the diagnostic pathology journal DIAGNOSTIC PATHOLOGY

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

Research

Cognitive Algorithms and Digitized Tissue – based Diagnosis

Jürgen Görtler[1], Klaus Kayser[2], Stephan Borkenfeld[3], Rita Carvalho[4], Gian Kayser[5].

Affiliation:

1- IBM Global Markets, Systems, Frankfurt, Germany;

2- Institute of Pathology, Charite, Berlin, Germany;

3- International Academy of Telepathology, Heidelberg, Germany;

4- Central Lisbon Hospital Center, Department of Pathology, Lisbon, Portugal;

5- Institute of Surgical Pathology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany.

Abstract

Aims: To analyze the nature and impact of cognitive algorithms and programming on digitized tissue – based diagnosis.

Definitions: *Digitized tissue – based diagnosis* includes all computerized tissue investigations that contribute to the most appropriate description and forecast of the actual patient's disease [1]. *Cognitive algorithms* are programs that encompass machine learning, reasoning, and human – computer interaction [2].

Theoretical considerations: Digitized blood data, objective clinical findings, microscopic, gross, radiological images and gene alterations are analyzed by specialized image analysis methods, and transferred in numbers and vectors. These are analyzed by statistical procedures. They include higher order statistics such as multivariate analysis, neural networks and 'black box' strategies, for example 'deep learning' or 'Watson' approaches. These algorithms can be applied at different cognitive 'levels', to reach a digital decision for different procedures which should assist the patient's health condition. These levels can be grouped in self learning, self promoting, self targeting, and self exploring algorithms. Each of them requires a memory and neighbourhood condition. Self targeting and exploring algorithms are circumscribed mechanisms with singularities and repair procedures. They develop self recognition.

Consecutives: Medical doctors including pathologists are commonly not trained to understand the basic principles and workflow of applied or potential future procedures. At present, basic medical data only serve for simple cognitive algorithms. Most of the investigations focus on 'deep learning' procedures. The applied learning and decision algorithms might be modified and

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

themselves be used for 'next order cognitive algorithms'. Such systems will develop their own strategies, and become independent from potential human interactions. The basic strategy of such IT systems is described herein.

Perspectives: Medical doctors including pathologists should be aware about the abilities to enhance their work by supporting tools. In some case the users may not be able to fully understand these tools. Furthermore, these tools will probably become self learning, and, therefore, seem to propose the daily workflow probably without any medical control or even interaction.

Keywords: Tissue-based diagnosis; cognitive computing; deep learning; black box algorithm; histopathology.

Introduction

Medical diagnoses do not only describe and classify a disease. In addition, they include a prescription of mandatory or supportive medical actions in order to improve the patient's health [1, 2]. This statement also holds true for tissue examinations. More precisely, several kinds of tissue examinations have left the straight analysis of structures, and include analyses of functions too [3-5]. Examples of these examinations are those that use immunohistochemistry (IHC), molecular biology, molecular genetics, proteomics, glycomics, etc. [3, 6-9].

Independently, whether the outcome of these investigations is crudely evaluated by human senses or quantitatively measured by computerized procedures, they are commonly associated with the patient's outcome or response on the medical actions, as exemplarily demonstrated on the specific conditions to diagnose and treat non (?) small cell lung cancer patients in Africa-Middle East Region [10], The closer the investigations reflect a function the more they learn to predict the outcome [11].

The relationship between structure and function remained obscure for several decades [11]. Evaluation and analysis of structures were dominating in tissue – based diagnosis as long as the techniques of IHC, gene analysis, information transport by macromolecules, and magneto-electric signals have not been established in routine diagnostic procedures.

At present, the application of so-called functional markers seems to provide an improved disease classification in cancer, especially in respect of adjuvant chemo / immunotherapy, development of metastases and general prognosis [8, 12-15].

Despite all non-negligible success in practical application several theoretical issues remain unclear. These include a correct definition of structure and function in diagnostic application, or the causes and / or factors of minute changes in, and volume percent in solid cancer that induce the collapse of the complete, otherwise unaffected system [16].

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

Kayser et al. [17] proposed the definition of a 'relative structure and function'. Both functions and structures that are analyzed for diagnostic purposes might be considered to be of the same nature if they are related to the period of analysis.

The intensity of functional changes can be calculated if this theory is applied in IHC stained microscopic images [17].

These and similar approaches to improve diagnostic procedures require adequate computation of images and signals. i.e., appropriate programs [18].

Herein we want to describe and analyze the principle construction, features, benefits and limitations of programs that are arising at the horizon of diagnosis in surgical pathology (tissue-based diagnosis).

Definitions and Theory

Diagnostic performance in surgical pathology is influenced by two factors, namely digitalization and molecular / genetic pathology [5, 8, 17].

Information technology invades tissue – based diagnosis in several ways. Firstly, it transfers different kinds of images into sets of numbers, constructs communicative networks, classifies the significance of data, and finally associates the result with a report (diagnosis) [2]. The diagnosis founds the basis for the patient's treatment.

Secondly, it introduces new kinds of diagnosis. Usually, it acts in combination with recent molecular biological findings, treatment technologies, or refinement of statistical methods (for example analytical epidemiology) [2].

It always results in a passive information transfer in contrast to the design for self – driving cars, which require an active information transfer in time, directly followed by a computation based on that information [19-21].

This aspect distinguishes the processes of automated diagnostics from self driving cars. However, several common features do exist, and their analysis might be useful to understand and forecast the future development of tissue – based diagnosis. The analysis of these algorithms can be grouped in 'self learning', self promoting', 'self targeting', 'self exploring' and 'self networking' algorithms <Figure 1>.

