Techniques in Pathology

Critical Comparison of 31 Commercially Available Digital Slide Systems in Pathology

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Advances in new technologies for complete slide digitization in pathology have allowed the appearance of a wide spectrum of technologic solutions for whole-slide scanning, which have been classified into motorized microscopes and scanners. This article describes technical aspects of 31 different digital microscopy systems. The most relevant characteristics of the scanning devices are described, including the cameras used, the speed of digitization, and the image quality. Other aspects, such as the file format, the compression techniques, and the solutions for visualization of digital slides, (including diagnosis-aided tools) are also considered. Most of the systems evaluated allow a high-resolution digitization of the whole slide within about 1 hour using a ×40 objective. The image quality of the current virtual microscopy systems is suitable for clinical, educational, and research purposes. The efficient use of digital microscopy by means of image analysis systems can offer important benefits to pathology departments.

Keywords: virtual microscopy; whole slide scanning; motorized microscope

T he term *virtual microscopy* is used to describe the acquisition and storage of microscopy digital images. The digital images may consist of a selected area or the whole histology or cytology slide, without being limited to just one or a few regions of interest. Virtual microscopy therefore allows access to all regions of interest within a sample slide by using a personal computer (PC) or digital device without use of the microscope.[1]

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Virtual microscopy is a general concept that includes different aspects related to this process spanning from the image acquisition to the visualization systems. Because the digital image is not less real than the one provided by the optical microscope, we believe that the term *virtual microscopy* is not an accurate term, and we prefer the term *digital microscopy*. Virtual microscopy systems are currently capable of complete digitization of the histology and cytology slides, a process known as whole-slide imaging (WSI). Nowadays, they are available in multiple formats and commercial solutions.

The history of these virtual devices is rather recent. The first virtual microscopy system was described in 1997 by the Computer Science Department at University of Maryland and the Pathology Department at Johns Hopkins Hospital, Baltimore, Maryland.[1,2] To the best of our knowledge, there are no recent reviews on the state of the art for possible virtual microscopy solutions. In 2003, the European Organization for Research and Treatment on Cancer (EORTC) published the results of a poll on virtual

microscopy systems to that date (3D Histech, Aperio, Histkom, InterscopeTech, Leica/Van Hopplynus, Olympus, Nikon, Samba, Syncroscopy, Trestlecorp, Zeiss and Zem).[3]

The objective of this work is to provide a comparative description of 31 solutions available on the market that are able to perform a whole slide digitization or assistance in complete slide review for anatomic pathology applications, together with other related products.

Digital Systems Classification

Digital imaging devices may be divided into 2 classes according to their purpose: the digital microscope (scan the whole slide) and diagnosis-aided systems.

The main objective of digital microscopes or WSI devices is to build digital slides. They are capable of digitizing slides at high magnifications. Diagnosis-aided systems are designed to help with the detection of the region of interest, and some are able to quantify biomedical signals. We include in this review those systems capable of whole-slide scanning or areas-of-interest scanning, at least with low magnification, and not just taking static images from a microscopic field.

By using a criterion based on the components of the device, it is possible to distinguish 2 groups: motorized microscopes and scanners. We have included within the group of motorized microscopes those in which the functionality and original components remain, such as eyepieces, multiple lenses, (motorized revolver), position, and spotlight control. The second main component of these systems is the camera joined up to the microscope. Another essential component is the software that controls the microscope and the camera. The progressive method, in which the final image is composed frame by frame, is the most common procedure used to scan the slides.

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. In this way, slide scanners become special devices for virtual microscopy. The scanners are closed systems. They are open only to introduce the slide tray to be scanned. The scanners are controlled by a PC, usually placed inside the scanner box, which includes an antivibration system. Table 1 shows a classification schema of digital microscopy devices.

Components of the Whole Slide Digitization Systems

All high-resolution virtual microscopy devices are composed of an optical microscope system, an acquisition system (photography), software that controls the scan process, and a digital slide viewer. Other optional components include the slide feeder or the image-processing program.

Cameras

The camera that takes the images is one of the critical components when analyzing the quality and speed of digital microscopy solutions. It is therefore very important to know the camera characteristics in detail.

Usually, these cameras have a charged coupled device (CCD) sensor that provides an analogue signal. Digital cameras convert analogue signals into digital. The main characteristic when analyzing digital camera quality is the image resolution or CCD size (number of pixels the sensor is able to detect) (Table 2).

Most digital cameras are connected to the PC through a FireWire port (LifeSpan Alias, Olympus SIS, Slide, Zeiss Mirax Scan). This may require the use of card adapters. Clarient ACIS uses the Matrox Meteor-II /multichannel card. The Hamamatsu C9600 NanoZoomer and Aperio ScanScope T2 use a CameraLink connection. The correction lens, located in the adaptor between the camera and the microscope, is ×1.0 (LifeSpan Alias, Olympus SIS .slide, Zeiss Mirax Scan) or ×0.63 (Zeiss Mirax Scan, Samba Naviqap). Some systems use an F-mount (LifeSpan Alias, Aperio ScanScope).

Stage

The high resolution and fast stages used in virtual microscopy are able to move at speeds of about 32 mm/s (Zeiss Mirax Scan), 38 mm/s (Aperio ScanScope T2), 41.22 mm/s (LifeSpan Alias), or even 180 mm/s (Olympus SIS .slide). The stage accuracy is about 1 µm to 3 µm, although some types are able to get an accuracy or minimum distance of 0.002 µm to 0.015 µm for the z-axis and 0.25 µm for the x-axis and y-axis (Syncroscopy SyncroScan and Montage Explorer, LifeSpan Alias, Bacus BLISS, Olympus SIS .slide). The most frequently used stages are

Table 1. Classification of Digital Microscopy Solutions

1. Digital microscopes (WSI): virtual slides creation	
A. Automated Microscopes (based on the following models)	Bacus BLISS (Olympus BX61; Zeiss Axioplan 2)
	LifeSpan Alias (Leica DM LA)
	Nikon Eclipse E600FN with EclipseNet-VSL
	Olympus SIS .slide (Olympus BX51)
B. Scanners	
Progressive Scanning	Nikon Coolscope with EclipseNet-VSL
	Zeiss Mirax Scan
	Zeiss Mirax Desk
Lineal Scanning	Aperio ScanScope T2
	Aperio ScanScope CS
Area transference (Time Delay and Integration - TDI)	Hamamatsu C9600 NanoZoomer
Optical matrix	DMetrix DX-40
C. Software and components for virtual slides management	Apollo Telemedicine ASAP Imaging and PathPACS
	Aurora mScope
	Fairfield PathSight
	MicroBrightField Virtual Slide System
	Samba Naviqap
	Syncroscopy SyncroScan
	SlidePath Digital Slidebox
	Trestle MedMicroscopy and Xcellerator
	Tribvn ICS WF
	VMscope
2. Diagnosis aided systems: image analysis and telepathology	
A. Automated Microscopes	Applied Imaging Ariol
	BioGenex iVision
	BioGenex GenoMx VISION
	CytoCore InPath Slide Based Test
	Imstar Pathfinder Morphoscan with E-Mage VS (virtual slide)
	Leica AS TPS2 (frozen section studies)
	MetaSystems Metafer
B. Scanners	
Progressive scanning	Clarient ACIS
	CyTyc ThinPrep Imaging System
Cytometry by laser	Compucyte iColor and Compucyte iCyte

Daedal 106004 model (Aperio ScanScope T2), Leica CTR MIC (LifeSpan Alias), and Maerzhauser scan 100*80 (Olympus SIS .slide). The stage of a motorized microscope may be controlled by means of a joystick (Olympus SIS .slide) or the Leica SmartMove (LifeSpan Alias).

Coolscope) or multispectral channels (LifeSpan Alias). The Zeiss Mirax Scan built-in white light has a complementary color temperature filter. It allows the use of dark field or fluorescence, similarly to Olympus SIS .slide, Hamamatsu NanoZoomer (since August 2006), and Applied Imaging (AI) Ariol.

Optical Equipment—Illumination

The illumination method most frequently used is the halogen lamp (100 W in Olympus SIS .slide). In the scanners, it can be an internal light source (EKE 150 W, Aperio ScanScope T2) or an external one (EKE 150 W, Aperio ScanScope CS). Other systems use light-emitting diodes (LEDs), with white light (Nikon

Hardware

Concerning the computer hardware, most solutions are based on workstations with 2 microprocessors (Xeon), 2.8 GHz to 3.6 GHz, and 4 gigabytes of RAM. The operative system used by the control devices and the workstations is usually Windows XP Professional (Microsoft, Redmond, Wash).

