Thesis

An innovative approach to deep learning used as an augmenting tool in the field of oncology

A review of the current literature

Submitted by

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To obtain the academic degree of

Doctor of medicine

(Dr. med. univ.)

At the

Medical University of Graz

Clinical institute of

Medical and chemical laboratory diagnostics

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Graz, February 16th, 2023

Statutory declaration

I declare that I have authored this thesis independently, that I have not used sources other than the declared sources, and that I have explicitly marked all material quoted either literally or by content from the used sources.

Graz, February 16th, 2023 *Sander Claeys eh.*

Acknowledgements

First of all, I would like to thank my supervisors, Priv.-Doz. Dr.med.univ. Dietmar Enko, MSc. MBA LL.M. , and Priv.-Doz. Mag. Dr.scient.med. Andreas Meinitzer, for their advice and support throughout the entire process of composing this thesis. They introduced me to the world of science and gave me the opportunity to perform extensive research on a prospering and interesting topic, which has the potential to change medicine in all of its domains.

At this point, I would like to express gratitude for my family's continuous encouragement and guidance through the different stages of my life. They have instilled in me indispensable qualities and personality traits, transforming me into the man I am today. In particular, I mention my extraordinary grandparents, who I deeply admire for their devotion and wisdom. Their visionary input inspired me to contrive the discussion for this thesis. Furthermore, I want to show my appreciation to my parents and sister for their unconditional love and warmth. They encouraged me to pursue my dreams and facilitated my interest in medicine.

Last but not least, I would like to give special thanks to my dear overseas friend, Jennifer Shepherd, for her support and linguistic assistance.

Thank you for being there for me!

Table of content

Glossary and abbreviations

Abbreviations	Full description
ATP	Adenosine triphosphate
AVC	Angiogenic vascular cell
AI	Artificial intelligence
ANN	Artificial neural network
BB	Black-blood
BI-RADS	Breast Imaging Reporting and Data System
CSC	Cancer stem cell
CAF	Cancer-associated fibroblast
CEA	Carcinoembryonic antigen
CRT	Chemoradiotherapy
CDFI	Colour doppler flow imaging
CT	Computer tomography
CADe	Computer-aided detection
CADx	Computer-aided diagnosis
CNN	Convolutional neural network
DL	Deep learning
DNA	Deoxyribonucleic acid
EMT	Epithelial-mesenchymal transition
EOC	Epithelial ovarian cancer
FDG-PET	Fluorodeoxyglucose-positron emission tomography
GM	Granulomatous mastitis
GPU	Graphics processing unit
H&E	Hematoxylin and eosin
IIC	Infiltrating immune cell
IBM	International Business Machines Corporation
ML	Machine learning

MRI	Magnetic resonance imaging
MeSH	Medical subject heading
MSI	Microsatellite instability
NLP	Natural language processing
NET	Neuroendocrine tumour
NIMA	Never in mitosis gene a
NEK7	NIMA-related kinase 7
NSCLC	Non-small-cell lung cancer
OPSCC	Oropharyngeal squamous cell carcinoma
PI	Proliferation index
PCa	Prostate cancer
PSMA	Prostate-specific membrane antigen
PW	Pulsed wave
pRb	Retinoblastoma protein
RNA	Ribonucleic acid
SA	Sclerosing adenosis
SL	Supervised learning
TCGA	The Cancer Genome Atlas
TIL	Tumour infiltrating lymphocyte
TME	Tumour microenvironment
TNM	Tumour-node-metastasis
US	Ultrasound
ULMS	Uterine leiomyosarcoma
VEGF	Vascular endothelial growth factor
WSI	Whole slide image

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Zusammenfassung

Hintergrund: Die Digitalisierung hat unsere moderne Welt revolutioniert, darunter auch die Medizin. Das exponentielle Wachstum medizinischer Daten wird zu einem zunehmenden Problem, das die manuelle Analyse und Extraktion aussagekräftiger Informationen fast unmöglich machen. Deep Learning (DL) ist in der Lage, Merkmale und wiederkehrende Muster in hochdimensionalen Datensätzen zu erkennen. Die Onkologie wäre daher die perfekte Umgebung. DL könnte zum Identifizieren und Charakterisieren von Krebs und zum Aufdecken neuer molekularer Mechanismen eingesetzt werden.

Ziel: Das Ziel dieser Arbeit besteht in einer umfassenden Synopsis neuer Erkenntnisse, die DL als ergänzendes Instrument in der Onkologie zusammenfassen. Somit wird eine Übersicht über die Entwicklungen in den verschiedenen Bereichen der Radiomics, computergestützte Pathologie und Multi-omics geschaffen.

Methoden: Mit den Suchmaschinen PubMed und Google Scholar wurde eine umfassende Literaturrecherche durchgeführt, die dem Ziel dieser Arbeit entsprechen. Ergänzende Informationen über DL und Tumorentstehung wurden hauptsächlich aus Lehrbüchern und Abhandlungen entnommen.

Ergebnisse und Diskussion: Diese neue Technologie markiert verdächtige Läsionen, prognostiziert die Malignität und überwacht abweichendes Gewebe. Darüber hinaus ist DL hervorragend in der Identifizierung treibender onkogener Mechanismen und Schwachstellen. Diese Entdeckungen können zur Entwicklung gezielter Therapien führen und fördern den Übergang zur Präzisionsmedizin. Der patientenzentrierte Ansatz ermöglicht es, die medizinische Behandlung auf die individuellen Variabilitäten abzustimmen. Somit werden die Behandlung und das klinische Ergebnis maximiert, während gleichzeitig die Nebenwirkungen minimiert werden.

Schlussfolgerungen: Die datengesteuerten Merkmale der DL erweisen sich als hervorragendes Instrument zur Unterstützung von Ärzt*innen in verschiedenen Bereichen ihrer klinischen Routine. Die Automatisierung repetitiver und administrativer Aufgaben wird den Schwerpunkt wieder auf die Gesundheitsversorgung legen und die menschliche Verbindung zwischen Ärzt*innen und Patient*innen stärken.

Abstract

Background: Digitalization has revolutionized our modern world, including the field of medicine. Unfortunately, the exponential growth of medical data forms an increasing problem, making it almost impossible to manually analyse and extract meaningful information. Deep learning (DL) is capable of detecting features and seeking recurring patterns in high-dimensional datasets. The field of oncology is, therefore, the perfect environment for the integration of DL to detect and characterize cancer cells and uncover molecular mechanisms.

Aim and objective: The aim of this thesis consists of comprehensive research and a summary of novel insights into DL as an augmenting tool in oncology. Hence, creating an overview of developments in the fields of radiomics, computational pathology and multi-omics.

Methodology: A comprehensive literature search for all published articles regarding the objective of this thesis was performed using PubMed and Google Scholar as search engines. Complimentary information about DL and tumorigenesis was mostly obtained from textbooks and papers**.**

Results and discussion: This novel technology marks suspicious lesions, predicts malignancies and monitors aberrant tissue. Furthermore, DL is outstanding at discovering driver oncogenic pathways and identifying cancer vulnerabilities, which could lead to the development of targeted therapy. The strength of this revolutionizing technology to quantify interconnected mechanisms of tumorigenesis and uncover patient-specific characteristics boosts the transition towards precision medicine. The patient-centric approach allows the tailoring of medical treatment to individual variabilities and enables the maximization of treatment response and clinical outcomes while minimizing side effects.

Conclusion: The data-driven characteristics of DL appear to be an excellent tool to augment physicians in different domains of their clinical routine. The automation of repetitive and administrative tasks will bring back the emphasis on healthcare again and will strengthen the human connection between physicians and patients.

1. Introduction

Digitalization has revolutionized our modern world, including the field of medicine. The wide adoption of wearable technology in the form of smartwatches, fitness bands and smartphone applications, facilitates the measurement of vital functions and provides an instant overview of one´s fitness. This data can subsequently be compared with patients of similar cohorts for disease prevention or optimization of current treatment plans. In health care, all kinds of information are acquired to help physicians in their daily routines, such as medical history, diagnoses, medications, treatment plans, radiology images, and laboratory results. These various kinds of data are compiled in easily accessible electronic health records.

Unfortunately, the exponential growth of medical data forms an increasing problem, making it almost impossible to manually analyse and extract meaningful information. Big data has been the thriving motor of a novel kind of technology, called deep learning (DL). Its data-driven characteristics enable the detection of features and seeking recurring patterns in high-dimensional datasets. The application of this scalable technology could revolutionize health care in all of its domains.

Cancer is characterized by uncontrollable cell growth and metastases. This multidimensional disease is dependent on a complex network of molecular and environmental components interacting at different levels within the cellular apparatus. The field of oncology is the perfect environment for integrating DL to detect and characterize cancer cells and uncover molecular mechanisms. Therefore, this thesis will explore the newest developments of DL used as an augmenting tool in oncology.

The first part of the background introduces the basic concept of artificial intelligence (AI) and machine learning (ML), building its way up to the technical aspects of DL. The second half explores the mechanisms cancer cells apply to get to their malignant state. The core of this thesis consists of three subchapters, each emphasizing the integration of DL in different domains of oncology. Starting with anomalies of organs and tissues, we dive deeper into morphological changes on the cellular level, to end our journey with molecular aberrations. Finally, these results will be summarised, and the potential future direction of this novel technology will be discussed.

1.1. Artificial intelligence

The alarm goes off, you wake up and command Alexa to play music. Spotify presents a playlist based on your previous songs. While listening, you unlock your phone with face recognition and screen through your emails. Your spam filter sorts out all irrelevant emails, so you can concentrate on the most important ones. After a duration of inactivity, your smartwatch alerts you to exercise. On this typical morning, you´ve already encountered five common applications of AI without even realizing it. Our modern world is surrounded by this innovative technology, but what does it represent?

