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Clinical applications of generative adversarial networks in medical image to image translation

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► ***Review article***

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ABSTRACT

Generative Adversarial Networks (GANs) have emerged as powerful tools within the realm of deep learning, particularly in the synthesis of artificial images, a capability that holds immense promise in the field of medical image-to-image translation. Recent years have witnessed significant strides in GAN development tailored for cross-domain image translation, largely driven by the availability of extensive datasets containing meticulously annotated medical images. Nonetheless, the process of annotating these images poses a formidable challenge, demanding a substantial number of specialized experts for supervised methods. To surmount this obstacle, cross-modality synthesis techniques have gained traction, offering an efficient approach to mitigate the complexities and costs associated with acquiring paired training data. This paper serves as an introductory exploration into the diverse array of GAN variants employed in image-to-image translation, subsequently delving into their applications within medical imaging. Specifically, it investigates the realms of cross-modality synthesis and conditional image synthesis, shedding light on their potential to revolutionize diagnostic precision and streamline the intricacies of medical imaging processes.

INTRODUCTION

Delivering superior-quality images of bodily organs and soft tissues holds significant importance in enhancing disease diagnosis and treatment across the medical field. Additionally, specific conditions, such as Alzheimer's disease, may evade detection when using low-resolution images (1, 2). Common medical imaging modalities encompass Magnetic Resonance Imaging (MRI), Computed Tomography (CT), ultrasonography, and Positron Emission Tomography (PET). Each modality presents unique challenges regarding imaging, dimensions, processing, and recording. Despite significant advancements, challenges persist in generating high-fidelity images, integrating dual-modal imaging like CT/PET, and automating medical image processing (3, 4).

In recent times, the medical community has shown growing interest in automating the processing of medical images and generating artificial images. Machine learning systems have played a pivotal role in complex decision-making for medical image analysis and synthetic data generation from the outset. However, the success of these systems heavily relies on access to extensive sets of labelled training data. Additionally, the process of generating medical data is laborious, time-intensive, and expensive, particularly when it comes to labelling medical images (5). In 2014, Ian Goodfellow transformed the landscape of synthetic image generation by unveiling the deep learning framework known as Generative Adversarial Networks (GANs) (6). GANs have unlocked new avenues for bridging the gap between image generation and supervised techniques due to their capability to replicate data distributions and generate images with unprecedented levels of detail and realism.

All GAN models work on the basis that the Generator makes an attempt to generate data utilizing a probabilistic input. As part of its task, the Discriminator Network strives to tell whether data input is real or fake by taking input either from the generator or from real sources. In addition to generating synthetic medical images, GAN models are used by radiologists for other challenges in medical imaging such as reconstruction, classification, segmentation, registration, detection, and denoising (figure 1) [4, 7].

In this review paper, conditional GAN models employed by physicians and radiologists to synthesize medical images and their potential applications are reviewed. Also, various medical studies in the field of image-to-image translation are discussed, which today have a promising role in the synthesis of medical images. A discussion of the advantages, disadvantages, and challenges of using these frameworks is also included.

The novelty of this article lies in its comprehensive review and critical evaluation of the transformative role of GANs in cross-modality medical imaging, emphasizing both technical advancements and clinical implications. Unlike existing reviews that often focus on single cross-modality translations, this article covers multiple modalities, including MRI-to-CT, CT-to-MRI, PET-to-CT, and MRI-to-PET, etc. It provides a holistic view of GAN applications across radiotherapy, oncology, and neurodegenerative disease diagnostics, enhancing diagnostic accuracy, improving soft tissue visualization, and reducing radiation exposure. The article also addresses key challenges in clinical trust regarding GAN-generated images, including the "black-box" nature of GANs, the need for standardized evaluation metrics, and the potential for anatomical inaccuracies. Furthermore, the article offers a balanced perspective on both the advantages and limitations of GANs, particularly in tackling data scarcity and producing high-quality synthetic images. By discussing the challenges related to interpretability and clinical adoption, it provides a nuanced view that adds depth to the review. The article also emphasizes the need for collaboration between AI developers, clinicians, and radiologists, presenting a novel interdisciplinary approach to integrating GANs into real-world clinical workflows. It bridges gaps between technical studies and clinical applicability, contributing significantly to the field of GAN-based medical imaging and offering a roadmap for overcoming barriers to clinical adoption. This broader, integrative perspective makes the article a valuable contribution to both medical and AI research communities.

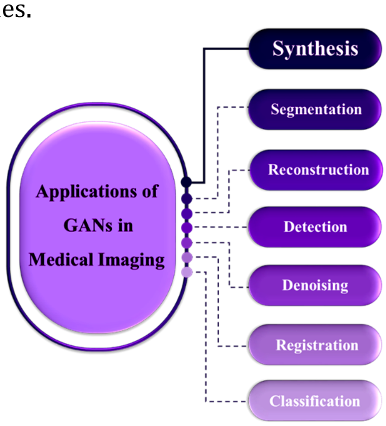

Figure 1. Different applications of GANs in medical image analysis.