Table 2.   Cameras Used in Some Slide Digitization Systems

Device	Model	CCD-CMOS Size	Sensor Pixel Size (μm)	Resolution (μm/pixel) ×20/×40 objective
Aperio ScanScope T2	Basler L301 kc (CCD)	Color, scanned 3-lineal RGB, 3 × 2098 pixels	14 ×14	0.47/0.23
Aperio ScanScope CS	Basler L301 kc (CCD)	Color, scanned trilateral RGB, 3 × 2098 pixels	14 × 14	0.5/0.25
Applied Imaging Ariol	Redlake MegaPlus ES 4.0/E (monochrome CCD)[a]	Interline CCD 2048 × 2048 pixels	7.4 × 7.4	0.368/0.184
Bacus BLISS	CCD	3 CCD Color 752 × 480 pixels	—	—/—
Clarient ACIS	Sony 3 CCDs 60 fps	Progressive scanning	—	0.0625 μm²/ pixel (×60)
DMetrix DX-40	DMetrix CMOS			
DM5760	24 mega-pixels	—	0.47/—	
Hamamatsu C9600 NanoZoomer	3 CCDs-TDI	4096 × 64 pixels	8 × 8	0.46/0.23
LifeSpan Alias	Diagnostic Instruments SPOT Xplorer 4MP Mono CCD	Monochromatic, 2048 × 2048 pixels (15.16 mm²)	7.4 × 7.4	0.37/0.185
Nikon Eclipse E600FN	Nikon DXM1200F (CCD) with Bayer mask	2/3" CCD. 3,840 × 3072 pixels	6.45 × 6.45	—/0.45
Nikon Coolscope	Nikon DS-5M	2/3" CCD. 2560 × 1920 pixels	8 × 8	—/—
Olympus SIS .slide	CCD. Peltier-cooled with Bayer mask. 12 bits/color	2/3" CCD. 1376 × 1032 pixels	6.45 μm × 6.45 μm	0.32/0.16
Zeiss Mirax Scan	Allied Vision Technologies Marlin F-146C	1392 × 1040 progressive CCD	4.65 μm × 4.65 μm	0.23/0.12 (optional: 0.32/0.16)

a. A range of cameras can be adapted, from 1392 × 1040 pixels (Jai CV-M4+ and CoolSnapEs), to 2048 × 2048 pixels (Redlake ES 4.0/E).

The recommended way for managing the storage is using centralized (enterprise) hospital storage servers. If the pathology department has to have its own storage, the following configuration is recommended: 6 disks, each of 300 gigabytes; 10k rpm hot swap for a total of 3.8 TB.

High-Resolution Monitors

All virtual microscopy solutions include a flat thin-film transistor (TFT) monitor, sized from 20 inches to 23 inches. These screens must be high resolution, such as Apple M9179 Cinema (Apple Computers, Inc, Cupertino, Calif), 30-inch liquid crystal display (LCD) TFT screen of 2560 × 1600 pixels, with 200-ppp resolution. This screen size allows a visual field 4 times larger than the classic microscope field of view. The Apple monitor is optional with Zeiss Mirax Scan, and it has a contrast ratio of 400:1 and a pixel pitch of 0.25 mm.

Aperio ScanScope includes 23-inch HP 2335 LCD monitors (Hewlett Packard, Palo Alto, Calif) (1920 × 1200 pixels, distance pixel 0.258 mm, contrast 500:1). Olympus SIS .slide includes a 20.1-inch NEC LCD2080UX+ monitor (Irving, Texas) (1600 × 1200 pixels, distance pixel of 0.255 mm, contrast 450:1). Bacus BLISS also includes a 20.1-inch LCD monitor.

The Digitization Process or Slide Scanning

Different aspects should be taken into account to evaluate the digitization process, such as the digitization speed, the maximum sample size, the focus quality, the digitization at different planes, the methods for scanning and image assembling, and the formats used to store the scanned samples. Table 3 includes some relevant aspects related to well-known digitization systems.

Digitization Speed

The digitization speed or total scanning time is one of the most important aspects to consider before

Table 3. Main Characteristics of Whole Slide Scanning Systems

Device	Slide Feeder	Viewer (Proprietary/Web)	Objective Lens	Image Stitching
Aperio ScanScope T2	120 (BCR)[a]	ImageScope/Zoomifyer	Olympus ×20/0.75 Plan Apo or ×40/0.75 Plan Fluor[d]	Stitching or ×40/0.75
Aperio ScanScope CS	5 (BCR)[a]	ImageScope/Zoomifyer	Olympus ×20/0.75 Plan Apo (×40 with "doubler").[e]	Stitching
Applied Imaging Ariol	50 (BCR)[a]	Web browser & Zoomifyer	Olympus (×1.25, ×5, ×10, ×20 and ×40)[f]	Stitching
Bacus BLISS	No	WebSlide viewer/Browser (applet java o Active X)	Olympus o Zeiss (×1.25, ×10, ×20 and ×40)	Tiling
Clarient ACIS	100 (BCR)[a]	—	Olympus ×4, ×10, ×20, ×40, ×60	—
DMetrix DX-40	40 (slipstream)	Digital Eyepiece	Matrix with ×80 objective lens, with N.A. = 0.65	Stitching
Hamamatsu C9600 NanoZoomer	210 (BCR)*	Fairfield PathSight File Viewer	Proprietary	Tiling during scanning
LifeSpan Alias	300 (BCR)[a] optional	Applet Java—Active X	Leica ×40 PL Fluotar 0.75 NA (and ×2.5, ×5, ×10, ×20, and ×63)	Stitching or Tiling
Nikon Coolscope	160 (Cool-Loader) optional	EclipseNet/Web DB (Bacus at USA)	×5, ×10, ×20 and ×40 or ×2, ×4, ×20, and ×40 (low-mag)	Stitching
Nikon Eclipse E600FN	No	EclipseNet/Web DB	Nikon CFI60 Plan Fluor ×40, CFI60 Plan Apochromat ×20, CFI60 Plan Fluor ×4	Stitching
Olympus SIS .slide	SL50, with BCR[a] or stage 4 slides optional	OlyVIA[c]/Zoomifyer	Olympus 40 UPLSAPO, ×2 PLAPON, ×10, ×20 (to 6)	Tiling
Zeiss Mirax Scan	300 (BCR)[a] optional	Mirax Viewer (free and full featured versions)[b]/ applet Java	Carl Zeiss Plan-Apochromat ×40 NA 0.95 or Zeiss Plan-Apochromat ×20, NA 0.8	Stitching (optional tiling)

a. BCR = includes a bar code reader.
b. Full featured version is 2,500 Euros/5 users license. The free viewer has every essential tool for digital slide viewing and only the additional application modules are missing, such as 3D reconstruction, TMA evaluation, and on-line teleconsultation.
c. OlyVIA (Olympus Viewer for Imaging Applications)
d. An optional ×40 Plan Apo may be used, but due to the extremely short working distance, some user interaction may be required for initial "macro focus," depending on glass slide thickness.
e. Optional objectives: ×40/0.75 Plan Fluor, or ×40/0.90 Plan Apo
f. Any objective may be used including ×60 and ×100.

choosing among these systems. An objective evaluation is quite difficult because it is dependent on factors such as:

- The area size to be scanned.
- The objective lens used (×20 or ×40). DMetrix DX-40 is able to take 3,000 images/s for the ×80 objective.
- The camera CCD size.
- The motorized stage model.
- The required time on the previsualization stage: panoramic view, selection of area of interest and focusing method.

- The number of focusing points needed. Slides with irregular surface require a higher number of points, which reduces the scanning speed.
- The number of planes at the z-axis to be digitized.
- The speed to obtain data from the camera to the PC and from the PC to the storage device.

For those devices with a slide feeder, the time to upload and download a slide is about 6 to 8 seconds. The total time, including the code bar reading, is around 15 seconds.

Tables 4 and 5 show the scanning time with ×20 and ×40 objective lens, respectively, sorted by

Table 4.   Required Time for Slide Scanning or Digitization With a ×20 Objective

Device	Area 10 × 10 mm	Area 15 × 15 mm	Whole: 25 × 50 mm
DMetrix DX-40	—	—	58 sec (ultra-speed mode)
Aperio ScanScope CS	2 min	2:45 min	4 min
Syncroscopy SyncroScan	—	—	5 min
Hamamatsu C9600 NanoZoomer	1 min	2.5 min	10 min
MicroBrightField	1 to 3 min	2 to 7 min	10-40 min
MetaSystems Metafer	—	—	11-14 min
Aperio ScanScope T2	2 min	5 min 16-30 min	
Trestle MedMicroscopy	—		16 min
Zeiss Mirax Scan	3.5 min[a]	2:25-6:45 min[b]	15 min
Olympus SIS .slide	2.5 min	6 min30 min	
Fairfield Imaging PathSight	4 min	8 min47 min	
Applied Imaging Ariol	7 min	16 min1 h 30 min	
LifeSpan Alias	8.5 min	20 min1 h 40 min	
Samba Naviqap	—	—	2 h 22 min
Nikon Eclipse E600FN	—	—	4 h to 12.5 h
Imstar Pathfinder E-Mage VM	—	—	5 min (5 mm^2)

a. Fluorescent scanning: 10 × 10 mm, ×20 objective, 0.23 μm/pixel, 3 channels with the following exposure times: 52, 100, and 48 milliseconds, 40:00 minutes.
b. With a ×0.63 camera adapter and focusing every 1 mm, scanning time is 3:05 minutes; if focus is made every 2 mm, scanning time is reduced to 2:25 minutes.