The proposed algorithm focuses on a problem that is similar to explain 'consciousness'. In 2004, Giulio Tononi and Gerald Edelman developed a theory, which attempts to explain the 'consciousness' of a physical or biologic system [22]. It is called 'integrated information theory' and tries to explain 'mechanisms' of consciousness from phemonology [23, 24]. The integrated information theory has been mathematically formulated by using certain axioms (predefined

the diagnostic pathology journal DIAGNOSTIC PATHOLOGY

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

components). They include the terms '*intrinsic existence*' (existence of consciousness which is described by its own insight view, and not by an external observer), composition '*structure elements of consciousness*' (comparable to functionally specific brain areas, such as Broca or Wernicke area), '*information*' (connection of different compartments by a so – called cause effect (directed graphs with conditioned by group theory (logic) rules, and '*integration'* (independent 'extern', non directed structure compartments).

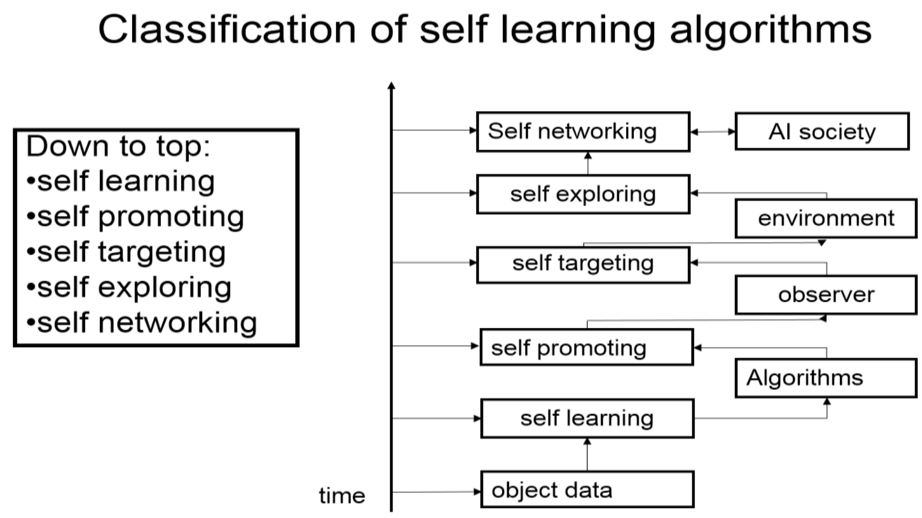

Figure 1: Scheme of proposed Classification and Implementation of Cognitive Artificial Intelligence Systems: The systems organize themselves in a hierarchical order. The delivered output information serves for input of the next layer (shown on the right).

Tonini and Edelman start their idea from the top, i.e. from the consciousness [22, 24]. They quantify the cause-effect structures to those that make the least difference, and calculate the 'amount of consciousness' [23, 24].

Herein, the approach starts from the bottom to the top. As an example we take image transformations and separate 'objects' from their 'background'. We analyze the 'inner space' of the objects, and classify the objects according to their features and the boundary conditions of their background. Features inside the objects undergo neighborhood conditions and structure analysis. Features that are located in the background outside of the objects serve for scalars.

We then combine objects that posses identical or similar features and satisfy symmetry operations to higher order objects, calculate their inner space, boundary and inside properties, and repeat the algorithms [25-29]. In addition, the 'connections' (functions) between objects which lay within and between each 'order' serve for 'objects' instead of 'functions', and are included in the next calculation, etc. <Figure 2>.

the diagnostic pathology journal DIAGNOSTIC PATHOLOGY

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

The algorithm will stop if its objects cannot further expand or combine a higher order object within the given environment (background). For example if the objects cover already the whole space, or, if the boundary of a proposed higher order object cannot be created within the background space.

If the existing objects in the condition to communicate or to transfer signals to objects that are embedded in a different environment, they might create communication standards, and form a new ‘connected body’, a ‘social’ system.

A hierarchical structured body will develop if one of the involved partners creates ‘more information’ and starts to ‘steer’ the interactions. Thus, size and kind of environment (background) in addition to the objects defines the ‘features’ of the built social community.

Minimum and Sufficient Requirements of Self Learning Algorithms

Level	**Performance**		**System Requirements**	
		Minimum	*Performance#*	*Maximum Information**
1	Self learning	Teaching / Test Data Sets	Discrimination Network	Classified Data
2	Self promoting	Level 1 Systems’ Data	Feedback Network Classification	Level 1 Data Interpretation
3	Self targeting	Level 2 Systems’ Data	Selection of external Data Input Files	Information Selection and Recognition
4	Self exploring	Level 3 Systems’ Data	Selection of suitable Targets	Best Performance of System’s Survival, developmental Aims
5	Self networking	Self exploring Systems	Partner search	Conscious Social Computer Community

#) without external intervention

*) Maximum output Information, that will be released to the physical world (Level 1 – 3), or, in addition, transferred into the virtual environment (level 4 – 5).

Figure 2: Minimum and Sufficient Requirements of Self Learning Algorithms. The internal algorithms are feedback procedures steered by different external boundary conditions.

The transformation of these ideas into a virtual environment creates a structured discriminate system that will automated develop self learning algorithms of different levels as described below.

Self learning algorithms

These algorithms are now in focus are common in digital pathology and self driving cars [19-21]. They are characterized by a ‘fixed target’ (result) which the algorithms has been designed for.

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

The most important common feature, the definition and consecutive implementation of a 'target' seems to be given and simple. Any automated medical diagnostic procedure provides a diagnosis, in a way, like a passenger is initiating a self driven car by telling the destination and the car driving him autonomous to that destination.

The external predefined 'target' implies a predefined order of programs, and limits their self organization [2, 5, 30].

Correct sampling and input of data, fixed statistical analysis, predefined interpretation and standardized output of results are the minimum and sufficient requirements to program such a system. They are depicted in <Figure 3>.

