Digital Pathology

Lumenera's Scientific-Grade Cameras Offer Imaging Solutions for Growing Digital Pathology Market

BACKGROUND

Intricately connected to all medical advancements has been the study and diagnosis of disease through examination of organs, tissues, and bodily fluids. Known as pathology, this field of study underwent a radical evolution in the mid-nineteenth century, as a result of new technology: the microscope. More readily available and with improved optics, microscopes quickly became a hallmark of the pathologist's work.

While microscopes still hold a central role in this science, another technological advancement stands as an equally critical evolution in this field: digital pathology. Digital pathology is the practice of digitizing glass slides and managing the resultant information for later educational, diagnostic, and analytic purposes. Telepathology is the act of performing pathology over a distance, and is predominantly performed using digital pathology representations. Consequently, both practices are closely related and enjoy considerable overlap.

CAMERA REQUIREMENTS

Central to any digital pathology application is imaging. The captured images are used for documentation, archiving, teaching, publication, and in the case of telepathology, to provide real-time consultation. To avoid dire consequences for patients, digital cameras used in pathology applications must be, above all else, highly reliable. Consumer-type cameras consistently fail to meet expectations in this regard.

The set of performance features that need to be taken into consideration when selecting a camera for a digital pathology application are outlined here:

High-Fidelity Color Reproduction and Consistency: Pathology is practiced by identifying and acting upon visual cues. In contrast to digital radiology, which is confined to grey-scale images, color plays a crucial perceptual role. For this reason, the colors captured by the camera should match human perception as much as possible. As well, color capture should be as consistent as possible from frame capture to frame capture and also from camera to camera.

Consequently, the fidelity and consistency of color capture is paramount in digital pathology applications. One key consideration is the means by which different color wavelengths are filtered prior to being captured by the image sensor. Crucial hardware design choices, such as whether to use mosaicing filters or three different pixel sensors for each RGB color, can affect color quality. As well, a great amount of care must be used to calibrate image sensors to human perception via the use of color charts and other tools. In terms of software, reproduction algorithms designed for specific types of pathology must also be carefully designed and tested. Finally, color quality and consistency are also affected by the monitor used to display the resulting image.

Low Noise: Every digital camera suffers from a degree of noise that degrades the image. Due to the stringent quality standards of digital pathology, cameras must exhibit a high signal-to-noise ratio in order to produce images acceptable for medical diagnosis and/or training.

Camera noise can be divided into fixed-pattern noise or temporal noise. Fixed-pattern noise is produced by variability between pixel to pixel. Using high-quality components and a careful production process can reduce this variability. Calibration can reduce or eliminate any inevitable variability that remains, meaning that the algorithms and testing methods used for this process play an acute role in limiting fixed-pattern noise.

Temporal noise is produced during the image capture process. One such source is optical, or shot noise, which is a fundamental and unavoidable property of photons. It is possible to mitigate shot noise through the use of software post-processing algorithms. Another key source is electronic noise, produced by the electronic circuitry and semi-conductors during the capture process. Aspects such as size

of the photodetector surface, integration time for linear sensors, and component quality all play a role. Another factor is nature and location of analog-to-digital conversion. The longer an analog signal has to travel before being converted to a digital value, the more opportunity is in place for noise to corrupt the signal.

Wide Dynamic Range / Large Bit Depth: The dynamic range of a camera refers to the range of light intensity that it can capture in one frame. Cameras still struggle to produce low noise images that can match the dynamic range of the human eye. In this specific application, especially when fluorescence specimens are used, it is crucial that both low- and high- intensity signals are captured and displayed to the medical professional.

The fundamental electronic circuitry of an image sensor is one key factor that can significantly impact dynamic range. For instance, linear response cameras typically do not enjoy the same wide dynamic range as logarithmic response cameras. However, linear response cameras typically have more favorable noise characteristics than logarithmic ones, reflecting a perennial trade-off faced by digital camera designers. Another key factor affecting dynamic range is the size of individual pixels. While smaller pixels do increase spatial resolution, they also reduce the number of photons hitting the image sensor, which limits the dynamic range of the resulting image.

