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SCHOOL OF INDUSTRIAL AND INFORMATION ENGINEERING
Master of Science – Computer Science and Engineering

Brain Magnetic Resonance Imaging Generation using Generative Adversarial Networks

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Acknowledgements

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Abstract

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Extended Abstract

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Chapter 1

Introduction

Medical imaging is crucial for clinical analysis and medical intervention since it gives important insights about some diseases whose structures might be hidden by the skin or by the bones. One of the most common techniques used nowadays is the Magnetic Resonance Imaging. **MRI!** (**MRI!**), ubiquitous in hospitals and medical centers, first because of its non-invasive nature, since, differently from other imaging technologies, doesn't make use of X-ray radiography and secondly due to recent improvements in the software and hardware instrumentation used. In this type of imaging, different sequences (or modalities) can be acquired and each sequence can give useful and different insights about a particular problem of the patient. For example the T1-weighted sequence can distinguish between gray and white matter tissues while T2-weighted is more indicated to highlight fluid from cortical issue.

The problem about MRI is that sometimes there isn't the possibility to acquire all the sequences that would be required in order to diagnose a disease and this is due to different reasons: sometimes there isn't enough time to collect all the needed sequences, sometimes it's too expensive to generate all of them. Furthermore, missing sequences might occur because of allergies from the patient that doesn't allow to obtain modalities where an exogenous contrast agent, a substance useful to increase the contrast between structures or fluids within the target area, is used to make the image clearer. It can also happen that, for a given patient, some scans might be unusable due to the presence of errors, corruptions or machine settings not defined in the proper way.

It would be useful, then, to find a way to generate a prediction of the missing sequences by using the modalities given as input for a given patient. These generated predictions then could be used either as direct aid to the doctor that has to make a diagnosis for a patient that maybe can't have injected into his body any kind of contrast agent, or could be used as one of the input pieces of a bigger pipeline.

Thanks to the recent improvements in Machine Learning, but more in particular in the **DL!** (**DL!**) field, the generation of missing modalities has become an objective feasible to reach, both in terms of efficiency of the obtained result and in terms of time spent in order to reach something meaningful.

1.1 Scope

In this work we approach the problem presented above using **GAN!** (**GAN!**), a special type of neural network that is used to synthesize the missing modalities given an certain input. [?]

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1.2 Related Work

1.2.1 Deep Learning in Medical Image Analysis

In the last few years interest toward Machine Learning and more in particular toward Deep Learning has grown exponentially: just to give an idea to the incredible spread that is having this **AI!** (**AI!**) research area, in the 2016 and 2017 over 400 contributions related to Deep Learning applied to Medical Image Analysis were published [?]. It has been shown that **DL!** has been able to reach very competitive results in many medical task: classification, detection, segmentation, registration of different areas and structures within the human body. Many progresses has been done and further are yet to come in order to reach results as accurate and precise as possible in crucial applications such as cancer cell classification, lesion detection, organ segmentation and image enhancement [?].

The most successful **DL!** architecture in medical analysis are **CNNs!** (**CNNs!**): neural networks with multiple hidden layers between the input and the output layers. The initial problem with this type of architecture was that researchers weren't able to train these deep neural networks in an efficient way. The watershed was the work described in [?] that represents a huge contribution to the field since the proposed CNN, called AlexNet, won the ImageNet competition in 2012 by a large margin. The peculiarity of AlexNet was that its competitive results and high performances were obtained in relative short time, due to the fact that the designer of this network made the training feasible by the utilization of **GPUs!** (**GPUs!**).

Another important breakthrough in the field was represented by the introduction of Generative Adversarial Networks, a new class of machine learning systems invented by Ian J. GoodFellow in 2014 [?].

1.2.2 Generative Adversarial Networks

A Generative Adversarial Network is a system composed by two neural networks, a generator and a discriminator, that, through an adversarial setting, try to learn the probability distribution of the data given as input and generates synthesized data that exhibits similar characteristics to the authentic data. GANs be used in many data domains, but the images one is for sure the one in which this type of neural network obtained the most significant results. The authors of the original paper relative to this architecture were the first to try a range of image datasets including MNIST [?], the Toronto Face Database [?] and CIFAR-10 [?]. A lot of work has been done also towards another task involving pictures: image-to-image translation where Isola et al., in order to explore the generality of their work [?], experimented with a variety of settings and datasets such as generating the night version of an image whose daily version was given as input to the network or synthesizing the picture of a building by only observing its relative architecture label as input after a training performed on CMP Facades (Figure ??).

