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The Benefits of Learning Morphological Cell Image Analysis for Medical Students

NevenkaVelickova

Faculty of medical sciences,
University «Goce Delcev» Stip, R.Macedonia
nevenka.velickova@ugd.edu.mk

Summary/Abstract

In the last decades, the combination of increase of ICT (information and communiication technology), computer power, high-quality of digital cameras and whole slide scanners with the development of image tools analysis, has allowed the possibility for fast and precise analyzing the slides in different field of medicine. Medical students in their practice on the course of histology can use digital images (slides) which has been transformed by the development of whole-slide imaging systems for the evaluation and interpretation of the cell and cell compartments of entire histologic sections. In this review, I will observe the benefits of learning morphological cell image analysis, their potential applications in the course of cytology and histology, and the use of digital image analysis by medical students, including theirs potential strengths, limitations, and considerations of these analysis. Some of the free downloaded software (Digimizer, Image tool ets.) provide basic informations about cell morphology, size, dimensions, nuclear/cytoplasm ratio ets. As a tools and analysis are easy-to-use by students and these are flexible image analysis software packages, that allows precise manual measurements as well as automatic object detection with measurements of cell features as a indicators for early diagnosis. Knowledge and utilization of these tools (in digital image analysis) and software is very important for medical students in their advance courses of study program, as a pathology, oncology, neurology ets. The review observe that learning morphological cell analysis has so many benefits. Image tools analysis becoming a standard method for defining morphologic changes in the cells and tissuues, with this analysis medical students and doctors can identify potential clinical biomarkers and can confirm the diagnosis.

Keywords: image analysis, morphological cell analysis, practice, software, students.

1. Introduction

Image analysis refers to the field of using algorithms to extract information from digital images. As a analysis involves different types of techniques, but the goal of most applications is to extract quantitative information from images. It can be applied in many areas including astronomy, medicine, archeology, technology ets. In the last decades, the combination of increase of ICT (information and communiication technology), computer power, high-quality of digital cameras and whole slide scanners with the development of image tools analysis, has allowed the possibility for fast and precise analyzing the bio-medical data. Interpreting tissue slides manually is labor intensive, involves the risk for human errors and subjectivity in interpretation of the results and report. Image tools analysis provide additional automatic, fast and reproducible analyses wich helping the histopathologist and other doctors to making an accurate diagnosis (Gurcan et al., 2009; Madabhushi, 2009). Identifying certain histological structures, such as nuclei, membranes or some of the cytoplasmic organelles in histological slides, is one of the great possibility of image analysis, because quantitative and qualitative data

approve the presence, extent, size and shape of these structures as a indicators for early diagnosis (Madabhushi, 2009).

Choosing the appropriate image tools analysis is dependent of the aim and field of the study, competitive od researchers, computer programming and image analysis expertise, and cost. In the field of histology and cytology, the quality of data obtained from image analysis methods depend of previously procedures and steps, such as tissue collection, fixation, processing, embedding, staining and digital image acquisition. For that point of view, the goal of image analysis is to increase the amount and quality of data preferably by providing quantitative measurements of histologic features. The cell and cellular compartments, as a nuclei and cytoplasm are visible structures in H&E (*Haemotoxylin and eosin*) stained histological slides. But, all these compartments has its own characteristics, shapes and dimensions ar very important as a indicators for different disease (Meijer et al., 1997; Irshad et al., 2014; Al‐Kofahi, 2010; Ballarò, 2008; Korde et al., 2009). For that reasons, the goal of image analysis is to achieve a quantitative representation of cell staining, morphology, and architecture that can be used to support early diagnosis. The process of define of cells or cellular structures is the first and most important step of many image analysis (Madabhushi, 2009). Also, examples of quantitative information relevant to some of the diagnosis can be the size, morphology and irregularity distribution of cells, or the ratio of cells as a diagnostic biomarker. A number of studies and researchers (Kuenen‐Boumeester, 1984; Larsimont et al., 1989; Aaltomaa et al., 1991; Pienta and Coffey, 1991; Baak et al., 1985) observe that morphological cell image analysis provide important informations to support diagnosis. Especially, nuclear area and shape, nuclear/cytoplasmic ratio, and automated mitotic detection carry prognostic value independent of other informations.

