenotypes and profiling treatments. Here, this review intended to provide an updated cell annotation system for histopathology images using the predetermined search strings and a set of inclusion criteria. Accordingly, 11 cell annotation systems (i.e., Image J, ASAP, Ilastik, Quanti.us, JS Segment Annotator, Labelme annotation tool, Labelbox, LabelImgTool, OpenSurfaces Segmentation UI, Cell Profiler and MATLAB Image Segmenter) was included. An in-depth discussion on the background of each included system was provided in this review alongside a brief comparison across different cell annotation systems.

1. Introduction

Histopathology involves the interpretation of cellular biology through visual analysis and is used for diagnostic purposes [1-4]. The field of digital pathology has emerged with the introduction of digitized images, allowing for the real-time sharing of images and video streams across different

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locations [5,6]. Digital images can be superimposed and linked together to enable spatial correlation beyond the limits of physical glass slides. These images are also suitable for computational pathology, including basic measuring and counting, as well as more advanced machine learning and deep learning tasks. With the advancement of artificial intelligence, sophisticated algorithms can now analyse digital images for features beyond traditional histopathology, such as linking images to clinical data for prognosis assessment [2-4,7,8].

Historically, digitization of histological images involved capturing single screenshots through a microscope's optics, primarily for research and teaching purposes [9,10]. However, in 1980, telepathology was introduced as a remote-operated system with a motorized microscope and a live view option of the slides. While it was only used for selected cases, technical advancements in scanning speed and cost reduction have made whole slide imaging (WSI) the future standard for large-scale, high-throughput digital pathology [6-8]. WSI requires dedicated equipment and IT infrastructure, including scanners, servers, bandwidth and workstations to minimize system downtime. It allows for tissue work-up, cutting, staining and immediate scanning of slides for access by pathologists on-site or remotely, but requires substantial IT capacity in large pathology departments [11-13]. Although orders for recuts, step-sections and additional histochemical or immunohistochemical stains can be electronically requested and subsequently scanned, the availability of glass slides upon request is still necessary for cases requiring polarization effect assessment, which cannot be performed on digital scans.

Segmenting single nuclei is a common challenge in the field of histopathology image processing as it is the initial step of numerous quantitative data analysis pipelines [9,10,14-17]. The accuracy of segmentation has a significant impact on the quality of tracking individual cells, extracting features and classifying cellular phenotypes [18].

Automated cell annotation is a technique that employs computer algorithms and prior biological knowledge to label cells or cell clusters [19]. This involves identifying a gene expression pattern or signature in a single cell or cluster that corresponds to a characteristic signature of a known cell type or state and assigning the corresponding label along with confidence scores. Figure 1 shows the overall applications of cell annotation and cell labelling in histopathology.

