Deep-learning-based image segmentation for uncommon ischemic stroke

From infants to adults

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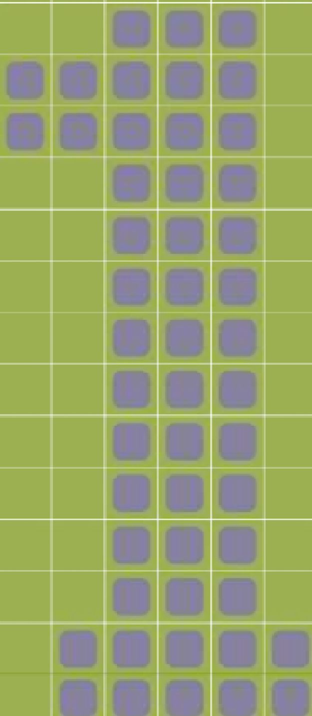

Chapter 1

Introduction

1

> There are other things to fear... apart from death, old age and madness. For example, apoplexy, that lightning bolt which strikes you down without destroying you, yet after which all is finished. You are still yourself but you are no longer yourself: from a near angel like Ariel, you have become a dull mass which, like Caliban, is close to the beasts.
>
> *Alexandre Dumas*, The Count of Monte Cristo. p.478

Stroke is defined as an acute neurological deficit that stems from injury to the central nervous system that is caused by an interruption of the circulatory system [13; 59]. The brain, with its high metabolic activity, is especially vulnerable to injury due to ischemia [15; 47]. Ischemic large vessel stroke, which is caused by an occluding thrombus in one of the large vessels of the brain, accounts for up to 46 percent of all cases of stroke in adult patients [40; 62]. Hence, ischemic large vessel stroke in adult patients has a poor prognosis, with only 33 percent of patients reaching functional independence 90 days after the stroke incident [8]. This has lead to stroke in adults being associated with a high financial cost. The global financial cost associated with stroke in adult patients was estimated at US $ 851 Billion [51].

Ischemic stroke occurs not only in adult patients, but also perinatally. Perinatal stroke is defined as a stroke that has occurred between 20 weeks of gestation up until 28 days after birth[20]. Perinatal Arterial Ischemic Stroke (PAIS) has the second highest incidence, after stroke in elderly patients [56]. The incidence rate of PAIS has been estimated to be between 1 per 3500 [1] and 1 per 7700 live births [25]. PAIS is associated with life time medical issues such as epilepsy, cerebral palsy, and cognitive and motor impairment [48].

The brain has two pathways that supply blood to it: The anterior and the posterior circulation. Anterior circulation large vessel ischemic stroke is more common than posterior circulation large vessel ischemic stroke, with 1 percent of large vessel ischemic strokes occurring in the posterior circulation. Posterior circulation large artery stroke involves an occlusion of the basilar artery, intracranial vertebral arteries or posterior cerebellar arteries. It is associated with a high risk of mortality and disability [29; 41; 61; 67].

During an ischemic stroke, the area of the brain that is ischemic can be subdivided into two regions. The first region is named the ischemic core. It is composed of tissue that has died due to insufficient blood flow and can no longer be salvaged. The second region is named the penumbra [5]. Due to a diminished blood supply, the neurons in the penumbra are no longer evoking action potentials. However, due to alternative routes, some blood can still be supplied to the penumbra, which can keep the tissue alive for several hours. Therefore, identifying the ischemic penumbra can help select patients that have the most salvageable tissue and would benefit the most from treatment [47].

