

Development of a guided tagging tool for Whole Slide Images

Master Thesis

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Preface

Hello, this is the preface

Abstract

This is the abstract.

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Chapter 1

Introduction

1.1 Motivation

The medical discipline of pathology is in a digital transformation. Instead of looking at tissue samples through the means of traditional light microscopy, it is now possible to digitize those samples. This digitalization is done with the help of a so called slide scanner. The result of such an operation is a *whole slide image* (WSI) [9]. The digital nature of WSIs opens the door to the realm of image processesing and analysis which yields certain benefits, such as the use of image segmentation and registration methods to support the pathologist in his/her work.

A very promising approach to image analysis is the use of *neural networks*¹. These are a group of computational models inspired by our current understanding of biological NN. The construct of many interconnected neurons is considered a NN (both in the biological and artificial context). Each single one of those neurons has input values and an output value. Once the input reaches a certain trigger point, the cell in the neuron sends a signal as output. The connections between the neurons are weighted and can dampen or strengthen a signal. Because of this, old pathways can be blocked and new ones created. In other words, a NN is capable of "learning" [48]. This is a huge advantage compared to other software models. While certain problems are "easier" to solve in a sequential, algorithmic fashion (say an equation or the towers of hanoi), certain problems (e.g. image segmentation or object recognition) are very complex, so that new approaches are needed, while other problems can not be solved algorithmically at all. With the use of adequate training samples, a NN can learn to solve a problem, much like a human.

In the recent past the use of NN enabled major breakthroughs, especially in the area of image classification and object recognition. Karpathy and Fei-Fei, for example, created a NN that is capable of describing an image or a scene using natural language text blocks [1] (see fig. 1.1 for a selection of examples).

¹See chapter 2.2

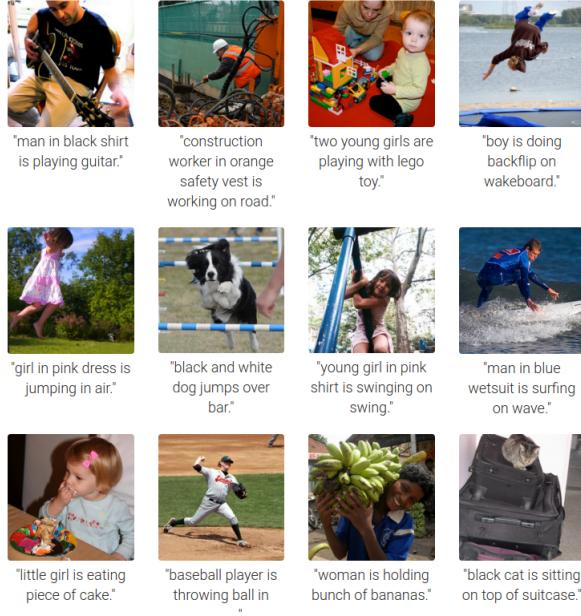


Figure 1.1: Example results of the in [1] introduced model (source: <http://cs.stanford.edu/people/karpathy/deepimagesent/>)

There is enormous potential in the use of NN in the digital pathology as well, but to transfer these models and technologies, certain obstacles must be overcome. One of those is the need for proper training samples. While generally there are large amounts of WSIs (e.g. publicly available at the Cancer Genome Atlas²), most of them will not be usable as a training sample without further preparation.

A possible way to prepare them is by using image annotation: tagging regions of interest (ROI) on an image and assigning labels or keywords as metadata to those tags. These can be added to the WSIs, stored and later used for training. The result of such an approach could be similar to the one of Karpathy and Fei-Fei [1], but with a medical context instead of daily situations.

Therefore the goal of this thesis is to provide tools for pathologists and data scientists to annotate WSIs and save those annotations in such a way that they will be usable later in combination with NN.

1.2 Research Objective

The objective of this thesis is the conceptualization and implementation of tools to prepare WSIs for the further use as training samples in NN. To achieve this,

²<https://gdc-portal.nci.nih.gov/>

a process chain with all the necessary steps needs to be established. The chain consists of the following tasks:

- (A) open WSI with a viewer tool
- (B) annotate opened WSI
- (C) extract annotations and prepare them for the use as training sample in a NN

There is no standardized WSI file format [9]. Hence, slide scanner vendors developed their own proprietary solutions. This either leads to

- (i) locking-in on a specific vendor or
 - (ii) separate handling of each proprietary format
- (i) would render the whole process chain vendor specific, limiting its use drastically. (ii) would not render the process chain vendor specific but call for a lot of additional work and maintenance, due to the separate handling of different formats. To counteract this, open file formats have been specified [9]:

- JPEG2000
- TIFF
- Deep Zoom Images (DZI)
- DICOM (supplement 145), without reference implementation as of yet [9]

Therefore, to achieve (A), the first step of the process chain is to establish a tool with which WSIs of various vendor specific formats can be turned into an open file format. This way, neither (i) nor (ii) will arise as a problem.

To achieve (A) and (B), it is also necessary to deploy a graphical user interface (GUI), that not only makes it possible to open and view a WSI (A), but also enables the user to annotate the WSI, as well as manage made annotations (B).

To achieve (C), another tool needs to be established, that is capable of turning saved annotations into training samples which are prepared for a further use in NN.

In summary: to reach the research objective of this thesis, tools to achieve the following tasks need to be established:

- (a) conversion of various WSI formats into an open format
- (b) annotation of WSIs and management thereof
- (c) extracting and preparing annotations as training samples for later use in NN

1.3 About this thesis

This thesis contains 6 chapters.

Chapter 1 - Introduction and *2 - Background* address the scope, background and vocabulary of this thesis.

The chapters 3 to 5 address the components described in the last section: *chapter 3 - Conversion Service* will describe a tool for image conversion, *chapter 4 - Annotation Service* will describe a tool for image annotation and *chapter 5 - Tessellation Service* will describe an extraction tool, to prepare the annotations made with the Annotation Service for the use in a NN.

Finally, *Chapter 6 - Conclusion* will discuss and conclude the findings of the aforementioned chapters.

Chapter 2

Background

2.1 Whole Slide Image Formats

Due to the amount of data stored in a raw, uncompressed WSI¹, file formatting and compression are required to make working with WSIs feasible. Since there is no standardized format for WSIs, vendors came up with their own, proprietary solutions, which vary greatly [9]. Efforts of standardization are being made through the *Digital Imaging and Communications in Medicine* (DICOM) Standard [14].

Usually, WSI files are stored as a multitude of single images, spanning multiple folders and different resolutions. Those files are used to construct a so called *image pyramid* [26] (see fig. 2.1 and subsection 2.1.1).

2.1.1 DICOM Supplement 145

Singh et al. [27] describe DICOM as follows:

"Digital Imaging and Communications in Medicine (DICOM), synonymous with ISO (International Organization for Standardization) standard 12052, is the global standard for medical imaging and is used in all electronic medical record systems that include imaging as part of the patient record."

Before *Supplement 145: Whole Slide Microscopic Image IOD and SOP Classes*, the DICOM Standard did not address standardization of WSI. Among others, the College of American Pathologist's Diagnostic Intelligence and Health Information Technology Committee is responsible for the creation and further advancement of this supplement [27].

It addresses every step involved in creating WSIs: image creation, acquisition, processing, analyzing, distribution, visualization and data management

¹ A typical 1,600 megapixel slide requires about 4.6 GB of memory on average [26]. The size of a H&E (hematoxylin and eosin) stained slide ranges typically from 4 to 20 GB [27].

[14]. It impacted the way how data is stored greatly [27], due to the introduction of a pyramid image model [14] (see fig. 2.1).

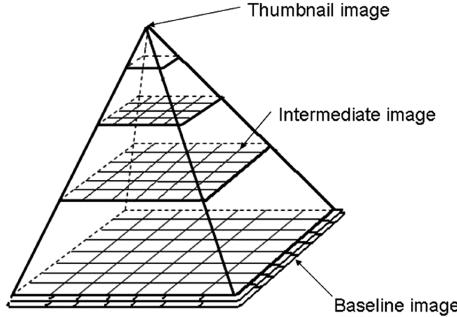


Figure 2.1: DICOMs image pyramid (source: [27])

The image pyramid model facilitates rapid zooming and reduces the computational burden of randomly accessing and traversing a WSI [27], [28]. This is made possible by storing an image in several precomputed resolutions, with the highest resolution sitting at the bottom (called the *baseline image*) and a thumbnail or low power image at the top (compare fig. 2.1) [14]. This creates a pyramid like stack of images, hence the name "pyramid model". The different resolutions are referred to as *layers* [14] or *levels* [27] respectively.

Each level is tessellated into square or rectangular fragments, called tiles, and stored in a two dimensional array [26].

Because of this internal organization, the tiles of each level can be retrieved and put together separately, to either form a subregion of the image or show it entirely. This makes it easy to randomly access any subregion of the image without loading large amounts of data [27].

2.1.2 Proprietary Formats

Vendors of whole slide scanners implement their own file formats, libraries and viewers (see tab. 2.1 for a list of vendors and their formats). Because of this, they can focus on the key features and abilities of their product. This generally leads to a higher usability, ease-of-use and enables highly tailored customer support. Furthermore, in comparison to open source projects, the longevity of proprietary software is often higher [40].

vendor	formats
Aperio	SVS, TIF
Hamamatsu	VMS, VMU, NDPI
Leica	SCN
3DHistech/Mirax	MRXS
Philips	TIFF
Sakura	SVSLIDE
Trestle	TIF
Ventana	BIF, TIF

Table 2.1: File formats by vendor

Since the proprietary formats have little to no documentation, most of the subsequently presented information was reverse engineered in [19] and [55]. All proprietary formats listed here implement a modified version of the pyramid model introduced in 2.1.1

Aperio

The SVS format by Aperio is a TIFF-based format, which comes in a single file [19]. It has a specific internal organization in which the first image is the baseline image, which is always tiled (usually with 240x240 pixels). This is followed by a thumbnail, typically with dimensions of about 1024x768 pixels. The thumbnail is followed by at least one intermediate pyramid image (compare fig. 2.1), with the same compression and tile organization as the baseline image [55]. Optionally, there may be a slide label and macro camera image at the end of each file [55].

Hamamatsu

Hamamatsu WSIs come in 3 variants:

- (1) VMS
- (2) VMU
- (3) NDPI

(1) and (2) consist of an index file ((1) - [file name].vms, (2) - [file name].vmu) and 2 or more image files. In the case of (2), there is also an additional optimization file. (3) consists of a single TIFF-like file with custom TIFF tags. While (1) and (3) contain JPEG images, (2) contains a custom, uncompressed image format called *NGR*² [55].

The random access support for decoding parts of jpeg files is poor [55]. To get around this, so called *restart markers*³ are used to create virtual slides [19]. The

²For more information on NGR, consult <http://openslide.org/formats/hamamatsu/>

³Restart markers were originally designed for error recovery. The markers allow the decoder to resynchronize at set intervals throughout the image [19].

markers are placed at regular intervals. The offset of every marker is specified in different manner. In the case of (1), it can be found in the index file. In the case of (2), the optimization file holds the information and in the case of (3), a TIFF tag contains the offset [55].

Leica

SCN is a single file format based on BigTIFF that additionally provides a pyramidal thumbnail image [19]. The first TIFF directory has a tag called "ImageDescription" which contains an XML document that defines the internal structure of the WSI [55].

Leica WSIs are structured as a collection of images, each of which has multiple pyramid levels. While the collection only has a size, images have a size and position, all measured in nanometers. Each dimension has a size in pixels, an optional focal plane number, and a TIFF directory containing the image data. Fluorescence images have different dimensions (and thus different TIFF directories) for each channel [55].

Brightfield slides have at least two images: a low-resolution macro image and one or more main images corresponding to regions of the macro image. Fluorescence slides can have two macro images: one brightfield and one fluorescence [55].

3DHistech/Mirax

MRXS is a multi-file format with complex metadata in a mixture of text and binary formats. Images are stored as either JPEG, PNG or BMP [19]. The poor handling of random access is also applicable to PNG. Because of this, multiple images are needed to encode a single slide image. To avoid having many individual files, images are packed into a small number of data files. An index file provides offsets into the data files for each required piece of data. [55].

A 3DHistech/Mirax scanner take images with an overlap. Each picture taken is then tessellated without an overlap. Therefore, overlap only occurs between taken pictures [55].

The generation of the image pyramid differs from the process described in 2.1.1 To create the n^{th} level, each image of the $n^{th} - 1$ level is divided by 2 in each dimension and then concatenated into a new image. Where the $n^{th} - 1$ level had 4 images in 2x2 neighborhood, the n^{th} level will only have 1 image. This process has no regards for overlaps. Thus, overlaps may occur in the higher levels of the image pyramid [55].

Philips

Philips' TIFF is an export from the native iSyntax format. An XML document with the hierarchical structure of the WSI can be found over the *ImageDescription* tag of the first TIFF directory. It contains key-value pairs based on DICOM tags [55].

Slides with multiple regions of interest are structured as a single image pyramid enclosing all regions. Slides may omit pixel data for TIFF tiles not in an ROI. When such tiles are downsampled into a tile that does contain pixel data, their contents are rendered as white pixels [55].

Label and macro images are stored either as JPEG or as stripped TIFF directories.

