
DIFFUSION MODELS FOR MEDICAL IMAGE ANALYSIS: A COMPREHENSIVE SURVEY

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ABSTRACT

Denoising diffusion models, a class of generative models, have garnered immense interest lately in various deep-learning problems. A diffusion probabilistic model defines a forward diffusion stage where the input data is gradually perturbed over several steps by adding Gaussian noise and then learns to reverse the diffusion process to retrieve the desired noise-free data from noisy data samples. Diffusion models are widely appreciated for their strong mode coverage and quality of the generated samples in spite of their known computational burdens. Capitalizing on the advances in computer vision, the field of medical imaging has also observed a growing interest in diffusion models. With the aim of helping the researcher navigate this profusion, this survey intends to provide a comprehensive overview of diffusion models in the discipline of medical image analysis. Specifically, we start with an introduction to the solid theoretical foundation and fundamental concepts behind diffusion models and the three generic diffusion modeling frameworks, namely, diffusion probabilistic models, noise-conditioned score networks, and stochastic differential equations. Then, we provide a systematic taxonomy of diffusion models in the medical domain and propose a multi-perspective categorization based on their application, imaging modality, organ of interest, and algorithms. To this end, we cover extensive applications of diffusion models in the medical domain, including segmentation, anomaly detection, image-to-image translation, 2/3D generation, reconstruction, denoising, and other medically-related challenges. Furthermore, we emphasize the practical use case of some selected approaches, and then we discuss the limitations of the diffusion models in the medical domain and propose several directions to fulfill the demands of this field. Finally, we gather the overviewed studies with their available open-source implementations at our [GitHub](#)¹. We aim to update the relevant latest papers within it regularly.

Keywords Generative models · Diffusion models · Denoising diffusion models · Noise conditioned score networks · Score-based models · Medical imaging · Medical applications · Survey