Applications of GANs in medical image-to-image translation

The GANs present a more accurate and better solution for augmenting training medical images and have been shown to lead to impressive effects. Therefore, the Research Community in the medical field has become increasingly interested in GANs as an approach to generating realistic medical images. The conditional GANs models have been able to help with important limitations such as restricting access to medical images for research purposes, improving image resolution, and reducing costs [8]. This paper evaluates the utility of using GAN-generated data for medical imaging and its richness and benefits. In this section, the performance of conditional GAN models in different modalities such as MR, CT, PET, etc, and the methods of image-to-image translation are reported (figure 2).

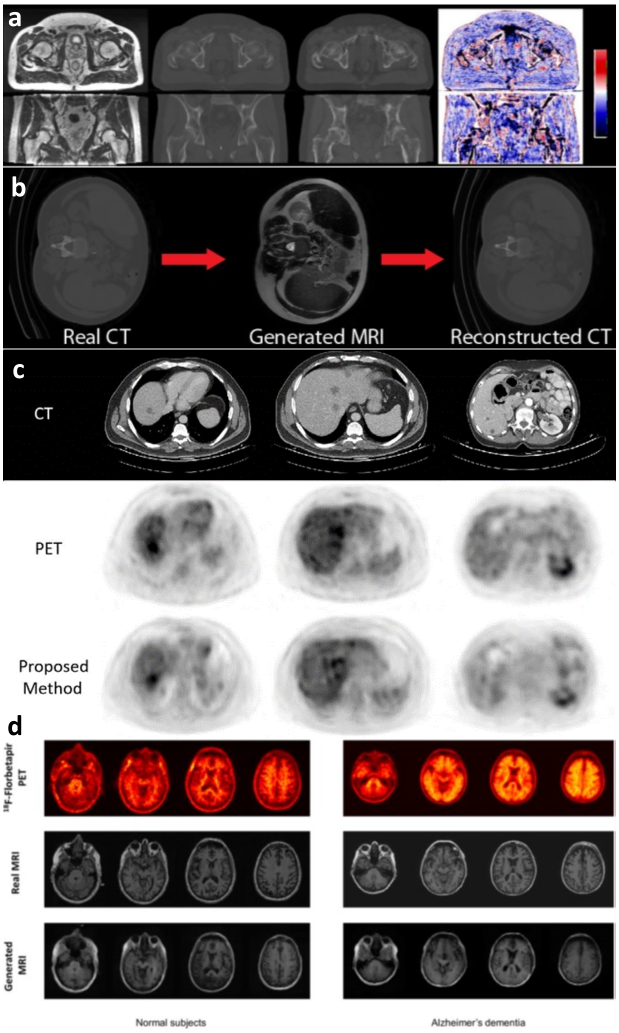

Figure 2. Examples of cross modality image to image translation. **a)** From left to right, MR image, CT, sCT and difference (CT – sCT). The images on top represent the axial plane, on the bottom, the frontal plane [11]. **b)** The intermediate results of the real, synthesized, and reconstructed images [12]. **c)** Sample results of the predicted PET using paper's method compared to the real PET with the corresponding CT images [13]. **d)** Generated MR images from amyloid PET images [14].

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Cross-modality synthesis, such as generating CT-equivalent images based on MR images, offers several advantages, including cost and time savings. However, the process of mapping between multiple domains is complex. A key challenge is the difficulty in obtaining paired images, as corresponding images may not always be available [9]. Image-to-image translation methods are broadly classified into supervised and unsupervised approaches. Pix2Pix belongs to the supervised category, utilizing paired images to learn a one-to-one mapping. It operates with two datasets: one serving as input and the other as the corresponding output. In contrast, unsupervised image-to-image translation does not rely on paired images to learn mappings between domains, making it a more commonly employed approach. CycleGAN and UNIT are two unsupervised methods used in more broad applications. Consequently, using these methods, a synthetic image of the target modality can be obtained by using the existing modality image and preserving all the anatomical structures or features [10]. Table 1 summarizes the articles related to the cross-modality synthesis of medical images.

Table 1. Cross-Modality synthesis.

