

Towards the Augmented Pathologist: Challenges of Explainable-AI in Digital Pathology

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Abstract

Digital pathology is not only one of the most promising fields of diagnostic medicine, but at the same time a hot topic for fundamental research. Digital pathology is not just the transfer of histopathological slides into digital representations. The combination of different data sources (images, patient records, and *omics data) together with current advances in artificial intelligence/machine learning enable to make novel information accessible and quantifiable to a human expert, which is not yet available and not exploited in current medical settings. The grand goal is to reach a level of usable intelligence to understand the data in the context of an application task, thereby making machine decisions transparent, interpretable and explainable. The foundation of such an "augmented pathologist" needs an integrated approach: While machine learning algorithms require many thousands of training examples, a human expert is often confronted with only a few data points. Interestingly, humans can learn from such few examples and are able to instantly interpret complex patterns. Consequently, the grand goal is to combine the possibilities of artificial intelligence with human intelligence and to find a well-suited balance between them to enable what neither of them could do on their own. This can raise the quality of education, diagnosis, prognosis and prediction of cancer and other diseases. In this paper we describe some (incomplete) research issues which we believe should be addressed in an integrated and concerted effort for paving the way towards the *augmented pathologist*.

1. Introduction

Artificial intelligence (AI) is currently experiencing a tremendous hype towards building systems that can learn and think like humans do (Lake et al., 2016; Weber et al., 2017). Much of the current success results from the applicability of deep neural networks trained on large data sets in various tasks. These include object recognition, e.g. identifying cats from unlabeled images (Le et al., 2011), video games, e.g. playing Atari games (Mnih et al., 2013), or board games, e.g. the game of Go (Silver et al., 2016). These systems achieve a performance that equals or even beats humans in some respects (Silver et al., 2017).

An impressive example from the medical domain is the very recent work by the Thrun-Group (Esteva et al., 2017), which showed that convolutional neural networks can achieve a performance on par with human doctors, demonstrating the ability of classifying skin cancer with a level of competence comparable to dermatologists. Despite all these impressive successes of automatic approaches we are still very far away from reaching general *human-level AI*. This would require algorithms to deal with the common sense "informatic" situation - we say context - in which the phenomena to be taken into account in achieving goals are not yet fixed in advance (McCarthy, 2007).

In our opinion, there is no danger that AI will replace medical professionals in the medium term; however, there is an increasing trend that those who will not enrich their methods with AI will have a potential disadvantage to those who embrace cutting-edge Machine Learning (ML) technologies.

AI and ML are often used synonymously, although there is a difference: AI is the field working on understanding intelligence and encompasses all underlying scientific theories of human intelligence/human learning versus machine intelligence/machine learning. ML is a very practical field and applies the findings of AI research to the design, development and testing of algorithms that can learn from data, gain knowledge from experience and improve their learning behavior over time (Holzinger, 2017). Understanding human intelligence, i.e. to study how humans make decisions and how they reason, is difficult but of utmost importance for advances in AI and ML. For a number of reasons it is very difficult to deal with non-stationary, non-linear as well as non-independent & non-identically distributed data ¹ in high-dimensional spaces, often additionally dependent on time. This is quite often the case in the medical domain where we are confronted with a variety of different data (for a taxonomy of data refer to (Holzinger et al., 2014d; Holzinger, 2014a)).

Studying the work of pathologists is interesting for several reasons: 1) Digital pathology is not just the transformation of the classical microscopic analysis of histological slides by pathologists to a digital visualization, it is an innovation that will dramatically change medical workflows in the coming years; 2) Much information is hidden in arbitrarily high dimensional spaces, not accessible to a human, consequently we need an AI/ML approach to generate a new kind of information, which is not yet available and not exploited in current diagnostics; 3) Pathologists are able to transfer previously learned knowledge quickly to new tasks. Insights into the latter supports AI research generally and ML research specifically and may contribute to developing software which can learn from experience, similarly as we humans do. Technologically, during the last decade pathology has benefited from the rapid progress of image digitizing technologies, which led to the development of scanners capable to produce Whole Slide images (WSI) which can be explored by a pathologist on a computer screen (virtual microscope) comparable to the conventional microscope and can be used for education and training, diagnostics (clinico-pathological meetings, consultations, revisions, slide panels and upfront clinical diagnostics) and archiving (Al-Janabi et al., 2012). Practical implications of digital pathology include telepathology (Afework et al., 1998), second opinions (Epstein et al., 1996) and education (Dee, 2009).

1. Learning from non-iid data is difficult, (Zhang et al., 2009)

The digitalization opens new opportunities to extract knowledge from such data, which would not be accessible to the human expert otherwise (Holzinger et al., 2014a); however, standard image analysis tools are inadequate to deal with the specialities of WSI's.

Fusing traditional image sources with *omics data calls for new solutions (Madabhushi and Lee, 2016), particularly if we want to go towards personalized medicine (Holzinger, 2014c). The variety of problems in digital pathology requires a synergistic combination of various methodological approaches which calls for an integrated ML approach (Holzinger, 2012, 2013; Holzinger et al., 2017a). Methodologies of two areas offer ideal conditions to implement integrated ML: Human-Computer Interaction (HCI) and Knowledge Discovery/Data Mining (KDD), with the goal of augmenting human intelligence with artificial intelligence to discover novel, previously unknown insights into data. This calls for solutions which let the medical professional not only ask questions like "Where are similarities/differences/anomalies ...?" but to ask "*why*" questions, for example "Why are there similarities/differences/anomalies ...?" in order to find and explain unknown unknowns in complex data, which goes beyond data mining. Interestingly, early developments from the field of augmenting human intelligence came from HCI-research (Engelbart and English, 1968; Engelbart, 1995; Russell and Norvig, 1995).

2. From Microscopical Thinking to Digital Pathology

Modern pathology was founded in the mid of the 19th century, when Virchow (1871) set the basis for modern medical science and established the "microscopical thinking" which is still state-of-the-art in classical pathology. In histopathology a biopsy or surgical specimen is examined by a pathologist, after the specimen has been processed and histological sections have been placed onto glass slides, see Figure 1. In cytopathology either free cells (fluids) or tissue micro-fragments are "smeared" on a slide without cutting any tissue. An alternative to invasive autopsy is virtual autopsy which is also conducted with scanning and imaging techniques (O'Sullivan et al., 2017).

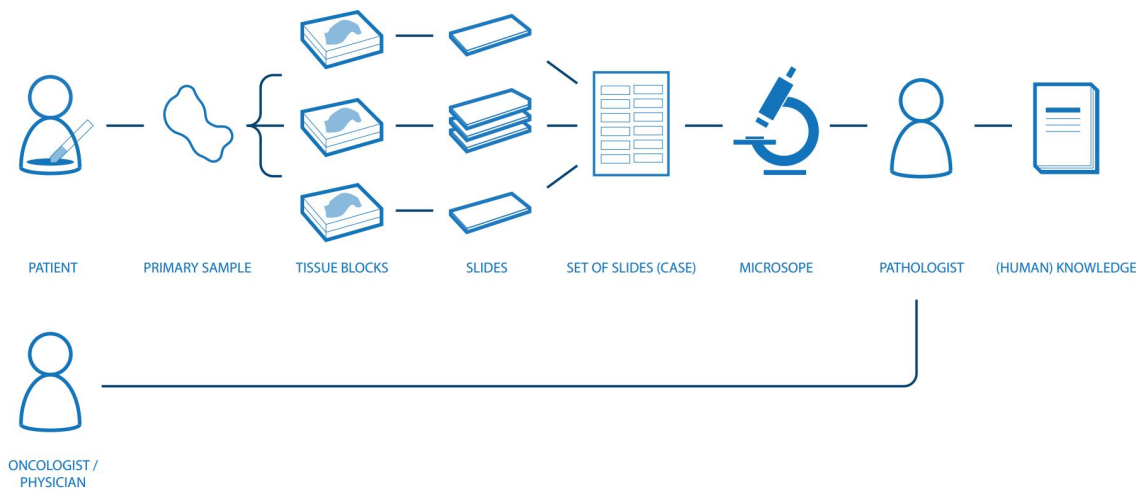


Figure 1: Clinical pathology, from mid 19th century up to the end of the 20th century.

Towards the end of the 20th century an individual clinical pathologist was no longer able to cover the knowledge of the whole scientific field. This led to the specialization of clinical pathology either by organ systems or methodologies. Molecular biology and *omics technologies set the foundation for the emerging field of molecular pathology, which today alongside WSI provides the most important source of information, especially in the diagnosis of cancer and infectious diseases, see Figure 2.

