Generative Adversarial Networks (GANs) for Retinal Fundus Image Synthesis

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Generative Adversarial Networks (GANs) for Retinal Fundus Image Synthesis

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Abstract. The lack of access to large annotated datasets and legal concerns regarding patient privacy are limiting factors for many applications of deep learning in the retinal image analysis domain. Therefore the idea of generating synthetic retinal images, indiscernible from real data, has gained more interest. Generative adversarial networks (GANs) have proven to be a valuable framework for producing synthetic databases of anatomically consistent retinal fundus images. In Ophthalmology, GANs in particular have shown increased interest. We discuss here the potential advantages and limitations that need to be addressed before GANs can be widely adopted for retinal imaging.

Keywords: Retinal fundus images · Medical imaging · Generative adversarial networks · Deep learning · Survey

1 Introduction

Computer-aided medical diagnosis is of great interest for medical specialists to assist in the interpretation of biomedical images. Harnessing the power of artificial intelligence (AI) and machine learning (ML) algorithms has sparked tremendous attention over the past few years. Deep learning (DL) methods – in particular – have been demonstrated to perform remarkably well for medical images analysis tasks [33]. Specifically, in Ophthalmology, DL systems with clinically acceptable performance have been achieved, for different end goals, including detecting different eye diseases, such as diabetic retinopathy (DR) [18,23,31,52,53], glaucoma [32], and age-related macular degeneration (AMD) [7,21]. These results show substantial potential for health-care and retinal applications, and possible implementation in screening programs.

However, there is a considerable need for large, diverse and accurately annotated data for further development, training and validation of DL models.

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High costs, in terms of money and time, are required to obtain high quality data from healthy and diseased subjects. Furthermore, as is the case for certain pathologies, the number of samples is often too limited to be statistically significant to conduct certain analyses. More importantly, legal concerns regarding patient privacy and anonymized medical records introduce critical limitations leading to possible bias to the research outcome, as seeking genuine patient consent is a fundamental ethical and legal requirement of all healthcare practitioners [12,56].

Nevertheless, one of the most interesting and innovative alternatives of using existing patient data, when dealing with medical images, is to artificially create new synthetic data, where generative models can potentially help overcome the aforementioned limitations. Here we focus on one of the recent breakthroughs in DL research, generative adversarial networks (GANs), and their applications in the field of retinal image synthesis. In particular, in this review paper, a broad overview of recent work (as of end of September 2018) on GANs for retinal images synthesis is provided. Potential clinical applications are also discussed.

2 Background

Synthesizing realistic images of the eye fundus is a challenging task since before the DL era. It was originally approached by formulating complex mathematical models of the anatomy of the eye [17,37]. Currently, the advances in technology have brought high computational power leading ML to neural networks with deep architectures. Considering recent progresses in DL algorithms, GAN represents a valuable framework. The rapid enhancement of GANs [15] facilitated the synthesis of realistic-looking images, leading to slightly anatomically consistent and reasonable visual quality colored retinal fundus images [5,13,14,22,24,60]. GAN is an unsupervised DL machine, introduced by Goodfellow et al. [20], based on two models: a generator and a discriminator. The generative model learns to capture the data distribution, taking random samples of noise, and generates plausible images from that distribution. The discriminative model estimates the probability that a sample comes from the data distribution rather than generator distribution, and therefore is tasked to discriminate between real and fake images (Fig. 1).

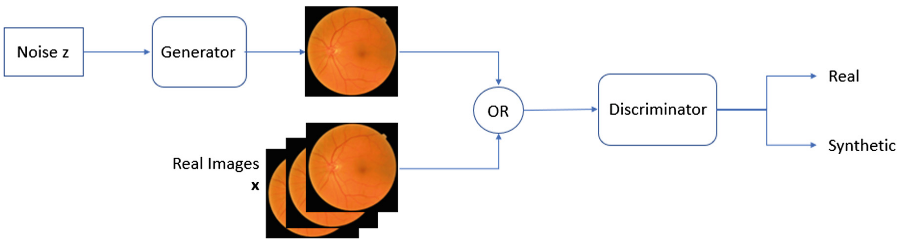

Fig. 1. GAN general scheme.