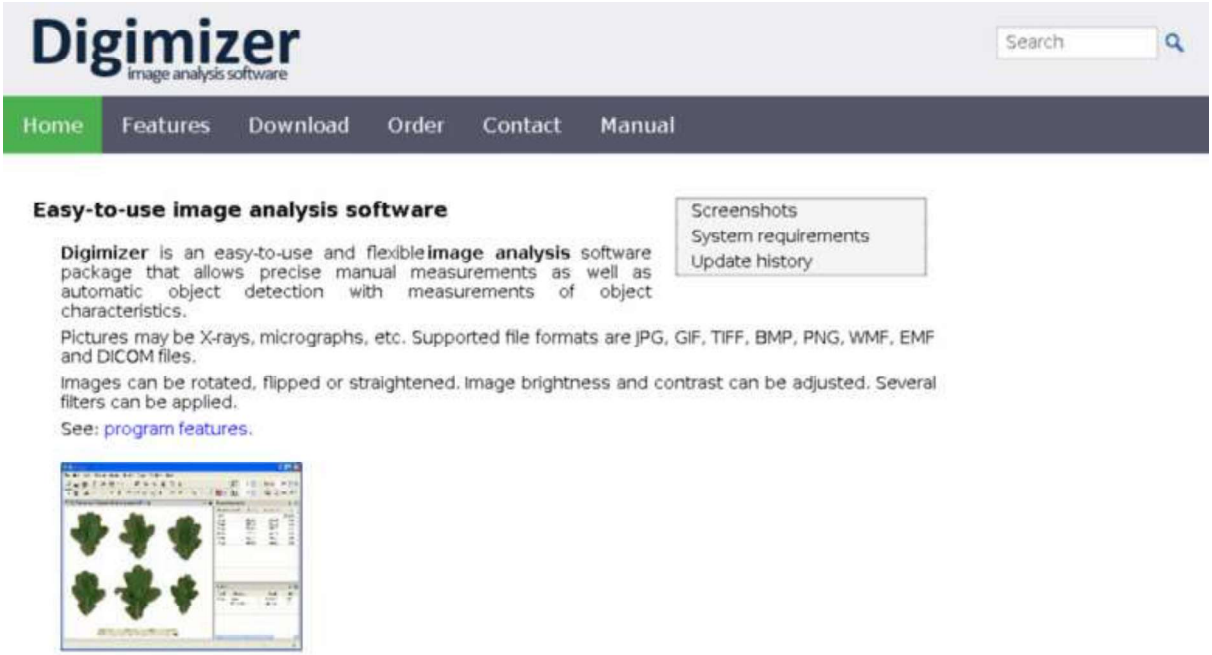
Medical students in their practice on the course of histology can use digital images (Velickova, 2018) which has been transformed by the development of whole-slide imaging systems for the evaluation and interpretation of the cell and cell compartments of entire histologic sections. Applications of whole-slide imaging include rapid transmission of the data basis for consultations and collaborations, standardization and distribution of the materials for education, tissue specimen archiving, and image analysis of histologic specimens. Morphological cell image analysis allows for the acquisition of objective measurements of histomorphologic, histochemical, and immunohistochemical properties of tissue sections (Webster and Dunstan, 2014). According to this, very usefull new technology for digital image analysis is virtual microscopy. It has several distinct advantages that can be used to address many of these challenges. Digital image files of histologic tissue sections can be created, placed on web servers, and made available to the entire student population. Since, all students evaluate the same digital histologic images, there is also elimination of slide-to-slide variability, thus ensuring that all students have the same opportunity and responsibility to evaluate the same lesion (Hamilton et al., 2012). Digital image analysis in medical training and practice in histopatology also creates unique learning opportunities because evaluation of histologic specimens on screens, increases interactions between students and facilitates classroom discussions (Webster and Dunstan, 2014). The image can be viewed through a computer interface that mimics the tools of a light microscope (Treanor, 2009). Depending on the marker of interest and specimen, microscopy may require different resolution imaging of x40, x60, or x100magnification. The benefits of digital image analysis is very suitable in the field of pathology, because it include ability to facilitate transmission of pathologic images and data worldwide and to facilitate qualitative and quantitative image analysis on pathologic specimens (Potts, 2009; Potts and al., 2010).

