Generative Adversarial Networks in Tumor-Related Research: A Review and Agenda for Moving Forward

(Note: Please include this section below and leave the author information blank on initial submissions to facilitate blind review)

Andrew J. Behrens
Dakota State University
Andrew.Behrens@dsu.edu

Cherie Noteboom
Dakota State University
Cherie.Noteboom@dsu.edu

ABSTRACT

Recent advances in Generative Adversarial Networks (GANs) have led to many new variants and uses of GANs. The latest advancements have allowed researchers and practitioners to apply this technique to tumor-related problems with limited data. One of the trends in this problem domain is to develop different variants of GANs suited explicitly to particular problems. The variants of GANs are numerous but share a common characteristic of expanding the dataset by creating synthetic data from the original dataset. This paper aims to develop a research agenda through a systematic literature review that investigates practitioners' and researchers' emerging issues and current works on the topic. Emerging implementation trends and limitations of GANs in tumor-related problems are explored.

Keywords

Generative adversarial network, tumors, healthcare, data-driven systems, decision support

INTRODUCTION

Generative Adversarial Networks (GANs) were proposed by Goodfellow et al. in 2014 (Goodfellow et al., 2014). GANs provide a way to learn deep representations without extensively annotated training data (Creswell et al., 2018). Their application and ability to synthesize and augment data stimulated their use within the medical imaging domain. GANs were considered a popular semi-supervised and unsupervised machine learning approach for medical image analysis. There are different architectures of GANs which are used as alternative approaches to problems. The various architectures are fully connected, convolutional, conditional, inference models, and adversarial autoencoders (Creswell et al., 2018). Consequently, there are significantly complex and efficient variants.

A gap between the development of GAN variants and their implementations currently exists. Practitioners are concerned with current challenges in their particular work settings, while academics develop more generalizable rules and understanding (Belanger et al., 2002). Academics focus more on understanding a rigorous comparison between different variants and practitioners focus on developing high-performing variants that solve specific problems.

There are two objectives in this paper:

1. To examine the gap between GAN variant development and implementation in tumor-related research; and
2. To identify a research agenda to address emerging issues and concerns relevant to the development and implementation of GANs in tumor-related research.

This study proceeds by examining the gap between GAN development and variant implementation through a systematic review. First, we define a specific methodology. Following that, a brief literature review is completed to summarize the current state of the literature and identify gaps. The results are presented and discussed. A brief research agenda is proposed in the discussion and identifies research gaps. The article will conclude with reflections on the findings following the agenda. The main contribution of this paper is to increase the understanding of the GAN variants, visualization procedures, datasets, and the medical tasks associated with tumor-related research.

METHODOLOGY

Overview

This review followed the PRISMA guidelines (Liberati et al., 2009) and the formatting style developed from Morid (Morid et al., 2021). Figure 1 details the PRISMA chart. Eligible articles were searched for in MEDLINE, IEEE, ScienceDirect, BSP, ACM, and ASP. The papers collected were from June 2014 and February 2021. The search strategy for each database was completed using the keywords "generative adversarial network" and "tumor." Original research studies were included that focused on the synthesis of medical tumor images that directly used GAN variants trained on the images.

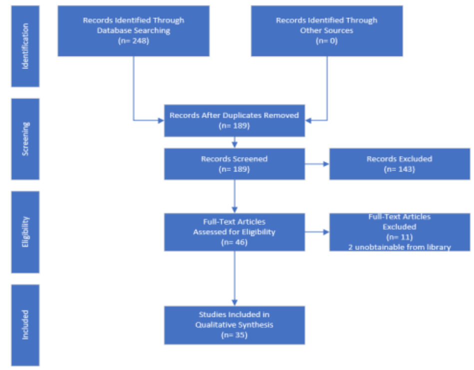

Figure 1. PRISMA chart

The studies that were excluded did not match the keyword in the title or abstract or met characteristics in Table 1. It is important to note that GANs were developed in 2014. Therefore, the research found before 2014 was excluded from the analysis. Inclusion eligibility was assessed individually by the researcher by evaluating the title and abstract of the article. The same researcher evaluated the full text of the included articles.