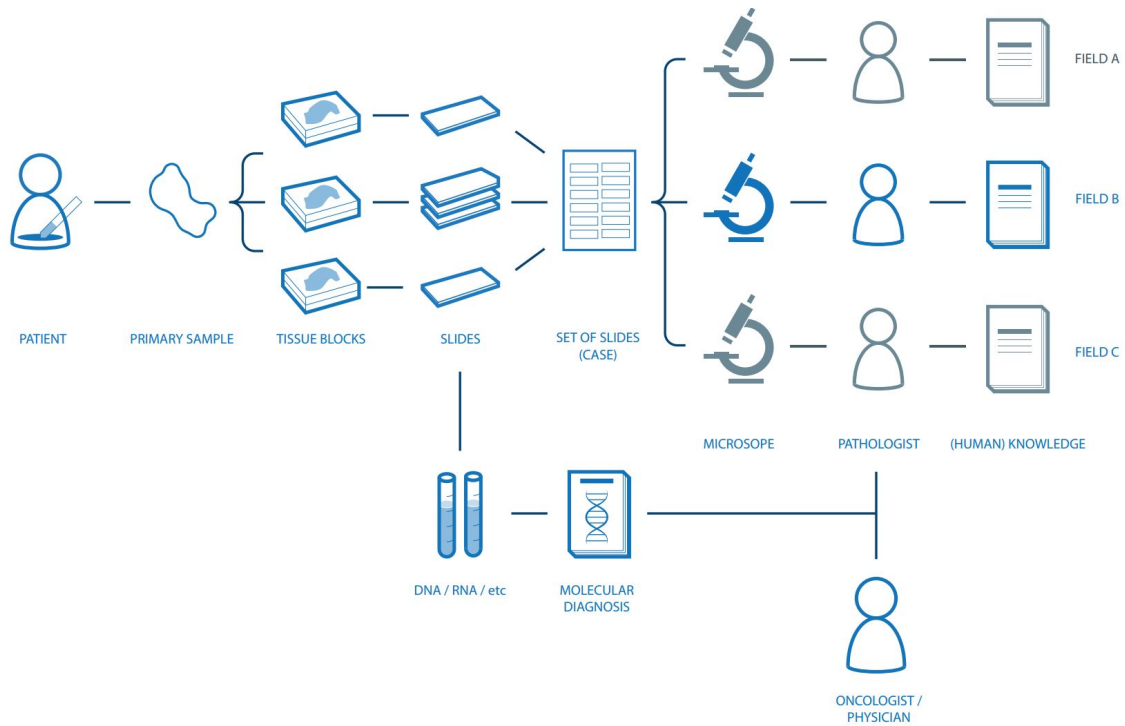


Figure 2: Today’s state-of-the-art (non digital) clinical pathology.

The roots of digital pathology go back to the 1960s in the context of telepathology, which was a remote-controlled light microscope attached to a video camera and a telecommunication link (Weinstein et al., 1987).

Later in the 1990s the principle of virtual microscopy (Weinstein et al., 2009) appeared in several life science research areas. At the turn of the century the scientific community gradually adopted the term ”digital pathology” (Barbareschi et al., 2000) to denote digitization efforts in pathology, see Figure 3.

The technical requirements (scanner, storage, network) in digital pathology are magnitudes higher than in radiology due to some general differences between those two fields: In radiology the image is primarily captured in digital format, whilst in pathology the scanning is done from preserved and processed specimens, for retrospective studies even from slides stored in biobanks (Huppertz and Holzinger, 2014). The integration of biobanks is of enormous importance for the realization of future precision medicine (Müller et al., 2015).

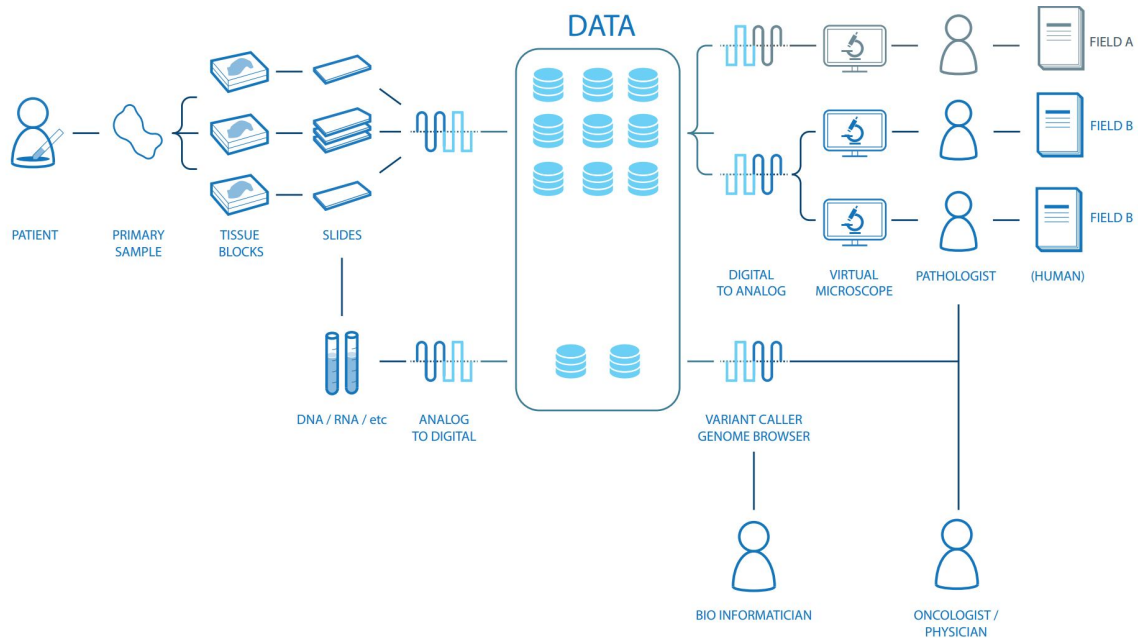


Figure 3: A digital pathology workflow always starts with the gross evaluation of the primary sample. Depending on the medical question and the material type, small tissue parts are extracted from the primary sample. The pathology lab cuts several slides from the tissue blocks, applies different staining methods and conducts additional histological and molecular tests. In addition to the set of whole slide images (each about 16 Gigapixels in size!), textual information from medical reports as well as molecular data are combined in the diagnosis-making process.

Besides some differences in pre-analytics workflows and metadata content, the required storage in digital pathology is two to three orders of magnitude higher than in radiology and places heavy demands on IT infrastructure (Huisman et al., 2010).

2.1 Virtual Case

A pathological workflow always starts with the overall evaluation of the primary sample. Depending on the medical question and the material type, small tissue parts are extracted from the primary sample and are either embedded in a paraffin block or cryo-frozen. From the tissue blocks the pathology lab cuts several slides, applies different staining methods and conducts additional histological and molecular tests. Finally, the pathologists evaluate all the slides together with the supporting gross- and molecular findings and makes the diagnosis. If in addition to the set of WSI all information is present in a structured digital format, we call this a virtual case. In a virtual case, the average number of slides and additional findings varies very much for different medical questions and material types.

The most demanding data elements in a virtual case are the whole slide images (WSI). Compared to radiology, where the typical file sizes are in the range from 500 KB to 50 MB, a single WSI scan with 80x magnification consists of approximately 16 Gigapixels (Note: for the calculation of the WSI file size and comparison of different scanner manufacturers, we use the de-facto standard area of 15mm x 15mm, with an optical resolution of 0.12 μ m, which corresponds to an 80x magnification).

With 8bit information for each color channel one WSI results in approx. 50GB stored in an uncompressed image format. Looking at the number of slides of a typical case, it is clear that some compression techniques must be applied to the image data, and luckily several studies reported that lossy compression with a high quality level does not influence the diagnostic results; Still there are unresolved questions (Holzinger et al., 2017a).

The newest generation of scanners (status as of October 2017²) is able to digitize a slide at various vertical focal planes, called z-layers, each the size of a single layer. The multi-layer image can be either combined by algorithms to a single composite multi-focus image (Z-stacking) or used to simulate the fine focus control of a conventional microscope. Z-stacking is a desirable feature especially when viewing cytology slides, however the pathologist should be aware that such an image can never be seen through an actual microscope.