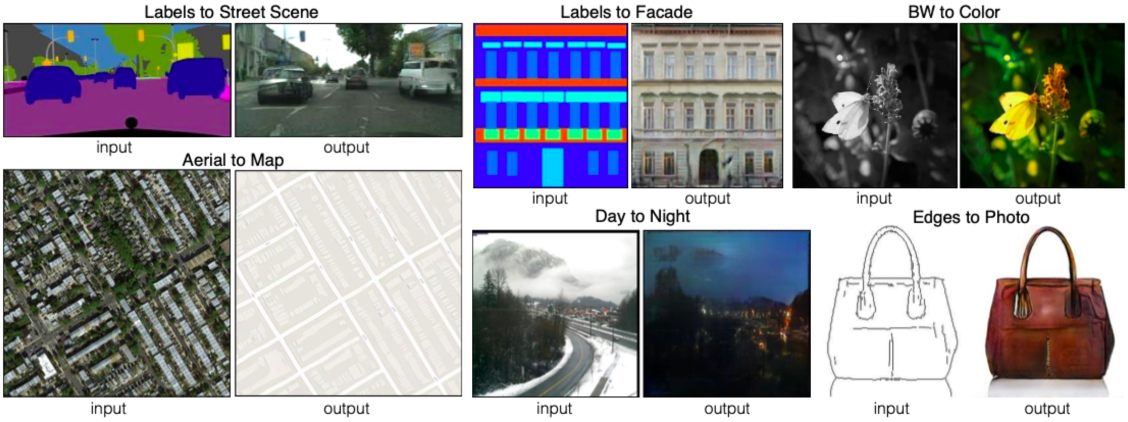

Figure 1.1. Examples of image-to-image translation from the work of Isola et al. [?]

1.2.3 GANs in Medical Imaging

GANs! (**GANs!**) have been applied in countless studies about image synthesis, where cross modality image synthesis (so the conversion of the input image of one modality to the output of another modality) is the most important application of this architecture. In 2018, was even published a paper of review [?] about all the work and progresses that have been done in the field of medical imaging through the application of **GANs!**. The authors described the magnetic resonance as the most common imaging modality explored in the literature related to this generative approach invented by GoodFellow and this is probably due to the fact that **GANs!**, through the cross modality synthesis, can reduce the excessive amount of time requested from **MR!** (**MR!**) acquisition.

Many different approaches and datasets have been used in the literature in order to overcome the problem of missing modalities. Orbes-Arteaga et al., in [?], since most of the datasets contain only T1 or T1/T2/PD scans due to logistical reasons, implemented a **GAN!** that generates T2Flair using the T1 modality. In [?], Camileri et al. developed a variant of the original GAN, called Laplacian pyramid framework (LAPGAN) that synthesizes images in a coarse-to-fine way. This methods, as the name suggests, is based on Laplacian pyramid and allows to generate initially an image with low resolution and then, incrementally, add details to it. Another approach to generate missing modalities was proposed in [?] where they presented two possible scenarios, based on the given dataset: they use a model called pGAN (that incorporates a pixel-wise loss into the objective function) when the multi-contrast images are spatially registered while they adopt a cycleGAN [?] in the more realistic scenario in which pixels are not aligned between contrasts. A cycleGAN is a variant characterized by the fact that has two generators, two discriminators and uses a cycle consistency loss. This model was trained in a unsupervised manner, meaning that the training made use of a collection of images from the source and target domain that didn't need to be related in any way.

Most of the papers about Generative Adversarial Networks, and also this work, though, are based on supervised generation, where the training is performed using paired examples, with input image and target image perfectly aligned.

Concerning the supervised generation, it's worth to cite also the work done by Anmol Sharma and Ghassan Hamarneh that were, to the best of their knowledge [**?**], the first to propose a many to many generative model, capable of synthesize multiple missing sequences given a combination of various input sequences. Furthermore, they were the first to apply the concept of curriculum learning, based on the variation of the difficulty of the examples that are shown during the network training.

MRI isn't the only imaging technique where **GAN!** has been applied to: in literature is possible to find various publications of generative models that use Positron Emission Tomography **PET!** (**PET!**), Computerized Tomography **CT!** (**CT!**) or Magnetic Resonance Angiography **MRA!** (**MRA!**) images. [**?**], for example, discuss about how generate **PET!** images using **CT!** scans through a fully connected neural network, whose output is improved and refined by a **cGAN!** (**cGAN!**) [**?**]. Olut et al., in 2018, demonstrated that **GAN!** works efficiently even when the source imaging technique is different from the target one: they were the first ones to synthesize **MRA!** images from T1 and T2 MRI modalities [**?**].