Modality	Method	Dataset	Remarks	Year	References
MR → CT	cGAN	Gold Atlas project (https://zenodo.org/record/583096)	Pelvic	2020	Kevin N D Brou Boni *et al.* [11]
	CycleGAN	SpineWeb Library (http://spineweb.digitalimaginggroup.ca)	Lumbar Spine	2020	Oulbacha *et al.* [49]
	ACGAN	MR-CT image data of 10 volunteers enrolled in an IRB-approved study at University Hospitals Cleveland Medical Center.	Abdomen	2020	Qian *et al.* [50]
	Augmentation of CycleGAN	Gold Atlas project (https://aapm.onlinelibrary.wiley.com/doi/10.1002/mp.12748), Institut Jules Bordet (IJB), Centre Oscar Lambret (COL)	Pelvic with prostate or rectal cancer	2021	Brou Boni *et al.* [51]
	cGAN	Real MRI/CT pairs head and neck imaging volumes coming from 36 patients (department of radiation oncology at the Center Hospitalier de l'Université de Montréal), sagital slices of 20 different patients	Head and Neck	2021	Touati *et al.* [52]
	CycleGAN	Weakly paired data from 90 cancer patients including CT and MR images of the pelvis, thorax, and abdomen	Pelvis, Thorax and Abdomen	2021	Kang *et al.* [53]
	Multi-Cycle GAN	CT and MR images of head, neck and shoulder submitted to Research Data Deposit (RDD) platform (www. researchdata.org.cn), with approval RDD number as RDDA2021001910.	Head, Neck and Shoulder	2021	Liu *et al.* [53]
	RTCGAN	MR and CT volumes of 19 subjects (https://aapm.onlinelibrary.wiley.com/doi/10.1002/mp.12748)	Pelvic	2023	Zhao *et al.* [16]
CT → MR	MR-GAN	Brain CT and MR images of 202 patients approved by the Institutional Review Board (IRB) of the Pusan National University Hospital, South Korea (IRB No. 1808-008-069)	Brain	2019	Jin *et al.* [52]
	cGAN	94 paired CT and MR scans as part of the ISLES 2018 Ischemic Stroke Lesion Segmentation Challenge	Brain	2019	Rubin *et al.* [17]
	ACGAN	9 healthy subjects for this IRB approved study including three types of MR images (i.e., fat, water and R2) and a corresponding CT scan	Brain	2020	Yang *et al.* [18]
	GAN	-	Brain	2022	Hu *et al.* [19]
MR ↔ CT	CycleGAN	-	Muscles around thigh, hip, pelvis, sacrum and femur bones	2018	Hiasa *et al.* [9]
	CycleGAN	Two-stage training and synthesis for abdominal image	Abdominal, Brain	2019	Huo *et al.* [12]
	uagGAN	Paired dataset: 367 MR-CT brain images from 18 patients (https://aapm.onlinelibrary.wiley.com/doi/10.1002/mp.12155) Unpaired dataset: MR-CT brain images from the Radiology Department of the Jordan University Hospital (JUH)	Brain	2021	Abu-Srhan *et al.* [20]
CT → PET	FCN+cGAN	25 pairs of PET/CT images	Liver	2017	Ben-Cohen *et al.* [21]
	FCN+cGAN	60 PET/CT scans from Sheba Medical center	Liver	2019	Ben-Cohen *et al.* [13]
	TransGAN	IXI dataset	Brain	2022	Li *et al.* [22]
PET → CT	cGAN, MedGAN	PET/CT images of 50 patients (SOMATOM mCT, Siemens Healthineers, Germany)	Brain	2018	Armanious *et al.* [23]
	cGAN	50 PET-CT studies from 50 lung cancer patients	Whole-body	2019	Dong *et al.* [24]
	WGAN	fortyfive sets of patient samples (26 males and 19 females)	Whole-body	2020	Hu *et al.* [25]

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Table 1. continued. Cross-Modality synthesis.

Modality	Method	Dataset	Remarks	Year	References
MR → PET	BMGAN	ADNI (http://adni.loni.usc.edu/)	Brain	2020	Hu *et al.* [26]
	GLA-GAN	ADNI-1 and ADNI-2 (http://adni.loni.usc.edu/)	Brain	2021	Sikka *et al.* [27]
	BPGAN	ADNI (http://adni.loni.usc.edu/)	Brain	2022	Zhang *et al.* [28]
PET → MR	pix2pix	ADNI (http://adni.loni.usc.edu/)	Brain	2017	Choi *et al.* [14]
	E-GAN	ADNI (http://adni.loni.usc.edu/)	Brain	2022	Bazangani *et al.* [29]
T1 ↔ T2 MR	cycleGAN	the MIDAS dataset, the IXI dataset, the BRATS dataset	Brain	2019	Dar *et al.* [40]
	rsGAN	the MIDAS dataset, the IXI dataset, the BRATS dataset	Brain	2020	Dar *et al.* [39]
	da-GAN	Kulaga-Yoskovitz	Brain	2020	Baoqiang Ma *et al.* [55]
	mustGAN	IXI Dataset, ISLES Dataset	Brain	2021	Yurt *et al.* [41]
	GAN	2,024 images scanned	Brain	2021	Kawahara & Nagata [56]
	cGAN	-	Brain	2022	Pan *et al.* [57]
T1 → FLAIR MR	Ea-GANs	The BRATS2015 and the non-skull stripped IXI	Brain	2019	Yu *et al.* [58]
	mustGAN	IXI Dataset , ISLES Dataset	Brain	2019	Yurt *et al.* [59]
	pix2pix	3220 MRI scans in 1450 patients with brain tumors	Brain	2021	Cont *et al.* [43]
T1, T2 → MRA	pix2pix	IXI dataset	Brain	2018	Olut *et al.* [44]
	DC GAN & WGAN-GP & WGAN-GP-SN	-	Brain	2020	Kossen *et al.* [45]
3T → 7T MR	Cascade GAN	-	Brain	2018	Nie *et al.* [46]
	cycle GAN (semi-supervised)	15 pairs of 3T and 7T T1 weighted MR brain images	Brain	2019	Qu *et al.* [47]
	SynGAN	33 healthy volunteers and 89 patients	Brain	2023	Duan *et al.* [48]
CBCT→CT	CycleGAN	CBCT images of 45 patients	Head and neck, thorax, pelvis	2020	Eckl *et al.* [32]
	CycleGAN	CBCT images of 30 patients	Pancreas	2020	Liu *et al.* [33]
	CycleGAN	12000 slice pairs of CT and CBCT	Pelvic head-and-neck	2020	Zhang *et al.* [34]
	Cycle-Deblur GAN & CycleGAN	9856 CBCT images	Chest	2021	Tien *et al.* [35]
	CycleGAN	120 paired CBCT images	Head and neck cancer	2022	Zhang *et al.* [60]
Domain adaption	DASGAN	-	Digital Pathology	2019	Kapil *et al.* [36]
	CycleGAN	HAM , MoleMap	Skin	2020	Gu *et al.* [37]
	WGAN	REFUGE , Drishti-GS1	Eye (Retinal Fundus imaging)	2020	Kadambi *et al.* [38]

