

AI (artificial intelligence) in histopathology – from image analysis to automated diagnosis

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Abstract: The technological progress in digitalization of complete histological glass slides has opened a new door in tissue – based diagnosis. The presentation of microscopic images as a whole in a digital matrix is called virtual slide. A virtual slide allows calculation and related presentation of image information that otherwise can only be seen by individual human performance. The digital world permits attachments of several (if not all) fields of view and the contemporary visualization on a screen. The presentation of all microscopic magnifications is possible if the basic pixel resolution is less than 0.25 microns. To introduce digital tissue – based diagnosis into the daily routine work of a surgical pathologist requires a new setup of workflow arrangement and procedures. The quality of digitized images is sufficient for diagnostic purposes; however, the time needed for viewing virtual slides exceeds that of viewing original glass slides by far. The reason lies in a slower and more difficult sampling procedure, which is the selection of information containing fields of view. By application of artificial intelligence, tissue – based diagnosis in routine work can be managed automatically in steps as follows: 1. The individual image quality has to be measured, and corrected, if necessary. 2. A diagnostic algorithm has to be applied. An algorithm has been developed, that includes both object based (object features, structures) and pixel based (texture) measures. 3. These measures serve for diagnosis classification and feedback to order additional information, for example in virtual immunohistochemical slides. 4. The measures can serve for automated image classification and detection of relevant image information by themselves without any labeling. 5. The pathologists' duty will not be released by such a system; to the contrary, it will manage and supervise the system, i.e., just working at a "higher level". Virtual slides are already in use for teaching and continuous education in anatomy and pathology. First attempts to introduce them into routine work have been reported. Application of AI has been established by automated immunohistochemical measurement systems (EAMUS, www.diag-nomX.eu). The performance of automated diagnosis has been reported for a broad variety of organs at sensitivity and specificity levels >85%). The implementation of a complete connected AI supported system is in its childhood. Application of AI in digital tissue – based diagnosis will allow the pathologists to work as supervisors and no longer as primary "water carriers". Its accurate use will give them the time needed to concentrating on difficult cases for the benefit of their patients.

Keywords: tissue – based diagnosis, artificial intelligence, smart pathology, virtual slides.

Introduction

The roots of surgical pathology range back into the medieval times. Prior, contemporary, and after the implementation of light microscopy, surgical pathology has been always a medical discipline that promotes medical knowledge and innovative treatment. Our

days belong to the so-called information century. Therefore, it is no surprise that surgical pathology is directly involved in developing and extending electronic information distribution and remote control performance [19]. Starting with telepathology at the end of the last century, its contribution to the communication scenery has matured to the establishment of virtual pathology institutions, that serve for daily routine diagnosis with electronic image transfer via the internet only [6,7]. Analysis of the basic diagnostic algorithms, implementation of quantification procedures

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such as quantitative immunohistochemistry, and videoconferencing systems for continuous education and case discussions have to be mentioned here [8, 16]. Within the last few years, machines are commercially available that require about 5 minutes to digitize a whole slide [9,23]. They are equipped with magazines for about 300 slides, and delegate the digitized, so – called virtual slides for further processes such as human diagnostics or automated measurements within eight to 10 hours (night duty). The virtual slides amount 2-3 Giga Bytes. The predominant technological task is to handle this huge amount of data in a fast and effective manner. In connection with a hospital information system (HIS) the virtual slides can be connected with the patients' data and clinicians' requests, and forwarded to the pathologist as an extended and integrated task [17-19,23].

In this article the existing main constraints and tools them are described that are essential to implement an innovative and effective AI based diagnostic system in a distributed manner. Most of the algorithms have been tested for accuracy and effectiveness; unfortunately, a definite implementation in routine workflow of surgical pathology is still missing. However, we are convinced that practical expertise is only a question of time; especially as the cost efficiency rates are turning to the favor of virtual slide technology [10].

