Open Implementation of DICOM for Whole-Slide Microscopic Imaging

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Abstract: This paper introduces an open implementation of DICOM for whole-slide microscopic imaging, following Supplement 145 of the DICOM standard. The software is divided into two parts: (a) a command-line tool to convert an whole-slide image to the DICOM format, and (b) a zero-footprint Web interface to display such DICOM images. The software architecture leverages the DICOM server Orthanc. The entire framework is available as free and open-source software. The existence of this software supports the development of digital pathology and telepathology in clinical environments, featuring a smooth integration with existing EHR and PACS solutions.

1 INTRODUCTION

Anatomopathology plays important medical roles by detecting preneoplastic lesions and by giving a diagnosis, prognosis and evaluation of therapeutic response based on visual observations of cellular or tissue samples. Telepathology is an application of telemedicine that allows the practice of the anatomopathology over a long distance with the use of images in an electronic format rather than viewing glass slides (Ling and Krishnappa, 2012). Telepathology is potentially useful for several applications:

- *Intraoperative Consultation*: Intraoperative consultations are emergencies in anatomopathology since the purpose of this examination is to guide immediate surgical management. For such consultations, the results should be given within 30 minutes (Ribback et al., 2014). Telepathology can be used in this context for obtaining consultation by a pathologist present in a remote physical location.
- *Secondary Consultation from Experts*: Secondary consultation refers to situations where a primary diagnosis has been performed on the primary material and further opinion is needed. Telepathology is beneficial by accelerating the process and by reducing the risks of material loss or break compared to postal services (Farahani and Pantanowitz, 2016).
- *Education and Research*: Telepathology is highly promising in medical education and clinical research. Currently, digital imaging starts to replace traditional glass slides and high quality microscopes to discuss interesting cases during lessons, symposia and conferences. Telepathology facilitates interactions between multiple users and allows the consistency and longevity of imaged materials (Marée et al., 2016).
- *Pathology Archiving*: The storage of histological slides is mandatory for a long period of time. Since the virtual slide perfectly reproduces the glass slide without any loss of information, telepathology could enable the storage of images in an entirely electronic way. As a consequence, the currently-used, costly physical archives could become legacy systems in the future (Webster and Dunstan, 2014).

Telepathology requires microscopic images to be put quickly and easily online, from a slide scanner onto a secured Web server. To this end, at least three technical difficulties must be overcome.

Firstly, any pathology laboratory requires high electronic storage capacities to store their whole-slide images, as the size of the latter may range from hundreds of megabytes to hundreds of gigabytes, depending on the scanning objective and the tissue sec-

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tion. A typical, uncompressed whole-slide image of 80,000×60,000 pixels acquired in 24-bit color (RGB) weights over 10GB (DICOM Standards Committee, Working Group 26, Pathology, 2010). Image compression (JPEG or JPEG 2000) can divide this size by a factor 10, but this still roughly corresponds to the size of 3D medical images (e.g. computed tomography or magnetic resonance imaging). Storing and indexing such a large amount of data on the long run is obviously not compatible with the manual administration of a filesystem: It implies the use of automated, scalable, enterprise-ready database systems similar to the PACS of the hospital (*Picture Archiving and Communication System*).

The second technical difficulty is the lack of interoperability between the proprietary ecosystems that are implemented by the manufacturers of slide scanners. A single hospital might host several scanners from different manufacturers, making it hard to consolidate all the whole-slide images inside a centralized tool because of a large variety of file formats. For the same reason, it is hard to link the EHR (*Electronic Health Record*) of a patient to her anatomopathology images. This lack of interoperability in the clinical workflow is also an obstacle to the exchange of images between hospitals, as well as to the use of standalone post-processing tools that are necessary for big-data analysis, medical research or education.

A possible solution to this problem consists in taking advantage of the DICOM standard for medical imaging (NEMA — National Electrical Manufacturers Association, 2016). Indeed, in 2010, the DICOM Committee defined a standard way of exchanging whole-slide microscopic imaging that is vendor-independent and that is fully compatible with existing PACS systems (DICOM Standards Committee, Working Group 26, Pathology, 2010). Unfortunately, there is currently no open implementation of this recent standard, most probably because of the existence of many patents (Cucoranu et al., 2014): As a consequence, even if any modern PACS can ingest such DICOM images, few will render them. There is also a lack of sample files, which strongly calls for an open infrastructure to share knowledge about this complex standard, to the benefit of hospitals, manufacturers and researchers.