¹<https://github.com/amirhossein-kz/Awesome-Diffusion-Models-in-Medical-Imaging>

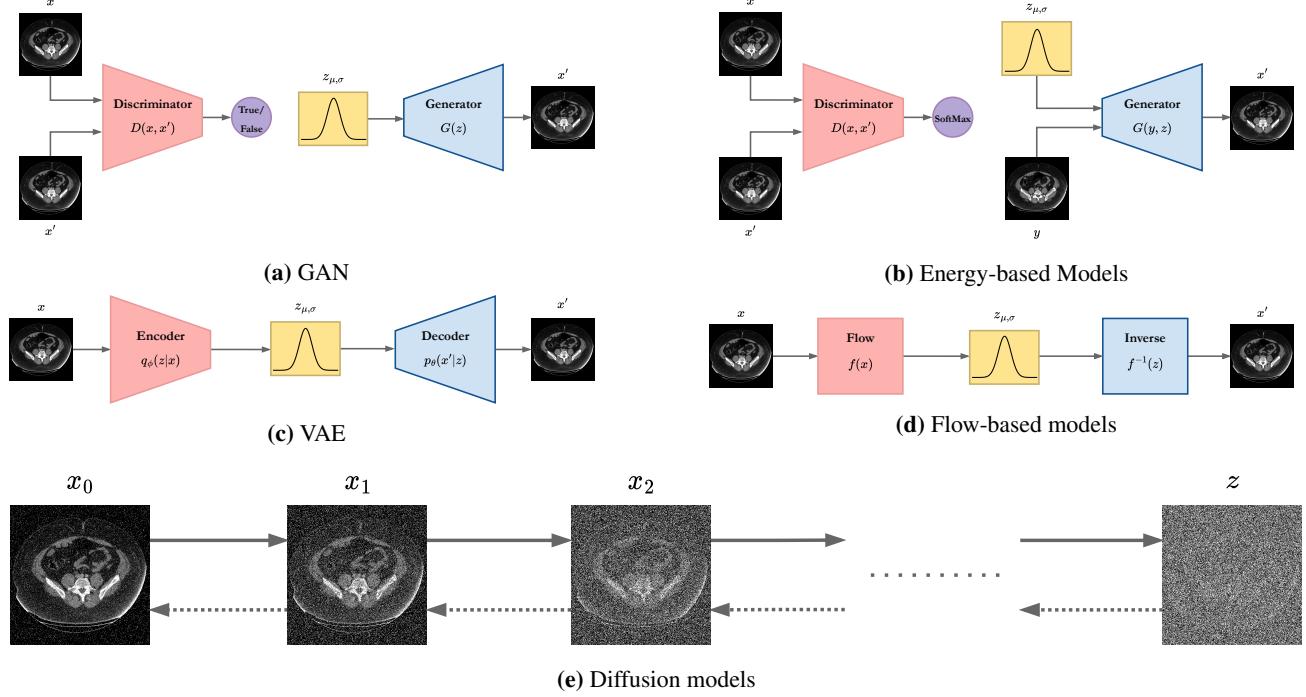


Figure 1: In this figure, We display the revolution of generative models and the insights behind them. (a) General Adversarial Network (GAN) [1] is an end-to-end pipeline that trains the generator in an adversarial manner to generate samples that the discriminator is capable of distinguishing from the real data sample. (b) Energy-based Model (EBM) [2], also known as non-normalized probabilistic models, trains in the same way as GANs with two major modifications. First, the discriminator learns a proper energy-based function that maps the data sample to a distribution space. Second, the generator utilizes a prior input to enhance the sample generation performance. (c) Variational AutoEncoder (VAE) [3] is a standalone network that follows a projection from a data sample to a low-dimensional latent space by the encoder and generates by sampling from it via a decoder path. (d) Normalizing flow (NF) [4] utilizes an invertible flow function to transform input to latent space and generate samples with the inverse flow function. (e) Diffusion Models intermingle the noise with the input in successive steps until it becomes a noise distribution before applying a reverse process to neutralize the noise addition in each step in the sampling procedure.

1 Introduction

Generative modeling using neural networks has been a formidable force in the past decade of deep learning. Since their emergence, generative models have made a tremendous impact in various domains ranging from images [5, 6], audio [7, 8], to text, [9] and point clouds [10]. From a probabilistic modeling viewpoint, the key defining characteristic of a generative model is that it is trained in such a way so that its samples $\tilde{\mathbf{x}} \sim p_\theta(\tilde{\mathbf{x}})$ come from the same distribution as the training data distribution, $\mathbf{x} \sim p_d(\mathbf{x})$. The pioneering energy-based models achieve this by defining an unnormalized probability density over a state space; however, these methods require Markov Chain Monte Carlo (MCMC) sampling during both training and inference, which is a slow iterative process [11]. Following the unprecedented surge of available datasets, as well as advances in general deep learning architectures, there has been a revolutionary paradigm shift in generative modeling. Specifically, the three mainstream generative frameworks include, namely, Generative adversarial networks (GANs) [1], variational autoencoders (VAEs) [12, 3], and normalizing flows [13] (see Figure 1). Generative models typically entail key requirements to be adopted in real-world problems. These requirements include (i) high-quality sampling, (ii) mode coverage and sample diversity, and (iii) fast execution time and computationally inexpensive sampling [14] (see Figure 2). Generative models often make accommodations between these criteria. Specifically, GANs are capable of generating high-quality samples rapidly, but they have poor mode coverage and are prone to lack sampling diversity. Conversely, VAEs and normalizing flows suffer from the intrinsic property of low sample quality despite being witnessed in covering data modes. GANs consist of two models: a generator and a critic (discriminator), which compete with each other while simultaneously making each other stronger. The generator tries to capture the distribution of true examples, while the discriminator, which is typically a binary classifier, estimates the probability of a given sample coming from the real dataset. It works as a critic and is optimized to recognize the synthetic samples from the real ones. A common concern with GANs is their training dynamics

which have been recognized as being unstable, resulting in deficiencies such as mode collapse, vanishing gradients, and convergence [15]. Therefore, an immense interest has also influenced the research direction of GANs to propose more efficient variants [16, 17]. Variational auto-encoders (VAEs) optimize the log-likelihood of the data by maximizing the evidence lower bound (ELBO). Despite the remarkable achievements, the behavior of Variational Autoencoders is still far from satisfactory due to some theoretical and practical challenges such as balancing issue [18] and variable collapse phenomenon [19]. A flow-based generative model is constructed by a sequence of invertible transformations. Specifically, a normalizing flow transforms a simple distribution into a complex one by applying a sequence of invertible transformation functions where one can obtain the desired probability distribution for the final target variable using a change of variables theorem. Unlike GANs and VAEs, these models explicitly learn the data distribution; therefore, their loss function is simply the negative log-likelihood [20]. Despite being feasibly designed, these generative models have their specific drawbacks. Since the Likelihood-based method has to construct a normalized probability model, a specific type of architecture must be used (Autoregressive Model, Flow Model), or in the case of VAE, an alternative Loss such as ELBO is not calculated directly for the generated probability distribution. In contrast, the learning process of GANs is inherently unstable due to the nature of the adversarial loss of the GAN. Recently, diffusion models [21, 22] have emerged as powerful generative models, showcasing one of the leading topics in computer vision so that researchers and practitioners alike may find it challenging to keep pace with the rate of innovation. Fundamentally, diffusion models work by destroying training data through the successive addition of Gaussian noise and then learning to recover the data by reversing this noising process.