General pathways to automated diagnosis in virtual (smart) pathology

Given the presentation of a completely digitized glass slide (virtual slide) the questions arises how to work with it in an appropriate manner. The final aims of the work should be a computerized extraction of image information that can be classified into the common scheme of medical diagnoses. This aim requires tools with standardized surfaces that can be combined to each other independently from potential future requirements [10,21,22]. These standards start with the virtual image and range to the diagnostic classification system. In detail, the necessary standardization tools include:

1. methods to standardize the images to be analyzed (image standardization tools). The unavoidable variation of glass slides in staining intensity or thickness of the cuts is directly transferred to the virtual slide, and has to be corrected electronically;
2. image pre-analysis systems that analyze the images for potential useful object segmentation;
3. sampling procedures that search for diagnostic significant fields of view;
4. texture analysis algorithms that analyze pixel – based image information such as image entropy, symmetries, translation figures, recursive formula data;

Table 1. The application of information not present in the image is a useful tool that can be applied for various purposes.

Knowledge of external (hidden) information is useful for	Search for diagnostic relevant areas
	Artificial construction of missed or incomplete segmented objects
	Appropriate image adjustment to diagnostic/measurement task (magnification)
	Evaluation of correct task performance
	Guide for additional similar tasks (flexible external information use)

5. segmentation algorithms that provide accurate magnification for object and structure associated information;
6. object segmentation, identification, and feature measurement;
7. structure analysis and feature extraction;
8. statistical analysis of measured parameters and classification systems;
9. continuous monitoring of results and readjustment of classification procedures.

The different tools comprise information that possesses the image itself, and information that is added from outside, so – called external information. In mathematical terms the external information serves as a set of parameters that define the result of the general function. For example, to measure nuclei in a histological slide, their size (and identification) strongly depends upon the microscope magnification, and it has to be known to the segmentation and identification algorithm at which pixel related size the objects are expected. Otherwise nucleolar features or clusters of nuclei would be identified instead of the wanted objects.

A survey of the described pathways is illustrated in Table 1.

Image standardization procedures

Image standardization requires a measure of the digitized image compared to a reference image or an image of "optimum quality" [15,20]. There do several algorithms exist how to compare images in between, most of them are designed to assure good quality image copies. [10,13,14]. Virtual slides often do not fulfil a homogenous illumination, and might be too "dark" or too pale dependent upon the staining procedure and scanner assessment. Therefore, measures of image quality are addressed to shading correction, normal distribution of gray values and absolute height of gray values (usual 8 bits). The mathematical correction procedures belong to the class of local dependent fil-

- Judgment of image compression (good values < 30-40 dB)
- Quality measurements of video stream (MOS), according to the recommendations of the International Telecommunications Union (ITU): *objective perceptual video quality measurement techniques for digital cable television in the presence of a full reference*

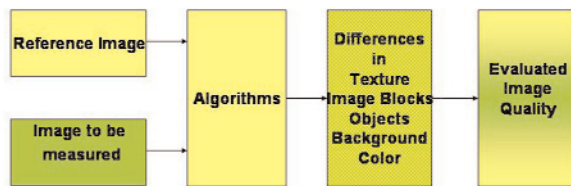


Fig. 1. Basic scheme of image quality measurements.

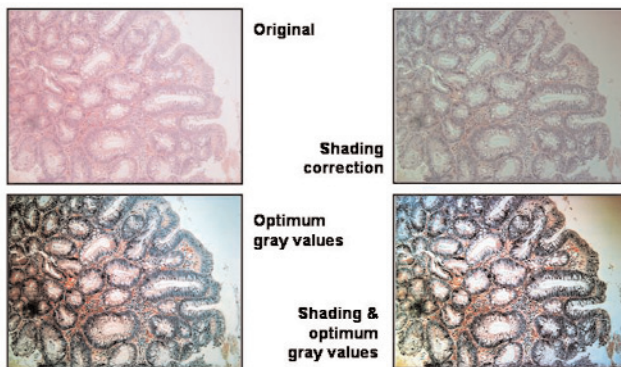


Fig. 2. Examples of commonly applied quality corrections of microscopic images.

ters [14,17]. These filter operations can be applied to the original virtual slide and its differentiated derivative. The differentiated image is mainly serves for segmentation algorithms. The difference of filter parameters are a measure of image quality, i.e., the smaller the image required filter parameters the better is the image quality [14]. The described algorithms are applied for each color space separately, especially if working with images presented in the red – green – blue (rgb) color space. The corrected and standardized image serves for further investigations. Examples of an original and a standardized derivative are given in Figs 1 and 2. The next step is addressed to evaluate potential segmentation thresholds.