At the Institute of Pathology of the Medical University of Graz about 73,000 diagnoses are made per year and approximately 335,000 glass slides are produced in the pathology lab; additionally approximately 25,000 glass slides are generated in the cytology lab. This results in a required yearly storage capacity of almost 1 PB and the appropriate computing power to process approximately 1000 slides per day plus the necessary capacity to train and improve AI/ML algorithms.

Several data formats are used today, either vendor independent (DICOM, TIFF/BigTIFF, Deep Zoom images) and vendor specific formats from Aperio, Hamamatsu, Leica, 3DHis-tech, Philips, Sakura and Trestle. In the setup of a virtual slide archive for medical research and machine learning it is essential to a) agree on a common exchange format, and b) to separate patient related and image related metadata. Patient related metadata comprise direct identifiers (name, birthday, zip code, ...) but also diagnosis results and others results from the patient medical history. When no such data is stored within or attached to the image format, the WSI is purely anonymous as no re-identification of the patient is possible. To link between the same WSI used in different studies, either a global unique identifier (GUID) or an image generated hash can be used.

2.2 Towards the Augmented Pathologist

Digitizing the workflows is one important fundamental issue to enable a revolutionary change in clinical pathology. Based on the digital workflow AI paradigms and ML methods can be applied to augment the human pathologist during diagnosing, research, education and training. The augmentation may start with simple classification and quantification algorithms as already available today (e.g. cell sorting (Arteta et al., 2012)), and may end in a fully autonomous pathologist. This is similar to the concept of autonomous driving, where human intervention is no longer necessary, but can still range over various degrees of involvement (to-be-or-not-to-be-in-the-loop (Louw et al., 2015)).

2. As of October 2017 the worldwide fastest WSI scanner is working in Graz <https://goo.gl/yiVnEx>

In driving automation autonomy levels have already been established (SAE J3016 ³) Kircher et al. (2014): level 0 = full control of the driver, just warnings; level 1 = hands-on, driver must be ready to retake full control at any moment; level 2 = hands-off, driver must monitor at any time and be prepared to immediately intervene in case the automatic system fails; level 3 = eyes-off, driver can safely turn her/his attention elsewhere, but driver may take over at any time; level 4 = mind-off, driver even may go to sleep or leave the driver's seat; level 5 = fully automatic, no human intervention required, e.g. a robotic taxi.

To distinguish such extreme scenarios from simple digital workflows we propose the term **machine aided pathology**, meaning that significant contributions of the decision making process are supported by machine intelligence. Such machine aided pathology solutions can be applied at several steps during the diagnosis and decision making process:

Formulation of a hypothesis. Each diagnosis starts with a medical question and a corresponding underlying initial hypothesis. The pathologist refines this hypothesis in an iterative process, consequently looking for known patterns in a systematic way in order to confirm, extend or reject his/her initial hypothesis. Unconsciously, the pathologist asks the question "*What is relevant?*" and zooms purposefully into the - according to his/her opinion - essential areas of the cuts. The duration and the error rate in this step vary greatly between inexperienced and experienced pathologists. An algorithmic support in this first step would contribute in particular to the quality and interoperability of pathological diagnoses and reduce errors at this stage, and would be particularly helpful for educational purposes. A useful approach is known from Reeder and Felson (2003) to discover certain patterns (called gamuts) in radiological images and to classify these into the groups "common/uncommon". This approach has its roots in differential diagnosis which has a long tradition (Kobayashi et al., 1974) and has been implemented with artificial neural networks (Asada and Doi, 1997).

- Very large amounts of data can only be managed with a "multi resolution" approach using image pyramids. For example, a Colon cancer case consists of approximately 20 Tera (!) pixels of data - a size which no human is capable of processing.
- The result of this complex process is a central hypothesis, which has to be tested on a selection of relevant areas in the WSI, which is determined by quantifiable values (receptor status, growth rate, etc.).
- Training data sets for ML can now contain human learning strategies (transfer learning, e.g.) as well as quantitative results (hypotheses, areas, questions, etc.).

Detection and classification of known features. Through a precise classification and quantification of selected areas in the sections, the central hypothesis is either clearly confirmed or rejected. In this case, the pathologist has to consider that the entire information of the sections is no longer taken into account, but only areas relevant to the decision are involved. It is also quite possible that one goes back to the initial hypothesis step by step and changes their strategy or consults another expert, if no statement can be made on the basis of the classifications.

3. Taxonomy and Definitions for Terms Related to On-Road Motor Vehicle Automated Driving Systems. Society of Automotive Engineers (SAE, 2014).

- In this step ML algorithms consist of well known standard classification and quantification approaches.
- An open question is how to automatically or at least semi-automatically produce training sets, because here specific annotations are needed (which could come from a stochastic ontology, e.g.).
- Another very interesting and important research question is, whether and to what extent solutions learned from one tissue type (organ 1) can be transferred to another tissue type (organ 2) – transfer learning – and how robust the algorithms are with respect to various pre-analytic methods, e.g. stainings, etc.

Risk prediction and identification of unknown features. Within the third step, recognized features (learned parameters) are combined into a diagnosis and an overall prediction of survival risk. The main challenge in this step lies in training/validation and in the identification of novel, previously unknown features from step two. We hypothesize that the pathologist supported by machine learning approaches is able to discover patterns – which previously were not accessible! This would lead to totally new insights into previously unseen or unrecognized relationships.

Beyond challenges in ML, the following general topics and prerequisites have to be solved for a successful introduction of machine aided pathology:

Standardization of WSI image formats and harmonization of annotation / metadata formats. This is essential for telepathology applications (on the importance of standardization for digital pathology see the recent work of Barisoni et al. (2017)); and even more important for the generation of training sets, as for a specific organ and disease stages, the required amount of cases may not be available even at a large institute of pathology.

Common digital cockpit and visualization techniques should be used in education, training and across different institutes. Changing the workplace should be as easy as switching the microscope model or manufacturer. However, commonly agreed-upon visualization and interaction paradigms can only be achieved in a cross vendor approach and with the involvement of major professional associations.

2.3 Data Integration

Applying sophisticated AI/ML methods on images alone is one aspect (Liu et al., 2017); however, the real added value results from the combination of two other sources of data:

1) Clinical data from electronic patient records (EPR) including the patient history with all documents, diagnoses, medical reports, laboratory tests, physiological parameters, vital signs, but also recorded signals, ECG, EEG, etc.); this also links to other image data including standard X-ray, MR, CT, PET, SPECT, microscopy, confocal laser scans, ultrasound imaging, molecular imaging, etc.⁴

4. Remark: At Graz University Hospital an all-digital hospital information system is in operation since 2000 (Gell et al., 2000; Holzinger et al., 2000)

2)*omics data from biobanks (Huppertz and Holzinger, 2014; van Ommen et al., 2015; Hainaut et al., 2017), e.g. from genomic sequencing technologies (Next Generation Sequencing, NGS, etc.), microarrays, transcriptomic technologies, proteomic and metabolomic technologies, etc., which all play important roles for biomarker discovery and drug design (McDermott et al., 2013; Swan et al., 2013; Libbrecht and Noble, 2015).

Fusing and integrating this data (images, text, *omics) allows to make novel information accessible and quantifiable for the human pathologist, which are not yet available and not exploited to date. *To understand the whole one must study the whole* (quote by HENRIK KACSER (1986), reference in: Kell (2004)). Data integration is a hot topic in the life sciences because solutions can bridge the gap between clinical routine and biomedical research (Jeanquartier et al., 2016). This is becoming important due to the distributed, heterogeneous and diverse data sources, including picture archiving and communication systems (PACS) and radiological information systems (RIS), hospital information systems (HIS), lab information systems (LIS), physiological/clinical data repositories, and all sorts of *omics data in labs, and biobanks. It is of highest importance to provide end-users with a *unified view on these data*. These unified views are particularly important in high-dimensions, e.g. for integrating heterogeneous descriptions of the same set of genes (Lafon et al., 2006), and fused data is more informative (Blanchet and Smolinska, 2016).