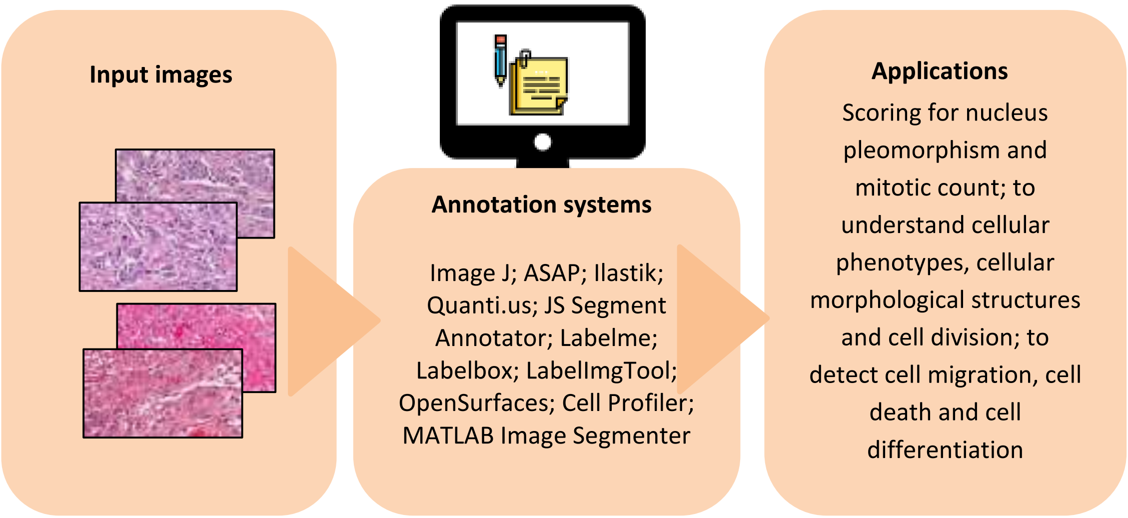

Fig. 1. Applications of cell annotation and labelling in digital pathology

The method can be applied to individual cells before or after clustering or to clusters of cells after clustering. In the case of cluster annotation, the gene expression profile of each cluster is determined by averaging the expression profiles of all cells within the cluster. Although annotating individual cells is preferred, heterogenous properties of the histopathology images with complex tissue architecture alongside overlapping cells (see Figure 2) make it challenging to accurately apply cell-based annotation [20,21]. Cluster-based annotation is faster and can be more reliable as it is based on expression level estimates averaged across all cells in a cluster. However, it may not be suitable for all cell types, particularly in dynamic systems such as developing tissues or tissues with gene expression gradients.

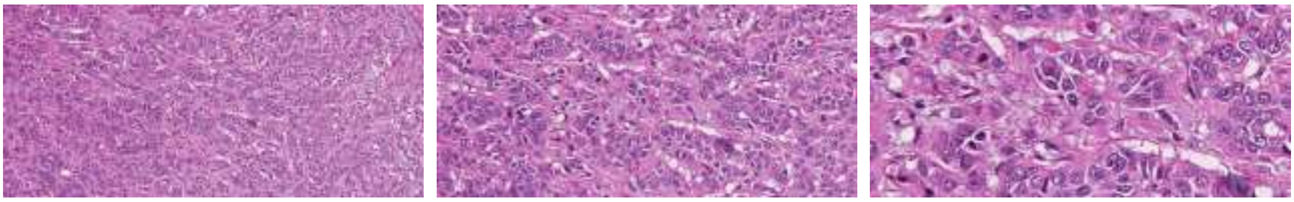
(a) (b) (c)

Fig. 2. Samples of histopathology images at different magnification level (a) 10x (b) 20x (c) 40x

2. Scope of Review

The main purposes of this review are to provide an updated insight and background into the included cell annotation systems, typically meant for cell annotation and labelling activities using histopathology images in the past decade. The included systems are meant for medical practitioners, biologists and newcomers into the field of histopathology, which is expected with limited background in information technology and computer programming. Also, the included cell annotation systems shall be adaptable and/ or specialized in biomedical applications, rather than general object labelling.

Similar to search method [22,23], to source the relevant cell annotation systems, an extensive search was performed in some of the dominant databases (i.e., Web of Science, Scopus, PubMed and Google Scholar), comprising papers from peer-reviewed journals, international conferences, book chapters and short communication. The search strings used are cell annotation; cell labelling; cell segmentation; and nuclei segmentation. To assure the included systems are aligned with the objective of this review, all the retrieved systems must abide by the predetermined inclusion criteria:

i. Systems shall reflect the scientific merit in cell annotation and/ or labelling activities while describing how the systems are used in the field of biomedical application
ii. Systems shall be a software or open interface that require minimum knowledge in information technology and computer programming
iii. Systems shall be user friendly with minimum difficulty in installation
iv. Systems shall be intended for commercial use, such that the systems do not restrict assignment to any specific scanners.

For this review, aided by the search strings and inclusion criteria aforementioned, 11 cell annotation systems were retrieved. The main objectives of these systems and sources are depicted in Table 1.