Table 5.   Required Time for Slide Scanning or Digitization With a ×40 Objective

Device	Speed (mm^2/s)	Area of 10 × 10 mm	Area of 15 × 15 mm	Whole: 25 × 50 mm
Hamamatsu C9600 NanoZoomer	0.35	4 min	9 min	40 min
Aperio ScanScope T2	0.66	6 min	13 min	1 h 15 min
Zeiss Mirax Scan	0.35	12.5-31 min	39 min	1 h 45 min
Olympus SIS .slide	0.18	11 min	25 min	1h 46 min
MicroBrightField	0.07-0.52	3.5-22 min	7.5-50 min	40 min-4 h 38 min
Applied Imaging Ariol	0.23	28 min	64 min	6 h
LifeSpan Alias	0.05	35 min	80 min	7 h 28 min
Nikon Coolscope	—	1 h	2 h 30 min	12 h 30 min

ascending order, according to the information provided by the manufacturer.

Slide Holder and Maximum Sample Size

All of the evaluated devices work with conventional slides 1 × 3 inches (25 × 75 mm) × 1 mm thick. Some systems, such as the first version of the Nikon Coolscope, do not work properly with round corner slides, whereas this is the type of slide recommended by Zeiss Mirax Scan.

The total scanning surface is constrained to the motorized stage used and to the histologic slide type. The scanners or motorized microscopes are usually able to go through all the slide width (27 mm), but usually they only go through the 60% to 70% of the slide length (50 mm); that is, they avoid the label area. The slide label is obtained by a special camera (Aperio ScanScope, LifeSpan Alias) or read by a code bar device (Zeiss Mirax Scan). For bar code reading with the Aperio ScanScope T2, we have obtained the best results using 2D Datamatrix code-bar of 8 points, generated with Tissue-Tek AutoWrite Glass Slide Printer. LifeSpan Alias can read multiple barcode formats

The Aperio ScanScope CS is able to work with large format slides (2 × 3 inches). This option is also available in Olympus SIS .slide.

The maximum scanning area of Aperio ScanScope T2 is 22.9 mm × 54.9 mm; for Aperio ScanScope CS, it is about 26.3 mm × 56.1 mm (50 mm × 57.1 mm for large slides); and for Zeiss Mirax Scan, it is about 27 mm × 50 mm.

The Mirax Scan digitization system is available with 2 configurations: Mirax Scan, for automatic digitization (several 50-slide cassettes), and Mirax Desk, a cheaper option intended for manual slide scanning.

Concerning the slide thickness, those slides mounted between 2 pieces of glass because of a break can be digitized with a conventional motorized microscope (Bacus BLISS, Olympus SIS .slide), but usually not with scanners such as Aperio ScanScope.

To hold the specimen slide, a mechanical attachment (Bacus BLISS), simple lateral pressure (Olympus SIS .slide), or vacuum system (LifeSpan Alias) can be used.

Focus Quality

The quality of the focusing may be evaluated by the following parameters:

- The focus range of movement (150 μm for Zeiss Mirax Scan.
- The time for adjusting the focus (0.1 second for Zeiss Mirax Scan).
- Minimum distance (least step) (0.15 μm for Zeiss Mirax Scan).
- The method applied to distance measurement: infrared laser light of 780-nm wavelength (Zeiss Mirax Scan) or the triangulation method, point by point (Aperio ScanScope T2).
- Movement resolution at the z-axis (0.3 μm with objective ×20 for Zeiss Mirax Scan and 0.1 μm for Aperio ScanScope T2 with objective ×40).

The number of focusing points (focusing map) may be manual or automatically set in Aperio ScanScope T2 and CS, AI Ariol, and Hamamatsu C9600 NanoZoomer. With this last device, it is also possible to adjust the number of focus points in the batch mode. Olympus SIS slide uses several options to choose different focusing algorithms.

Systems based on motorized microscopes (Table 1) are particularly suitable to scan focus difficult areas within the slide because they allow higher control over the stage position. However, scanners may also
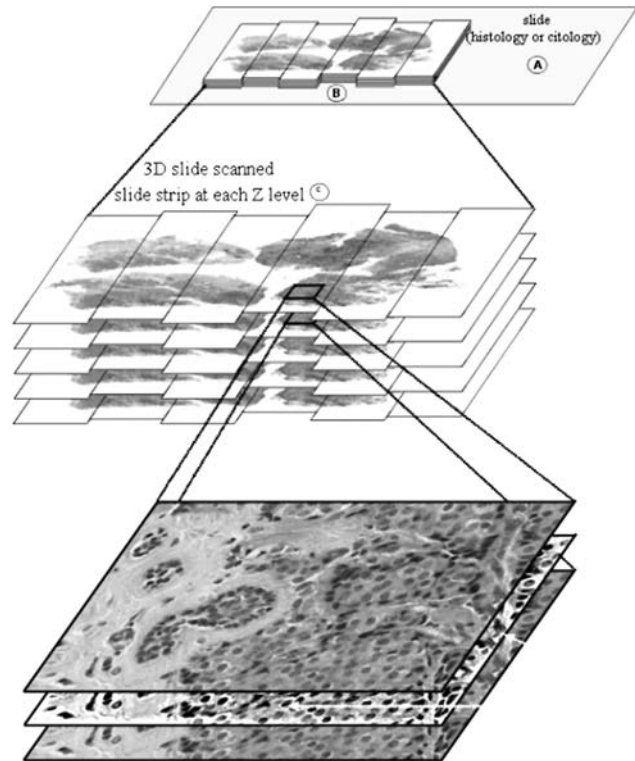
Figure 1.   Multiple focus planes digitization from a histology slide.

have an observation mode that allows the focus to be manually adjusted over a set point.

Multiple Planes Digitization Through the Z-Axis

Visualizing multiple planes is a requirement for pathologists in cases such as thick tissue slides or cytology slides with 3-dimensional (3D) clusters. Therefore, the scanning system should be able to digitize different focused planes through the z-axis in a way similar to that used by pathologists with the microscope fine focus control (Figure 1).

Different systems are able to provide the digitization through the z-axis, at least on one area of the slide. These are the Aperio ScanScope CS (Remote Revisit), Bacus BLISS, LifeSpan Alias, Nikon Coolscope with EclipseNet-VSL, and Hamamatsu NanoZoomer (since August 2006).

It is sometimes possible to obtain a perfect focus image even if the system is not able to produce z-axis

scanning by means extended focal imaging (EFI), which is optimal focus over all points (Olympus SIS .slide). Syncroscopy SyncroScan also integrates a similar system for plane focusing.

## Whole Slide Scanning Method and Stitching

The first step of the digitization process is to decide whether it is necessary to scan the whole slide or only arbitrarily selected areas, or automatically detected tissue or cytology fields. This can be achieved using a previsualization tool (available in most systems), by taking an overview slide picture with a digital camera or webcam (Aperio ScanScope, Zeiss Mirax Scan), or by digitalizing the whole slide at the lowest available magnification (×2.5 for LifeSpan Alias; ×2 for Olympus SIS .slide; ×1.25 for Bacus BLISS and AI Ariol). The Hamamatsu C9600 NanoZoomer uses an additional high-resolution camera (1344 × 1024 Interline CCD) to create the slide map. It is a quick process that usually takes less than 15 seconds (Zeiss Mirax Scan, Olympus SIS .slide).

It is also possible to manually select several regions of interest (Olympus SIS .slide, and AI Ariol) or draw up the estimated shape of one or several regions to be scanned (LifeSpan Alias, Nikon EclipseNet VS).

The second step is to adjust the focus point (focus map) for the selected region (see Focus Quality) and adjust image settings, such as white balance.

The third step is the scan. This process consists on taking different fields of the original slide and joining the different strips (virtually on the screen or in a real file on the PC) to create a seamless virtual slide. This process can be set manually or automatically (batch mode or one touch) in all described systems, as well as in a mixed way, available in NDP Scan 1.2 software of the Hamamatsu NanoZoomer, where the user corrects the focus options or the regions of interest that the system uses in batch mode (Figure 2).