Treatment

Approved treatments for adult patients suffering from acute ischemic stroke aim to reperfuse the ischemic area by removal of the occluding thrombus. Two treatments have proven to be both safe and effective for ischemic stroke. First, the occlusion can be dissolved by means of thrombolytic therapy. Thrombolytic therapy involves the intravenous administration of recombinant Tissue Plasminogen Activator (rTPA). It is effective if administered within 4.5 hours after stroke onset [19]. Second, the occlusion can be removed by means of mechanical thrombectomy. Mechanical thrombectomy involves navigating a stent-retriever or an aspiration catheter from a puncture in the femoral artery to the occluding thrombus in the brain and removing it. Mechanical thrombectomy in addition to thrombolytic therapy has become the recommended treatment for patients arriving to the hospital within 6 hours of the time the patient was last known to be well. When the patient arrives between 6 and 24 hours after the patient was last known to be well, mechanical thrombectomy can often still be performed. This is the case if there is a sufficiently large mismatch between the volume of the infarct core and the penumbra or the infarct core and the clinical deficit [2; 49; 54; 66].

For infant patients suffering from PAIS, there are currently no approved treatments. Thrombolytics and mechanical thrombectomy are not given due to a lack of evidence regarding their effectiveness in neonates [57]. All patients suffering from PAIS should be given neuroprotective measures and supportive care. Examples of supportive care are controlling seizures, ensuring adequate oxygenation and, correcting any anemia or dehydration, as well as reducing fever [20; 57].

The current focus of research that focuses on developing therapies for PAIS are novel stem-cell based neuro-regenerative treatments [68]. This is because neonates suffering from a PAIS have a greater ability to recover from the ischemic injury, due to their brains having greater plasticity than adult brains [10]. Moreover, animal models of the neonatal brain show a greater response to stem cell therapy than animal models of adult brains [69].

Neuro-imaging

Brain imaging is recommended for patients suspected of suffering from an acute ischemic stroke [54]. Brain imaging serves multiple purposes during a workup of acute ischemic stroke [30; 46]. First, to differentiate between hemorrhagic and ischaemic stroke. Second, to determine the extent of the ischemic core. Third, to determine the size of the penumbra. Fourth, to exclude stroke mimics, such as migraines or tumors as the cause of the symptoms. Fifth, to assess the large arteries in the head and neck. Sixth, to guide interventions, such as selecting which patients are eligible for a thrombectomy.

Computed Tomography (CT) is the preferred imaging modality in adult patients with stroke due to widespread availability, short scan times and high sensitivity for differentiating hemorrhagic from ischemic stroke. Specifically, Non-Contrast Computed Tomography (NCCT) is used to detect hemorrhagic stroke and the presence of hyper-dense artery sign. During Computed Tomography Angiography (CTA) a bolus of contrast is administered to the patient to visualize the arteries and to quantify the vascular disease burden (the degree of stenosis, thrombus length etc.) caused by the occluding thrombus [17; 34].

Magnetic Resonance Imaging (MRI) can also aid in the diagnosis of stroke. MRI is as accurate as NCCT at the detection of acute hemorrhage and more accurate than CT at detecting chronic intracerebral hemorrhage [21; 32; 53]. Furthermore, diffusion weighted imaging (DWI), an MRI sequence that shows the diffusion of water, has been shown to be accurate at diagnosing acute ischemic stroke [11; 22; 24].

For neonatal patients with PAIS, MRI is preferred over CT. This is due to the low sensitivity of CT at detecting small or posterior circulation infarcts, the rarity of hyper-dense artery signs in neonatal stroke patients, and the radiation produced by CT scanners [9]. A radiological workup of PAIS patients consists of several MRI sequences. These sequences include Diffusion Weighted Imaging (DWI) and apparent diffusion coefficient, susceptibility weighted imaging, and magnetic resonance angiography. T2- and T1-weighted sequences are optionally added [9; 20; 33]. To evaluate the treatment efficacy of novel neuro-regenerative treatments information from images can be used, such as final lesion volume on follow-up MRI. [7].

Brain imaging data collected from stroke patients also has an important role in stroke research. Features extracted from these images, can be used as an alternative outcome measure to assess treatment efficacy. Examples are ischemic lesion volume on baseline and follow-up scans in adult patients [12; 70] in perinatal arterial ischemic stroke [7]. Image features, such as ischemic lesion volume, rely on its accurate segmentation. However, its manual segmentation is a time consuming task. Therefore, automated deep learning based segmentation methods have the potential to reduce the time required to create segmentations.