Table 1
Current cell annotation systems included in this work

Annotation systems	Main objectives	Sources			Search strings
		WOS	Scopus	Other	
Image J	Annotation-oriented systems	√	√		Cell annotation; cell labelling; cell segmentation; nuclei segmentation
Automated Slide Analysis Platform (ASAP)				√	
Ilastik		√	√		
Quanti.us		√	√		
JS Segment Annotator		√	√		
Labelme annotation tool		√	√		
Labelbox				√	
LabelImgTool				√	
OpenSurfaces Segmentation UI		√	√		
Cell Profiler	Analysis-oriented systems with optional annotation feature	√	√		
MATLAB Image Segmenter				√	

3. Systems for Current Cell Annotation Systems

The core output of the cell annotation systems is to generate the ground truth for training the selected classifier(s) or neural network architecture(s) that serve as the core of computer-aided diagnosis and prognosis systems. The ground truth comprises the creation of output masks or text files that contain object border coordinates, based on various inputs such as point labels, squiggles, rough regions/ areas covered, bounding box coordinates or closed bounding polygons that are carefully curated/ demarcated to the borders of the objects of interest.

3.1 ImageJ

ImageJ, developed by Wayne Rasband, a software tool that utilizes the Java programming language [24]. It supports image stacks, which are a series of images that can be processed in parallel on multi-CPU hardware due to its multi-threaded nature. ImageJ is capable of calculating area and pixel value statistics, measuring distances and angles, creating density histograms and line profile plots, as well as performing standard image processing functions such as logical and arithmetical operations between images, contrast manipulation, convolution, Fourier analysis, sharpening, smoothing, edge detection and median filtering. It can also perform geometric transformations such as scaling, rotation and flips and can support any number of images simultaneously depending on system memory availability.

AnnotatorJ is a plug-in for ImageJ that combines deep learning with manual annotation to accurately and reliably identify and segment individual cells in microscopy images in 2D [25,26]. It can be used as a semi-automatic tool to annotate cells or objects of interest and is particularly useful in creating datasets that reduce the manual labour of hand-annotating cells. By applying U-Net-based pre-segmentation, AnnotatorJ can help find the true contour of individual objects, significantly improving the accuracy of state-of-the-art solutions such as deep learning or when used as training data. The quality of cellular analysis affects subsequent analysis steps, such as expression measurements, which can be carried out more precisely and without bias with the help of AnnotatorJ.

3.2 Automated Slide Analysis Platform (ASAP)

The Computation Pathology Group, which is part of the Diagnostic Image Analysis Group at Radboud University Medical Centre in Nijmegen, developed ASAP in 2018 [27]. This software is an Automated Slide Analysis Platform that provides a rapid and seamless viewer for digitized histopathology images with multiple resolutions. The image I/O and processing libraries are wrapped in Python to facilitate the use of machine learning tools.

ASAP offers a range of intuitive annotation tools that allow users to create annotations such as dots, rectangles and polygons. These annotations are saved in human-readable XML format. Furthermore, the software can display image analysis and machine learning results, such as segmentation masks and likelihood maps, as overlays, which can be customized using lookup tables [28].

The primary focus of ASAP is on providing a fast and user-friendly interface for viewing images and creating annotations. The software has two main components: an I/O library for reading and writing multi-resolution images and a viewer component for visualizing such images. It also offers point, polygonal and spline annotation tools that allow for the annotation of whole-slide images, with annotations stored in simple, human-readable XML format for easy use in other software.

ASAP can read scanned whole-slide images from several different vendors, including Aperio, Ventana, Hamamatsu and Olympus and supports fluorescence images in Leica LIF format [29]. It can also write generic multi-resolution tiled TIFF files for ARGB, RGB, Indexed and monochrome images, with support for different data types such as float.

The input/ output (IO) library is wrapped in Python, which allows access to multi-resolution images through Numpy arrays. Additionally, basic image primitives or patches can be fed to image processing filters. A Qt-based viewer is also included to display whole-slide images quickly and smoothly.

Lastly, the viewer and reading library can be extended by implementing plugins using one of four interfaces: tools, filters, extensions or file formats. The software can also perform on-the-fly image processing while viewing, such as colour deconvolution and nuclei detection.