The performance of both networks simultaneously improves over time during the training process: while the generator tries to fool the discriminator by generating images as realistic as possible, the discriminator tries to not get fooled by the generator by improving its discriminative capability. Equation 1 represents one of the widely used GAN general loss function.

$$\min_G \max_D V(D,G) = \mathbf{E}_{\boldsymbol{x} \sim p_{(data)}(\boldsymbol{x})}[logD(\boldsymbol{x})] + \mathbf{E}_{\boldsymbol{x} \sim p_{(z)}(\boldsymbol{z})}[log(1 - D(G(\boldsymbol{z})))] \quad (1)$$

A variety of prominent extensions have been proposed, including DCGAN [42] and cGAN [38], to the most recent WGAN [3], LSGAN [36], AC-GAN [40], cycleGAN [62]. The adoption of GAN into medical imaging field covers applications such as denoising [57], reconstruction [48], detection [1], classification [46], segmentation [43], synthesis [4].

Concerning retinal fundus images field, GANs have been widely used for segmentation [30,35,47,49,50] purposes, and relatively less explored in synthesis [5,13,14,22,24,60] and super-resolution tasks [34].

3 Retinal Image Synthesis: Current Status

GANs have demonstrated capabilities to generate synthetic medical images with impressive realism. Existing work on GANs for the synthesis of colour retinal fundus images [5,13,14,22,24,60] is described in this section (Table 1).

Costa et al. [13] paired retinal fundus images with vessel tree segmentation. The binary maps of retinal vasculatures were obtained using U-Net [45] architecture. The pairs were used to learn a mapping from a binary vessel tree to a new retinal image (512×512 pixel), using image-to-image translation technique (Pix2Pix [25]). They used the general GAN adversarial loss and a global L1 loss, controlling low-frequency information in images generated by the generator. The training set consisted of 614 image pairs from the Messidor-1 dataset. For evaluation of their synthetic results, they adopted two no-reference retinal image quality metrics, Image structure clustering (ISC) [39], and Q_v [29] scores. While the latter score focused more on the assessment of contrast around vessel pixels, the former performed a more global evaluation.

Notably, Costa et al. proposed a follow-up work [14], where the authors trained jointly an Adversarial autoencoder (AAE) for retinal vascularity synthesis and a GAN for the generation of colour retinal images. Specifically, the VAE was used to learn a latent representation of retinal vessel trees and subsequently generate the corresponding retinal vessel tree masks, by sampling into a multi-variate Normal distribution. In turn, the adversarial learning mapped the vessel masks into colour fundus images, by sampling a multi-dimensional Gaussian distribution using the adversarial loss. The L1 loss promoted the consistency of global visual features, such as macula and optic disc. Again, 614 healthy macular-centered retinal images from Messidor-1 dataset were downscaled to 256×256 and used for the training phase. The authors performed qualitative and quantitative experiments comparing real and synthetic database containing the same number of pairs. They found that the model did not memorize the training data: the synthetic vessels resulted in images visually different from the closest on the real database. The authors decided to adopt again the ISC metric. Also, they evaluated U-Net [45] performance when trained to segment first real images only, and then synthetic data only. They found that training with only synthetic data lead to only slightly inferior AUCs values. However, combining synthetic and real images for training led to decreased performance. Some synthetic results are shown in Fig. 2.

Fig. 2. Examples of synthetic images, reproduced with permission [14].

Similarly, Guibas et al. [22] proposed a two-stage pipeline, consisting of a DCGAN [42] architecture trained to synthesize retinal vasculature from noise, and a second cGAN (Pix2Pix [25]) to generate the corresponding colour fundus image, trained with Messidor fundus images. To evaluate the reliability of their synthetic data, the authors trained the same U-Net [45] with pairs of real images from DRIVE and pairs of synthetic samples. By computing F1 scores, they found that training with only synthetic data leads to only slightly inferior values. They also calculated the difference between the synthetic and real datasets with KL divergence score, to demonstrate that the synthetic data are diverse from the real sets and do not copy the original images. Some synthetic results are shown in Fig. 3.