Alan M. Turing, often seen as the founder of computer science, asked the question of whether machines can think. Therefore, he proposed the idea of a test in his paper "Computing machinery and intelligence" to prove a machine´s intelligence, later called the Turing test (1). An interrogator can write with a human foil and a computer about any topic or question. His goal is to determine which one of both is the computer. If the interrogator is deceived several times, the computer wins the game (1,2). To prove its intelligence a computer must master certain skills such as the ability to communicate in the English language, store knowledge, and use this information to draw new logical conclusions. Additionally, it must extract recurring patterns and adapt to new circumstances (3).

In the early days of AI, scientists tried to duplicate human intelligence. They pursued the idea of making a thinking machine like Alan M. Turing suggested, to explain human cognition. To this day, AI is nowhere near the human level. It could be compared with an analogy to flying (3).

> The quest for "artificial flight" succeeded when the Wright brothers and others stopped imitating birds and started using wind tunnels and learn about aerodynamics. Aeronautical engineering texts do not define the goal of their field as making "machines that fly so exactly like pigeons that they can fool even other pigeons" (3 p3).

Just like the goal of aerodynamics to understand the concept of flying, AI´s ultimate concept is not necessarily the creation of human intelligence, but rather creating problem-oriented agents. The modern approach to AI is building intelligent systems, which solve problems in a narrow field of expertise (3). MYCIN was one of these early expert systems specializing in blood infections. It was programmed to diagnose patients based on their symptoms and laboratory tests. As a result, it would recommend the appropriate treatment plan and had the ability to explain its reasoning. MYCIN´s expertise reached the level of human specialists in this field, confirming the strength of this technology (4).

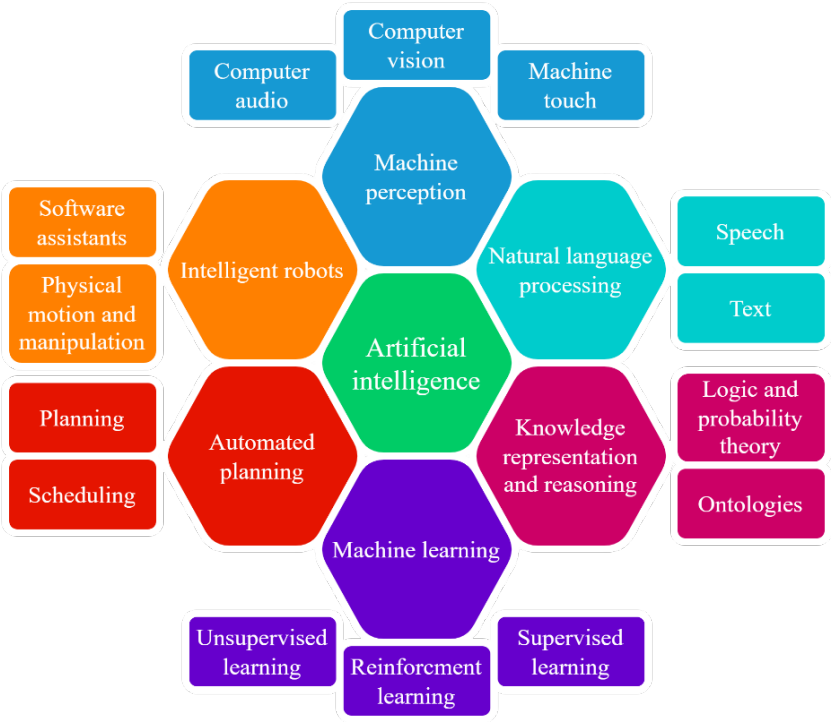

Figure 1: Domains of artificial intelligence, modified after (5)

AI can be seen as a broad term for various domains within the field of computer science and engineering (5). Many of these domains, illustrated in figure 1, have already been implemented in the healthcare system. The technology of natural language processing (NLP), which is often based on ML algorithms, is used for speech recognition, text analysis, and translation. In the clinical setting, NLP is used to convert unstructured patient information, in form of physician notes or electronic recordings, into structured and classified data (6).

Surgical robots are getting more sophisticated with the application of AI technology. They are improving the surgeon´s performance by optimizing optical settings and enabling precise and minimally invasive incisions (6). The outcome of connecting vessels in the field of super-microsurgery is limited by the precision of a surgeon's hand. Microsure is a commercially available robot, which filters tremors and scales down motions of the surgeon´s hand to overcome these human limitations (7).

Whether not following the recommended exercise or forgetting to take prescribed drugs, non-compliance is a major problem generally known by physicians. With the advancement of wearable technology in the form of smartwatches, fitness bands, and smartphone applications, users are more likely to comply. These personalized devices alert patients to take their medication and motivate them to exercise. Furthermore, wearables can measure vital functions and compare this data with patients of similar cohorts for disease prevention or optimization of current treatment plans (6).

Repetitive tasks in administration can be easily replaced by implementing AI. Chatbots interact with patients by making appointments and refilling prescriptions. Other administrative applications manage patient records, billing, and revenue cycles (6). Paradoxically, the implementation of AI applications and automatization of healthcare can free caregivers from mundane tasks to emphasize the human connection.

ML, however, provides the greatest advancements and promises to revolutionize healthcare. This domain of AI is specialized in the detection of features and extraction of meaningful patterns in extensive datasets and shows enormous potential in the field of oncology. With the integration of medical imaging and clinical variables, ML can mark suspicious lesions and predict their malignancy. Furthermore, this technology shows to be excellent at discovering driver oncogenic pathways and identifying cancer vulnerabilities, which could lead to the discovery and development of targeted therapy. Therefore, this thesis will explore the newest developments of this prospering technology in oncology.

1.2. Machine learning

The biggest achievements of AI are in the field of ML which seek recurring patterns in data, to fulfil simple tasks. This technology enabled the development of machine translation, face and speech recognition, gene prediction and beyond, but shows even greater potential in the field of oncology. To achieve these phenomenal results, ML has to be trained first (8).

In the training phase, ML adjusts its function by analysing every data sample, which can be anything from tables to pictures. The function represents a mapping of identical features in the given data, which will be encoded in a computer program. Subsequently, the model is evaluated on its performance in the inference, by applying the function to unseen data. The spam filter is a real-life application of a ML algorithm, which analyses e-mails to differentiate between normal and malware. After finding commonalities associating the data to either one of both groups, it creates a function, classifying malware e-mails and finally moving them to the spam box (8).

Three ways of learning to train ML algorithms could be implemented, called supervised learning (SL), unsupervised learning, and reinforcement learning. The first one is the most common form of ML and the most relevant for this thesis. Each input in the training phase of SL is manually labelled with the expected output value by data scientists, which could be the annotation of objects in an image. The algorithm knows the outcome, but still has to learn the patterns to differentiate between different objects, like a dog and a bird. Using the difference between the estimated and correct outcomes, the model will update its function to minimize the error. Ultimately, the algorithm will find the correct function that differentiates between objects and classifies them correctly (8).

Unsupervised learning categorizes unlabelled datasets into clusters. The algorithm tries to group examples with high similarities into the same cluster, without knowing its correct output value. The objective of this method is to achieve a great diversity between clusters while maintaining a high correlation within the group. This type of technology is mostly useful for companies, such as Amazon, which desire the clustering of people with the same interests and purchases. This way they can recommend products to these specific groups and target them with marketing campaigns (8).

The basic concept of reinforcement learning has been influenced by the work of Allan M. Turing. He philosophized about whether a machine should be programmed like a child´s mind and stated that the machine would be much easier to program this way. Like a child,

the algorithm would learn by getting punishments and rewards for certain actions, eventually reaching the level of an adult´s mind (1).

This technology is most needed in control tasks, such as robotics and gaming, in which it aims to get rewarded for its actions. It will reinforce a certain action that led to a positive reward and will weaken those, which led to a negative reward (8). For instance, if certain moves of a chess game led to victory, it will save them for further games. In 1997, chess proved to be a perfect environment for reinforcement learning. The chess computer of International Business Machines Corporation (IBM) beat the world champion of chess, Garry Kasparov (2). Thirty years after this victory, ML beat the world champion in the board game Go. This game is much more complex than chess, because of the extensive number of board configurations. AlphaGo was programmed with a new ML concept, called DL, which proves the potential of this emerging technology (8).

1.3. Deep learning

The exponential growth of data in our digital world has been the thriving motor of a novel kind of technology, called DL. This subfield of ML specializes in the automated detection of features and recurring patterns in high-dimensional datasets, such as pictures. DL is put through a training phase with labelled or unlabelled datasets, in which the same principles of ML are applied. Subsequently, the model is evaluated on its performance in the inference, by applying the function to unseen data (8).

DL has only emerged recently because of the development of more efficient algorithms and the invention of faster hardware, called graphics processing units (GPUs). The coherence of the three factors, illustrated in figure 2, facilitates the computational power needed to calculate its elaborate network and boosts further development (9).

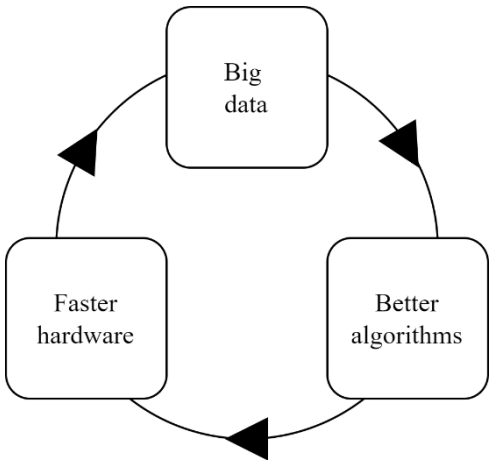

Figure 2: Vicious cycle driving deep learning, modified after (9)

1.3.1. Artificial neural network

The function of DL is based on the neural network of our brain, in which each nerve cell performs a simple task to create a problem-solving network. A neuron, exemplified in figure 3, consists of a cell body, multiple dendrites, and an axon with axon terminals. The synapse connects an axon terminal of one neuron with a dendrite of the neighbouring neuron. Information is passed to the following neurons in the form of electrical currents, in which dendrites operate as input channels and axons as output channels. Only if a certain threshold is exceeded, the next neuron will be fired and pass an electrical signal to connected neurons. Consequently, a neuron will either pass its set of inputs to the next neuron or produce no output (10).