3.3 Ilastik

Ilastik is developed by Christoph Sommer and team back to 2011 [30,31]. Ilastik is an object annotation software that enables users to annotate an unlimited number of classes in images via a mouse interface. Users can train a random forest classifier using these annotations and generic (nonlinear) image features. Additionally, Ilastik has a Cell Profiler module to use Ilastik classifiers to process images within a Cell Profiler framework. This software supports image classification and segmentation.

The Ilastik repository provides a framework for creating GUI applications that utilize lazyflow-based computation pipelines and the volumina 5D image viewing kit. The Ilastik framework aims to facilitate the rapid development of user interfaces for image processing pipelines. The framework defines a straightforward GUI "shell" that functions as a container for combining a portion of a lazyflow pipeline with the GUI elements to configure it.

Pre-built binaries for Ilastik are available for all major platforms and developers and power-users can run their own Python scripts with the provided interpreter.

3.4 Quanti.us

Quanti.us was created by Hughes *et al.,* [32], is an image processing and analysis platform that utilizes crowd-based image annotation to offer an accurate solution for challenging image analysis problems. Users can take advantage of Quanti.us for medium-throughput image analysis tasks and by doing so, they can save 10-50 times more analysis time than what a single expert annotator would require for the same task. Both Quanti.us-derived and expert-derived annotations show similar deep learning performance, allowing for the integration of tailored machine learning algorithms at scale. The Annotation collection can be performed using Quanti.us, with annotations being overlaid onto images and postprocessed with custom scripts in Matlab R2015b. The machine learning system in Quanti.us has the ability to predict the centre locations of cell nuclei in 500x500 pixel images. The Quanti.us software was written using custom code in Matlab R2015b and built with Python 2.7 and Django 1.11. A comprehensive Matlab pipeline, including instructions and example images, which covers automated image pre-processing for uploading to Quanti.us, as well as several annotation post-processing and overlay options, is publicly available at https://github.com/quantius-science/. This repository contains code for the Quanti.us pre-processing pipelines, post-processing pipelines and machine learning pipeline.

3.5 JS Segment Annotator

JS Segment Annotator is a web-based image annotation tool that relies on image segmentation [33]. Users can label image regions using a mouse. To use JS Segment Annotator, users need a browser that supports HTML canvas. This software is a client-side implementation of image segmentation and users can start using it by preparing a JSON file that includes the labels and imageURLs fields. JS Segment Annotator is written in vanilla JavaScript, CSS and HTML, with a dependency on require *.js (packaged). The most recent software release occurred in March 2019.

3.6 Labelme Annotation Tool

Labelme is a web-based image annotation tool designed for graphical image annotation, taking inspiration from http://labelme.csail.mit.edu [34]. It allows users to label the identity of objects and their occurrence in images. The software has been widely used to generate high-quality annotations across various object categories for a large set of high-resolution images.

The tool incorporates advanced features like WordNet and heuristics to recover object parts and depth ordering to improve the quality, breadth and depth of the dataset. The dataset's quantitative results reflect the quality of the annotations and their potential for new research in object recognition and computer graphics.

Labelme is coded in Python and uses Qt for its graphical interface. It offers a range of annotation options, including polygons, rectangles, circles, lines and points. The software also supports image flag annotation for classification and cleaning, as well as video annotation [35]. The GUI can be customized with predefined labels or flags, auto-saving, label validation and more.

Labelme supports exporting VOC-format datasets for semantic and instance segmentation, as well as COCO-format datasets for instance segmentation. The latest software release occurred in March 2022.

3.7 Labelbox

Labelbox is an AI platform that facilitates the creation and deployment of artificial intelligence applications through efficient data annotation [22,36]. It offers a data-centric infrastructure that enables modern AI teams to quickly create training data with minimal human intervention, leading to improved model performance [37-40]. Labelbox supports various functionalities such as Catalog, Annotate, Model Training, Model Diagnostics and Boost, all of which aid in image annotation and processing. Custom Editor can be set up by users in Labelbox to further enhance their workflow. It is primarily designed to help AI teams build and operate production-grade machine learning systems. Labelbox is developed by the Labelbox company and has a stable software release as of October 2021, which uses Python SDK as its programming language.