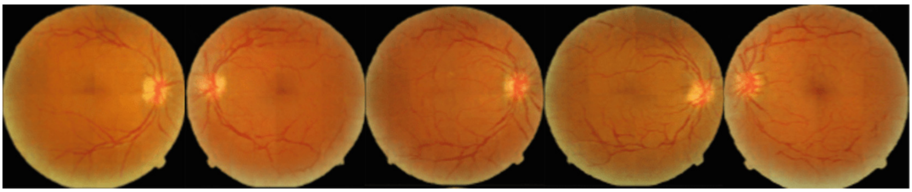

Fig. 3. Examples of synthetic images, reproduced with permission [22].

Zhao et al. [60] developed Tub-GAN, a framework capable of producing different outputs from the same binary vessel segmentation, by varying a latent code z. The model can learn from small training sets of 10–20 images. The authors deployed the method by Isola et al. [25] to generate retinal fundus images from binary segmentation masks. They built the generator with an encoder-decoder strategy allowing the introduction of latent code in a natural manner, without need of dropout. Along with this, they implemented a Tub-sGAN incorporating style transfer into the framework. This is made possible by introducing a style image as an additional training input. Thus, in terms of the optimization problem, the approach incorporates other two perceptual loss components [19]: style loss and content loss, as well as a total variation loss. The authors trained the models with 20 DRIVE images (resized to 512×512), 10 STARE images (resized to 512×512), 22 HRF images. As HRF raw images are of very large size (3304×2336), they resized the data to 2048×2048 instead. The authors extensively validated of the quality of their synthetic images and observed that 90% of the synthetic images are realistic looking. Zhao et al. carried out many experiments to evaluate the performance of different segmentation methods (a patch-based CNN and a re-implementation of DRIU [35]), demonstrating, from F1 scores, that by training the same model with both real and synthetic images, the segmentation performance improves (compared to Costa et al. work). They also considered an evaluation scheme in which the same trained segmentation model is applied on both synthetic and real images. Furthermore, to provide a quality assessment, the Structural similarity image quality metric (SSIM [55]) were applied, showing that SSIM scores were higher compared to Costa et al. results. Some synthetic results are shown in Fig. 4.

In another recent work, Zhao et al. [61] aimed at the generation of a synthetic fundus image dataset for vessels segmentation purposes. The authors explored a variant of gater recurrent unit [11], a recurrent neural network. Multiple styles of images can be reproduced taking advantage of recurrence.

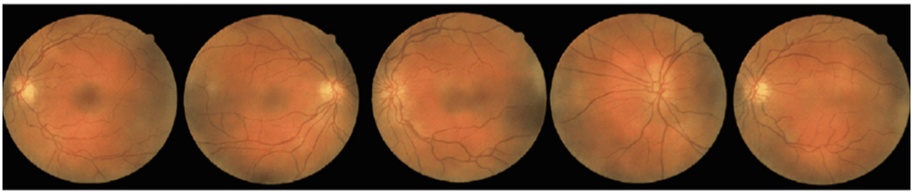

Fig. 4. Examples of synthetic images, reproduced with permission [60].

Similarly, Iqbal et al. [24] proposed MI-GAN for generating synthetic medical images and their segmented masks, from only tens of training samples. The authors proposed a variant of the style transfer, and considered DRIVE and STARE database. They updated the generator twice than discriminator to get faster convergence and overall training time was reduced significantly. The framework helped to enhance the image segmentation performance when used as additional training dataset.

Beers et al. [5] investigated the potential of progressive growing GANs (PGGANs [26]) for synthesizing fundus retinal images associated with retinopathy of prematurity. The GAN was trained in phases and the generator initially synthesized low resolution images (4×4 pixels). Additional convolutional layers were iteratively introduced to train the generator to produce images at twice the previous resolution, until the desired 512×512 pixels, considering interpolation between nearest neighbour upsampling. They deployed Wasserstein loss. The authors also showed that including segmentation maps as additional channels enhanced details; the segmentations were obtained with a pretrained U-Net [45]. They used 5,550 posterior pole retinal photographs, resized to 512×512, collected from the ongoing multi-centre Imaging and Informatics in Retinopathy of Prematurity (i-ROP) cohort study. The authors evaluated the vessels quality of the synthesized images considering a segmentation algorithm trained on real images and tested on real and generated images. Furthermore, to explore the variability of the synthetic results, they also trained a network for encoding synthetic images to predict the latent vector which produced them. They demonstrated that it was able to qualitatively approximate the global vessel structure. Some synthetic results are shown in Fig. 5.

