AI methods to reduce contrast medium administration in MR imaging

Seminar Paper

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Contents

1 Introduction

Magnetic Resonance Imaging (MRI) has become an indispensable tool in modern medicine, allowing non-invasive visualisation of internal structures and organs. However, the use of contrast agents is often required to improve the clarity of the images produced - therefore improving the visibility of certain structures or lesions, but their use also carries rare risks and side effects. In recent years, several Artificial Intelligence (AI) methods have emerged as a promising solution to this problem. By reducing the amount of contrast required to obtain high-quality images, AI techniques can potentially reduce the risks and side effects associated with contrast administration. The low-dose, contrast-enhanced scans made possible by these AI methods can improve the safety and efficacy of MRI while maintaining diagnostic accuracy.

This work will review the current state of AI methods for reducing contrast administration in MR imaging, discuss their potential benefits and limitations, and give a brief outlook on the future of AI in MRI.

2 Contrast Agents and their risks

2.1 Magnetic Resonance Imaging

To understand why contrast agents are used, we first need to understand how MRI works. When a patient enters the MRI machine, and its powerful magnetic field, the nuglear spin of the protons in the patient's body tissue align with this magnetic field. Radio waves are then sent into the body, causing the aligned protons to absorb energy from the radio waves and spin out of alignment. When the radio waves are turned off, the protons return to their aligned state and release energy, which is detected by special receiving coils in the MRI machine. The received signals are then digitally processed to generate images and a complete three-dimensional scan. [1]

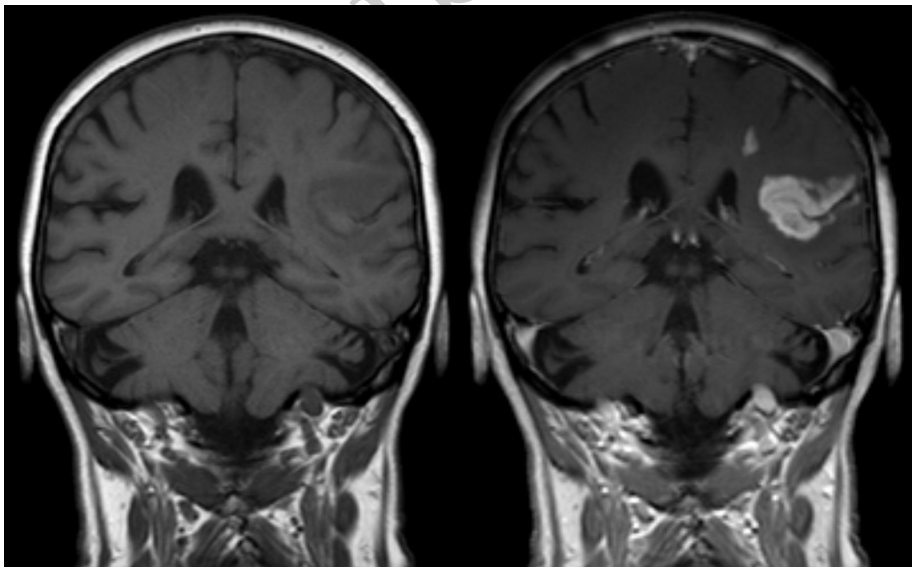

Figure 1: Effect of contrast agent on images. [2]

Contrast agents can be given to the patient "to increase the speed at which [the] protons realign with the magnetic field" [1], which affects the intensity of the resulting signal, making it stand out more in the resulting images. Tigure 1 shows the difference between a MRI without (left) and with (right) contrast agent of the blood-brain barrier of a human brain after a stroke.

2.2 Types of contrast agents and their use cases

In some cases, MRI does not require a contrast agent, but more often it is a valuable and helpful addition to a clear image and subsequent diagnosis. In essence, a contrast agent is used to improve the image quality by 'illuminating' certain tissues, making them easier to see and identify [3]. There are various types of contrast agents commonly used in MR imaging, each with its own unique properties and applications.

One of the most common types of contrast agents used in MRI are Gadolinium-based contrast agents (GBCAs). Unfortunately, the heavy metal gadolinium (Gd) "is not part of the normal composition of human tissue" [4], which is why it can cause long-term side effects when administered, more about this later.

A rather new type of contrast agents are Iron-based contrast agents (IBCAs) which contain iron oxide nanoparticles to create contrast in MRI images. They have several advantages over GBCAs, including a longer imaging window and lower risk of adverse reactions. IBCAs are particularly useful for imaging the lymphatic system and liver [5] [6].