MR → CT

Kevin *et al.* (2020) proposed a novel multi-scale approach using conditional GAN (cGAN) with paired data to generate synthetic CT images from MRIs across multiple sites, focusing on cases of rectal or prostate cancer with CT and pelvic MR images from the Gold Atlas project dataset. Despite the limited dataset, the study achieved high efficiency through a combination of feature matching loss and LSGAN loss [11].

In 2021, Liu *et al*. introduced a Multi-Cycle GAN technique for synthesizing head and neck region CT images from MRI scans, employing a Pseudo-Cycle Consistent module to enhance target generator performance and a domain control module to improve stability and image quality. Utilizing Z-Net to replace the generator yielded enhanced performance and synthesis accuracy, with exceptional results in synthetic accuracy and image quality, requiring no additional computational resources or time [15].

Zhao *et al*. (2023) presented the Residual Transformer Conditional GAN (RTCGAN), a new methodology that combines Convolutional Neural Networks (CNN) to refine local texture details and Transformer for enhancing global correlations in extracting multi-level features from MR and CT images. Additionally, this study employs feature reconstruction loss to regulate potential image features, mitigate over-smoothing, and minimize local distortion in the generated CT images. Experimental findings indicate that RTCGAN yields visually more aligned results with reference CT images and delivers promising results in mitigating local mismatches in tissues [16].

CT → MR

Rubin *et al.* (2019) used the conditional mapping method by training GANs that are able to map computed tomography perfusion (CTP) infarcted zones to clearly delineate hyperintense areas in produced MR images. The dataset used in this study consisted of 94 paired MR and CT scans. Results showed that the infarcted core regions can be accurately mapped to the hyperintensities aligned

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with the ground-truth MR 's corresponding areas by using the CGAN model. And also segmentation performance quantitatively improved in this method (17).

Yang *et al*. (2020) introduced CAE-ACGAN, a novel GAN-based method merging Auxiliary Classifier Generative Adversarial Network (ACGAN) and Variational Auto-Encoder (VAE) strengths. Applied to CT to MR image translation using brain datasets from nine healthy subjects, approved by the Institutional Review Board (IRB), the approach surpassed WGAN-GP and pix2pix, achieving superior accuracy while preserving clear anatomical topography and internal organ structures' gross features (18).

In another study, Hu *et al*. (2022) utilized a GAN model to produce synthetic MR brain images from the corresponding CTs in patients with suspected acute ischemic stroke and investigated the possibility of detecting suspected lesions using synthetic MRI images. The introduced model achieved high performance in translating non-contrast CT images to synthetic MR and demonstrated considerable accuracy in detecting patients with suspected acute ischemic stroke (19).

MR ↔ CT

Hiasa *et al*. (2018) expanded the CycleGAN method by incorporating gradient consistency (GC) loss to improve images edge alignment in two domains (613 CT and 302 MR volumes) to overcome wide ranges of data and accuracy enhancement. The results showed that a lot of the training data resulted in statistically remarkable enhancements based on paired t-tests in Mutual information. The gradient consistency loss also led to a raise in mutual information between the MR and the synthetic CTs (9).

In 2019, Huo *et al.* introduced SynSeg-Net, an end-to-end synthetic segmentation network capable of training on target imaging modalities without manual labelling. SynSeg-Net utilizes unpaired intensity images from both target and source domains, with manual labels solely in the source domain. Integration of CycleGAN and Deep Convolutional Neural Networks (DCNN) facilitated SynSeg-Net's development. Evaluation, based on Dice similarity coefficient (DSC), compared segmentation outcomes against ground truth across different methods. Performance assessment involved two experiments: (1) MRI to CT abdominal images and (2) CT to MRI brain images, with SynSeg-Net achieving notably high performance relative to other methods, particularly when utilizing target modality labels (12).