Lumenera® corporation

7 CAPELLA COURT, OTTAWA, ON, CANADA K2E 8A7 | TEL (613) 736-4077 | FAX (613) 736-4071 | WWW.LUMENERA.COM | MARKETING@LUMENERA.COM

Excellent Sensivity: Related to dynamic range, the sensitivity is the lowest light intensity a camera can capture where the amount of noise is still less than the true light signals. Human eyes typically have lower sensitivity than cameras, explaining why a flash is needed for consumer photography in conditions that seem well-lit to the human eye. Like all imaging applications, high sensitivity is desirable in digital pathology. In particular, fluorescence imaging, with its frequent low-intensity signals, has demanding needs for high-quality images under challenging conditions.

Physical components, such as the size of the aperture, can affect the sensitivity of an imaging system. As well, the darkening effects of the magnifying optics also restrict the practical sensitivity of the imaging system. In terms of the camera itself, the most significant factor affecting sensivity is the size of pixels since larger pixels capture more photons. Since the dominating noise close to the sensitivity is electronic noise, electrical component quality, analog-to-digital conversion, and the design of the pixel itself are also important contributing components.

High Spatial Resolution: A high spatial resolution, meaning the smallest details the imaging system can capture, is a desirable feature of most imaging applications. However, many digital pathology applications, such as certain types of tissue processing, necessitate stringent resolution demands for visual cues and this can push against the theoretical optical resolution limit of visible light.

In terms of camera design, pixel pitch, or the size of individual pixel sensors, is perhaps the most critical element in spatial resolution. Nonetheless, as pixel decreases, the performance demands of the image sensors become more challenging to meet, placing practical limits on the size of individual pixels. As well, the spatial resolution of the imaging system is affected by components beyond than the camera since the quality of the magnifying optics play a crucial role.

Large Optical Sensor: The size of the camera sensor affects how much of the microscopy field of view that a pathologist or technician can capture at one time. In many types of digital pathology, it is important to capture as much as possible the same field of view. For static imaging, this allows the medical professional to view the same amount of specimen area he or she would view directly using the microscope. For whole-slide imaging, the larger the field of view, the quicker an entire slide can be imaged. To match the microscope's field of view, the optical sensor must typically be a medium- or large-format camera sensor.

Fast Frame Rates: Whole-slide imaging requires high frame rates (90 fps or higher) to keep the digital scanning process as fast as possible. In order to match these fast frame rates, the image sensor quality, including many of the factors explained above, must be high enough to perform effectively under these quick conditions. As well, memory storage capabilities and data transfer rates must also be able to handle the fast frame rates.

Standard and High-Speed Data Interface: In order to allow a fast transfer of the image data, the camera must be equipped with a high-speed data interface. High bit depth requirements reinforce this need for high-speed data transfer. An industry standard data interface can allow a lab to mix-and-match modules and more easily upgrade its system in future. USB 3.0 is ideal for pathology applications since it is readily available on virtually every desktop computer around the world and allows for applications of almost 4 Gbps.

SOFTWARE

As mentioned previously, the software used in a telepathology system must not only be capable of reliably importing, stitching, and compressing images, it must also be intuitive for its users. Further, it must offer the ability to annotate and measure images. Lumenera offers a general purpose software solution, which is included with most INFINITY microscopy cameras.

Lumenera's INFINITY microscopy cameras include INFINITY ANALYZE software, allowing complete camera control and advance image acquisition and analysis. Also included is INFINITY CAPTURE, an intuitive user interface that contains all of the basic features needed to control the camera and capture images.