Sakura

WSIs in the SVSLIDE format are SQLite 3 database files. Their tables contain the metadata, associated images and tiles in the JPEG format. The tiles are addressed as a tuple of (focal plane, downsample, level-0 X coordinate, level-0 Y coordinate, color channel). Additionally, each color channel has a separate grayscale image [55].

Trestle

Trestles TIF is a single-file TIFF. The WSI has the standard pyramidal scheme and tessellation. It contains non-standard metadata and overlaps, which are specified in additional files. The first image in the TIFF file is the baseline image. Subsequent images are assumed to be consecutive levels of the image pyramid with decreasing resolution [55].

Ventana

Ventanas WSIs are single-file BigTIFF images, organized in the typical pyramidal scheme. The images are tiled and have non-standard metadata, as well as overlaps. They come with a macro and a thumbnail image [55].

2.1.3 Open Formats

As mentioned in 2.1.2, proprietary formats typically come without much or any documentation. Furthermore, a vendor's viewer is usually the only way of viewing WSIs of a particular format. This creates a vendor lock-in, where users can not take advantage of new improvements offered by other vendors. Furthermore, most viewers only provide support for Windows platforms. While, in a clinical setting, Windows may dominate the market, a significant amount of users in medical research prefer Linux or Mac OS X [19]. The use of mobile platforms, such as iOS or Android tablets may also have a great influence of the work flow in the future. Some vendors try to compensate for this fact with a server-based approach, which hurts performance by adding a network round-trip delay on every digital slide operation [19].

To resolve these issues, open image formats have been suggested, which will be discussed further in the following subsections.

Deep Zoom Images

The DZI format is an XML-based file format, developed and maintained by Microsoft [52]. A DZI is a pyramidal, tiled image (see fig. 2.2), similar to the one described in 2.1.1 (compare 2.1 and 2.2), with two exceptions:

1. the baseline image is referred to as the highest level, instead of the lowest; this either turns the image pyramid or its labeling upside down
2. tiles are always square, with the exception of the last column/row

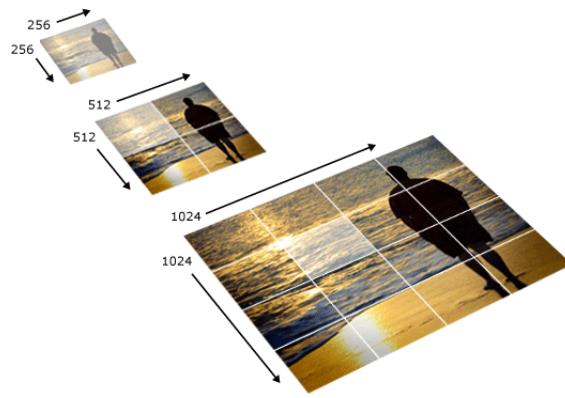


Figure 2.2: DZI pyramid model example (source: [52])

A DZI consists of two main parts [52]:

- (1) a describing XML file ([file name].dzi) with the following metadata:
 - format of individual tiles (e.g. JPEG or PNG)
 - overlap between tiles
 - size of individual tiles
 - height and width of baseline image
- (2) a directory ([file name]_files) containing image tiles of the specified format
 - (1) and (2) are stored "next" to each other, so that there are 2 separate files. (2) contains sub directories, one for each level of the image pyramid. The baseline image of a DZI is in the highest level. Each level is tessellated into as many tiles necessary to go over the whole image, with each tile having the size specified in the XML file. If the image size is no multiple of the specified tile size, the width of the n^{th} column of tiles will be $(width \bmod tile\ size)$ pixels. Equally, the height of the m^{th} row will be $(height \bmod tile\ size)$ pixels. Thus, the outermost right bottom tile $t_{n,m}$ will be of $(width \bmod tile\ size) \times (height \bmod tile\ size)$ pixels.

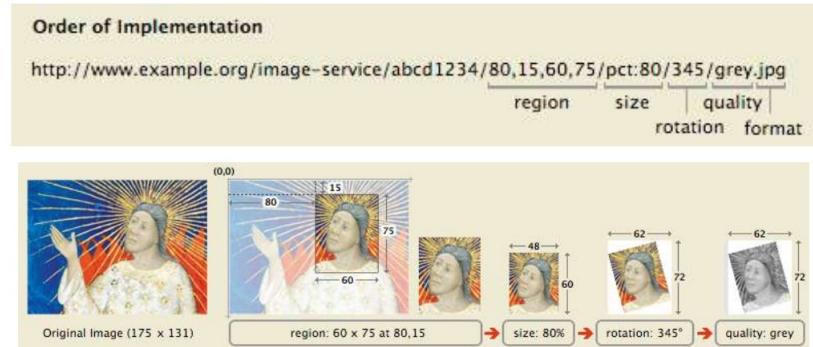
International Image Interoperability Framework

The International Image Interoperability Framework (IIIF) is the result of a cooperation between The British Library, Stanford University, the Bodleian Libraries⁴, the Bibliothèque Nationale de France, Nasjonalbiblioteket⁵], Los Alamos National Laboratory Research Library and Cornell University [10]. Version 1.0 was published in 2012.

IIIF's goal is to collaboratively produce an interoperable technology and community framework for image delivery [38]. To achieve this, IIIF tries to:

- (1) give scholars access to image-based resources around the world
- (2) define a set of common APIs to support interoperability between image repositories
- (3) develop and document shared technologies (such as image servers and web clients), that enable scholars to view, compare, manipulate and annotate images

IIIF Image Delivery API



<http://library.stanford.edu/iiif/image-api>

Figure 2.3: Example of iiif request (source:<http://www.slideshare.net/Tom-Cramer/iiif-international-image-interoperability-framework-dlf2012?ref=https://www.diglib.org/forums/2012forum/transcending-silos-leveraging-linked-data-and-open-image-apis-for-collaborative-access-to-digital-facsimiles/>)

⁴Oxford University

⁵National Library of Norway

The part relevant for this thesis is (2), especially the image API [24]. It specifies a web service that returns an image in response to a standard web request. The URL can specify the region, size, rotation, quality and format of the requested image (see 2.3). Originally intended for resources in digital image repositories maintained by cultural heritage organizations, the API can be used to retrieve static images in response to a properly constructed URL [37]. The URL scheme looks like this⁶:

```
1 {scheme}://{server}/{prefix}/{identifier}/{region}/{size}/{rotation}
   }/{quality}.{format}
```

The *region* and *size* parameters are of special interest for this thesis. With them, it is possible to request only a certain region of an image in a specified size.

The *region* parameter defines the rectangular portion of the full image to be returned. It can be specified by pixel coordinates, percentage or by the value “full” (see tab. 2.2 and fig. 2.4).

Form	Description
full	The complete image is returned, without any cropping.
x,y,w,h	The region of the full image to be returned is defined in terms of absolute pixel values. The value of x represents the number of pixels from the 0 position on the horizontal axis. The value of y represents the number of pixels from the 0 position on the vertical axis. Thus the x,y position 0,0 is the upper left-most pixel of the image. w represents the width of the region and h represents the height of the region in pixels.
pct:x,y,w,h	The region to be returned is specified as a sequence of percentages of the full image’s dimensions, as reported in the Image Information document. Thus, x represents the number of pixels from the 0 position on the horizontal axis, calculated as a percentage of the reported width. w represents the width of the region, also calculated as a percentage of the reported width. The same applies to y and h respectively. These may be floating point numbers.

Table 2.2: Valid values for *region* parameter (source: [24])

If the request specifies a region whose size extends beyond the actual size of the image, the response should be a cropped image, instead of an image with added empty space. If the region is completely outside of the image, the response should be a ”404 Not Found” http status code [24].

⁶For detailed information on all parameters see the official API: <http://iiif.io/api/image/2.0>



Figure 2.4: Results of IIIF request with different values for region parameter (source: [24])

If a region was extracted, it is scaled to the dimensions specified by the size parameter (see tab. 2.3 and fig. 2.5).

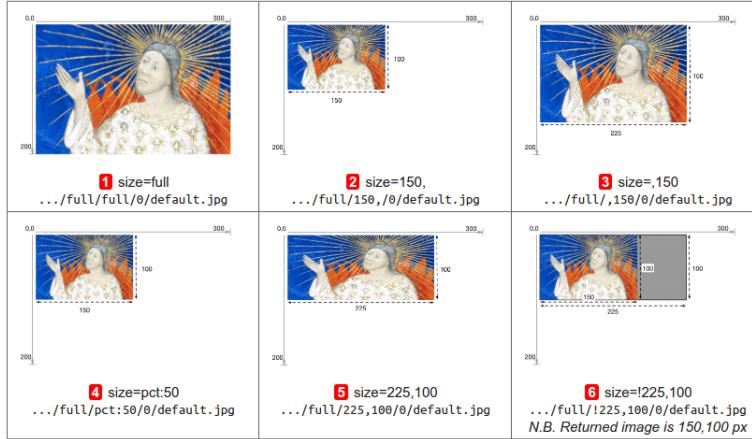


Figure 2.5: Results of IIIF request with different values for size parameter (source: [24])

If the resulting height or width equals 0, then the server should return a "400 Bad Request" http status code. Depending on the image server, scaling above the full size of the extracted region may be supported [24].

Form	Description
full	The extracted region is not scaled, and is returned at its full size.
w,	The extracted region should be scaled so that its width is exactly equal to w, and the height will be a calculated value that maintains the aspect ratio of the extracted region.
,h	The extracted region should be scaled so that its height is exactly equal to h, and the width will be a calculated value that maintains the aspect ratio of the extracted region.
pct:n	The width and height of the returned image is scaled to n% of the width and height of the extracted region. The aspect ratio of the returned image is the same as that of the extracted region.
w,h	The width and height of the returned image are exactly w and h. The aspect ratio of the returned image may be different than the extracted region, resulting in a distorted image.
!w,h	The image content is scaled for the best fit such that the resulting width and height are less than or equal to the requested width and height. The exact scaling may be determined by the service provider, based on characteristics including image quality and system performance. The dimensions of the returned image content are calculated to maintain the aspect ratio of the extracted region.

Table 2.3: Valid values for *size* parameter (source: [24])

To use the IIIF API, a compliant web server must be deployed. Loris and IIPIImageserver are examples for open source IIIF API compliant systems [37]:

- **Loris**, an open source image server based on python that supports the IIIF API versions 2.0, 1.1 and 1.0. Supported image formats are JPEG, JPEG2000 and TIFF.
- **IIPIImage Server**, an open source Fast CGI module written in C++, that is designed to be embedded within a hosting web server such as Apache, Lighttpd, MyServer or Nginx. Supported image formats are JPEG2000 and TIFF [38].

OpenStreetMap/Tiled Map Service

OpenStreetMap (OSM) is a popular tile source used in many online geographic mapping specifications [37]. It is a community driven alternative to services such as Google Maps. Information is added by users via aerial images, GPS devices and field maps. All OSM data is classified as *open data*, meaning that it can be used anywhere, as long as the OSM Foundation is credited [34].

Tiled Map Service (TMS) is a tile scheme developed by the Open Source Geospatial Foundation (OSGF) [37] and specified in [33]. The OSGF is a non-profit organization whose goal it is to support the needs of the open source geospatial community. TMS provides access to cartographic maps of geo-referenced data. Access to these resources is provided via a "REST" interface, starting with a root resource describing available layers, then map resources with a set of scales, then scales holding sets of tiles [33].

Both, OSM and TMS, offer zooming images, which in general, have the functionality necessary, to be of use for this thesis. Unfortunately, they are also highly specialized on the needs of the mapping community, with many features not needed in the context of this thesis.

JPEG 2000

[46] describes the image compression standard JPEG 2000 as follows:

"JPEG 2000 is an image coding system that uses state-of-the-art compression techniques based on wavelet technology. Its architecture lends itself to a wide range of uses from portable digital cameras through to advanced pre-press, medical imaging and other key sectors."

It incorporates a mathematically lossless compression mode, in which the storage requirement of images can be reduced by an average of 2:1. On top of that, there is a visually lossless compression mode⁷ with compression rates between 10:1 to 20:1 [41]. JPEG 2000 code streams offer mechanisms to support random access at varying degrees of granularity. It is possible to store different parts of the same picture using different quality [13].

In the compression process, JPEG 2000 partitions an image into rectangular and non-overlapping tiles of equal size (except for tiles at the image borders). The tile size is arbitrary and can be as large as the original image itself (resulting in only one tile) or as small as a single pixel. Furthermore, the image gets decomposed into a multiple resolution representation [50].

This creates a tiled image pyramid, similar to the one described in subsection 2.1.1.

The encoding-decoding process of JPEG 2000 is beyond the scope of this thesis. Therefore, it is recommended to consult either [41] for a quick overview or [50] for an in depth guide.

⁷At visually lossless compression rates, even a trained observer can not see the difference between original and compressed version [41].

TIFF/BigTIFF

The Tagged Image File Format (TIFF) consists of a number of corresponding key-value pairs (e.g. *ImageWidth* and *ImageLength*, who describe the width and length of the contained image) called *tags*. One of the core features of this format is that it allows for the image data to be stored in tiles [18].

Each tile offset is saved in an image header, so that efficient random access to any tile is granted. The original specification demands a use of 32 bit file offset values, limiting the maximum offset to 2^{32} . This constraint limits the file size to be below 4 GB [18].

