Digital Pathology: The Time Is Now to Bridge the Gap between Medicine and Technological Singularity

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Abstract

Digitalization of the imaging in radiology is a reality in several healthcare institutions worldwide. The challenges of filing, confidentiality, and manipulation have been brilliantly solved in radiology. However, digitalization of hematoxylin- and eosin-stained routine histological slides has shown slow movement. Although the application for external quality assurance is a reality for a pathologist with most of the continuing medical education programs utilizing virtual microscopy, the abandonment of traditional glass slides for routine diagnostics is far from the perspectives of many departments of laboratory medicine and pathology. Digital pathology images are captured as images by scanning and whole slide imaging/virtual microscopy can be obtained by microscopy (robotic) on an entire histological (microscopic) glass slide. Since 1986, services using telepathology for the transfer of images of anatomic pathology between detached locations have benefited countless patients globally, including the University of Alberta. The purpose of specialist recertification or re-validation for the Royal College of Pathologists of Canada belonging to the Royal College of Physicians and Surgeons of Canada and College of American Pathologists is a milestone in virtual reality. Challenges, such as high bandwidth requirement, electronic platforms, the stability of the operating systems, have been targeted and are improving enormously. The encryption of digital images may be a requirement for the accreditation of laboratory services—quantum computing results in quantum-mechanical phenomena, such as superposition and entanglement. Different from binary digital electronic computers based on transistors where data are encoded into binary digits (bits) with two different states (0 and 1), quantum computing uses quantum bits (qubits), which can be in superpositions of states. The use of quantum computing protocols on encrypted data is crucial for the permanent implementation of virtual pathology in hospitals and universities. Quantum computing may well represent the technological singularity to create new classifications and taxonomic rules in medicine.

Keywords: Digital pathology, Medicine, Singularity, Quantum, Artificial Intelligence, Bioinformatics

1. Introduction

In the past two decades, we experienced some new inventions in technology with the development of quad-core processors (four independent units called cores able

to read and execute central processing unit instructions) and 5G networks. This environment in information technology (IT) allows us a more efficient, stable, and faster communication than ever. Currently, the 5G network is considered the milestone that will open the conversation to the next level. There is crescent popularity, widespread use and increasing dependency on wireless technologies in our societies, both Western and Eastern civilizations. This demand has produced an unimaginable industrial revolution that may show some spectra of Orwellian nature [1]. There is increasing public exposure to broader and higher frequencies of the electromagnetic spectrum and data are transmitted as fast as never before [2]. The evolution from current 2G, 3G, and 4G to 5G wireless technologies is increasing worldwide. However, the promise of a convenient and comfortable lifestyle with a massive 5G interconnected telecommunications network has raised not only the expansion of broadband with shorter wavelength radiofrequency radiation but also highlighted the concern that health and safety issues may remain unknown [2]. Currently and in the future, the effects of radiofrequency electromagnetic radiation are and will be challenging if not impossible to identify epidemiologically. This challenge relies on the lack of an unexposed control group. Nevertheless, it is inconceivable to carry out some steps in our daily life without using the telecommunication network. In this chapter, some of the new exciting aspects of the evolution of digital pathology in diagnostics and teaching are discussed.

2. Digital pathology

Digital pathology (DP) can be shortly demarcated and, probably, clearly defined as the digitalization of gross and microscopic tissue specimens subject to electronic capture of the photons as well as the management, analysis, and distribution of images. DP has been considered a terrific technology that is transforming the benchmark and protocols of work of pathologists after the impressive revolution operated in imaging radiology a decade earlier. Telemetric measurement of body temperatures in experimental animals implanted with commercially available transmitters has been automated using the Commodore C-64 microcomputer since the 1980s [3]. Also, in the 1980s, digitalization of 2D gels started, and high-performance liquid chromatographic system based on the Commodore 64 personal computer were common [4, 5]. The routine work of pathologists involves the identification of data and patterns in gross and microscopic tissue sections to deliver a diagnosis that can be rendered to the clinician and to the patient for further investigation or for starting therapy. The work of the pathologist is not quite different from the radiologist's job focusing on images, although most of the radiologic images are on black and white, while the pathologists use some dyes to facilitate the discrimination of morphologic structures on the tissue. The work of the pathologist is crucial in closing the loop, and reaching the diagnosis. The pathologist is also focusing on teaching. In the past, cases valuable for teaching were cut and mounted on glass slides that have been used to be projected using a film-based camera mounted on light microscopes and archival slides used for clinical rounds or multidisciplinary clinical team meetings as well as educational seminar presentations. This analog presentation was also used for forensic (medico-legal) purposes being broadly accepted in court proceedings for both civil and criminal law systems. Currently, archival tissue collections and new teaching cases are scanned and converted to static digital images. The images of gross and microscopic pathology specimens are continuously captured by digital cameras, tablets, iPads, phablets, and smartphones and the images downloaded via media card, universal serial bus (USB) interphase or wireless connections into personal computers or

university servers for storage ready for teaching or discussion in the setting of multidisciplinary team clinical meetings. The digitized images may have different extensions such as tiff, jpg, and gif and the quality of the image increases proportionally with the number of pixels of the image or a digitized static image. The term "virtual microscopy" has been used to describe the acquisition, management, and storage of digitalized microscopic images [6]. Virtual microscopy systems are capable of complete digitization of the histology and cytology slides. This process is also known as whole-slide digitation or whole-slide imaging (WSI). In 1997, the first virtual microscopy system was described by the Computer Science Department at the University of Maryland and the Pathology Department at Johns Hopkins Hospital, Baltimore, Maryland [7, 8]. Fifteen years ago, in 2003, the European Organization for Research and Treatment of Cancer (EORTC) printed the results of a poll on virtual microscopy systems to that date [9]. Rojo et al. [10] provided a comparative description of 31 potential solutions available on the market as early as 2006 that can perform a whole slide imaging (WSI) or assistance in complete slide review for anatomic pathology applications. Digital imaging can be subdivided into two classes according to the aim, including the digital microscope and virtual microscopy-aided systems. The digital microscopes aim to create a digital image from an analogic image detected with a light microscope. Conversely, diagnosis-aided systems can detect the region of interest (ROI) and give data arising from the analysis of biomedical signals. There are two different devices including the motorized microscopes and scanners. In the motorized microscopes, there are two classes of components. The first class includes pieces of proper light microscopy (e.g., eyepieces, multiple lenses, motorized revolver, position control, and spotlight control), while the second component deals with the capture of the images using a camera joined up to the microscope. The virtual microscopy devices include an optical microscope system, an acquisition system (photography/camera), a software program that controls the scan process, and a digital slide viewer. Optional components of the virtual microscopy include the slide feeder or image-processing programs. The most critical components are the light microscope and the acquisition camera. Good microscopy needs to have an optical quality of high level. The optical quality is largely determined by the quality of the lenses (objective) and by the class of the eyepieces. Good, quality objective lenses have a standard, which are achromatic lenses. Since diverse colors refract through a curved lens at different angles, an achromatic lens produces an enhanced, "flatter" specimen image of the specimen than it would otherwise be obtained. However, achromatic lenses are of less quality than semi-plan or plan objectives, which are "perfect lenses" and are typically required for sophisticated biological research with double the price of achromatic objectives. Also, it is useful to confirm that the objectives are DIN (Deutsch Industry Norm) compatible. DIN objectives are convenient since they are interchangeable. They are transposable from one DIN compatible microscope to another. The wider the eyepieces are, the easier the viewing. Thus, "widefield" (WF) or "super wide field" (SWF) eyepieces are crucial, although the wider the lens, the smaller eye ports, which means there is a decrease of the size of the magnification power. There are four primary categories of illumination: tungsten, fluorescent, halogen, and light-emitting diode (LED). Tungsten is the basic illumination for entry-level microscopes, but halogen and LED microscopes are of higher quality. Halogen produces strong, white light and usually, includes a variable rheostat with adjustable light intensity, while LED, especially if used with rechargeable batteries, makes the microscope fully portable with the opportunity to use it in environments with limited electrical outlets. Fluorescent lighting or epi-fluorescent microscopes are for biological research and similar applications. Moreover, the microscope should have an iris diaphragm and good quality condenser—preferably,