The following features were extracted from each of the included studies to answer each of the research questions in Table 1 based on the description of the problem, the input, the process, and the output. The studies included were summarized based on the research questions and attributes laid out in Table 1. The visualizations provided will convey the frequency of different approaches based on the medical task, anatomical site, dataset, preprocessing, variant, approach, and visualization method.

Table 1. Question and attribute table

Research Question	Category	Feature	Description
(1) What GANs are being used for tumor-related tasks?	Problem	Medical task	Medical task performed
		Anatomical site	Organ or body area
(2) What modalities are being used most frequently with the application of GANs and their variants?	Input	Image type	Modality used in the study
		Dataset used	Data type and name
(3) Which GAN architectures are used and what are the most prevalent?	Process	GAN variant	Type of GAN
(4) What visualization method was used for interpretation?	Output	Visualization	Technique used for interpretation of the GAN

LITERATURE REVIEW

Previous literature in the field focuses on the broader topic of GANs in medical imaging and creating artificial images for radiology applications using GANs (Sorin et al., 2020; Yi et al., 2019). Another paper investigates a similar issue from a different perspective by looking into general deep learning models applied to electronic health records (Xiao et al., 2018). Previous papers have not investigated which variants are being used to solve specific tumor-related problems. In (Aggarwal et al., 2021), the authors discuss the current state of GANs in their paper and detail an increase in articles written from 378 in 2019 to 1392 in 2020. While there is an increase in articles, there are no distinct review articles that investigate specific applications and visualization of GANs or their variants and how they are used to solve that problem in the tumor problem domain.

GANs and their extensions have carved open many exciting ways to tackle well-known and challenging medical image analysis problems such as medical image de-noising, reconstruction, segmentation, data simulation, detection or classification (Kazeminia et al., 2020). The improvements being made in this study area are due to: (1) GANs maximizing the probability density over the data generating distribution by exploiting density ratio estimation (Isola et al., 2017) in an indirect fashion of supervision; and (2) GANs can discover the high dimensional latent distribution of data, which has led to significant performance gains in the extraction of visual features (Kazeminia et al., 2020). These improvements are helpful, but significant research must be completed further to understand the implementation and utility of their variants.

RESULTS

The search resulted in 248 studies. Fifty-nine duplicate records were removed. The screening stage involved a title and abstract review of the remaining 198 records resulting in 143 exclusions. The eligibility process started with 46 articles for the full review. Eleven articles did not qualify after further review. There were 35 studies included in the detailed literature review.

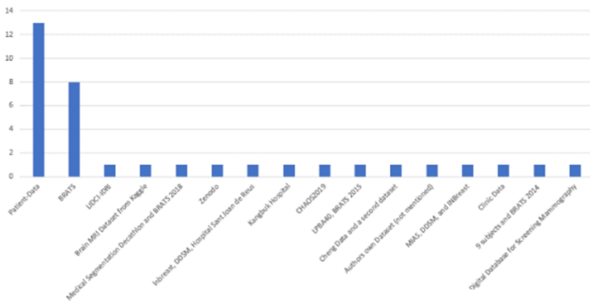

Figure 2. Datasets used in papers

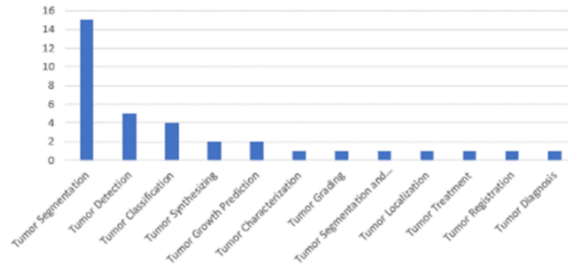

Figure 3. GAN tasks used in papers

Figure 2 details the two prominent datasets used. The most frequent dataset was generalized as patient data with a frequency of 37%. These studies incorporated a patient study. This was the most frequent due to the researcher's access to patient data and patients. The second most frequent dataset was the use of BRATS (Brain Tumor Segmentation) at 23%. The anatomical site most frequently investigated is the brain with 45% of occurrences. The second is lung at 14% and the third is breast at 11%.

Figure 3 shows the number of articles counted by the medical task. The most common task GANs were involved with was related to tumor segmentation with 43%. Tumor detection and classification were the second and third with 14% and 11%, respectively. Tumor synthesis and growth prediction individually made up 5% of the tasks. The remaining tasks individually made up 3% of the tasks investigated.