This constraint led to the development of BigTIFF. The offset values were raised to a 64 bit base, limiting the maximum offset to 2^{64} . This results in an image size of up to 18,000 peta bytes [15].

TIFF and BigTIFF are capable of saving images in multiple resolutions. Together with the feature of saving tiles, the image pyramid model (as described in subsection 2.1.1) can be applied [16].

2.2 Short Introduction to Neural Networks

The objective of the workflows introduced in chapter 1.2 is to create training samples for NNs. Before going into other details, it is necessary to clarify what NNs are, how they work, why they need training samples and what they are used for⁸.

Artificial NNs are a group of models inspired by Biological Neural Networks (BNN) . BNNs can be described as an interconnected web of neurons (see 2.6), whose purpose it is to transmit information in the form of electrical signals. A neuron receives input via dendrites and sends output via axons [59]. An average human adult brain contains about 10^{11} neurons. Each of those receives input from about 10^4 other neurons. If their combined input is strong enough, the receiving neuron will send an output signal to other neurons [12].

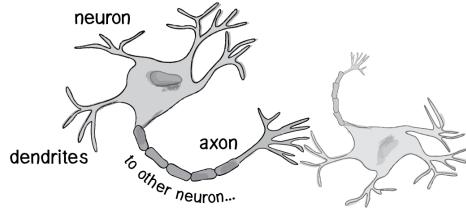


Figure 2.6: Neuron in a BNN (source: [59])

⁸ An in-depth introduction into the field of NNs is far beyond the scope of this work. For further information about NNs, consultation of literature (e.g. [8], [12], [25], [48], [59]) is highly recommended.

Although artificial NNs are much simpler in comparison⁹, they generally work in the same fashion.

One of the biggest strengths of a NN, much like a BNN, is the ability to adapt by learning¹⁰. This adaption is based on *weights* that are assigned to the connections between single neurons. Fig 2.7 shows an exemplary NN with neurons and the connections between them.

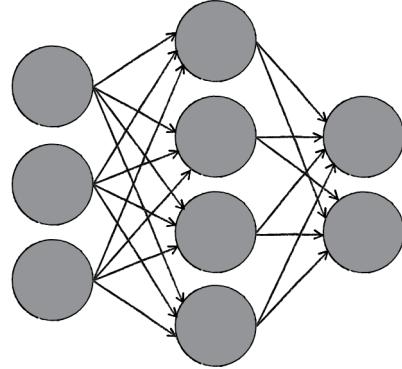


Figure 2.7: Exemplary NN (source: [59])

Each line in fig. 2.7 represents a connection between 2 neurons. Those connections are a one-directional flow of information, each assigned with a specific weight. This weight is a simple number that is multiplied with the incoming/outgoing signal and therefore weakens or enhances it. They are the defining factor of the behavior of a NN. Determining those values is the purpose of training a NN [12].

According to [59], some of the standard use cases for NN are:

- Pattern Recognition
- Time Series Prediction
- Signal Processing Perceptron
- Control
- Soft Sensors
- Anomaly Detection

2.2.1 Methods of Learning

There are 3 general strategies when it comes to the training of a NN [12]. Those are:

⁹Usually, they do not have much more than a few dozen neurons [12].

¹⁰As humans, NN learn by training [59].

1. Supervised Learning
2. Unsupervised Learning
3. Reinforcement Learning (a variant of Unsupervised Learning [57])

Supervised Learning is a strategy that involves a training set to which the correct output is known, as well as an observing teacher. The NN is provided with the training data and computes its output. This output is compared to the expected output and the difference is measured. According to the error made, the weights of the NN are corrected. The magnitude of the correction is determined by the used learning algorithm [57].

Unsupervised Learning is a strategy that is required when the correct output is unknown and no teacher is available. Because of this, the NN must organize itself [59]. [57] makes a distinction between 2 different classes of unsupervised learning:

- reinforced learning
- competitive learning

Reinforced learning adjusts the weights in such a way, that desired output is reproduced. An example is a robot in a maze: If the robot can drive straight without any hindrances, it can associate this sensory input with driving straight (desired outcome). As soon as it approaches a turn, the robot will hit a wall (non-desired outcome). To prevent it from hitting the wall it must turn, therefore the weights of turning must be adjusted to the sensory input of being at a turn. Another example is *Hebbian learning* (see [57] for further information).

In competitive learning, the single neurons compete against each other for the right to give a certain output for an associated input. Only one element in the NN is allowed to answer, so that other, competing neurons are inhibited [57].

2.2.2 The Perceptron

The perceptron was invented by Rosenblatt at the Cornell Aeronautical Laboratory in 1957 [58]. It is the computational model of a single neuron and as such, the simplest NN possible [59]. A perceptron consists of one or more inputs, a processor and a single output (see fig. 2.8) [58].

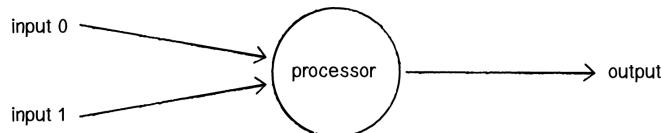


Figure 2.8: Perceptron by Rosenblatt (source: [59])

This can be directly compared to the neuron in fig. 2.6, where:

- input = dendrites
- processor = cell
- output = axon

A perceptron is only capable of solving *linearly separable* problems, such as logical *AND* and *OR* problems. To solve non-linearly separable problems, more than one perceptron is required [58]. Simply put, a problem is linearly separable, if it can be solved with a straight line (see fig. 2.9), otherwise it is considered a non-linearly separable problem (see fig. 2.10).

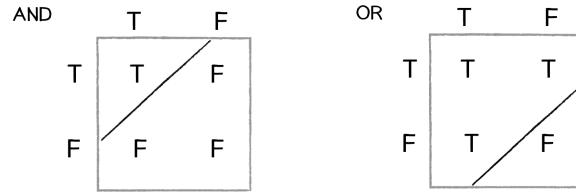


Figure 2.9: Examples for linearly separable problems (source: [59])

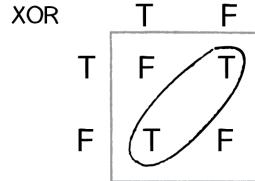


Figure 2.10: Examples for non-linearly separable problems (source: [59])

2.2.3 Multi-layered Neural Networks

To solve more complex problems, multiple perceptrons can be connected to form a more powerful NN. A single perceptron might not be able to solve *XOR*, but one perceptron can solve *OR*, while the other can solve $\neg AND$. Those two perceptrons combined can solve *XOR* [59].

If multiple perceptrons get combined, they create layers. Those layers can be separated into 3 distinct types [8]:

- input layer
- hidden layer
- output layer

A typical NN will have an input layer, which is connected to a number of hidden layers, which either connect to more hidden layers or, eventually, an output layer (see fig. 2.11 for a NN with one hidden layer).

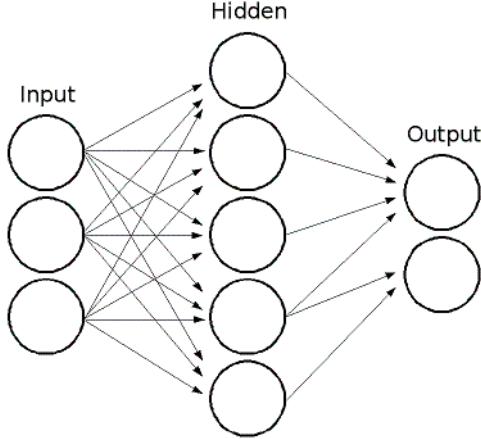


Figure 2.11: NN with multiple layers (source: http://docs.opencv.org/2.4/_images/mlp.png)

As the name suggests, the input layer gets provided with the raw information input. Depending on the internal weights and connections inside the hidden layer, a representation of the input information gets formed. At last, the output layer generates output, again based on the connections and weights between the hidden and output layer [8].

Training this kind of NN is much more complicated than training a simple perceptron, since weights are scattered all over the NN and its layers. A solution to this problem is called *backpropagation* [59].

Backpropagation

Training is an optimization process. To optimize something, a metric to measure has to be established. In the case of backpropagation, this metric is the accumulated output error of the NN to a given input¹¹. There are several ways to calculate this error, with the *mean square error*¹² being the most common one [12].

Finding the optimal weights is an iterative process of the following steps:

1. start with training set of data with known output

¹¹To do so, it is necessary to know the right answer. Therefore, backpropagation is part of the supervised learning process.

¹²Mean square error is the average of the square of the differences of two variables, in this case the expected and the actual output.

2. initialize weights in NN
3. for each set of input, feed the NN and compute the output
4. compare calculated with known output
5. adjust weights to reduce error

There are 2 possibilities in how to proceed. The first one is to compare results and adjust weights after each input/output-cycle. The second one is to calculate the accumulated error over a whole iteration of the input/output-cycle. Each of those iterations is known as an *epoch* [12].

2.3 Microservices

The following section elaborates on the concept of *Microservices* (MS), defining what they are, listing their advantages and disadvantages, as well as explaining why this approach was chosen over a monolithic approach. A monolithic software solution is described by [45] as follows:

”[...] a monolithic application [is] built as a single unit. Enterprise Applications are often built in three main parts: a client-side user interface (consisting of HTML pages and javascript running in a browser on the user’s machine) a database (consisting of many tables inserted into a common, and usually relational, database management system), and a server-side application. The server-side application will handle HTTP requests, execute domain logic, retrieve and update data from the database, and select and populate HTML views to be sent to the browser. This server-side application is a monolith - a single logical executable. Any changes to the system involve building and deploying a new version of the server-side application.”

2.3.1 Definition

MS are an interpretation of the Service Oriented Architecture. The concept is to separate one monolithic software construct into several smaller, modular pieces of software [62]. As such, MS are a modularization concept. However, they differ from other such concepts, since MS are independent from each other. This is a trait, other modularization concepts usually lack [62]. As a result, changes in one MS do not bring up the necessity of deploying the whole product cycle again, but just the one service. This can be achieved by turning each MS into an independent process with its own runtime [45].

This modularization creates an information barrier between different MS. Therefore, if MS need to share data or communicate with each other, light weight communication mechanisms must be established, such as a RESTful API [56].

Even though MS are more a concept than a specific architectural style, certain traits are usually shared between them [56]. According to [56] and [45], those are:

- (a) **Componentization as a Service:** bringing chosen components (e.g. external libraries) together to make a customized service
- (b) **Organized Around Business Capabilities:** cross-functional teams, including the full range of skills required to achieve the MS goal
- (c) **Products instead of Projects:** teams own a product over its full lifetime, not just for the remainder of a project
- (d) **Smart Endpoints and Dumb Pipes:** each microservice is as decoupled as possible with its own domain logic
- (e) **Decentralized Governance:** enabling developer choice to build on preferred languages for each component.
- (f) **Decentralized Data Management:** having each microservice label and handle data differently
- (g) **Infrastructure Automation:** including automated deployment up the pipeline
- (h) **Design for Failure:** a consequence of using services as components, is that applications need to be designed so that they can tolerate the failure of single or multiple services

Furthermore, [7] defined 5 architectural constraints, which should help to develop a MS:

(1.) **Elastic**

The elasticity constraint describes the ability of a MS to scale up or down, without affecting the rest of the system. This can be realized in different ways. [7] suggests to architect the system in such a fashion, that multiple stateless instances of each microservice can run, together with a mechanism for service naming, registration, and discovery along with routing and load-balancing of requests.

(2.) **Resilient**

This constraint is referring to the before mentioned trait (h) - *Design for Failure*. The failure of or an error in the execution of a MS must not impact other services in the system.

(3.) **Composable**

To avoid confusion, different MS in a system should have the same way of identifying, representing, and manipulating resources, describing the API schema and supported API operations.

(4.) **Minimal**

A MS should only perform one single business function, in which only semantically closely related components are needed.

(5.) **Complete**

A MS must offer a complete functionality, with minimal dependencies to other services. Without this constraint, services would be interconnected again, making it impossible to upgrade or scale individual services.

2.3.2 Advantages and Disadvantages

One big advantage of this modularization is that each service can be written in a different programming language, using different frameworks and tools. Furthermore, each microservice can bring along its own support services and data storages. It is imperative for the concept of modularization, that each microservice has its own storage of which it is in charge of [62].

The small and focused nature of MS makes scaling, updates, general changes and the deployment process easier. Furthermore, smaller teams can work on smaller code bases, making the distribution of know-how easier [56].

Another advantage is how well MS plays into the hands of agile, scrum and continuous software development processes, due to their previously discussed inherent traits.

The modularization of MS does not only yield advantages. Since each MS has its own, closed off data management¹³, interprocess communication becomes a necessity. This can lead to communicational overhead which has a negative impact on the overall performance of the system [62].

2.3.1(e) (*Decentralized Governance*) can lead to compatibility issues, if different developer teams chose to use different technologies. Thus, more communication and social compatibility between teams is required. This can lead to an unstable system which makes the deployment of extensive workarounds necessary [56].

It often makes sense to share code inside a system to not replicate functionality which is already there and therefore increase the maintenance burden. The independent nature of MS can make that very difficult, since shared libraries must be build carefully and with the fact in mind, that different MS may use different technologies, possibly creating dependency conflicts.

