Digitalisation of histological images

Digitalisation of histological images has caused a revolution in the pathology world and has become a reality of the daily functioning of the hospital laboratory and of the research and scientific communities

Oihana Belar
Roberto Bilbao
Basque Biobank for Research, Basque Foundation for Health Innovation and Research, Barakaldo, Spain

The histological image is at the core of microscopic study of diseased tissue in anatomy pathology departments. Over past decades, the evolution of information technology has directly affected the practice of pathologists in improving the production, accuracy, collaboration and data integration with clinical records. In this regard, the dramatic increase in computational power and telecommunications has seen the development of services based on advanced forms of telepathology and the improvement of image analysis algorithm.[1]

First, telepathology was used in the 1980s to share images at different locations with different applications, for example, (a) teleconsultation via e-mail or web-based tools, (b) distant education and (c) virtual microscope management consultations. Unfortunately, the limitations resulting from the low bandwidth and hence low responsiveness for real-time applications and inadequate security and privacy delayed the development of telepathology.[2] However, recent internet improvements have partially solved these restrictions, making the use of telepathology more prevalent in hospitals worldwide. Moreover, pathology departments are moving to computerised diagnostic pathology in terms of work-flow integrative telepathology and virtual laboratory. As a result, the histological sections are scanned and digitalised for diagnosis on the computer screen, leaving the traditional microscope removed during the process. Furthermore, new services associated with histological digital analysis have been developed, offering innovative solutions for research.

The present paper reviews the requirements and use of digitalised histological images in medical practice and new advances in image analysis for research and tissue biobanks.

Telepathology

Telepathology uses telecommunications technology to facilitate the transfer of image-rich pathology data between distant locations for the purposes of diagnosis, education and research. Performance of telepathology requires that a pathologist select the video images for analysis and third opinion. In the 1980s, telepathology was made possible with the introduction of video cameras mounted on microscopes, meaning that live images could be shared with people at different locations.[3] As affordable digital cameras became available, efficient capturing of still digital images at high resolution came into effect. During the past decade, digital slide scanners have been introduced and have gradually taken their place, first in anatomical pathological labs and later in biobanks, as a ‘digital age’ alternative to the conventional microscope.[4]

Digital pathology is much more than just the capturing of a digital image of a glass slide. As described by the Digital Pathology Association, it means the creation, viewing, management, sharing, analysis and interpretation of these images and includes management and workflow considerations unique to a digital imaging environment.[5]

The process of glass slide digitalisation has been improved significantly during recent years, offering different types of product (mostly table-top devices) that take glass slides as input and produce whole-slide images (WSI) or region of interest images as output, in a cost- and time-efficient manner.[6] The goal of WSI, coupled with whole-slide image viewers, is to simulate slide viewing by a conventional microscope on a computer screen. This digital workflow is often referred to as Pathology 2.0.[7] The last step toward a complete digital workflow has been the integration of WSI into the regular workflow, indeed replacing the conventional diagnosis procedure.

Histological image digitalisation platforms

There are two main digitiser systems: one focused on whole-slide digitalisation (digital microscope) and the other on diagnosis-aided systems that are designed to digitalise and help with the detection of the region of interest and biomedical signal

Table 1. Integrating digitalisation into practice	
Current patient care application	
Frozen section interpretation	Remote interpretation of a frozen section slide(s) via digital pathology
Digital image analysis	Automated interpretation of IHC (for example, HER2, ER/PR) or ISH assays, the automated algorithms that quantify intensity or percent positivity and rare events, for example
Intra-practice	Consultation within a practice, for example, sending a slide to a sub-specialty pathologist within the practice
Archiving	Fast and convenient slide retrieval; back-up documentation for legal purposes; comparison with previous biopsies; preservation of virtual slides in which tissue may be used for testing (for example, molecular)
Diagnostic pathology report	WSI links on traditional pathology report; incorporation of WSI into integrated report; incorporation of WSI into hospital EMR
Consultation/ expert second opinion	Expert second opinion of challenging cases by national or international expert pathologists (between practices)
Quality assurance (QA)	More conventional slide sharing and re-reads; allows for a robust QA system for auto-selection of random cases; tracking of slide review to ensure all areas of virtual slides are assessed
Clinical conferences	Use of DP to present cases to tumour boards or pathology conferences
Emerging patient care application	
International in-sourcing	Slides received digitally from an international source based upon a partnership whereby the US pathologist is viewing the slides for primary diagnosis and/or consultation
Future patient care application	
Multiplex high medical value assays	Multiplex assays delivering prognostic or companion diagnostics information through analysis of multiple analytes simultaneously on a slide
Computer-aided diagnosis	Automated interpretation of H&E stains (for example, mitotic figures, rare event detection)
Primary diagnosis	Primary histopathologic diagnosis rendered from digital, not glass, slide; may be limited to specific types of practice settings, such as a remote hospital or a clinic with insufficient volume to support an on-site pathologist, or sub-specialty practices that are at different locations

quantification.[8]