The acquisition of microscopic fields is usually square-by-square, from the slide's upper left corner to the lower right one (Figure 3A). Thus, the final image is a mosaic composed of multiple files. Other systems use linear cameras (Aperio ScanScope), where the acquisition file corresponds to a strip set of the same length than the slide or area of interest width (Figure 3B).
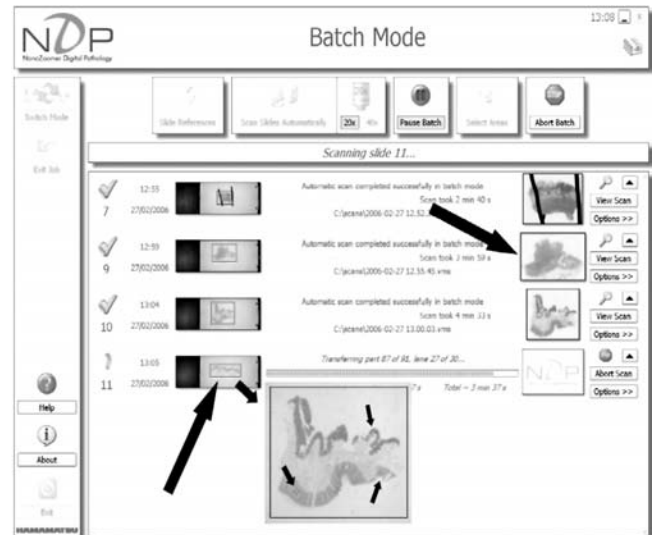
Figure 2. Batch mode in Hamamatsu NanoZoomer allows automatic region of interest selection and focusing points and manual adjustments for editing and amending failed scans.

The first method (square matrix acquisition) takes a high number of image frames (tiles). For instance, it is estimated that for an area of 15 mm × 10 mm at ×40, the Olympus SIS .slide needs about 1253 pictures.

The use of monochromatic cameras (LifeSpan Alias, and AI Ariol) requires three scanners (R, G, B) for each area. At 2048 × 2048 pixels CCD (LifeSpan Alias), each acquisition will be 4 MB in size, therefore 12 MB per frame.

Aperio ScanScope uses a lineal scanner and adjusts the focus from one line to the next at a high frequency rate. Moreover, the line scanned is always at the optical axis, thus avoiding 2D optical aberrations. At a ×20 objective, each uncompressed tagged image file format (TIFF) file with a scanned image stripe is 200 mega-pixels in size when Aperio ScanScope is used.

The assembling process of the slide squares may be done in 2 different ways:

1. Mechanical adjustment: Tiling the borders of each fragment. This method is available in most systems.
2. Software adjustment: Stitching between the images. The images are acquired with some overlapping between them and the common regions are matched by software. This method
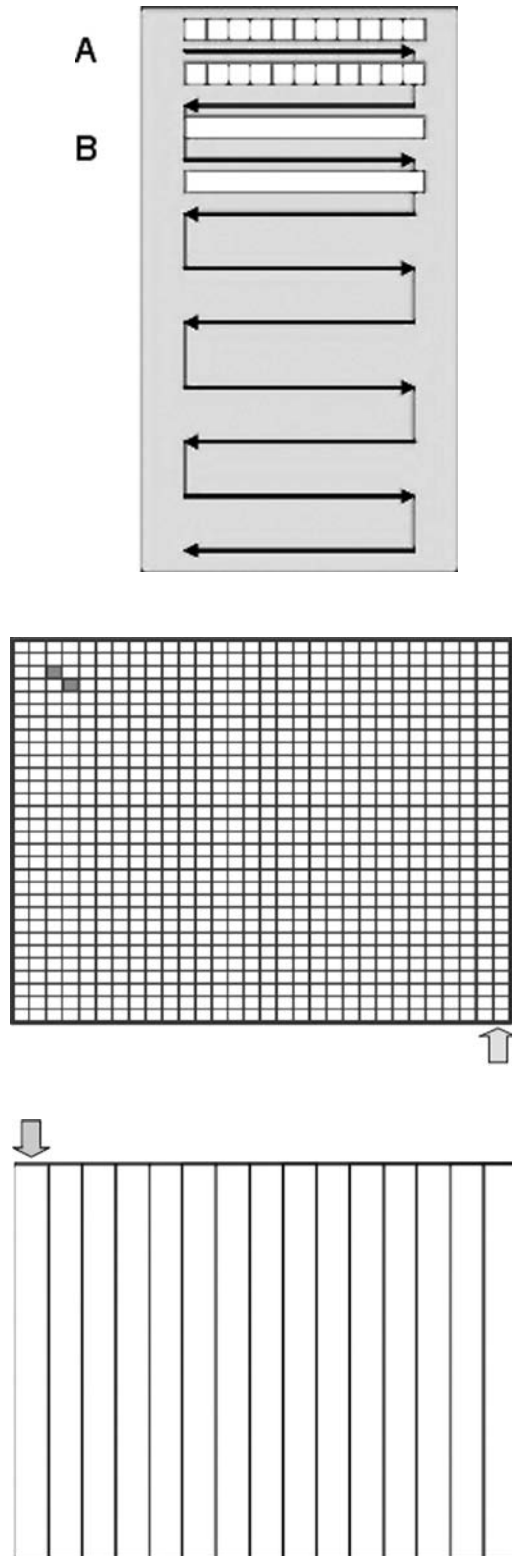
Figure 3. (A) Scanning based on the sequential microscope individual fields capture (squared matrix) where an image is obtained by each field. (B) Lineal scanning, where each file groups all fields within a line.

is available in Aperio ScanScope, AI Ariol, DMetrix, LifeSpan Alias, and Zeiss Mirax Scan.

File Formats

The final result obtained after a digital slide has been created may be physically as follows:

- Multiple files—usually thousands of Joint Photographic Experts Group (JPEG) files— in one or several folders. Usually, each folder corresponds to a different magnification (SlidePath, Bacus Bliss). It is also possible to generate files with bitmaps without compression (LifeSpan Alias). These files are particularly useful for image analysis.[4]
- Several files with one or multiple resolutions (usually JPEG). This is the method used by Zeiss Mirax Scan and Zoomifyer viewer.[5]
- A single compressed file (JPEG2000, JPEG).

It is possible to obtain a single file with multiresolution information. When this solution is implemented, all the information, including the panoramic image or thumbnail and the captures to different resolutions, is stored in a single physical file. Often, the structure of these files is pyramidal[6] and may be TIFF (Aperio ScanScope), JPEG2000, Flashpix (MicroBrightField Virtual Slide), or other (VSI extension in Olympus SIS. slide).

Table 6 summarizes the various compression techniques and file formats used by different manufacturers. To facilitate transmission through communications networks, high-resolution images are stored partitioned in small chunks (240×240 pixels in Aperio ScanScope T2 and CS).

The maximum compression for JPEG2000 is usually double than that of JPEG at the same percent compression ratio, but it requires double computational time. Therefore, some solutions, like Aperio ScanScope CS, use JPEG2000 compression by hardware.

Digital Slide Visualization and Processing

Ideally, the movements to be carried out by the pathologist when visualizing a virtual slide on the

Table 6.   Compression Methods and File Formats

Device	Default Compression Method	JPEG2000 Compression Available	Other Optional Compression Methods	Available Uncompressed Format	File Type	File Size ×40
Aperio ScanScope T2	JPEG (libjpeg)	Lossless (1:20). Matrox Imaging algorithm	LZW (lossless)	TIFF	.SVS (modified TIFF 6.0, pyramidal)	1.5 GB
Aperio ScanScope CS	JPEG (libjpeg)	By hardware	LZW (lossless)	TIFF	.SVS (modified TIFF 6.0, pyramidal)	1.5 GB
AI Ariol	JPEG	Yes	No	BMP, JPEG2000, and PNG	JPEG	—
Bacus BLISS	JPEG	No	—	No	JPEG	—
Hamamatsu C9600 NanoZoomer	JPEG	No	No	Under	JPEG development	2 GB
LifeSpan Alias	JPEG o JPEG2000	Yes (Aware Jpeg2000 SDK)	JPEG	TIFF	.TIF	2 GB
Nikon EclipseNet-VSL	JPEG	Yes (max 350 MB)	No	TIFF, BMP	.VSL (JPEG) and :JP2 (JPEG2000)	2 GB (JPEG)
Olympus SIS .slide	CMW (Leadtools Wavelet compressed 1:15)	Yes (with or without loss)	JPEG	TIFF, but not RAW	.VSI (pyramidal, up to 9 resolutions)	1.5 GB
Zeiss Mirax Scan	JPEG	Third party (VMscope)	No	BMP, PNG	.DAT (JPG)	1.5 GB

screen should be the same as those made when a conventional microscope is used. They are:

- X-axis and y-axis movements → lateral and vertical displacement through the screen.
- Objective shifting or zoom.
- Z-axis displacement (focusing and focus planes).
- Other functions.