INFINITY ANALYZE software allows customized image processing and archiving enabling users to:

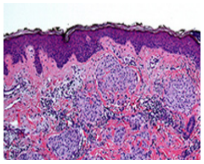
- Quickly process, archive and save images in a variety of formats
- Apply and reproduce customized measurements and annotations with ease
- Effortlessly manage and retrieve images within the built-in database

Additional software highlights include:

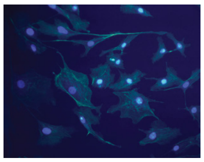
- Real time video preview
- Measurement and annotation
- RGB image composition including Look-Up Tables (LUT)
- Single capture and time lapse
- Image stitching
- Automatic/manual exposure and white balance
- Hue, saturation, gain, contrast, brightness and gamma controls
- Advanced image processing
- Customize interface for specific applications
- Thumbnail worksheet
- Drag and drop measurement data to
- Microsoft Excel for analysis
- Save and restore camera settings
- Context sensitive help for all functions
- Optional focus enhancement
- Interactive color composition
- Available in 9 languages

These applications are compatible with 32 and 64-bit operating systems running Windows 10, 8, 7, XP, and Vista as well as MAC OS X 10.7.

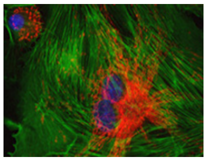
A selection of images taken with Lumenera's scientific megapixel cameras . With 5 families of cameras ranging from 1.3 through 32 megapixel, Lumenera cameras are well suited for digital pathology.



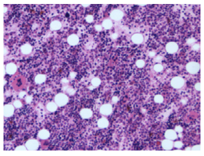
INFINITY*2-5*
Cellular Neurothekeoma



INFINITY*3-1*UR
Fluorescence



INFINITY*3-3*UR
BPAE Fixed Cell



INFINITY*3-6*UR
Mammal Bone Marrow

Third Party Software

Many image capture and report preparation software packages aimed at pathology will include the ability to capture from a camera through a TWAIN interface. Lumenera INFINITY cameras can be used in this manner, as the software installs a TWAIN plug-in that launches a custom version of the INFINITY CAPTURE application. Since the main software package typically requires several mouse clicks (or keystrokes) to invoke the image capture package, it is important to consider streamlining a sequence of instructions into hotkeys / macros.

Programming Keyboard Shortcut Keys for INFINITY Cameras

Keyboard shortcuts can greatly improve efficiency when performing repetitive sequences. When there's a requirement to perform image acquisition to add an image to a patient record or test report, consider recording the required menu operations into a single keyboard operation.

The INFINITY CAPTURE and INFINITY ANALYZE software packages each include menu shortcuts that can be invoked using the <Alt> key and a corresponding keyboard character. This also applies to the TWAIN interface version of INFINITY CAPTURE.

There are a number of options available to setup macro key sequences, but one easy technique can be found by using the free, 3rd-party tool, available from www.AutoHotKey.com *(*see additional references below)*

Hands-free operation with INFINITY Cameras

There are times when hands-free operation is critical, such as performing a sterile procedure, or working with a grossing station, while conducting certain types of lab research, or possibly while inspecting delicate electronic components when your hands are preoccupied and it is simply unsafe or inconvenient to reach your hand out to a keyboard or mouse to capture an image.

In cases like this, a hands-free solution would be to use INFINITY cameras with their application software, and add a footswitch to your PC. A footswitch allows for pedals to emulate a sequence of keyboard functions. It can be programmed to perform a single operation, or to send a string of key strokes to the application software for more complex operations. The best part about integrating such a device is that users don't need a large amount of experience with electronics or computer programming to set it up.

A programmable foot switch lets your foot activate any keyboard command. These devices are available with either a USB interface or a standard PS/2 connection and available from a number of third party sources.