2.3.3 Conclusion

The tools needed to achieve the research objective stated in subsection 1.2 will be implemented by using the MS modularization patterns. Due to the implementation being done by a single person, some of the inherent disadvantages of MS are negated (making them a favorable modularization concept):

¹³See subsection 2.3.1 - *Decentralized Data Management*

- Interprocess communication does not arise between the single stages of the process chain, since they have a set order¹⁴
- Different technologies may be chosen for the single steps of the process chain, however, working alone on the project makes technological incompatibilities instantly visible
- The services should not share functionality, therefore there should be no need for shared libraries

This makes the advantages outweigh the disadvantages clearly:

- different languages and technologies can be used for every single step of the process chain, making the choice of the most fitting tool possible
- WSIs take a heavy toll on memory and disk space due to their size; the use of MS allows each step of the chain to handle those issues in the most suitable way for each given step
- separating the steps of the process chain into multiple MS leads to well separated modules, each having a small and therefore easy to maintain codebase
- other bachelor/master students may continue to use or work on this project in the future, making the benefit of a small, easily maintainable code base twice as important

2.4 Process Chain

This section and its following subsections are dedicated to establish the process chain necessary to accomplish the research objectives stated in 1.2. The usual procedure look as follows:

- (1.) convert chosen WSI img_i^{wsi} to open format img_i^{cvrt}
- (2.) open img_i^{cvrt} in a viewer V
- (3.) annotate img_i^{cvrt} in V
- (4.) persist annotations A_i on img_i^{cvrt} in a file $f_{(A_i)}$
- (5.) create training sample ts_i by extracting the information of A_i in correspondence to img_i^{cvrt}

While it only makes sense to run (1.) once per img_i^{wsi} to create img_i^{cvrt} , steps (2.) - (4.) can be repeated multiple times, so that there is no need to finish the annotation of an image in one session. That makes it necessary to

¹⁴E.g. it would not make sense trying to extract a training sample without converting or annotating a WSI first.

not only save but also load annotations. Therefore, the loading of already made annotations can be added as step (2.5). This also enables the user of editing and deleting already made annotations. Because of this, step (5.) also needs to be repeatable (see fig. 2.12).

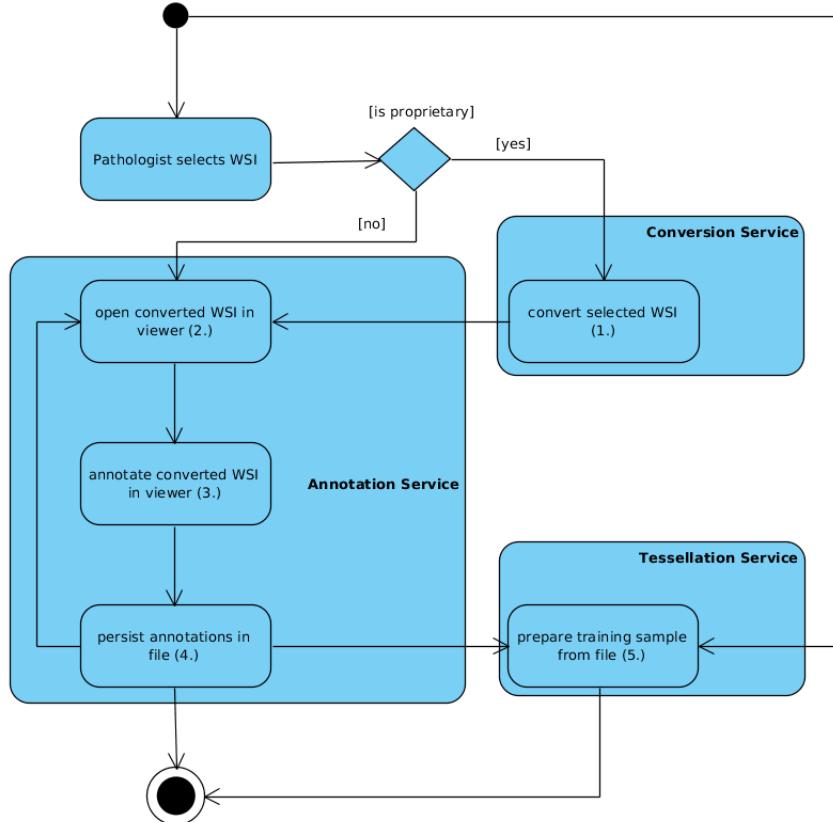


Figure 2.12: Activity diagram of the process chain

The single steps of the process chain will be sorted into semantic groups. Each group will be realized as its own MS. The semantic groups are: conversion (1.), extraction (5.) and viewing and annotation (2. - 4.).

A MS will be introduced for each group in the subsections 2.4.1 - 2.4.3). Those are:

- **Conversion Service**

This service will be responsible of the conversion from img_i^{wsi} to img_i^{cvrt} (1.).

- **Annotation Service**

This service will offer a GUI to view a img_i^{cvrt} , as well as make and manage annotations (2. - 4.)

- **Tessellation Service**

This service will be responsible for extracting a ts_i from a given A_i and img_i^{cvrt} (5.).

2.4.1 Conversion Service

The devices which create WSIs, so called *whole slide scanners*, create images in various formats, depending on the vendor system (due to the lack of standardization [9]). The Conversion Service (CS) has the goal of converting those formats to an open format¹⁵ (see fig. 2.13).

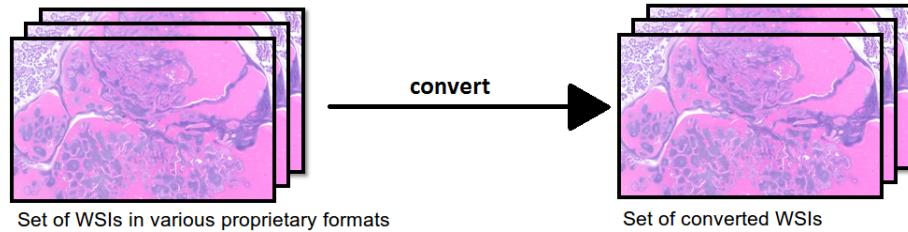


Figure 2.13: Visualization of the Conversion Service

Upon invocation, the CS will take every single WSI inside a given directory and convert it to a chosen open format. The output of each conversion will be saved in another specified folder. Valid image formats for conversion are:

- .bif
- .mrxs
- .ndpi
- .scn
- .svs
- .svslide
- .tif
- .tiff

¹⁵Compare subsections 2.1.2 and 2.1.3

- .vms

- .vmu

2.4.2 Annotation Service

As mentioned in 2.4, the Annotation Service (AS) will provide a graphical user interface to view a WSI, create annotations and manage those annotations. This also includes persisting made annotations in a file (see fig. 2.14).

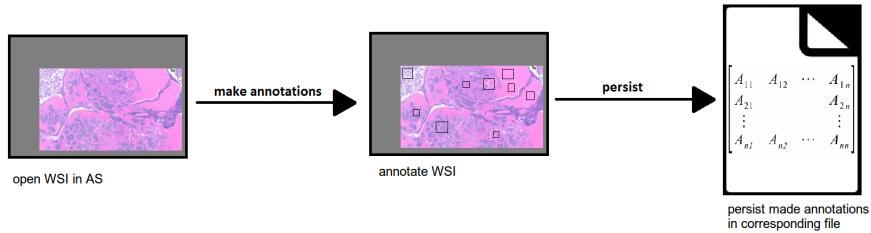


Figure 2.14: Visualization of the Annotation Service

The supplied GUI will offer different tools to help the user annotate the WSI, e.g. a ruler to measure the distance between two points. The annotations themselves will be made via drawing a contour around an object of interest and putting a specified label on that region. To ensure uniformity of annotations, labels will not be added in free text. Instead they will be selected from a predefined dictionary.

2.4.3 Tessellation Service

The task of the Tessellation Service (TS) is to extract annotations and their corresponding image data in such a fashion that they will become usable as training samples for NN.

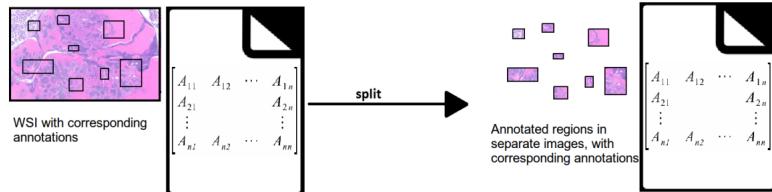


Figure 2.15: Visualization of the Tessellation Service

Let there be a WSI Img and a corresponding set of annotations A . The TS will achieve the extraction by iterating over every $a_i \in A$, creating a sub-image

img_i which is the smallest bounding box around the region described by a_i (see fig. 2.15). To be used as training sample, the TS must keep up the relationship between img_i and a_i .

Chapter 3

Conversion Service

3.1 Methodology

As stated in section 2.1, there is no standardized format for WSIs. Supplement 145 of the DICOM standard tries to unify the whole process around WSIs, but vendors still push their proprietary formats. For the reasons mentioned in subsection 2.1.3, it is necessary to establish a common format for all the WSIs which are subject to the process chain established in section 2.4. Therefore, the goal of the CS is to convert WSIs of proprietary formats into a common open format.

To make the conversion as convenient and fast as possible, the CS should only have brief user interaction. For this purpose it will not have a GUI. Instead the CS will be implemented as a console script. Furthermore, the CS should be capable of converting multiple WSIs after one another, so that no restart is necessary between conversions. Therefore, the CS will take an input directory as parameter and convert all WSIs of valid format inside that directory. Another parameter will be the output folder, in which the converted DZIs are stored.

vendor	formats
Aperio	SVS, TIF
Hamamatsu	VMS, VMU, NDPI
Leica	SCN
3DHistech/Mirax	MRXS
Philips	TIFF
Sakura	SVSLIDE
Trestle	TIF
Ventana	BIF, TIF

Table 3.1: File formats by vendor

Tab. 3.1 gives an overview of file formats, sorted by vendor, which are viable

as input for the conversion.

3.1.1 Selection of Image Format

A format or service must be chosen as conversion target for the CS. Choices have been established in 2.1.3. These are:

- (1) BigTIFF
- (2) DZI
- (3) IFFF
- (4) JPEG 2000
- (5) TMS/OMS

To convert a WSI, a conversion tool is needed. Tab. 3.2 shows a listing of possibilities for that purpose. Listed are the name of the tool, the technology used and the output format. The table indicates, that DZI has a great variety of options, while the alternatives have little to none (Map Tiler for TMS, Kakadu for IFFF and none for the others).

Deep Zoom Composer	deskstop app for Windows	DZI
Image Composite Editor	panoramic image stitcher from Microsoft Research for the Windows desktop	DZI
DeepZoomTools.dll	.NET-library, comes with Deep Zoom Composer	DZI
deepzoom.py	Python	DZI
deepzoom	Perl utility	DZI
PHP Deep Zoom Tools	PHP	DZI
Deepzoom	PHP	DZI
DZT	an image slicing library and tool written in Ruby	DZI
MapTiler	desktop app for Windows, Mac, Linux	TMS
VIPS	command line tool and library for a number of languages	DZI
Sharp	Node.js, uses VIPS	DZI
MagickSlicer	shell script (Linux/Mac)	DZI
Gmap Uploader Tiler	C++	DZI
Node.js Deep Zoom Tools	Node.js, under construction	DZI

OpenSeaDragon DZI Online Composer	Web app (and PERL and PHP scripts)	DZI
Zoomable	service, offers embeds; no explicit API	DZI
ZoomHub	service, under construction	DZI
Kakadu	C++ library to encode or decode JPEG 2000 images	IIIF
PyramidIO	Java (command line and library)	DZI

Table 3.2: Overview of conversion options for zooming image formats (source: [37])

Since the CS should only consist of brief user interaction and be as automated as possible, desktop and web applications are not valid as tools for conversion. This excludes *Deep Zoom Composer*, *MapTiler*, *OpenSeaDragon DZI Online Composer* and *Zoomable* as possible choices (therefore also excluding (next to the reasons given in subsection 2.1.3), TMS as possible format).

One of the reasons not to use proprietary formats was the support of only certain operating systems, eliminating Windows-only tools. Those are *Image Composite Editor* and *DeepZoomTools.dll*.

Furthermore, reading the proprietary formats is a highly specialized task, eliminating most of the leftover choices: *deepzoom* [5], *DZT* [17], *sharp* [35], *MagickSlicer*, *Node.js Deep Zoom Tools*¹, *Gmap Uploader Tiler* [53], *Zoomhub* [36] and *PyramidIO* [32].

Kakadu can only encode and decode JPEG 2000 images [37], making it no valid choice either.

This leaves *deepzoom.py* and *VIPS*, both creating DZI as output. Through the use of OpenSlide, they are both capable of reading all proprietary formats stated in tab. 3.1 [55].

3.1.2 Deepzoom.py

*Deepzoom.py*² is a python script and part of Open Zoom³. It can either be called directly over a terminal or imported as a module in another python script. The conversion procedure itself is analogous for both methods.

If run in a terminal the call looks like the following:

```
1 $ python deepzoom.py [options] [input file]
```

¹MagickSlicer and Node.js Deep Zoom Tools use ImageMagick to read images, which does not support any of the proprietary WSI formats [39].