X-Axis and Y-Axis Movements

One of the main problems in digital microscopy systems is the low screen refreshment during the horizontal and vertical displacements. This is due to the large amount of data that need to be transferred between the different parts of computer (central processing unit, hard disk, graphics card, memory) or through the communication network. It is therefore possible to watch during this process how the pieces of each slide's region start uploading into the screen. This effect may be quite disturbing for pathologists, who are used to going quickly through the slide with only the limitation of their eyes' accommodation.

To avoid this problem, the proposed solution is partitioning large images into small pieces according to the required magnification and buffering adjacent pieces (prefetching) in the viewer. In most cases, the microscopy viewer includes a thumbnail image to get a picture of the entire slide (Figure 4). Some solutions bring this image into a resizable window (LifeSpan Alias, Olympus SIS .slide).

Pointer and Tracking Devices

The mouse is not a comfortable device for pathologists to use to review the slide because they are used to a wheel system to control the fine movements and focus. It is therefore likely that devices similar to the SmartMove, designed by Leica Microsystems (Figure 5), will become popular in the near future.

Objective Shifting or Zoom

The virtual slide viewers allow pathologists to work in a way similar to that used with conventional microscopes, by using ×4, ×10, ×20, ×40, or ×60
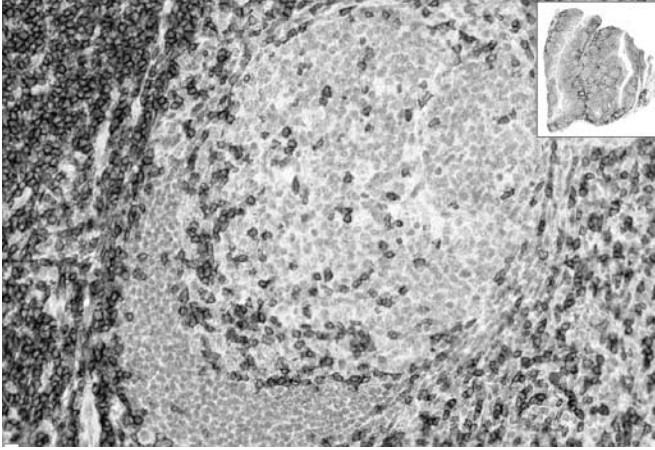
Figure 4.   The thumbnail image (slide map) at the right upper corner, allows identifying the zone to be seen into detail (CD3 in normal tonsil).

Figure 5.   SmartMove controller by Leica Microsystems.

objectives. In addition, most viewers have additional tools to facilitate the everyday work, such as:

- Continuous sliding bar that allows adjustment of the zoom in a flexible way.
- Digital zoom to quickly visualize at higher magnifications small selected regions of interest.
- Opening 2 windows of the same slide at different magnifications.

Z-Axis Displacement (Focusing and Focus Planes)

Histology slides, and especially cytology slides, may require the capture of multiple z-planes to get a perfectly focused image. It is particularly interesting to obtain a complete view of some structures, such as papillary structures on cytology smears.

In general, digitization of multiples planes at the z-axis is usually available for motorized microscopes but not for scanners. However, Aperio ScanScope CS has an option called "Remote Revisit," that allows for the capture a set of z-planes ("z-stack") composed of small regions of interest within the digital slide that can be selected with a remote connection to the scanner. This allows focusing on real-time selected areas from the slide. Those z-stack images are kept on the server together with the high-resolution 2D image. It is during the visualization process that the z-stack images are overlapped and matched all together.

Others Functions

Simultaneous and synchronized displacement on multiple windows: This is an especially useful tool that allows movements performed on one slide to be reproduced in all the other opened slides. This function helps to compare different sections from the same paraffin block stained with different markers, even if the sections have undergone rotation and translations. This option is available on several described systems, such as Aperio ScanScope (Aperio SmartSync), Zeiss Mirax Scan, Olympus SIS .slide, and AI Ariol. The link between multiple scans may be used by the Ariol system to define the regions for capturing and analyzing over all of the linked slides. For example, the hematoxylin and eosin slide may be used to select the tumor regions on all slides in an immunohistochemistry panel.

Track of visiting areas: Some viewers (Zeiss Mirax Scan) keep track of the visited regions within the slide.

Digital bookmarks: It is possible to include bookmarks on digital slides, facilitating the retrieval of interesting positions in subsequent case reviews. These bookmarks can be in text or in graphic format (ie, arrows, circles). The bookmark list with labeling options should allow a viewer to go directly to the right magnification and coordinates of the slide with a simple click of the mouse. Another interesting option, not always available, is identifying the author

of the bookmark. Aperio ScanScope, Zeiss Mirax Scan and Olympus SIS .slide include digital bookmark options.

Teleconsultation and conferencing: Virtual slides can be visualized and commented on simultaneously by several pathologists. This virtual "multihead microscope" allows all users to review the same areas when one of the users takes control of the session, or different pathologist can review different parts of the same slide at the same time. Moreover, discussions and comments are available by means of a dialog window. With session control tools, it is possible to assign a role to each participant of the conference.

Remote conference tool: This is available on several systems, such as Aperio ScanScope, Bacus BLISS, Zeiss Mirax Scan, and Olympus SIS .slide. This tool facilitates the use of digital slides in multicenter quality assurance protocols.[7] ScanScope CS and Ariol, and Mirax Scan allow remote logging onto the system, and running the system using Remote Desktop over the Internet.

Image Analysis: Apart from the Tissue Micro-Array (TMA) specific modules described below, some of the digitization solutions (Mirax Scan, Aperio ScanScope) have modules to conduct quantitative analyses of regions of interest within digital slides,[8] such as quantification of positive immunohistochemistry pixel detection, positive nucleus, cellular membrane detection and micrometastasis detection. Except for specialized solutions (AI Ariol, Clarient ACIS), the image analysis provided by most of virtual slides solutions is limited to some edition, visualization, and management options. It is also possible, however, to perform image analysis in digital slides with other compatible software (Olympus AnalySIS).

Three-dimensional reconstruction: Zeiss Mirax Scan (3D Mirax) has an optional module that gives the possibility of creating 3D reconstructions from virtual slides.

Software for Tissue-Micro Arrays: Tissue Micro-Array slides require specific management tools. For this reason, some manufactures have integrated specific TMA modules, such as Aperio TMALab or SIS .slide. Specific solutions, such as AI Ariol and Clarient ACIS, can be more suitable for TMA management.

File Format Export Options: The digital image visualization module must be able to manipulate them (ie, rotate, resize, contrast modification, filtering) and, above all, it must be able to export them in different formats such as JPEG, TIFF (without compression), and raw format. For instance, Olympus SIS .slide is able to export the slide to a standard Web page, generating multiple JPEG, each one of 512×512 pixels, that may be read by Zoomifyer.

The resulting files in the exporting options, which can include annotations, are good-quality images, and they are most valuable for scientific papers, congress presentations, or pathology reports. For example, the ImageScope viewer from Aperio is able to provide images of 1.676×926 pixels (96 ppp).

Available Systems on the Market

Bacus Bliss
http://www.bacuslabs.com/

Bacus BLISS is a pioneer system of virtual slides. Besides a good image quality, Bacus BLISS incorporates numerous tools for virtual slides management and visualization via Web, also used by other manufactures. Contact: Bacus Laboratories, Inc, 410 Eisenhower Lane N, Lombard, IL 60148; phone: 630-424-9750; fax: 630-424-9754; e-mail: info@bacuslabs.com.

The image gallery is available at the Web site http://66.106.109.242/blipathology/index.html (it requires Java installation).