To date, diffusion models have been found to be useful in a wide variety of areas, ranging from generative modeling tasks such as image generation [23], image super-resolution [24], image inpainting [25] to discriminative tasks such as image segmentation [26], classification [27], and anomaly detection [28]. Recently, the medical imaging community has witnessed exponential growth in the number of diffusion-based techniques (see Figure 4). As shown in Figure 4, a wealth of research is dedicated to the applications of diffusion models in diverse medical imaging scenarios. Thus, a survey of the existing literature is both beneficial for the community and quite timely. To this end, this survey sets out to provide a comprehensive overview of the recent advances made and provides a holistic overview of this class of models in medical imaging. A thorough search of the relevant literature revealed that we are the first to cover the diffusion-based models exploited in the medical domain. We hope this work will point out new paths, provide a road map for researchers, and inspire further interest in the vision community to leverage the potential of diffusion models in the medical domain. Our major contributions include:

- This is the first survey paper that comprehensively covers applications of diffusion models in the medical imaging domain. Specifically, we present a comprehensive overview of all available relevant papers (until October 2022).
- We devise a multi-perspective categorization of diffusion models in the medical community, providing a systematical taxonomy of research in diffusion models and their applications. We divide the existing diffusion models into three categories: denoising diffusion probabilistic models, noise-conditioned score networks, and stochastic differential equations. Moreover, we group the applications of diffusion models into seven categories: anomaly detection, denoising, reconstruction, segmentation, image-to-image translation, image generation, and other applications.
- We do not restrict our attention to application and provide a new taxonomy (see Figure 4) where each paper is broadly classified according to the proposed algorithm along with the organ concerned and imaging modality, respectively.
- Finally, we discuss the challenges and open issues and identify the new trends raising open questions about the future development of diffusion models in the medical domain in both algorithms and applications.

Paper Organization. In Section 2.1, we present a detailed overview of the concepts and theoretical foundations behind diffusion models, covering three sub-categories with a similar baseline definition. Sections 3.1 to 3.7 comprehensively cover the applications of diffusion models in several medical imaging tasks, as shown in Figure 3, whereas Section 3.8 provides a comparative task-specific overview of different literature work. We conclude this survey by pinpointing future directions and open challenges facing diffusion models in the medical imaging domain in Section 4.

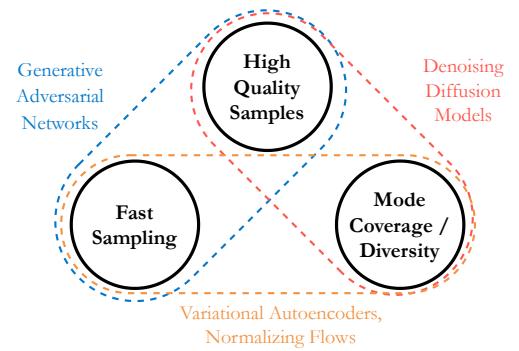


Figure 2: Generative learning trial [14]. Despite the ability of GANs to quickly generate high-fidelity samples, their mode coverage is limited. In addition, VAEs and normalizing flows have been revealed to have a great deal of diversity; however, they generally have poor sampling quality. Diffusion models have emerged to compensate for the deficiency of VAEs and GANs by showing adequate mode coverage and high-quality sampling. Nevertheless, due to their iterative nature, which causes a slow sampling process, they are practically expensive and require more improvement.