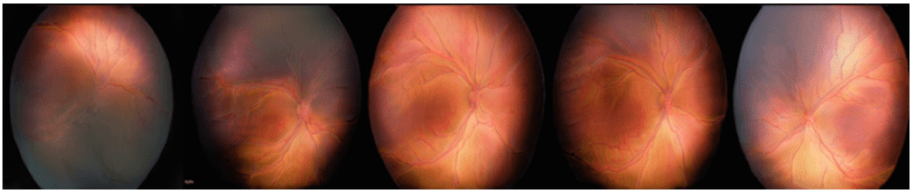

Fig. 5. Examples of synthetic images, reproduced with permission [5].

3.1 Limitations

In the AI field, the synthesis of medical images based on the general idea of adversarial learning has recently seen dramatic progress. Although adversarial techniques have achieved a great success in the generation of retinal fundus images, their application to retinal imaging is still very new and their adoption into clinical field is so far very limited or non-existent. There are many limitations concerning the proposed approaches that should be the subject of future research.

First, GAN can work with retinal images of size often lower than the resolution provided by current retinal fundus image acquisition systems. This can lead to a possible lack of quality of the synthesized datasets.

Second, it can be observed that the global consistency of the synthetic images is quite realistic-looking. Also, optic disc and fovea can be quite reasonably reconstructed, suggesting that GAN can automatically learn and reproduce intrinsic features, without any explicit human intervention. However, the consideration that optic disk and macula appear correctly located is a necessary but not sufficient condition: plausible diameter and geometry are critical in a clinical context. Important diseases are related to macula and optic disc, such as diabetic macular edema (DME) and glaucoma.

Table 1. List of papers on synthesis of coloured retinal fundus images.

	Datasets	Methods	Validation
Costa et al. [13]	-Messidor 512 × 512	-cGAN(Pix2Pix)	-ISC, Q_v
Costa et al. [14]	-Messidor 256 × 256	-AAE -cGAN(Pix2Pix)	-Segmentation -ISC
Guibas et al. [22]	-Messidor 512 × 512	-cGAN(Pix2Pix)	-Segmentation -KL divergence
Zhao et al. [60]	-Drive -Stare 512 × 512 -HRF 2048 × 2048 -Style references	-cGAN(Pix2Pix) -Style transfer	-Segmentation -SSIM
Iqbal et al. [24]	-Drive -Stare 512 × 512 -Style references	-cGAN(Pix2Pix) -Style transfer	-Segmentation
Beers et al. [5]	-i-ROP 4 × 4 ... 512 × 512	-PGANS	-Segmentation -Latent space espression

Third, all the existing approaches attach importance to retinal vascularity, showing that the generated images preserve the retinal vessels morphology. However, although high plausibility is shown, often the synthetic vessel networks are not clinically acceptable because of abnormal interruptions, unusual width variation along the same vessel, and lack of distinction between veins and arteries [14]. This could hinder the proper detection and preservation of retinal conditions such as arteries/vein occlusions and retinal emboli.

Fourth, while synthetic retinal images generated with GANs have overall consistent appearance, retinal lesions, instead, cannot be replicated properly. Zhao et al. examined some clinical pathological case (Fig. 6), using as style reference retinal images with DR, artery occlusion and cataract: the results are very far to be considered clinically acceptable. Also, the synthetic retinal images associated with retinopathy of prematurity by Beers et al. suffer of anatomical un-realism.