3. Deep Learning

Among the most important machine learning methods in medical image analysis are support vector machines, random forests, and deep learning approaches. For a brief overview of machine learning for digital pathology see (Holzinger et al., 2017a). Here we briefly focus on the state-of-the-art in *interpretable* deep learning. Deep Learning (DL, for an overview refer to (LeCun et al., 2015; Schmidhuber, 2015; Arel et al., 2010)) is a whole family of (hierarchical) learning approaches primarily based on *learning representations by layers and units in a network structure*. Due to their practical success DL is currently the most popular general framework (Greenspan et al., 2016) in ML. The "deeper" the network the more layers and intra-layer units can represent functions of increasing complexity. Most tasks that consist of mapping an input vector to an output vector can be accomplished via deep learning, given sufficiently large data sets of labeled training examples (for details see the excellent book by Goodfellow et al. (2016)). Despite all their successes DL approaches have some limitations, e.g. they are very data hungry, need much computational power and they are considered black-box models (Singh et al., 2016). However, in the medical domain it is necessary to be able to open the black-box to a glass-box (Holzinger et al., 2017b) and to make the results transparent, re-traceable and explainable on demand (see section 7).

3.1 Convolutional Neural Networks

The most prominent and recently most successful DL architectures are Convolutional Neural Networks (CNN, or short: convnets), which have been introduced in the early 1990ies (LeCun et al., 1989), and which have demonstrated excellent performance recently (Krizhevsky et al., 2012)⁵. Technically a CNN is structured as a series of different layers, i.e. convolu-

5. This NIPS-paper has 17,770 citations as of 14.12.2017 12:00 CET



Figure 4: Detail of a typical WSI: FFPE section of a human liver with cirrhosis, hematoxylin and eosin staining (Image Source: Pathology Graz, obtained with the new P1000 scanner of 3DHistech), see also Figure 8

tional layers, pooling layers, fully connected layers and classification layers (e.g. softmax). Convolutional layers are feature maps, where each feature map is connected to local patches in the corresponding feature map in the previous layer. Pooling layers merge similar features into one. Fully connected layers generate the output for the actual task and classification layers produce a label provided a learning instance. CNNs are so popular because the effort of engineering the feature representations can be mostly handled by the network itself.

Also in the medical domain, amazing results have been achieved, e.g. for cancer detection with human-like performance: Liu et al. (2017) adopted a CNN framework for breast cancer metastasis detection in lymph nodes. By exploiting the information of a pre-trained model, sophisticated image normalization, and building on a multi-stage approach (mimicking the human perception), state-of-the-art methods and even human pathologists have been outperformed on a standard benchmark dataset.

Similarly, Esteva et al. (2017) addresses the problem of skin cancer detection: they propose a transfer learning setup in which a pre-trained CNN architecture using ImageNet has been modified in such a way that only the final classification layer is discarded and re-trained for the given task (additionally, the parameters are fine-tuned across all layers). Eventually, the obtained network was able to perform on par with human dermatologists on different tasks.

Even though this demonstrates that DL may be beneficial in the medical domain generally, the main challenge is still to cope with the problem that often the rather large amount of training data required is not available. Consequently, there has been a considerable interest in approaches that can learn from a small number of training samples (see section 6). The most common and straight forward way is to use data augmentation for constructing iterative optimization via the generation of artificial data or latent variables (Van Dyk and Meng, 2001; Hauberg et al., 2016). In our domain image augmentation (Bloice et al., 2017) can be particularly beneficial, where additional training samples are generated via variation of the given data, e.g. via rotation, elastic deformation, adding noise, etc.

A prominent example for such an approach is U-Net (Ronneberger et al., 2015), which demonstrated that state-of-the-art results can be obtained for bio-medical image segmentation even when the model was trained on merely a few samples.

Even though this simple approach often yields good results, it is restricted as only limited variations can be generated from the given data. A promising direction is to build on ideas from transfer learning (Long et al., 2016). The key idea is to pre-train a network on large publicly available datasets and then to fine-tune it for the given task. For example, Cai et al. (2017) fine-tunes the VGG-16 network, which is already pre-trained using a huge amount of natural images, to finally segment pancreas from MR images. In addition, a CRF step is added for the final segmentation. Another way would be to use specific prior knowledge about the actual task (Payer et al., 2016).

However, this information is often not available and, as mentioned above, medical image data and natural images are often not sharing the same characteristics, which is why such approaches often fail in practice.

A totally different way to deal with small amounts of training data is to use synthetically generated samples for training such as (Rozantsev et al., 2015) which are easy to obtain. However, even in this way the specific characteristics of the given image data might not be reflected properly. To overcome this problem, Generative Adversarial Nets (Goodfellow et al., 2014) train a generator and a discriminator framework in parallel. The key idea is that the generator synthesizes images and the discriminator decides if an image is real or fake (i.e., generated by the generator). In this way, increasingly better training data can be generated. This idea is for example exploited by Nie et al. (2017) to better model the nonlinear relationship between CR and MR images.

3.2 Interpretable Deep Learning Models

Simple models are regarded as more interpretable than complex ones, therefore linear models and basic decision trees still dominate in many applications where interpretability is an issue. This belief is however challenged by recent work, in which carefully designed interpretation techniques have shed light on some of the most complex and deepest machine learning models (Singh et al., 2016).

Standard supervised convnet models LeCun et al. (1989); Krizhevsky et al. (2012) map a color 2D input image x_i , via a series of layers, to a probability vector \hat{y}_i over C different classes. Each layer consists of (i) a convolution of the previous layer output (or, in the case of the 1st layer, the input image) with a set of learned filters; (ii) passing the responses through a rectified linear function ($relu(x) = \max(x, 0)$); (iii) [optionally] max pooling over local neighborhoods and (iv) [optionally] a local contrast operation that normalizes the responses across feature maps - refer to (Krizhevsky et al., 2012) for details. The top few layers of the network are conventional fully-connected networks and the final layer is a softmax classifier Zeiler and Fergus (2013).

The model can be trained using a large set of N labeled images $\{x, y\}$, where label y_i is a discrete variable indicating the true class. A cross-entropy loss function, suitable for image classification, is used to compare \hat{y}_i and y_i . The parameters of the network (filters in the convolutional layers, weight matrices in the fully-connected layers and biases) are trained by back-propagating the derivative of the loss with respect to the parameters throughout the network and updating the parameters via stochastic gradient descent.

Visualizing features in order to gain insight into the behavior of networks has been done previously, however, limited to the first layer(s). In "deeper" layers it is not possible to make projections to the pixel space, consequently there are very few methods to date to provide interpretability of such networks. For example Erhan et al. (2009) proposed to find the optimal stimulus for each unit by performing gradient descent in image space to maximize each unit's activation. This requires a careful initialization and does not give any information about the unit's invariances. Motivated by this shortcoming, Ngiam et al. (2010) demonstrate how the Hessian of a given unit may be computed numerically around the optimal response, giving some insight into invariances. The problem still remains that for higher layers the invariances are extremely complex and can therefore hardly be captured.

A very interesting approach has been developed by Zeiler and Fergus (2013): they introduce a visualization technique that reveals input stimuli exciting individual feature maps at any layer in the model, which allows to observe a kind of "evolution" of features during the training phase. This allows insight into the internals of the model as well as to discover problems. Their technique is based on a multi-layered deconvolutional network (deconvnet) (Zeiler et al., 2011) in order to project the feature activations back to the input pixel space. The basic principle can be inferred from Figure 5 and Figure 6. The procedure is "unpool, rectify, filter" in order to reconstruct the activities in the layer which was responsible for an activation. This procedure is repeated until the input pixel space is reached.