²See <https://github.com/openzoom/deepzoom.py> for further details

³See <https://github.com/openzoom> for further details

The various options and their default values can be seen in 3.3. If called without a designated output destination, deepzoom.py will save the converted DZI in the same directory as the input file.

option	description	default
-h	show help dialog	-
-d	output destination	-
-s	size of the tiles in pixels	254
-f	image format of the tiles	jpg
-o	overlap of the tiles in pixels (0 - 10)	1
-q	quality of the output image (0.0 - 1.0)	0.8
-r	type of resize filter	antialias

Table 3.3: Options for deepzoom.py

The resize filter is applied to interpolate the pixels of the image when changing its size for the different levels. Supported filters are:

- cubic
- bilinear
- bicubic
- nearest
- antialias

When used as module in another python script, deepzoom.py can simply be imported via the usual *import* command. To actually use deepzoom.py, a Deep Zoom Image Creator needs to be created. This class will manage the conversion process:

```

1 # Create Deep Zoom Image Creator
2 creator = deepzoom.ImageCreator(tile_size=[size],
3     tile_overlap=[overlap], tile_format=[format],
4     image_quality=[quality], resize_filter=[filter])

```

The options are analogous with the terminal version (compare tab. 3.3). To start the conversion process, the following call must be made within the python script:

```

1 # Create Deep Zoom image pyramid from source
2 creator.create([source], [destination])

```

In the proposed workflow, the ImageCreator opens the input image img^{wsi} and accesses the information necessary to create the describing XML file for the DZI⁴. The needed number of levels is calculated next. For this, the bigger value

⁴Compare subsection 2.1.3

of height or width of img^{wsi} is chosen (see eq. 3.1) and then used to determine the number of levels lvl^{max} (see eq. 3.2) necessary.

$$max_dim = max(height, width) \quad (3.1)$$

$$lvl^{max} = \lceil \log_2(max_dim) + 1 \rceil \quad (3.2)$$

Once lvl^{max} has been determined, a resized version img_i^{dzi} of img^{wsi} will be created for every level $i \in [0, lvl - 1]$. The quality of img_i^{dzi} will be reduced according to the value specified for -q/image_quality (see tab. 3.3). The resolution of img_i^{dzi} will be calculated with the *scale* function (see eq. 3.3) for both, height and width. Furthermore, the image will be interpolated with the specified filter (-r/resize_filter parameter, see tab. 3.3).

$$scale = \lceil dim * 0.5^{lvl^{max}-i} \rceil \quad (3.3)$$

Once img_i^{dzi} has been created, it will be tessellated into as many tiles of the specified size (-s/tile_size parameter, see tab. 3.3) and overlap (-o/tile_overlap parameter, see tab. 3.3) as possible. If the size of img^{wsi} in either dimension is not a multiple of the tile size, the last row/column of tiles will be smaller by the amount of (*tile size* - ([height or width] mod *tile size*)) pixels.

Every tile will be saved as [column]_[row].[format] (depending on the -f/file_format parameter, see tab. 3.3) in a directory named according to the corresponding level i . Each one of those level directories will be contained within a directory called [filename]_files. The describing XML file will be persisted as [filename].dzi in the same directory as [filename]_files.

3.1.3 VIPS

VIPS (VASARI Image Processing System) is described as "[...] a free image processing system [...]" [11]. It includes a wide range of different image processing tools, such as various filters, histograms, geometric transformations and color processing algorithms. It also supports various scientific image formats, especially from the histopathological sector [11]. One of the strongest traits of VIPS is its speed and little data usage compared to other imaging libraries [43].

VIPS consists of two parts: the actual library (called libvips) and a GUI (called nip2). libvips offers interfaces for C, C++, python and the command line. The GUI will not be further discussed, since it is of no interest for the implementation of the CS.

VIPS speed and little data usage is achieved by the usage of a fully demand-driven image input/output system. While conventional imaging libraries queue their operations and go through them sequentially, VIPS awaits a final write command, before actually manipulating the image. All the queued operations will then be evaluated and merged into a few single operations, requiring no additional disc space for intermediates and no unnecessary disc in- and output. Furthermore, if more than one CPU is available, VIPS will automatically evaluate the operations in parallel [42].

As mentioned before, VIPS has a command line and python interface. In either case, a function called *dzsave* will manage the conversion from a WSI to a DZI. A call in the terminal looks as follows:

```
1 $ vips dzsave [input] [output] [options]
```

When called, VIPS will take the image [input], convert it into a DZI and then save it to [output]. The various options and their default values can be seen in tab. 3.4.

option	description	default
layout	directory layout (allowed: dz, google, zoomify)	dz
overlap	tile overlap in pixels	1
centre	center image in tile	false
depth	pyramid depth	onepixel
angle	rotate image during save	d0
container	pyramid container type	fs
properties	write a properties file to the output directory	false
strip	strip all metadata from image	false

Table 3.4: Options for VIPS

A call in python has the same parameters and default values. It looks like this:

```
1 image = Vips.Image.new_from_file(input)
2 image.dzsave(output[, options])
```

In line 1 the image gets opened and saved into a local variable called *image*. While being opened, further operations could be done. The command in line 2 writes the processed image as DZI into the specified output location.

3.2 Implementation

As stated before, the CS should be implemented as a script.

The first iteration was a python script using deepzoom.py for the conversion. This caused severe performance issues. Out of all the image files in the test set⁵, only one could be converted⁶. Other files were either too big, so the process would eventually be killed by the operating system, or exited with an IOError concerning the input file from the PIL imaging library.

The second iteration uses VIPS python implementation, which is capable of converting all the given test images.

The script has to be called inside a terminal in the following fashion:

```
1 $ python ConversionService.py [input dir] [output dir]
```

⁵See section 3.3

⁶CMU-3.svs from Aperio, see appendix A.1

Both the input and the output directory parameter are mandatory, in order for the script to know where to look for images to convert and where to save the resulting DZIs.

Upon calling, the *main()* routine will be started, which orchestrates the whole conversion process. The source code is as follows:

```

1 def main():
2     path = checkParams()
3     files = os.listdir(path)
4     for file in files:
5         print("-----")
6         extLen = getFileExt(file)
7         if(extLen != 0):
8             print("converting " + file + "...")
9             convert(path, file, extLen)
10            print("done!")

```

checkParams() checks if the input parameters are valid and, if so, returns the path to the specified folder or aborts the execution otherwise. Furthermore, it will create the specified output folder, if it does not exist already. In the next step, the specified input folder will be checked for its content. *getFileExt(file)* looks up the extension of each contained file and will either return the length of the files extension or 0 otherwise. Each valid file will then be converted with the *convert(...)* function:

```

1 # convert image source into .dzi format and copies all header
2 # information into [img]-files dir as metadata.txt
3 # param path: directory of param file
4 # param file: file to be converted
5 # param extLen: length of file extension
6 def convert(path, file, extLen):
7     dzi = OUTPUT + file[:extLen] + ".dzi"
8     im = Vips.Image.new_from_file(path + file)
9     # get image header and save to metadata file
10    im.dzsave(dzi, overlap=OVERLAP, tile_size=TILESIZE)
11    # create file for header
12    headerOutput = OUTPUT + file[:extLen-1] + "-files/metadata.txt"
13    bashCommand = "touch " + headerOutput
14    call(bashCommand.split())
15    # get header information
16    bashCommand = "vipsheader -a " + path + file
17    p = subprocess.Popen(bashCommand.split(), stdout=subprocess.PIPE,
18                         stderr=subprocess.PIPE)
19    out, err = p.communicate()
20    # write header information to file
21    text_file = open(headerOutput, "w")
22    text_file.write(out)
23    text_file.close()

```

The name for the new DZI file will be created from the original file name, however, the former extension will be replaced by ".dzi" (see line 7). *OUTPUT* specifies the output directory which the file will be saved to. Next, the image file will be opened with Vips' Image class. Afterwards, *dzsave(...)* will be called, which handles the actual conversion into the dzi file format. *OVERLAP* and

TILESIZE are global variables which describe the overlap of the tiles and their respective size. Their values are 0 (*OVERLAP*) and 256 (*TILESIZE*). The output will be saved to the current working directory of *ConversionService.py*, appending ”/dzi/[*OUTPUT*]”.

When a WSI gets converted into DZI by the CS, most of the image header information is lost. To counteract this, a file *metadata.txt* is created in the [name]_files directory, which serves as container for the header information of the original WSI (see line 12 and 13).

The console command *vipsheader -a* is responsible for extracting the header information (see line 17 - 18). The read information (*out* in line 18) is then written into the *metadata.txt* file (Line 20 - 22).

3.3 Test

To test the correct functionality of the CS a test data set was needed. OpenSlide offers a selection of freely distributable WSIs⁷, which can be used for that purpose.

Since the size of the WSIs is big, they are not delivered via the CS repository⁸. Instead they need to be downloaded separately from the OpenSlide homepage. For a complete listing of the used test data see Appendix A.

3.3.1 Setup

To create a controlled environment for the test, a new directory will be created, called *CS_test*. A copy of *ConversionService.py* as well as a directory containing all the test WSIs (called *input*) will be placed in that directory.

Input contains the following slides:

- (1) CMU-2 (Aperio, .svs)
- (2) CMU-1 (Generic Tiled tiff, .tiff)
- (3) OS-3 (Hamamatsu, .ndpi)
- (4) CMU-2 (Hamamatsu, .vms)
- (5) Leica-2 (Leica, .scn)
- (6) Mirax2.2-3 (Mirax, .mrxs)
- (7) CMU-2 (Trestle, .tif)
- (8) OS-2 (Ventana, .bif)

⁷See OpenSlides Homepage: <http://openslide.cs.cmu.edu>, or directly for the test data: <http://openslide.cs.cmu.edu/download/openslide-testdata/>

⁸See <https://github.com/SasNaw/ConversionService>

Because of their structure, (4), (6) and (7) will be placed in directories titled with their file extension. Fig. 3.1 shows the content of the input folder.

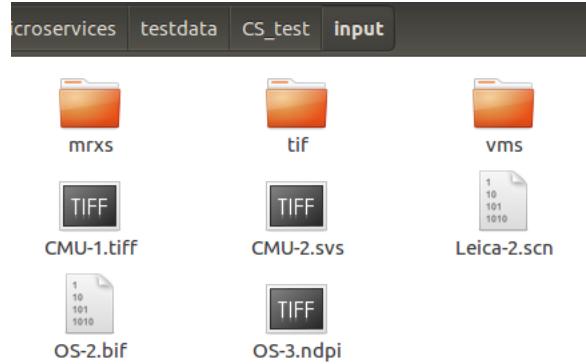


Figure 3.1: Content of input directory

This makes multiple calls of the CS necessary. The calls, in that order, are:

```

1 $ python ConversionService.py input/ out_1/
2 $ python ConversionService.py input/mrxs out_2/
3 $ python ConversionService.py input/tif out_3/
4 $ python ConversionService.py input/vms out_4/

```

3.3.2 Result

All runs of `ConversionService.py` were successful. Tab. 3.5 shows an overview of the results:

input	output	time (sec)
input/	CMU-1.dzi, CMU-2.dzi, Leica-2.dzi, OS-2.dzi, OS-3.dzi	1992
input/mrxs/	Mirax2.2-3.dzi	500
input/tif/	CMU-2.dzi	56
input/vms/	CMU-2-40x - 2010-01-12 13.38.58.dzi	305

Table 3.5: Results of Conversion Service Test

The vast difference in file size of the test data accounts for the different run times of the tests. While the first test converted 5 WSIs (399 sec/WSI), every other test converted a single one. The conversion of (6) was much faster, since the file was smaller in size (304.22 MB) compared to the others (1495.24 MB on average).

Chapter 4

Annotation Service

4.1 Objective of the Annotation Service

As described in 2.4.2, the goal of the AS is to provide a user with the possibility to:

- (1) view A WSI
- (2) annotate a WSI
- (3) manage made annotations

In order to achieve objective (1) - (3), a GUI needs to be deployed which supports the user in working on those tasks. (3) also adds the need for file persistence management.

It became clear during the development process that the support of only DZI was impractical for the real life environment of the AS, thus making it necessary to support proprietary formats as well. A solution has to be found, that still addresses the vendor and platform issues stated in 1.2 and 2.1.3.

4.2 Functionality of the Annotation Service

The goal of viewing a WSI (1) is a straight forward task. (2) and (3) are more elusive. For that reason, this subsection elaborates on the functionality needed to help achieve those objectives.

Annotations will be created by drawing directly onto the viewed WSI. If the user spots a region of interest, a contour can be drawn around it. This can either be done in *free hand* or *polygon mode*. In free hand mode, the contour will be drawn along the path of the mouse pointer, until the mode is disabled again. Upon deactivation, the contour will be closed. In polygon mode, the user can place coordinates which will be connected from one to another in the order they are placed in. A contour in this mode considers to be closed, once

a point on the contour is clicked a second time. A marked region of interest is simply called *region* from this point on.

The information what a region is surrounded by can be as valuable as the information about the region itself [4]. Therefore, every region will have a *context* trait, which lists every label of regions it touches, crosses, surrounds or is surrounded by (see fig. 4.1).