The work related to the generation of medical image is huge and new papers about the topic are being published every week. Many approaches have been already tested and many datasets have been used but there are still lots of challenges that need to be resolved in order to be able to be employed in medical imaging [**?**] and since there is still room for improvements in the application of generative models in medical imaging, we present in this work a complete study about different architectures of **GAN!** and about the information that passes through the inner channels and through the skip connections of the generator networks.

1.3 Thesis Structure

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1.4 Summary

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Chapter 2

Theoretical Background

In this chapter we introduce the theoretical aspects our work is based upon, while giving the reader an overview of the tools and techniques we applied in our models, in order to better understand the setting in which our work takes place.

2.1 State-of-the-art review

The main model used in our work is the Generative Adversarial Network whose architecture is partially based on the Convolutional Neural Network: a deep neural network with many hidden layers that nowadays is the workhorse of the **DL!** field in many application going from Image Recognition to Video Analysis, passing through Natural Language Processing, Anomaly detection, Drug Discovery, etc.

2.1.1 Convolutional Neural Network

The 1980, period in which David H. Hubel and Torsten Wiesel gave crucial insights about the structure of the visual cortex (the authors are winners of the 1981 Nobel Price in Physiology or Medicine for their work), is the starting point from which *convolutional neural networks* started to gradually evolve into what is today the architecture most used in **DL!**, composed by traditional building blocks such as fully connected layers and sigmoid activation functions but also convolutional layers and pooling layers that were first introduced by the pioneering work of Yann LeCun in 1998 that developed a model, LeNet-5, to identify handwritten digits for zip code recognition in the postal service [**?**].

The most important building block is the convolutional layer that is based on the mathematical operation from which **CNNs!** take their name. This layer allows to extract features by convolving the input with a certain number of filters, producing a stack of feature maps, one per each filter that was convolved with the input image. Each filter basically tries to capture, in the first layers of the network, low-details of the image by producing this feature map that highlights which are the areas on the input that were activated by the filter the most. In the the next hidden layers this small low-level features are assembled into higher-level features and this hierarchical structure is one of the reason why **CNNs!** work so well and are so widely used [**?**]

2.1.2 GAN

Generative Adversarial Network was proposed in 2014 by Ian J. GoodFellow [?] and represents a new framework for estimating generative models in an adversarial setting. The system is composed by a couple of neural networks: a generator G, whose architecture is similar to an autoencoder's decoder, and a discriminator D, typically a **CNN!** (**CNN!**), that are trained simultaneously. In particular, G is trained to capture the data distribution while the discriminative model estimates the probability that a sample came from the training data rather than G.

In this adversarial setting, the two networks compete with each other in a game (corresponding to what is called minimax two-player game in Game Theory [?, p. 276]) where the G is the analogous to a counterfeiter that tries to fool D, the analogous of the police whose objective is to be able to discover the true images, the ones belonging to the input dataset, from the ones generated by the generator. Equation **??** shows the losses for D and G used in the original architecture [?].

$$
\begin{aligned}
L_D^i &\leftarrow \frac{1}{m}\sum_{i=1}^{m} \log[D(x^i) + \log(1 - D(G(z^i)))] \\
L_G^i &\leftarrow \frac{1}{m}\sum_{i=1}^{m} \log(1 - D(G(z^i)))
\end{aligned}
\tag{2.1}
$$

where z^i is a batch of random noise and x^i is a batch of true data samples. The two networks are trained alternately using *Backpropagation*, in such a way that the generator can learn to synthesize the images based on the discriminator feedback.

It's important to highlight that the G never sees real images: it just learns the gradients flowing back through the discriminator. The better the discriminator gets, the more information about real images is contained in these secondhand gradients, so the generator can make significant progress [?]. As the training advances, the **GAN!** may end up in a situation that is called by the theorists *Nash equilibrium*, so a situation in which the generator produces perfectly realistic images while the discriminator is forced to guess (50% real and 50% fake). Unfortunately it's not that simple: it's not enough to just train a **GAN!** for a long time and there is no guarantee to reach this equilibrium.