3.8 LabelImgTool

LabelImg is a tool for graphical image annotation that utilizes a Python codebase and Qt graphical interface [41,42]. Annotation files created by the tool are saved in XML format and conform to the PASCAL VOC format, which is identical to ImageNet format.

3.9 OpenSurfaces Segmentation UI

OpenSurfaces is a crowdsourced database of surfaces that have been segmented from consumer photographs of interiors and annotated with material parameters (such as reflectance and material names), texture information (including surface normal and rectified textures) and contextual information (such as scene category and object names) [43]. It is a large and growing resource that offers rich information about real-world surfaces.

3.10 Cell Profiler

Cell Profiler is an open-source software developed by the Broad Institute's Imaging Platform [44]. The software is developed using Python programming language, intended to perform automated detection, analysis and measurement of a wide range of biological objects in images. Image thresholding and machine learning are of the common algorithms used for segmentation (i.e., object identification), recognition, segregation of overlapping objects and merging or removing of objects based on morphological features (e.g., size or shape).

The software is capable to perform automatic counting and measuring as well as to record various measurements for each object [45-47]. Common features of such including object’s location within the image, size, shape, colour intensity, degree of correlation between colours, texture and number of neighbours. Cell Profiler can process small numbers of images automatically on a personal computer or hundreds of thousands using a computing cluster. This easy-to-use software is free and enables biologists to comprehensively and quantitatively address questions that would have previously required custom programming, thereby facilitating discovery in various biological fields of study.

The resulting measurements can be viewed using Cell Profiler's built-in viewing and plotting data tools or exported in a tab-delimited spreadsheet format that can be opened in programs like Microsoft Excel and OpenOffice.org Calc. Additionally, the measurements can be exported in a format that can be imported into a database such as Oracle or MySQL or opened in MATLAB.

3.11 MATLAB Image Segmenter

MATLAB is a proprietary programming language and numeric computing environment developed by MathWorks [48,49]. It allows for matrix manipulations, function and data plotting, algorithm implementation, user interface creation and interfacing with programs written in other languages. The environment provides numerous functions that can be easily integrated into existing programs. MATLAB Image Segmenter enables users to interactively explore various segmentation techniques using apps and simplify image analysis workflows using built-in image segmentation algorithms. Users can also design and train semantic segmentation networks with a collection of images and corresponding labelled images [50]. MATLAB was invented by Cleve Moler and the latest software release was in March 2022. The program can call functions and subroutines written in C++ or Fortran and MEX files are the dynamically loadable object files created by compiling such functions. MATLAB also supports two-way interfacing with Python, which has been increasing since 2014.

4. Systems Analysis

The 11 cell annotation systems included herein are not all exclusively meant for biomedical application. Some, for example, Image J, JS Segment Annotator, Labelme annotation tool, OpenSurfaces Segmentation UI and MATLAB Segmenter, are designed for general applications, such as identifying common objects like animals, clothes and cars. However, these systems can be adapted for biomedical application by using their segmentation tools to demarcate individual cells in a similar manner to identify common objects. However, it should be noted that these systems may not be able to tackle some of the known challenges in cell segmentation, such as overlapping or clumped cells. Therefore, cell annotation systems specifically designed for biomedical application, such as ASAP, Ilastik, Quanti.us and Cell Profiler, may be superior to the aforementioned annotation systems.

As health practitioners and biologists are the primary users of these systems, ease of installation and a user-friendly layout is essential. Therefore, systems such as Image J, ASAP, Ilastik, Labelbox, LabelImg Tool and Cell Profiler are among the top choices, whereas, systems that required knowledge in information technology and computer programming such as Quanti.us, JS Segment Annotator, Labelme annotation tool and OpenSurfaces Segmentation UI may not be favoured. In terms of applicability, ASAP, Ilastik and Cell Profiler can perform multicellular segmentation, which is crucial for separating overlapping or clumped cells and/or nuclei, making them the preferred options for cell annotation and labelling procedures. Table 2 summarises the analysis of the 11 cell annotation systems.