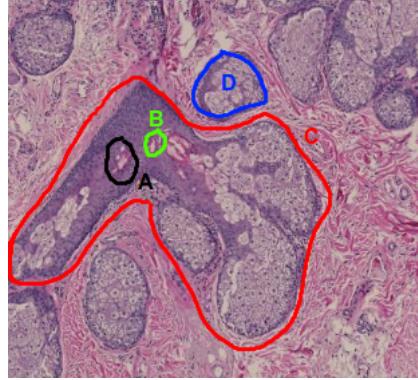


Figure 4.1: Example of context regions (B, C are context of A; A, C are context of B; A, B are context of C; D has no context region)

Another way of creating regions will be so called *points of interest* (POI). A POI will be placed with a mouse click. After that, an external script will be invoked to run an automated segmentation in the proximity of the POI and return with a contour which will be marked as region. The segmentation approaches may differ drastically in different scenarios [49], therefore the script will be interchangeable¹.

Each region has a *label* associated to it. A label is a predefined string, which describes what the region just created shows. The labels available will be determined through a *label dictionary*, which is a container that offers a list of strings to select from. This approach guarantees a unified labeling, independent of a specific WSI or pathologist. The option to choose between multiple available label dictionaries opens up the possibility of creating dictionaries which are specialized on certain cases or studies. Again, to keep up labeling integrity, labels can only be selected from one dictionary per WSI.

Users will be able to create new, empty dictionaries, if the need arises. Furthermore, they will be able to add entries to existing and new dictionaries alike, to further advance or specialize them. To delete single entries or whole dictionaries, file access to the server is necessary. This is due to the fact, that

¹There are many different ways of how to approach the topic of segmentation (e.g. [22], [23], [29], [44] for cell segmentation alone). Writing a fully working segmentation script is worth another thesis by itself, therefore only a dummy implementation will be delivered with this work.

knowledge can be added without direct negative consequences. Deleting existing knowledge influences all WSIs on which this knowledge was used, may it be as a label or a whole dictionary.

To support the user in annotating a WSI, a distance measurement tool will be usable as well. This tool can measure the distance between 2 pixels in μm .

4.3 Methodology

As stated in 2.1.3, most vendors have proprietary image formats and their own implementation of a viewer for those, thus creating a vendor lock-in. Further do vendors often support only Windows platforms, ignoring other operating systems [9], [14], [26]. To avoid this, a solution must be found that is independent of operating system and vendor.

Independence from an operating system can be achieved by using web technologies, especially when running an application in a web browser, since those are supported by all modern operating systems and even mobile platforms [21].

To develop the AS as a web application means to become subject to *cross-origin resource sharing* (CORS) [47] and the *same-origin policy* (SOP) [51]. The SOP is a security concept of the web application security model, that only allows direct file access if the parent directory of the originating file is an ancestor directory of the target file [51]. Since the local WSI file will not have the same origin, CORS is needed. CORS is a standard that defines mechanisms to allow access to restricted resources from a domain outside of the origin, when using the HTTP protocol [47]. Since the WSI is a local file, HTTP can not be used to retrieve the file.

The restrictions of SOP and CORS can be worked around by deploying a server as so called *digital slide repository* (DSR). A DSR manages storage of WSIs and their metadata [9]. This way, WSIs would share the same origin as the viewer and their retrieval would be possible.

Using a DSR has additional advantages:

- WSIs are medical images and as such confidential information. Their access is usually tied to non-disclosure or confidentiality agreements (e.g. [54] or [61]). A DSR eliminates the need to hand out copies of WSIs, which makes it easier to uphold the mentioned agreements.
- WSIs take up big portions of storage [27]. The local systems used by pathologists in the environment of the AS are usual desktop computers and laptops. As such, their storage might be insufficient to hold data in those quantities. A DSR can be set up as a dedicated file server, equipped for the purpose of offering large amounts of storage.
- A DSR enables centralized file management. Pathologists don't access local their local version of a WSI and its annotations, but share the same data pool.

- Depending on the network setup, other advantages become possible, e.g. sharing of rare cases as educational material and teleconsultation of experts independent of their physical position [20].

Chapter 3 established a service to convert WSIs of various, proprietary formats to DZI, addressing the need to implement multiple image format drivers. But, as stated in 4.1, a solution to serve proprietary image formats without explicit conversion must be found.

OpenSlides Python provides a DZI wrapper. This wrapper can be used to wrap a proprietary WSI and treat it as a DZI [55]. A DSR can use this to serve a proprietary WSI as DZI to a viewer.

For the reasons mentioned above, the AS will be implemented as a web application. To do so, it will be split into 2 parts: a DSR and a viewer.

4.4 Parts of the Annotation Service

As described in section 4.3, the AS will be realized in 2 separate parts:

- a DSR, called *Annotation Service Server* (ASS)² (see subsection 4.4.1)
- a viewer, called *Annotation Service Viewer* (ASV) (see subsection 4.4.2)

The ASS will be responsible for data management, supplying image data and serving the ASV to the client. The ASV will supply a GUI, including a WSI viewer and all functions specified in section 4.2.

The two components interact as follows: once the client requested a valid image URL, the ASS will check if the requested WSI is a DZI and, if so, render a ASV with the image path, MPP and file name of the WSI. If the WSI is proprietary, it will be wrapped by OpenSlide. The remaining procedure is then identical to the DZI case.

The ASV is returned to the client and requests the data necessary to view the WSI and its annotation if they should already exist (this includes configurations, annotations, labels and the image tiles for the current view).

Once loaded, the client can change the current view to maneuver through the different levels and image tiles available, which will be requested by the ASS whenever needed. Additionally, annotations can be made and persisted at any time.

See fig. 4.2 for a diagram of how the ASS and ASV interact with each other.

4.4.1 Annotation Service Server

As described in section 4.3, the ASS serves as a DZR. As such it is responsible for the storage of WSI files and their related metadata [9]. Additional data managed by the ASS will be:

- annotation data

² ASS is pronounced "A2S".

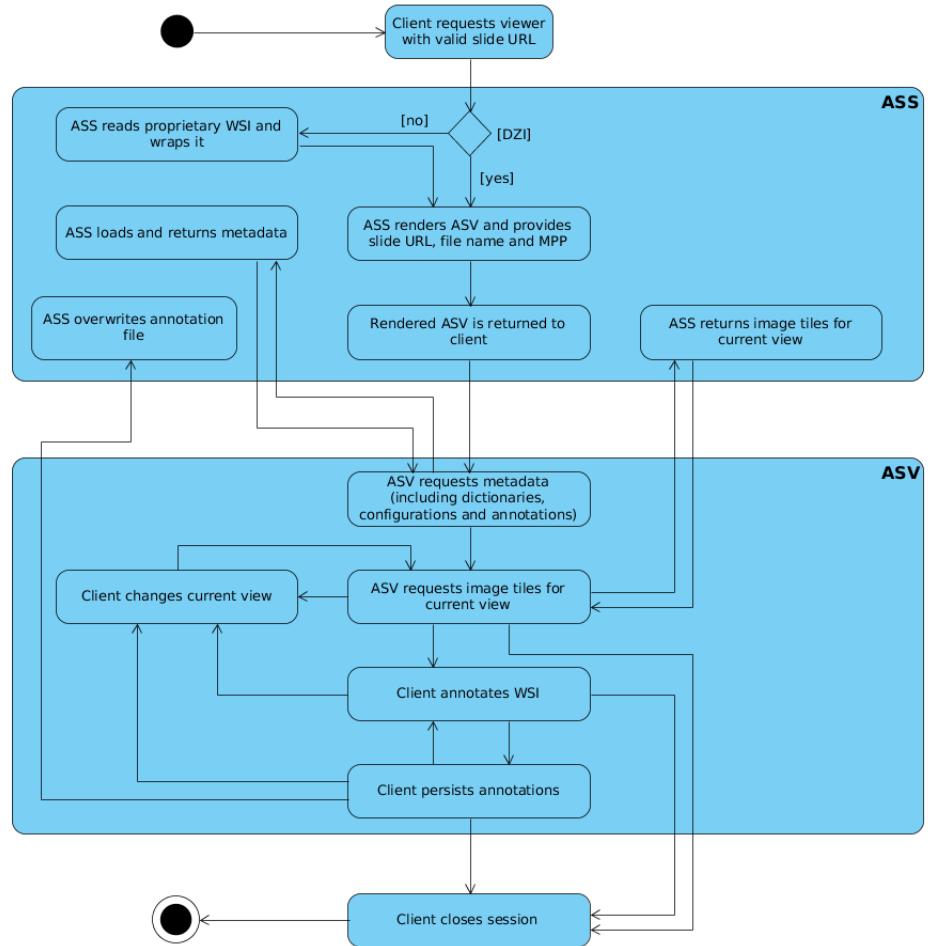


Figure 4.2: Activity diagram of ASS and ASV

- the ASV's configuration data
- dictionary data

Communication with the ASS directly is only necessary to request the rendering of an ASV with a WSI. Once the ASV is rendered, communication can be handled through shortcuts in the ASV.

Communication between ASS and client, as well as ASS and ASV, will be realized over a RESTful API³ offered by the ASS.

The development of a fully functional web server is not within the scope of this thesis. Therefore, the ASS will run as a local web server. This works around many of the common issues when hosting a web server (e.g. inefficient caching, load balance issues, gateway issues, poor security design, connectivity issues) [2].

4.4.2 Annotation Service Viewer

The ASV is developed to deploy a GUI through which the pathologist is enabled to view a WSI and annotate it (see section). The ASV is developed in an iterative approach with the help of selected pathologists. After each iteration, the GUI and user experience (UX) will be evaluated. This way, the ASV can be adapted to the needs of a real life environment based on the pathologists feedback.

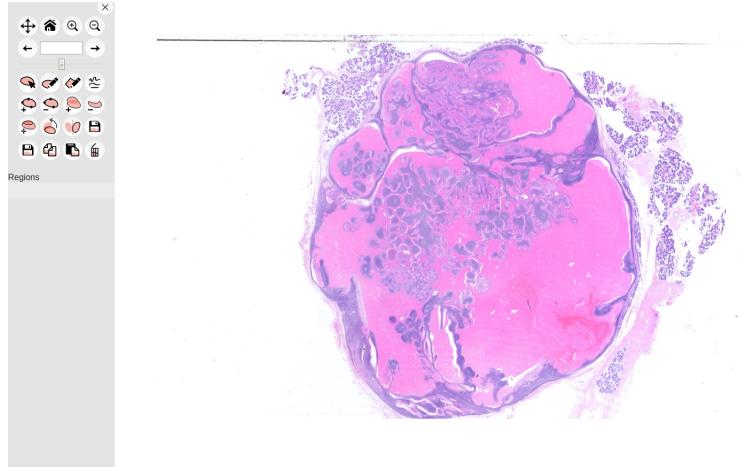


Figure 4.3: Microdraw GUI with opened WSI

The first iteration of the ASV will be based on an open source project called *MicroDraw*⁴ (see fig. 4.3 for MicroDraws GUI). MicroDraw is a web application to view and annotate "*high resolution histology data*" [3]. The visualization is based on another open source project, called *OpenSeadragon* [37]. Annotations

³ *Representational State Transfer* (REST) is an architectural style for developing web applications. It was established in 2000 by Fielding in [30]. A system that complies to the constraints of REST can be called RESTful. Typically, RESTful systems communicate via the HTTP protocol [30].

⁴See <https://github.com/r03ert0/microdraw> for more information on the MicroDraw project

are made possible by the use of *Paper.js*⁵. This delivers a baseline for the functionality specified in 4.2 and can be further adjusted to the needs of the ASV.

Apart from the frameworks used, MicroDraw is written in JavaScript using HTML5, CSS3 and jQuery⁶.

4.5 Annotation Service Server Implementation

The ASS is a local server, implemented in python (*as_server.py*). It offers a RESTful styled API for communication (see subsection 4.5.4). To improve functionality, the following frameworks were used:

- Flask (see subsection 4.5.1)
- OpenSlide Python (see subsection 4.5.2)

All code snippets in the following subsections have been taken from *as_server.py*. A detailed documentation of the individual functions can be found in appendix B.1.

4.5.1 Flask

To give ASS its server capabilities, Flask was used⁷. It provides a built-in development server, integrated unit testing, RESTful request dispatching and is Web Server Gateway Interface⁸ (WSGI) compliant [31].

Flask's so called *route()* decorator provides a simple way to build a RESTful API for server client communication:

```

1 @app.route('/loadJson')
2 def loadJson():
3     ...
4
5 @app.route('/createDictionary')
6 def createDictionary():
7     ...
8
9 @app.route('/getDictionaries')
10 def getDictionaries():
11     ...

```

Decorating a function with `@app.route([URL])` will bind it to the supplied URL. When the client requests that bound URL, the server will call the decorated function [31]. The code snippet above shows exemplary how to use decorators.

⁵See <http://paperjs.org/> for more information on Paper.js

⁶See <https://jquery.com/> for more information on jQuery

⁷ See Flasks homepage for additional information: <http://flask.pocoo.org/>

⁸ The WSGI is a standard interface for the communication between web servers and web applications or frameworks in python. The interface has a server and application side. Basically, the server side invokes a callable object that is provided by the application side. The specifics of providing this object are up to the individual server [6].