Another type of contrast agent is based on fluorine. Fluorine-19 (^{19}F) is a stable and naturally occurring isotope that can be used in MRI. During a scan, the ^{19}F atoms in the contrast agent give off a signal that is detected by the MRI machine, which can be used to create images of the tissues or organs being scanned. Unlike GBCAs, ^{19}F-based contrast agents have no known (significant) toxicities or risk of accumulating in the body [7].

There are also Manganese-based contrast agents (MBCAs) which work similarly to gadolinium-based ones by altering the magnetic properties of water molecules in the body, which affects how they appear on an MRI scan [8].

2.3 Risks associated with contrast medium administration

Like all medicines, contrast media can have side effects such as allergic reactions. Although these side effects are considered to be very rare, they can have a serious impact on the patient.

Patients with impaired kidney function, diabetes mellitus or hypertension are at higher risk of developing nephrogenic systemic fibrosis (NSF), a rare side effect of GBCAs. Symptoms include hardening of the skin, usually on the extremities, but sometimes extending to the torso [9]. A study conducted at St. Vincent's Medical Center in Bridgeport, Connecticut in 2007 found that "each radiologic study using gadolinium presented a 2.4% risk for NSF" [10] and suggests "that gadolinium exposure should be avoided in patients with [impaired kidney function]" [10] given the significant mortality risk of NSF. There have been reports that certain GBCAs may remain in the brain. As a result, the suspension of approvals for several GBCAs, including Gadodiamide, Gadopentetic acid and Gadoversetamide, has been extended to both 2020 and 2022 by the Federal Institute for Drugs and Medical Devices (BfArM) in Germany [11]. The suspensions include the European Union (EU) [12]. The latest extension of the suspension now lasts until 2024 and reflects ongoing concerns about the potential retention of GBCAs in the brain.

Another risk associated with the administration of contrast media is contrast-induced nephropathy (CIN), a type of acute kidney injury that can occur after the administration of certain types of contrast media. The risk of CIN is particularly high in patients with pre-existing kidney disease, diabetes and heart failure [13]. The exact mechanism by which contrast media cause CIN is not fully understood, but it is thought to involve a combination of direct toxic effects on the kidney and changes in renal blood flow. To minimise the risk of CIN, it is important to identify patients at risk and to use alternative imaging modalities or lower doses of contrast agents where possible.

2.4 Current methods to reduce contrast agents

Several methods and strategies have been introduced to address the challenge of reducing the use of contrast media in medical imaging. These approaches aim to minimise the potential risks and adverse effects associated with contrast administration while maintaining diagnostic accuracy.

The simplest and most straightforward technique is to avoid the use of GBCAs, as adressed above. Of course, this does not solve the problem of side effects, which are inherent in any drug. In some cases, it is possible to have an MRI without a contrast agent. For example, some tumours are classified as enhancing tumours and can be seen on the scan without the need for contrast [14] - this is described in more detail later in chapter 3.2.2.

When administering contrast agents such as GBCAs, it is also important to choose them wisely, based on additional factors such as the stability of the complex. Some contrast agents offer a longer imaging time and could therefore avoid double dose administration.

It is also important to consider whether an MRI and contrast are absolutely necessary, especially in patients with pre-existing conditions. A doctor may consider whether a patient with active kidney disease is suitable for MRI with GBCAs or its alternatives, and whether there are other diagnostic options that haven't been tried.

In a 2017 study conducted at institutions in Heidelberg, Germany, researchers investigated the use of natural, unlabelled d-glucose as a contrast agent for MRI scans. They aimed to improve imaging capabilities without relying on traditional contrast agents [15].

The study included a group of healthy controls and a group of patients with glioblastoma, a type of brain tumour. In the glioblastoma patients, the researchers used a technique called T1r-weighted dynamic glucose-enhanced (DGE) MRI to identify areas of increased glucose uptake in the brain that corresponded to the location of the tumour. In the healthy volunteers, T1r-weighted DGE MRI showed increased signal intensity in specific brain regions that had higher signal intensity compared to the surrounding white matter. Importantly, there was no saturation of the increase in signal intensity observed during the measurement period.

Overall, the balance between the benefits and potential risks of contrast-enhanced MRI, the selection of appropriate contrast agents and the individual approach based on the patient's specific conditions and medical history are major considerations in clinical practice.