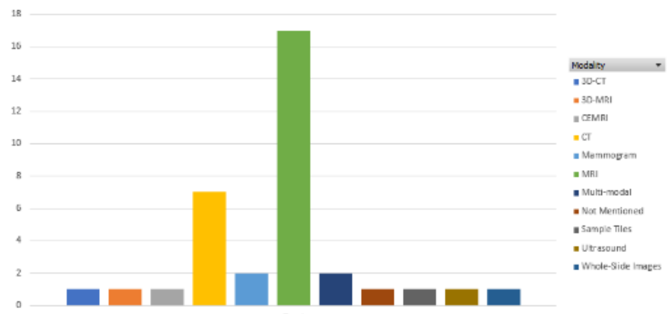

Figure 4. Modalities used in papers

Figure 4 shows the input modality frequency statistic for each article. Magnetic resonance imaging (MRI) and computed tomography (CT) were the most used image inputs with 49% and 26%, respectively. Two modalities were tied for the third, which were multi-modal and mammograms, individually ranking at 6%.

Figure 5 shows which GAN variants were used based on the anatomical site. Conditional GAN (cGAN) was the most frequently employed technique at 23%. That variant also was used in 6 different anatomical sites. 46% of the variants used focused on solving the brain tumor task which is the most common problem that researchers investigated. The lung tumor task at 11% was the second most targeted task. This problem has used four different approaches to GAN to solve the problem.

Figure 6 highlights that image comparison was the most used visualization measured at 43%. Other studies incorporated some

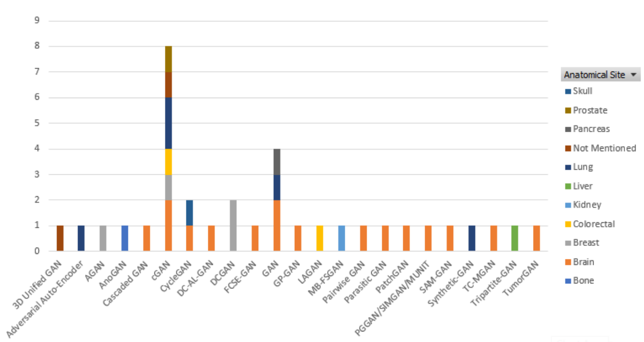

Figure 5. GANs used by anatomical site

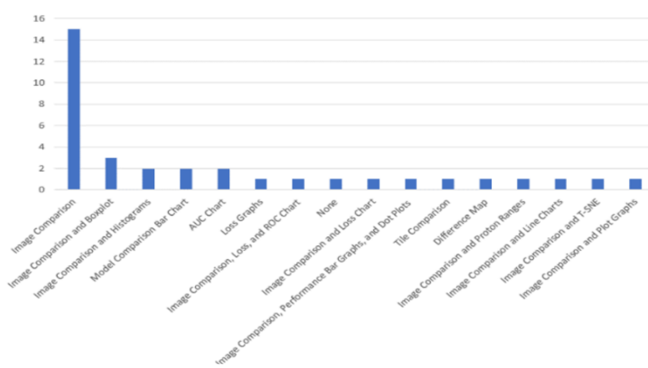

Figure 6. Visualizations used in papers

type of image comparison and another type of visualization made up 40%. Other models included AUC charts, loss graphs, ROC charts, and specific measures related to the modalities.

DISCUSSION

One article used GANs in tumor-related research during 2018 (B. Yu et al., 2018). This was the first article that used GANs. The discussion below can be used to guide researchers to identify potential approaches to specific tumor-related analysis problems that may warrant further research.

Generative adversarial network variants

The most prevalent GAN used was the conditional GAN (cGAN). This was used in tumor segmentation with MRIs and mammograms (B. Yu et al., 2018; Singh et al., 2020), tumor detection with sample tiles (Tavolara et al., 2019), growth prediction using CTs (A. Liebgott et al., 2019), localization with a 3D-CT (Wei et al., 2020), and diagnosis with whole-slide tiles (Rana et al., 2020), suggesting that cGANs may be the most effective GAN used for different types of medical tasks with different types of input modalities. cGANs are used to capture auxiliary information (B. Yu et al., 2018). This variant is broad in nature and has been used to supplement other models (Teki et al., 2019). While benchmarks generally are used to see how well the variant performs, in 50% of the articles that used cGAN, none applied a benchmark to compare to other variants (A. Liebgott et al., 2019; Rana et al., 2020; Wei et al., 2020). Figure 7 presents the other various GAN variants used to solve medical tasks.