In this review, I will discuss morphological cell image analysis, their potential applications in the course of cytology and histology, and the use of digital image analysis by students, including theirs potential strengths, limitations, and considerations of these analysis.

2. Material and Methods

As I mention previously (Velickova, 2018) students today, are all highly computer competent, and greatly appreciate the advantages of the VM (*virtual microscopy*) systems. The delivery of the slides can easily be incorporated into existing e-learning resources that have been developed on the faculty. VM (virtual microscopy) technologies use the platform of hardware accompanying with the software and include pre-and post-image processing, compression, transmission and visualization of the slides. VM allows on-line access to entire scanned sections of tissue that can be viewed on a computer in exactly the same way as conventional glass slides with a microscope and can be explored by the learner at several magnifications. It is provide substantial educational benefits esspecialy to part-time students (Velickova, 2018).

The morphological cell image analysis is highly relevant for medical students in the process of analysis of histological images or slides. Some of the tools of image analysis are focuses on the segmentation of sub-cellular structures, such as the nuclei or cell membranes, and another on classifying different staining patterns. Very usefull image analysis software, very acceptable and easy to use for medical student in the bascic course of cytology and histology is Digimizer (*Picture 1*).



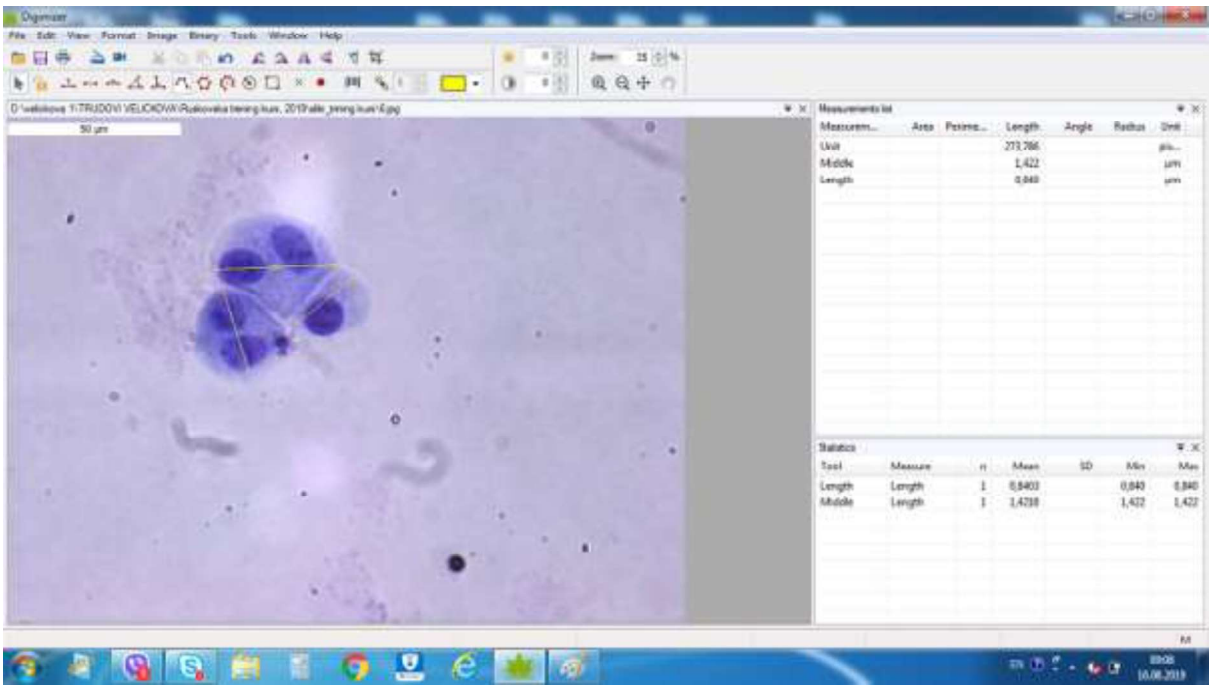
Picture 1. Screenshot of Digimizer image analysis software