To integrate digitalisation systems into routine practice, an infrastructure needs to be developed into the pathology department and/or biobank. This infrastructure consists of: (i) hardware for scanning of slides, storing of the scanned images, transmission of the images to pathologists, and those interfaces necessary to display the images and report interpretations; and (ii) software to facilitate the workflow of the image movement, display and reporting of the results.[4]

Scanning platforms

Motorized microscopes

In these types of system, the functionality and original components remain fixed: eyepieces, multiple lenses, position and spotlight control. The camera is joined to the microscope and the software controlling both items is integrated.

The progressive method, in which the final images is composed frame by frame, is the most common procedure used to scan the slide.

Scanners

Slide scanners include components similar to those used in automated microscopes but with some modifications, such as absence of eyepieces and absence of position and focus control: they are closed systems.

Different aspects should be taken into account when evaluating the digitalisation process, such as the digitalisation speed, the maximum sample size, the focus quality, the digitalisation at different planes, the methods for scanning and image assembling, and the formats used to store the scanned samples (for example, JPEG and TIF).

Application

As described in the CAP Pathology Resource Guide: Digital Pathology, digital pathology can be used in different current/ emerging application areas:[9]

Innovative solutions

Innovative investigation into digital histological images is driving the development of new tools. Until now, in most pathology labs, doctors have diagnosed disease over tissue slices on glass microscope slides, based on subtle visual features, mainly morphological, that are difficult to quantify. But this is starting to change. Just as lenses revealed what had been previously invisible to the human eye, different new software is opening up a new window on biology. The latest digital tools make it possible to do a visual search in microscopy images, to automate diagnosis, and to synchronise image data with the genomic profiles of tumours.[10]

For example, in 2011, Harvard Medical School pathologist Andrew Beck built a tool called C-Path (for Computational Pathologist) by feeding learning software with images of breast-cancer biopsies from 248 patients, along with survival data. The software learned to grade the severity of breast cancer and predict patient survival based on a comparative analysis of identified features related to both a sample's global structure and its fine-scale details. In conclusion, Beck found that the morphology of the stroma was a better predictor of survival than that of the cancer cells alone.[11]

Others have developed a tool called SVIQ software, which highlights similar features in the one histological image, helping pathologists to find sites of interest in the visually overwhelming landscape of a digital slide; moreover, the author suggests that it could be integrated into the process of screening patients for cancer clinical trials.[12]

Histological digital imaging has also opened new opportunities for biobanks. In this regards, OECI-TuBaFrost (www.tubafrost.org) was a key European Commission-funded project to develop an image database for research that would be available to the scientific community through a Virtual Microscope system. Basically, it consisted of sending glass slides for digitisation to the Tumor Bank office at the European Organisation for the Research and Treatment of Cancer in Brussels. Afterwards, the virtual slide images would be stored on an image server under directories linking it to records within the TuBaFrost Central database. After digitization was completed, the glass slides were returned to the collector institute.

BIOPOOL

A further step towards the era of web 3.0 has been taken with a novel innovative project called BIOPOOL (www.biopoolproject.eu), funded by the 7th Frame Program of the European Commission and leaded by the Basque Foundation for Health Innovation and Research (www.basquebiobank.com). Despite the high number of Biobanks, due to its geographical dispersion, linguistic differences or lack of updated catalogues on line, researchers struggle to find specific samples, especially in the case of rare diseases. The BIOPOOL platform is a biological sample search service for a network of biobanks, which enables the sharing of different histological images as well as associated clinical data among member biobanks.