an Abbe condenser which allows for greater adjustments and most good quality microscopes include iris diaphragms and Abbe condensers as standard. Finally, a mechanical stage is also valuable for compound microscopes. This situation is critical particularly when viewing specimens at high magnifications. A good camera is also a crucial component and a charged coupled device (CCD) sensor in the camera provides an analog signal. Digital cameras convert the analog signal into digital. It is important to choose the right image resolution or CCD size, i.e., the number of pixels the sensor can detect. The connection of the camera with the personal computer is through a FireWire port, and card adapters may be needed. In virtual microscopy, the high resolution can move at different speeds. There is about 32 mm/s (Zeiss Mirax Scan), or more at 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 1–3 µm, although some types can get accuracy or minimum distance of 2 nm (0.002 µm) to 15 nm (0.015 µm) for the z-axis and 250 nm (0.25 µm) for the x-axis and y-axis. About the computer hardware, most DP solutions should be based on workstations with at least two microprocessors, 2.8–3.6 GHz or higher, and at least 4 GB of random-access memory (RAM). The operating system used by the control devices and the workstations is usually Windows XP Professional, Vista, 7, 8 or 10 (Microsoft Redmond, Wash.). The endorsed way for handling the storage is using centralized (enterprise) storage servers of the hospital or healthcare institution. This solution may not be an option if IT personnel or healthcare administrators raise security issues. Thus, alternatives would use intranet servers or with storage up to 100 terabytes (TB). Recently, the Nimbus Data company unveiled a new 100 TB solid-state drive (SSD) making it the world's largest SSD currently available. Different from the hard-disk drive (HDD), an SSD is like a memory stick. There are no moving parts and information is stored in microchips. Nimbus Data developed advanced flash memory solutions that power data-driven innovation and one of these solutions include ExaFlash® All-Flash Arrays and ExaDrive® Solid State Drives. This solution is accelerating data storage, simplifying data management, and improving data protection for cloud infrastructure, data analytics, AI-rich content, high scientific computing, and numerous other applications that may be considered unconceivable currently. However, the minimum recommended configuration should include six disks, each of 300 GB (0.3 TB); 10 k rpm hot swap for a total of 3.8 TB. All virtual microscopy solutions comprise a flat thin film transistor (TFT) monitor (20–23 inches). These screens must be high resolution with a TFT screen of 2560 × 1600 pixels, with 200-ppm resolution. This screen size allows a visual field four times larger than the standard microscope field of view. Different aspects should be considered during the digitalization process, such as the digitization speed, the maximum size of the sample, the focus quality, the digitization at diverse planes, the procedures for slide scanning and image assembling (with or without correction), and the formats used to store the scanned samples. The digitization speed, also known as total scanning time, is probably one of the most important aspects to consider before choosing among these systems. The evaluation should be based on specific factors. It is wise to list the area size to be scanned and the objective lens used (e.g., ×20 or ×40 as objective). Further, we list the charge-coupled device (CCD) camera size, the model of motorized stage, the required time on the previsualization stage, the time for a panoramic view, the selection of the area of interest, the choice of focusing method, as well as the number of points (focusing) needed. It is crucial to remember that slides with irregular surface require a higher number of points, which reduces the scanning speed. Moreover, it is important to consider the number of planes at the z-axis to be digitized, the speediness to obtain data from the CCD camera to the personal computer (PC), and the transfer from the PC to the storage device.

Devices with a slide feeder have time to upload and download a slide in about 6–8 seconds, which is a good time for many laboratories. The total time, including the code bar reading, maybe around 15 seconds. The total scanning surface is forced to the motorized stage used and to the histologic slide type. The number of focusing points, also known as "focusing map" may be manual or automatically set. Multiple planes digitization through the z-axis may be a requirement for visualizing thick tissue slides or cytology slides with 3D clusters. Thus, the scanning system should work similar to the microscope fine focus control of the light microscopy on conventional histologic slides. Different systems can provide the digitization through the z-axis, at least in one area of the slide. For diagnostic purposes, scanning only a region of interest is not an option, because the pathologist may need to scan on the whole slide. Thus, WS Scanning method and stitching may be an option in some cases. Typically, the acquisition of microscopic fields is square-by-square, from the slide's upper left corner to the lower right one and the final image is a mosaic composed of multiple files. The assembling procedure of the slide squares may be performed in two different ways. We can use a mechanical adjustment tiling the borders of each fragment. Alternatively, we can use some software adjustment, which stitches the images. The final result may be considered as multiple files (typically thousands of Joint Photographic Experts Group or JPEG files)—in one or several folders, several files with one or multiple resolutions with the method used by Zeiss Mirax Scan and Zoomify viewer, and/or a single compressed file (JPEG2000, JPEG, TIFF). Flashpix (MicroBrightField Virtual Slide), or other formats (VSI extension in Olympus SIS.slide, .svs) may be encountered. SVS files are used by some medical/microscope scanners such as Aperio, scan scope (AxioVision), and others. They are essentially based upon the TIFF format and utilize the tiled image capabilities. Digital Slide Visualization and processing include x-axis and y-axis movements (lateral and vertical) displacement through the screen, objective shifting or zooming, displacement of the z-axis, and the x-axis and y-axis movements. One of the original problems was the low screen refreshment during the horizontal and vertical displacements. This disadvantage was due to the large amount of data that needed to be transferred between the different parts of the computer (central processing unit, hard disk, graphic card, and memory) or through the communication network. The fragmentation of the images may be quite disturbing for the pathologist who needs to review several files for diagnostic purposes. A solution is partitioning large images into small pieces according to the required magnification and buffering adjacent pieces (prefetching) in the viewer. However, quad-core processor based computer and 5G networks may be part of the solution as well. Histological slides, and especially cytopathology slides, may require the capture of multiple z-planes to get a perfectly focused image. Simultaneous and synchronized displacement on multiple windows is also useful options. Moreover, it is possible to include bookmarks on digital slides, facilitating the retrieval of interesting positions in subsequent case reviews. Virtual slides can be visualized and interpreted simultaneously by several consultants in pathology creating the virtual "multi-headed microscope" allowing innumerable users to review the same areas considering that not only one takes control of the session. Thus, different pathologists can review different parts of the same slide at the same time. Most of the systems can scan a digital slide using the highest image quality available (objective ×40) in about 1 hour. This time may be a limiting factor and shortening to 10–15 minutes should be a choice in the future. Future systems should improve the technical aspects, such as the scanning speed, the necessary bandwidth on networks, requirements for storage, user interfaces, improvement of focusing, and detection of tissue or cytology areas. The intellectual process of analyzing and interpreting pathology images to provide a final diagnostic is one of the central