Digimizer is a product of MedCalc Software, a developer of medical and statistical software. Digital image file sizes vary depending on the scanning objective and tissue size but commonly range from approximately 200 MB to 1 GB.42. The last version of the software Digimizer 4.3.0 can be free download https://digimizer.en.downloadastro.com/download/

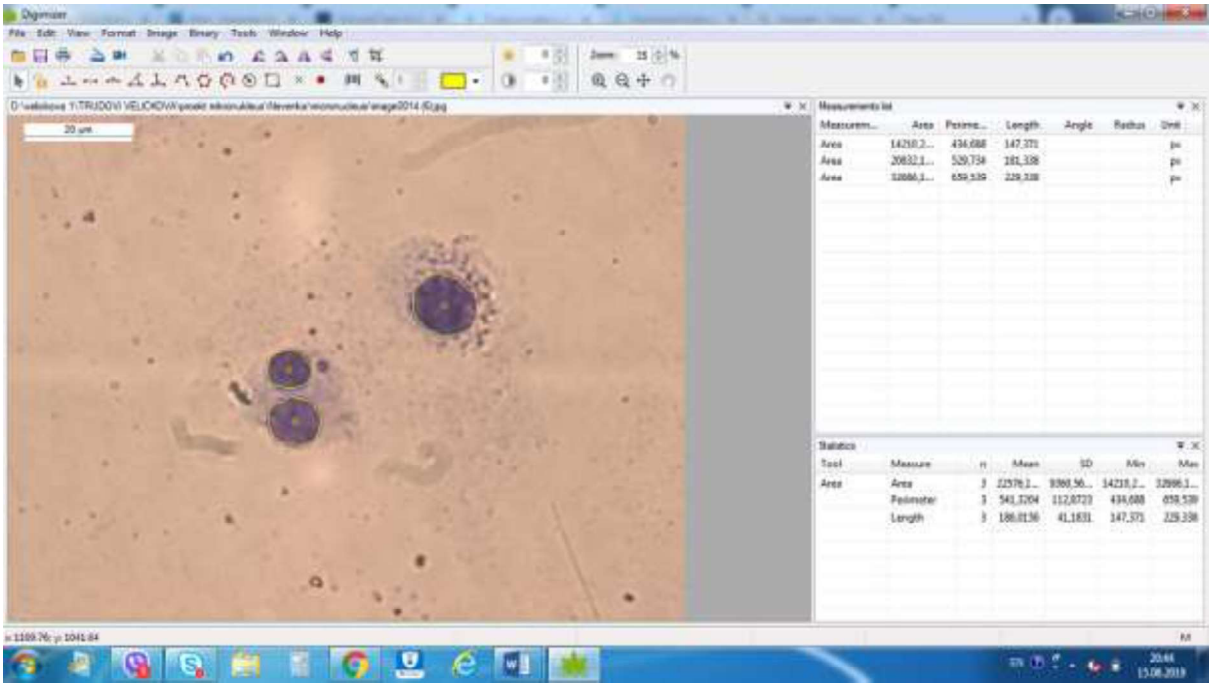
As a tools and analysis are easy-to-use and flexible image analysis software packages, that allows precise manual measurements as well as automatic object detection with measurements of object characteristics. Pictures may be X-rays, micrographs, etc. Supported file formats are JPG, GIF, TIFF, BMP, PNG, WMF, EMF and DICOM files. Images can be rotated, flipped or straightened. Image brightness and contrast can be adjusted. Several filters can be applied.