The third technical challenge for telepathology consists in serving the images over Internet. Because of the size of whole-slide images, a raw transfer of the files would not be compatible with real-time constraints or mobile applications. It is also highly desirable to avoid the installation of some heavyweight client software on the computers of an hospital, as this operation is often prevented for security reasons: A telepathology viewer should therefore be able to run entirely inside a standard Web browser, as such a browser is almost always installed by default on any computer. A Web application also has the advantage of being compatible with mobile devices. The OpenSlide software can already serve whole-slide images generated by commonplace scanners onto the Web (Goode et al., 2013). Similarly, the Cytomine software builds upon the OpenSlide experience to provide an advanced collaborative analysis framework for research and education in digital pathology (Marée et al., 2016). Unfortunately, neither of those platforms currently supports the DICOM standard that is mandatory for clinical workflow.

The previous discussion calls for the engineering of a framework built upon the DICOM standard that would support the development of workflow for digital pathology and telepathology in clinical environments, featuring a smooth integration with existing hospital information systems (EHR and PACS). The needed software would be able to convert whole-slide images encoded using proprietary formats, to a standard DICOM file in accordance with the "*VL Whole Slide Microscopy Image Information Object Definition (IOD)*", as specified in the "*PS3.3: Information Object Definitions*" part of the DICOM standard (NEMA — National Electrical Manufacturers Association, 2016). It would then be able to forward the converted images to a generic PACS system, while serving them directly over Internet, using a zero-footprint Web client.

This paper introduces such an innovative framework and makes it available as free and open-source software to support the development of digital pathology and telepathology in hospitals.

2 SYSTEM AND METHODS

According to the Introduction section, our software framework for digital pathology and telepathology is divided into two separate components:

- A standalone command-line tool that takes as input a non-DICOM whole-slide microscopic image, and that generates a compliant DICOM file.
- A DICOM server that can easily publish such images on the Web.

This section will fully describe our technical solution, after an introduction to the DICOM file format for whole-slide microscopic imaging.

2.1 DICOM for Visible Light Whole-Slide Microscopic Images

Because images for digital pathology are very large (possibly dozens of gigabytes), they most often cannot entirely fit inside the memory of a standard computer. For this reason, whole-slide images are in practice divided as a regularly-spaced set of *tiles*, each tile being a small patch taken from the full image. A tile is most often a square whose sides contain between 256 and 1024 pixels. Each individual tile can be accessed separately, allowing a digital pathology application to bring a tile into memory only when needed.

Compressing some whole-slide image amounts to compressing each individual tile either using a lossless algorithm (JPEG 2000), or a destructive algorithm (JPEG). Furthermore, to enable the navigation over the entire whole-slide image, the full-sized image is downscaled several times, leading to a *pyramid* of images with decreasing spatial resolutions. Each level of the pyramid is encoded as a separate tiled image. This process is illustrated in Figure 1. Note that similar encoding schemes are also commonly used to serve cartography maps on the Web.

The DICOM standard models the real world as follows: A given *patient* benefits during her life from a set of medical imaging studies. Each *study* is made of a set of series. Each *series* is in turn a set of *instances*, the latter being a synonym for a DICOM file. A single DICOM instance can be multi-frame, meaning it can store several independent images (provided all of its individual frames share the same size). As a consequence, the whole-slide pyramid represented in Figure 1 corresponds to one DICOM series, whose parent study might contain other series acquired during the same clinical episode, possibly coming from other medical imaging modalities. This series is made of several instances (the DICOM files), each instance storing the individual tiles of one given pyramid level as separate frames. A single instance is not allowed to store tiles from multiple pyramid levels, yet the same level can be spread over multiple instances, so as to prevent the appearance of huge DICOM files.

Besides its individual frames, each DICOM instance is associated with clinical data under the form of a recursive key-value associative array. Such keys are called the *DICOM tags* and are indexed with two 16-bit hexadecimal numbers. The DICOM standard lists which DICOM tags are mandatory, conditional or allowed for whole-slide images in the so-called "*VL Whole Slide Microscopy Image IOD*" (NEMA — National Electrical Manufacturers Association, 2016, PS3.3, Section A.32.8).