aspects of the pathologist's work. Therefore, both image and report must always include the name of the consultant pathologist and department where that intellectual work has been performed. The enterprise-centralized and electronic storage is the best option and should be based on what is labeled the Picture Archiving and Communication System (PACS), which will permit an efficient way of seeking pathology images. This aspect will be possible, thanks to the Digital Imaging and Communications in Medicine (DICOM) image format, which is being used for radiology images and adapted to be also used for pathology images.

3. Whole slide imaging/virtual microscopy

The introduction of whole slide imaging (WSI) has created some wonderful opportunities for the pathologist or generally speaking for the morphologist or biologist. It allowed capturing images of the entire pathology slide without the need to select only a few regions of interest. The new platforms with 64 bit and quad-core processors and the development of high-resolution cameras allowed the manufacturing of digital slides at high resolution harboring uniquely multiple magnifications and focal planes. This set of data processed in a computer allows a full simulation of light microscopy. The operator (e.g., pathologist or technologist) can scan the slides rapidly and focus zooming in and out in the monitor using the keyboard, mouse, or his/her finger determining the quality of the image and gathering information to make the diagnosis. The robotic microscopic scanner mechanically scans histologic glass slides containing the tissue already processed and stained. A software combines individual scanned fields into a composite digital image [11–14]. The acquisition time has been reduced since a scanner was commercialized and time, which has been a limiting factor, will shorten even further in the future. The operator may be able to open the final file using several viewing software with optional user-friendly interfaces. This procedure makes it possible for the operator to navigate to various areas of the virtual slide or zoom in/out changing the magnifications without operating a revolver. The new technology applied with the WSI can be used for primary diagnosis by the pathologist, for publication of scientific data in peer-reviewed biomedical journals, to capture static images for reporting, archiving or computer-aided analysis, and educational activities in the setting of new concepts for universities and hospitals. A few decades ago the introduction of multi-headed microscopy allowed multiple viewers to follow the operator navigating a light microscope connected with few guest binoculars. This simple step was multiplied using a camera connecting the microscope with a big screen able to open the participation of guests from dozens to hundreds. However, the virtual microscopy has opened the scenario to unrestricted access to viewing, no need to recut slides for teaching and overcome the quality deterioration of staining. The WSI slides are obviously more interactive than static images. They are easier to share with multiple users on several platforms, they can work on diverse operating systems, anywhere and at any time. Training materials can be standardized. Moreover, files can be made available by hyperlinks using restricted codes to access specific file servers [11–14]. Since the introduction of virtual microscopy, we have faced numerous and virtually unlimited educational activities, including graduate schools, training in different medical specialties, E-learning, and tele-education for remote communities that are not easily accessible. Education has not been limited to medical only but involved dental, biological, and veterinary schools worldwide [15]. There are e-learning and virtual workshops with virtual atlases on the web that have been able to be a primary source for hundreds or thousands of new doctors. The virtual microscopy has started a revolution promoting knowledge, which is web-based learning and made available by several societies

including the United States and Canadian Academy of Pathology (USCAP), the International Academy of Pathology, and the International Academy of Cytopathology (IAC) [16]. In the United Kingdom (UK), the National Health Service (NHS) promotes Clinical Governance and clinical excellence with a specific institute nationwide labeled National Institute for Health and Care Excellence (NICE) [17]. Clinical governance describes a systematic approach to maintain and improve the quality of patient care. In similarity to the plan-do-check-act cycle, which is also known as Deming or Shewhart cycle, the clinical governance constitutes an official and unique framework through which the NHS is accountable for the ongoing improvement of quality of the clinical service with the aim safeguarding high standards of clinical care and creating a crucial environment focused on clinical excellence. Although communication failure is the most likely cause for medical errors, a substantial number of errors may be linked to a decrease of professional skills contributing to fatalities in healthcare. In 1999, Quality System Essentials were promoted to laboratory practices by the National Committee specifically for Clinical Laboratory Standards (now Clinical Laboratory Standards Institute [CLSI]). The essentials identify 10 or more major laboratory activities that are important components of a laboratory quality program [2, 3]. The updated and modernized quality system essentials that should be provided to each operator (e.g., pathologist) include updated equipment, smooth improvement of the diagnostic process, regular assessment and measurement of safety, and professional and personal development among others. All of these essentials were established to guarantee that data reported from the diagnostic laboratory unit are as accurate as possible. They should serve the requirements of both patients and clinicians. An imperative component in the control of any laboratory procedure is the constant and diligent participation of the operator in an external quality assurance (EQA) or proficiency testing program to validate that the operator is updated with the diagnostic criteria and skills are maintained. An EQA plan in place allows the healthcare to provide (University or hospital) to be certain that quality indicators are in place. There are numerous EQA programs worldwide, and they constitute a fundamental part of continuing professional development (CPD) of health care professionals [4]. The purpose of EQA in pathology is both to maintain good running standard operating procedures and to improve the performance of all sub-specialties. It will ensure that patients have access to a high-quality service wherever they live without constraints of physical barriers. Previously, we compared four slide survey programs from four geographical regions (United Kingdom, Germany, USA-Canada, and Australasia) concerning the EQA in pathology for pediatric pathologists in the setting of continuing professional development [17]. We found that the United Kingdom scheme, which has specific time frames (2 circulations/year, 30 slides), partial confidentiality, and numerous sources of data and assessors, can be used as an archetypal for revalidation. The US-Canadian and Australasian schemes only partially seem to fulfill the revalidation requirements. The German IAP scheme appears to be essentially an educational program and may be unsuitable for revalidation. WSI is widely implemented in the Australasian QA programs of the Royal College of Australia. The diagnostic scores of the pathologists undergoing the College promoted Performance Improvement Program (PIP) in Surgical Pathology online only without using histological glass slides do not appear compromised by the converting to WSI [18]. Pathology is in the center of a radical transformation in medicine, which is driven by many factors. Foremost, there is the advancement of precision medicine, an imbalance of pathology jobs across regions, and a need for more efficiency and effectiveness in the diagnostic workflow. In healthcare, technological innovation and its implementation at several sites are growing at an increasingly fast pace across specialties. Pathologists spend 30–40% of their work with administrative duties, and the frustration may exasperate with an