3. Results and Discussion

With this software package medical students can measure objects in the image (in their practice/histological slides) using any of the following **Measurement tools.** The Image can be manipulate, resize, crop, zoom, stretch histogra, convert to grayscale na color ets. As a software this can define unit of measurement, measure distances and lengths of line segments or paths (*Picture 2*), perimeters, area, angles, find center and calculate characteristics of circular objects ets. (*Picture 3*). With this Image analysis we can analyze the objects: object detection with measurement of perimeter and area.

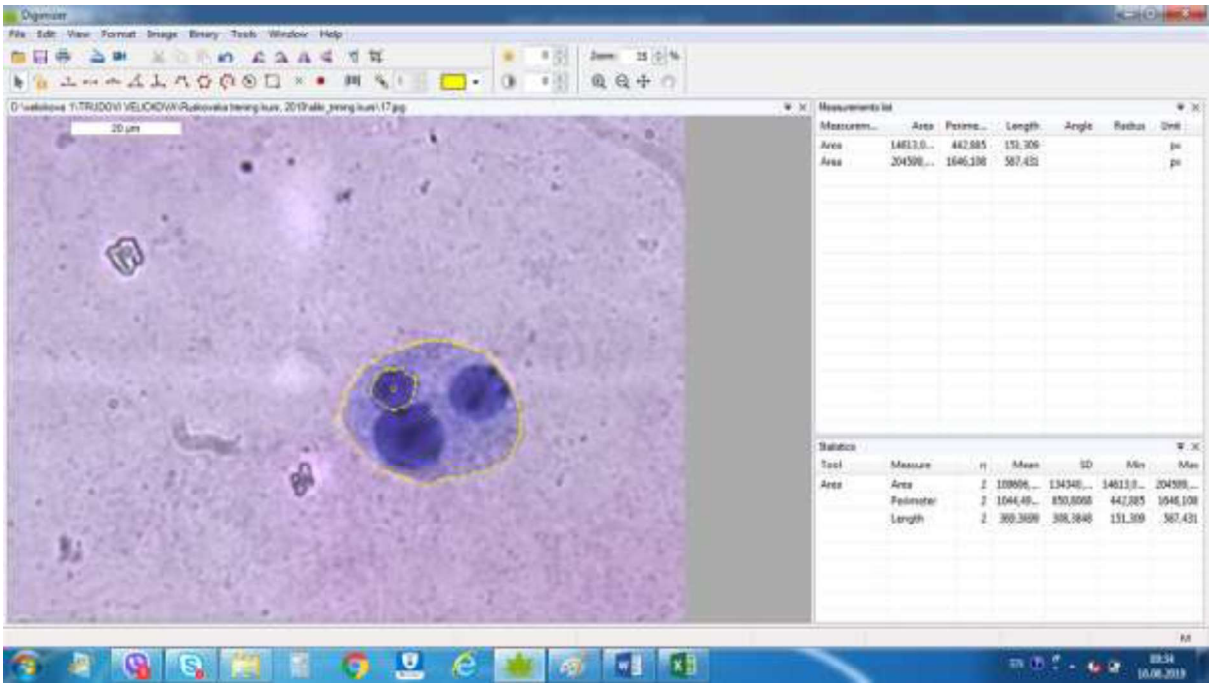


Picture 2. (Screenshot of mesurments of the lengths of human lymphocites)



Picture 3. (Screenshot of mesurments of the center and calculate characteristics of human lymphocites)

These software, provide basic informations about cell morphology, size, dimensions, esspecially nuclear/cytoplasm ratio as a very important parameter or indicator for some of the disseas and early diagnosis. Also, the integrated statistics window displays statistics (n, mean, SD, minimum and maximum) of the measurements in the Measurements list. (*Picture 4*).