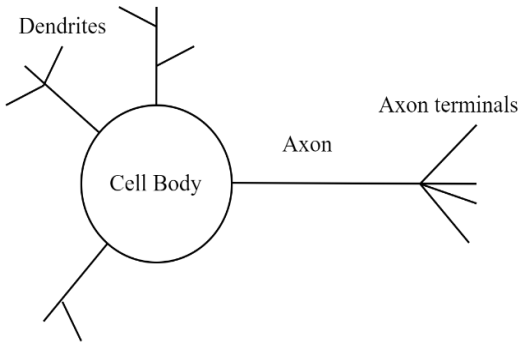

Figure 3: Structure of a neuron, modified after (10)

The building blocks of DL are “digital” neurons, connected in an artificial neural network (ANN). Each neuron, represented as circles in figure 4, consists of a computing unit, learns a simple function and therefore solves a little piece of the puzzle. It maps the input values to a single output value and presents them as input values for neurons in the next layer. The hierarchical combination of these simpler functions through a neural network creates a complex model that solves the overall problem (10,11).

The structure of a simple ANN is based on three layers. The neurons in the first layer, represented as squares, have no computing function but introduce datasets, such as images or tables, to the network. They can be seen as sensing neurons, representing the value of their input to neurons in the next layer. The output layer represents the results of processed information by the hidden layers, which are formed by multiple layers of interconnected computing units (10). The superficial layers learn to recognize simple features like edges, corners, and lines. These features will be combined in deeper layers to recognize more

complex features such as noses and mouths, which are merged in the final layer to identify faces. The results will be presented in the output layer (12).

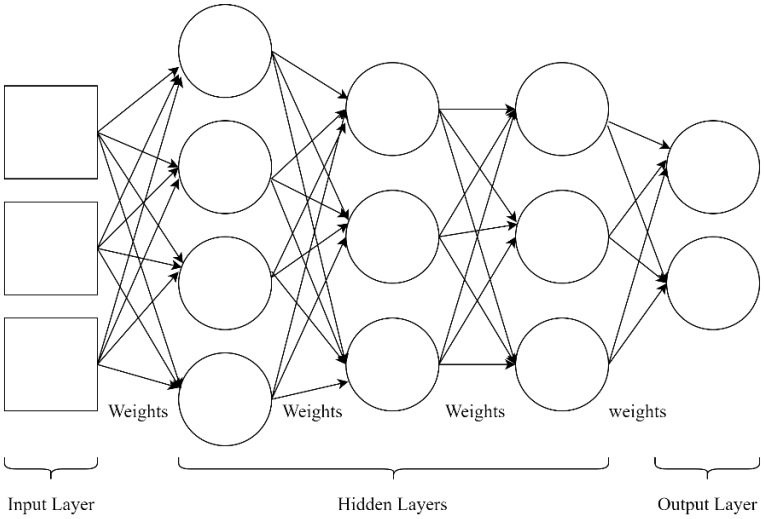

Figure 4: Illustration of a simple neural network, modified after (10)

The core idea of DL is based on Hebb´s postulate, which explains the creation of learning. The connection between neurons will strengthen, due to their repeated activation. A strong connection points out the importance of these neurons in the network (9). Analogically to the strengthening of neural connections in the brain, DL tries to figure out which connections contribute more to determine the output value. To strengthen or weaken a connection, a certain value or weight is given to each link. Through learning the appropriate weights, a correct function is extracted, which will ultimately lead to the right classification (10).

Figure 5 illustrates the technical detail of a neural connection in an ANN. A neuron maps the input values of previous neurons to a single output value, which is in turn presented as an input value for neurons in the next layer. The computing unit processes information from previous layers by multiplying the input values from each neuron in the previous layer by its according weight (input value 1 multiplied by weight 1 and so forth). These resulting values are subsequently added to each other to form the so-called weighted sum (10,11). An artificial neuron must decide whether a neuron is valuable to the network and should pass its information or not. Therefore, a final calculation is performed, transforming the weighted sum into an activation function. The neuron will fire and pass its information to the next layer when the output value exceeds a certain threshold (10).

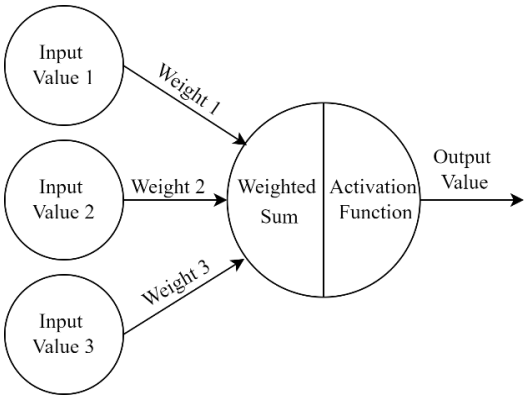

Figure 5: Structure of an artificial neuron, modified after (10)

In the case of an image classifier, a picture is introduced in an ANN, in which each pixel is presented to a different neuron in the input layer. The input value, which is the intensity value of that pixel, will be multiplied by its weight. It does this for every connection and adds all the results together. The activation function of the weighted sum will determine if the information in that picture is valuable enough to contribute to the correct classification of images.

The objective of ANNs is to find the correct weights, enabling the detection of specific features. At first, the model is inaccurate, because of the random setting of the weights. The model will compare its predicted output with the correct output, given by SL, and tries to minimize the error between these values. It does this by the technique of backpropagation, by calculating the amount of blame each connection has for the error. The computer starts from the output layer until it reaches the first hidden layer. As a result, the algorithm updates its weights accordingly and learns the correct function (9). If the error is zero, the weights stay the same. If the error is positive, the weights will be decreased, in proportion to their blame. If the error is negative, the opposite occurs (11).

For instance, at first, a mole classification system labels an image of a melanoma mole as a common mole because it does not know yet what these different moles look like. In the training phase, the model learns and extracts features of the annotated input images, such as the asymmetry of a mole´s form, colour, diameter and borders of moles. Normal moles showed to be either black, cinnamon or brown, whereas melanoma moles were commonly associated with a diameter greater than six mm. The algorithm will update its weights accordingly to the value of these extracted features, thus improving its performance. A fully trained network will be capable of accurately differentiating between normal moles from melanomas (13).

1.3.2. Convolutional neural network

A convolutional neural network (CNN) is a specialized ANN in the field of image classification. In 2012, a CNN, called AlexNet, proved the potential of these expert systems as the winner of the ImageNet large-scale visual recognition challenge. This annual competition in image processing, recognition, and labelling, provides researchers with ImageNet´s extensive database of annotated images to develop their DL algorithm (9).

The architecture of CNNs has been influenced by another analogy of the brain, the visual cortex. Hubel and Wiesel inserted electrodes into the brains of sedated cats to study the brain's response to visual stimuli. They found that certain cells in the visual cortex would rapidly respond to specific visual patterns, like lines at a certain angle (9). A single cell would only respond to stimuli in a certain location in the visual field of the cat, called the receptive field of this neuron. In addition to these simple cells, they found another type of cell, which would respond to the same stimuli regardless of its position. They concluded that there must be some sort of hierarchical projection of the simple cells onto complex cells. The receptive field of a complex cell would therefore be the summation of the receptive fields of several simple cells (9).

Like the simple cells of the visual cortex, specialized detectors of CNNs look for local visual features like a flashlight in a dark room. The lighted areas are the receptive fields of these neurons, which are combined in hierarchical layers to classify pictures. The goal of a CNN is to learn the appropriate set of weights to optimize the feature detection function. The network must, for instance, be trained to detect unique features that differentiate dogs from birds (12,14).

Figure 6 illustrates a simplified version of a CNN, containing input, hidden and output layers. The hidden layers consist of various convolutional layers, which are a sequence of a convolution mask, a feature map, a layer of activation functions and a pooling layer. Each one of these layers performs an individual task, contributing to feature detection and image classification (12).

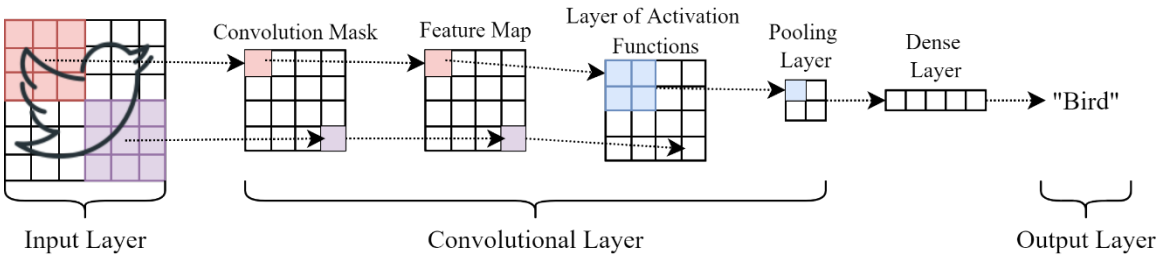

Figure 6: Illustration of a convolutional neural network, modified after (12)

The first layer is called a convolution mask or kernel. This filter detects only one specific feature, like curves, straight edges, or simple colours. A curve detector, for instance, is a filter with a pixel structure, in which the area resembling a curve will have higher weight values. Like in figure 6, the convolution mask screens systematically through the picture, beginning with the first neuron in the left corner until the last neuron in the convolution is reached. The receptive field of each neuron will inspect a different portion of the image for this specific feature. By combining the receptive fields of these neurons, just like the complex cells of Hubel and Wiesel, a convolution covers an entire image (12,14).