increasing rate of burnout colleagues in several countries. The number of duties may be simplified, and technological innovation may help the pathologist to decrease the burden of the diagnostic procedures, but also install a system to red flags situations that may be borderlines. The introduction of AI in WSI will be the next step and will help to increase the accuracy of pathology diagnosis and reporting. The introduction of algorithms that allow the machine to follow the diagnostic procedure operated by the pathologist using an eye tracking system and algorithms able to identify the discrepancies of pathology reports before signing out will help in the aim to reach extreme accuracy in medicine. The breakdown of geographical barriers operated by WSI will be implemented by the next step of a new healthcare system where AI will support the diagnostic procedure. There will be an enhanced collaboration allowing pathologists to seek second opinions more quickly, collaborating with multidisciplinary care teams more effectively, and distribute workloads across sites more evenly. Data from patient's history and unique risk factors will be studied by a background algorithm allowing the pathologist to have a companion for suggested differential diagnoses. The integration of data across clinical systems, lab examinations, and radiology with pathology images applying artificial intelligence to derive understandings is called computational pathology, which is far more convoluted than a file with stacked images of a glass slide. This revolution will implement the highest levels of accuracy and can be implemented to any specialty. This scenario is happening now as evidenced by the most recent congress of European urologists. Prof. Guo from Nanjing, China, claimed that smart software could diagnose prostate cancer as well as a pathologist (https://eau18.uroweb.org/smart-software-can-diagnose-prostate-cancer-as-well-as-a-pathologist/). All these algorithms seem to reconnect to the Bayes' theorem, which benefits us finding the probability of an event A given event B, written P(A|B), in terms of the probability of B given A, written P(B|A), and the single probabilities of A and B. Consequently, P(A|B) = P(A) * P(B|A)/P(B). Thus, in this scenario, event A is the event the patient has a specific disease, and event B is the event that the patient's test is positive. Thus, P(B|notA) represents the probability of a "false positive" rate, i.e., the patient's test is positive even though the patient does not have the disease. If the specific disease has an incidence of one in 10,000 people and a specific test has an accuracy of 99%, P(B|A) = 0.99, P(A) = 0.0001, and P(B) may be consequent by conditioning on whether event A does or does not occur, i.e., P(B) = P(B|A) * P(A) + P(B|notA) * P(notA) or 0.99 * 0.0001 + 0.01 * 0.9999. Thus, the ratio the pathologist gets from Bayes' theorem is less than 1%. This result relies on the disease, which is very rare. The number of false positives significantly surpasses the people who truly have the disease.

4. Gross pathology imaging and 3D printing

Three-dimensional (3D) printing uses 3D data to produce 3D physical models has been a powerful discovery and engine in science and medicine. Starting with computer-aided design (CAD) models for industry, 3D manufacturing is entering at the full title in medicine for undergraduate and postgraduate education [19]. Computer software can build up the model from a series of photographs on cross-sections that resemble to realistic sections from the original model. 3D printing is attained by placing down consecutive layers of powdered material or liquid plastic resins which are used to build 3D models at high temperature and sliced with laser technology. In the setting of 3D printing, the most critical techniques include ink-jetting, deposition modeling, laminated object manufacturing (LOM), and laser sintering. The ink-jet technique uses a method similar to two-dimensional (2D) inkjet printers whereby it deposits liquid plastic resins in striated lines. Infused deposition modeling a technique

is applied to extruding and layering filaments of thermoplastic materials, which are melted. LOM uses a laser cutter technique of shaping and sticking (gluing) layers of plastic films or paper. Finally, laser sintering includes stereolithography and selective laser sintering with curing photopolymers by a UV laser (stereolithography) and fusing small particles such as thermoplastic metal, ceramic, or glass by high-power laser (selective laser sintering) [20]. 2D digital photographs, sequential X-rays, and images of computed tomography (CT)/magnetic resonance imaging (MRI) are useful to create 3D CAD models by software reconstruction and laser scanning of objects. MRI was used in the past in guiding dissection of specimens for teaching purposes [21]. 3D printing has been used in orthopedic surgery and vascular surgery to guide surgeons during procedures [22–24]. The 3D reconstruction may revive anatomic pathology museums with the possibility to create several 3D models for undergraduate and postgraduate teaching. These specimens can be scanned by CT or MRI and the information provided be used to develop singular 3D models that may be produced for hundreds of learners. The advantages are that the learners do not need to be exposed to toxic solutions, such as formaldehyde, that students do not need to overcrowd a classroom or a museum hall, but they have no hassle in examining each specimen with time and investigate details. It may be very encouraging and reassuring when learners discover and participate in the inspection of the sample at the same time. There is the advantage to go back to the sample at any time. These specimens are durable, not infectious, and not fragile like the original ones. The robustness of these specimens will also allow the reproducibility of teaching in classes of the future. There is also the opportunity to utilize precious digital photographic collections in building 3D models of specimens that are not available anymore. 3D printing can create realistic models of almost any complex profile or geometric feature with extreme accuracy and opportunities are invaluable at this time. Some 3D printers with price ranging from hundreds of dollars to several thousands of dollars are commercially available. 3D printed models can then be used to demonstrate very complex lesions such as congenital heart defects of different age, including the transposition of the great arteries and hypoplastic ventricles. There will be enormous resources for learning using 3D printed models for undergraduate and postgraduate students, anatomic pathology residents, radiology residents, and other medical practitioners such as surgeons for educational and training purposes. Teaching curricula can be implemented with 3D models. While we expect the cost of living increases over time, in the next couple of decades the rate at which the price of a college education has gone up is utterly alarming. A 3D model may cost approximately $ 500, but the price may increase to several thousand in case of extreme accuracy. Production costs of 3D models do not need to spike up the admission fees to college and universities enormously. With increased demand, 3D computing and modeling will potentially become more affordable on mass production. At rounds or multidisciplinary clinical team meetings, 3D models can be used to teach topography of pathological lesions and adopt the best therapy possible. Current 3D printing of human anatomic pathology specimens is a reality but merits further investigations for application in teaching college and university students. The increase in complexity of CAD software will allow reaching that level of accuracy for the complete satisfaction of the learning process.