Picture 4. (Screenshot of nuclear/cytoplasm ratio in human lymphocites)

Currently, numerous histologic image analysis software solutions are commercially available. Some of them can be free downloaded but, some of them are very expensive. ImageJ

should be the first program you become familiar with when looking for image analysis software. It can do simple things like crop, label, and alter the brightness and contrast of fluorescence images (visit their website: http://imagej.nih.gov/ij/**.)** FIJI (FIJI Is Just ImageJ) is a bundle of the top plugins available for ImageJ **(**visit their website: http://fiji.sc/Fiji. Cell Profiler can extract quantitative measurements from thousands of images through a custom pipeline that can first process and then analyze your images. Other Image Analysis acceptable and very usefull in the study of biomedicine are:

- **AFNI** - Software for Analysis of Functional NeuroImages
- **Bio7** - Ecological Modeling, Scientific Image Analysis, and Statistical Analysis
- **BioImage Suite** - Integrated Image Analysis Software Suite of Yale University
- **BioImageXD** - Analysis, Processing, Visualization of Multi-Dimensional Microscopy Images
- **CellProfiler** - Cell Image Analyis Software Developed at the Broad Institute
- **Crystal Image** - Software Program for Image Processing and Analysis
- **CVIPTools** - Software Package for Exploration of Computer Vision and Image Processing
- **DIPimage & DIPlib** - Toolbox and Library for Digital Image Processing
- **Endrov** - Framework for Image and Data Analysis in Microscopy
- **Fiji** - Fiji Is Just ImageJ - Batteries Included
- **FSL** - Library of Analysis Tools for fMRI, MRI, DTI Brain Images
- **Icy** - Open Community Platform for Bioimage Informatics
- **Ilastik** - Interactive Image Classification, Segmentation, and Analysis
- **ImageJ** - Java Tool for Image Processing and Analysis
- **IMAL** - Image Measurement and Analysis Lab
- **KNIME** - Data Analytics, Reporting, and Integration Platform
- **NEFI** - Tool for Network Extraction From Images
- **PhenoRipper** - Software for Microscopy Data Exploration and Interpretation
- **SPM** - Software for Statistical Parametric Mapping
- **QuPath** - Open Source Software for Quantitative Pathology
- **ORBIT** - Whole Slide Image Analysis

The morphological cell image analysis is very suitable for side-byside viewing allows for direct comparisons between two or more specimens or evaluations of differently stained sections. Each image analysis software package has its unique advantages and disadvantages. No single package is perfect for every laboratory.

4. Conclusion

The use of digital image analysis in medical education, especially in the course of histology has numerous benefits. The collection of teaching quality specimen or histological slides, free from artifacts is very important in this analysis. Also, there must be enough tissue available to produce representative sections for an entire class. Image analysis tools provide objective measures for research end points. In a fact that segmentation of sub-cellular structures in tissue is an important pre-requisite for quantitative and qualitative assessment of the expression of biomarkers. Morphological image cell analysis can be used for the extraction and quantification of sub-cellular data, e.g., nuclei, cytoplasm, membrane and gene probes, from whole slide histological slides. Knowledge and utilization of these tools (in digital image analysis) and software is very important for medical students in the advance course of their

study program, as a pathology, oncology, neurology ets. Image tools analysis becoming a standard method for defining morphologic changes in the cells and tissuues, can identify potential clinical biomarkers and can confirm the diagnosis.

5. References

Aaltomaa, S., Lipponen, P., Eskelinen, M., Kosma, V.M., Marin, S., Alhava, E, et al. *(*1991). The significance of nuclear morphometric variables as prognostic predictors in breast cancer. *Anticancer Res*;11:1663‑9.

Al‑Kofahi, Y., Lassoued, W., Lee, W., Roysam, B. (2010). Improved automatic detection and segmentation of cell nuclei in histopathology images. *IEEE Trans Biomed Eng;*57:841‑52.