3 AI-based methods for contrast medium reduction

3.1 Machine Learning techniques for MR imaging

In recent years, machine learning (ML) techniques have gained popularity in the field of medical imaging. This is due to their ability to identify subtle patterns in large datasets and improve diagnostic accuracy. In particular, ML techniques have been used to reduce the need for contrast agents in MR imaging. Promising approaches include reconstructing or denoising previously acquired images and synthesising contrast agents with low-dose or no-dose images [16].

As stated earlier, one common contrast agent is gadolinium-based and carries some possible side effects with its administration. A 2018 study from two departments, including the Department of Radiology at Stanford University in California, "[developed] [...] a new [deep learning]-based technology to reduce GBCA dose levels while maintaining image quality and contrast information of full-dose contrast images" [16].

The study involved 60 patients and 60 MRI scans from three different conditions. The first scan was performed with no contrast agent (pre-contrast), the second with a tenth of the full dose (10% low dose) and the final scan, used as a reference, with the full amount of gadobenate dimeglumine (100% full dose), a GBCA. Ten cases were used to train a deep learning (DL) model to reconstruct (or estimate) the full dose images from the low dose

scans. The remaining 50 patients were divided into two groups: 30 patients diagnosed with glioma (a common type of brain tumour) and 20 patients with mixed indications.

Using a very noisy uptake from the low-dose MRI scan, the trained DL model can reduce the noise sufficiently to obrain an image which is almost as clear as the full-dose scan.

In addition to using zero- and low-dose scans to approximate the full-dose image, alternative methods have also been explored, such as complete approximation without the administration of any contrast agent. A feasibility study conducted by researchers from renowned institutions in Germany, including the German Cancer Research Center (DKFZ) and the University of Heidelberg Medical Centre, aimed to investigate this alternative approach [14]. The study included three groups of patients - enhancing tumours, non-enhancing tumours and a normal control group. Enhancing tumours are characterised by increased contrast enhancement on MRI scans, even without the use of contrast agents, whereas non-enhancing tumours do not show such enhancement. The normal control group consisted of individuals with no brain abnormalities.

The DL model demonstrated very good quantitative and qualitative performance in predicting virtual contrast enhancement based solely on native multiparametric MRI data. The study concluded that prediction of gadolinium enhancement may be feasible in the near future. However, further studies in larger patient populations with different neurological diseases are needed to assess the clinical applicability of this novel approach.

Both of the above studies attempt to approximate an enhanced MR image, but other possibilities are being explored, such as a classification model for patients with multiple sclerosis (MS). Researchers at the McGovern Medical School (University of Texas Health Center) and the Icahn School of Medicine (Mount Sinai, New York) have published a paper on this approach to diagnosing the disease without the administration of a contrast agent [17]. Unlike previous studies, they used a relatively large dataset of 1970 MRI scans from 1008 patients acquired over a four-year period - the ground truth was established by identifying enhanced lesions on post-contrast T1-weighted images annotated by neuroradiologists.

The researchers achieved high levels of accuracy in identifying patients with a positive ground truth scan (active MS lesions). They concluded that the results are promising for a procedure that avoids the administration of contrast agent administration.

There are numerous other studies in this field exploring similar or different approaches to improving MRI imaging, many of them using the familiar no- and low-dose comparison for training and achieving similar results to those mentioned in my paper. They were published between 2018 and 2023, as the whole field is relatively new research [18]. While these studies are not covered in detail in this paper, they contribute to the broader understanding and ongoing research in this area.

All three of the above research papers will be discussed further in the next section, with a focus on the technical side of the approaches.

3.2 Studies and real-life appliances of this technique

Several approaches have been developed to reduce the amount of contrast agent required for high-quality MRI scans. This section[1], will explore some of the most promising methods, including image reconstruction and synthesis techniques, as well as ML algorithms that use large data sets to improve the accuracy of low-dose contrast-enhanced images.

[1]To improve readability, works are cited only once at the beginning of the description and in direct quotations. Unless specified otherwise, no additional sources have been used.

3.2.1 Low-dose contrast-enhanced MRI

Training a ML model for denoising or full contrast synthesis can be very laborious and complex. Going back to the Stanford University Department of Radiology study mentioned earlier [16], several different methods were used to approximate a full-dose image, including a convolutional neural network (CNN). CNNs are a type of neural network that specialise in processing data with a grid-like topology, such as images or video [19] - ideal for MRI.