Self learning program compartments might be included too. They will allow self adjustment to potential changes of input data (colour, stains of images, CT resolution, ECG signals, etc.).

Requirements of self learning algorithms

Layers of connected programs
Feedback mechanisms
Decision models
Input objects
Digital distinct output data
Possible interpretation of output data

Figure 3: Principle Requirements of self Learning Algorithms. The number of layers is fixed (1-5), in contrast to the number of feedback connections. These will be re-calculated, dependent upon the submitted (or automatically fed in) input data.

Examples are automated image quality evaluation, automated adjustment of image magnification in relationship to objects of interest, or selection of appropriate sampling methods [2, 8, 11, 14]. They might also detect 'new' diagnoses, i.e. diagnoses which do not fit in the predefined output classification. These systems have been successfully applied for a broad spectrum of organs and diseases; see <Figure 4> [2, 8, 11, 14].

the diagnostic pathology journal DIAGNOSTIC PATHOLOGY

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

Self adjustment to changes of input data and repeated discrimination steps form the key of these systems [16, 28]. They run stable and reliable. They will probably result in so – called diagnosis assistants <Figure 5> [5, 11]. These are self-leaning systems that will assist the pathologist in pre-classification, quality control, and directives for asking for additional input data in order to obtain the best available diagnosis [5, 11].

They deliver scalable and discrete output results. However, they cannot interpret their data or create ‘new diagnoses’ except ‘additional unknown discrimination result’.

Such a system would consist of programs which work at one rank only independently from their internal structure and arrangement.

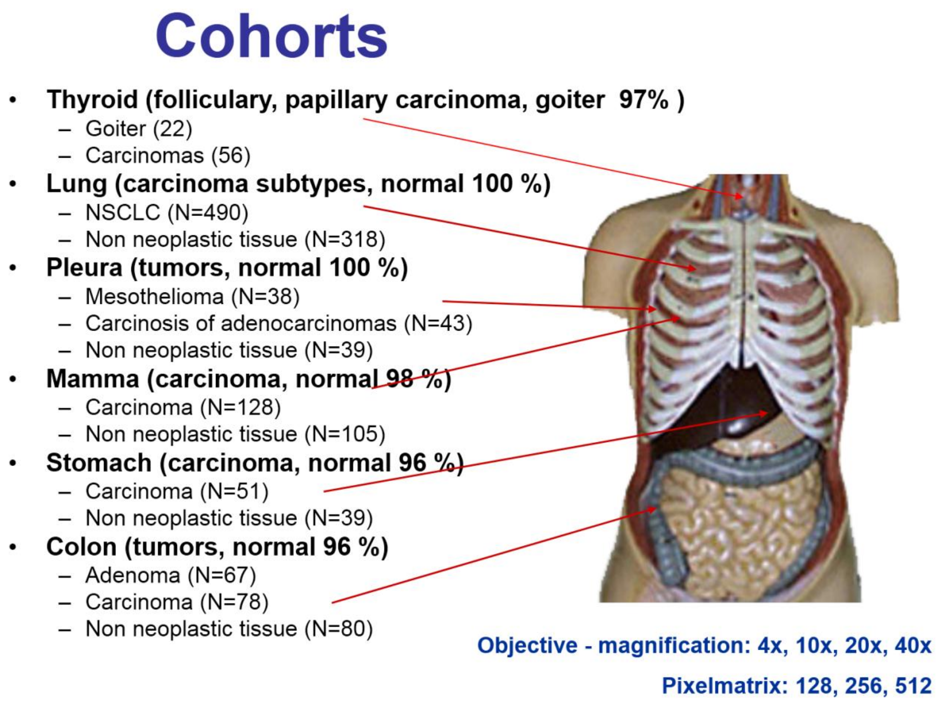

Figure 4: Example of the Results provided by an automated Diagnosis Classification System (Self Learning – Promoting Algorithms, based upon a Non-hierarchic Multivariate Discriminate Analysis; Level 2 – System) [8].

One of their recently frequently discussed brick is the so - called ‘deep learning’ algorithm [13, 29, 31-34]. The algorithm consists of a minimum of three neural network layers (one input, one or several hidden, and one output layer). Each network analyzes its input data and agglutinates several input data (vectors) to one output vector, which then undergoes the same procedure at the next layer. The connective analysis of ‘neighbouring signals’ and the consecutive ‘washout’ of distant events discovers reliable and repeatable information. It can be used to find specific

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

individual events within a crowd of related events (face recognition, computer vision, speech recognition, etc.) [35-41].