Evaluation of potential segmentation thresholds

There do exist several segmentation algorithms such as edge – , color – , gradient – , region – based, or dynamic segmentation. All of these algorithms require gray value differences independently form the specific performance. Thus, the summarized differences in height of gray values are associated with the segmentation accuracy, and can be displayed in gray value histograms. Figs 3 and 4 exemplary demonstrate the potential segmentation thresholds in an original and a derived standardized image. The evaluated number

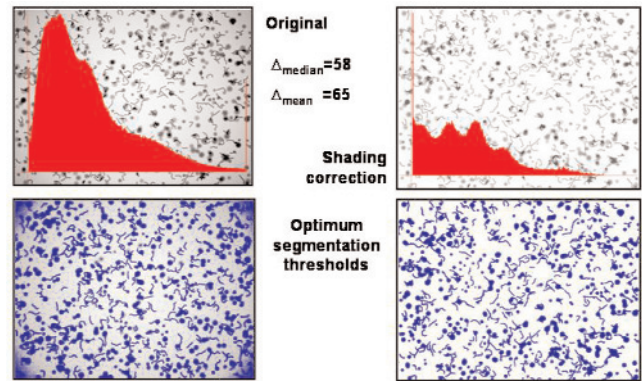


Fig. 3. Effect of shading correction on segmentation procedures.

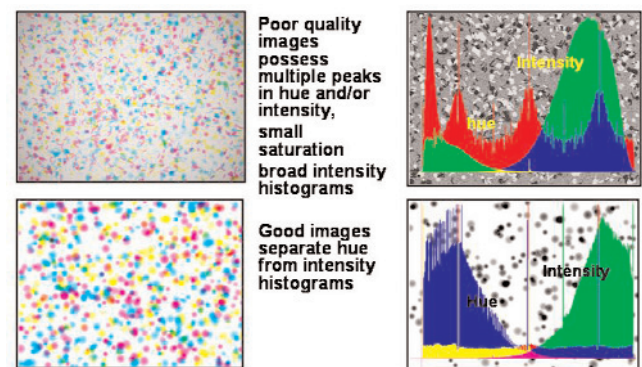


Fig. 4. Example of image quality correction in the hue – saturation – intensity color space.

and gray value heights of these thresholds are a measure of image quality too.

Sampling algorithms of field of view

The well known sentence: “You can only see what you want to see” can be translated into the sentence: “You have to define what you want to see before you start viewing at an image”. In other words, external information is required for appropriate segmentation and identification of the items you are interested in (objects) [15]. In histopathology we are dealing with still images, most frequently with closed figures such as nuclei, cells, vessels, glands, etc. The features of those units are related to area size, gray value distribution within the areas, and length of circumference. Within certain limits they basically define the specific object such as cancer cell, lymphocyte, giant cell, capillary, or normal gland. These limitations are known and can be used

1. to adjust the most appropriate magnification
2. to search for fields of view displaying the most significant information.

The task “screen for potential cancer” requires at its end stage the identification of cancer cells (and the magnification to unambiguous detect objects that pres-

ent cancer cells), in contrast to the task “measure the density of small vessels” which needs a different (lower) image magnification. A potential algorithm to adjust the optimum image magnification to the object identification task is shown in Fig. 5. In principle it is a self – adjusting segmentation algorithm which can be expanded to several features of the objects searched.

If expanding this algorithm to (externally provided) functions such as structural arrangement of a set of objects it will display the detected fields of view in association with the list of tasks. In other words, screening the virtual slide for vascular lesions will display those areas the are suspicious for these lesions. An additional different screening task will display those areas that might present cancer. Such a system will be probably implemented in a distributed manner such as a Grid [10].