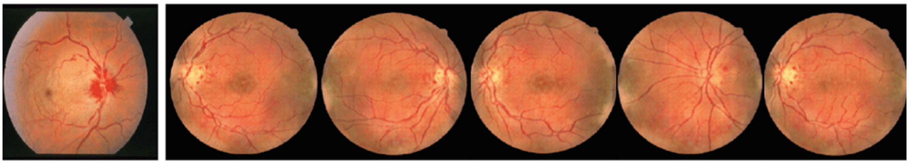

Fig. 6. Synthetic retinal images with pathology. The first image is style reference [60].

Fifth, although many quality evaluation approaches were explored, from segmentation methods to image quality metrics, they cannot be considered gold standard validation systems. In fact, first of all, realism and reliability of synthetic results should always be judged by retinal experts and ophthalmologists. Only after clinical assessment a synthetic retinal image can be considered clinically acceptable and then useful for further technical analysis purpose.

Appan et al. [2,41] have recently proposed novel solution for generating retinal images with hemorrhages using a GAN, obtain quite reliable results. The authors used both lesion and vessels annotations for training the model. Hence, they developed a DL system for the synthesis of retinal image with different severity, by providing their corresponding lesion masks, is feasible.

3.2 GAN and Variational Autoencoder

Along with GAN, another class of deep generative models to be explored for medical imaging tasks is Variational Autoencoder (VAE) [27]. The input for GAN is a latent (random) vector. It is not easy to manipulate the output of GAN to generate synthetic images with desired characteristics/features. VAE has been proposed to address this problem. There are two parts for a VAE, namely an encoder and a decoder. The encoder will encode input images by a multilayer convolutional neural network into a latent vector of random variables with corresponding mean and standard deviation. Unlike GAN starting with a random signal, VAE samples from the input-related latent vector and passes it to the decoder to reconstruct the original input image. Therefore, we can directly control VAEs to generate desired synthetic output images by selecting relevant input images. However, the output from original VAE may look blurry as the loss function to measure the similarity between input and output is mean squared error (MSE). In order to address this issue, Rezende et al. [44] add in adversarial network for similarity metrics, by combining both the merits of VAE and GAN. The use of VAE in medical imaging is very novel [8,54] and merits to be explored more fully for retinal image analysis.

4 Potential Clinical Applications

One of the most interesting application of GAN is image augmentation and the main motivation of existing work is the growing need for annotated data in medical image analysis area. Database of synthetic images could tremendously facilitate the development of robust DL systems. This is essential for the scenario of rare eye diseases: small population datasets with limited diversity could be amplified by approximating and sampling the underlying data distribution. Heterogeneity and size of training databases would dramatically increase with use of GANs. Several areas may potentially benefit from GANs, from common conditions with less severe spectrum, to less common conditions.

The common condition of DR has a wide spectrum of disease severity (Figs. 7, 8 and 9). Among patients with diabetes, approximately 70%–80% have no

DR and 10–20% have mild non-proliferative DR (NPDR) [16,59]. Mild NPDR (Fig. 7) is characterized by presence of microaneurysms (dilations of the retinal capillary) in the retina; given their variability in terms of locations and size, it is hard to obtain a diverse and large dataset to train algorithms dealing with mild NPDR. The application of GAN in this scenario may work if the artificially synthesized retinal images can simulate various examples of mild NPDR retinal images. Considering a more sever spectrum, within patients with diabetes, less than 5% have visual-threatening DR (VTDR), defined as proliferative DR (PDR, Fig. 10) and DME (Fig. 11) [16,59]. Although in the retinal fundus some changes can be quite obvious, they can also be quite variable, ranging from having the presence of new vessels at the optic disc to anywhere in the retina, presence of hard exudates at the centre of the macula and etc. Given the lack of prevalence, it is hard to build a robust model to detect these conditions and GAN could help to augment datasets of VTDR eyes.

Fig. 7. Mild NPDR.

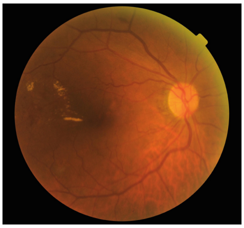

Fig. 8. Moderate NPDR.