LifeSpan Biosciences Alias
http://www.lsbio.com/products/automatedimage capture/

The main characteristic of LifeSpan Alias is the high image quality, due to the numerous modifications the manufacturers have done to the Leica microscope. The system includes an illumination system based on 4 colors LED (RGB + amber). A recent modification of ALIAS was the addition of the 63x objective. Contact: LifeSpan Biosciences Inc, 2401 4th Ave,
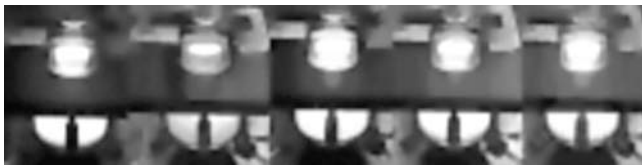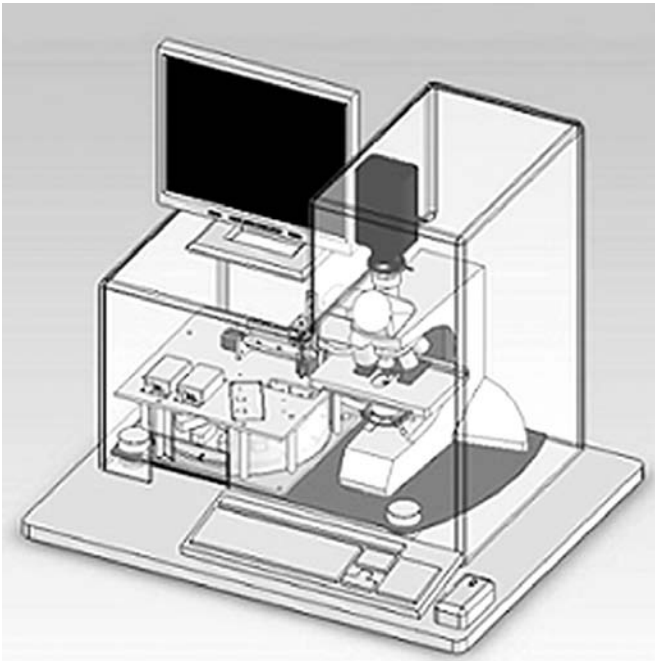
Suite 900, Seattle WA 98121; phone: 206-374-1175; fax: 206-464-1723; e-mail: Rajesh.Krishnan @LifeSpanBiosciences.com; Web page: http://www .lsbio.com/.

Olympus-Soft Imaging System .slide
http://www.soft-imaging.net/rd/english/3412.htm

This system is easy to use and provides a very good image quality. Its outstanding software includes numerous modules (ie, slide review, conferencing, measurements). Since 2004, Soft Imaging System (SIS) is part of Olympus Europe. The contact address is local to each country by Olympus Optical: http:// www.olympus-global.com/en/global/
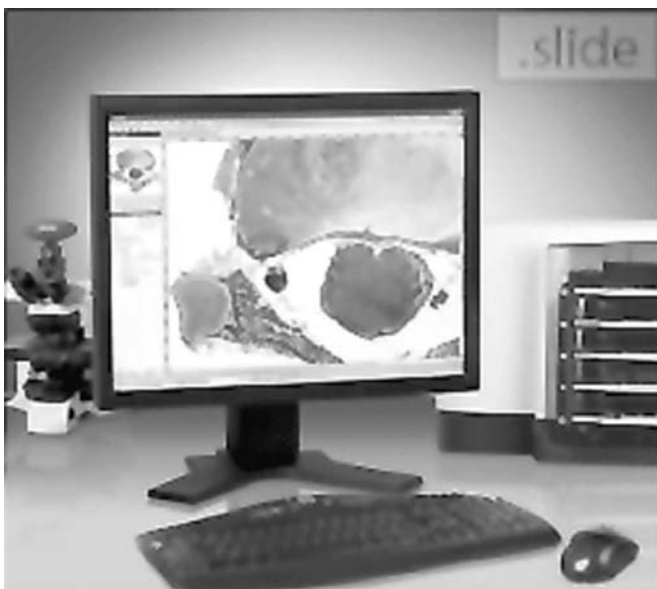
A gallery of digital SIS slides is at http://www .dotslide.soft-imaging.de/

Nikon Eclipse E600FN with EclipseNet-VSL
http://www.nikon-instruments.com/uk/products/ imaging.html and http://www.lim.cz/index.php?lang= en&inc=enet_vsl

This system is proposed by Nikon for a complete slide digitization. The digital slides are kept on database of a workstation or in any other network PC. EclipseNet performs all the capture and storage processes. The EclipseNet Web DB database allows reviewing the slides using a web browser. EclipseNet VSL works with all Nikon digital cameras (see also Nikon Coolscope below).

In the near future, EclipseNet will be replaced by Nikon Imaging Software (NIS) Elements, the Nikon worldwide software platform. At present, NIS does not include an instrument for creating or managing virtual slides.

Nikon Coolscope with
EclipseNet-VSL or Bacus Coolscope VS
http://www.coolscope.com/ and http://www.eclipsenet .info/

Nikon Coolscope digital microscope is a compact system that includes the functionalities of an optical microscope and a PC. It allows transferring images from slides using standard hypertext transfer protocol (http) and file transfer protocol (ftp). In the United States it is provided with software from Bacus (Coolscope VS). This system is also available in Europe as an alternative to EclipseNet VSL. EclipseNet VSL is able to drive Coolscope and also a microscope with a scanning stage. The latter option allows more flexibility for lens selection; for instance, using oil immersion lenses is not available for the Coolscope. The Coolscope slide loader (Cool-loader) is designed for telepathology purposes, not for VSL creation. Contact (international): http://www.nikon-instruments.jp/eng/contact/ContactTop.aspx

The LUCIA Net VSL digital slide gallery is available at http://www.lim.cz/webdb/index.php?dsn=SampleDatabase&dbid=27&jmeno=guest, or sample databases at http://www.lim.cz/index.php?lang=en&inc=webdb.

Carl Zeiss Mirax Scan and Mirax Desk
http://www.zeiss.de/mirax

Mirax Scan is based on the Hi-Scope (http://www.3dhistech.com/) developed in Hungary by Dr Bela Molnar's team, from Semmelweis University at Budapest. The system is able to digitalize automatically a large number of sample slides. This is one of the few systems with fluorescent scanning capabilities. Up to 10 filter cubes can be mounted in Mirax Scan. The obtained virtual slide is always a folder with several files with .dat extension. A Software Development Kit will be soon available to access the slide data by third-party programmers. A smaller model Mirax Desk is also available. It is equivalent

to Mirax Scan in speed, resolution, and image quality in bright field, but has no fluorescence and it can only scan one slide.

More information is available at the Web site. A contact form and international section is at http://www.zeiss.com/explore.

Several examples are available at the 3D Histech Web sites: http://www.3dhistech.com/viewer2/; Zeiss', http://www.zeiss.de/mirax; and PathoNet site: http://www.pathonet.org/

Aperio ScanScope T2 and CS
http://wwww.aperio.com/ and http://www.scanscope.com/

The Aperio Company has 2 different ScanScope scanners: T2 and CS. They are remarkable for their good quality/speed ratio, the efficient virtual slides data base management, including tools like Workflow Manager, and for the easy publication of virtual slide both on the Internet and the hospital intranet. The company has released a new pathology information system, called Spectrum, to help the integration of gross study images, microscopy digital slide images, reports, clinical histories, and other associated documents and images.

Aperio Technologies Headquarters is at 1430 Vantage Court, Suite 106, Vista, CA 92081; phone: 760-539-1100; fax: 760-539–1116; e-mail: info@aperio.com. The European office address is Charwell House, Wilsom Rd, Alton, Hampshire GU34 2PP, UK; phone: +44-0-1420-540-271; e-mail: europeinfo@aperio.com.

The image gallery is available at http://images2.aperio.com/ and http://images.scanscope.com/.

Other examples are available at California Medical Center at California University on Davis (http://ccm.ucdavis.edu/imagearchive/), Leeds University (http://www.virtualpathology.leeds.ac.uk/), and Hospital General de Ciudad Real (http://www.hgcr.es/html/).

Hamamatsu C9600
NanoZoomer Digital Pathology
http://jp.hamamatsu.com/products/node.do?dir=/application/medical/pa195&lang=en&ext=html

This is a fast slide scanner that can handle more than 200 slides. Files obtained with NanoZoomer can be published in Web sites using Bacus WebSlide software. Contact e-mail: salesmaster@hq.hpk.co.jp.