2.1.3 Deep Convolutional GAN (DCGAN)

The problem with the original **GAN!** paper [?] is that GoodFellow et al. experimented with convolutional layers but only with small images. In the following months researchers tried to work with deeper neural networks for larger images and, in 2015, Radfrod, Metz and Chintala presented an improved version of the original architecture with some tricks and variations [?].

The guidelines proposed, that we followed in our work, in order to obtain a stable training even with large images, are:

- Replacement of any pooling layers with strided convolutions in the discriminator and with transposed convolutions in the generator.

- Batch normalization [?] in every layer (with the exception of the generator output layer and the discriminator input layer).
- Remove fully connected hidden layers, both in G and D.
- ReLu activation functions [?] in G for all layers except for the output, which uses Tanh.
- LeakyReLu in D for all layers.

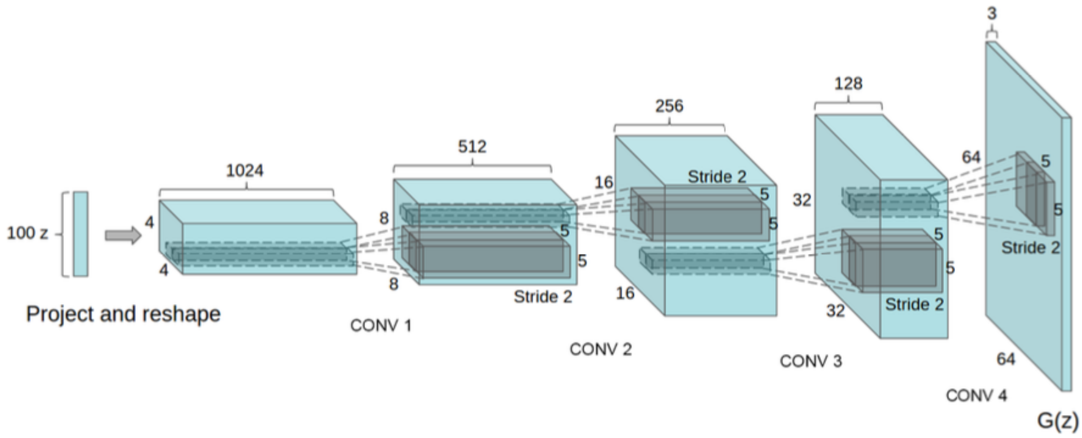

Figure 2.1. DCGAN generator used in the work of Radford, Metz and Chintala.

2.1.4 Conditional GAN

In the *Conclusions and future work* of the original **GAN!** paper [?], GoodFellow et al. suggested that the proposed framework could have been extended by conditioning the input of both G and D. This extension was realized by Mehdi Mirza and Simon Osindero that developed a Conditional Generative Adversarial Net. The authors explain that in a unconditioned generative setting there is no possibility to control the modes of the data that is generated, while by conditioning the input with some extra information y it's possible to direct the data generation process [?].

y can be any kind of auxiliary information, such as class labels or data coming from other modalities (in our work we conditioned the input with images as the extra information), so the prior noise z is combined to y as input to the generator while the discriminator takes as input data x and y.

2.1.5 Image-to-Image translation with Conditional GAN

Image-to-Image translation is the task of translating one possible representation of a scene into another one. After the publication, in 2015, of *Conditional Adversarial Nets* [?], many researchers started to apply this kind of architecture to the *Image-to-Image translation*, using images as auxiliary information to control the data generation. An important contribute was given by Phillip Isola et al. that developed a general framework that is not application-specific, generally known as Pix2Pix [?].

Pix2Pix works so well in many domains because of several architectural choices that were adopted both in the generator and in the discriminator.

Figure 2.2. Thermal images translated to RGB photos: an example of Image-to-Image translation using Pix2Pix [?]

None of these architectural choices were introduced for the first time by the authors of Pix2Pix: they have been already explored in many papers related to **GAN!** and focused on specific applications, but for the first time they have been used for a general-purpose solution to image-to-image translation. The neural networks chosen by Isola et al. are the same ones that have been used in our work: a "U-Net"-based architecture [?] as generator and a "PatchGAN" classifier, similar to the one proposed in [?], as discriminator.