5. Telepathology

The introduction of microscope-integrated telepathology systems enables geographically remote stakeholders to view the live tissue histology slide as seen by the study pathologist within the local microscope. Telepathology is the practice of pathology at a distance using technologies. Although the concept and first

telepathology devices are now more than 20 years old [25–27], the introduction of quad-core processors and 5G technologies is renovating this nearby field of virtual microscopy. Simultaneous online viewing and dialog between study pathologist and remote operators in high-speed intranet or internet platform is becoming a reality in many countries. Telepathology is an efficient and cost-effective means for inter-professional histopathology consultation, pathology working groups, and peer review, facilitating collaboration and sound science and economic benefits by enabling more timely and informed clinical decisions. In 1986, the mane of telepathology was coined by Dr. Ron Weinstein. Differently, from the meta- or diachronous virtual microscopy, telepathology is a singular specifically synchronous two-way communication between the host and recipient. Telepathology has also been variously named: teleconsultation, telemicroscopy, teleconferencing, remote robotic microscopy, and web conferencing. In 1987, Weinstein first reported telepathology and the network of pathology diagnostic services on breast tissues by remote workstation-controlled light microscope attached to a high-resolution video camera and a telecommunication linkage [28]. Since the 1990s, similar analog technologies have been used for remote intraoperative frozen section services in northern Norway of Scandinavia [29, 30]. Telepathology is currently used for several fields of pathology, including cytopathology and ultrastructural pathology [31–36]. The approval of the Food and Drug Administration of the United States (US FDA) of these different methodologies has broadened a field in laboratory services, which was not known before [37, 38]. The three major telepathology supported systems currently used are static, real-time, and, of course, virtual microscopy. In the static system, pre-captured still digital images are deposited on a secure server with encryption. The disadvantages of static telepathology are that the operator controls everything including acquiring the images, while the audience is passive participants. In teleconsultation, the consultant histopathologist has no remote control of the physical microscopic glass slide and has limited fields of view to examine. Static TP systems are, nevertheless, welcome in some parts of the world with limited resources, shortages of particularly trained personnel, and lack of continuing professional education programs [39]. Tele-oncology has been proved to facilitate access to care and decrease health care costs with teleconsultations may take place in a syn-, asynchronous, or blended format. There are a few examples of successful applications that include cancer telegenetics, bundling of cancer-related telepathology-supported applications, remote chemotherapy supervision, symptom management, survivorship care, palliative care, and multidisciplinary approaches to increase access to cancer clinical trials [40]. It is careful to be a simple, cost-effective, reliable and efficient means to provide diagnostic and educational support to pathologists in the developing world improving pathology and laboratory medicine in low-income and middle-income countries. New technologies, including point-of-care testing and telepathology, can partake a substantial role in service delivery of laboratory medicine and pathology if used appropriately [41]. The physical geography of Canada is extensively varied with boreal forests prevailing throughout the country and ice areas prominently in northern Arctic regions and through the Rocky Mountains, and the flat Canadian Prairies in the southwest of the country. There is the vast distance between some parts of the country and telepathology is playing a significant role in some areas [42–44]. In the University Health Network (UHN), is a multi-site academic institution in Toronto. The UHN comprises several downtown hospitals and remote hospitals in Northern Ontario, WSI has been effectively utilized for telepathology in primary intraoperative frozen section diagnosis and secondary/tertiary teleconsultation [43, 45]. Likewise, in the Province of Quebec, the implementation of the telepathology project (Eastern Quebec) provides uniform frozen section diagnosis and teleconsultation services

across a vast geographic region comprising up to 21 sites [44]. Real-time and WSI/ virtual microscopy in telepathology systems may be implemented in the Prairies as well as in Northern Western territories. The future may be brighter because of faster networks and fast digitalization.

6. Social media and mobile device use

There is a terrific increase of time pathologists spend on the internet to search for pathologies, criteria or images that may help them in narrowing the differential diagnosis of challenging cases. The advances in computing power, cheaper prices for single device, and the exponential growth of web search for online learning resources have permitted the launch of platforms that are internet-based that are helping for publication and digital education. There are numerous digital atlases online, and there is a proliferation of multiple web-based technologies for continuing professional development of human and veterinary pathologist at a pace that we were not thinking before [46–57]. Telepathology using smartphones and tablets with Skype and its alternatives, including FaceTime, Viber, Talky, WeChat, and WhatsApp, among others, for live, synchronous online communication are feasible for clinical and educational uses [58]. The purpose of an iPad tablet or similar android device to download digitalized images of gross and microscopic pathology from a Web server for E-learning has been found to provide a satisfactory solution in low-resource countries as well as in the middle- and high-resource countries, because the pathologist can directly access the information at fingertip [59]. In a review of social media use in medical education, the incorporation of social media tools boosted the engagement of the learners, feedback from the audience and tighter collaboration and professional development [60–64]. Although probably up to a few years ago, the most commonly cited challenges were technical issues, variable learner motivation, and privacy/security concerns, currently, the high-speed internet, the increased competition among learners in a highly competitive world, and the use of https protocols with 2-key authentication seem to have demolished the above-raised challenges.

7. Artificial intelligence as the "third revolution in pathology"

In the 1980s the introduction of immunohistochemistry or the application of immunologic methods using antibodies against specific epitopes in situ directly on the tissue allowed a complete change of various diagnoses based exclusively on morphologic criteria. The identification of cell of origin and differentiation pathways allowed the re-classification of numerous pathologies, e.g., malignant Non-Hodgkin's lymphomas with the acquisition of knowledge that will shape the advancements in hematology and hematopathology for decades [65, 66]. The introduction of genomic and proteomic platforms may also represent an important revolution, probably, the second one after the immunohistochemistry. The genomic and proteomic medicine identified a new niche in medicine that has been focused for years from investigators of public health issues, i.e., precision medicine [67–71]. The "Third Revolution" in pathology is probably represented by the artificial intelligence (AI) [72]. AI is defined as intelligence demonstrated by machines, differently from the natural intelligence displayed by humans and specific animals. Thus, any device that perceives its surroundings and takes actions that maximize its chance of successfully achieving its goals may be considered showing an AI behavior. The correct acquisition and interpretation of external data and the integration of such data and results with the surrounding is the principle of the adoption by the machine of flexible adaptation.