In the second layer, the input values of the picture will be multiplied by the weights of the curve detector and result in a so-called feature map. This layer represents all locations where this certain feature, here a curve, is detected. Like neurons in ANNs, these weighted sums must be transformed by an activation function, which will determine if the information in that picture is valuable enough to contribute to correctly classify images. The last layer in this sequence is called the pooling layer, in which the gathered information is downsized and simplified. (12).

A CNN consists of many convolutional layers, which are combined in a fully connected layer. Note that only one of these feature detectors is represented in figure 6. The dense layer enables the combination of simple features to form complex features, like paws and wings. Finally, this layer looks at the outputs of these high-level features and determines which features correlate most to a particular class. If the activation maps have high values in features representing wings and beaks, the network will label the image with “bird” (12,14).

The pre-process of CNNs is a critical step to assure a network's credibility and reduce bias. One common method is transfer learning. Using images from a large collection of annotated natural objects, such as ImageNet, a network is introduced with basic features such as shapes and edges. After this process, disease-specific data is introduced to the model, enabling it to finetune its parameters in the last layers. An alternative technique is based on an autoencoder, which learns background features from representative images and encodes a compressed representation of these basic features, which are later used to initialize CNNs. The Cancer Genome Atlas (TCGA) is one of the most comprehensive databases, including a large number of data types, such as genomics, epigenomics, proteomics, histopathology and radiology images. This enables researchers to improve their model based on a large number of annotated images and by integrating diverse types of data, like genomes and proteomes (15).

In 2016, the CAMELYON competition was introduced to propose solutions to detect and classify breast cancer metastases in sentinel lymph nodes. Most of the submitted algorithms were CNNs and the best classification models were exclusively based on the method of transfer learning, indicating the significance of this technology. The large dataset of annotated whole slide images (WSI) of this challenge was a game changer in the field of oncology comparable to the impact of ImageNet on the computer vision community. CAMELYON nourished the interest of scientists in this advanced technology and stimulated further research and development of DL algorithms in the field of oncology (15,16).

1.4. Oncology

Cancer is a diverse disease, identifiable by its uncontrolled cell growth and its character of spreading to distant body parts. This highly complex disease depends on a large number of molecular and environmental components interacting at various levels to shape its ultimate phenotype. Driven by alterations of the genome and epigenome in the cellular machinery, tumour cells acquire functional capabilities to get to their malignant state. Surprisingly, these aberrant cells reprogram and corrupt normal cells, creating an optimal environment to support tumour development and progression. Understanding these interconnected mechanisms and molecular pathways of tumour behaviour is crucial for discovering and developing novel targeted therapy.

1.4.1. Hallmarks of cancer

Hanahan and Weinberg proposed the concept of hallmarks of cancer, which are biological capabilities, that normal cells must acquire during the multistep process of tumorigenesis, to enable them to become tumorigenic and ultimately malignant. This concept makes it possible to organize the complexity and variety of tumour types and subtypes into a set of cellular parameters. The diversity of this broad spectrum of phenotypes is a result of tissue-specific barriers, which had to be circumvented during tumorigenesis (17,18).

The hallmarks, summarised in figure 7, include the acquired capabilities for sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing/ accessing vasculature, activating invasion and metastasis, reprogramming cellular metabolism, and avoiding immune destruction. Each of these capabilities serves a role in the development, progression, and persistence of tumours, although not all hallmarks have to be acquired to become aberrant (17,18).

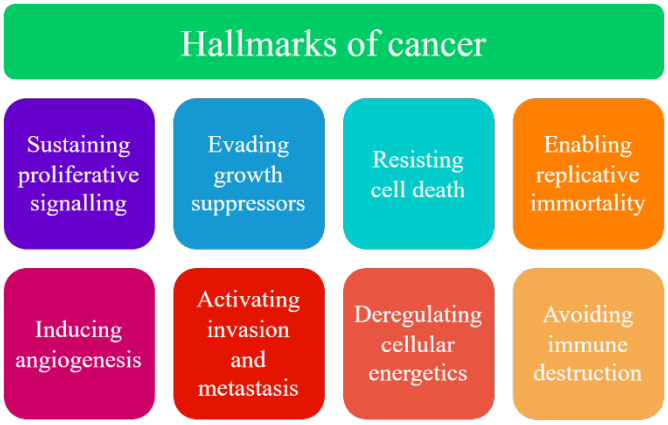

Figure 7: Hallmarks of cancer, modified after (17)

The main characteristic of cancer cells is the ability to grow uncontrollably. By deregulating the production and release of growth-promoting signals they become masters of their own destinies. ´Driver mutations´ convert normal genes into oncogenes, which alter signal transduction circuits to stimulate and sustain the progression of cells without constraint. In some instances, autocrine and paracrine signalling circuits can also be deregulated by epigenetics, which involves changes in the gene activity and expression, rather than mutations in the deoxyribonucleic acid (DNA) sequence (17,18).

Another mechanism cancer cells have to circumvent to proliferate indefinitely, is the controlling apparatus of the cell division cycle, which consists of two essential gatekeepers. The retinoblastoma protein (pRb) is one of the direct regulators of the cell cycle. Through a complex mechanism of intra- and extracellular signals, pRb decides whether the cell should proceed with its growth-and-division cycle. Contrary to the pRb, which mostly responds to extracellular signals, the p53 protein reacts to intracellular stress and abnormalities, doing so by shutting down the cell division until the conditions have been normalized. If a degree of damage to the genome is irreparable or the intracellular conditions are alarming, p53 will induce a form of programmed cell death, called apoptosis. By shutting down these pRb and p53 pathways, through genetic mutations and epigenetic mechanisms, cancer cells are a step closer to the full freedom of division and proliferation (17,18).

Our body has thought of programmed cell death as another barrier to cancer development. As mentioned above, apoptosis forms one of these barriers, inducing the suicide of aberrant cells. It does this by degrading cellular organelles, shrinking the cell and its engulfment by macrophages. As a result of this fast process, apoptotic cell bodies do not release subcellular components, that could provoke an immune response. Necrotic cells, on the contrary, induce

an inflammatory reaction, by bloating and exploding. Therefore, releasing their contents in the immediate environment can have both tumour-promoting and tumour-antagonizing effects. Autophagy is a third method of the body to respond to cellular stress. This program breaks down cellular organelles and recycles them as metabolites and nutrients. To survive, cancer cells must think of smart ways to bypass this natural barrier (17,18).

A built-in mechanism in our DNA, called the telomers, prevents the indefinite proliferation of cells. These multiple tandem hexanucleotide repeats protect the ends of chromosomal DNAs from end-to-end fusions and eventually unstable chromosomes. By every cycle, the length of the telomeres shrinks and will ultimately surpass a certain threshold. This leads to cell death or senescence, which is the irreversible entrance into a non-proliferative state. Hence, this limits normal cells to a certain amount of cell cycles. To overcome the barrier of limited replication, the majority of cancer cells have found a way to maintain these telomeres. Most of them use the enzyme telomerase, which adds telomeric DNA at healthy lengths (17,18).

Cancer cells may seem invincible, however, like normal cells, they need a steady supply of oxygen, glucose and other nutrients along with the ability to evacuate metabolic waste. These needs are fulfilled by angiogenesis, which is the process of developing new blood vessels. In a healthy adult, angiogenesis is transiently activated in phases of wound healing and female reproductive cycling. Unfortunately, ´the angiogenic switch´ in cancer is almost always activated, due to the help of stimulating proteins like vascular endothelial growth factor (VEGF) and the fibroblast growth factor. Hence, new vessels are continually sprouting and helping to sustain the expansion of malignant cells. Pathologists report that tumour neovasculature is often aberrant in both its morphology and functionality. These blood vessels are dilated and leaky and contain precocious capillary sprouting and abnormal blood flow (17,18).

The development of new blood vessels is not the only functional capability to sustain their proliferative state. Cancer cells change their energy metabolism and process glucose in a far less efficient way than normal cells do. The reason for this transformation is, besides the production of cellular energy in form of adenosine triphosphate (ATP), the assembly of additional building blocks for cell growth and division. Lactate, for instance, was for a long time considered a toxic waste. However, this molecule has tumour-promoting capabilities and is utilized as an energy source and biomaterials (17,18).

Although it remains unclear whether metastasis is beneficial for primary tumours, this well-known phenomenon counts as one of the hallmarks of cancer. This process is a sequence of discrete steps leading to the ultimate invasion and metastasis of distant tissues. At first, cell-biological changes enable local invasion, which is followed by the intravasation into nearby blood and lymphatic vessels and the dissemination throughout the whole body. After escaping the vascular and lymphatic systems, these cancer cells form micro metastasis, which will eventually lead to colonization and macroscopic tumours. Research suggests that these aberrant cells use the developmental programme, called the epithelial-mesenchymal transition (EMT), which normally occurs only in embryogenesis and organogenesis. These transformed epithelial cells lose their cell polarity and cell-cell adhesion by losing their adherens junctions and therefore gaining the capability of migrating (17,18).

Our immune system is the last obstacle preventing malignant proliferation and metastases. Cancer cells must acquire immune-evasive strategies to overcome this active surveillance. As the immune system develops a tolerance toward self-antigens, the possibility exists that these aberrant cells may pass under the radar if expressing such antigens. Immune phenotyping of tumours could become beneficial in more accurate predictions of prognosis and treatment decisions (17,18).

These hallmarks enable the interpretability of tumour behaviour and help to unravel pathophysiological mechanisms, which can be used for developing targeted therapeutics. This originates from the idea that if a hallmark is truly important for a tumour's existence, its inhibition will impair the growth and progression of cancer cells. Unfortunately, alternative mechanisms are mostly involved in the acquisition of capabilities. Thus, a drug targeting one key pathway may not inhibit the complete hallmark, allowing cancer cells to survive and adapt to the selective pressure. This acquired drug resistance can even lead to reduced dependence on this particular hallmark. One solution could be to target multiple hallmarks at once, increasing the difficulty for cancer cells to develop resistance mechanisms. By further exploring the molecular and cellular pathways of tumorigenesis, vulnerabilities can be elucidated for drugs to target. However, the development and application of these therapeutics have to be carefully considered to avoid drug resistance (17,18).