A bound URL can also contain variable sections, which are marked as *<variable name>*. Optionally, a converter can be used to only accept variables of a certain type. This becomes possible by specifying the converter in front of the variable: *<converter:variable name>* [31]. The following code snippet shows possible examples for URLs with variables (see tab. 4.1 for a list of available converters):

```

1 @app.route('/wsi/<path:file_path>.dzi')
2 def index_dzi(file_path):
3     ...
4
5 @app.route('/wsi/<path:file_path>')
6 def index_wsi(file_path):
7     ...
8
9 @app.route('/<slug>.dzi')
10 def dzi(slug):
11     ...
12
13 @app.route('/<slug>-files/<int:level>/
14 <int:col>,<int:row>.<format>')
15 def tile(slug, level, col, row, format):
16     ...

```

To bind a URL with one or more variables, the corresponding function must be parameterized with same variables (compare line 1 and 2 or 13 - 14 and 15) [31].

name	accepted input
string	any text without a slash (default)
int	integer values
float	floating point values
path	like string, but also accepts slashes
any	matches one of the items provided
uuid	UUID strings

Table 4.1: Available converters in Flask (source: [31])

HTTP knows different methods for accessing URLs (such as GET or POST) [60]]. Flask will answer only GET requests by default. Any other method is answered with a "405 Method not allowed" HTTP status code [31]. This can be changed by adding the *methods* argument to the decorator:

```

1 @app.route('/saveJson', methods=['POST'])
2 def saveJson():
3     ...

```

4.5.2 OpenSlide Python

To read a WSI, ASS uses OpenSlide Python, which is a python interface to the OpenSlide C library. Besides providing an interface to read a WSI, it offers a DZI wrapper [55], called *DeepZoomGenerator* (DZG). The DZG can be used to create Deep Zoom tiles on demand. The following formats are supported by OpenSlide [55]:

- BIF
- NDPI
- MRXS
- SCN
- SVS
- SVSLIDE
- TIF
- TIFF
- VMS
- VMU

This list is identical to the list of image formats supported by the CS (compare chapter 3. This is due to the fact that *VIPS* uses OpenSlide to read WSIs as well [11].

OpenSlide can read a proprietary WSI as a so called *OpenSlide* object (see line 4):

```
1 from openslide import open_slide
2 from openslide.deepzoom import DeepZoomGenerator
3
4 slide = open_slide(slide_path)
5 dzg = DeepZoomGenerator(slide[, tile_size, overlap, limit_bounds])
```

An OpenSlide object offers methods to access available metadata, image tiles, the thumbnail image and associated images, if available⁹. The OpenSlide object can be wrapped with a DZG to enable DZI support (see line 5) [55]. A number of optional parameters can be passed into the constructor as well (see tab 4.2 for parameters and their default values).

⁹ See the OpenSlide documentation for further information: <http://openslide.org/api/python/>

parameter	type	description (default value)
osr	OpenSlide, ImageSlide	the slide object (mandatory)
tile_size	integer	the width and height of a single tile (254)
overlap	integer	the number of extra pixels to add to each interior edge of a tile (1)
limit_bounds	boolean	true to render only the non-empty slide region (false)

Table 4.2: DZG parameters (source: [55])

The DZG¹⁰ generates all data necessary, to work with a proprietary WSI as if it would be a DZI [55]. Of special importance are the `get_dzi(format)` and `get_tile(level, address)` functions.

`get_dzi(format)` generates a string containing the complete metadata of a DZI XML file¹¹. The parameter (`format`) specifies the format (PNG or JPEG) of the individual Deep Zoom tiles.

`get_tile(level, address)` returns an image of the tile corresponding to the provided parameter values (see tab. 4.3). The tiles are returned either as PNG or JPEG, depending on which format was chosen for `get_dzi(format)`,

name	type	description
level	integer	the DZI level to get the tile from
address	tuple	the address of the tile within the level as a (column, row) tuple

Table 4.3: Description of `get_tile(level, address)` parameters (source: [55])

The use of the DZG enables ASS to create DZI metadata and Deep Zoom tiles from proprietary WSI files on demand.

4.5.3 Setup

To provide static files to Flask a `static/` directory must be present at the root level of the ASS. This directory contains the CSS, JavaScript, dictionary, configuration and WSI files. To make a WSI accessible to the ASV, it must be placed in `static/wsi/`. From there, the file path is arbitrary.

To provide a segmentation script, it must be placed in `static/segmentation`. Furthermore, the name of the script must be adjusted in the configuration file (`"segmentationScript"` in `configuration.json`, see tab. 4.4 for a list of all configurable parameters).

¹⁰ For an in-depth list of functions, see <http://openslide.org/api/python/>

¹¹ Compare subsection 2.1.3 - Deep Zoom Images

parameter	description	standard
defaultFillAlpha	Default alpha value for regions	0.5
defaultStrokeColor	Default color for region strokes	black
defaultStrokeWidth	Default width for region strokes	1
dictionary	Name of currently active dictionary	example.json
hideToolbar	Hide toolbar when ASV is rendered	false
segmentationScript	Script used for segmentation of POIs	opencv.py

Table 4.4: Configurable parameters in configuration.json

The ASS can be started from a terminal through the use of a python interpreter:

```
1 $ python as_server.py
```

Alternatively, python's -m switch can be used:

```
1 $ export FLASK_APP=as_server.py
2 $ python -m flask run
```

When started, the server will listen on 127.0.0.1:5000 by default. Another port (-p, --port) or IP address (-l, --listen) can be specified when starting the ASS. Additionally, DZG-related parameters can be changed (see tab. 4.5).

parameter	description	default
-B, --ignore-bounds	render only the non-empty slide region	false
-e, --overlap	set overlap between adjacent tiles in pixels	0
-f, --format	set tile format (PNG or JPEG)	JPEG
-l, --listen	set IP address to listen to	127.0.0.1
-p, --port	set port to listen to	5000
-Q, --quality	set JPEG compression quality in %	100
-s, --size	set tile size	256

Table 4.5: Parameters for as_server.py

To retrieve a WSI from the ASS, the URL must be pointed to it in the following manner: *http://[host]:[port]/wsi/[file path]* (see fig. 4.4 for an example).



Figure 4.4: Example URL to retrieve WSI (<http://127.0.0.1:5000/wsi/CMU-1.svs>) ; WSI source: OpenSlides freely distributable test data (see appendix A.1)

4.5.4 RESTful API

To communicate with the ASS a RESTful API was deployed. This is realized with Flasks route() decorators¹². The listing below gives an overview over the URLs that the ASS RESTful API offers (in the style of **URL** (method): *function(parameters)*), followed by a brief description of the functionality¹³:

- (1) - **/wsi/<path:file_path>.dzi** (GET): *index_dzi(file_path)*

This URL is used to request a viewer with a specified DZI from the ASS. The ASS then renders an ASV and passes the DZIs file path, its microns per pixel (MPP) and its name to it. The ASV feeds the path to OpenSeadragon, which then views the DZI. The MPP are used to calculate the actual image size in μm for the scale. Lastly, the file name is used to change the name of the browser tab accordingly.

- (2) - **/wsi/<path:file_path>** (GET): *index_wsi(file_path)*

Works similar to (1), except that the requested image is not of the DZI format. To view it in OpenSeadragon anyway, an instance of the DZG is created which wraps the proprietary WSI. Then, a specific path ("/*slide.dzi*") is handed to the ASV.

¹²See subsection 4.5.1

¹³See appendix B.1 for a detailed documentation of the ASS functions

(3) - /<slug>.dzi (GET): *dzi(slug)*

Once the ASV requests slide.dzi, the DZG builds a response with the descriptive DZI file, created from the proprietary WSI format (via its *.get_dzi(format)* function, with *format* being the file format of the tiles) and serves it to the ASV.

(4) - /<slug>.files/<int:level>_<int:col>_<int:row>.<format> (GET): *tile(slug, level, col, row, format)*

If an original DZI is requested, there is a */wsi/* in front of the URL. Therefore, this URL only triggers if (3) was called before. This way OpenSeadragon requests the separate tiles needed to fill the current view of the user. This is done via the DZG *.get_tile(level, address)* function. *Level* describes the requested level, while *address* is a tuple with the x (col) and y (row) position of the requested tile.

(5) - /saveJson (POST): *saveJson()*

This URL is used when the user wants to save made annotations. The name of the JSON file and the content to write into it will be send via the POST request. The content of the POST request can be accessed via Flasks *Request* object [31] in the following fashion:

```
1 post_data = request.form  
2 source = post_data.get('file', default='')  
3 content = post_data.get('content', default='{}').  
4 encode('utf-8')  
5
```

(6) - /loadJson (GET): *loadJson()*

(6) is used to load a JSON file, may that be the *configuration.json*, a dictionary or saved annotations. The name of the source is passed as parameter (*?src=[file]*) to the ASS. Similar to (5), it can be accessed with the Request object [31]: *request.args.get(parameter, default value)*.

(7) - /createDictionary (GET): *createDictionary()*

If the user sends the command to create a new dictionary, this URL is called. The ASS then creates a new, empty dictionary file. The name of the dictionary is passed as a URL parameter (*?name=[name]*) and then acquired in the same fashion as in (5). The ASS also opens the configuration file and changes the currently selected dictionary to the newly created one.

(8) - /getDictionaries (GET): *getDictionaries()*

When called, the ASS looks up the content of its *dictionaries* folder and returns a list with the found file names or -1 in the case of an error.

4.6 Annotation Service Viewer Implementation

Chapter 5

Tessellation Service

- 5.1 Methodology
- 5.2 Implementation
- 5.3 Test
 - 5.3.1 Setup
 - 5.3.2 Result

Chapter 6

Conclusion

- 6.1 Results**
- 6.2 Conclusion**
- 6.3 Future tasks**

Appendices

Appendix A

Listing of Conversion Service Test Data

The test data for the Conversion Service can be found at OpenSlides homepage, at the freely distributable test data section¹. Various slides can be found there. The following subsections A.1 - A.8 give listings of all used WSIs, sorted by vendor and file format.

A.1 Aperio (.svs)

name	size (MB)	description
CMU-1-JP2K-33005.svs	126.42	Export of CMU-1.svs, brightfield, JPEG 2000, RGB
CMU-1-Small-Region.svs	1.85	Exported region from CMU-1.svs, brightfield, JPEG, small enough to have a single pyramid level
CMU-1.svs	169.33	Brightfield, JPEG
CMU-2.svs	372.65	Brightfield, JPEG
CMU-3.svs	242.06	Brightfield, JPEG
JP2K-33003-1.svs	60.89	Aorta tissue, brightfield, JPEG 2000, YCbCr
JP2K-33003-2.svs	275.85	Heart tissue, brightfield, JPEG 2000, YCbCr

Table A.1: Aperio data set (source: <http://openslide.cs.cmu.edu/download/openslide-testdata/Aperio/>)

¹<http://openslide.cs.cmu.edu/download/openslide-testdata/>

A.2 Generic Tiled tiff (.tiff)

name	size (MB)	description
CMU-1.tiff	194.66	Conversion of CMU-1.svs to pyramidal tiled TIFF, brightfield

Table A.2: Generic Tiled tiff data set (source: <http://openslide.cs.cmu.edu/download/openslide-testdata/Generic-TIFF/>)

A.3 Hamamatsu (.ndpi)

name	size (MB)	description
CMU-1.ndpi	188.86	Small scan with valid JPEG headers, brightfield, circa 2009
CMU-2.ndpi	382.14	Brightfield, circa 2009
CMU-3.ndpi	270.1	Brightfield, circa 2009
OS-1.ndpi	1,860	H&E stain, brightfield, circa 2012
OS-2.ndpi	931.42	Ki-67 stain, brightfield, circa 2012
OS-3.ndpi	1,370	PTEN stain, brightfield, circa 2012

Table A.3: Hamamatsu data set (.ndpi, source: <http://openslide.cs.cmu.edu/download/openslide-testdata/Hamamatsu/>)

A.4 Hamamatsu (.vms)

name	size (GB)	description
CMU-1.zip	0.62	Brightfield
CMU-2.zip	1.13	Brightfield
CMU-3.zip	0.91	Brightfield

Table A.4: Hamamatsu data set (.vms, source: <http://openslide.cs.cmu.edu/download/openslide-testdata/Hamamatsu-vms/>)

A.5 Leica (.scn)

name	size (GB)	description
Leica-1.scn	0.28	Brightfield, single ROI, 2010/10/01 schema
Leica-2.scn	2.1	Mouse kidney, H&E stain, brightfield, multiple ROIs with identical resolutions, 2010/10/01 schema
Leica-3.scn	2.79	Mouse kidney, H&E stain, brightfield, multiple ROIs with different resolutions, 2010/10/01 schema
Leica-Fluorescence-1.scn	0.02	Fluorescence, 3 channels, single ROI, 2010/10/01 schema

Table A.5: Leica data set (source: <http://openslide.cs.cmu.edu/download/openslide-testdata/Leica/>)