8. Artificial intelligence and classroom

AI may be able teachers to identify students that may need some additional help or individuals with special needs that may struggle in a typical classroom. AI algorithms have been designated to increase the production of learning and the efficiency and effectiveness in learning. There are some paramount roles of AI in education. They include automation of grading with an approach tailored explicitly to short answered question other than multiple choice questions, teacher's support using chatbot able to communicate directly with students, student's aid with future students having an AI lifelong learning companion starting from high-school to university and postgraduate education adopting a new model of AI-controlled continuing professional development. Moreover, AI may be able to identify each student's strengths and weaknesses in a way that may be more standard than conventional teaching, which may be linked to the current motivation of the teacher. There is a personalized learning curriculum with an AI machine able to help students with special needs by adapting teaching material to lead them to success without being downscaled for mental r physical barriers. AI will allow teachers to Act as learning motivators and help to mentor undergraduate and postgraduate students to the best suitable path for them. As AI takes on more of an education role by providing students with the necessary information, this procedure will change the position of teachers in the classroom. Educators will move into the role of classroom supervisor, facilitator or learning motivator and adopt a previously unimaginable relationship with the students. Some examples of classroom-based AI include Thinkster Math, brain, and Content Technologies Inc. Thinkster Math (http://get.hellothinkster.com/why-tabtor-is-now-thinkster/), which is a math tutor able to identify the level of each student allowing each student to improve the logic process by providing video assistance for stuck students and immediate, personalized feedback. Brainly (https://brainly.com/) is the social media site for classroom questions allowing users to ask questions and receive verified answers from fellow students. Content Technologies, Inc. (http://contenttechnologiesinc.com/) is an AI company using Deep Learning to create customized textbooks. Teachers carefully import curricula (syllabi) into a CTI engine. The CTI equipment then masters the content and uses specific algorithms to create tailored books and coursework based on core concepts. Mika (https://www.carnegielearning.com/products/software-platform/mika-learning-software/) is another AI based on math, and like Thinkster Math, Carnegie Learning's Mika harbors AI-based tutoring tools for learners, who may be too busy for after-school tutors. This solution has also been promoted for students who require personalized attention. Finally, Netex Learning (http://www.netexlearning.com/en/) teachers design curriculum across a variety of digital platforms and devices (iPad, android or surface devices). The use of Netex allows teachers to create customized materials to be published on any digital platform while providing tools for video sessions, adapted assignments, and learning analytics (https://www.thetechedvocate.org/5-examples-artificial-intelligence-classroom/). There will be plenty of apps in the future able to target pathology residents in their curriculum preparation and the proposed limitation of the pathology education to core-competencies only is a tragic evolution. The identification and implementation of these technologies should form the basis for venture companies able to shape the transforming platform of work of pathologists. An application to improve pathology teaching is the use of eye-tracking technology [73, 74]. During the teaching of histopathology skills to medical students and postgraduates, the use of eye tracking allowed a better performance at the final score in learners that took advantage of this technique compared to learners that did not utilize it.

9. Challenges of digital pathology education

DP is far from the niche described a few years ago. DP is a stable platform in many universities and colleges. Radiology images are chiefly acquired as digital data and saved in robust picture archiving systems [75]. Hartman et al. [75] describe the challenges using digital pathology for second opinion intraoperative consultations for over 10 years implementing an incremental rollout for digitalization in pathology on subspecialty benches. They began with cases that contained small amounts of tissue (biopsy specimens). The authors successfully scanned over 40,000 slides through their digital pathology system and emphasized that a successful conversion to digitalization in pathology requires pre-imaging adjustments, integrated software, and post-imaging evaluations. The limitations in the implementation of digital pathology include: (1) Infrastructure and resources support, although the cost of acquisition and maintenance of DP equipment, networking equipment, and staffs expenses are cheaper than a few years ago. (2) Integration into an existing laboratory information system (LIS) or Provincial Health Network (PHN) portals such as the upcoming Epic software implementation in several regions (e.g., Alberta, Canada) [76–79] rather than a stand-alone DP education system may attract investments from the government or the private sector or creating public-private partnerships. (3) Acceptance of digital pathology images in the diagnosis (4) Engagement of all pathologists in practice or training.

10. Artificial neural networks in medicine

Artificial neural networks (ANN) are increasingly a desirable technique for solving machine learning and AI issues. The variety of neural network type and their use of diagnosis and therapy in medicine requires skilled knowledge to choose the most appropriate approach. ANN may be considered as simplified models of the human brain neuronal networks. In both natural and artificial, the essential requirement for a system is that it should attempt to capture the necessary information for further processing. The simplest ANN that may be listed here is the threshold logic unit or TLU. A processing unit for numbers with n inputs x_1, x_2,…, x_n and one output y constitute the TLU. In the TLU, there is a threshold θ, and each input x_i is associated with a weight w_i. A TLU computes the function and then output a "1" if this sum exceeds a threshold, and a "0" otherwise. TLUs mimic the thresholding comportment of biological neurons *in vivo*. This simple logical unit may become more complicated and apply to various areas of medicine, such as diagnostic systems, biochemical analysis, image analysis, and drug development. ANNs are very useful in medicine and applications to have been described in the literature dealing with problems in cardiology and oncology. ANNs are an AI technique that uses a set of nonlinear equations to mimic the neuronal connections of biological systems. ANNs are useful for pattern recognition and outcome prediction applications and have the potential to bring AI techniques to the personal computers of practicing pathologist, assisting them with a variety of diagnostic procedure, such as hepatocellular carcinoma [80–83]. The benefits to utilize ANNs is that they are not affected by external factors such as fatigue, working conditions and emotional or mood state. ANNs may represent a useful AI companion in the routine diagnostic pathology as it has been used in several other fields in medicine, such as to analyze blood and urine samples, track glucose levels in diabetics, and determine ion levels in body fluids. There are numerous applications including tumor detection in ultra-sonograms, classification of chest X-rays, blood vessel classification in MRI, determination of skeletal age from X-ray images, and determination of brain maturation, among others. ANNs are also useful in the

development of drugs for treating cancer and AIDS and in the process of modeling biomolecules. There is also the ability of ANNs to provide sensor fusion which is the combining of values from several different sensors. Sensor fusion empowers the ANNs to acquire complex relationships among the individual sensor values, which would otherwise be lost if the values were independently analyzed. Pathology is an imaging-based discipline in medicine which deals with the nature of disease like radiology. Pattern recognition starts with the idea of classifying input data into identifiable classes by use of significant feature attributes of the data, where the feature attributes are extracted from a background of irrelevant detail. This pattern recognition has been used primarily in radiology [84–92]. ANNs are used in pattern recognition because of their ability to learn and to store knowledge, and they can achieve very high computation rates which are vital in an application like telemedicine. Another approach for applications of image-driven machine learning is a "deep learning" architecture labeled as convolutional neural networks (CNNs). CNNs are a deep learning architecture procedure constituted by a set of layers of individual modules able to extract progressively and sequentially higher levels of abstraction from input images. This procedure is far more sophisticated than the human eye and can discern immediately features that are important for a classification task. AlexNet [93–98] and GoogLeNet [95, 97–107] became quite popular most recently. Their uptake has been speeding up by the availability of open source software such as Caffe, Theano, and Tensorflow. These frameworks of deep learning interface efficiently with Graphical Processing Units (GPUs) to provide speed improvements at which models can be developed and tested. Neural networks together with random forests (RF), and support vector machines (SVMs) are machine learning algorithms. Esteva et al. were able to create and train a CNN to differentiate between benign and malignant skin lesions obtaining an accuracy pretty similar as dermatologists on a test set of cases verified by follow-up biopsies [108]. In **Table 1**, some relevant terms of machine learning in pathology are grouped.