In 2021, Abu-Srhan *et al.* introduced the Unsupervised Attention Guided Generative Adversarial Network (uagGAN) approach, designed to translate CT images to MR images and vice versa using small-sized datasets, both paired and unpaired. This model addresses the misalignment issue inherent in unpaired training and mitigates the challenge of generating blurred images during paired data training. The outcomes demonstrate the model's high efficiency in MR-to-CT image translation. However, further improvements are needed for CT-to -MR image translation (20).

CT → PET

In oncology, diagnosis and classification are regularly made based on PET images. Moreover, PET and CT imaging have become key assessment apparatus for drug development. Furthermore, in recent years, many medical imaging analysts have been trying to produce artificial PET data in a direct way from CT images, because PET devices are costly and include radioactivity, and in this way put patients in danger (13).

In 2017, Ben-Cohen *et al*. utilized fully convolutional networks (FCN) in conjunction with conditional generative adversarial networks (cGAN) to anticipate PET-like images from CT images. The cGAN model was constructed following the framework introduced by Isola *et al*. This approach successfully achieved high tumor detection rates through the use of synthetic PET images generated from the cGAN combined with FCN (21).

In another study, Ben-Cohen *et al*. (2019) employed 60 PET/CT scans from the Sheba Medical Center dataset to generate synthetic PET images of the liver using the FCN-cGAN model. By integrating this model with an existing lesion detection software, positive outcomes were observed in terms of both restoration measures and detection measures (13).

Another study introduced a transformer-enhanced GAN for generating synthetic CT images from PET scans and introduced a loss function based on image gradient differences to enhance the quality of the generated CT images (22).

PET → CT

The study published in 2018, introduced a new GAN-based method, called MedGAN. Armanious et al. used different models for the translation of medical images, which are based on an end-to-end approach. The results showed that the MedGAN framework has the most adequate performance in translating PET images into artificial CT images. Also, it was determined that the classic adversarial loss CGAN is ineffective (23).

Dong *et al*. (2019) used CycleGAN model to generate synthesize CT images from whole-body NAC PET. The synthesized CT images show high similarity to real CT images and strong contrast on lungs, soft tissues, and bone. In the absence of structural details, this model shows tremendous potential for whole-body PET attenuation correction (24).

PET imaging necessitates CT imaging for precise anatomical delineation and attenuation correction (AC) maps, crucial for accurate PET quantification, albeit escalating ionizing radiation exposure. In 2020,

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Hu *et al.* introduced a WGAN model to mitigate radiation dosage while acquiring high-resolution PET and CT data concurrently. The model first addresses noise and artifacts in non-attenuation-corrected (NAC) PET data to produce synthetic AC PET images for whole-body PET/CT scans. It subsequently synthesizes CT images from the synthetic AC PET images obtained in the initial stage [25].

MR → PET

Hu *et al.* (2020) proposed Bidirectional Mapping GAN (BMGAN), an end-to-end 3D network, that latent vector and image contexts were efficiently applied and optimized to predict PET brain images from MR images. The model is evaluated on a subset of the ADNI database. Both quantitative and qualitative results prove the advantages of utilizing 3D convolutional operations instead of the common 2D operations. The experimental results demonstrated the effectiveness of the method in generating high-quality synthetic images, underscoring the significance of adversarial training in 3D BMGAN. The advantages of the proposed BMGAN are clearly shown in this scenario. The proposed network has shown acceptable performance for MR to PET translation task [26].

In another study, Sikka *et al*. (2021) introduced a globally and locally aware GAN model for MRI to PET cross-modality image translation in order to facilitate diagnosis of. Experimental results show the advantage of GLA-GAN both in generating synthetic PET images with enhanced quality and utility in clinical studies for improving Alzheimer's disease diagnosis compared to other novel models [27].

In 2022, Zhang *et al*. noted that multi-modal medical images, such as MRI and PET scans, are commonly used for diagnosing brain disorders like Alzheimer's disease. A novel method called BPGAN is proposed for synthesizing PET scans from MRI images, improving the accuracy of AD diagnosis. The experimental findings reveal that the synthetic PET images generated by BPGAN exhibit high quality and offer complementary information for Alzheimer's disease (AD) diagnosis. The proposed method surpasses other state-of-the-art techniques by generating diverse and high-quality PET scans [28].

PET → MR

Choi *et al*. (2018) developed a model to translate amyloid PET images into structural MR images, trained on paired data comprising MR images and amyloid PET scans from Alzheimer's disease (AD) and mild cognitive impairment (MCI) patients, as well as normal controls. Utilizing a model architecture featuring two convolutional neural networks, a discriminator, and a generator, data from the ADNI database were gathered. Results indicated that normal PET template-based and PET segmentation-based models exhibited greater bias in AD patients, whereas the multi-atlas-based model demonstrated less bias than the former. Furthermore, both normal PET template-based and PET segmentation-based models showed significant underestimation compared to MR-based models, regardless of the subject's diagnosis or cortical regions of interest [14].

