Computational Technology with Artificial Intelligence and Machine Learning: What Should a Cytologist Do with It?

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There has been both hope and hype for computation, artificial intelligence (AI), and machine learning (ML) technologies in the medical field, specifically in pathology, and especially cytopathology. In 2019, the US Food and Drug Administration (FDA) released a white paper proposing a regulatory framework for AI (software) medical technologies as medical devices (software medical devices), and the report stated that AI/ML-based software medical devices will deliver safe and effective software functionality that will improve patient care [1]. For the community and academic cytologist, many questions, uncertainties, and challenges remain. What can this evolving multidisciplinary science contribute to cytology? Will this computational technology be the “third wave” or “third revolution” augmenting the first immunocytochemistry wave and the second molecular diagnostics wave? Does this technology hold a “false promise” with little, if any, practical clinical value? Alternatively, will this discipline “replace” our cytology profession and evaporate like the telephone booth as those in this technology industry often claim?

For most of us, our own life experiences serve as the foundation for our future vision. I came to the USA in early 1987 as a postdoctoral research fellow to pursue my medical career and work on fundamental cancer biomarker studies. My mentor, Dr. George P. Hemstreet III, an urologist and a pioneer in digital imaging field, developed a technique called “quantitative fluorescence image analysis (QFIA).” This system, as illustrated in Figure 1,

interfaced a fluorescence microscope (Leitz) connected to a video camera, a monitor, and a computer (TAS-Plus) that was taller than myself (I am 5'7"). It was quite sophisticated at that time. The microscope was programmed automatically to scan the entire slide to capture cellular images (mainly cellular nuclei stained with Hoechst 33258), the fluorescence intensity was measured, and the image was stored in the disk (eight-inch disk, Fig. 1). The entire disk storage space was 64 kilobytes, barely enough to store 1 nuclear image, and the image analysis was “hard wired.” As a comparison, a meniscus-sized iPhone chip (relative to the 8-inch disk) had a 128-gigabyte capacity. Figure 1 shows a MorphoGo system (Hangzhou, China), a combined fully automatic scanner with built-in morphology-driving cell analysis algorithms. The MorphoGo system has the capability of scanning the entire cytology slide with selected automatic single-cell acquisition, automatic optimal focusing, and automatic convolutional neural network for cellular classification. The system was originally designed to analyze bone marrow smears, including both differential count and initial diagnostic interpretation; analyze 27 slides per batch, at about 20 min per slide; and store up to 100 individual cell images per slide. More recently, the MorphoGo has been modified to analyze other less formidable sample preps, including urine, lumbar puncture fluid, and peripheral blood smears.

While the advancement of computation technologies, including computer power, the Internet, and mathematic algorithms, makes the computation cytology possible, a

Fig. 1. Image of the QFIA system (upper left), the corresponding disk (upper right), and the MorphoGo system (bottom). QFIA, quantitative fluorescence image analysis.

technological advancement crucial for this journey is standardized sample preparation techniques, that is, liquid preparation methods. These standardized preparations produced a cell monolayer with minimum lab-to-lab variations. The combination of computation technology and the liquid-based preparation poises cytology for AI technology success, as exemplified by the cervical Pap story, elegantly reviewed by Madelyn Lew et al. in this special issue.

On the other hand, one must recognize that cellular morphology, or morphometrics, as a sole diagnostic benchmark, has its limit. Techniques that only analyze morphometrics, no matter how sophisticated the technique might be, by definition, has limitations. What I mean by that is while we can train the system to accurately distinguish cancer from non-cancer cells, it is highly unlikely that morphometrics can determine if a particular cell has HPV16 infection (not HPV18 or other type), a P53 mutation, or PDL1 overexpression purely based on morphometrics alone. In other words, in the foreseeable future, there is still a need for an educated operator (cytologist) to perform initial morphology-based examination, to determine what additional biomarkers or ancillary studies are necessary to probably perform those studies, and to integrate all the diagnostic information to guide appropriate patient management. But if the system can distinguish cancer from non-cancer cells more accu-

rately and consistently, or give us a quantitative measurement of specific biomarker expression so that a targeted drug can be more effective, then why not?

These so-called AI technologies may be used in conjunction with other important diagnostic commodities, such as immunohistochemical or immunofluorescence staining and molecular analysis, to eventually derive the most accurate and clinically meaningful diagnosis on the cytology materials, provided the cytologists know how to apply the technology and can assemble the information together in their interpretation.

This issue reflects a first step to educate our readers and to conceptualize our creativities to optimize decisional intelligence which will mold this new science, providing high-quality validated data for economic resource utilization to develop “Digital and Computational Cytology: What Is in the Horizon”? This special edition includes a mixture of review and original research of application of AI systems for the cytological diagnosis of various organ systems. While the concept of computation and AI technologies is very broad, this treatise focuses on ML, either supervised or unsupervised, in cytological diagnosis, and areas such as ROSE or telecytology are not included. As McAlpine and Michelow [2] pointed out in their recent review: “Cytopathologists need to become informed consumers of these AI algorithms by understanding their workings and

limitations, how their performance is assessed and how to validate and verify their output in clinical practice.” I cannot agree more with this statement. The combination of digital morphology with quantitative biomarker analysis at the single cell level utilizing computational and AI approaches, a dream that has been relentlessly pursued by Dr. Hemstreet over 3 decades [3], may soon be realized.

References

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