The variety of variants that have been used demonstrates that researchers and practitioners are trying to find new ways to achieve the highest performance. Many of the variants used have attempted to combine two or more GAN methods to complete their studies' objective(s). In fact, in 2018, the only published study used cGAN and five studies in 2019 used cGANs. Aside from that, only three studies used GAN without any additional variants (Gao & Wang, 2019; Ghassemi et al., 2020; O'Briain et al., 2020), 77% of the other studies reviewed attempted to use an ensemble GAN technique to achieve higher accuracy. A substantial amount of work has been conducted to optimize GANs by taking on an ensemble approach. High-quality datasets are crucial to tackling smaller datasets that plague the tumor-related research problem domain. For example, (C. Ge et al., 2020) claims that the development of GANs will assist with tackling the commonly encountered problems of insufficiently large brain tumor datasets and incomplete modality of images.

Dataset size and collection method

Very few studies had extensive datasets in each publication. This is to be expected as the primary purpose of GANs is to try to augment the data to provide a larger set of data to work with. Four studies did not report dataset size (Elazab et al., 2020; Lee et al., 2020; N. Xi, 2019; T. E. & K. Saruladha, 2020). The most common dataset size was 200-300 images which accounted for 28% of the articles. Additionally, 69% of the articles studied held less than 1000 images. Many of the GAN variants were developed to better understand and use for specific problem domains.

While performance was reported in all studies, there was no common metric to compare across each study. Therefore, it is not exactly clear whether the size of the study had a significant impact on the findings (Morid et al., 2021). This creates a defined gap in the research where the understanding of optimal dataset thresholds should be understood, analyzed, and reported to understand better if dataset size has a significant effect on the performance of deep learning or machine learning approaches on the replicated datasets created from the GANs. The utility of GAN is not limited by the dataset collection method. 63% of the studies investigated used public data to develop new variants and study current GANs, while the other 37% of the studies used patient data from their organizations.

Visualization techniques

A majority (77%) of the reviewed studies visualized the results through image comparison. About 43% of the studies incorporated just image comparison. The other 34% of the studies incorporated image comparison and a statistical visualization such as a boxplot detailing further details about the technique used. These visualization techniques should be incorporated into any GAN study. They can help provide insight into how well the GAN presented a newly created image based on previous data which will assist with establishing trust in the medical community when considering the utilization of GANs (Borjali et al., 2020).

Research Agenda:

- Further investigation into each anatomical site to understand how each modality reacts to the implementation of GANs.
- Tumor detection and segmentation were the most prevalent tumor-related studies. The other problem domains should be investigated further to see if GANs are as effective in those environments.
- Determine if GANs or one of its variants can augment data from different study modalities.

- Identify which GAN variant performs the best in which study domain.
- Further, investigate what makes each GAN variant useful for each tumor-related implementation.
- Determine whether GAN variants can perform specific tumor tasks or if they are generalizable to other tasks.
- Identify a framework to help formalize the GAN development and allow for more generalizability between studies.
- Identify whether there is an optimal size of the dataset and how it impacts the performance of the GAN.
- Determine which is the most effective visualization for GAN troubleshooting and development.

This study yielded significant results but still had some limitations. Many problem domains regarding image modality and the anatomical site had limited studies completed. A single researcher classified and identified each article during the systematic review. The systematic review was also limited by only having access to Academic Search Premier, Association for Computing Machinery, Business Source Premier, IEEE, PubMed, and ScienceDirect. Future research should address a standardized benchmarking method and GAN variant to enable increased comparability among studies. Further, researchers should attempt to aggregate GAN variants from different domains to understand what each variant can provide or what it cannot. There is a significant need to understand why each GAN was applied to different problems and if that can be applied to similar problem domains.