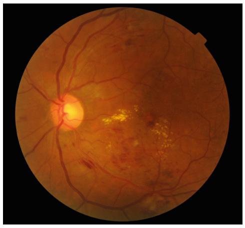

Fig. 9. Severe NPDR.

Concerning AMD (Fig. 12), the diseases can be classified as early and late AMD. Specifically, the prevalence of early, late and any AMD is shown to be 8%, 0.4%, and 8.7% respectively [58]. While early disease is mainly defined as either any soft drusen and pigmentary abnormalities or large soft drusen, the late disease is defined as the presence of any of geographic atrophy or pigment epithelial detachment, subretinal haemorrhage or visible subretinal new vessel, or subretinal fibrous scar or laser treatment scar. Given the variety of manifestations and the lower prevalence, GAN could help to enhance database of AMD eyes.

Fig. 10. PDR.

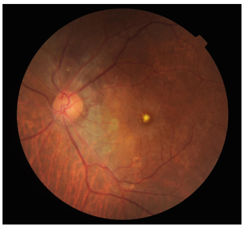

Fig. 11. DME.

Similarly, glaucoma (Fig. 13) is the leading cause of global irreversible blindness, with an overall global prevalence of 3.5% [51]. In details, while prevalence and risks vary among races and countries, prevalence is limited to 3% for primary open-angle glaucoma and 0.5% for primary angle-closure glaucoma. Glaucoma is associated with characteristic damage to the optic nerve and manifests itself in retinal images as optic disc dimension and shape variation and pixel level changes.

In the challenging case of rare diseases, GANs could potentially be functional in increasing the size of datasets of positive cases such as retinal vein occlusion (RVO) (Fig. 14) [28] and retinal emboli [10], where the prevalence is less than 1%. Also, epiretinal membrane (ERM) [9] disease could be considered.

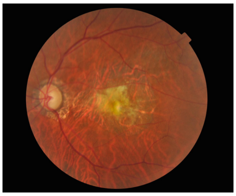

Fig. 12. AMD.

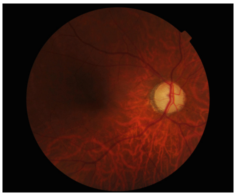

Fig. 13. Glaucoma.

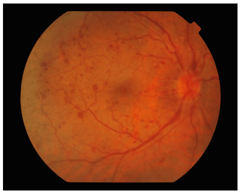

Fig. 14. RVO.

It is quite common that a well-trained AI model for retinal images may not be able to generalize well and to achieve expected performance when being deployed on dataset collected from different devices, fields of view, resolutions, cohorts, ethnic groups, as in the case of retinal fundus images. This is commonly referred as domain adaption problem in ML [6]. GAN can be used to generate synthetic images with characteristics which are unique on target domain to achieve desired performance in this scenario.

5 Conclusion

GANs have seen tremendous progress over the past few years and the synthesis of retinal images via GANs has recently also seen increased interest. Limitations such as lack of large annotated datasets and high costs for high quality medical data collection may be overcome via these techniques. Also, legal concerns regarding patient privacy and anonymized medical records could be addressed via these generative approaches. However, GAN applications to medical imaging field are still growing and the results are far from clinically deployable still. In fact, retinal images provide vital information about the health of patients, therefore any synthetic generation has to be consistent carefully in the context of synthetic generation considering the special anatomy of colour retinal fundus images.

Existing approaches of retinal image synthesis attach importance to retinal vascularity and show that while optic disc and fovea can be reconstructed rather well, lesions must be replicated with high fidelity as well, which is a problem of continued investigation. Meaningful and appropriate assessment of the generated images degree of realism must be carried out by experts and ophthalmologists, in order to get efficient quality validation. Furthermore, as previous studies suggest, quantitative evaluation can be conducted by performing methods based on the problem domain. Therefore, in the future, the introduction of manual annotations for retinal lesions on training datasets of less than 50 images will be the first natural extension of the current models. This would have the goal to produce realistic-looking synthetic images and the new annotated data could be applied to develop novel retinal image analysis techniques, or to enhance existing database with meaningful data. Also, the flexibility of GAN suggests these can be used for deploying these methodologies used for retinal synthesis purpose to different medical images.

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