Texture analysis

Texture and texture analysis should be clearly distinguished from structure and its evaluation. Structure is created by the spatial arrangement of objects, and requires external knowledge. Texture is a pixel based gray value distribution and not related to any external limitations or setups [13,15]. The definition of a texture is often crude and not reproducible [19], detailed definitions are related to recursive formulas or locally dependent and independent image transformations [27]. Well known are Fourier, Hough, Hadamard transformations, or those that follow gradient properties such as thinning, erosion, dilation, *etc.* [27]. The advantage of texture analysis is its evaluation of solely image related features without any pre-existing knowledge, its disadvantage is its strong dependence upon image size, and results that are commonly only useful for image comparison (for example between images belonging to different diagnoses). Application of texture analysis has been reported to distinguish between images of different lung cancer cell types, mesothelioma versus metastatic carcinoma into the pleura, and cancer cell types of various origins [12]. It is of substantial value when creating automated diagnosis algorithms [20].

Segmentation algorithms

After standardization of the virtual slide, confirmation of gray values suitable for segmentation, and automated assessment of the most appropriate magnification, the image objects have to be identified in type and position. Histological images are composed of two different non overlapping spaces: 1: those that might but not necessarily have to contain objects (object space), and 2. those that will not, i.e., the so called back-

ground. [11]. A simple gray value thresholding is often sufficient to determine the object space, which is then subject for object segmentation and identification. Known object features allow the object identification, object segmentation often requires artificial extension (deletion) of detected units that might represent objects. This procedure is similar to the application of external knowledge and uses features and spatial arrangement of already identified objects to complete detected items within the object space [11]. All different algorithms applied by several authors try to detect the object boundaries [19]. The authors use a method related to non random dynamic sampling, a method that work with variable gray value limits of the proposed object boundary combined with features of neighboring, already clearly identified objects. The method is described in detail in [11], and is implemented in the electronic automated measurement user system (EAMUS, www.diagnomx.eu).

Structure analysis

The spatial position of objects (which can be of different types) forms the basis to further analyze the structure. Structures are derived from "the position" of objects, which can be spatial or associated to any feature [19]. They require a neighbourhood condition and a mathematical procedure for its analysis. Most frequently Voronoi's tessellation and graph theory approaches are applied [26,27]. The method results in a set of features that can be used to build up new objects (for example glands formed by goblet cells), that can be considered as "new objects at a different magnification level", and serve for feature extraction as described above. The algorithm has been called orders of structure [12]. It is related to symmetry operations and reaches in normal glandular organs several levels in contrast to common cancer [12].

Statistical analysis for automated diagnosis

Numerous authors reported a close relationship between measured features of objects, and structures with different organs, commonly diseases of the same organ [2,4,5] Less frequently texture parameters have been analyzed [25]. The statistically significant features are often described in detail; a practical use of the reported results is, however, missing to a great extent [12]. Every approach of deriving a diagnosis from results based upon image measurements should be aware that the detected discriminating features are of little practical value, and, therefore, only important if they are relevant for disease explanation or classification. If the statistically significant features are only important for the specific task, they can be exchanged and replaced by others in a different task. The more

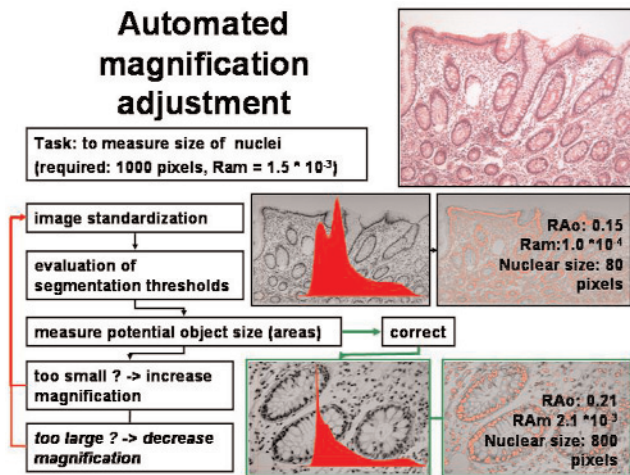


Fig. 5. Algorithm of automated optimum image magnification applied for object segmentation and measurement.

practical approach is then to forget about the specific meaning of any feature, and focus only on its statistical significance for the individual approach. The measures of objects, structures and textures are limited, and comprise together about 120 different features. The selection of those features that contribute for distinguishing the different diagnoses is performed according to the highest significance of the individual features with a maximum number of five features per dimension (object, structure, texture). The remaining features disregarded for the specific task, unless they improve in significance during the experiment. The contribution of a specific feature to separate diagnosis A from diagnosis B may be completely different for separating diagnosis C from diagnosis B.