Furthermore, the authors found beneficial to mix the **GAN!** objective to a more traditional loss such as the L1 loss. So, while the objective of a conditional GAN can be expressed as

$$\mathcal{L}_{cGAN}(G, D) = \mathbb{E}_{x,y}[\log D(x, y)] + \mathbb{E}_{x,z}[\log(1 - D(x, G(x, z)))], \tag{2.2}$$

where G tries to maximize the objective against the adversarial D that tries to minimize it, a L1 loss was used in order to measure the distance between the ground truth image and the generated image:

$$\mathcal{L}_{L1}(G) = \mathbb{E}_{x,y,z}[\|y - G(x, z)\|_1]. \tag{2.3}$$

L1 loss is preferred to the L2 one, since it produces results less blurred. The final objective, then, is:

$$G^* = \arg\min_G \max_D \mathcal{L}_{cGAN}(G, D) + \lambda\mathcal{L}_{L1}(G). \tag{2.4}$$

Pix2pix is the model whose performances are used as baseline in our work and, because of this, we present below further details on the U-Net architecture and on the PatchGAN architecture, in order to make more understable the next chapters.

U-Net

Pix2pix adopts as generator a "U-net" architecture [?], used also in this work, that allows to obtain better results with respect to the ones reached by generators composed by an encoder-decoder network.

The important problem in image-to-image translation, so in a setting where we need to map a high resolution input grid to a high resolution output grid by maintaining the same underlying structure between an input and output image that differ in surface appearance [?], is that using an encoder-decoder network the input image is simply downsampled progressively until a bottleneck layer after which the process is reserved and the information pass through many upsample layers.

Because of this bottleneck layer, it would be preferable to have to shuttle all this information directly across the net: this is obtained adding to the network some links, called **skip connections** between, for example, the *i* layer and the *n-1* layer, where *n* is the total number of layers. Skip connections result very useful in tasks such as image colorization, where input and output share the location of the prominent pixels and are able to prevent the problem of losing information through the bottleneck.

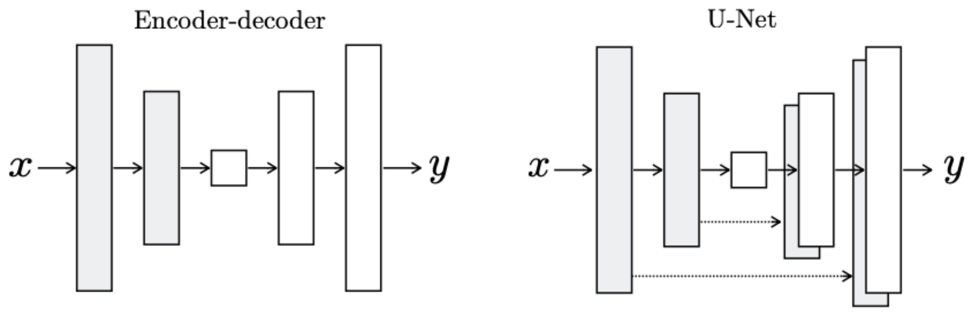

Figure 2.3. Two choices for the generator architecture. U-Net has skip connections between mirrored layers [?].

PatchGAN

Isola et al. explain that, since L1 loss (Eqn. **??**) is able to capture accurately low-level frequencies, it's sufficient to restrict the **GAN!** discriminator focus only on the high frequencies. High frequencies can be captured by using a classifier, *Patch*GAN, that is able to discriminate small local *NxN* patches of the images and assign to these a fake or true label. Averaging all the responses across the image provide then the ultimate output of D [?].

The authors demonstrate, after testing various kinds of patches, such as a 1x1 "PixelGAN" and a 286x286 "ImageGAN", that a 70x70 PatchGAN gives the best results in terms of blurriness, sharpness, general quality of the image and presence of any artifacts.

Figure 2.4. Path size variations going from 1x1 "PixelGAN" to "286x286" "ImageGAN" passing through the 70x70 PatchGAN that produces sharp results in both the spatial and spectral (colorfulness) dimensions [?].

Furthermore, scaling the patch beyond 70x70 doesn't improve the quality of the output and has the downside of a longer training needed, because of the larger number of parameters.

2.2 Summary

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Conclusions

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Appendix A

First Appendix

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Acronyms

AI	Artificial Intelligence
cGAN	conditional GAN
CNN	Convolutional Neural Network
CNNs	Convolutional Neural Networks
CT	Computerized Tomography
DL	Deep Learning
GAN	Generative Adversarial Network
GANs	Generative Adversarial Networks
GPUs	Graphics processing units
MR	Magnetic Resonance
MRA	Magnetic Resonance Angiohraphy
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography

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