Machine Learning and Deep Learning

Machine learning is the study and development of computer algorithms that are capable of learning. In this definition, learning is defined as the ability of the algorithm to improve its performance at tasks with experience [43].

For example, an algorithm that learns how to play chess would have its performance measured by its ability to win at the group of tasks that involve playing chess games and by gaining experience through playing games of chess against itself or others.

Deep learning is a sub-field of machine learning that utilizes layers of non-linear processing of information, also known as Artificial Neural Network (ANN), to solve learning problems [18]. The most basic neural network has five key components; weights, biases, an activation function, an output function, a loss function, and an optimizer. The goal of training a neural network is to minimize the loss function given the input data. The process by which the neural network is taught how to minimize the loss function is referred to as training. Before training, the weights and biases are initialized by assigning them random numbers. The input data is transformed by multiplication of the data with the weights and addition of the biases. Next, the result is transformed by applying the activation function. The resulting matrix of numbers is referred to as the features. This process is repeated a pre-specified number of times. When the final layer is reached, the output function is applied. The output function varies per image analysis task, for example classification uses the softmax output function and regression uses the linear activation function. Next, the value of the loss function is computed on the basis of the output. By using the optimizer the weights and biases are updated to reduce the value of the loss function. This process continues until the loss value has reached a stable value. See figure 1.1 for a schematic representation of this process.

In recent years, deep learning has been applied to solve multiple medical image analysis tasks [36]. Specifically, the network architecture that is commonly used to create solutions for medical image analysis are Convolutional Neural Networks (CNN) [27]. CNNs have their weights organised in convolutional kernels, which are slid over and multiplied with the underlying input data as opposed to matrices that are multiplied with the input data. A graphical representation of how convolutions work in a neural network can be found in figure 1.2. This allows local correlations between for example pixels in images to be more easily used. Examples of medical image analysis