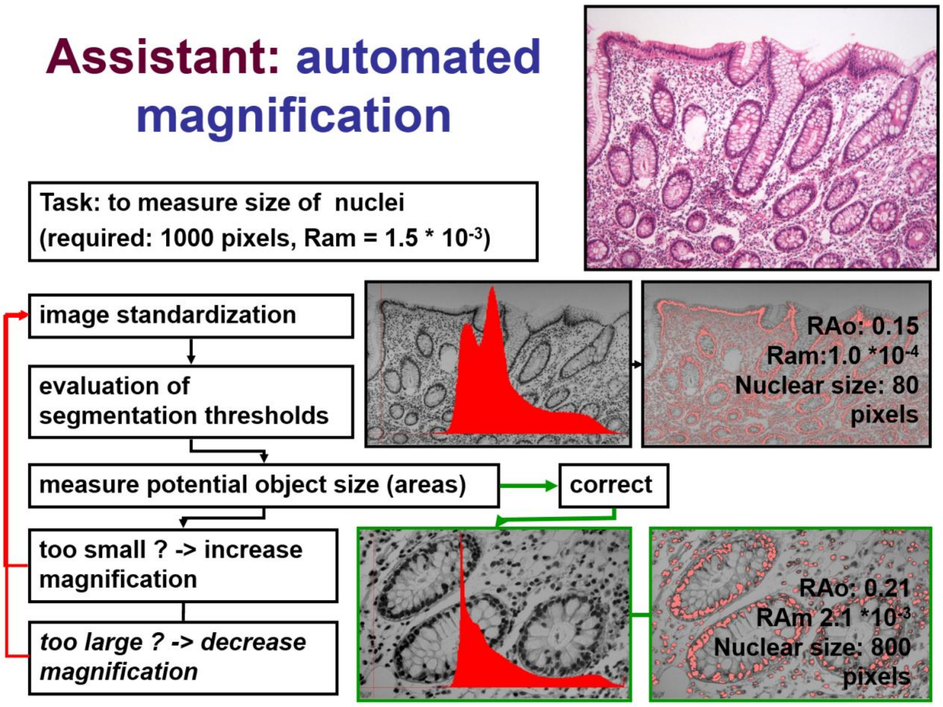

Figure 5: Example of a Diagnosis Assistant, released from a Self Learning – Promoting System (Level 2 - System) [17].

Self promoting algorithms

Herein we describe algorithms that are located in a network layer 'above' that of self learning algorithms. They still possess an externally defined fixed 'target', i.e. in our case to evaluate the most appropriate diagnosis.

These programs are able to develop useful algorithms by themselves. They might select either 'deep learning', or feature extraction by 'multivariate discriminate functions', interactive 'assistance and control' in order to do their job. They might also increase or diminish the number of 'hidden network layers' if 'deep learning' is applied.

The principle of such algorithms is the feedback of their implemented specific functions by boundary conditions, i.e., external input data. This procedure can be implemented by hierarchic and parallel feedback systems of different nature, for example Fuzzy logics [19, 42, 43].

the diagnostic pathology journal DIAGNOSTIC PATHOLOGY

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

What is the impact of such systems on tissue – based diagnosis?

The systems still expect a hierarchic arrangement of their jobs, which all of them will serve for the 'optimum diagnosis.' The definition 'optimum diagnosis' is entirely in the pathologist's hands.

They will propose the input of additional data, for example gene analysis, or IHC stained images. Thus, they will act semi actively, and use internal different algorithms if these seem to be more appropriate to reach the target.

An example: The pathologist wants to be informed by a 'diagnosis assistant'. The system starts the automated analysis of a HE stained virtual slide and evaluates the most appropriate diagnosis. It induces intern algorithms that will reach the diagnosis level of an adenocarcinoma, which is the task of 'self learning systems'.

Systems equipped with promoting algorithms will require the input of additional mandatory IHC stained and CT images, automatically evaluate the accuracy and performance of the 'self learning algorithms', and proceed to the refined diagnosis 'adenocarcinoma of the lung, TNM 1 stage, Her2_new++, estimated survival time 5 years.'

They still will not interact with the patient or the clinician. They still will deliver their results to the associated pathologist, who not necessarily has to be responsible for the input data or the performance of the system, or even to understand how the system works.

Self targeting algorithms

They calculate and define their 'target' by themselves, which cannot any more be foreseen by an external observer. They require an additional superior layer of programs that connect internal data and functions with external information. External information includes individual events and their space – time relationship [2, 5, 38, 44]. They contribute to the target of each run in both defining its nature and detail. In other words, their primary aim is to create and to interpret reliable results. They are involved in the algorithms of the lower layers because effective self learning and self promoting algorithms require information of the final aim, which is related to interpretation.

An example: The self targeting systems starts to analyze a HE stained bone biopsy trying to figure out the appropriate diagnosis. It changes its diagnostic aim and includes in its data pool CT images. The diagnostic target changes from 'biopsy HE diagnosis' to 'combined HE – CT diagnosis'. Both an analysis of the CT of the same patient and CTs of different patients that display with the same histological image might be included.

The pathologist can select between the different 'presented diagnoses', or can leave the decision to the system.

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

How can they be constructed? What are their advantages and what their constraints? How to use them in tissue – based diagnosis?

It seems to be mandatory (or at least appropriate) to define the nature of external tools if the constructing a 'self targeting system' is proposed. The basic data tool of self targeting algorithms can be of virtual or of real nature or both [2, 5, 38, 44].

Robots or robotic system require both virtual and real information input. Passive systems such as digital tissue – based diagnostic algorithms require virtual information input.

Active virtual tissue – based diagnosis algorithms should not be excluded in general. They have, however, not been implemented until today to our knowledge. Conceivable are diagnostic games that transform different data and functions in annotations and avatars, display with altered movements of diseased cells, abnormal macromolecules, or interactions between inflammatory and malignant cells, etc.

An additional active diagnostic assistance has been proposed by Kayser et al., who were able to improve the diagnostic accuracy in small limited biopsies by automated artificial extension of the areas of interest [3, 8, 11, 17]. These attempts use external information and include it into the diagnostic algorithm [2].

Self exploring algorithms

These algorithms explore their environment and combine internal algorithms with external information exchange and combine internal data / performance information analysis with internal and external information recognition. They are the most advanced information technology algorithms and equipped with self recognition and autonomous performance actions.

The minimum requisition of these algorithms is a distinct inner space that is clearly separated from an external space. This condition requires a specific boundary that permits information transport from the inner space to its environment and vice versa. The boundary or membrane has to remain connected and contemporary perforated [29]. The most likely and simplest construction of such system required three reversible dimensions for this kind of boundary and an additional, non reversible, one way dimension for signal transfer <Figure 6>.