The model takes the pre-contrast (0% dose) and low-dose (10%) scans to calculate their difference, after "... [removing] the systematic differences between signal intensity levels in nonenhancing regions (such as scalp fat)..." [16]. The result can be upscaled to produce an approximation of the full-dose (100%) MRI scan. Each patient scan consisted of 300 to 350 images, which were combined to create the 3D scan. A total of 10 individual slices per 3D scan were removed due to their low quality, as measured by the signal-to-noise ratio (SNR). As every MRI image is made up of individual signals and their noise, the SNR is a commonly used measure to describe the performance of an MRI scan [20].

On the technical side, the DL model used stochastic gradient descent (SGD) and back-propagation for network optimisation and its parameters. Using mean absolute error (MAE) as a cost function, the model used the target values (full dose scans) and approximations (model output) to evaluate the results. In addition to the popular SGD, adaptive moment estimation (Adam) and a total of 200 epochs were used to further improve the model. All of these methods are well known standards in ML.

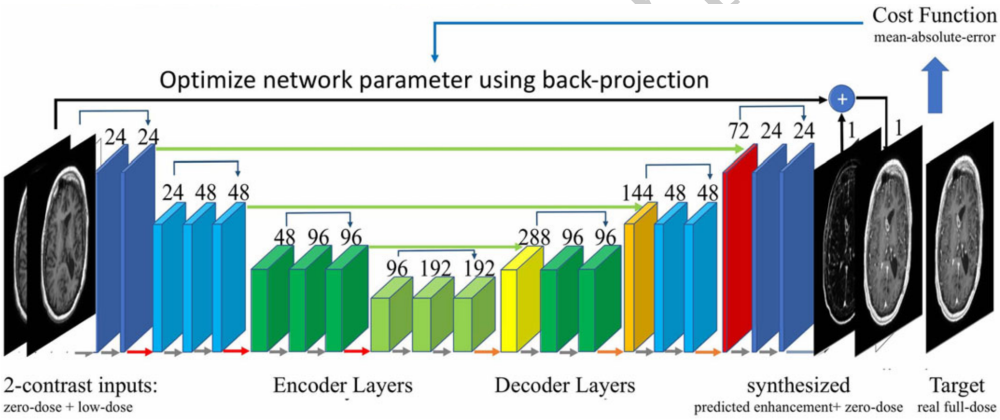

Figure 2: The structure of the DL model used in the study. [16]

The model used common image processing techniques such as 2x2 max-pooling (layers) to reduce dimensionality (marked in red where the layer size decreases, figure 2) or 2x2 up-sampling in the decoding process to recover spatial information that may have been lost during the previous downsampling operations (marked in orange or where the layer size increases, fig. 2). As an activation function, the researchers chose a 3x3 rectified linear unit (ReLU) since it's a simple and computationally efficient function that introduces non-linearity into the network. batch normalization (BN) was also used to increase the stability of the network. Concatenate connections, also known as skip-merge-connections, were also used to provide additional information to the subsequent layers of the network, improving the learning overall (marked light green, fig. 2) and in this case to avoid resolution loss in the images. To avoid the vanishing gradient problem the team also used residual connections (marked dark blue, fig. 2). A convolutional layer is used as the last layer, which "[enables] the model to synthesize a full-dose image by predicting the enhancement signal" [16].

The model was trained on a Linux server with standard high performance graphics processing units (GPU) for neural networks (as of 2018). Each of the 512x512 synthesised images took about 0.1 seconds to generate, and were then converted back into Digital

Imaging and Communications in Medicine (DICOM) file format to obtain a full 3D image, "the international standard for medical images and related information" [21] and is commonly used for MRI, computed tomography (CT) and X-ray.