A full enumeration of this set of DICOM tags is obviously out of the scope of this paper, and the interested reader is kindly invited to refer to the DICOM standard. In the context of this paper, it is sufficient to know that each single instance must specify the size of the pyramid level it is related to: The DICOM tag "*Total Pixel Matrix Columns*" `(0x0048,0x0006)` stores the width of the pyramid level, whereas "*Total Pixel Matrix Rows*" `(0x0048,0x0007)` stores its height. These two tags allow to know to which level of the pyramid a given DICOM instance belongs.

Similarly, because the tiles of one pyramid level can be shuffled over several multi-frame DICOM instances, each frame is associated with the (x,y) position of the corresponding tile in the corresponding pyramid level: The tag "*Column Position In Total Image Pixel Matrix*" `(0x0048,0x021e)` contains the x-position of one frame, and "*Row Position In Total Image Pixel Matrix*" `(0x0048,0x021f)` its y-position. This information is collected for each frame of the DICOM instance inside the tag "*Per Frame Functional Groups Sequence*" `(0x5200,0x9230)`. Our framework almost exclusively relies on this set of tags.

2.2 DICOM-izer

The first component of our software framework for telepathology is the tool that converts a whole-slide image from a non-DICOM format to DICOM. This tool will be referred to as the *DICOM-izer*. It takes the form of a standalone, cross-platform command-line tool, so that it can easily be integrated into any pathology department.

The DICOM-izer features built-in support to read the most widespread open file format for whole-slide imaging (i.e. hierarchical TIFF), as well as commonplace image formats (PNG, JPEG and JPEG 2000). It is also able to decode proprietary file formats for slide scanners (SVS, BIF, VMS...) through the OpenSlide toolkit (Goode et al., 2013)[1]. It extracts as much clinical information as possible from the meta-data of the input image (such as the scanner manufacturer), but additional information that is not verbatim available inside the source file must be provided alongside (e.g. the identifier of the patient, or the optical parameters of the acquisition). The output of the DICOM-izer is a set of compliant DICOM files that can be sent to any DICOM modality, including the PACS of the hospital, thanks to the standard DICOM C-Store command.

If the input image does not contain the full pyramid but only its finest level, the DICOM-izer can automatically generate all the upper levels of the pyramid. Similarly, the DICOM-izer can change the com-

[1] Note that OpenSlide does not support the generation of DICOM files by itself.