Bazangani *et al.* (2022) introduced a cross-modality generation technique termed Elicit Generative Adversarial Network (E-GAN) to tackle challenges related to insufficient databases and unbalanced data in medical image applications. Key innovations include the implementation of separable convolution for learning 3D features, a fusion strategy resembling a self-attention mechanism, integration of a Sobel filter for conveying geometrical information, and the adoption of a weighted version of a hybrid loss function to enhance learning stability. Evaluation results demonstrate superior performance in capturing both structural and textural information compared to existing methods. However, limitations such as prolonged training times due to feature mixing operations and the utilization of a min-max strategy were noted [29].

CBCT→CT

Cone-Beam Computed Tomography (CBCT) images are used to measure the dose of adaptive radiation therapy. Physicians' challenges in this area are inaccurate Hounsfield units (HU) and large artifacts [30]. The ideal solution to these challenges is to produce CT images from CBCT images. Using deformed planning CT images leads to artifacts' significant decrease and HU values corrected while maintaining anatomical accuracy. Currently, the GAN models have illustrated considerable success in image -to-image translation tasks [31].

Eckl *et al*. (2020) utilized a cycleGAN-based method for CBCT to synthetic CT conversion, assessing image quality, dosimetric accuracy, and segmentation on a dataset of 15 patients. Despite closely resembling pCT images and exhibiting accurate dosimetry, the model faced challenges regarding low soft-tissue contrast [32].

Similarly, Liu *et al.* (2020) employed CycleGAN to generate CBCT-based sCT images, employing a patch-based approach for image generation and achieving comparable accuracy to planning CT for dose calculation [33].

Zhang *et al.* (2020) explored AI-driven enhancement of CBCT image quality using an unsupervised deep-learning method, demonstrating effectiveness through metrics like MAE of Hounsfield units and PSNR, offering efficiency gains in terms of time and cost [34].

In 2022, Tian et al. applied conditional GANs to synthesize CT images from CBCT scans of head and neck cancer patients, conducting a comparative evaluation with U-Net and CycleGAN to assess

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synthetic CT image quality [35].

Domain adaption

Kapil *et al.* (2019) introduced an end-to-end training framework called DASGAN (Domain Adaptation and Segmentation GAN), which simultaneously conducts semantic segmentation and unpaired image-to-image translation. The training dataset comprised 56 stained whole slide images (WSI) of non-small cell lung cancer (NSCLC) subjects and 69 whole slide images of the same indication stained with the SP263 PD-L1 clone. These images were unpaired and originated from two independent patient cohorts. DASGAN facilitated the optimization of domain transfer networks, aiming to generate realistic PD-L1 images while enhancing the performance of the segmentation network [36].

Gu *et al*. (2020) proposed employing a CycleGAN as a domain adaptation technique and novel cross-domain recognition method for skin disease imaging translation between datasets. The study utilized HAM and MoleMap datasets to validate the approach, revealing improved model performance with CycleGAN domain adaptation. However, despite minimizing distribution shift, residual variances persisted due to factors such as labelling noise, which remained unrecoverable [37].

Kadambi *et al*., 2020 presented a segmentation approach based on domain adaptation utilizing Wasserstein distance inspired by WGAN adversarial domain adaptation for classification tasks. Utilizing REFUGE and Drishti-GS1 datasets, the method demonstrated higher Dice and IOU for cup and disc segmentation compared to neural network's domain-adversarial training and adversarial discriminative domain adaptation, with more pronounced improvements over direct transfer learning. Efficiency was notably enhanced compared to other patch-based discriminator methods [38].

T1 ↔ T2 MR

In medical imaging, physicians use T1-weighted images to examine organs such as white and gray matter of the brain. T2-weighted images provide physicians with more complete and accurate information about fluid and cortical tissues. However, multi-contrast imaging is often impractical due to limited scan time or excessive artifacts related to patient movement. Therefore, the use of artificial intelligence models can be efficient [39].

A study working on the image contrast is one conducted by Dar *et al*., (2019). They introduced a method performing end-to-end training, working on multi-contrast MRI synthesis utilizing cGANs. This method employed images of the source contrast to create target contrast. Their proposed method demonstrated a promising performance regarding multi-contrast MRI synthesis in clinical practice [40].

Dar *et al*., (2020), introduced a novel method for under sampled multi-contrast acquisitions using reconstructing-synthesizing GAN (rsGAN). Their method represented a high-level performance compared to pure reconstruction and synthesis methods, boosting the quality and scan efficiency of multi-contrast MRI exams [39].

In their study in 2021, Yurt *et al.* also worked on T2-weighted image synthesis from T1-weighted images. To do this, they employed a multi-stream GAN architecture (mustGAN). In this method, the information from multiple source contrasts is accumulated through a combination of multiple one-to-one streams and a joint many-to-one stream. The advantage of this method is that it presents a higher performance in terms of quantity and quality [41].