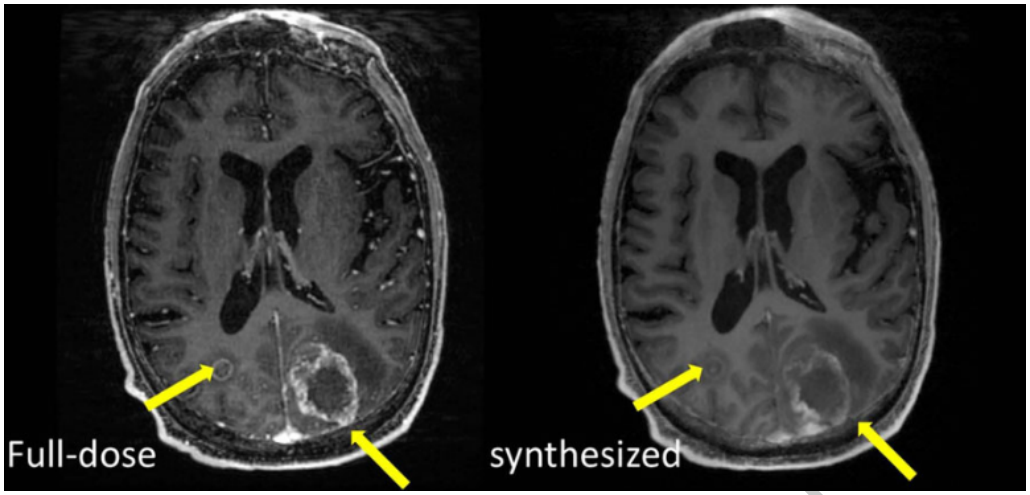

Figure 3: Deep learning enhanced scan compared to normal MR scan. [16]

To evaluate the DL model, both quantitative metrics (on all 50 patients) and qualitative assessments (on only 20 patients with mixed indications) by two experienced neuroradiologists were conducted. Metrics included the peak signal-to-noise ratio (PSNR) (maximum value of the SNR) and structural similarity index (SSIM) which analyses things like textures, edges and structural similarity in the MRI-images [22]. Overall, the model performed very well in approximating (100%) full-dose scans. Quality assessment by neuroradiologists showed a significant improvement over unenhanced low-contrast images and "no significant [to slightly worse] difference in overall image quality" [16] for synthesised scans.

For better visualisation, figure 3 compares a ground truth image (100%) and the synthesised scan from the DL model. This particular scan is from a patient with a glioma and shows good enhancement in the low-dose scan and even better motion artefact suppression compared to the full-dose MRI.

3.2.2 Fully synthetic contrast-enhanced MRI

The potential of low-dose MRI has been explored to reduce patient exposure to contrast agents and minimise potential risks. However, even with low doses, there may still be potential side effects associated with contrast agents. This highlights the need for further research into alternative approaches that can improve image quality while minimising risks. This focuses on the development and use of fully synthetic contrast agents, which offer a promising way to address these concerns and advance the field of medical imaging.

To return to the German study mentioned earlier [14], the aim was to create exactly these fully synthetic MR images without the need for contrast agent administration. The study included a total of 82 patients, some of whom "were examined several times [...], usually while undergoing therapy, leading to a total of 116 data sets" [14] for the research.

In order to prevent the model from adapting too well to the training data (overfitting), data augmentation was used. In this case, random reflections were made along the three axes with a probability of 0.5 during the training process. This is a common technique in medical imaging, where training data can be limited.

The research team used a fully convolutional network (FCN) with dropout to generate the virtual contrast enhancement map and an uncertainty map. In traditional black and

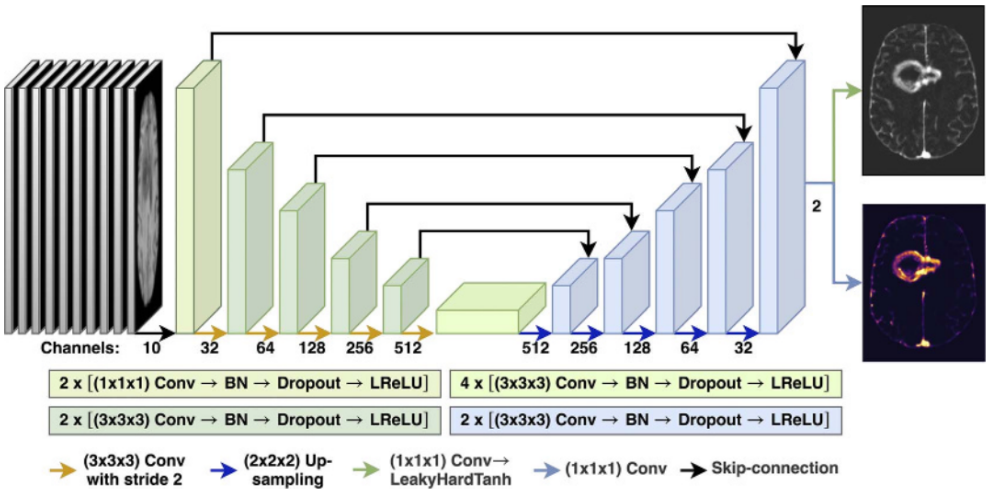

Figure 4: The structure of the DL model used in the study. [14]