Sample images scanned with Hamamatsu NanoZoomer are available at Bacus Laboratories Web site at http://www.bacuslabs.com/blog/products/WebSlideBrowser.html

Dmetrix DX-40
http://www.dmetrix.net/

This innovative device, developed at Tucson, Arizona, is defined as an "array microscope" because it includes an 80-lens or miniature objectives array combined in the same scanner. In this fashion, the whole slide image is obtained in one shot (9,10). Contact: DMetrix, Inc, 1141 West Grant Rd, Suite 100, Tucson, AZ 85705

Apollo Telemedicine
http://www.apollotelemedicine.com/

Apollo Telemedicine software is used by MicroBrightField and DMetrix solutions. Some of their products are ASAP Imaging, to share virtual slides and work in a remote way with the same slide, facilitating the second opinion (consult); Apollo LIVE for videoconference; and PathPACS for storage management and virtual slide retrieving. An image gallery is available at http://216.204.84.52/
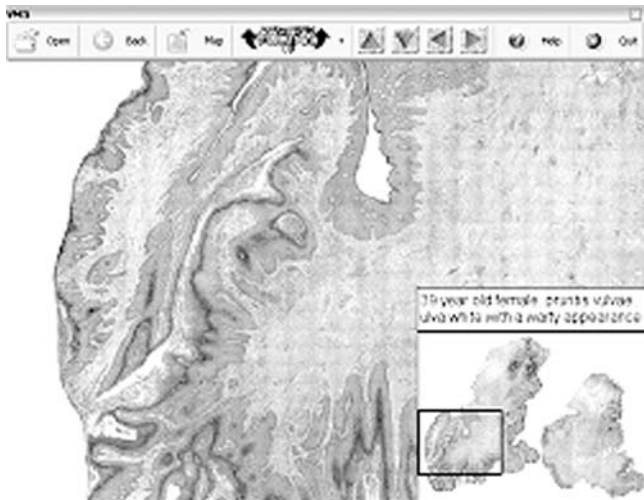
Aurora mScope
http://www.mscope.net

Aurora MSC is a company specialized in software for pathology image management. Its products are compatible with different scanners, including Aperio, Trestle, and Nikon, among others. Some of the modules available are Scanner Interface Manager for image generation, file conversion, data base, and work list management; Distributed Digital Slide Server, and image server optimized for the use of digital slides, using a wavelet compression which is 25% more efficient than JPEG; Laboratory Image Workflow Manager for images follow-up from their generation, including storage and integration within the pathology workflow process; and Authoring and Publishing Server with educational tools in pathology. Contact: Aurora MSC, 505 University Ave, Suite 1603. Toronto, Ontario M5G 2P1, Canada; e-mail: rwilk@mscope.net.

Fairfield PathSight
http://www.fairfield-imaging.co.uk/

PathSight is a flexible system, capable of both semi-automatic and automatic working modes. The java-based viewer is free. Fairfield is a British company funded on 1989 located at Nottingham, UK, and since 1995 it has belonged to Medical Solutions Group (e-mail: info@medical-solutions.co.uk). They provide an image gallery at http://www.fairfield-imaging.co.uk/fairfield/mikewells/ and http://interpath1.uio.no/telemedisin/

MicroBrightField Virtual Slide System

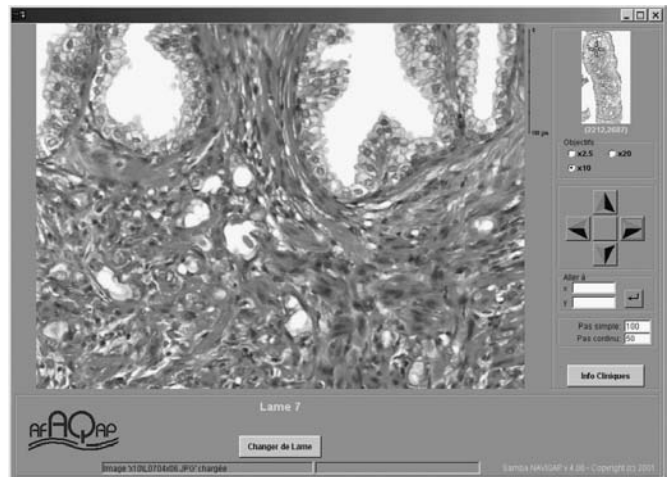http://www.microbrightfield.com/products/virtual
slide/whitepaper.html

Virtual Slide System is a software module to be added to microscopy solutions of some manufactures, such as Neurolucida or Stereo Investigator. Contact (Europe): MicroBrightField Europe, E.K. Matthissonstrasse 6, D-39108 Magdeburg, Germany; phone: +49-391-732-6989; fax: +49-391-732-6989; e-mail: rbraul@online.de.

Samples of virtual slides can be found at Neuroinformatica Web (http://neuroinformatica.com/) and Virtual Slidebox (http://www.path.uiowa.edu/virtualslidebox/).

Samba Naviqap

http://www.sambatechnologies.com/ProduitsUS1.htm

Samba uses the automatic microscopy workstation AcCell, with a control PC that may be combined with a digital slide server (PDB2000). Contact: Samba Technologies, Zirst, 53 chemin du Vieux Chêne, 38240 Meylan, France; phone: +33-0-476-04-00-50; fax: +33-0-476-04-15-98; e-mail: samba@sambatechnologies.com.

An example of a virtual slide is at http://www.molecular-dx.com/1_investors/3_samba/40_virtual SlideViewer.html

Syncroscopy SyncroScan

http://www.syncroscopy.com/syncroscopy/syncro
scanshort.asp

SyncroScan is a system based on software for automatic microscopy that is possible to install on different microscopes. Syncroscopy Europe Office contact: Beacon House, Nuffield Rd, Cambridge CB4 1TF, United Kingdom; phone: +44-0-1223-727127; fax: +44-0-1223-727101; e-mail: eurosales@syncroscopy.com; international: intlsales@syncroscopy.com.

Some examples of digital slides are at the Web site http://www.syncroscopy.com/syncroscopy/microscopy
.asp

SlidePath Digital Slidebox

http://www.slidepath.com/

The Digital Slidebox is a management system for digital slides that allows users to create their own Web-based pathology resource, with application for external quality assurance. Contact: SlidePath, The Innovation and Enterprise Centre, Dublin City University, Dublin 9, Ireland; phone: +353-0-1-700-7576; fax: +353-0-1-700-7555; e-mail: info@SlidePath.com.

Trestle MedMicroscopy and Xcellerator

http://www.trestlecorp.com/medmicro_sysdiagram
.asp and http://www.trestlecorp.com/Xcellerator.asp

The Trestle MedMicroscopy software is used combined with motorized microscopes, such as Olympus BX-40 or Olympus BX-50 (11). Moreover, Xcellerator is a set of software toolkits for digital image archiving and management. It may incorporate tools for image analysis such as those developed by BioImagene (http://www.bioimagene.com). Contact: Trestle Corporation, 199 Technology Dr, Suite 105, Irvine, CA 92618; phone: 800-823-3203, 949-673-1907; fax: 949-673-1058; e-mail: info@trestlecorp.com.

Tribvn ICS WF
http://www.tribvn.com/tribvn/med/stations.htm

The French company Tribvn has developed a module for virtual slides that can also be used in its telepathology platform, TeleSlide. These systems may be used with several devices, either motorized microscopes or scanners (Aperio ScanScope, Nikon Coolscope) and are able to export proprietary files to JPEG2000 format. Contact: Tribvn 39, rue Louveau. 92320 Châtillon, France; phone: +33-0-1-55-58-05-20; fax: +33-0-1-55-58-05-30; e-mail: info@tribvn.com; Web page: http://www.tribvn.com/

VMscope
http://www.vmscope.com/

The VMscope GmbH was founded in 2004 by members of the University Hospital Charité in Berlin. Its products are VM Slide Server, which provides the virtual slides for fast transmission over Internet, and VM Slide Explorer for the client side. It offers different services, such as slide scanning, slide databases, and publishing slides on the Internet, with several authoring tools (Learning Portal, VM TMA Module). The VM Slide Converter creates virtual slides in the standard format JPEG2000 from the data format of several slide scanners, such as Zeiss Mirax. Contact: VMscope GmbH, am Campus Charité Mitte, Schumannstr 20-21, 10117 Berlin, Germany; phone: ++49-0-30-450-536188; fax: ++49-0-1212-579320-483; e-mail: info@vmscope.de.

BioGenex iVISION and GenoMx VISION
http://www.biogenex.com/

In addition to scanning facilities, iVISION includes automated imaging analysis, enabling the user to capture images and quantify results in immunohistochemistry and in situ hybridization applications. The GenoM VISION System is designed for tissue microarray core image acquisition, management (archiving, retrieval, and cataloging), and analysis. Contact: BioGenex Headquarters. 4600 Norris Canyon Rd. San Ramon, CA 94583; phone: 1-925-275-0550, 1-800-421-4149 (in the US); fax: 1-925-275-0580; e-mail: info@biogenex.com.

CytoCore InPath Slide Based Test
http://www.molecular-dx.com/2_laboratorians/2_inpath/270_inCell_HPV.html

Formerly Molecular Diagnostics, this company has developed a screening for cervical dysplasia and

cervical cancer screening technology that includes an analysis of cytology slides through use of an automated instrument for detection of any material indicative of "not normal." Contact: CytoCore, Inc, 414 N Orleans St, Suite 800, Chicago, IL 60610; phone: 312-222-9550; fax: 312-222-9580; e-mail: info@molecular-dx.com.