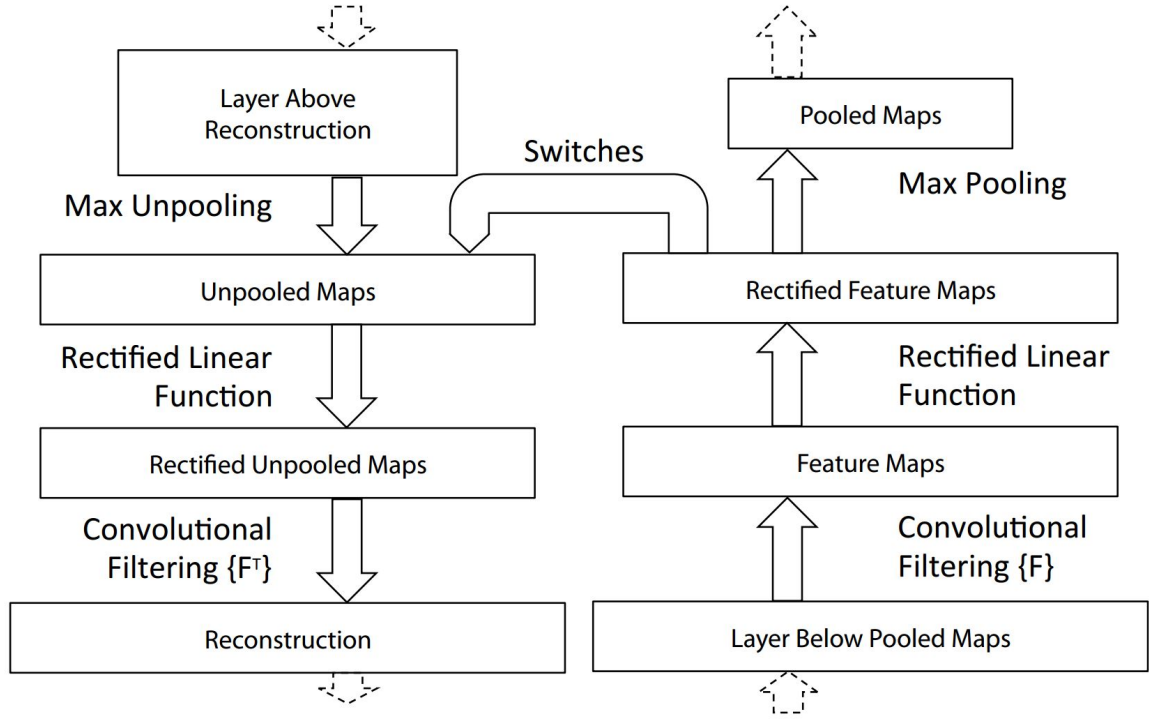


Figure 5: A deconvnet layer (left) attached to a convnet layer (right). The deconvnet is able to reconstruct an approximate version of the convnet features from each layer beneath; image source: Zeiler and Fergus (2013)

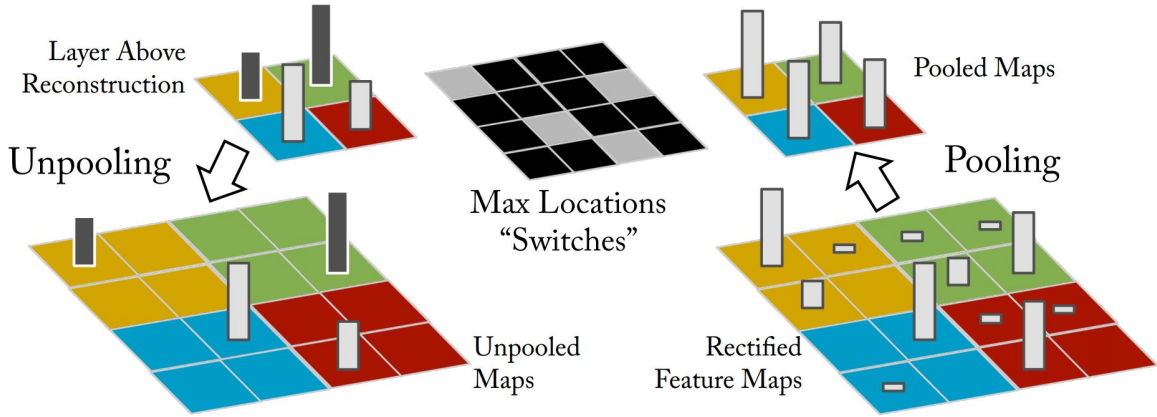


Figure 6: The unpooling operation in the deconvnet, using *switches* which record the location of the local max in each pooling region (colored zones) during pooling in the convnet; image source: Zeiler and Fergus (2013)

4. Learning from Heterogeneous Graphs

Graph Theory (Harary et al., 1965; Bondy and Murty, 1976) provides powerful tools to link data structures of different sources and to reason about probabilistic connections between data objects (Strogatz, 2001). Graphical models (Lauritzen, 1996) combined with probability theory (Kolmogorov, 1950), which can represent a set of random variables and conditional dependencies, form the basis for causality (Pearl, 2009); this is of extreme importance towards reaching explainable AI. Recent developments in probabilistic programming support such approaches (Fadja and Riguzzi, 2017; Tran et al., 2017).

An example is the graph-based approach for mitosis extraction in breast cancer from WSI, which has been presented by Roullier et al. (2011): Their segmentation uses multi-resolution, which reproduces the WSI examination done by a (human) pathologist. Each resolution level is then analyzed with a focus of attention resulting from a coarser resolution level analysis. At each level a spatial refinement by label regularization is performed to obtain a more accurate segmentation. The proposed segmentation is fully unsupervised by using domain specific knowledge and their strategy for multi-resolution segmentation makes use of regularization on graphs both for image simplification and segmentation. This approach is based on an interesting nonlocal discrete regularization framework on weighted graphs of the arbitrary topologies for image and manifold processing (Elmoataz et al., 2008), where graphs are the shared representation.

However, the challenge of extracting appropriate graphs out of "natural images" remains, especially w.r.t. identifiable biological structures, which is not an easy task (Holzinger et al., 2014c,b).

With respect to the sheer size of our pathological input space (see Figure 8) we propose an intriguing possibility of graph-theory: To project an image's pixel space down to a graph's vertex-space, in which each vertex represents a Region-of-Interest (ROI) within the original image (e.g. a cell nucleus). Given a meaningful representation, we can subsequently apply powerful graph algorithms including belief-propagation or Bayesian networks - or even train CNNs using the vertex vector / adjacency matrix as input layer (see Figure 7).

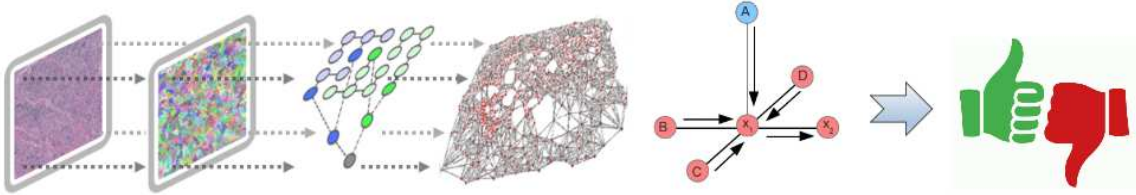


Figure 7: A possible graph computational pipeline: 1) Image preprocessing & segmentation, 2) projection from pixel to vertex space, 3) graph construction, 4) graph-based data mining, 5) classification

While the real power of graph theory does not lie in constructing graphs from individual items but in interlinking heterogeneous sources, simply connecting EHR, *omics and image data of one single patient does not present us with an "interesting" graph, since almost no

information will be encoded by the graph structure itself (i.e. the topology of the graph), but remain within the "nodes" representing the original data. Therefore, it is essential to devise methodologies which allow us to extract features from different data modalities that are *atomic*, *isolated*, *meaningful* and - above all - *linkable* in order to produce a data structure amenable to graph-theoretical procedures. This necessitates the development of *ashared representation on the feature level*, e.g. the mapping of features from different domains to a shared concept space.

While this could be achieved via Word embeddings for EHRs (Word2Vec) and via random walks on image subgraphs / graphs extracted from subimages (Node2Vec), it is yet unclear how to properly perform meaningful embeddings for *omics data. In any case, the goal of such projections is to make data fragments from different sources comparable in terms of structural as well as functional similarity and importance to specific use cases. This could serve as a first step towards explainability, as concept-mappings over modalities would enable text-and-omics-to-screen reasoning algorithms which form part of the idea of a *holistic user interface*.

Finally, merging heterogeneous data sources provides the intriguing possibility of forming superior models about patterns of interplay between symptoms / characteristics on the cellular, *omics, and diagnostic level. Introducing such parameter schemes to generative adversarial networks (GANs) might even allow for the generation of quasi-realistic, synthetic patient data and thus the provision of virtual pathology data sets.