1.4.2. Emerging hallmarks

Besides the core hallmarks described above, additional hallmarks are thought to have some role in the multistep process of tumour pathogenesis. These emerging hallmarks, summarised in figure 8, comprise acquiring functional capabilities such as unlocking phenotypic plasticity, non-mutational epigenetics reprogramming, polymorphic microbiomes and senescent cells. They may contribute to a more holistic understanding of the complex mechanisms and manifestations of this disease. However, to become included in the core hallmarks, evidence has to validate their contribution to malignancy (19).

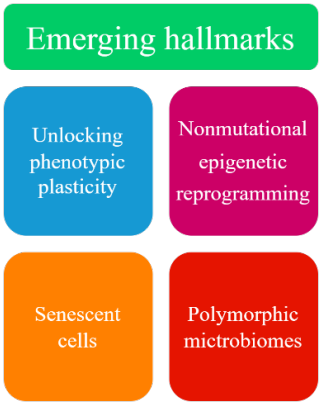

Figure 8: Emerging hallmarks, modified after (19)

Terminal differentiation, in which cells cease further differentiation, forms a natural barrier against neoplasia. However, recent evidence shows that cancer cells evade this restriction by unlocking phenotypic plasticity. They acquire the ability to dedifferentiate from their fully differentiated states back to progenitor-like cell states or even change regulatory circuits to block further differentiation. A third functionality cancer cells may use, is the one of trans-differentiation, allowing cells of one differentiation pathway to switch to entirely different developmental programs. Gaining the ability to evade terminal differentiation and change their cellular programming facilitates cancer cells to become masters of their own destiny (19).

Mutations and genome instability are widely accepted to enable the acquisition of hallmarks and form the fundamental components of tumorigenesis. However, another independent enabler of cancer development has arisen. The so-called non-mutational epigenetic reprogramming relies on changes in DNA methylation, epigenetic histone and chromatin

structures and the triggering of gene expression switches. Evidence has shown that cells of the tumour microenvironment (TME) can cause changes in the epigenome, which can result in the acquisition of hallmark capabilities. Hence, cancer cells and their environment are closely associated with the reprogramming and corruption of normal cells to further support tumour development and progression (19).

Each tissue and organ are associated with its characteristic microbiome, which has its typical diversity and population dynamics. Increasing evidence shows that the ecosystem created by microorganisms may have a protective effect on cancer development and malignant progression. Some bacterial species have been identified to directly stimulate the hallmark of proliferative signalling and modulate growth suppression by altering tumour suppressor activity. They might even be involved in the acquisition of drug resistance. The mechanisms of these phenomena still have to be elucidated (19).

Cellular senescence forms an alternative to programmed cell death and is induced by microenvironmental stress and damage to DNA, organelles, and other cell components. This mechanism instructs cells to shut down their cell division cycle, release bioactive proteins, and evoke changes in cell morphology and metabolism to maintain tissue homeostasis. Cellular senescence has long been thought to be a protective mechanism against cancer, however, evidence suggests the contrary. In certain cases, senescent cells contribute to acquiring hallmarks such as proliferative signalling, avoiding apoptosis, inducing angiogenesis, and stimulating invasion and metastasis (19).

These emerging hallmarks help to further elucidate the complex pathophysiologic mechanisms of this disease and may contribute to the discovery of cancer vulnerabilities. However, these four parameters must be further explored and validated to be established as worthy hallmarks and potential targets.

1.4.3. Enabling characteristics

Cancer acquires functional capabilities, driven by two enabling characteristics in the cellular machinery. The first major mechanism is based on alterations in the genome. DNA is constantly exposed to a variety of mutagens, such as environmental factors and reactive by-products of normal metabolism. Our DNA-maintenance machinery tries to detect and repair these unavoidable mutations and inactivates or intercepts mutagenic molecules. p53, also called the guardian of the genome, is such a repair system and induces apoptosis by irreparable damage. Unfortunately, forty percent of all cancers have mutations in their alleles transcribing p53. Without this protein, DNA is left unrepaired and leads to genomic instability, which enables an escalation of mutations within a cell lineage (17,18).

Not being subjected to cell cycle inhibitors, cancer cells undergo more divisions than normal cells would be able to do. Therefore, the mutation-generating replication errors rise exponentially, resulting in potential hallmark-enabling mutations. The high number of cell divisions is problematic for a second reason. If not maintained properly, telomers shorten and gain the ability to fuse with other chromosomes and become unstable, resulting in the amplification or deletion of chromosomal segments. Another pathway of enabling hallmark capabilities is through the epigenome, which consists of heritable changes in chromatin, without changing the nucleotide sequences, as mutations do. Currently, an astonishing amount of data is being generated by genomic technology. The major challenge is to determine, which alterations contribute to hallmark-enabling mutations. DL could be assisting us in looking for a needle in a haystack of data (17,18).

Tumour-promoting immune infiltrations are held as the second major enabling characteristic. Although aberrant cells must evade the adaptive immune system to assure their survival, research has shown that most cancers are surrounded by so-called infiltrating immune cells (IICs) helping cancer to acquire hallmarks. These mediators of inflammation release proliferative signals and pro-angiogenic factors, enabling them to proliferate, invade local tissue and eventually lead to metastasis. Tumour infiltrating lymphocytes (TILs), which are specific IICs, promote angiogenesis and actively suppress cytotoxic T-lymphocytes. Additionally, they release reactive oxygen species in their direct environment to accelerate the state of malignancy. Pre-existing inflammatory conditions are, therefore, fertile breeding grounds for many cancer types (17,18).

1.4.4. Tumour microenvironment

For a long time, cancer cells have been thought to be relatively homogeneous. Recent histopathological founds, surprisingly, have shown the complexity of these cells surpassing that of normal tissue. Many tumours contain regions with various degrees of differentiation, proliferation, vascularity, inflammation and invasiveness. Currently, a lot of interest is taken in the field of TME, because of its crucial role in the acquisition of cancer hallmarks. The TME consists of three important classes of stromal cells (17,18).

Firstly, cancer-associated fibroblasts (CAFs) are cells secreting proteases and signalling ligands, which can liberate epithelial cells from growth suppression. They have the additional capacity to stimulate tumour-promoting inflammation, which is an enabling characteristic of cancer. Other abilities in their array are the provision of fuel, inducing angiogenesis and helping cancer cells to evade attacks by the immune system (17,18).

The second type of stromal cells are angiogenic vascular cells (AVCs), which are responsible for forming tumour-associated vasculature. Using the concept of the angiogenic switch, which is introduced in the hallmark of angiogenesis, endothelial cells are programmed to construct new blood vessels. The final group of cells contributing to the TME are the IICs, which are explained in the previous subchapter (17,18).

A special category of cells has also been discovered in the TME, cancer stem cells (CSCs). Because of their slow pace of proliferation, they may seem to be lacking tumour initiation. However, slowly proliferating CSCs are more resistant to existing anti-cancer drugs and can initiate the regrowth of the tumour after initial treatment (17,18).

Mapping different stromal cell types and understanding the interconnected mechanisms of the TME to reprogram and corrupt normal cells is crucial for discovering cancer vulnerabilities and the development of targeted therapy.

2. Methodology

A comprehensive literature search for all published articles regarding the integration of DL technology as an augmenting tool in the field of oncology was performed using PubMed and Google Scholar as search engines. Additional information about the novel technology of DL is mainly based on the textbook written by Kelleher JD. The theoretical background of tumorigenesis is mostly determined by the innovative ideas of Hanahan D and Weinberg RA. Further access to textbooks and relevant online material was primarily gained through the library of the Medical University of Graz.

Studies were screened and assessed regarding the relevance of their title and abstract to the purpose of this thesis. The following filters were applied to narrow down the number of search results:

- Only articles that were available in a full version for free were considered.
- The publication date was set at a limit of five years to include only the latest findings on this topic.
- Only articles in English and based on human studies were examined.

Adequate medical subject heading (MeSH) terms were used in different combinations, by applying quotation, truncation, parentheses and the Boolean operators “AND”, “OR”, and “NOT” to specify the search and to cover relevant synonyms and interchangeable terms. The following words and MeSH terms were used in this research: “Deep Learning”, “Artificial Intelligence”, “Neoplasms”, “Oncology”, “Cancer”, “Radiology”, “Pathology”, “Radiomics”, “Genomic”, “Transcriptomic”, “Proteomics”, “Pharmacogenomics”, “Multi-omics”, “Precision Medicine”, and “Targeted Therapy.”

Additional literature was gathered by evaluating the bibliographic reference lists of the reviewed papers to identify relevant publications that were missed during the initial search. Mendeley Cite was chosen as a citation program and used as a means to manage the references.

3. Results

Cancer is a multidimensional disease, driven by alterations of the genome and epigenome. These changes in hereditary information facilitate the acquisition of functional capabilities to shape their ultimate, malignant state visible to the human eye through several imaging techniques. Radiologists examine structural anomalies of organs and tissues. DL shows to be an excellent augmenting tool in this field of expertise, providing pre-screened images with automated detection of suspicious lesions and predicting their malignancy.

Zooming in on these structural anomalies, the world of histology presents morphologic changes on a cellular level. By detecting and quantifying mitotic activity, vascular invasion and metastasis, tumour behaviour can be closely observed. DL can assist pathologists in detecting and characterizing the abundant information presented on histopathological slides, due to its data-driven property.

Tumour behaviour is dependent on a complex network of molecular and environmental components interacting at different levels within the cellular apparatus. Quantifying these interconnected mechanisms is crucial for discovering and developing novel targeted therapy. DL is capable of analysing associations between multiple types of data, extracting information to identify prognostic biomarkers and predict clinical outcomes and responses to targeted therapeutics.