* For additional information on programming macro hot-keys and a footswitch for use with INFINITY applications, please visit: http://www.lumenera.com/media/wysiwyg/support/pdf/FootswitchAccessory.pdf

LUMENERA'S EXTENSIVE PRODUCT LINE

Lumenera has been providing imaging solutions to pathologists for a number of years from our portfolio of scientific cameras. Our most popular models, as chosen by pathologists, include the 5 megapixel INFINITY2-5, the higher performance 3 megapixel INFINITY3-3UR, and 6 megapixel INFINITY3-6UR. All three models have a maximum bit depth of 14 bits and output color-accurate raw images. The quantum efficiency and dynamic range vary per camera model, with the INFINITY3-6UR coming out on top with a peak QE of 66% and dynamic range of 68.6dB. Similarly, the INFINITY3-3UR has a dynamic range of 68.8dB and a peak QE of 61% and the INFINITY2-5 has a peak QE of 42% and a dynamic range of 58dB. Clinical pathologists can address imaging and budgetary requirements with Lumenera's wide range of USB 2.0 and USB 3.0 INFINITY cameras.

FEATURED CAMERAS

INFINITY2-5 Highlights

- 5.0 MP Sony Super HAD CCD sensor
- 9 fps at full resolution
- Wide dynamic range, high sensitivity
- ROI support for even high frame rates
- Selectable 8 or 14-bit pixel data
- Full image analysis software included
- USB 2.0 interface

Lumenera's **INFINITY2-5** digital CCD USB 2.0 camera offers excellent sensitivity, high resolution and a global electronic shutter. With 2448 X 2048 resolution and onboard processing, the INFINITY2-5 delivers outstanding image quality and excellent color reproduction. Live video preview provides for real-time focus while auto exposure and auto white balance efficiently capture your optimal image.

ORDERING OPTIONS:
INFINITY2-5C 5.0 Megapixel CCD Color Camera
INFINITY2-5M 5.0 Megapixel CCD Mono Camera

INFINITY3-3UR Highlights

- 2.8 MP Sony EXview HAD II CCD sensor
- 53 fps at full resolution, 66 fps at full HD
- Low noise, high sensitivity
- Selectable 8 or 14-bit pixel data
- Full image analysis software included
- USB 3.0 interface

The **INFINITY3-3UR** is a high-speed, high sensitivity, research-grade camera with a resolution of 2.8 megapixel. Featuring Sony's EXview HAD II technology, this camera is well suited for applications requiring optimal color reproduction, extreme sensitivity, increased resolution and high speed, such as clinical pathology. The INFINITY3-3UR delivers outstanding image quality via a high-speed USB 3.0 interface.

ORDERING OPTIONS:
INFINITY3-3URC 2.8 Megapixel CCD Color Camera
INFINITY3-3URM 2.8 Megapixel CCD Mono Camera

INFINITY3-6UR Highlights

- 6.0 MP Sony EXview HAD II CCD sensor
- 27 fps at full resolution
- Large field of view
- High sensitivity, high speed
- Selectable 8 or 14-bit pixel data
- Full image analysis software included
- USB 3.0 interface

Lumenera's **INFINITY3-6UR** is a high-speed, high sensitivity research-grade camera with a 6 megapixel resolution. The INFINITY3-6UR incorporates Sony's remarkable ICX694 CCD sensor, that provides high dynamic range and speed. Full resolution 6.0 MP images are sent to a host computer at up to 27 frames per second (fps). The result is an industry-leading, high-performance, low noise digital camera, alone in its class.

ORDERING OPTIONS:
INFINITY3-6URC 6.0 Megapixel CCD Color Camera
INFINITY3-6URM 6.0 Megapixel CCD Mono Camera

LUMENERA MICROSCOPY CAMERAS:

To view Lumenera's full INFINITY product line, visit us online: www.lumenera.com/products/microscopy.html

Lumenera corporation

7 CAPELLA COURT, OTTAWA, ON, CANADA K2E 8A7 | TEL (613) 736-4077 | FAX (613) 736-4071 | WWW.LUMENERA.COM | MARKETING@LUMENERA.COM