T1 → FLAIR MR

In 2019, Yu *et al*. introduced Edge-Aware Generative Adversarial Networks (Ea-GANs), which serve the purpose of translating T1-weighted images into FLAIR-MR images. These networks incorporate edge information, which reflects the textural structure of image content and delineates the borders of various objects, thereby reducing gaps. The model consists of a generator-induced Ea-GAN (gEa-GAN) and a discriminator-induced Ea-GAN (dEa-GAN). Both frameworks utilize their generators to integrate the edge information, with dEa-GAN additionally employing its discriminator [42].

Also, Yurt *et al.* (2019) used a different method of GAN for generating FLAIR image synthesis from T1- and T2-weighted images. The mustGAN can enhance the synthesis accuracy in numerous regions that are suboptimally recovered by competing methods by capturing information from both one-to-one and many-to-one streams. As a whole, mustGAN decrease noise and artifacts of fake images of white-matter of brain tissues, and provide more accurate representations of gray-matter tissue boundaries [41].

Cont *et al.* (2021) devised a GAN to generate missing FLAIR images from T1-weighted images, intended for utilization in a brain tumor segmentation model that necessitated multiple MRI series [43].

T1, T2 → MRA

In 2018, Olut *et al.* showcased an sGAN approach for generating magnetic resonance angiography (MRA) contrast from multi-contrast T1- and T2-weighted MRI data, relying on spin-lattice and spin-spin relaxation effects. Their study revealed that the sGAN outperformed the standard GAN method in terms of comparable PSNR values and enhanced visual perceptual quality [44].

In 2020, Kossen *et al*. conducted a study focusing on MRA among various modalities. Their research centered on training three GAN frameworks using a dataset of subjects with cerebrovascular disease. The study design involved training DCGAN, Wasserstein-

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GAN with gradient penalty (WGAN-GP), and WGAN-GP with spectral normalization (WGAN-GP-SN) on time-of-flight (TOF) MRA patches to generate image-label pairs. Performance evaluation occurred in two stages: first, through visual inspection and quantitative comparison to real data, and second, by employing the "half U-net" and classical augmentation techniques. The results evolution indicated the superior performance of WGAN-GP-SN (45).

3T → 7T MR

For generating artificial medical images, Nie *et al.* in 2018 presented the supervised GAN. Their presented model comprised a generator network which is a fully convolutional network and discriminator network which is a CNN. Fully convolutional network was planned to include an image-gradient-difference that led to creating more real-like target images. In addition, a context-aware convolutional adversarial network was performed utilizing the Auto-Context Model. The designed model was just employed for 3T-to-7T synthesis task. The accuracy obtained by this model was acceptable (46).

In 2019, Qu *et al.* designed a new approach based on information in both spatial and wavelet domains using Semi Wave framework for 7T MR image synthesis. This framework is a semi-supervised cycleGAN. The first mapping function of cycleGAN is a basic 3T-to-7T mapping and another is a twofold 3T-to-7T mapping. This model consists of a wavelet coefficient extractor and two associated adversarial discriminators. Thorough qualitative and quantitative tests demonstrated better 7T MR images in terms of anatomical details compare with fully-supervised methods (47).

In 2023, Duan *et al.* demonstrated the feasibility of generating synthetic 7T images with similar quality to acquired 7T images using a synGAN model (48).

DISCUSSION

The reviewed literature highlights the transformative potential of Generative Adversarial Networks (GANs) in cross-modality medical imaging. For MRI-to-CT translation, models such as CycleGAN and Residual Transformer Conditional GAN (RTCGAN) have shown the ability to produce high-quality synthetic CT images that align closely with reference CTs, aiding applications like radiotherapy planning and reducing patient radiation exposure. Similarly, CT-to-MRI translation using models like ACGAN enhances soft tissue visualization and improves diagnostic precision for conditions like stroke and oncology (16, 18). PET-to-CT and CT-to-PET conversions demonstrate the value of GANs in creating synthetic images for attenuation correction and tumour detection, effectively lowering costs and minimizing reliance on radiation-heavy imaging protocols (21, 24). MRI-to-PET translation, facilitated by models like BMGAN, has shown promise in generating functional PET-like images, enabling non-invasive diagnostics for neurodegenerative diseases such as Alzheimer's (26).

Despite these advancements, challenges persist, including difficulties in acquiring paired datasets, computational complexity, and the potential for anatomical inaccuracies in synthesized images. Clinician trust in synthetic images remains a significant hurdle due to the risk of artifacts and the opaque mechanisms of GAN models (59). However, the advantages, such as reducing imaging costs, enhancing diagnostic workflows, and improving accessibility to advanced imaging techniques, make GAN-based image synthesis a promising solution for overcoming current limitations in medical imaging (8).