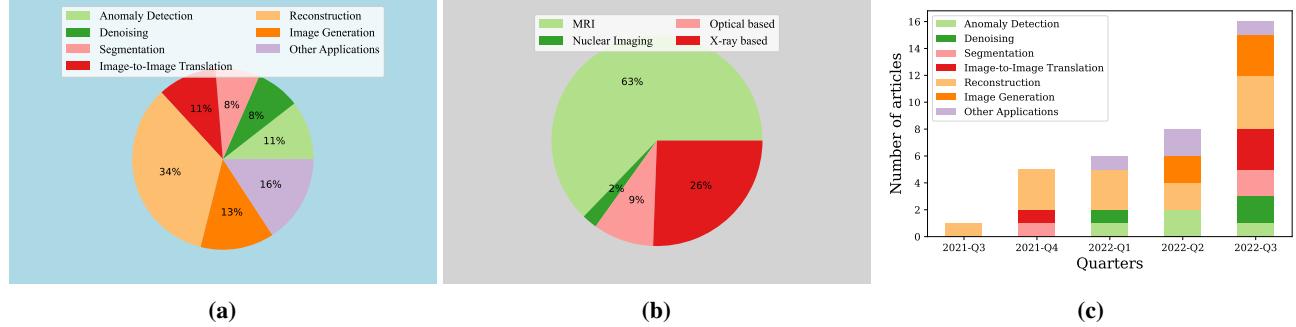


Figure 3: The diagram (a) shows the relative proportion of published papers categorized according to their application and (b) according to their imaging modalities. (c) indicates the number of diffusion-based research papers published in the medical domain. The growth rate per year reveals the importance of diffusion models for future work.

2 Taxonomy

Generative approaches have undergone significant advances in medical imaging over the past few decades. Therefore, there have been numerous survey papers published on deep generative models for medical imaging [29, 30, 31]. Some of these papers focus on a specific application only, while others concentrate on a specific image modality. There is, however, a lack of comprehensive surveys on the applications of diffusion models in medical imaging. To this end, in this survey, we devise a multi-perspective vision of diffusion models in which we discuss existing literature based on their applications in the medical domain. Nonetheless, we do not restrict our interest to the applications but describe the underlying working principles, the organ, and the imaging modality of the proposed method. We further discuss how this additional information can help researchers attempt to consolidate the literature across the spectrum. A brief outlook of our paper is depicted in Figure 4.

2.1 Algorithm

There are at least three sub-categories of diffusion models that comply with the baseline definition of diffusion models [60]. First, there are denoising diffusion probabilistic models (DDPMs) [21, 22], which are a class of latent variable models inspired by considerations from nonequilibrium thermodynamics. The second sub-category is represented by noise-conditioned score networks (NCSNs) [61], which is fundamentally based on estimating the derivative of the log density function of the perturbed data distribution at different noise levels. Stochastic differential equations (SDEs) [62] form the third sub-category, which encapsulates previous approaches and can be viewed as a generalization over DDPMs and NCSNs. We hereinafter elaborate on the details of each category.

2.1.1 Denoising Diffusion Probabilistic Models (DDPMs)

Forward Process. DDPM defines the forward diffusion process as a Markov Chain where Gaussian noise is added in successive steps to obtain a set of noisy samples. Consider $q(x_0)$ as the uncorrupted (original) data distribution. Given a data sample $x_0 \sim q(x_0)$, a forward noising process p which produces latent x_1 through x_T by adding Gaussian noise at time t is defined as follows:

$$q(x_t | x_{t-1}) = \mathcal{N}(x_t; \sqrt{1 - \beta_t} \cdot x_{t-1}, \beta_t \cdot \mathbf{I}), \forall t \in \{1, \dots, T\} \quad (1)$$

where T and $\beta_1, \dots, \beta_T \in [0, 1]$ represent the number of diffusion steps and the variance schedule across diffusion steps respectively. \mathbf{I} is the identity matrix and $\mathcal{N}(x; \mu, \sigma)$ represents the normal distribution of mean μ and covariance σ . Considering $\alpha_t = 1 - \beta_t$ and $\bar{\alpha}_t = \prod_{s=0}^t \alpha_s$, one can directly sample an arbitrary step of the noised latent conditioned on the input x_0 as follows:

$$q(\mathbf{x}_t | \mathbf{x}_0) = N(\mathbf{x}_t; \sqrt{\bar{\alpha}_t} \mathbf{x}_0, (1 - \bar{\alpha}_t) \mathbf{I}) \quad (2)$$

$$\mathbf{x}_t = \sqrt{\bar{\alpha}_t} \mathbf{x}_0 + \sqrt{1 - \bar{\alpha}_t} \epsilon \quad (3)$$