3.1. Radiomics

Based on education and experience, radiologists detect, characterize and monitor diseased tissue. Unfortunately, the workload of physicians increases exponentially because of the disproportionate growth of imaging data, resulting in inevitable errors (20). Radiomics, an emerging field in medicine, aims to extract and analyse features from medical images to improve diagnosis, prognosis and clinical decision support (21).

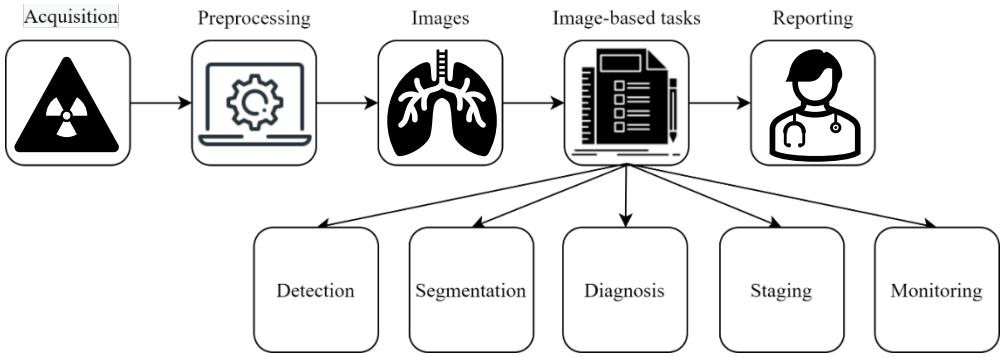

Figure 9: Workflow in radiology, modified after (20)

The clinical workflow in radiology, illustrated in figure 9, starts with the acquisition of images based on different scanning technologies. These scans are introduced to a pre-processing program, reducing noise and enhancing image quality to improve the diagnostic performance of radiologists. Jun et al. constructed a CNN, which could effectively suppress blood vessels while retaining metastases in magnetic resonance imaging (MRI) of the brain. Blood vessels have the same high signal intensity as metastatic lesions and can therefore easily be mistaken for metastases. In clinical routine black-blood (BB) imaging is used to suppress such vessel signals. Unfortunately, this additional scan is time-consuming and sensible to motion-related artefacts. The model enables effectively synthesising BB imaging while obtaining metastases, without the need for additional scans (22).

To detect possible irregularities, radiologists scan through images, while modifying viewing planes, window widths and level settings. Relying on their knowledge and experience, they are trained to distinguish between healthy and abnormal radiographs. To some degree, this can be subjective and therefore unreproducible (20). This problem can be solved with the help of the so-called computer-aided detection (CADe), which can screen a large number of

medical images and mark suspicious lesions. These pre-screened images are then suggested to the radiologist for further evaluation (23).

Lung cancer, of which eighty percent are non-small-cell lung cancer (NSCLC), has the highest incidence of malignant tumours and has become the leading cause of tumour-related death. Unfortunately, this type of cancer is associated with a lack of clinical manifestations in its early stages, silently progressing its malignancy as a consequence. Studies have suggested the five-year survival rate increases significantly if detected and treated early. This shows the importance of early diagnosis and treatment to improve the prognosis and quality of life of these patients. Chen et al. proposed a film reading system with automatic nodule detection in the diagnosis of NSCLC. They concluded that this system has a higher sensitivity for the diagnosis than radiologists, the false positive rate, however, was relatively high. With some improvements, this CADe could be used as an auxiliary detection tool for screening NSCLC in the near future (23).

After being detected, malignant lesions must be segmented from healthy tissue. Delineation is a very time-consuming process and is strongly dependent on the precision of the practitioner. This procedure is essential, especially in the planning of radiation therapy (20). RayStation, a commercially available DL system, is programmed to automatically delineate anatomical structures in computer tomography (CT) and MRI datasets in under a minute. The CNN is trained on a large number of previously segmented image sets and can additionally be trained on external datasets to promote generalizability (24).

Based on quantitative characteristics, such as size, maximum diameter, sphericity, internal texture, and margin definition, radiologists classify abnormalities, as benign and malignant (20). Liu and colleagues developed a combined DL model incorporating mammographic data and clinical variables to predict malignancy. A dataset of Breast Imaging Reporting and Data System (BI-RADS) 4 breast microcalcifications, which is an early suspicious indicator, detected by radiologists has been used to train the CNN. Additionally, risk factors, like age, family, history of breast cancer, menopausal status, and further mammographic features such as breast composition, location, distribution, and morphology of microcalcification have been included in the training. The performance of the model rivalled the senior radiologists and outperformed junior radiologists with a significant difference. Furthermore, the study indicated an increase in the performance of junior radiologists provided with DL assistance, proving the value of DL as an educational tool (25).

Yu et al. went a step further and trained a CNN to not only distinguish between benign and malignant tumours of the breast, but also between sclerosing adenosis (SA) and granulomatous mastitis (GM), which are non-cancerous pathologies of the breast. Three models were proposed to compare diagnostic accuracy between three common ultrasound (US) settings. 2D images contain information about the intensity of the tissue, 2D- colour doppler flow imaging (CDFI) has additional information about the surrounding blood flow and 2D-CDFI with pulsed wave (PW) images measure the velocity of blood in a precise area within the lesion. The CNN proved to be superior to all ultrasonologists, even showing a shorter time and higher accuracy. The researchers concluded the classification to be more accurate for identifying benign and malignant tumours than for GM and SA, in which the 2D-CDFI model performed better compared to the other models (26). This so-called computer-aided diagnosis (CADx) system could help physicians in the accurate prediction of malignancy, resulting in a reduction of unnecessary biopsy and treatment. Consequently, these systems will be capable of replacing the second independent reader instead of the current double-human reading system and contribute to the reduction of physicians´ workload (20, 25).

The last step is staging aberrant tissue, by relying on information from previously segmented and diagnosed areas. The most widely used staging system in oncology is the tumour-node-metastasis (TNM) classification. T describes the primary tumour site and size, N describes the infiltrated regional lymph nodes, and M describes whether metastasis is present. TNM classification enables the prediction of prognosis and survival likelihood, and accordingly, appropriate treatment is chosen (20).

Although the automation of staging systems is still in its infancy, researchers developed a CNN predicting lymph node infiltration in prostate cancer (PCa), combining CT and a radiotracer targeting prostate-specific membrane antigen (PSMA), which is a marker correlated to aggressive PCa. A common problem within DL is its unexplainable decision-making, provoking scepticism among physicians and researchers. To overcome this problem, Hartenstein and his team used a heatmap, which is a feature map of the CNN, visualizing their decision-making by highlighting important regions by colour. Examples of such heatmaps showed that the CNN was able to learn features within the lymph node but also by anatomical features surrounding the lymph node. The team noted that the anatomical context of images should be carefully considered when building CNNs, as undesirable features might influence the performance of the model and be biased as a consequence (27).

While TNM classification forms a good foundation for predicting patient prognosis and treatment outcomes for most tumours, occasionally, it presents some limitations. In patients with oropharyngeal squamous cell carcinoma (OPSCC) treatment selection is based on this staging system, however, a recent study reported it to be suboptimal. Fujima et al. investigated the value of DL analysis, predicting the treatment outcome of OPSCC patients. The model was learned from fluorodeoxyglucose- positron emission tomography (FDG-PET) images, which are based on the disrupted glucose metabolism of tumours and shown to be highly accurate and superior to the T-stage and clinical classification. They found that an increase in intra-tumoral heterogeneity indicated a poor prognosis, which could reflect the biological difference in sensitivity to chemoradiation therapy (CRT). Additionally, tumour morphology was investigated and found to be an important prognostic marker. These features are not captured in the current TNM classification and suggest the implementation of other, more accurate staging systems, especially in OPSCC (28).

Perhaps the most crucial task of radiologists is to track subtle changes in the aberrant tissue in order to evaluate treatment response and thus monitor cancer. Diseased tissue is aligned across multiple scans and subsequently evaluated carefully utilizing a data comparison protocol. This involves the quantifying of changes in tumour size, shape, and cavitation. However, some features are just not identifiable by the human eye such as texture and heterogeneity, resulting in a suboptimal assessment of tumour monitoring (20).

The standard treatment for locally advanced rectal cancer consists of neoadjuvant CRT, followed by radical surgery. By examination of surgically removed tissue, research showed that 15- 27% of patients would have a pathologic complete response, which is defined as the lack of residual cancer cells after CRT. Due to this fact, non-operative management would have been a better choice for these patients, considering the complications associated with surgery and surgical removal (29).

Jin et al. developed a DL network to predict treatment response before surgery. The first component of the model is a CNN, which simultaneously segments tumours and extracts features. This is then followed by a Siamese subnetwork, which combines the extracted features from three different network layers. The latter allows the integration of structural and functional information at all levels to finally compare pre/post-treatment MRI. This process enables the model not only to learn tumour features, but also dynamic changes caused by treatment. Among several other traits, depth of tumour invasion and extramural

vascular invasion were found to be correlated with high risk. While having similar feature maps in pre-treatment images, these features were substantially decreased in responders compared to non-responders, proving the effectiveness of the model. Furthermore, these researchers integrated the carcinoembryonic antigen (CEA). This blood-based biomarker commonly used for treatment monitoring showed to increase the performance of the network (29).

Another common molecular biomarker used to predict the treatment response of patients with rectal cancer is microsatellite instability (MSI). Due to a loss of one or more mismatch repair genes, which correct errors during DNA replication in normal cell division, an accumulation of mutations occurs. This ultimately results in the synthesis of repeated sequences of DNA. MSI was the first of its kind to be approved as a predictive biomarker for immunotherapy, enabling the development of individualized therapies and maximising the response rate. Zhang et al. developed a non-invasive method predicting MSI status of preoperatively magnetic resonance imaging, including clinicopathological characteristics such as differentiation degree, T-stage and levels of the biomarker CEA. The combined model showed better predictive performance compared to the image model alone, indicating the need for the integration of multiple sources of data to boost performance. Being a non-invasive method to the routinely performed genetic analysis of biopsies, this model showed to be a great alternative in predicting MSI status and contributes to the trend of personalizing treatment plans (30).