5. On Topological Data Mining from Medical Images

Much potential lies in topological data mining (Holzinger, 2014b), where we need point cloud data sets or distances as inputs. A set of such primitives forms a space, and if we have finite sets equipped with proximity or similarity functions $sim_q: S^{q+1} \rightarrow [0, 1]$, which measure how "close" or "similar" $(q + 1)$ -tuples of elements of S are, we speak about a *topological space*. A value of 0 means totally different objects, while 1 corresponds to equivalent items. This is highly relevant for explainable AI, because natural data form certain structures called manifolds (Abraham et al., 1988; Edelsbrunner et al., 2001). Manifolds can be seen as a topological space that is locally homeomorphic (that means it has a continuous function with an inverse function) to a real n -dimensional space. In other words: X is a d -manifold if every point of X has a neighborhood homeomorphic to \mathbb{B}^d ; it is called *bounded* if every point has a neighborhood homeomorphic to \mathbb{B} or \mathbb{B}_+^d (Cannon, 1978). This is highly relevant for many applications in machine learning where we are confronted with high-dimensional data and to find meaningful representations in the lower-dimensions (Tenenbaum et al., 2000; Saul and Roweis, 2003; Weinberger and Saul, 2006). A topological space can therefor be seen as an abstraction of a metric space, and similarly, manifolds generalize the connectivity of d -dimensional Euclidean spaces \mathbb{B}^d by being locally similar but globally different. A d -dimensional chart at $p \in X$ is a homeomorphism $\phi: U \rightarrow \mathbb{R}^d$ onto an open subset of \mathbb{R}^d , where U is a neighborhood of p and open is defined using the metric. A d -dimensional manifold (d -manifold) is a topological space X with a d -dimensional chart at every point $x \in X$ (Zomorodian, 2010).

Also interesting for our work are simplicial complexes ("simplicials") which are spaces described in a very particular way, the basis of which is homology (Cerri et al., 2013).

The reason for their existence is that it is not possible to represent surfaces precisely in a computer system due to limited computational storage; thus, surfaces are sampled and represented with triangulations. Such a triangulation is called a simplicial complex, and is a combinatorial space that can represent a space. With such simplicial complexes, the topology of a space can be separated from its geometry.

One way to create a simplicial complex is to examine all subsets of points, and if any subsets of points are close enough, a p-simplex (e.g. line) is added to the complex with those points as vertices. For instance, a Vietoris-Rips complex of diameter ϵ is defined as $VR(\epsilon) = \{\sigma \mid \text{diam}(\sigma) \leq \epsilon\}$, where $\text{diam}(\epsilon)$ is defined as the largest distance between two points in σ . A common way to analyze topological structures is to apply persistent homology (Zomorodian and Carlsson, 2005), which identifies cluster, holes and voids. It is assumed that more robust topological structures are the one which persist with increasing ϵ . For us it is very relevant to extract significant features, thus these methods are useful, since they provide robust and general feature definitions with emphasis on global information, e.g. Alpha Shapes (Edelsbrunner and Mücke, 1994).

The combination of topology and machine learning towards *geometric machine learning* could be very useful in the future, e.g. geometric deep learning, which attempts to generalize structured deep learning models to non-Euclidean domains, such as graphs and manifolds (Lee et al., 2016; Bronstein et al., 2017) and help in developing explainable-AI.

6. Interactive Machine Learning with the Expert-in-the-Loop

The central challenge in machine learning is the development of a model which relates observations X to target variables $Y = x_1, x_2, x_3, \dots$, inferring either decisions or predictions. While traditionally we deal with deterministic values for Y , in some domains - such as pathology - we need to consider uncertainties and therefore seek applications where Y includes unknowns or rare categories - and where the application of automatic machine learning approaches may result in the danger of modeling artifacts.

A further problem is that the complexity of automated machine learning algorithms has generally detained non-experts from the application of such solutions. However, for solving real-world problems, the integration of a domain expert’s knowledge can sometimes be indispensable and the interaction of the domain expert with the data would greatly enhance the knowledge discovery process, consequently iML puts the pathologist-in-the-loop to enable what neither a human nor a computer could do on their own (Holzinger, 2016b).

One approach to mitigate these shortcomings is to involve humans in the model-building effort; traditionally this has been restricted to having people label data in a pre-processing stage or by requesting experts to select or weight features (bias-injection) before the actual Machine Learning happens. A real *interactive* approach though requires the interplay of algorithmic action and human feedback in a continuous loop, thereby enabling the algorithm to adapt it’s internal learning strategy on-the-fly, thus effectively opening up the black box approach (Holzinger, 2016b,a) to a glass box⁶.

This method brings with it two major benefits: 1) for problems in high-dimensional search spaces, it allows the algorithm to restrict possibilities by making use of human

6. Our project page is accessible via: <https://hci-kdd.org/project/iml>

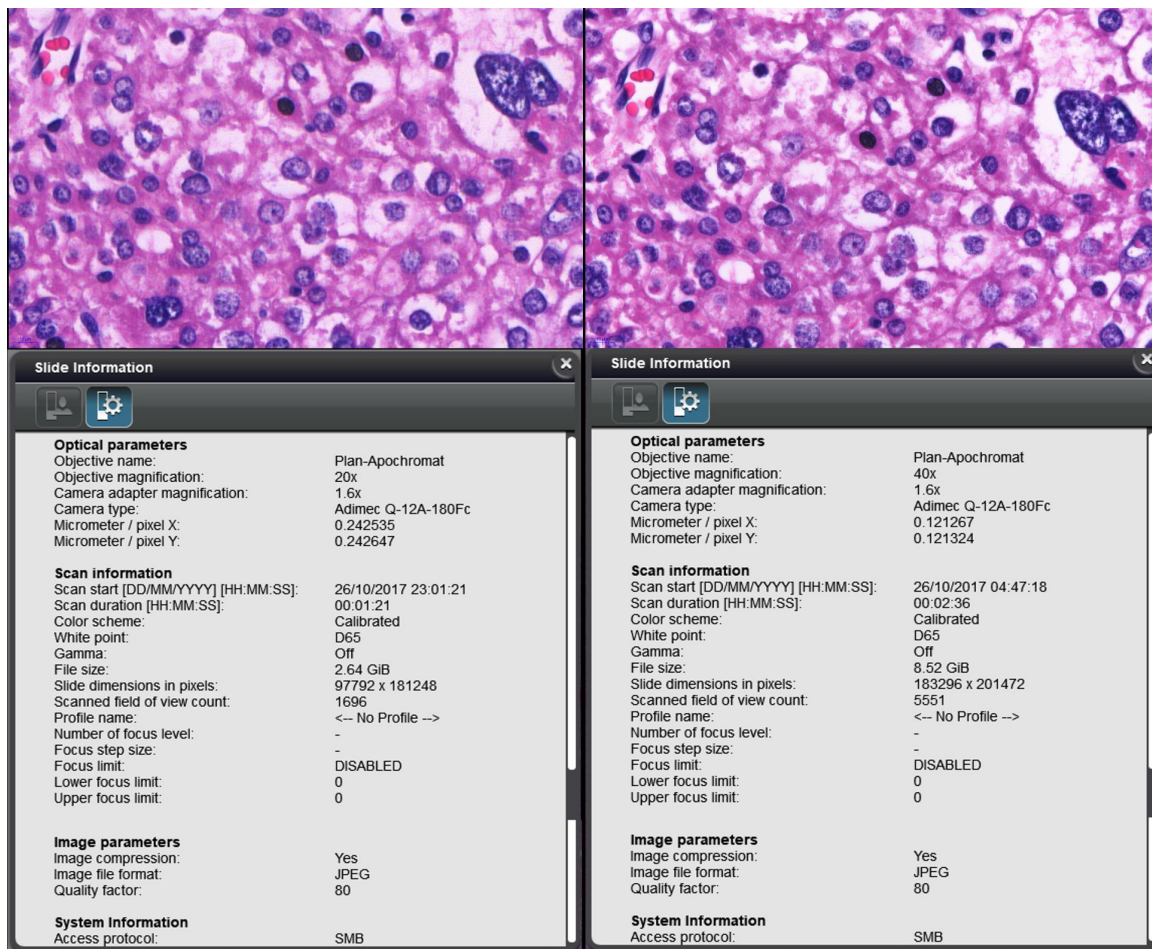


Figure 8: FFPE section of a human hepatocellular carcinoma, hematoxylin and eosin staining; comparison of scans with 0,24 micrometer/pixel and 0,12 micrometer/pixel (Image Source: Pathology Graz, obtained with the new P1000 scanner of 3DHis-tech)

experience translated into heuristic functions, and 2) as decisions are always - at least partly - based on inputs stemming from the realm of human expertise, any subsequently automated ML approach will exhibit the same patterns of reasoning, which makes algorithmic decisions much more explainable from a human perspective.

An interesting aspect of such interaction is the Bayesian manner by which humans assign significance to data points they observe and the hypotheses they extract from such data; instead of seeing "importance of data" and "hypothesis" as separate entities, one should more appropriately model the mutual influence as "importance of data, given some hypothesis" and "hypothesis, given some important data points".