Table 2
Analysis of the 11 cell annotation systems

Systems	Years	Platforms	Detection approaches	Advantages and disadvantages	Applications
Image J [24]	2020	Software	Various objects	Advantages: Good performance when the object of interest is in similar size and shape Disadvantages: Not suitable for 3D input image; low performance in thresholding algorithm; object tracking is pixel-oriented, hence, susceptible to noise	General; adaptable to biomedical application

ASAP [27]	2018	Software	Cell, nuclei and multicellular	Advantages: Software written in phyton to facilitate wide range of machine learning tools; fast and user-friendly Disadvantages: Not suitable for 3D input image	Biomedical application
Ilastik [30]	2019	Software	Cell, nuclei and multicellular	Advantages: Provide interactive operation; user-friendly and require minimal knowledge in machine learning to operate the software Disadvantages: High consumption of computer random-access memory (RAM)	Biomedical application
Quanti.us [32]	2018	Source code	Various objects	Advantages: A crowd-based image-annotation website; high accuracy Disadvantages: Require efforts from groups of experts; require funding to support the annotation service	General and biomedical application
JS Segment Annotator [33]	2017	Source code	Various objects	Advantages: User-friendly; allow image labelling using a mouse Disadvantages: Java Script dependent; low accuracy in complex object annotation (e.g., nucleus cells)	General; adaptable to biomedical application
Labelme annotation tool [34]	2005	Source code	Various objects	Advantages: Lightweight; user-friendly; open-source visual annotation tool Disadvantages: Limited application; effective only in the polygonal annotation	General; adaptable to biomedical application
Labelbox [36]	2023	Software	Various objects	Advantages: User-friendly; valuable tools for data annotation with collaborative features Disadvantages: Complex UI navigation; limited technical support; expensive pricing	General; adaptable to biomedical application
LabelImgTool [41]	2015	Software	Various objects	Advantages: Simple to use.	General; adaptable to biomedical application
OpenSurfaces Segmentation UI [43]	2013	Source code	Various objects	Advantages: Simple and lightweight software; very useful for small-scale applications; simple installation Disadvantages: Limited features for expert application (e.g., medical image annotation); semi-automated annotation tools; annotation quality dependent on the training dataset	General; adaptable to biomedical application

Cell Profiler [44]	2021	Software	Cell, nuclei and multicellular	<u>Advantages:</u> Build for biomedical applications; responsive technical support team; high accuracy <u>Disadvantages:</u> Required knowledge in image processing for effective software operation	Biomedical application
MATLAB Image Segmenter [48]	2022	Software	Various objects	<u>Advantages:</u> Flexible; high accuracy <u>Disadvantages:</u> High RAM consumption; required knowledge in image processing for effective software operation	General; biomedical application

5. Conclusion

In this review, with the aid of search strings and inclusion criteria, 11 cell annotation systems are included. These systems are Image J, ASAP, Ilastik, Quanti.us, JS Segment Annotator, Labelme annotation tool, Labelbox, LabelImgTool, OpenSurfaces Segmentation UI, Cell Profiler and MATLAB Image Segmenter. Overall, these systems can be clustered into two major groups: general applications with the capability to adapt to the biomedical application or biomedical-oriented applications. Cell annotation is known to be tedious, laborious and time-consuming. There is a requirement for annotation tools that are both user-friendly and reliable. Additionally, there is a need for software that can be easily used by pathologists and can save annotations in a format that can be readily interpreted by any deep learning system. These systems should also have the capability for multinomial classification of labelled objects and allow for quick and effortless manual correction of labels. While most of the existing software has sustainable features, there is still a lack of a universal standard for annotations despite their extensive usage in deep learning problems. It is our belief that the creation of a shared annotation standard would enhance the scientific community by facilitating the exchange of annotations and the pre-processing of data for deep learning training.

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