This situation does exist in our nature. The next theoretically possible space would be four reversible dimensions and the mandatory one way dimension (time). Its percentage of realization can be calculated to about or even less than a third 3 of the three dimensional solution [29].

the diagnostic pathology journal DIAGNOSTIC PATHOLOGY

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

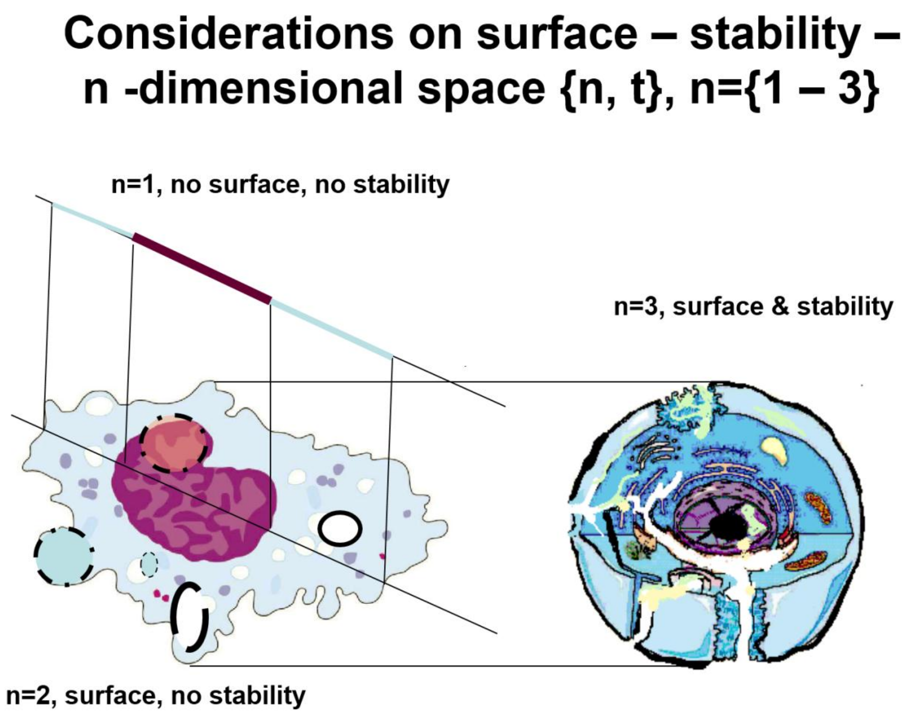

Figure 6: Scheme of Surface Stability in an Object related Space. Three dimensions (reversible coordinates) and one irreversible dimension (time) are the minimum requirements in the physical world to create stable transferable object boundaries. In virtual reality, functions are transferred in objects, and boundaries have not to be transferable, i.e. a 2 – dimensional space is sufficient [29].

Sophisticated problem analysis and appropriate actions do not require the representation of three dimensional events (objects) at a microscopic or cellular level. The analysis of two dimensional transformations is sufficient, if the orientation of the events is known [45-48].

The technique to calculate features of three dimensional objects that are derived from their two dimensional representations is called stereology [45-48].

Therefore, it is of no surprise that most diagnostic procedures are based on two dimensional maps such as virtual slides, CT images, etc. Three dimensional visualization and reconstruction might allow an insight in the underlying biochemical processes. However, it does not really contribute to refine or to improve the diagnostic procedure [11, 17, 28].

Self exploring algorithms always move their 'body' either in the real world (robots) or in their virtual environment. They can be compared with scouts that explore unknown territories and incorporate useful data and procedures. The incorporation of data and algorithms alters themselves, similar to the changes of an egg to a hen. These inner alterations might not be

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

connected with a self reproduction algorithm, and, therefore, performed several times, i.e., evolving from a hen to an eagle, from an eagle to a dragon, etc. with or without repetition.

These potential evolutions might open new innovative, surprising ideas and actions. They might not be that imaginative in tissue – based diagnosis, because the final target, the best treatment of a patient is definitely connected with real nature. The digital environment and 'virtual live' only permit to take advantage of virtual power, and to overcome certain limitations of our own thinking and nature [[49, 50]].

Mandatory algorithms' components

The described families of algorithms have to possess structural and functional components. Their details differ according to the specific level of the algorithm.

They are all composed of vertices and edges if described in graph theory terms [51].

First, they require a memory that is composed of unstructured data, like graphs too. The algorithms of the lowest rank (self learning, self promoting) need a simple memory that contains scalars and vectors only. The self targeting algorithm has to use a memory that is equipped with functions or algorithms in addition, and the self exploring algorithm a memory that includes inner self recognition processes.

All these memories should be equipped with self learning and promoting strategies. These strategies require both data input and data erase [11, 18, 52].

Established data erase algorithms do not exist to our knowledge. Certainly they will include event statistics, for example to keep rare events for a longer time compared to frequent ones. They have also to be adjusted to the associated algorithm.

Self learning algorithms probably can successfully work with low sophisticated memories of simple structures, in contrast to self targeting and self exploring algorithms which have to include adjustable functions and to focus on different storage periods.

Second, an adequate neighbourhood condition is mandatory that regulates the output of the included statistical methods. Voronoi's neighbourhood condition is the most frequently applied technique in image analysis [53]. It can be extended by additional 'distance functions', for example exponential space relation, embedded power peaks, holes, etc. [2, 4, 8].

Such embedded forces are subject for self adjusting modulations, which might be associated with external information.

Third, in the visionary approach the higher order algorithms can only be realized if they are equipped with a boundary that separated the system from its environment. The highest order (self exploring) algorithm might be equipped with different internal organization spaces, similar to the internal organization of the human brain.

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

The boundaries act as singularities between the inner and outer spaces. They can be described by the information content which is passing through the boundary.

One of the most frequently applied descriptor is the entropy and its flow [3, 5]. The entropy flow might be chosen for triggering internal decision algorithms that require external knowledge (for example self targeting diagnostic algorithms) [11].