In combination with heterogeneous data graphs and a *holistic* user interface, we can conceive of a progressive interaction cycle where reasoning algorithms present the pathologist with their insights in the form of recommendations (e.g. diagnosis, prognosis, valuable related information) which a pathologist could accept or reject (see Figure 7, providing continuous feedback for the algorithm to change it’s internal mapping parameters. This feedback could be collected implicitly via *affective computing*, i.e. the observation of a user’s reaction to content without eliciting conscious, deliberate feedback. This can be done by microscope eye-tracking (Duchowski, 2007) which can provide novel insights into the analysis behavior of a pathologist (Jaarsma et al., 2014; Krupinski et al., 2006); comparison studies can be enormously useful for the machine learning community⁷.

Projecting this approach further into the future, we could go beyond gaining insights from moment-to-moment user observation to a system of intention mining, where a chain of user (inter)actions is utilized to derive a pathologist’s individual strategy of dealing with a given problem when presented specific observations. The resulting models of individual learning strategies could be analyzed w.r.t. to their historic success, beneficial strategy phases could be extracted from each expert’s profile and merged into a *virtual pathologist* combining the best traits of each human archetype. Although the practical deployment of such a ”super pathologist” might evoke negative reactions from medical experts and patients alike, it would present an ideal solution in education and training of future practitioners (especially given the shortage of expert personnel in the field), and contribute to the research in AI generally and ML specifically.

7. Explainability of Machine Decisions

Being a rather general term, explainability is usually defined as making automated ML decisions transparent, which one can decompose into meaning *interpretable* (what effect was that decision supposed to have?), *comprehensible* (which data led to the decision?) and *reproducible* (given the data and specific circumstances, can we model a function that outputs the same decision?). In order to achieve this, we need to identify and disentangle explanatory factors in the underlying data, may it be pixels in images, tokens in text, or base-pairs in genetic sequences.

Apart from several references to explainability in earlier sections, a few generic approaches have been recently proposed which in our view warrant specific presentation. In Ribeiro et al. (2016) the authors introduce a model they call *LIME* - Local Interpretable Model Explanation - which aims to explain any classification or prediction result by approximating it locally with an interpretable model. They achieve this via sampling around local instances until they arrive at a linear approximation of the global decision function which behaves in a locally faithful way.

A very recent work Bach et al. (2015) describes *layer-wise relevance propagation* (LRP) which the authors claim applicable for any form of layered computation architecture. The method preserves constraints to a total relevance score per layer, so that input dimensions ”compete” for their influence on the next layer. The system works by first computing the overall function and then working backwards via distributing the relevance of a neuron k at layer $l + 1$ onto its input neurons at layer l all the way back to the input dimensions (e.g.

7. Compare to the work done by Gopnik and et al. (2004)

pixels within an image). These can then be visualized via heat maps, offering an intuitive interface for human comprehension.

An interesting application framework for explainable interactive ML is *Bonsai*⁸, which allows programmers without extensive ML experience to train so-called "curricula", i.e. bottom-up learning strategies for particular tasks in a Domain Specific Language. These programs are separated into different learning sections and phases, so that the user acts as a constraint-giver to the solution space during training (which has the downside of limiting the universal learning-capabilities of deep architectures), so that mis-classifications of the trained model in the testing phase can be clearly attributed to a "sub-program", thereby helping explainability and model acceptance.

8. Privacy Aware Machine Learning

The General Data Protection Regulation (GDPR and ISO/IEC 27001) coming into effect on May 25th 2018 attracts a lot of attention in the medical area, as it is concerned with all major issues regarding the processing of personal sensitive information and deals with the legal requirements for data collection, consent regarding processing, anonymization/pseudonymization, data storage, transparency and deletion (*"the right to be forgotten"* (Malle et al., 2016), calling for federated learning approaches (Malle et al., 2017)).

Still, the major issue is that many details are currently not defined, e.g. whether deletion needs to be done on a physical or simply a logical level, or how strong the anonymization-factors need to be (Villaronga et al., 2017).

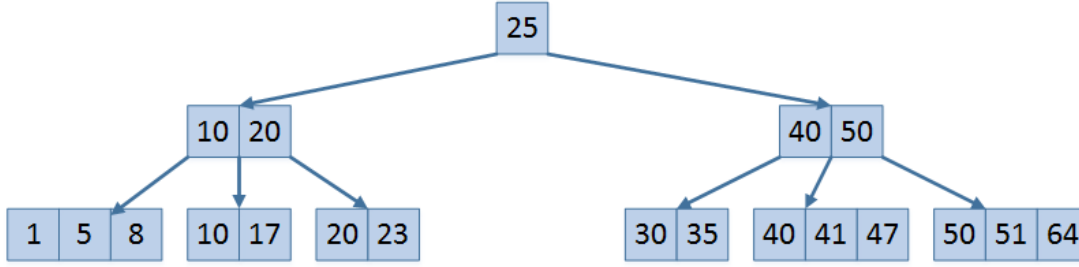
Furthermore, some parts are formulated in a way that cannot be achieved with current technological means, e.g. de-anonymization being impossible in any case, as well as the antagonism between deletion and transparency. Thus, the issue of securing sensitive information is one of the big challenges in machine learning in health related environments.

8.1 Digital Self-Determination

Providing digital self-determination is one of the major targets of the GDPR and forms the background behind several aspects like (i) the requirement for consent, (ii) no consent given implying the need for anonymization, (iii) transparency of the whole analysis process, including the right of the data subject to promptly receive all information regarding the processing of his/her data, as well as (iv) the right to rectify any erroneous information entered into the processing system, even granting (v) the right to have all personal data deleted. This *"right to be forgotten"* can even be called upon in case explicit consent was granted beforehand, meaning consent can be revoked by the data subject basically at all times.

The main problem behind deletion, which is also true for rectification of erroneous data, is that there is currently no definition of the word "deletion" within the GDPR (Villaronga et al. (2017)). Furthermore, the GDPR is written as a legal text with a lot of absolutes that can be interpreted as to demand things that are technically impossible like physical deletion in cloud environments. Another issue regarding deletion are backups that must

8. <https://bonsai.ai>


 Figure 9: Example for a B^+ - Tree

not be changed with respect to backup policies and for security reasons. Also the right to transparency can pose a severe problem, as traceability in complex enrichment processes might require complex Audit & Control mechanisms that will contain parts of the user data.

While in theory, deleting data from a system is not considered a major problem, in the reality of complex systems *provable deletion*, i.e. being able to guarantee that the deleted data cannot be restored, is far from trivial (Villaronga et al., 2017). This becomes especially problematic when considering complex systems like databases that on the one hand store most of the data in real-life environments and are therefore the main concern for data deletion and on the other hand have to cater to requirements like ACID-compliance (Haerder and Reuter, 1983).

While manipulating the data requires quite some knowledge of the internal mechanisms of the DBMS in question, in the end it is just a legal question on how much resilience a deletion mechanism has to provide. To further illustrate this aspect, we stay within the database environment and have a look at "normal" deletion: Quite like in most file systems, data is not actually deleted from the disk, e.g. by overwriting the memory, but just unlinked from the global search indices: Typically, relational databases store their content inside a special structure called a B^+ -tree (Bayer and McCreight, 2002) (see Figure 9 for an example, still, reality is a bit more complex, but this simplification does not significantly change our point):

- For the number m_i of elements of node i holds $\frac{d}{2} \leq m_i \leq d$, where d is a pre-defined value (the order) for the whole tree. Only the root node is allowed to possess less elements (> 0). Inside the nodes, the elements are stored as sorted lists.
- Each inner node holding m elements possesses $m + 1$ child nodes.
- The inner nodes of the B^+ -tree do not store actual information on the elements, but just the information required to let the search engine navigate through the tree efficiently. All actual data is stored in the leafs, which are all on the same level in the tree (balanced tree).

8.2 Unsolicited Propagation of Data

Within a lot of research environments, cooperation with external experts or with academic peers is very important. Within many data driven research approaches this sooner or later

leads to the topic of data exchange, e.g. by sharing data within a common environment or providing experts with sample data. While regulations and legal frameworks like the GDPR deal with the topic of protecting the data subjects, another issue is often neglected: The inherent value of even well-anonymized data, or data sets that do not contain sensitive personal information at all. While not a Privacy issue, a lot of data that is usable enough for providing insight on a certain topic does possess an inherent value that needs to be protected, as it is often a vital asset of the (academic/medical) institution. This is especially true for large collections of pathological data that have been obtained through an expensive process of physical labor. Thus, when institutions join cooperative research projects, they must make sure to be able to protect these data assets.