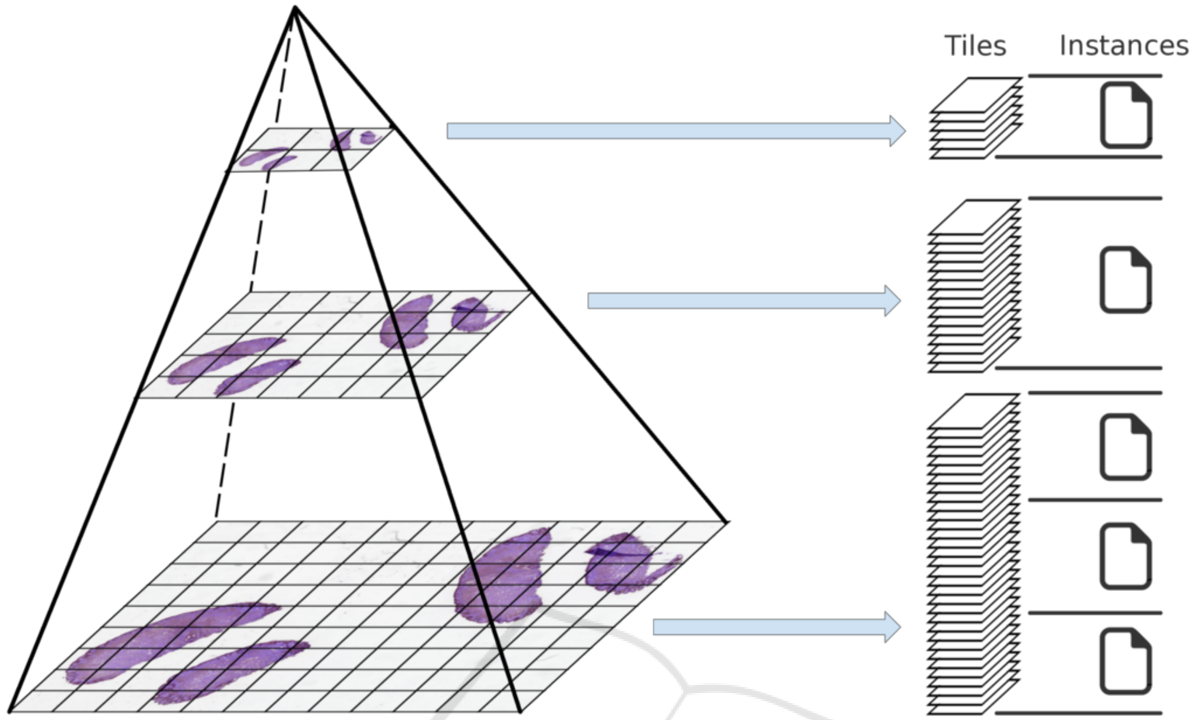

Figure 1: Mapping a multi-resolution pyramid according to the DICOM standard (DICOM Standards Committee, Working Group 26, Pathology, 2010). Each level of the pyramid is a downscaled version of the whole-slide image, and is decomposed as a set of tiles. The tiles are encoded as separate frames of multi-frame DICOM instances (files).

pression scheme of the input image to one of the algorithms supported by the DICOM standard (i.e. no compression, JPEG or JPEG 2000). Unsurprisingly, decoding a proprietary format, changing the compression, and/or rebuilding the pyramid are CPU-intensive re-encoding operations that can last dozens of seconds, even though our DICOM-izer efficiently takes advantage of multi-threading. However, the baseline process of simply transcoding a hierarchical TIFF to DICOM only takes a few seconds, with almost no CPU usage.

Note that microscopy images are often stained or multi-spectral. This means that multiple channels might be needed to store the full microscopy image. The DICOM standard requests to store the various spatial and spectral channels in separate DICOM series. In such situations, the DICOM-izer can be separately invoked for each channel, which will generate a set of DICOM series, all belonging to the same parent DICOM study.

2.3 Orthanc Plugin for Whole-Slide Imaging

The second component of our software framework for telepathology allows laboratories to immediately publish the DICOM images that are produced by the DICOM-izer over Internet. As argued in the Introduction, this component is a necessary companion to the DICOM-izer, as most PACS do not currently support the rendering of whole-slide images. Because our framework is designed to be as open as possible to the benefit of the worldwide community of pathology laboratories and researchers, this component leverages a free and open-source DICOM server.

The two most well-known free and open-source DICOM servers are DCM4CHE (Warnock et al., 2007, written with Java and JBoss) and Orthanc (Jodogne et al., 2013, written in C++). Besides its small footprint, Orthanc has the advantage of proposing a RESTful API that makes it ready for Web applications (Fielding, 2000), and to propose a plugin mechanism that can be used by third-party developers to extend the core REST API without using an additional Web server. As a consequence, our Web publishing component is built upon the Orthanc vendor neutral archive, and takes the form of a C++ plugin.

Our Orthanc plugin is a shared library that is dynamically loaded by Orthanc during its startup, and that is responsible for:

1. Transparently indexing all the tiles of a given DICOM series as a whole-slide pyramid.

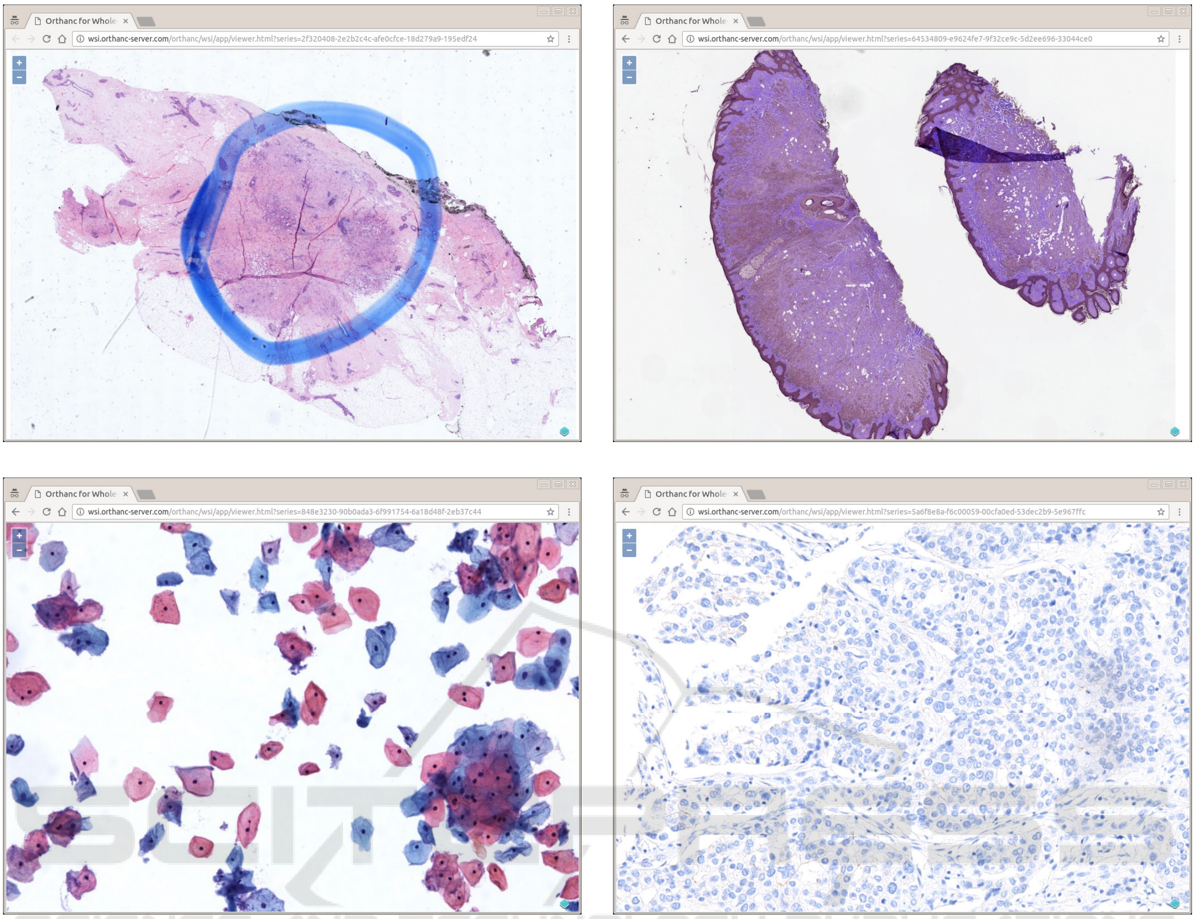

Figure 2: Some screenshots of a Web browser displaying real-world pathology images stored inside Orthanc, at various zoom levels. The Web application is zero-footprint: It is entirely written in JavaScript, and no heavyweight client must be installed (all is done by the Web browser). The Web interface is built upon OpenLayers version 3, a free and open-source JavaScript library for displaying raster tile maps (Open Source Geospatial Foundation, 2010). Note that the Web application can be served through the HTTPS protocol, meaning that the medical communication can be secured through proper authentication and encryption.

2. Serving the individual tiles according to their (x,y,z) location (z corresponds to the level of the tiles in the pyramid), after dynamically transcoding them to an image format that is compatible with Web browsers (either PNG for uncompressed or losslessly-compressed whole-slide images, or JPEG for destructively-compressed images).

3. Publishing all the HTML and JavaScript static resources that are necessary for the Web viewer.

The indexing process of Step (1) first groups the instances according to the size of their associated pyramid level z, then extracts the (x,y) position of each frame in these instances, only by considering the DICOM tags that were introduced at the end of Section 2.1. Figure 2 shows screenshots of a Web browser accessing our viewer of DICOM whole-slide images[2].

The DICOM-izer can be configured to automatically push its output images to any Orthanc server through its RESTful API. Note also that because Orthanc is a fully-featured vendor neutral archive, it can be used to re-transmit (resp. query/retrieve) the whole-slide images to (resp. from) other DICOM modalities, including the PACS of the hospital. Finally, an official plugin is available to make Orthanc use a PostgreSQL database, making it fully scalable and enterprise-ready if need be.

[2] The demonstration server from which these screenshots were taken is publicly available online at: http://wsi.orthanc-server.com/demo/. This demonstration server illustrates the fact that the Web interface is entirely zero-footprint: Any modern Web browser will display it out-of-box, without having to install any additional software.