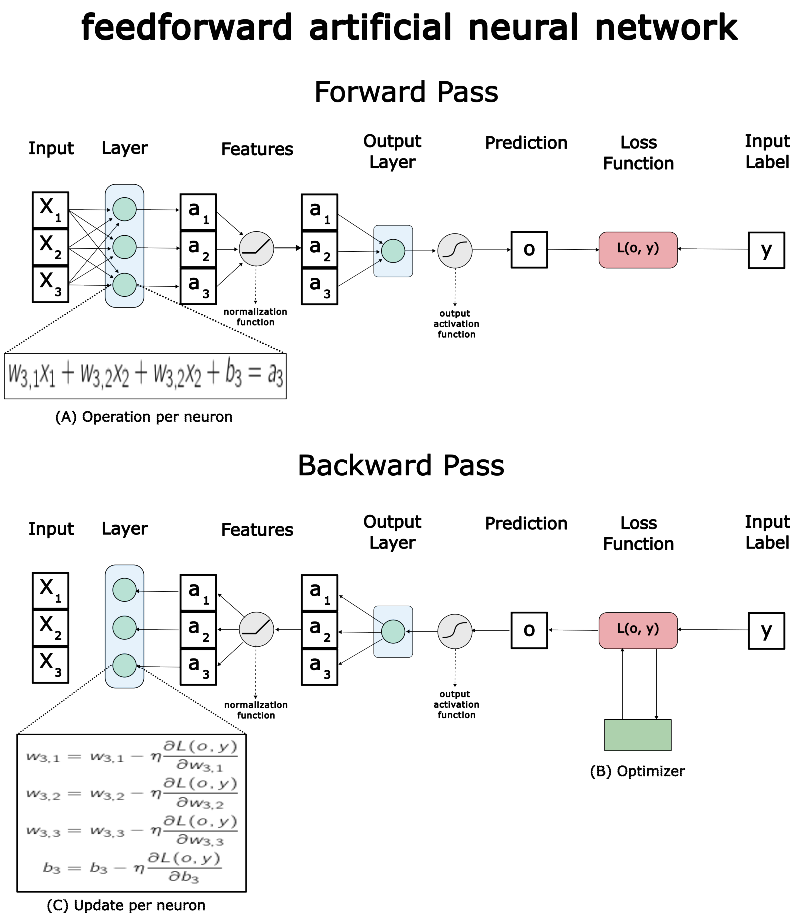

Figure 1.1: Forward (top) and backward pass (bottom) of a simple two-layered artificial neural network(ANN). The neural network consists of an input layer which is composed of three neurons. The input layer is followed by an activation function, which is followed by the output layer consisting of one neuron. Finally, the output layer is followed by a sigmoid activation function and the cross-entropy loss. During the forward pass the neural network is given the input data and the input label. **(A)** Each neuron in the input layer multiplies one of its weights ($w_{l,n}$) with one of the input values(x_n), sums the result and adds a bias value (b_n) to calculate the features (a_n). The features are normalized and passed to the output layer. The output layer repeats the process and normalizes the result as is required for the specific task. The loss value is calculated using the input label and network result. During the backward pass the optimizer **(B)** is used to calculate the gradient updates to minimize the loss function. To achieve this the gradients are passed through the network such that all of the weights and biases are updated **(C)**.

tasks are segmentation of brain tissue on MRI [44], image registration [16] and lung nodule detection [28].

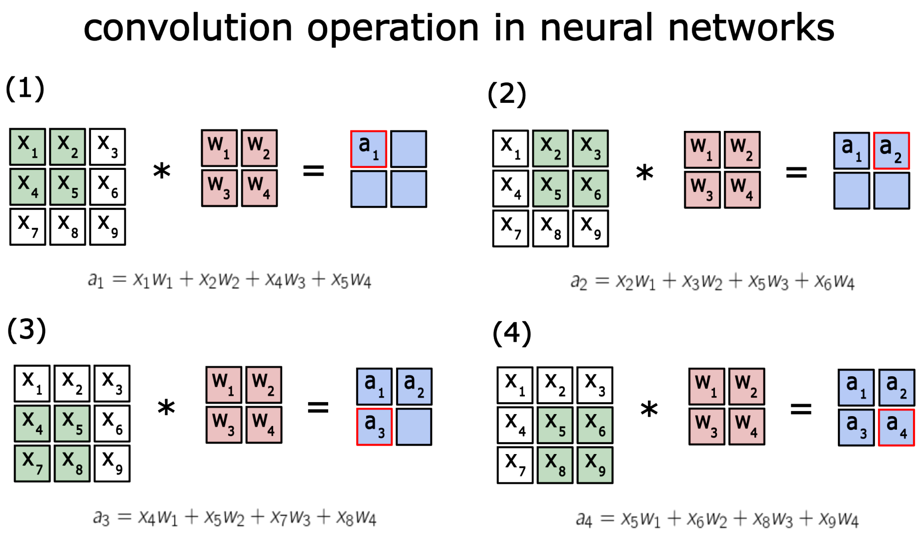

Figure 1.2: Example of how the convolution operation is used in a convolutional neural network (CNN). Shown in each of the four panels from left to right is the input data (green and white), the kernel that is parameterized by weights (red), and the resulting features (blue). The kernel is multiplied element-wise with the part of the input data that is shaded green. The formula below shows the resulting calculation for each feature. Steps 1 through four show how the kernel is moved over the input data to calculate all of the features. The weights in the kernel are updated such that spatial correlations in an image are captured by the network.