Artificial intelligence (AI)	A context where a machine executes the execution of cognitive tasks
Artificial neural networks (ANNs)	Computing structure with several stacked layers that analyze information from the input to the desired output, with mathematical optimization that is at the basis for a process driving knowledge extraction and learning from the data (input) concerning the production (output).
Convolutional neural networks (CNNs)	An ANN-like architecture, but devoid of the constraint of every stacked layer and applicable for image recognition tasks.
Machine learning (ML)	An AI field, which stresses the use of algorithmic approaches to train machines in performing tasks such as classification, prediction, and pattern recognition.
Deep learning (DL)	An AI and ML subfield that controls large-scale datasets and consecutively complex mathematical architecture to fulfill a machine learning task.
ImageNet	A dataset of large-scale (10 million) images annotated by nouns in the photos with several degrees of granularity.
Technological singularity	An event showing a singular technological advance or sum of innumerable technological advances that in aggregate could lead to a break in the psychologic and somatic evolution of humans with entirely unpredictable results.

Table 1.
The most useful definitions of frameworks of machine learning and beyond.

Image recognition in pathology has used a discrete number of hand-crafted features, which are time-consuming and are limited in scope, while deep learning identifies its elements from a large number of training examples able to identify patterns that may be unrecognized by humans. There are three tasks in "deep learning" that need to be differentiated, including detection, segmentation, and classification. Litjens et al. trained a CNN for prostate and breast biopsies to improve the objectivity and efficiency of histologic (microscopic) slide analysis. All slides containing prostate cancer and micro- and macro-metastases of breast cancer could be recognized automatically. Moreover, 30–40% of the slides containing benign and normal tissue could be excepted without the use of any additional immunohistochemical marker or human intervention [109]. Murthy et al. investigated the automated classification of the nuclear shapes and visual attributes of cells of glioma, a tumor of the central nervous system, using CNNs on pathology images of automatically segmented nuclei, proposing three methods that improve the performance of a previously-developed semi-supervised CNN. On a dataset of 2078 models, the combination of the proposed approaches was able to cut the error rate and shape classification by 21.54% and 15.07%, respectively [110]. It is not inconceivable that computers in the future will exceed human decision making demonstrating their superiority over humans in identifying new categories [60, 111].

11. Artificial intelligence and basic research

Image-based recognition of developmental pathways has been a pillar in identifying several milestones in developmental biology [112–119]. In systems biology, networks and network-based methods are starting a new analysis of the functional organization of gene networks [120]. In translational bioinformatics, there is the union of translational medicine and bioinformatics. In this setting, translational medicine moves fundamental discoveries of biology from the research bench into the patient-care setting and iteratively uses clinical observations to inform basic biologists. Translational medicine is focusing on patient care, including the creation of new diagnostic procedures, prognostic markers, prevention strategies, and therapeutic protocols based on biological discoveries with an explicit goal of affecting profoundly clinical care [121]. AI is helping to decipher non-coding genes after that 17 years ago the sequencing of the human genome was reached. Currently, one in eight of the 22,210 coding genes listed by the Ensembl/GENCODE, RefSeq and UniProtKB reference databases are differently marked across the three sets [122]. Mappings of tumor-infiltrating lymphocytes (TILs) based on histological images through computational staining using a convolutional neural network trained to classify patches of images will be important in identifying the interaction of cancer with the surrounding environment [123]. The fabrication of functional DNA nanostructures operating at a cellular level could be crucial in determining the pathways to check how more natural-like orchestration is present at cellular level comparing to the rigid and restrictive conventional approaches adopted so far [124]. Currently, we are witnessing a renewed interest in adapting ANN for pharmaceutical research and computer-assisted drug discovery, and design will be a daily task in the future [125]. We specially emphasize deep neural networks, restricted Boltzmann machine networks, and convolutional networks. The Virtual Physiological Human and research studies into nanotechnology will confidently produce yet more unpredictable opportunities, leading to substantial changes in biomedical research and practice [126].

12. Quantum computing and pathology imaging

The language called "R" is a free open source programming language, which is mainly used for data analytics and statistical analysis. Compared with commercial software, open source software allows the operator to become a programmer and change the code. R is enabling users to develop custom AI apps to arrange within their organization with applications for predictive modeling, deep learning, extracting mission-critical information from reams of text, and several other applications. A revolutionary concept in digital data processing is quantum computing, which is based on the fundamental principles by which nature operates, i.e., quantum mechanics [127]. In a classic computer, the process works with bits, which at any given time can be in one of two states, i.e., 0 or 1. Conversely, quantum computers use qubits. These units can exist in any superposition of states 0 and 1 and are represented by a complex number, which is a number that can be expressed in the form a + bi, where a and b are real numbers, while i is a solution of the equation $x^2 = -1$, and it is called imaginary number, because no real number satisfies this equation. When N qubits are in superposition, a combination of 2^N states are created. While a traditional computer can only hold one of these states at a time, quantum computers can perform significant operations on superpositions of states. The most basic operations performed on qubits are defined by quantum gates, which are pretty similar to logical gates used in standard computers using bits. The state of a quantum computer, a set of qubits called quantum register, can be visualized in some ways, typically as a 2D or 3D graph, on which points or bars represent superpositions of qubits, while their color or bar height represent amplitude and phase of a given superposition. Instituted in 1999, D-Wave Systems is considered as the world's first quantum computing company. D-Wave is the leader in the progress and distribution of quantum computing systems and software, and a few applications have been recently reported [128–131]. Quantum computing users have already developed over 100 early applications in areas including image analysis, optimization, machine learning, pattern recognition, anomaly detection, cybersecurity, financial analysis, software/hardware verification, and validation, bioinformatics/cancer research, traffic flow, manufacturing processes, and internet advertising. However, quantum computing is a work in progress, because D-Wave quantum computers do not currently perform arbitrary quantum gate operations on sequences of qubits. Quantum Computing Playground (http://www.quantum-playground.net/#/home) is a browser-based WebGL Chrome platform. It features a graphics processing unit (GPU)-accelerated quantum computer with a simple integrated development environment (IDE) interface and its scripting language with debugging and 3D quantum state visualization features. Quantum Computing Playground can resourcefully simulate quantum registers up to 22 qubits, run some algorithms (e.g., Grover's and Shor's algorithms), and has a variety of quantum gates built into the scripting language itself. All currently known and useful quantum algorithms that can run on quantum computers are based on the ability of the quantum system, upon specific rearrangement, to behave in unison. Large chunks of data can be processed at once, operating primarily on only a few particles, that is, in a massively parallel manner. This aspect will allow tasks that would require centuries of computing on a standard computer to require only a few minutes on a quantum computer. A key challenge for quantum computers is to provide and maintain isolation of individual qubits involved in the computation. Extreme and stable cooling is required to make wire circuits behave in a quantum fashion. Operated by an electrical signal from a classical computer, these systems must be maintained at these extremely low temperatures by a vast refrigeration apparatus involving a rare helium-3 isotope. Standard encryption methods rely on