The data-driven characteristics of DL could become a major assisting tool in the emerging field of radiomics, providing radiologists with pre-screened images and automatically identified features. An increase in efficiency and a decline in errors could be expected as a result (20).

3.2. Computational pathology

Radiology and pathology both capture morphologic data but on a different biological scale. While radiologists concentrate on anomalies of organs and tissues, pathologists analyse morphologic changes on the cellular level. Histopathological images are much larger in terms of pixels and possess greater structural information than radiological images. They present cells with genetic alterations and epigenetic modifications through their phenotypes and their spatial arrangements. By way of detecting and quantifying mitotic activity, vascular invasion and metastases, tumour behaviour can be closely observed (31).

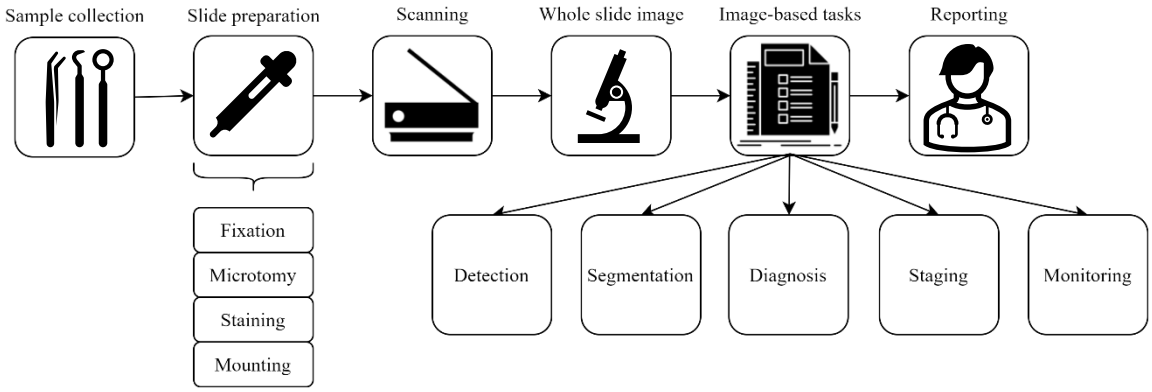

Figure 10: Workflow in pathology

The clinical workflow in pathology, represented in figure 10, starts with tissue removal as a biopsy or during surgery, for diagnostic and research purposes. The sample needs to be fixed through embedding in paraffin or freezing in an optimal cutting temperature compound, to prevent tissue degradation and preserve morphological structures. It is then precisely cut into slices of 2- 10 micrometres and mounted onto a glass slide. As tissue normally is transparent, staining is necessary to increase contrast and visualise cell structures by creating a chromatic distinction. Hematoxylin and eosin (H&E) is a staining combination commonly used as a routine stain, because of its easy maintenance and good performance. A variety of other stains are used to accentuate other cell components and thus help in the evaluation of specific disease entities. Masson´s trichrome is one of these special stains and is routinely used to view connective tissue. Other examples are periodic acid-Schiff, which highlights basement membranes and the Jones methenamine silver, which helps to contrast glomerular architecture (32).

Frequently, these special stains are required after an evaluation with H&E. As a result, the tissue has to be destained and re-stained again, which takes a longer preparation and much more effort to obtain. De Haan and colleagues developed a virtual staining technique, transforming histopathological images based on H&E into images with special stains. They introduced different staining procedures, reagents and scanners to the network to simulate the variability between labs and equipment, hence improving its generalizability. By commercializing such systems, preparation time, costs, and resources can be decreased. Additionally, the destruction of tissue samples through the process of de- and re-staining is eliminated. Without the need for chemical staining in the near future, which is often biased by the variability of inter-technician, inter-lab and inter-equipment, stain normalization can be introduced, enabling better detection and characterization of malignant cells (32).

In the modern era digitalization has been introduced to pathology, enabling the acquisition of WSIs by microscopic scanning devices. These digital slides are high-resolution representations of glass slides, enabling the examination on a computer with an enormous range of magnification levels compared to the traditional microscope. In addition, this digitalization introduced the concept of computational pathology, which analyses tissue sections with the help of AI applications (16).

Relying on their knowledge and experience, pathologists carefully assess digital histological slides. Because of the increasing amount of data, this time-consuming task demands the integration of assisting tools to detect and classify aberrant tissue. Ho et al. developed two DL frameworks for these purposes on an annotated dataset of colonic biopsy WSIs. The first model was trained to segment and identify potentially high-risk regions. These segmentations allow the calculation of tumour area and the detailed visualization of multiple parameters, compared to using only heat maps. The architecture was not only able to differentiate between areas with likely normal, dysplastic and malignant tissue, but also represented blood vessels and inflammation. Each parameter was colour-coded to enhance interpretability. The output of the segmentation model is, subsequently, used in the slide classification model to label slides as either high or low risk. This DL algorithm validates to function as an excellent CADe and CADx tool to assist pathologists in their daily routines (33).

Mitosis is an important prognostic biomarker of proliferation, directly representing the process of cell division. Cancers such as uterine leiomyosarcoma (ULMS) are examined on their different mitotic rates to differentiate between benign and malignant. The detection of this cellular phenomenon is highly dependent on the experience of pathologists. Mitotic activity can vary from region to region within the same tumour, making the assessment vulnerable to bias. Therefore, it is important to identify the most mitotically active areas and count mitoses in these areas to prevent misrepresentation of reality. Researchers trained a DL system to detect mitotically active regions in histopathologic images of ULMS. The great variability of mitosis patterns and the strong resemblance to other tumours, like leiomyomas, were found to be disturbing factors for the learning process. Despite these challenges, this study opens a new door by providing a baseline for future methods to accelerate the diagnosis process (34).

An alternative representation for proliferating cells is the Ki-67 proliferation index (PI). After highlighting Ki-67 by the process of immunohistochemical staining, the percentage of tumour cells expressing this prognostic biomarker is determined to grade tumours accordingly. To eliminate manual counting, which is labour-intensive and often biased by inter- and intra-observer variation, Vesterinen et al. developed a DL algorithm. Their model was based on immunohistochemical labelled images of neuroendocrine tumours (NETs). They presented a framework for the automated assessment of the Ki-67 PI, which is critical in the grading of NETs and treatment selection. This CADe offers a foundation for the high-capacity analysis of Ki-67 PI with more reproducible outputs to augment pathologists (35).

To sustain their proliferative character, cancer cells induce angiogenesis with the help of proangiogenic factors, such as VEGF. Inhibiting these angiogenic pathways have recently been established as a good alternative to chemotherapy-resistant cancers. Despite its promising effect, this drug should be carefully considered due to its high costs and potential toxicity. To accurately predict the therapeutic effect of an anti-VEGF antibody, Wang et al. developed a DL framework based on patients with epithelial ovarian cancer (EOC). The model was able to differentiate between patients gaining positive therapeutic effects with low cancer recurrence from patients with disease progression after treatment. Furthermore, they found a possible correlation between antiangiogenic therapy and an antigen of the inflammasome, which promotes angiogenesis. The expression of this antigen could potentially lead to its implementation as a biomarker. This study highlights the potential of DL as a predictive method to guide physicians in the selection of targeted treatment (36).

In recent years, stromal cells of the TME have increasingly gained interest because of their ability to reprogram and corrupt normal cells. They create an optimal environment to support tumour development and progression. To increase the prognosis of tumour behaviour, Saltz and colleagues investigated the importance of spatial context and cellular heterogeneity within the TME. Therefore, two CNNs were trained based on WSIs from 13 different cancer types. One CNN segmented regions of necrosis and the other detected and classified regions with TILs. Patches with remarkable tissue were presented as heatmaps for the pathologists to review and refine. In this manner, the system was updated and increased its sensitivity. They assessed the clustering patterns of TILs to improve our understanding of the TME. Local and overall patterns were differentially represented in different tumour types, immune subtypes, and molecular subtypes. The study suggests that the spatial arrangement of TILs may be reflective of certain aberration states of tumour cells. Additionally, it indicates that survival and immune response is encoded into these structural patterns. The implementation of automated TILs quantification could lead to tailoring immunotherapy to the individual (37).

DL proves to be an excellent tool to quantify the extensive information presented on histopathological slides. Besides automating mundane and time-consuming tasks of pathologists, it is cable of discovering novel biomarkers to identify patients who are most likely to derive therapeutic benefits. Furthermore, DL presented novel insights into the configuration of the TME and could play a crucial role in the discovery of novel immunotherapy.

3.3. Multi-omics

Detecting, characterizing and monitoring tumours through their phenotypical appearance at both macro- and microscopic levels is one way of gaining information about cancer. Malignant cells, however, are much more complex than these superficial features, considering the myriad of molecular and environmental components interacting at different levels to shape their ultimate constitution. Tumour behaviour is dependent on many factors, including genetic and epigenetic aberrations, alterations in gene expression and protein synthesis, variations in the response to cellular signalling, metabolic changes and beyond. To uncover inter-molecular mechanisms and identify cancer vulnerabilities, new fields of research have emerged, commonly referred to as multi-omics. This technology, summarised in figure 11, enables the quantification of biomolecular systems at several levels, such as the genome, epigenome, transcriptome, proteome, metabolome and beyond. (38).