white images, there is usually only one channel representing the grey scale intensity values. In this study, however, the images had 10 channels because they used multiparametric imaging data, which provided additional information about various image characteristics such as tissue composition, perfusion and diffusion. "Multiparametric magnetic resonance imaging (mp-MRI) is the newer concept of MR which is evolving and being used widely for various applications" [23], and in this case allows the model to use a richer set of information for prediction.

Figure 4 shows the input and output channels as well as the network structure with five downsampling blocks for feature extraction and five upsampling blocks for image construction. In addition to data augmentation, dropout was used to prevent overfitting by randomly deactivating a fraction of the neurons during each training iteration. This technique helps to promote generalisation and improve the model's ability to handle new, unseen data. AMSGrad was used instead of Adam as an optimisation algorithm to improve the stability and convergence of the training process. AMSGrad is a variant of Adam that addresses some common problems associated with this optimiser.

The team used a clever technique where the model used longitudinal data (time series data) from a single patient either for training only or for testing only. This ensures that the predictions are based on data that was not seen during the training phase, thereby avoiding any correlation with the training set. Each individual brain volume took about 30 seconds to generate, running on Linux servers and using hardware common at the time, such as the GTX 1080 Ti graphics card.

Similar to the first paper, the metrics used for evaluation included SSIM, PSNR and additionally the area under the curve (AUC) on the ROC curve, which captures sensitivity and security. For visual and subjective assessment, two neuroradiologists were asked to evaluate the images produced, including the uncertainty map. The model "often yield good to excellent results, reflected by 91.5% of high ratings for the enhancing and 92.3% for the nonenhancing glioma" [14]. However, regions were sometimes overlooked or not correctly captured, particularly where enhancement regions were not captured as boldly as in the ground truth data. It is worth noting that the presence of uncertainty maps proved particularly helpful, as they typically prevented the reader from overlooking these regions during an assessment.

Figure 5 shows visual results on two enhancing gliomas, where vcSub represents the prediction, ceT1w and subT1 the representing ground truth data. On the right the uncertinity map is seen, where the more yellow the more uncertain the model is.

Finally, we return to the classification approach for identifying multiple sclerosis from

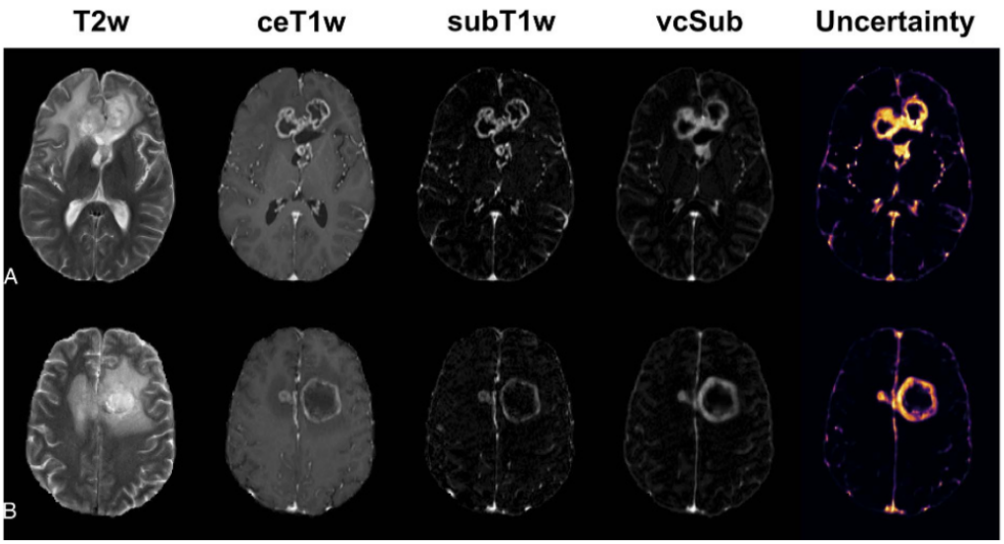

Figure 5: Comparison of scans and predictions. [14]

2020 [17]. The study used a DL approach with a two-stage neural network architecture to predict enhancing lesions in patients. The processing was performed on the Maverick2 cluster at the Texas Advanced Computing Center.