a code for the operator to access encrypted data. However, the key must be shared and can be decoded by unauthorized persons seeking to 'hack' a system using several software programs (most of them open-source) available in internet. With quantum computing, the core and the data can be secured indefinitely with guaranteed unbreakable encryption. Such strong security is possible because quantum encryption relies on the laws of nature (quantum mechanics) to furnish it. Thus, cryptography is expected to be the first application of quantum computing to enter medical practice to secure medical records and communication. "Big data" research and machine learning are likely to be one of the fields to advance quickly with the advent of real-world functional quantum computers. A statistical model requires rational decisions about variable definitions and their inter-relationships. In machine learning, there are few assumptions and algorithms are derived from computer programs that evaluate millions of data elements and all their potential directions of effect and interactions. The more an algorithm is derived from raw data and with less human input, the more it fits into machine learning. Machine learning that informs clinical practice in real time depends on growing databases containing regularly updating medical record information and linked to other sources of data (e.g., wearable technology). To deal with this complexity future machine learning programs will require computational power of quantum computing to deliver results in real time. It is expected that a quantum MRI machine will generate extremely precise imaging allowing even the visualization of single molecules. Using artificial intelligence, quantum computing can be applied to interpreting diagnostic images, histology images other than radiology images. Not only will image detail be exponentially improved but the physician can be aided in understanding results because active machine learning can train a quantum computer to identify abnormal findings with a precision better than the human eye. Combining "big data" (i.e., data that are too complicated to work on using traditional data processing application software) with quantum computing will provide access to the current evidence and enable meaningful use of the electronic data continuously generated in the delivery of care. Realization of personalized medicine will need to draw on analysis of mega-data and bring together measures of physiology, imaging, genomics, wearable technology, screening measures, patient records, environmental measures and more. Currently, we realize that we may be at the dawn of a revolution in computing. We have numerous examples of machine learning algorithms and artificial intelligence that may leverage the power of quantum computing to deliver real time results.

13. Technological singularity

The technological singularity may be considered an event that shows a single technological advance or may represent a sum of many technological advances that in aggregate could lead to a break in the psychologic and physical evolution of humans with entirely unpredictable and unfathomable results [60]. In this hypothesis, there is the concept that artificial superintelligence will abruptly prompt blockbusting technological growth, resulting in impenetrable changes to human civilization. Currently, it is not inconceivable that AI may generate software-based AI learning with "deep learning" on "big data" to enter a phase of self-improvement cycles, with each new and more intelligent generation appearing algorithms will be installed becoming operative. It may swiftly create an intelligence burst resulting in a powerful superintelligence that would, qualitatively, far surpass the human intelligence. Such time is already started and may coincide with the progress of quantum computing (**Figure 1**).
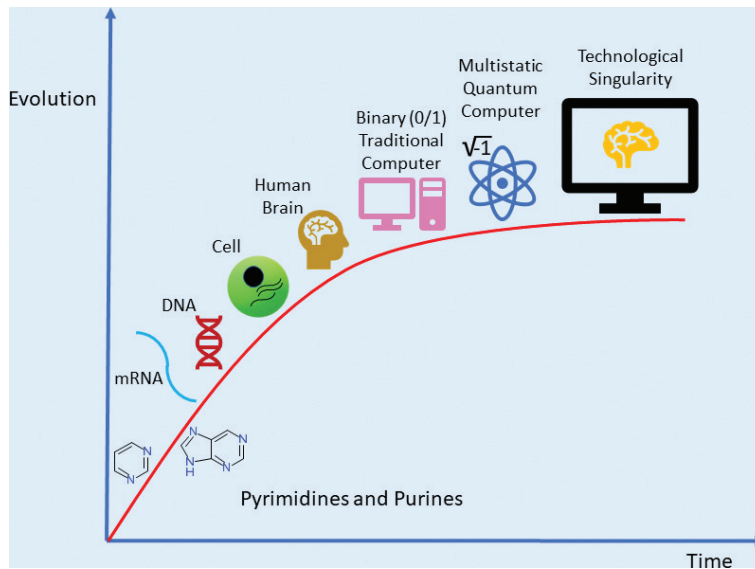
Figure 1.
Evolutionary framework.

In the last few decades, there has been accelerating progress of technology and changes in the mode of human life. These states may give the appearance of approaching some essential singularity in the human history signalizing fears and concerns that the new superintelligence would continue to upgrade itself and annihilate humans considered ineffective and inefficient. Apart of science fiction, there is substantial ground that technological singularity started already with some applications of D-wave and processes of hidden Markov model (HMM) that run most of our daily and professional life [132]. HMM are useful in everyday life in many activities, such as speech recognition (e.g., Siri or Cortana), speech synthesis, speech tagging, machine translation, partial discharge, handwriting recognition, activity recognition, transportation forecasting. HMM is also useful in our professional life in activities, including single-molecule kinetic analysis, gene prediction, alignment of bio-sequences, deoxyribonucleic acid (DNA) motif discovery, time-series analysis, protein folding, chromatin state discovery, document separation in scanning solutions, sequence classification, metamorphic virus detection, solar irradiance variability, and computational finance. Although most individuals may suggest that the artificial superintelligence may be fully functional around 2050, there is no certainty that this may really happen. Multifractality and HMM-based integrated framework may represent two of the pathways to discover it in the nearest future.

14. Conclusions

In conclusion, the rapid advancement of information technology has allowed the gradual acceptance of DP in diagnostic routine and education. The use of digital pathology in clinical services may go back to the early steps using personal computers, such as Commodore 64, but is now well recognized in multi-site medical centers with more than one location as well as in geographically very diverse health sites. The use of quad-core processing, 5G technologies, and quantum biocomputing will change the image of colleges and universities in the 3rd decade of this

century. It is up to us to use these new technologies to build students at the highest level of teaching. The initial limitation of funding should be overcome using private donations from charities or benefactors or instituting public-private partnerships.

Acknowledgements

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