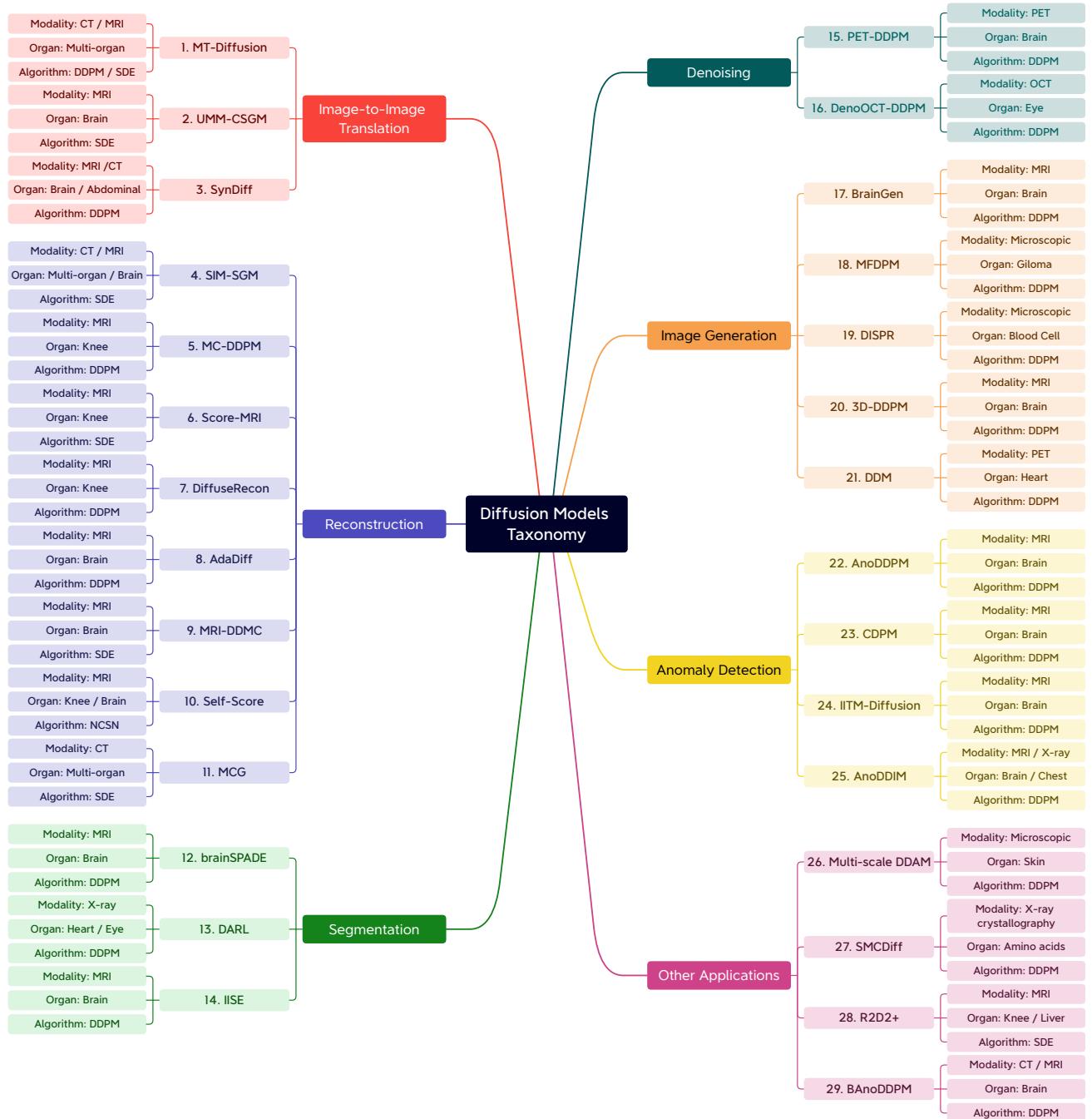


Figure 4: The proposed taxonomy for diffusion-based medical image analysis research is built on seven sub-fields: I) Image-to-Image Translation, II) Medical Image Reconstruction, III) Image Segmentation, IV) Medical Image Denoising, V) Image Generation, VI) Anomaly Detection and VII) multi-disciplinary applications, named Other Applications. For the sake of brevity, we utilize the prefix numbers in the paper's name in ascending order and denote the reference for each study as follows: 1. [32], 2. [33], 3. [34], 4. [35], 5. [36], 6. [37], 7. [38], 8. [39], 9. [40], 10. [41], 11. [42], 12. [43], 13. [44], 14. [45], 15. [46], 16. [47], 17. [48], 18. [49], 19. [50], 20. [51], 21. [52], 22. [53], 23. [54], 24. [55], 25. [28], 26. [56], 27. [57], 28. [58], 29. [59].