CONCLUSION

The current state of the literature shows there are still significant contributions to the GAN and tumor-related research field. Significant benefits of using GANs in tumor-related research are the ability to synthesize data, augment data, and create synthetic data to more successfully train and test models. Given the popularity of GANs and how significant tumor-related research is, in-depth research on this topic is quite limited. Understanding the benefits in depth will enable GANs and their variants to be effectively implemented into tumor-related research.

REFERENCES

1. A. Liebgott, D. Hindere, K. Armanious, A. Bartler, K. Nikolaou, S. Gatidis, & B. Yangl. (2019). Prediction of FDG uptake in Lung Tumors from CT Images Using Generative Adversarial Networks. *2019 27th European Signal Processing Conference (EUSIPCO)*, 1–5. https://doi.org/10.23919/EUSIPCO.2019.8902935
2. Aggarwal, A., Mittal, M., & Battineni, G. (2021). Generative adversarial network: An overview of theory and applications. *International Journal of Information Management Data Insights*, 100004. https://doi.org/10.1016/j.jjimei.2020.100004
3. B. Yu, L. Zhou, L. Wang, J. Fripp, & P. Bourgeat. (2018). 3D cGAN based cross-modality MR image synthesis for brain tumor segmentation. *2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018)*, 626–630. https://doi.org/10.1109/ISBI.2018.8363653
4. Belanger, F., Watson-Manheim, M. B., & Jordan, D. H. (2002). Aligning IS research and practice: A research agenda for virtual work. *Information Resources Management Journal*, *15*(3), 23.
5. Borjali, A., Chen, A. F., Muratoglu, O. K., Morid, M. A., & Varadarajan, K. M. (2020). Deep Learning in Orthopedics: How Do We Build Trust in the Machine? *Healthcare Transformation*, heat.2019.0006. https://doi.org/10.1089/heat.2019.0006
6. C. Ge, I. Y. Gu, A. S. Jakola, & J. Yang. (2020). Enlarged Training Dataset by Pairwise GANs for Molecular-Based Brain Tumor Classification. *IEEE Access*, *8*, 22560–22570. https://doi.org/10.1109/ACCESS.2020.2969805
7. Creswell, A., White, T., Dumoulin, V., Arulkumaran, K., Sengupta, B., & Bharath, A. A. (2018). Generative Adversarial Networks: An Overview. *IEEE Signal Processing Magazine*, *35*(1), 53–65. https://doi.org/10.1109/MSP.2017.2765202
8. Elazab, A., Wang, C., Gardezi, S. J. S., Bai, H., Hu, Q., Wang, T., Chang, C., & Lei, B. (2020). GP-GAN: Brain tumor growth prediction using stacked 3D generative adversarial networks from longitudinal MR Images. *Neural Networks*, *132*, 321–332. Academic Search Premier.
9. Gao, X., & Wang, X. (2019). Deep learning for World Health Organization grades of pancreatic neuroendocrine tumors on contrast-enhanced magnetic resonance images: A preliminary study. *International Journal of Computer Assisted Radiology and Surgery*, *14*(11), 1981–1991. https://doi.org/10.1007/s11548-019-02070-5
10. Ghassemi, N., Shoeibi, A., & Rouhani, M. (2020). Deep neural network with generative adversarial networks pre-training for brain tumor classification based on MR images. *Biomedical Signal Processing and Control*, *57*, 101678. https://doi.org/10.1016/j.bspc.2019.101678
11. Goodfellow, I. J., Pouget-Abadie, J., Mirza, M., Xu, B., Warde-Farley, D., Ozair, S., Courville, A., & Bengio, Y. (2014). Generative Adversarial Networks. *ArXiv:1406.2661 [Cs, Stat]*. http://arxiv.org/abs/1406.2661
12. Isola, P., Zhu, J.-Y., Zhou, T., & Efros, A. A. (2017). Image-to-Image Translation with Conditional Adversarial Networks. *2017 IEEE Conference on Computer Vision and Pattern Recognition (CVPR)*, 5967–5976. https://doi.org/10.1109/CVPR.2017.632