The procedure permits an automated and flexible selection of those parameters that are introduced into the diagnosis classification process.

Automated diagnosis assessment

The selected significant features serve for the final disease classification. The most frequently used statistical classification methods are 1. multivariate analysis, and 2. neural networks. The efficiency of both methods has been reported to be similar; there are teams that prefer neural networks, others prefer multivariate discriminate analysis [27]. Classification based upon multivariate analysis offers the possibility to apply different classification schemes (classifiers), such as error correction method, hierarchic classification, or parallel epipedon classification.

All classification methods require a learning set that serves for computation of an n-dimensional space that classifies the disease. The test cases are then grouped according to these boundaries, and can serve

Cohorts

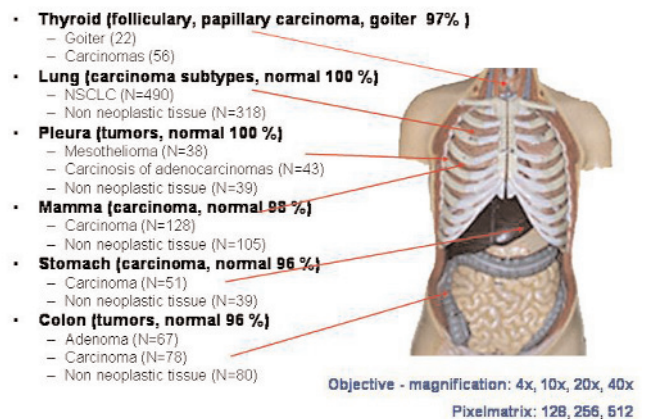


Fig. 6. Results of automated prospective disease classification in different organs by application of the same algorithm.

for further calculations too. Such a system is self-learning and can adjust itself to any future changes [15].

Preliminary results

A model of the described system has been computed and tested for diseases of several organs, which are listed in Figure 6. The aim was to introduce the system for tissue screening purposes, and most of the classifications differentiate between cancer and "normal", *i.e.* non-cancerous tissue. The corresponding results are shown in Figure 6. Only 10 cases per diagnosis group were randomly selected from the basic cohorts. The specificity of the applied system was computed to range between 95% and 100%. Even difficult to diagnose images were correctly classified (mesothelioma versus metastatic adenocarcinoma of pleura).

Discussion

Without any doubt surgical pathology undergoes great changes in workflow and diagnostic challenges. Molecular biology approaches and gene analysis have led to a new understanding of several diseases combined with newly developed therapeutic strategies. These methods focus on functional aspects that are usually not assessable in the light microscopic range. One should, however, keep in mind, that the structural arrangement of the biologically most important units, the cells, requires a strict and sensitive regulation that derives from the molecular biological functions. A detailed and reproducible analysis of object and structure features can be an appropriate (and cheap) tool to direct those investigations that are time consuming and expensive.

It seems to be appropriate (if not necessary) that the implementation of an automated diagnosis or pre-screening system consists of several modules that should work independently from each other. To start with, a control and evaluation of the objective image quality is necessary [20]. An evaluation of subjective image quality might be neglected at those levels that do not include human image evaluation. It can be adjusted to the needs of the pathologist at the stage of diagnostics.

The sequences of next two modules of search for diagnostic relevant fields of view and computation of possible thresholds for object detection can be left open. It seems more appropriate first to define the number and value of thresholds; however, the opposite sequence of searching for fields of view and afterwards defining the thresholds might be more efficient. The sequence probably depends upon the clinical task, the kind of tissue specimen, and the laboratory conditions. To our knowledge no investigations in this question have been performed until now.