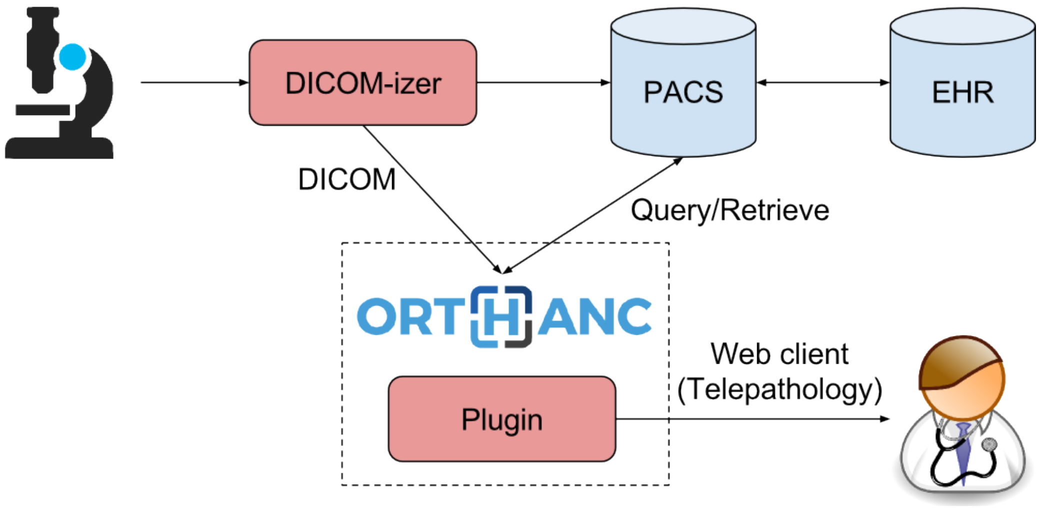

Figure 3: Possible clinical workflow for digital pathology. The innovative contributions introduced by this paper are highlighted in red.

3 APPLICATIONS

Figure 3 illustrates a real-world clinical workflow that becomes possible thanks to our open framework for digital pathology and telepathology. In this workflow, the pathology department sends its images to the PACS of the hospital, which enables the continuous integration with the electronic health record (EHR) of the patient: This would solve the "*pathology archiving*" objective explained in the Introduction.

In parallel, the DICOM-izer also sends its output images to an Orthanc server equipped with our plugin. As soon as the DICOM images are received by Orthanc, they are immediately made available online for real-time viewing: Opening an image in the browser takes less than one second, and the user experience is similar to well-known Web mapping systems. This allows telepathologists to quickly and easily review whole-slide images remotely, using any standard Web browser. This remote, read-only access is also possible using a smartphone or a tablet.

The CPU power that is required by the Orthanc server is very low if the images are encoded using JPEG, which is the most common case: As Web browsers natively support JPEG, the plugin can serve the compressed tiles without decoding them. Furthermore, as the telepathology plugin is entirely Web-based, the network administrators of the hospital can setup a reverse proxying system and HTTPS encryption to ensure the proper authentication and confidentiality for the access to the medical information: This would solve the "*intraoperative consultation*" and "*secondary consultation*" objectives. Also note that Orthanc can query/retrieve images archived in the PACS so as to put them back online.

Finally, whole-slide images that are found to be of interest for research or education, can be exported as hierarchical TIFF directly from our Web viewer to a richer Internet application for collaborative analysis such as Cytomine (Marée et al., 2016). This would solve the "*education and research*" objective.

4 CONCLUSION

This paper introduces an implementation of the "*VL Whole Slide Microscopy Image IOD*", as specified in the "*PS3.3: Information Object Definitions*" part of the DICOM standard (NEMA — National Electrical Manufacturers Association, 2016), in order to support the development of digital pathology and telepathology in clinical laboratories and hospitals. The source code of our framework is provided as free and open-source software, under the terms of the AGPL license[3]. It is notably compatible with Microsoft Windows, Apple OS X and GNU/Linux environments.

To the best of our knowledge, this is first public, open, reference implementation of DICOM for whole-slide microscopic imaging. Our framework consists of a standalone DICOM-izer, that converts

[3] The source code is accessible from the official homepage of Orthanc: http://wsi.orthanc-server.com/. Full technical documentation of the framework and of the underlying open Web API is part of the Orthanc Book: http://book.orthanc-server.com/.

whole-slide images to compliant DICOM files, together with a dedicated plugin extending the vendor neutral archive Orthanc. The latter plugin extends Orthanc with a lightweight, zero-footprint Web viewer of whole-slide images. This viewer can be accessed remotely from any Web browser or mobile device.

It has also been discussed how our framework for telepathology can be integrated inside a typical hospital workflow to meet real-world challenging objectives such as remote consultation, education, clinical research, or long-term archiving. Future work will consist in taking advantage of our framework to support a multi-centric clinical study that will develop and assess new algorithms to quantify relevant biomarkers on digitized immunostained slides of neoplastic lesions.

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