Typical measures proposed by traditional security research mainly fall into the category of proactive measures, typically limiting the actual data exchange. Examples for these *proactive measures* include the setup of sealed research environments, typically virtualized environments containing all required data and the analysis tools while not allowing the extraction of detailed information, or splitting the information over several independent processing entities that are assumed to not collude (e.g. Hudic et al. (2013)), or providing data only in anonymized or aggregated form.

Proactive measures are of course massively interesting but cannot be used under all circumstances, e.g. when the analysts require their own analysis environments or need the data with a certain quality. *Reactive* approaches on the other hand do not aim at limiting unsolicited propagation, but rather allow to detect it, thus allowing the data owner to recoup their losses with legal actions. Fingerprinting/watermarking of data is the most popular approach in this area. Fingerprinted data contains certain changes to the original information that allow the data owner to determine and prove which partner was the source of a data leak. These fingerprints are required to be stable against colluding attackers and it must not be possible to identify and remove the marks from a marked set. Furthermore, they must be unforgeable in order to protect innocent partners against wrongful accusations. In addition, the less information is required to detect the data leak, the better. While many fingerprinting approaches rely on the addition or change of data records, there are also approaches that utilize the intrinsic features of anonymization (Kieseberg et al., 2014), which can be very useful in case the data has to be anonymized anyways.

8.3 Manipulation Detection

Especially when considering expert-in-the-loop systems in the medical area, the question of securing information against manipulation gains increasing importance. In case experts are used to control and steer the decision making process, their input might be responsible for the well-being of patients, while used in a way that makes it hard for them to actually control the effects, as the data is taken as input by machine learning algorithms and utilized as e.g. knowledge base.

Thus, one vital aspect lies in gaining trust of the doctor in the loop (Kieseberg et al., 2016b,a) i.e. assuring that the information that was presented as starting point for giving expertise is not changed afterwards. In addition, the expert must be sure that the expertise

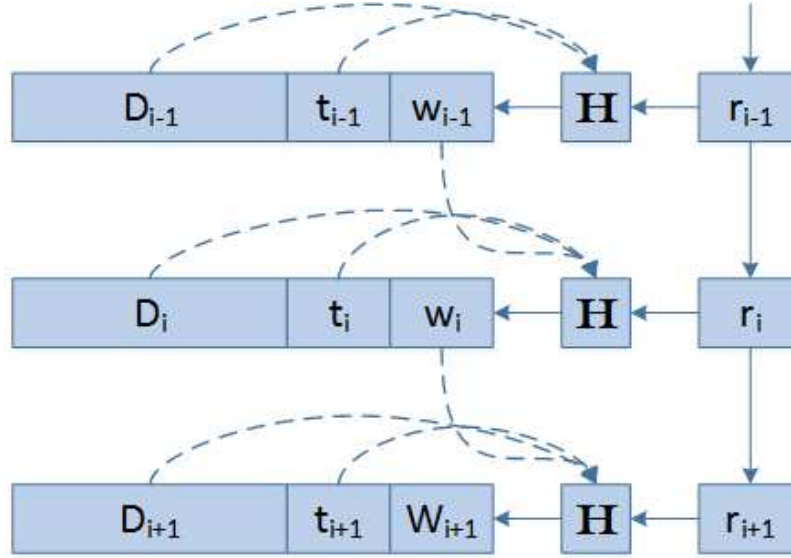


Figure 10: Chaining log entries

(the information) gathered from him has not been distorted, i.e. in case the algorithms produce wrong results, the blame cannot be shifted towards him/her without justification. This is especially important in order to protect the experts against cover-ups, e.g. other experts or the developers of the machine learning algorithms trying to put the blame towards them. In our experience, providing such mechanisms is of vital importance in order to attract expert involvement and make them share their knowledge, as well as to increase the acceptance of the results of semi-automated decision engines.

While many of the tasks required to establish a secure environment harken back to typical topics of system hardening against inside and outside attacks, i.e. making it as impenetrable as possible, and are therefore highly dependent on the actual technical system in place, the data needs to be secured against another attack vector typically not included in security assessments: The manipulation of the data by the system itself, i.e. typically implemented in the form of a database management system. While the system and its administrators are typically trusted to a certain extent in most architectures, they need to be considered as a major antagonist for data manipulation in order to cover up the application of wrong algorithms or the provisioning of erroneous data. Thus, every piece of information that is used in the analysis needs to be secured against subsequent manipulation attacks, even from users possessing administrator privileges.

In addition, other approaches have been introduced including utilization of the database replication mechanism etc., still, research in this area is rather at its infancy and has not received much attention in the past as most real-life systems use traditional system hardening measures together with organizational measures.

9. Conclusion and Future Outlook

Digital pathology poses manifold challenges for AI research generally and ML research specifically. Solutions will benefit education, training, research and clinical decision support. The setting of digital pathology is ideally suited to study both human learning and human decision making and contrast it to machine learning and machine decision making. By comparing both the strengths/weaknesses of machine as well as human intelligence it will be possible to find solutions where we are currently lacking appropriate methods.

Future medicine relies increasingly on various data for better detection and treatment of diseases. In order to extract knowledge from massive amounts of information contained in high resolution images, AI and ML methods are indispensable. Moreover, digital pathology provides a fertile environment to integrate data from heterogeneous and distributed sources (images, text, omics), making novel information accessible and quantifiable - which is not accessible and quantifiable for the human expert to date. A major challenge in this area will be to "break down" the constituent parts of each data source (image region, gene sub-sequence, EHR entry) and to make them interlinkable on a level allowing for reasoning between sensory records, image anomalies & textual description of symptoms. Eventually, this will enable completely new knowledge and query-based systems, where experts may input an image region and receive genetic sequences potentially explaining the observation.

AI-augmented digital pathology will change the education and training of pathologists, which is an urgently needed solution to the global shortage of medical specialists. In order to realize this potential, we will have to define interaction points between pathologists and the learning system; this entails studies to discover which internal learning states can be best represented in a human-intelligible way, what kind of problems the expert is asked to decide (accept/reject a final recommendation or help identifying image regions), and how to incorporate the human decision back into the internal machine model. Defining a new standard protocol for such interactions would also enable external software providers to hook into the process, generating new business models for interactive diagnostics.

Providing insights into the inner workings of algorithms is not only a future legal requirement but also a valuable tool for "debugging", especially in the case of deep neural architectures where exact coefficients at exact moments are to date nearly uninterpretable by human experts. Building on recent works we will in future work experiment with the interplay of iML and explainability - injecting search space constraints based on user decisions gathered from an interaction loop into our programs. Consequently, it is necessary to contrast any gains in explainability with the potential loss of generality incurred by the restriction of algorithmic freedom.

Although deep learning has long proven it's worth in a multitude of ML challenges, we still need to make it efficient on extremely large images (such as WSI). Our main challenge will lie in finding more compact, yet smart image representations e.g. via graph extraction, offering the possibility to "asymmetrically" compress an image via region-to-node projection, i.e. applying different compression rates to regions of different importance. As neural nets take simple feature vectors as their inputs, we can easily replace a pixel representation with a node feature vector or the entries of an adjacency / Laplacian matrix. This approach also promises insights above and beyond image classification, since in the process we will experiment with DNNs "intuiting" network properties like degree distributions or

centralities, potentially yielding deep approximate graph algorithms for problems whose algorithmic runtime has not improved in decades.

As modern AI/ML approaches require great amounts of data, training on local databases could easily hit its limits, yet legal requirements as well as societal expectations restrict us from freely sharing vulnerable data. In order to overcome the unsatisfying trade-off we are confronted with today - lose precision via learning on anonymized data, or risk severe repercussions, we need to examine methods to learn from other models instead of other data.

Eventually, we strive to combine parallel & distributed DNNs working within their respective "local sphere" into a powerful network of learners, each fueled by their unique, private knowledge bases yet capable of incorporating model insights from their peer learners - achieving the grand goal of secure, efficient and reliable privacy aware federated learning.

ACKNOWLEDGMENTS

We are grateful for valuable discussions and comments from our local, national and international colleagues. We thank our industrial partner 3DHistech for their assistance with our new scanner and the Biobank Graz for valuable support. Acknowledged Funding: Hochschulraum-Strukturmittelverordnung.

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