Imstar Pathfinder Morphoscan and E-Mage
http://www.imstar.fr/products/pathology/emage/

Imstar Pathfinder provides automated assessment of molecular cell markers in cytology and histology, including tissue arrays. Two modules are available: E-Mage VS for creation of virtual slides, and E-Mage VM (virtual microscope) for interactive browsing of selected area of virtual slide images. Contact: IMSTAR SA, 60 rue Notre Dame-des-Champs 75006 Paris, France; phone: +33-0-1-42-34-93-70; fax: +33-0-1-46-34-51-57; e-mail: info@imstar.fr.

Leica AS TPS2
http://www.leica-microsystems.com/

Leica AS TPS2 is a telepathology system especially designed to obtain a second opinion and providing telepathology facilities for frozen section diagnosis. It is neither a virtual slide system nor an automatic image analysis solution, but we have included this system because of its multiple integrated tools (patient-related case data, telepathology case database, remote control, shared pointer, and video and audio conference, amongst others). Contact: Leica Mikrosysteme Vertrieb GmbH, Lilienthalstr 39-45, D-64625 Bensheim, Germany; phone: +49-6251-136 0; fax: +49-6251-136-155. Contact Web address: http://www.leica-microsystems.com/contact.

MetaSystems Metafer
http://www.metasystems.de/

This company has converted an automatic metaphase finder into a "multipurpose scanning platform" that can be of use also in pathology, for instance, in fluorescence in situ hybridization (FISH) imaging. These are two examples: the MetaCyte module analyzes cells in single cell preparations and in tissue sections, and the RCDetect module finds rare cells. Contact: Robert-Bosch-Str 6, 68804 Altlussheim, Germany; phone: +49-6205-39610; fax: +49-6205-32270; general e-mail: info@metasystems.de.

Applied Imaging Ariol
http://www.aicorp.com/products/02path.htm

Ariol is a system for automatic image analysis. It has been developed to quantify immunochemical and FISH techniques. Thus, it allows using conventional microscopy and fluorescence.[12] A complete TMA package is available. The Sanger Institute (http://www.sanger.ac.uk/) is the UK reference site.

In some countries, this system is distributed by Olympus resellers. Corporate offices (sales for Americas and Pacific Rim): Applied Imaging Corporation, 120 Baytech Dr, San Jose CA 95134-2302; phone:

+1-408-719-6400; fax: +1-408-719-6401; e-mail: info@aicorp.com. International operations (sales for Europe, Middle East and Africa): Applied Imaging International, Ltd, Bioscience Centre, Times Square, Scotswood Rd, Newcastle upon Tyne NE1 4EP, United Kingdom; phone: +44-191-202-3100; fax: +44 191 202 3101; e-mail: info@aii.co.uk.

Examples of bright field and fluorescent TMA analysis are available at http://www.sanger.ac.uk/Teams/Team86/icc_group_intro.shtml

Clarient ACIS (Chromavision)

http://www.chromavision.com/product/acis1.htm
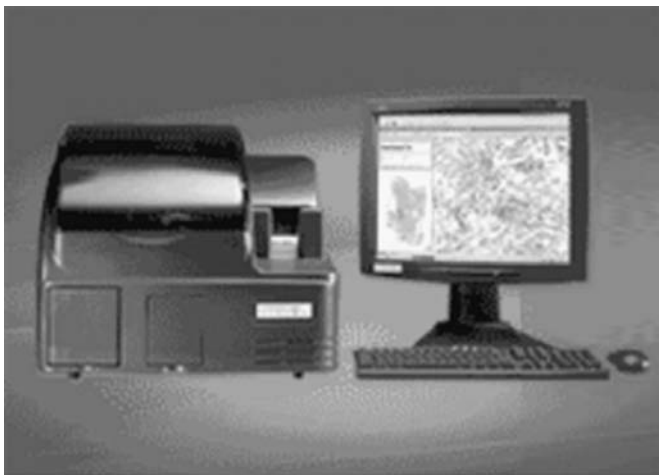
ACIS stands for Automated Cellular Imaging System, and it was developed by Chromavision. ACIS has been designed for immunohistochemistry image analysis.[13] In July 2005, Dako and Clarient signed an ACIS development and distribution agreement. Clarient Headquarters: Clarient, Inc. 31 Columbia, Aliso Viejo, CA 92656; phone: 949-443-3355, ext 295; fax: 888-443-3345; e-mail: info@clarientinc.com.

CyTyc ThinPrep Imaging System

http://www.cytyc.com/lab/lab_cervical_cancer_thinprepimaging.shtml

This solution is designed for gynecologic cytology and it allows processing of up to 300 slides per day. The system only stores the coordinates of the interesting or abnormal areas, together with the slide identification. Contact: Cytec Corporation. 85 Swanson Rd, Boxborough, MA 01719; phone: 1-888-ThinPrep. European headquarters' e-mail: uk@cytyc.com.

Compucyte iColor and Compucyte iCyte

http://www.compucyte.com/icolor.htm and http://www.compucyte.com/icyte.htm
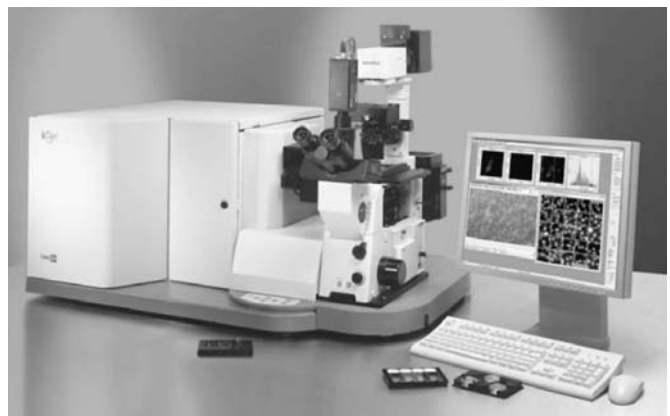
iColor allows simultaneous analysis of fluorescent and chromatically-stained specimens. iColor combines functions of flow cytometry, fluorescence image analysis, and immunohistochemistry.

The iCys Research Imaging Cytometer first performs scanning (with simultaneous acquisition of multiple-fluorescence and bright-field laser-scatter images) and analysis of the slides, and then the

microscope stage may be automatically moved to the location of any features of interest. Headquarters: CompuCyte Corporation, 12 Emily St, Cambridge, MA 02139; phone: +1-617-492-1300; fax: +1-617-577-4501; e-mail: salesinfo@compucyte.com.

Conclusions

After analyzing the main features of the anatomic pathology slide digitization systems available on the market, we conclude that these systems are able to scan a digital slide using the highest image quality available (objective ×40) in about 1 hour. These digital slides may be used for diagnosis, digital records, second opinion, medical education, professional training, quality assurance, image analysis, and research. Most of the reviewed systems can be provided with some software for TMA analysis.

Digital slides allow the retaining of a permanent file of the slide that avoids daily problems such as breakage, loss, or fading of stain and fluorescent signals.

Some devices include warnings about their use being "only for research and not for clinical diagnosis purposes," even when their commercial material includes descriptions about their use in clinical field. The US Food and Drug Administration may take action when this practice is detected.[14]

Future systems should improve some technical aspects, such as the scanning speed, the necessary bandwidth on communication networks, large requirements for storage, user interfaces (which are also different from the conventional microscope), improvement of focusing, and detection of tissue or cytology areas. Many of the systems are not suitable for use with polarization light (amyloid or crystals detection), but in the near future, most systems will incorporate the necessary filters.

Another drawback to current systems is their high cost, usually between 60 000 to 180 000 Euros, ($75 000 to $230 000), except Nikon Coolscope with a lower price of about 15 000 Euros ($20 000).

We believe that current technology is allowing a progressive shift towards a complete microscopic image digitization in pathology. Even if today's systems are suitable only for the digitization of a certain number of selected cases, in the near future, all the technical problems are likely to be solved, and all cases studied by the pathology department will be digitized. Keeping in mind all the presented difficulties, during the First Virtual Slide Congress on the Internet, our group confirmed that pathologists find themselves quite comfortable working with virtual slides.[15] Many other authors have confirmed the utility of virtual slides.[16]

It is already possible to integrate links to the virtual slide into the pathology final reports. The pathologist may sign the forms at the same time the corresponding images are visualized. This facilitates a double-checking and validation (text and images) before the final report is sent.

The intellectual process of analyzing and interpreting pathology images to provide a final diagnostic is one of the fundamental aspects of the pathologist's work; therefore, both image and report always must include the name of the pathologist and department where that intellectual work has been done. Only those images corresponding to validated and signed reports should be available in the patient's clinical record.

The enterprise-centralized and automated storage is the best option and should be based in what is called the Picture Archiving and Communication Systems, which will permit an efficient way of seeking pathology images. This will be possible, thanks to the Digital Imaging and Communications in Medicine (DICOM) image format, which is being adapted to be used also for pathology images.

Acknowledgments

References

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