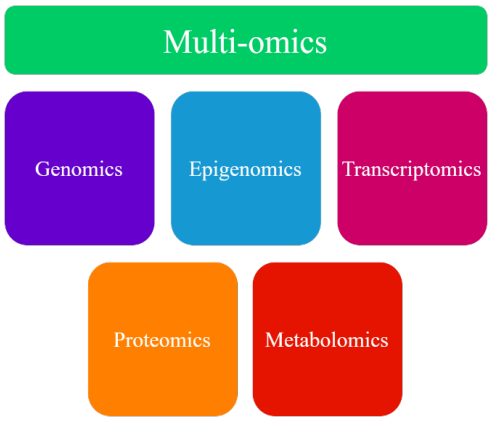

Figure 11: Multi-omics

Driven by alterations of the genome and epigenome in the cellular machinery, tumour cells acquire hallmarks to get to their malignant state. This indicates the need for a better understanding of the essential genes for tumours to proliferate and survive. Researchers presented Deep DEP to predict this gene dependency based on genomic profiles of both tumour and cell line samples. The unsupervised model generated a pan-cancer dependency map, which was capable of identifying frequent interactors of oncogenes and thus presenting novel possibilities for drug therapies. Furthermore, it revealed predominant mitochondrial functions in genes essential in chemo-resistant tumours. This confirms their need for an alternative energy metabolism to survive the damage induced by chemotherapeutic drugs and forms another opportunity for targeting therapy to overcome their chemo-resistant

capabilities. Finally, the model analysed the association between certain tumour-suppressive genes and the overall survival of patients with different cancers and identified a prognostic role in some of these genes (39).

The change of hereditary information stored in our DNA results in a cascade of alterations in other molecular sub-levels, beginning with the abnormal gene expression in form of ribonucleic acid (RNA) (40). The transcriptome, which includes all RNA molecules transcribed from the genome of a cell, represents the biological state of its phenotype. This means, that by studying these molecules through transcriptomics, one directly captures regulatory changes within tumour cells (38). Hong et al. developed a multitasking DL model, classifying transcriptomic data. It was capable of accurately differentiating the disease state based on gene expression between non-neoplastic, peri-neoplastic and neoplastic tissue. Additionally, the network was able to classify tissue origin and neoplastic subtypes. This unique technique of tissue profiling offers an advantage in detecting cancers of unknown primary, compared to traditional pathologic examination (41).

Another layer affected by the mutational DNA is the sub-level of proteins, which are directly encoded from RNAs. These molecules control most of the biological processes and thus show the dynamic molecular behaviour of cells. To better understand the relationship between genotype and phenotype, Gonçalves and colleagues introduced a proteomic map quantifying multiple proteins across a pan-cancer cell line. The network was able to characterize protein expression patterns that could not be captured by the transcriptome, validating the benefit of this technology. Through visualization of protein intensities, the model showed a general alignment of the proteomic data with cell lineage, revealing the cell type of origin. Additionally, it identified EMT markers, which are known to induce metastasis and therapy resistance. The group of researchers developed another DL architecture to identify cancer vulnerabilities by integrating proteomic data with drug responses and gene essentiality screens. This program assessed all possible drug-protein and gene essentiality-protein associations to identify potential protein biomarkers (42).

Each one of these omics data reveals information about its appropriate field of expertise, contributing to the understanding of the pathophysiology of malignant cells. However, cancer is a multiscale pathology, requiring a multidimensional approach to understand its complete picture. Multi-omics data integration emerged as a promising solution to analyse multiple levels of complexity and extract meaningful conclusions out of these different kinds

of data. Malik et al. introduced a neural network with omics integration to predict clinical outcomes and responses of an individual to a variety of drugs. Including clinical features like age, pathologic stage, and number of affected lymph nodes, the model was able to accurately classify patients into high-risk and low-risk classes. Additionally, it showed an increased performance when adding multiple omics types compared to the traditional single-omics approach, indicating the need for integration of this type of data. Ultimately, the drug response model captured the relationship between multi-omics data and known breast cancer drugs and could assist in screening a pool of drugs based on patients' sensitivity (43).

The accurate prediction of drug response is crucial in cancer treatment, especially in immunotherapy, where only a small proportion of patients are sensitive and will benefit from this therapy. Due to this problem, Ma et al. developed a DL network to predict immune attributes of genes in responding to immunotherapy. The model was able to uncover new immune-related genes based on their protein-protein interaction, giving a probability of each gene belonging to a specific immune category. It revealed the association of some of these genes with immune cell infiltration and confirmed their role as regulators of the TME, which could affect immunotherapeutic sensitivity. Furthermore, tumour-promoted genes were found to be encoding defensins for antimicrobial and cytotoxic function, and immune-inhibited genes were detected, contributing to regulating cellular functions, such as motility, signalling, growth, and protein synthesis. These results suggest their diagnostic capability in predicting drug responsiveness of immunotherapy (44).

The low response rate of immunotherapy is not the only problem leading to ineffective treatment. Either by inducing an immunosuppressive TME or modifying themselves, cancer cells acquire the capability to evade the antitumour immune response. They become invisible to the immune system and resistant to immunotherapy. Xie and colleagues aimed to uncover these molecular mechanisms with the help of an unsupervised DL architecture. Based on multi-omics datasets, they successfully categorized tumours into 4 genomic clusters, each associated with a unique immune landscape. The model was able to highlight the complex interaction between genomics and host antitumour immunity and estimate their response to immunotherapy (45).

The discovery and development of novel therapeutics are very time-consuming and costly, which is why pharmaceutical industries apply drug repurposing as an attractive alternative. One way is by identifying an analogue with a similar structure to an existing drug molecule, which shares similar mechanisms of action and can discover alternative targets. The other way is by finding related transcriptomic signatures, which most likely share the same indications. A study supervised by Li et al. introduced transcriptomics in combination with structural information of chemical structures to the network to find alternative drugs for NSCLC. They started to identify approved drugs and found a promising chemotherapy analogue, sharing similar biological and pathway signatures with the existing drug. The drug was originally an anti-dyskinesia agent, which was used to reduce uncontrolled movements. To validate the proposed candidate for repurposing, additional experiments were conducted, testing the antitumour activity. This model shows the possibilities of clinical adaptation to the time-consuming task of drug development (46).

Besides the technology of repurposing drugs, structure-based virtual screening of large libraries of compounds plays a vivid role in drug discovery and development. Researchers developed a model combining DL and molecular docking technology to find specific inhibitors of the never-in mitosis gene a (NIMA)-related kinase 7 (NEK7), which is a crucial regulatory protein involved in DNA repair and controlling cell division. After completion of virtual screening, four compounds were found to have better docking scores and binding affinity compared to an approved drug. These top hits were further analysed on their inhibiting potential, by assessing their structural configuration and molecular interaction. Additionally, molecular dynamics of these top hits were investigated to determine the stability of protein-ligand complexes under accelerated conditions, suggesting their potential as targeted inhibitors of NEK7 (47).

Currently, an astonishing amount of data is being generated by omics technology. DL is capable of analysing associations between these multiple types of data, extracting information to identify prognostic biomarkers, and predict clinical outcomes and responses to targeted therapeutics. The adoption of DL in the field of multi-omics is the thriving motor behind the development of precision medicine.

4. Discussion

The workload of doctors increases exponentially as a consequence of the disproportionate growth of medical data, resulting in inevitable errors. The data-driven characteristics of DL facilitate the automatic detection of features and recurring patterns in high-dimensional datasets, presented in electronic health records. This novel technology shows to be an excellent tool to augment physicians in different domains of their clinical routine.

The field of oncology is especially suited for the adoption of DL, due to the variability and complexity of this disease and the availability of extensive datasets. CNNs are capable of marking suspicious lesions and predicting their malignancy. The adoption of such CADe and CADx systems can drastically improve the clinical workflow. By providing physicians with pre-screened images, they could replace the current double-human reading procedure and consequently increase efficiency and reduce inevitable human errors.

Another application of DL is the automated assessment of tumour monitoring by quantifying changes in tumour size, shape, and other features unidentifiable to the human eye, such as texture and heterogeneity. Additionally, CNNs show to be excellent at discovering novel structural patterns and biomarkers which are associated with immune response and survival rate. These findings are crucial to predict patients' outcomes and maximizing their therapeutic response.

Multi-omics is a promising field of research in oncology, analysing multiple levels of this high-dimensional disease. The integration of this kind of data presents a unique technique to profile tissue. CNNs are competent in discovering driver oncogenic pathways and elucidating cancer vulnerabilities, which could lead to the discovery and development of targeted therapy. Furthermore, DL can assist in the virtual screening of potential compounds and uncover analogue drugs, which are superior to the existing drug. Hence, making the time-consuming task of drug development much more efficient.

DL indicates to be a promising tool in the field of oncology; however, it is still in its infancy. This novel technology is known for its dependence on scalable data, increasing the accuracy and performance of the model. Unfortunately, researchers are only scratching the surface of this technology´s potential, due to the lack of manually annotated data in the training phase. The adoption of new strategies should enable an automated curation and provide DL with a greater dataset.

Another common challenge of this technology is the lack of understanding in the decision-making process of DL, better known as the black box. This phenomenon is a troublesome obstacle in medicine which could lead to harmful consequences. Every decision, from detection to treatment plan, has to be comprehended to justify the following measures. Researchers are intensively developing alternative solutions to solve this problem. One example of explainable AI is the use of feature maps, which highlight important regions by colour to visualize interpretability.

Despite these challenges, DL proves to be an excellent augmenting tool, with the potential to revolutionise medicine in all of its domains. The strength of this novel technology to quantify interconnected mechanisms of tumorigenesis and uncover patient-specific characteristics boosts the transition toward precision medicine. The patient-centric approach allows the tailoring of medical treatment to individual variabilities, rather than the one-size-fits-all approach. This strategy enables maximizing treatment response and clinical outcome while minimizing side effects.

Paradoxically, DL could strengthen the human connection between doctors and patients. The automation of repetitive and administrative tasks will bring back the emphasis on healthcare again. The role of physicians will transform towards communicators, in which their empathy and human interaction are accentuated. These features are indispensable for the acquisition of essential information for patients. Machines may not detect the overall appearance or emotions of patients, which are fundamental in the decision-making process of physicians. These decisions have to be communicated and further elucidated to get the full compliance of patients. The integration of DL could, therefore, improve healthcare extensively and emphasise human connection.

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