Reverse Process. Leveraging the above definitions, we can approximate a reverse process to get a sample from $q(x_0)$. To this end, we can parameterize this reverse process by starting at $p(\mathbf{x}_T) = \mathcal{N}(\mathbf{x}_T; \mathbf{0}, \mathbf{I})$ as follows:

$$p_\theta(\mathbf{x}_{0:T}) = p(\mathbf{x}_T) \prod_{t=1}^T p_\theta(\mathbf{x}_{t-1} | \mathbf{x}_t) \quad (4)$$

$$p_\theta(\mathbf{x}_{t-1} | \mathbf{x}_t) = \mathcal{N}(\mathbf{x}_{t-1}; \mu_\theta(\mathbf{x}_t, t), \Sigma_\theta(\mathbf{x}_t, t)) \quad (5)$$

To train this model such that $p(x_0)$ learns the true data distribution $q(x_0)$, we can optimize the following variational bound on negative log-likelihood:

$$\begin{aligned} \mathbb{E}[-\log p_\theta(\mathbf{x}_0)] &\leq \mathbb{B}_q \left[-\log \frac{p_\theta(\mathbf{x}_{0:T})}{q(\mathbf{x}_{1:T} | \mathbf{x}_0)} \right] \\ &= \mathbb{E}_q \left[-\log p(\mathbf{x}_T) - \sum_{t \geq 1} \log \frac{p_\theta(\mathbf{x}_{t-1} | \mathbf{x}_t)}{q(\mathbf{x}_t | \mathbf{x}_{t-1})} \right] \\ &= -L_{\text{VL.B}} \end{aligned} \quad (6)$$

Ho et al. [22] found it better not to directly parameterize $\mu_\theta(\mathbf{x}_t, t)$ as a neural network, but instead to train a model $\epsilon_\theta(\mathbf{x}_t, t)$ to predict ϵ . Hence, by reparameterizing Equation (6), they proposed a simplified objective as follows:

$$L_{\text{simple}} = E_{t, x_0, \epsilon} \left[\|\epsilon - \epsilon_\theta(\mathbf{x}_t, t)\|^2 \right] \quad (7)$$

where the authors draw a connection between the loss in Equation (6) to generative score networks in Song et al. [61].

2.1.2 Noise Conditioned Score Networks (NCSNs)

The score function of some data distribution $p(x)$ is defined as the gradient of the log density with respect to the input, $\nabla_x \log p(x)$. To estimate this score function, one can train a shared neural network with score matching. Specifically, the score network s_θ is a neural network parameterized by θ , which is trained to approximate the score of $p(x)$ ($s_\theta(x) \approx \nabla_x \log p(x)$) by minimizing the following objective:

$$\mathbb{E}_{x \sim p(x)} \|s_\theta(x) - \nabla_x \log p(x)\|_2^2 \quad (8)$$

However, due to the computational burden of calculating $\nabla_x \log p(x)$, score matching is not scalable to deep networks and high dimensional data. To mitigate this problem, the authors of [61] propose to exploit denoising score matching [63] and sliced score matching [64]. Moreover, Song et al. [61] highlight major challenges that prevent a naive application of score-based generative modeling in real data. The key challenge is the fact that the estimated score functions are inaccurate in low-density regions since data in the real world tend to concentrate on low-dimensional manifolds embedded in a high-dimensional space (the manifold hypothesis). The authors demonstrate that these problems can be addressed by perturbing the data with Gaussian noise at different scales, as it makes the data distribution more amenable to score-based generative modeling. They propose to estimate the score corresponding to all noise levels by training a single noise-conditioned score network (NCSN). They derive $\nabla_x \log(p_{\sigma_t}(x))$ as $\nabla_{x_t} \log p_{\sigma_t}(x_t | x) = -\frac{x_t - x}{\sigma_t}$ by choosing the noise distribution to be $p_{\sigma_t}(x_t | x) = \mathcal{N}(x_t; x, \sigma_t^2 \cdot \mathbf{I})$ where x_t is a noised version of x . Thus, for a given sequence of Gaussian noise scales $\sigma_1 < \sigma_2 < \dots < \sigma_T$, Equation (8) can be written as:

$$\frac{1}{T} \sum_{t=1}^T \lambda(\sigma_t) \mathbb{E}_{p(x)} \mathbb{E}_{x_t \sim p_{\sigma_t}(x_t | x)} \left\| s_\theta(x_t, \sigma_t) + \frac{x_t - x}{\sigma_t} \right\|_2^2 \quad (9)$$