13. Kazeminia, S., Baur, C., Kuijper, A., van Ginneken, B., Navab, N., Albarqouni, S., & Mukhopadhyay, A. (2020). GANs for medical image analysis. *Artificial Intelligence in Medicine*, *109*, 101938. https://doi.org/10.1016/j.artmed.2020.101938
14. Lee, H., Jo, J., & Lim, H. (2020). Study on Optimal Generative Network for Synthesizing Brain Tumor-Segmented MR Images. *Mathematical Problems in Engineering*, 1–12. Academic Search Premier.
15. Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Medicine*, *6*(7), e1000100.
16. Morid, M. A., Borjali, A., & Del Fiol, G. (2021). A scoping review of transfer learning research on medical image analysis using ImageNet. *Computers in Biology and Medicine*, *128*, 104115. https://doi.org/10.1016/j.compbiomed.2020.104115
17. N. Xi. (2019). Semi-supervised Attentive Mutual-info Generative Adversarial Network for Brain Tumor Segmentation. *2019 International Conference on Image and Vision Computing New Zealand (IVCNZ)*, 1–7. https://doi.org/10.1109/IVCNZ48456.2019.8961008
18. O'Briain, T. B., Yi, K. M., & Bazalova-Carter, M. (2020). Technical Note: Synthesizing of lung tumors in computed tomography images. *Medical Physics*, *47*(10), 5070–5076. Academic Search Premier.
19. Rana, A., Lowe, A., Lithgow, M., Horback, K., Janovitz, T., Da Silva, A., Tsai, H., Shanmugam, V., Bayat, A., & Shah, P. (2020). Use of Deep Learning to Develop and Analyze Computational Hematoxylin and Eosin Staining of Prostate Core Biopsy Images for Tumor Diagnosis. *JAMA Network Open*, *3*(5), e205111. https://doi.org/10.1001/jamanetworkopen.2020.5111
20. Singh, V. K., Rashwan, H. A., Romani, S., Akram, F., Pandey, N., Sarker, M. M. K., Saleh, A., Arenas, M., Arquez, M., Puig, D., & Torrents-Barrena, J. (2020). Breast tumor segmentation and shape classification in mammograms using generative adversarial and convolutional neural network. *Expert Systems with Applications*, *139*, 112855. https://doi.org/10.1016/j.eswa.2019.112855
21. Sorin, V., Barash, Y., Konen, E., & Klang, E. (2020). Creating Artificial Images for Radiology Applications Using Generative Adversarial Networks (GANs) – A Systematic Review. *Academic Radiology*, *27*(8), 1175–1185. https://doi.org/10.1016/j.acra.2019.12.024
22. T. E. & K. Saruladha. (2020). Design of FCSE-GAN for Dissection of Brain Tumour in MRI. *2020 International Conference on Smart Technologies in Computing, Electrical and Electronics (ICSTCEE)*, 1–6. https://doi.org/10.1109/ICSTCEE49637.2020.9276797
23. Tavolara, T. E., Niazi, M. K. K., Arole, V., Chen, W., Frankel, W., & Gurcan, M. N. (2019). A modular cGAN classification framework: Application to colorectal tumor detection. *Scientific Reports*, *9*(1), 18969. https://doi.org/10.1038/s41598-019-55257-w
24. Teki, S. M., Varma, M. K., & Yadav, A. K. (2019). Brain Tumour Segmentation Using U-net Based Adversarial Networks. *Traitement Du Signal*, *36*(4), 353–359. Business Source Premier.
25. Wei, R., Liu, B., Zhou, F., Bai, X., Fu, D., Liang, B., & Wu, Q. (2020). A patient-independent CT intensity matching method using conditional generative adversarial networks (cGAN) for single x-ray projection-based tumor localization. *Physics in Medicine and Biology*, *65*(14), 145009. https://doi.org/10.1088/1361-6560/ab8bf2
26. Xiao, C., Choi, E., & Sun, J. (2018). Opportunities and challenges in developing deep learning models using electronic health records data: A systematic review. *Journal of the American Medical Informatics Association*, *25*(10), 1419–1428. https://doi.org/10.1093/jamia/ocy068
27. Yi, X., Walia, E., & Babyn, P. (2019). Generative Adversarial Network in Medical Imaging: A Review. *Medical Image Analysis*, *58*, 101552. https://doi.org/10.1016/j.media.2019.101552