CNNs have been applied to image analysis tasks related to stroke in adult patients. Prior work has developed deep learning-based algorithms to identify patients with a large-vessel occlusion stroke in CTA images [4; 42; 60; 63] and to detect or segment thrombi in the anterior circulation on NCCT scans [35; 45; 64]. Other work has focused on developing algorithms to segment diffusion abnormalities during an acute ischemic stroke on DWI [37; 72]. Zhang et al. used a 3D DenseNet to segment the ischemic region on DWI [72]. In addition, Zhang et al. evaluated their method on data from the open-source Ischemic Stroke LEsion Segmentation (ISLES) challenge[39], making their method easily comparable to other existing methods. Liu et al. developed a method that outperformed existing methods, specifically on small lesions. Algorithms have also been developed to segment chronic stroke lesions on T1-weighted MRI scans by using variations of U-Net [58]. Tomita et al. used a UNet which was trained by using zoomed-in sub volumes, the zoom factor was decreased as training progressed. They speculated that their training strategy improved performance due to improved regularization [65]. Qi et al. replaced the standard U-Net convolutional blocks with feature-similarity modules that more effectively utilize dependencies between distantly placed voxels [55]. Finally, Zhou et al. used a specific convolutional block to fuse 2D and 3D features and they used a novel mixing loss to more effectively address the class imbalance between foreground and background voxels [73]. Algorithms have also been developed to segment ischemic lesions due to an anterior circulation stroke on follow-up NCCT [6] and baseline CTA [50]. All previously mentioned studies have focused on segmentation of lesions on the same scan that was used to create the ground truth annotation. However, Yu et al. developed a method that predicts the follow-up lesion segmentation from baseline multi-sequence MRI [71]. Their method achieved a moderate overlap and a good volumetric agreement between the ground truth and predicted segmentation.

Transfer Learning

A limitation of CNNs is that they require large amounts of annotated data to learn how to accurately segment objects in images. However, creating large amounts of annotations is a time-consuming task. Moreover, large amounts of scan data may not always be available for uncommon diseases. Hence, reducing the amount of annotated data that is required for the development of CNN based algorithms is an active area of research.

Transfer learning is a method that can be used to improve CNN performance in settings where available annotated data is scarce [52]. Transfer learning aims to re-use a CNN that has been pre-trained on a different source task with a large amount of available data on a new target task [36]. The task of a neural network refers to the specific application such as segmentation, classification or regression. In addition to the task, another relevant aspect of transfer learning is the source and target domain [52]. The domain refers to the type of data on which the neural network is trained or to which the neural network is applied.

Prior studies on transfer learning have evaluated the effect of different source tasks and domains on target medical MRI segmentation tasks in a limited manner. On the natural image source domain, studies have only assessed the source tasks classification [3; 26] and segmentation [31], but not self-supervised tasks. On the medical image source domain the only source tasks that were evaluated, were segmentation [14; 23; 38] and self-supervised tasks [74]. Classification source tasks were not yet evaluated. Moreover, all the studies evaluated the the effect the source tasks and domains had on target task performance on different data-sets, which makes a fair comparison difficult. Hence, a fair evaluation of the effect that the source task and domain have on the target medical segmentation tasks could allow for a effective application of transfer learning.

Aim of this thesis

Both posterior circulation large vessel and perinatal arterial ischemic stroke are uncommon types of stroke. Hence, few data is available to train algorithms to perform complex segmentation tasks. The aim of this thesis is to investigate, develop, and evaluate deep learning-based algorithms for automatic segmentation of images of these types of stroke.

Thesis outline

In **chapter 2**, we evaluate transfer learning for medical image analysis tasks. Specifically, we focus on evaluating the overlap and detection accuracy of source-tasks and domain combinations for target segmentation tasks on MR scans. We apply transfer learning to two segmentation tasks related to posterior circulation large vessel ischemic stroke in **chapter 3** and **chapter 4**. In **chapter 3**, we develop and evaluate algorithms for automated segmentation of posterior circulation stroke lesions on follow-up scans. In **chapter 4**, we develop and evaluate an automatic method for localization and segmentation of thrombi in the posterior circulation stroke on baseline scans. In **chapter 5** a method is developed that automatically segments brain tissues and the ischemic lesion per hemisphere on baseline and follow-up MR brain scans of patients suffering from a perinatal arterial ischemic stroke. Finally, in **chapter 6** we discuss the results.

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