Object-, structure-, and texture derived features contribute in a different manner to the assessment of a diagnosis [12]. Texture derived parameters strongly depend upon the image size, which should be kept constant within the system [13,14]. Dependent upon the available computation power the image size could be set to 2 k×2 k pixel; however an image size of 0.5 k ×0.5 k pixels was sufficient in our measurements [15]. Quadratic images sizes are mandatory to applying specific transformations such as Hough or Hadamard transformation [27].

Structure derived features such as structural entropy or current of structural entropy are less dependent upon the image size; however, it should be kept constant too [27]. The image size should not be chosen below 0.2 k × 0.2 k pixels; the number of objects should exceed 100 objects per object class (for example cell type). Structure analysis based upon graph theory approaches has been reported as really powerful method to estimating survival in patients with cancer of various origins and cancer stages [12].

Object derived features are measured on the basis of the space (in pixels) an object covers [20]. Thus, the magnification or size of an object within the image (and object space) is the main criterion of accuracy. Objects covering only 102 pixels possess a circumference of about 20 pixels. Due to digitalization each of these pixels present with an accuracy of only $\sqrt{2}$, thus, the expected error of this experiment would range between 10 – 15%. Therefore, object sizes should possess an area >103 pixels allowing a measurement accuracy of about 3% [20]. These calculations explain the object magnification (×20) which is mainly used in conventional microscopy viewing cells (quite seldom

Table 2. A general use of automated pre-screening in virtual slides can be expected in the near future.

Present stages of testing and implementation of automated diagnosis modules	
Image standardization, quality control	available
Image pre-analysis for segmentation	available
Automated image magnification	available
Automated selection of fields of view	test phase
Texture analysis	available
Object segmentation and identification	available
Structure analysis	available
Automated classification algorithms	available
Continous monitoring and readjustment of results	test phase

an object *40 is chosen), and the most significant contribution to discriminating between different diagnoses in multivariate analysis [15].

The final step of diagnosis assessment is a statistical approach that calculates the differences between the measured features and classifies the diagnoses according to these results. In the literature, numerous data have been published of object derived features that discriminate between several diseases with a great statistical significance [1,3] Unfortunately nearly none of these systems has been practically applied in routine diagnostic work [19]. The reasons are subject for speculations, such as non available measurement system, inadequate user performance, difficulties in implementing such a system into the daily workflow, or image sources of different properties such as broad variety in staining, fixation, etc. In addition, most of the reported classification systems such as neural networks, or multivariate discriminate analysis (and its variants) are constructed in a non flexible manner; i.e. the expect data sets that remain constant in their roots (image features and other data). This is correct in limited experiments; however far away from any routine experiences. Therefore, any classification system to be introduced into routine laboratory work has to take into account remarkable changes in its data input sets. In other words, it has to be a self learning and adjusting system [1,2,17,20]. It should be noted that this idea is different from the so – called self adjusting neural networks that adjust themselves to a boundary to that the input data and their outcome must convert. To our understanding the meaning of a self learning classification system adjusts the "rules" to a given final outcome (for example the weight of input data according to their "input age", and the creation of a "new diagnosis" if a final classification cannot be obtained after several

approaches and obtaining several similar situations [15]. Such a system will remain stable (*i.e.*, keep its installed diagnoses) and expand its knowledge in the future. Thus, it is close to human performance of gathering ideas and knowledge [15].

A summary of the supposed input modules and the present stage of testing and implementing is given in Table 2. Most of the modules have been tested in still images of various sizes with pre-selected image areas. The significant module of automated assessment of the most significant field of view is in its test phase, and preliminary results are promising [20]. A different approach of Oger et al. using fraction analysis has to be mentioned here too [24]. This approach offers a new strategy and should be tested in future too.

There are good reasons to believe that automated slide screening and automated diagnosis assessment will be available in the near future. No pathologist should be afraid in losing his position due to these changes in pathology: To the opposite: his knowledge, advise and supervise will become more important. In addition as tissue based examinations will grow rapidly and faster than the number trained pathologists, such systems will liberate our colleagues from the growing amount of "easy to diagnose" cases and will give them the necessary, at present often not available time to focus on those cases which need them the most: patients suffering from unusual, difficult to diagnose diseases.

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