Challenges

Converting medical images from one modality to another using Generative Adversarial Networks (GANs) presents several challenges. The scarcity of paired data due to variations in patient positioning and scan timing makes it difficult to train accurate models, with unpaired translation leading to less reliable results. Anatomical accuracy is often compromised during conversion, especially in complex tissues, as synthesized images may lack fine details critical for diagnosis. Computational complexity and the high resource demands of GANs limit their clinical application, while overfitting can occur when datasets are small or unrepresentative (9, 20). Additionally, the lack of interpretability and trust in GAN-generated images, due to their "black-box" nature and potential for artifacts, remains a significant hurdle for clinical adoption. Finally, the absence of standardized evaluation metrics complicates the assessment of GAN performance in clinical contexts. Despite these challenges, ongoing improvements in GAN models continue to enhance their feasibility for medical image conversion (59).

Advantages

In medical image processing, a GAN model can produce high-resolution images from low-resolution medical images and image colouring with more than 90% accuracy. Also, annotating medical images is very expensive, and medical datasets often suffer from class imbalances. The aforementioned problems challenge the use of supervised deep learning methods. Moreover, transferring learning methods, like most other areas of machine learning, lack medical imagery. On the one hand, producing real images is costly, and on the other hand, traditional data augmentation techniques can only produce data that is closely distributed with the original samples. But, the use of GAN models offers a solution to the lack of data in medical image analysis. One of the

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main applications of GANs is their use in cross-modality image synthesis. Sometimes two or more medical images are needed for a complete diagnosis; however, the physician's access is limited due to some problems. The contrast of more images can provide necessary and additional information to the physician. For example, in contrast to T1-weighted images, T2-weighted images can better distinguish inflammation from normal tissues and present more complete information for diagnosis [41].

In addition, to obtain reliable results from automated image analysis, it is essential to optimize image quality before extracting diagnostic information. In some circumstances, it may be possible to generate additional image information based on information that has already been collected without further examination. Hence, the development of an image translation framework would be useful for medical professionals and patients; this enhanced diagnostic efficiency shortens the diagnostic procedure by minimizing the need for additional scans. However, it should be noted that translating an image from one modality to another can be challenging, with the risk of introducing untrue information and rendering fake images unreliable for diagnostic use. Translated images, in some cases, are used to enhance the quality of further post-processing tasks rather than to aid in diagnosing. Translation of PET images to synthetic CT images is an example where synthesized CT images are not used directly for analysis and diagnostic purposes, but rather for PET attenuation correction (AC) [23].

Disadvantages

The use of GAN models sometimes has its drawbacks and limitations, some of which are mentioned here. When a model is applied in a medical environment, it will not be accurate if it does not take into consideration characteristics that clinicians consider for prognosis and diagnosis. One of these disadvantages is poor interpretability due to the use of deep neural networks to produce synthetic images in GAN models. Although GANs perform better than deep neural networks models in many contexts, they are difficult to interpret; this is the main problem that prevents practical application within the medical profession. Also, if the database does not have enough data, the accuracy of the model decreases. Designing Gan models, the data flow, and lost functions to minimize the possibility of collapse or non-convergence of the model must be designed carefully [61].

One of the main challenges is to rely on the data generated by these models and gain the trust of physicians and radiologists. Especially, the mechanism of GAN models is not sufficiently understood. Typically, intensities in medical images have some meaning. For instance, in CT images, every intensity can be mapped to the Hounsfield-scale, so each intensity identifies a specific tissue. These associations are missing from the current GAN models leading to distrust of the healthcare system. However, the outcome in the computer version is more satisfactory [30].

Future clinical applications of GANs

As we envision future possibilities, GANs can be used to improve radiology workflow and patient care, as shown in this paper. The generation of artificial medical images and image-to-image translation by GANs could have other useful and practical developments. Among the applications of cGANs that should be considered in the future in the field of medical image processing is the addition of makeup removal presented by Chang *et al.* [62]. This technique can be used to reduce image artifacts; for example, improving bone X-ray images by removing artifacts. It may help radiologists and physicians assess the details and diagnose fractures and determine bone healing progress. Another example of the development of image-to-image translation can be attributed to the improved restoration of MR. Children may be less likely to retake their exams if MRI images acquired with motion artifacts can be restored; it also reduces the workload of radiologists [39].

One of the new applications of GANs that was introduced by Bodnar in 2018 is Generating images from natural language. The images produced by this method can create a new approach in the processing of medical images. For example, using this generated dataset, medical image classification tasks can be trained on supervised neural networks [63].

In summary, despite the remarkable results, GANs still cannot be used as a reliable source for medical diagnosis. There are many challenges in this regard. However, despite all this, it cannot be ignored that GANs are part of the medical future.

Concluding remarks

In conclusion, GANs hold significant potential to transform medical imaging by enabling efficient image-to-image translation across modalities, reducing costs, and improving diagnostic workflows. Their ability to generate high-quality synthetic images can enhance clinical decision-making, reduce patient exposure to radiation, and improve accessibility to advanced imaging techniques. However, further validation, optimization, and trust-building are essential for their widespread clinical adoption. Overcoming challenges such as data limitations, computational demands, and the need for interpretable models will be crucial for integrating GAN-based solutions into routine medical practice.

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