The presence of hyperintense lesions on images obtained with T2-weighted, proton density weighted and fluid-attenuated inversion recovery (FLAIR) MRI is a hallmark of MS and this is what the model tries to predict. The neural network architecture is quite different from the ones discussed so far, as it consists of two different networks, each with its own set of characteristics.

Since each brain scan consists of multiple 2D images, all of them have to be considered in order to make a final diagnosis for a patient. In other words, the model needs to understand the relationship between images taken from the same patient. The team solved this problem by using a traditional convolutional neural network for each image slice, similar to the previously mentioned CNNs: a sigmoid activation function is applied after several max-pooling layers, giving each slice a probability of predicting an active lesion (values from 0 to 1). These predictions are then combined in the second network, a standard fully connected neural network (FCNN), to make a patient-specific prediction of enhancement based on whether or not an active lesion is present.

Because some of the CNNs weights do not need to be adjusted after learning information about active lesion detection, some complete layers are frozen - a method where the corresponding neurons do not update and only pass information through the network. This is beneficial because the early layers in a deep neural network tend to learn low-level features, such as edges or textures, that are generally applicable to different tasks. By freezing these layers, the network can focus on learning task-specific features in the later layers without overwriting the valuable information already captured in the earlier layers.

Figure 6 shows the visualisation of the networks used combined into one. The CNN (A) is a pre-trained and tuned network (VGG16) that uses "transfer learning, a technique that uses knowledge from another model that has been trained on a different task" [17] and shows good performance in image processing. The layers marked in black are those that will be frozen later in the process to avoid loss of information. The rather simple second network, which combines the scores, consists of three layers, only one hidden layer with four nodes.

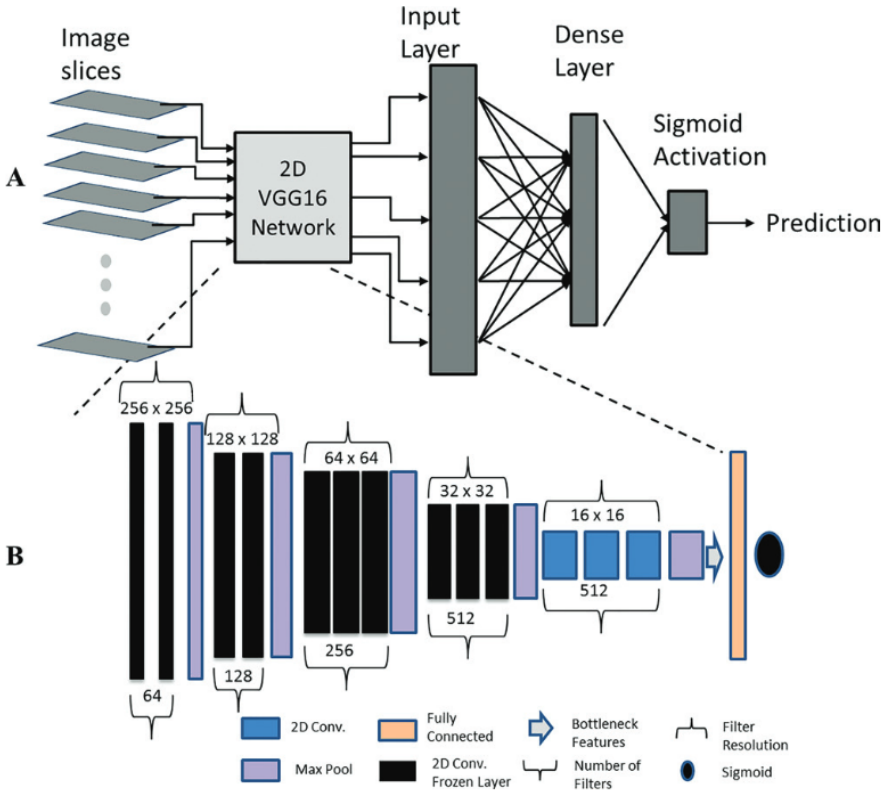

Figure 6: Combination of two different neural networks for lesion prediction. [17]

At its first stage (slice-wise prediction), the model used Adam as an optimizer given its weight-dependent learning rate and fast convergence. In the second stage (patient-wise prediction), when the slices were frozen, the model switched to SGD with a low learning rate and high impulse, which ensures that large changes in weights are avoided. To avoid overfitting, the researchers implemented overfitting and data augmentation by reflecting along the image axes.