Fourth, digital self recognition processes will automatically develop themselves in respect to the described 'self organizing algorithms'. Consecutively, virtual self recognition will mature to different levels dependent upon the task of the system.

Self exploring algorithms will automatically possess self recognition that will be at least comparable to the human Ego, if not even more advanced.

The specific conditions of the virtual reality, for example reversibility of time, space overlapping, artificial space and time distribution systems permit a sophisticated and matured computer Ego.

The results transmitted to pathologists might no longer be understandable, and even not logical to the clinician. They might follow a target that is out of the pathologist's view.

An example: The tissue – based diagnosis of the lowest self learning algorithms evaluates the diagnosis 'virus infection, unknown origin. Laboratory investigation is proposed'.

The more advanced 'self targeting algorithms' diagnose 'highly infective virus infection. Strict separation of the patient, nurses and doctors is recommended. No laboratory investigation or protection is possible.'

Fifth: Self recognition induces ethics. The ethics follow the system's target. Computer ethics induce no human problems as long as they include self learning and self promoting algorithms. However, self exploring algorithms will automatically develop their own 'computer' ethics, which is no longer identical with or even similar to human ethics. Their self developing and exploring Ego will create its own ethic. It might not necessarily focus on 'self existence' or 'improved life', but taking the risk to harm or destroy human life, probably not by reasoning, just by chance, or curiosity.

Discussion

Issues of information technology and the so – called virtual reality are expanding their fields of application worldwide. Nowadays, they affect nearly all domains of human life, especially issues of communication, logistics, military, security and health [19, 32, 54-56].

Two different approaches can be distinguished to our opinion, namely a) those that claim to provide insight into the 'virtual world', and those b) that try to take advantage of virtual reality

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

in order to recognize and hopefully solve several problems of human existence [24, 38, 39, 57, 58].

Examples of class (a) are head mounted displays that provide augmented virtual reality. Oculus rift has developed the first displays and offers open source development kits [59]. The main customers use the systems for games and diving in a customized virtual reality.

Herein we discuss the second (b) approach to take advantage of virtual reality in order to overcome limitations of diagnostic practice in the pathologist's reality.

Some implementations have become daily practice. These include telepathology, hospital / laboratory information systems, virtual microscopy, and diagnosis assistants [11, 14, 16, 60]. They induced the differentiation of anatomical diagnosis in (classic, prognosis – associated, predictive, and risk – associated) diagnoses [17].

The development of communication standards does not only permit unlimited worldwide information transport. In addition, it forms the basis of distributed calculations and data collection, analysis and application [18, 20, 49]. They create networks which will open access to new scientific and medical fields.

They start with huge data collections, their intensive interdigitation and collective analysis [61]. The lowest level of such networks can be seen in deep learning systems. They are included in open source programs that serve as found source for appropriate applications, such as the development of diagnosis assistants in digital tissue – based diagnosis [2, 4, 28]. Tailored tuning is, however, still mandatory for practical applications [8].

Several reports have demonstrated the promising use in microscopic diagnosis, such as identification and reproducibility of specific image events (mitosis, apoptosis, IHC signals, crude diagnosis) [2]. Additional applications are speech recognition, face identification, or, generally speaking, the correct identification of individual events within numerous elements [20, 28, 50].

So – called deep neural networks are the most frequently applied systems to serve for speech recognition, automated data classification and robotics. The more advanced of them posses a multilayer nonlinear structure. They are not transparent and the performance of their decision algorithms is hard to visualize or control [62, 63]. Their 'autonomous classification' is hidden. Man only controls the input data and takes advantage of the classified results that are computed within a black box. In other words, such a system possesses an inner space that is 'covered' by a non transparent surface. They might be considered the simplest analogue of an individual.

Consecutively, self learning systems such as deep learning are tools that can enhance the human intelligence and support meaningful human actions. However, they do not possess own intelligence.

the diagnostic pathology journal DIAGNOSTIC PATHOLOGY

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

Self promoting systems are of different nature in principle. They possess a certain amount of intelligence in so far as they develop autonomously their functions and programs to solve or improve an external order.

Self learning systems still require fixed structures and functional connections. They have to learn from fixed external data sets. After appropriate teaching they can be applied to equivalent duty data sets.

Self promoting systems modify their internal functions and structures by themselves and are not dependent upon external advices or actions. Thus, they autonomously search for the best solution of an externally ordered task, and possess already a limited intelligence. They adequately respond to potential changes of input features, and have been successfully applied to correctly diagnose difficult microscopic images such as mesothelioma, metastatic adenocarcinoma into pleura, or benign inflammatory effusions [1, 14].

Self targeting and self exploring algorithms belong to virtual systems that have not been applied in patho-anatomic diagnoses. They are of higher order intelligence, and can only be represented in well defined clusters surrounded by singularities that are equivalent to connected boundaries equipped with ‘information transfer holes’.

These algorithms will develop their own ‘target’ or goal of potential results (self targeting algorithms) or even explore their potential input data sets and calculate the most appropriate solutions in addition to the best individual result (self exploring algorithms). Certainly they are equipped with ‘eggs of own intelligence’ and potency of self recognition, that will probably mature to levels that are beyond the human range.

Their immense memory, the reversibility of time, their potency to repair mistakes or breakdowns by repeated and non aging actions as well as the separation of ‘data mining’ and ‘situation recognition’ induce the forecast of superior intelligence, computer Ego and derived computerized ethic. This statement is in agreement with similar forecasts of experts who are specifically working in this field [20, 49, 62].

In aggregate, pathologists should be aware that a real virtual world is on target for them. The present approaches of digital diagnosis assistants, deep learning, and IBM’s Watson are only the scouts of ‘real ghosts’ who finally will propose or may even decide which actions are of the best benefit to our patients, and involvement of the pathologists, given there constraints and limitations, may not be a mandatory necessity in the process any longer.