A.6 Mirax (.mrxs)

name	size (GB)	description
CMU-1-Exported.zip	2.02	Export of CMU-1.mrxs with overlaps resolved, brightfield, JPEG, CURRENT_SLIDE_VERSION 2.3
CMU-1-Saved-1_16.zip	0.003	Quick save of CMU-1.mrxs at 1/16 resolution (multiple positions per image), brightfield, JPEG, CURRENT_SLIDE_VERSION 1.9
CMU-1-Saved-1_2.zip	0.14	Quick save of CMU-1.mrxs at 1/2 resolution (multiple images per position), brightfield, JPEG, CURRENT_SLIDE_VERSION 1.9
CMU-1.zip	0.54	Brightfield, JPEG, CURRENT_SLIDE_VERSION 1.9
CMU-2.zip	1.22	Brightfield, JPEG, CURRENT_SLIDE_VERSION 1.9
CMU-3.zip	0.65	Brightfield, JPEG, CURRENT_SLIDE_VERSION 1.9
Mirax2-Fluorescence-1.zip	0.06	Fluorescence, 3 channels, JPEG, CURRENT_SLIDE_VERSION 2
Mirax2-Fluorescence-2.zip	0.04	Fluorescence, 3 channels, JPEG, CURRENT_SLIDE_VERSION 2
Mirax2.2-1.zip	2.61	HPS stain, brightfield, JPEG, CURRENT_SLIDE_VERSION 2.2
Mirax2.2-2.zip	2.38	HPS stain, brightfield, JPEG, CURRENT_SLIDE_VERSION 2.2
Mirax2.2-3.zip	2.77	HPS stain, brightfield, JPEG, CURRENT_SLIDE_VERSION 2.2
Mirax2.2-4-BMP.zip	0.95	Brightfield, BMP, CURRENT_SLIDE_VERSION 2.2
Mirax2.2-4-PNG.zip	1.01	Brightfield, PNG, CURRENT_SLIDE_VERSION 2.2

Table A.6: Mirax data set (source: <http://openslide.cs.cmu.edu/download/openslide-testdata/Mirax/>)

A.7 Trestle (.tiff)

name	size (MB)	description
CMU-1.zip	158.87	Brightfield
CMU-2.zip	304.22	Brightfield
CMU-3.zip	223.11	Brightfield

Table A.7: Trestle data set (source: <http://openslide.cs.cmu.edu/download/openslide-testdata/Trestle/>)

A.8 Ventana (.bif)

name	size (GB)	description
OS-1.bif	3.61	H&E stain, brightfield
OS-2.bif	2.53	Ki-67 stain, brightfield

Table A.8: Trestle data set (source: <http://openslide.cs.cmu.edu/download/openslide-testdata/Trestle/>)

Appendix B

Annotation Service Documentation

The following two sections document the implemented functions of the ASS (section B.1) and ASV (section B.2) in detail. Both files can be found in the AS' repository at:

<https://github.com/SasNaw/AnnotationService>.

B.1 Annotation Service Server

index_dzi()

If the client requests a DZI (URL ends in ".dzi"), `index_dzi()` renders an ASV and passes the necessary information (slide URL, file name, MPP) to it.

It builds the file name and slide URL (line 3 and 4) for a requested DZI. A metadata.txt will be present in the [slide name]_files directory, if the DZI was created with the CS. If so, the function will try to fetch the metadata information about MPP and calculate the average height of a pixel (line 6 - 16). If the MPP metadata could not be fetched, it is set to 0 (line 17 - 18). File name, URL and MPP are then passed onto the ASV, which then is rendered with the given information (line 19).

```
1 @app.route('/wsi/<path:file_path>.dzi')
2 def index_dzi(file_path):
3     file_name = file_path + '.dzi'
4     slide_url = '/wsi/' + file_name
5     # read dzi file
6     try:
7         with open('static/wsi/' + file_path + '_files/metadata.txt') as
8             file:
9                 mpp_x = 0
10                mpp_y = 0
11                metadata = file.read().split('\n')
12                for property in metadata:
```

```

12     if openslide.PROPERTY_NAME_MPP_X in property:
13         mpp_x = property.split(':')[1][1]
14     elif openslide.PROPERTY_NAME_MPP_Y in property:
15         mpp_y = property.split(':')[1][1]
16     slide_mpp = (float(mpp_x) + float(mpp_y)) / 2
17 except IOError:
18     slide_mpp = 0
19 return render_template('as_viewer.html', slide_url=slide_url,
    slide_mpp=slide_mpp, file_name=file_name)

```

index_wsi()

When the client requests a proprietary WSI (URL *does not* end in ".dzi"), `index_wsi()` renders an ASV and passes the necessary information (slide URL, file name, MPP) to it. Furthermore, it wraps a DZG around the proprietary WSI and adds that to the WSGI object.

Line 22 - 27 create a map with the optional DZG parameters (compare tab. 4.2) and turn them into a dictionary. Line 28 reads the proprietary WSI. A DZG with the supplied parameters¹ is created, which wraps the proprietary slide object to add Deep Zoom support (line 29 - 31). The created DZG is added to the WSGI object (line 29). Line 32 - 37 fetch associated images, the metadata (line 33), wrap the associated images with a DZG of their own and add this, together with the metadata, to the WSGI object. Line 39 - 43 fetch the MPP metadata and calculate the average MPP (or set it to 0, if not found). Line 44 creates a URL for the DZG object with Flasks `url_for(endpoint, **values)` function. This URL is passed, together with the MPP and file path, to an ASV which then gets rendered (line 45).

```

1 @app.route('/wsi/<path:file_path>')
2 def index_wsi(file_path):
3     config_map = {
4         'DEEPEZOOM_TILE_SIZE': 'tile_size',
5         'DEEPEZOOM_OVERLAP': 'overlap',
6         'DEEPEZOOM_LIMIT_BOUNDS': 'limit_bounds',
7     }
8     opts = dict((v, app.config[k]) for k, v in config_map.items())
9     slide = open_slide('static/wsi/' + file_path)
10    app.slides = {
11        SLIDE_NAME: DeepZoomGenerator(slide, **opts)
12    }
13    app.associated_images = []
14    app.slide_properties = slide.properties
15    for name, image in slide.associated_images.items():
16        app.associated_images.append(name)
17        slug = slugify(name)
18        app.slides[slug] = DeepZoomGenerator(ImageSlide(image), **opts)
19    try:
20        mpp_x = slide.properties[openslide.PROPERTY_NAME_MPP_X]
21        mpp_y = slide.properties[openslide.PROPERTY_NAME_MPP_Y]
22        slide_mpp = (float(mpp_x) + float(mpp_y)) / 2
23    except (KeyError, ValueError):

```

¹Compare tab. 4.5

```

24     slide_mpp = 0
25     slide_url = url_for('dzi', slug=SLIDE_NAME)
26     return render_template('as_viewer.html', slide_url=slide_url,
27                           slide_mpp=slide_mpp, file_name=file_path)

```

dzi(slug)

If `index_wsi()` was called before, a URL was generated for the WSI. This URL will be requested from the ASS by OpenSeadragon, which causes `slug(dzi)` to be called. `slug(dzi)` creates the DZI metadata and returns it to OpenSeadragon.

The `dzi` parameter is the slide URL generated in `index_wsi` (line 44).

Line 48 retrieves the format for the individual Deep Zoom tiles. Line 49 - 52 try to create a response. If a response can not be created, because the requested DZG is unknown, a "404 Not Found" http status code will be returned instead. If the DZG could be found, a response with the DZIs metadata will be created via the DZGs `get_dzi(format)` function (line 50, compare subsection 4.5.2).

```

1 @app.route('/<slug>.dzi')
2 def dzi(slug):
3     format = app.config['DEEPZOOMFORMAT']
4     try:
5         resp = make_response(app.slides[slug].get_dzi(format))
6         resp.mimetype = 'application/xml'
7         return resp
8     except KeyError:
9         # Unknown slug
10        abort(404)

```

tile(slug, level, col, row, format)

If a response for OpenSeadragon was created via `slug(dzi)`, OpenSeadragon will request the individual image tiles in such a way, that, through the use of the `route()` decorator, `tile(slug, level, col, row, format)` will be called.

As in `slug(dzi)`, the `slug` parameter is the slide URL generated in `index_wsi` (line 44). The parameters `level`, `col` and `row` describe the DZI level and address of the requested image tile. `format` is the image format of the tile.

If the format is not JPEG or PNG, the ASS return a "404 Not Found" http status code (line 58 - 61).

If the format is either JPEG or PNG, the requested tile is generated through the use of the DZGs `get_tile(level, address)` function (line 63). If it was not possible to generate the tile, a "404 Not Found" http status code will be returned.

The generated tile is then saved into a PIL image object², stored in either a JPEG or PNG image and returned as response to OpenSeadragon (line 70 - 74).

²See <http://pillow.readthedocs.io/en/3.3.x/reference/Image.html>

```

1 @app.route('/<slug>_files/<int:level>/<int:col>,<int:row>.<format>',
2           )
3 def tile(slug, level, col, row, format):
4     format = format.lower()
5     if format != 'jpeg' and format != 'png':
6         # Not supported by Deep Zoom
7         abort(404)
8     try:
9         tile = app.slides[slug].get_tile(level, (col, row))
10    except KeyError:
11        # Unknown slug
12        abort(404)
13    except ValueError:
14        # Invalid level or coordinates
15        abort(404)
16    buf = PILBytesIO()
17    tile.save(buf, format, quality=app.config['DEEPZOOM_TILE_QUALITY'])
18    resp = make_response(buf.getvalue())
19    resp.mimetype = 'image/%s' % format
20    return resp

```

saveJson()

When the client sends JSON data to save, the `saveJson()` function is called.

The associated request is a POST request. This means that the posted data needs to be extracted. This can be done via Flasks *request object*³ (line 77 - 79). The file path will be transmitted as "source", the content to save as "json".

If there is something to save (line 80), the content will be written into the provided file. If the file does not exist yet, it will be created (line 81 - 82).

```

1 @app.route('/saveJson', methods=['POST'])
2 def saveJson():
3     dict = request.form
4     source = dict.get('source', default='')
5     json = dict.get('json', default='{}').encode('utf-8')
6     if len(source) > 0:
7         with open('static/' + source, 'w+') as file:
8             file.write(json)
9     return 'Ok'

```

loadJson()

When the client requests JSON data, `loadJson()` is called.

The source of the JSON data is passed in the URL as parameter ("src=/path to source/"). The src parameter can be extracted via Flasks request object⁴ (line 86). If the provided source is a file, the content will be read and returned as JSON data (line 87 - 90). Otherwise an empty JSON list is returned (line 91 - 92).

³Compare subsection 4.5.1

⁴Compare subsection 4.5.1

```

1 @app.route('/loadJson')
2 def loadJson():
3     source = 'static/wsi/' + request.args.get('src', '')
4     if os.path.isfile(source):
5         with open(source, 'r') as file:
6             content = file.read()
7             return jsonify(content)
8     else:
9         return jsonify([])

```

createDictionary()

When the client requests the creation of a new dictionary, `createDictionary()` is called. The name of the new dictionary is passed as URL parameter (`name=[name]`). The name parameter can be extracted via Flasks request object⁵ (line 95).

Once the name was extracted, the function checks if a dictionary with the provided name already exists. If so, "error" is returned (line 96 - 99). Otherwise a new, empty dictionary is created (line 101 - 102). To switch to the newly created dictionary, the configuration file must be updated (line 103 - 107).

As response, the name and path of the newly created dictionary is returned (line 108 - 109).

```

1 @app.route('/createDictionary')
2 def createDictionary():
3     name = request.args.get('name', '')
4     path = 'static/dictionaries/' + name
5     if os.path.isfile(path):
6         # dictionary already exists
7         return 'error'
8     else:
9         with open(path, 'w+') as dictionary:
10             dictionary.write("[]")
11             with open('static/configuration.json', 'r') as config:
12                 content = json.loads(config.read())
13                 content['dictionary'] = name
14             with open('static/configuration.json', 'w+') as config:
15                 config.write(json.dumps(content))
16             response = {"name": name, "path": path}
17             return response

```

getDictionaries()

The `getDictionaries()` function is called, when the client requests a list of all available dictionaries.

If no dictionaries could be found, "-1" will be returned, otherwise a JSON list of all available dictionaries.

⁵Compare subsection 4.5.1

```
1 def getDictionaries():
2     dir = 'static/dictionaries/'
3     if os.path.isfile(dir):
4         # no dictionaries found
5         return '-1'
6     else:
7         # return dictionaries
8         return json.dumps(os.listdir(dir))
```

B.2 Annotation Service Viewer

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Nomenclature

AS	Annotation Service
ASS	Annoation Service Server
ASV	Annotation Service Viewer
BNN	Biological Neural Network
CS	Conversion Service
DICOM	Digital Imaging and Communications in Medicine
DSR	Digital Slide Repository
DZG	DeepZoomGenerator
DZI	Deep Zoom Image
GUI	Graphical User Interface
IIIF	International Image Interoperability Framework
MPP	Microns per Pixel
MS	Microservice
NN	Neural Network
OSGF	Open Source Geospatial Foundation
OSM	OpenStreetMap
POI	Point of Interest
ROI	Region of Interest
SOP	Same-Origin Policy
TIFF	Tagged Image File Format
TMS	Tiled Map Service
TS	Tessellation Service
UX	User Experience
VIPS	VASARI Image Processing System
WSGI	Web Server Gateway Interface
WSI	Whole Slide Image