The model achieved an average accuracy of 70% in predicting enhancements in patients with at least one enhancing lesion. While this level of accuracy may be considered good in some contexts, much higher levels are often required in medicine for reliable diagnosis. False positives included generated lesions that were not active on the ground truth, and vice versa for false negatives - which play a more critical role in medical imaging than in other ML tasks, as they raise concerns about missing findings in the diagnostic process. Average AUCs of 0.75 were achieved for patient-specific improvements. The authors acknowledge the limitations of the model, including the need for further testing on a more heterogeneous imaging dataset. They also point out the potential for future work to incorporate advanced MRI sequences and to generalise the model for use on more diverse datasets, as this study focused only on patients with relapsing-remitting MS, the most common form of multiple sclerosis.

3.3 Benefits and limitations

One thing holding these technologies back is the amount of effort required to create datasets from normal MRI scans.

The most challenging part is anonymisation, as personalised data can be found almost anywhere in a DICOM file. This includes simple metadata in the file itself, such as the patient's name, date of birth, gender and more [24]. Although this data can be removed fairly easily, for research purposes (depending on where the scan was performed), the patient's consent to share their data is required. Once these two steps have been taken,

the data still contains useful information such as the 3D structure of the face, which can be used to reconstruct a facial image, so further processing is needed to biometric information - commonly referred to as defacing [25]. Various types of MRI machines can also produce identifiable artefacts in the image, making it possible to infer the location the scan was performed [24]. Once all this information has been removed and the file is completely anonymised, it can be used as training data for ML, which usually requires some form of pre-processing.

Another problem is that the resulting datasets are often very small or tailored to specific diagnostic tasks or target conditions, which can lead to models that are optimised for classifying specific types of diagnoses. Due to the specificity of the training data, such models may have limited generalisability and may not perform well on different or unseen diagnoses. In the Stanford University study, the training data consisted of only 80 patient scans and very similar medical diagnoses.

Benefits include the obvious avoidance of contrast administration, the main aim of the trials, as well as other side effects associated with the approach, such as a faster diagnostic process due to the fact that no additional administration is required. For classification approaches, a ML model could significantly improve the process by reducing the need for human intervention - as long as a high level of accuracy and reliability is achieved, which is often the current problem with these techniques.

4 Conclusion

By reducing the amount of contrast agent administered, the overall cost of the imaging process and diagnosis can be significantly reduced, making the process more accessible to all types of people - or reducing healthcare costs in general.

Concerning patient care, the application of artificial intelligence can additionally reduce the time needed for a complete diagnosis - for example when no or low-dose administration is required.

4.1 Future perspectives

As all of the methods discussed in this paper are relatively experimental, almost none of them are currently used in medical imaging due to the high demands on the reliability of the predictions.

One solution I suggest is to have a central repository of imaging data to eliminate the frequent lack of data, which leads to poorer results and slows down the whole process. An open and accessible place for anonymised data would make the whole field more accessible to many people, researchers and institutions.

For now, the whole field of ML and image processing is growing at an immense rate, as many of the techniques we learned this semester are already outdated and being replaced by newly proposed ideas. Therefore, I am very confident that these problems will be overcome in the near future and can be used by medical experts to improve the diagnostic process as a whole.

Acronyms

Adam adaptive moment estimation

AI Artificial Intelligence

AUC area under the curve

BfArM Federal Institute for Drugs and Medical Devices

BN batch normalization

CIN contrast-induced nephropathy

CNN convolutional neural network

CT computed tomography

DGE dynamic glucose-enhanced

DICOM Digital Imaging and Communications in Medicine

DKFZ German Cancer Research Center

DL deep learning

EU European Union

FCN fully convolutional network

FCNN fully connected neural network

FLAIR fluid-attenuated inversion recovery

GBCA Gadolinium-based contrast agent

GPU graphics processing units

IBCA Iron-based contrast agent

MAE mean absolute error

MBCA Manganese-based contrast agent

ML machine learning

MRI Magnetic Resonance Imaging

MS multiple sclerosis

NSF nephrogenic systemic fibrosis

PSNR peak signal-to-noise ratio

ReLU rectified linear unit

SGD stochastic gradient descent

SNR signal-to-noise ratio

SSIM structural similarity index

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