At present, researchers must contact several biobanks in order to find the needed samples; there is no agile mechanism that eases the search. The BIOPOOL aim is to provide a tool that will allow the search for biological samples, which is similar to that used as a reference by the search engine. BIOPOOL will provide the set of relevant samples ranked by similarity as well as their location and diagnosis (Figure 1). In this manner, researchers will be able to have quicker access to many more samples, which will help speed both the time of research and the diagnosis while, at the same time, reducing associated costs.

The BIOPOOL platform can be accessed through the internet, and can be searched both for image content and for text. The most innovative characteristic of this platform is the image search engine, which has been developed based on the histological images of colon, breast and lung cancer. The entry image is compared by means of its mathematical description against the database in order to find the most approximate values. The more similar they are, the more similar the images will be between them and, therefore, so will be the first results that are retrieved as a result of the search.

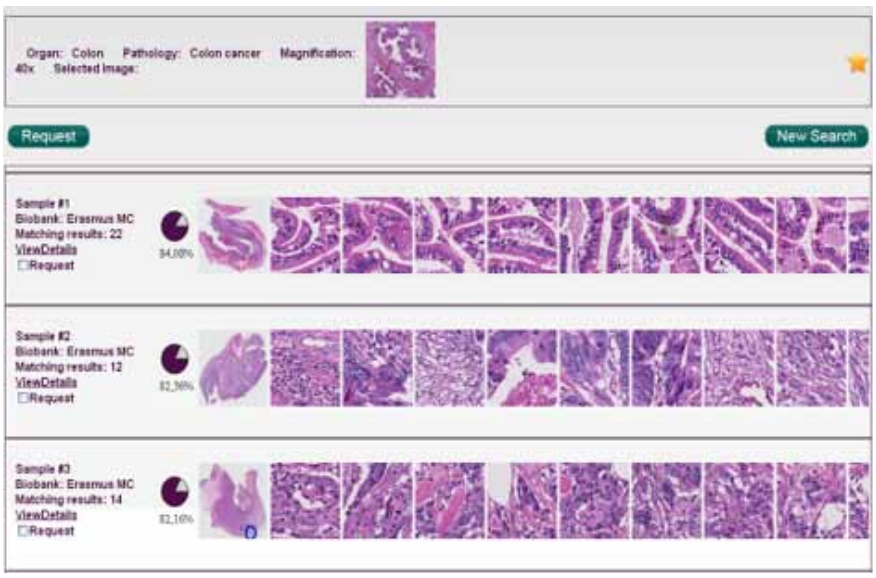

Fig.1: Results from BIOPOOL platform

Conclusions

The histological digitalised image overcomes drawbacks inherent in work with traditional preparations, passing from descriptive microscopy to their quantitative analysis. Diagnosis and research have benefited from new approaches that are coming from new technology and the development of fast and more secure communications: the medical image will one day become the new '-omic'.

References

1. Gabril MY, Yousef GM. Informatics for practicing anatomical pathologists: marking a new era in pathology practice. Mod Patho. 2010;23:349–58.
2. Della Mea V, Beltrami CA. Current experiences with internet telepathology and possible evolution in the next generation of Internet services. Anal Cell Pathol 2000;21:127–34.
3. Weinstein RS. Prospects for telepathology. Human Path 1986;17: 433-4.
4. Pantanowitz L et al. Review of the current state of whole slide imaging in pathology. J Pathol Inform 2011;2:36.
5. Glossary of Terms https://digitalpathologyassociation.org/glossary-of-terms_1.
6. Teodorovic I et al. TuBaFrost 6: Virtual microscopy in virtual tumour banking. Eur J Cancer 2006;42:3110–6.
7. Schreiber WE, Giustini DM. Pathology in the era of Web 2.0. Am J Clin Pathol 2009;132:824–8.
8. Rojo MG et al. Critical comparison of 31 commercially available digital slide systems in pathology. Int J Sur. Pathol 2006;14:285–305.
9. Digital Pathology Resource Guide - dp_resource_guide.pdf, n.d. http://www.cap.org/apps/docs/membership/dp_resource_guide.
10. Bourzac, K. Software: The computer will see you now. Nature 2013;502: S92–S94.
11. Beck AH et al. Systematic Analysis of Breast Cancer Morphology Uncovers Stromal Features Associated with Survival. Sci Transl Med 2011;3:108–13.
12. Hipp JD et al. Spatially Invariant Vector Quantization: A pattern matching algorithm for multiple classes of image subject matter including pathology. J Pathol Inform 2011;2:13.