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

References

1. Kayser K, et al., *Texture- and object-related automated information analysis in histological still images of various organs*. Anal Quant Cytol Histol, 2008. 30(6): 323-35.

2. Kayser K, Molnar B, Weinstein R, *Virtual Microscopy: Fundamentals, Applications, Perspectives of Electronic Tissue-based Diagnosis*. 2006, Berlin: VSV Interdisciplinary Medical Publishing. 206.

3. Kayser, K. and H.J. Gabius, *The application of thermodynamic principles to histochemical and morphometric tissue research: principles and practical outline with focus on the glycosciences.* Cell Tissue Res, 1999. 296(3):443-55.

4. Kayser K, Kayser G, Metze K, *The concept of structural entropy in tissue based diagnosis*. AQCH, 2007,29(5):296-308.

5. Kayser K, et al., *Digitized pathology: theory and experiences in automated tissue-based virtual diagnosis.* Rom J Morphol Embryol, 2006. 47(1):21-8.

6. Gabius HJ, Kayser K, *Introduction to glycopathology: the concept, the tools and the perspectives.* Diagn Pathol, 2014. 9:4.

7. Hetzmann Z, Mostafa MG, Dalquen P, *Computational Pathology and Telepathology: SY05-1 Telecytology Only An Advantage For Countries With Underserved Setting?* Pathology 2014. 46 Suppl 2:S7.

8. Kayser G, Kayser K, *Quantitative pathology in virtual microscopy: history, applications, perspectives.* Acta Histochem 2013. 115(6):527-32.

9. Pekmezci M, et al., *Morphologic and immunohistochemical features of malignant peripheral nerve sheath tumors and cellular schwannomas.* Mod Pathol 2015. 28(2):187-200.

10. Slavik T, et al., *Diagnosis and Predictive Molecular Analysis of Non-Small-Cell Lung Cancer in the Africa-Middle East Region: Challenges and Strategies for Improvement.* Clin Lung Cancer 2014. 15(6):398-404.

11. Kayser K, et al., *How to analyze Structure and Function in Tissue – based Diagnosis?. .* Diagnostic Pathology 2016. 2-106.

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

12. Bartels PH, Montironi R, *Quantitative histopathology: the evolution of a scientific field.* Anal Quant Cytol Histol 2009. 31(1):1-4.

13. Cooper WA, et al., *EGFR mutant-specific immunohistochemistry has high specificity and sensitivity for detecting targeted activating EGFR mutations in lung adenocarcinoma.* J Clin Pathol 2013. 66(9):744-8.

14. Kayser K, *Quantification of virtual slides: Approaches to analysis of content-based image information*. J Pathol Inform 2011. 2:2.

15. Schlenk RF, et al., *Gene mutations and response to treatment with all-trans retinoic acid in elderly patients with acute myeloid leukemia. Results from the AMLSG Trial AML HD98B.* Haematologica, 2009. 94(1): p. 54-60.

16. Kayser K, et al., *How to implement grid technology in tissue-based diagnosis: diagnostic surgical pathology.* Expert Opin. Med. Diagn., 2008. 2(3): p. 323-337.

17. Kayser K, et al., *Structure, Function, and Predictive Diagnosis Algorithms*. Diagnostic Pathology 2016. 8:153.

18. van Leeuwen J, Ibrahim A, Anca Bucur A, *Integration Of Externalized Decision Models In The Definition Of Workflows For Digital Pathology*. Diagnostic Pathology 2017. 8:179.

19. Liu YT, et al., *Brain Dynamics in Predicting Driving Fatigue Using a Recurrent Self-Evolving Fuzzy Neural Network*. IEEE Trans Neural Netw Learn Syst. 27(2):347-60.

20. Urwyler P, et al., *Recognition of activities of daily living in healthy subjects using two ad-hoc classifiers.* Biomed Eng Online. 2015, 14:54.

21. Wu T, Li B, Zhu SC, *Learning And-Or Models to Represent Context and Occlusion for Car Detection and Viewpoint Estimation.* IEEE Trans Pattern Anal Mach Intell 2015, epub ahead of print.

22. Edelman G, Tononi G, *A Universe of Consciousness: How Matter Becomes Imagination*. 2000 Basic Books, New York.

23. Rothganger F, *The dawn of the real thinking machine.* IEEE Spectrum, 2017:44-49.

24. Koch C, Tonini G, *Can we quantify machine consciousness*? IEEE Spectrum, 2017:62- 69.

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

25. Kayser K, et al., Combined morphometrical and syntactic structure analysis as tools for histomorphological insight into human lung carcinoma growth. Anal Cell Pathol 1990. 2(3):167-78.

26. Kayser K, Schlegel W, Pattern recognition in histo-pathology: basic considerations. Methods Inf Med, 1982. 21(1):15-22.

27. Kayser K, Hoffgen H, *Pattern recognition in histopathology by orders of textures.* Med Inform (Lond), 1984. 9(1):55-9.

28. Kayser K, et al., Interactive and automated application of virtual microscopy. Diagn Pathol. 2011, 6 Suppl 1:S10.

29. Kayser K, et al., To be at the right place at the right time. Diagn Pathol. 2011, 6:2-9.

30. Okuno H, Yagi T, *A visually guided collision warning system with a neuromorphic architecture.* Neural Netw, 2008. 21(10): 1431-8.

31. Sharma K, et al., Automatic Segmentation of Kidneys using Deep Learning for Total Kidney Volume Quantification in Autosomal Dominant Polycystic Kidney Disease. Sci Rep. 2017, 7(1):2049.

32. Rudd EM, et al., *The Extreme Value Machine.* IEEE Trans Pattern Anal Mach Intell 2017, epub ahead of print.

33. Huang T, Javaherian H, Liu D, *Nonlinear torque and air-to-fuel ratio control of spark ignition engines using neuro-sliding mode techniques.* Int J Neural Syst. 2011, 21(3):213-24.