Baak, J.P., Kurver, P.H., De Snoo‑Niewlaat, A.J., De Graef, S., Makkink, B., Boon, M.E., et al.(1982). Prognostic indicators in breast cancer – Morphometric methods. *Histopathology*; 6:327‑39.

Baak, J.P., Van Dop, H., Kurver, P.H., Hermans, J. (1985). The value of morphometry to classic prognosticators in breast cancer. *Cancer*; 56:374‑82.

Ballarò, B., Florena, A.M., Franco, V., Tegolo, D., Tripodo, C., Valenti, C., *et al.* (2008). An automated image analysis methodology for classifying megakaryocytes in chronic myeloproliferative disorders. *Med Image Anal*;12:703‑12.

Gurcan, M. N., Boucheron, L. E., Can, A., Madabhushi, A., Rajpoot, N. M., Yener, B. (2009). Histopathological image analysis: A review, *Biomedical Engineering, IEEE Reviews in* 2. 147–171.

Hamilton, P.W., Wang, Y., McCullough, S.J. (2012). Virtual microscopy and digital pathology in training and education. *APMIS*.;120(4): 305–315.

Irshad, H., Veillard, A., Roux, L., Racoceanu, D. (2014). Methods for nuclei detection, segmentation, and classification in digital histopathology: A review‑current status and future potential. *IEEE Rev Biomed Eng*;7:97‑114.

Korde, V.R., Bartels, H., Barton, J., Ranger‑Moore, J. (2009). Automatic segmentation of cell nuclei in bladder and skin tissue for karyometric analysis. *Anal Quant Cytol Histol*;31:83‑9.

Kuenen‑Boumeester, V., Hop, W.C., Blonk, D.I., Boon, M.E. (1984). Prognostic scoring using cytomorphometry and lymph node status of patients with breast carcinoma. *Eur J Cancer Clin Oncol;*20:337‑45.

Larsimont, D., Kiss, R., d'Olne, D., de Launoit, Y., Mattheiem, W., Paridaens, R., et al. (1989). Correlation between nuclear cytomorphometric parameters and estrogen receptor levels in breast cancer. *Cancer*; 63:2162‑8.

Madabhushi, A. (2009). Digital pathology image analysis: opportunities and challenges, *Imaging in Medicine* 1 (1) 7–10.

Meijer, G.A., Belien, JAM, van Diest, P.J., et al. (1997). Image analysis in clinical pathology. *J Clin Pathol*.;50(5):365–370.

Pienta, K.J., Coffey, D.S. (1991). Correlation of nuclear morphometry with progression of breast cancer. *Cancer;* 68:2012‑6.

Potts, S.J. Digital pathology in drug discovery and development:multisite integration. Drug Discov Today. 2009;14(19–20):935–941.

Potts SJ, Young GD, Voelker FA. The role and impact of quantitative discovery pathology. Drug Discov Today. 2010;15(21–22): 943–950.

Treanor, D. Virtual slides: an introduction. *Diagn Histopathol*. 2009;15(2):99–103.

Velickova, N. Virtual microscopy as a learning method in part-time medical education, EDUvisin 2018 »Modern Approaches to Teaching the Coming Generations« pp. 1885-1889

Webster, J.D., and Dunstan, R.W. (2014). Whole-Slide Imaging and Automated Image Analysis: Considerations and Opportunities in the Practice of Pathology, *Veterinary Pathology*. Vol 51(1) 211-223.

About the author

Nevenka Velickova works as an Associate Professor on Faculty of medical sciences, University "Goce Delcev" in Stip, R. Macedonia. She has gained experience in cytology and histology, mainly in the field of effect of pollutants on human cells. Also her research interests include e-learning and teaching strategies, according to her previous experience as a teacher in high school and in communications technology in education. She participated in many conferences at home and abroad (over 150) and she published (at home and abroad) over 50 academic papers in the field of biomedicine.