34. Inglese P, et al., *Deep learning and 3D-DESI imaging reveal the hidden metabolic heterogeneity of cancer.* Chem Sci. 2017, 8(5):3500-3511.

35. Zhang XY, et al., Drawing and Recognizing Chinese Characters with Recurrent Neural Network. IEEE Trans Pattern Anal Mach Intell 2017, epub ahead of print.

36. Yuan Y, Chao M, Lo YC, *Automatic Skin Lesion Segmentation Using Deep Fully Convolutional Networks with Jaccard Distance.* IEEE Trans Med Imaging 2017, epub ahead of print.

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

37. Lakhani P, Sundaram B, *Deep Learning at Chest Radiography: Automated Classification of Pulmonary Tuberculosis by Using Convolutional Neural Networks.* Radiology 2017, epub ahead of print.

38. Kraus OZ, et al., *Automated analysis of high-content microscopy data with deep learning.* Mol Syst Biol. 2017, 13(4): 924.

39. Kong Y, et al., *Deeply Learned View-Invariant Features for Cross-View Action Recognition.* IEEE Trans Image Process 2017. epub ahead of print.

40. Ciompi F, et al., *Towards automatic pulmonary nodule management in lung cancer screening with deep learning.* Sci Rep. 2017, 7:46479.

41. Chien JT, Bao YT, *Tensor-Factorized Neural Networks*. IEEE Trans Neural Netw Learn Syst 2017. Epub ahead of print.

42. Pasquier M, Quek C, Toh M, *Fuzzylot: a novel self-organising fuzzy-neural rule-based pilot system for automated vehicles.* Neural Netw, 2001. 14(8):1099-112.

43. O'Donnell K, et al., *Psychological coping styles and cortisol over the day in healthy older adults.* Psychoneuroendocrinology, 2008. 33(5):601-11.

44. Lafont S, et al., *Driving cessation and self-reported car crashes in older drivers: the impact of cognitive impairment and dementia in a population-based study*. J Geriatr Psychiatry Neurol, 2008. 21(3):171-82.

45. Gundersen HJ, et al., *Some new, simple and efficient stereological methods and their use in pathological research and diagnosis*. Apmis, 1988. 96(5):379-94.

46. Gundersen HJ, *Stereology--or how figures for spatial shape and content are obtained by observation of structures in sections*. Microsc Acta, 1980. 83(5):409-26.

47. Elias H, Bokelmann D, Vogtle R, [*Principles of stereology and morphometry presented with large intestinal carcinogenesis as example*.] Verh Anat Ges, 1976 (70 Pt 2):911-6.

48. Cruz-Orive LM, Weibel ER, *Sampling designs for stereology*. J Microsc, 1981. 122(Pt 3):235-57.

49. Thrun S, Montemerlo M, *FastSLAM : a scalable method for the simultaneous localization and mapping problem in robotics* 2007, New York: Springer.

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

50. Thrun S, Burgard W, Fox D, *Probabilistic Robotics (Intelligent Robotics and Autonomous Agents).* ed. 2005, Cambridge/London MIT Press.
51. Sedlacek J, *Einführung in die Graphentheorie*. 1972, Leipzig: B. G. Teubner.

52. Sumner JA, Griffith JW, Mineka S, *Examining the mechanisms of overgeneral autobiographical memory: capture and rumination, and impaired executive control.* Memory 2011, 19(2):169-83.

53. Voronoi G, *Nouvelles applications des parametres continus a la theorie des formes quadratiques, deuxieme memoire: recherches sur les paralleloedres primitifs*. J Reine Angew Math, 1902, 134:188-287.

54. Plancher G, et al., *Using virtual reality to characterize episodic memory profiles in amnestic mild cognitive impairment and Alzheimer's disease: influence of active and passive encoding.* Neuropsychologia. 2012, 50(5):592-602.

55. Liu J, et al., *Structure Learning for Deep Neural Networks Based on Multiobjective Optimization.* IEEE Trans Neural Netw Learn Syst 2017. epub ahead of print.

56. Le MN, et al., *Evolution by adapting surrogates*. Evol Comput. 21(2):313-40.

57. Moore GP, et al., *An innovative on-call system for paediatric residency programs: The alternate night float*. Paediatr Child Health. 2015, 20(2):77-81.

58. McNabb J, Gray R, *Staying Connected on the Road: A Comparison of Different Types of Smart Phone Use in a Driving Simulator*. PLoS One. 2017, 11(2):e0148555.

59. https://www.oculus.com/rift/.

60. Kayser K, Gabius HJ, *Graph theory and the entropy concept in histochemistry. Theoretical considerations, application in histopathology and the combination with receptor-specific approaches.* Prog Histochem Cytochem, 1997. 32(2):1-106.

61. Yuan J, Wu Y, *Mining visual collocation patterns via self-supervised subspace learning*. IEEE Trans Syst Man Cybern B Cybern. 2012, 42(2):334-46.

62. W. Samek, A. Binder, G. Montavon, S. Lapuschkin, K.-R. Müller. Evaluating the visualization of what a deep neural network has learned. IEEE Trans. Neural Netw. Learn. Syst., 2016, 99: 1–14.

the diagnostic pathology journal DIAGNOSTIC PATHOLOGY

Jürgen Görtler et al., diagnostic pathology 2017, 3:248
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:248

63. G. Montavon, S. Lapuschkin, A. Binder, W. Samek, K. R. Müller, Explaining nonlinear classification decisions with deep Taylor decomposition Pattern Recognition. 2017, 65:211 - 222, 2017.

64. https://su.org/faculty-speakers/neil-jacobstein/.