where $\lambda(\sigma_t)$ is a weighting function. The inference is done using an iterative procedure called "Langevin dynamics" [65, 66]. Langevin dynamics design an MCMC procedure to sample from a distribution $p(\mathbf{x})$ using only its score function $\nabla_{\mathbf{x}} \log p(\mathbf{x})$. Specifically, to move from a random sample $\mathbf{x}_0 \sim \pi(\mathbf{x})$ towards samples from $p(\mathbf{x})$, it iterates the following:

$$x_i = x_{i-1} + \frac{\gamma}{2} \nabla_{\mathbf{x}} \log p(\mathbf{x}) + \sqrt{\gamma} \cdot \omega_i \quad (10)$$

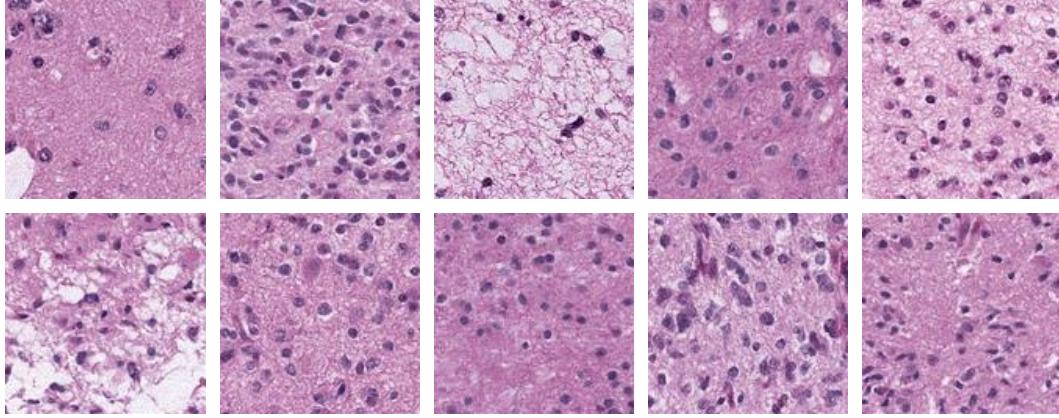


Figure 5: Ten synthetic histopathology images generated by MFDPM [49].

where $\omega_i \sim \mathcal{N}(0, \mathbf{I})$, and $i \in \{1, \dots, N\}$. When $\gamma \rightarrow 0$ and $N \rightarrow \infty$, \mathbf{x}_i samples obtained from this procedure converge to a sample from $p(\mathbf{x})$. The authors of [61] propose a modification of this algorithm nomenclature as the annealed Langevin dynamics algorithm since the noise scale σ_i decreases (anneals) gradually over time to mitigate some pitfalls and failure modes of score matching [67].

2.1.3 Stochastic Differential Equations (SDEs)

Similar to the aforementioned two approaches, score-based generative models (SGMs) [62] transform the data distribution $q(x_0)$ into noise. However, by generalizing the number of noise scales to infinity, one can view the previous probabilistic models as a discretization of an SGM. We know that many stochastic processes, such as the diffusion process, are the solution to a stochastic differential equation (SDE) in the following form:

$$d\mathbf{x} = \mathbf{f}(\mathbf{x}, t)dt + g(t)d\mathbf{w} \quad (11)$$

where $\mathbf{f}(\cdot, t)$ is the drift coefficient of the SDE, $g(t)$ is the diffusion coefficient, and \mathbf{w} represents the standard Brownian motion. Let \mathbf{x}_0 be the uncorrupted data sample, and \mathbf{x}_T denote the perturbed data approximating standard Gaussian distribution. For the given forward SDE, there exists a reverse time SDE running backward where, by starting out with a sample from p_T and reversing this diffusion SDE, we can obtain samples from our data distribution p_0 . The reverse-time SDE is given as:

$$d\mathbf{x} = [\mathbf{f}(\mathbf{x}, t) - g^2(t)\nabla_{\mathbf{x}} \log p_t(\mathbf{x})] dt + g(t)d\bar{\mathbf{w}} \quad (12)$$

where dt is the infinitesimal negative time step, and $\bar{\mathbf{w}}$ is the Brownian motion running backward. In order to numerically solve the reverse-time SDE, one can train a neural network to approximate the actual score function via score matching [61, 62] to estimate $s_\theta(\mathbf{x}, t) \simeq \nabla_{\mathbf{x}} \log p_t(\mathbf{x})$ (denoted red in Equation (12)). This score model is trained using the following objective:

$$\mathcal{L}(\theta) = \mathbb{E}_{\mathbf{x}(t) \sim p(\mathbf{x}(t) | \mathbf{x}(0)), \mathbf{x}(0) \sim p_{\text{data}}} \left[\frac{\lambda(t)}{2} \|s_\theta(\mathbf{x}(t), t) - \nabla_{\mathbf{x}(t)} \log p_t(\mathbf{x}(t) | \mathbf{x}(0))\|_2^2 \right] \quad (13)$$

where λ is a weighting function, and $t \sim \mathcal{U}([0, T])$. Notably, $\nabla_{\mathbf{x}} \log p_t(\mathbf{x})$ is replaced with $\nabla_{\mathbf{x}} \log p_{0t}(\mathbf{x}(t) | \mathbf{x}(0))$ to circumvent technical difficulties.

2.2 Clinical Importance

Generative models have significantly impacted the field of medical imaging, where there is a strong need for tools to improve the routines of clinicians and patients. Concretely, the complexity of data collection procedures, the lack of experts, privacy concerns, and the compulsory requirement of authorization from patients create a major bottleneck in the annotation process in medical imaging. This is where generative models become advantageous [68]. Several perspectives have driven our interest in generative diffusion models for medical imaging. In the medical field, many datasets suffer from severe class imbalance due to the rare nature of some pathologies. Diffusion models can alleviate this restriction by generating diverse realistic-looking images to leverage in the medical field. Furthermore, generating synthetic medical images has substantial educational value. With its ability to produce a limitless source of unique instances of different medical imaging modalities, diffusion models can satisfy educational demands by constructing distinct synthetic samples for teaching and practice. Additionally, these artificial images can mitigate data security concerns associated with using patient data in public

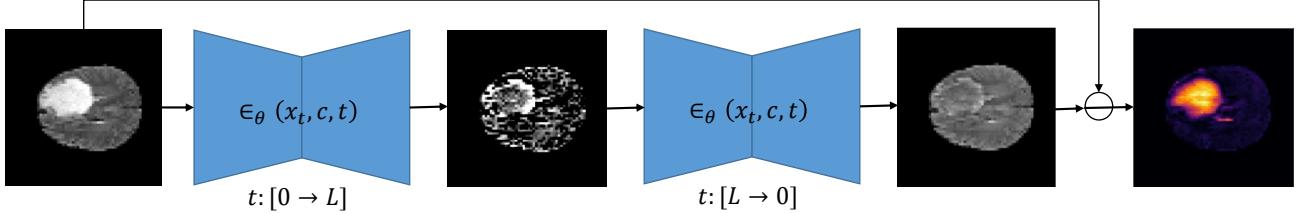


Figure 6: An overview of CDPM [54]. Iteratively applying diffusion models using an unconditional model ($c = \emptyset$) encodes the input image into a latent space. Then, reversing the diffusion process from the latent space decodes a healthy state image. The decoding process is guided by conditioning it on the healthy state and \emptyset . The anomaly heatmap is generated by subtracting the input image from the generated counterfactual.

settings. These artificial images can also solve a particular significant difficulty in training deep neural networks for medical applications. Generally, the annotation of medical images is a lengthy and costly process that necessitates the assistance of an expert. Hence, using diffusion models to generate synthetic samples can alleviate the problem of medical data scarcity to a great extent. A case study using [49] to generate histopathology images with rare cancer subtypes is described in Figure 5.

3 Diffusion Models in Action

Providing a taxonomy for diffusion models more or less follows the same route as other techniques for medical imaging analysis. We provide, however, detailed additional information for each sub-category paper in Figure 4. In this section, we explore diffusion-based methods, which are proposed to solve any disentanglement from the medical imaging analysis in **seven** application categories, as in Figure 4: **(I)** Image-to-Image Translation, **(II)** Image Segmentation, **(III)** Anomaly Detection, **(IV)** Medical Image Reconstruction, **(V)** Image Generation, **(VI)** Medical Image Denoising and **(VII)** multi-disciplinary applications, named Other Applications. Figure 4 represents a collection of numerous studies for each category with extensive information on each study, such as the modality of study, the organ of interest, and the specific algorithm utilized in the reverse process of the diffusion model for study. Finally, in Section 3.8, we discuss the overall algorithms used in the studies and try to shed light on the main novelty and contribution of the papers in Table 1.

3.1 Anomaly Detection

Medical anomaly detection is an important topic in computer vision, aiming to highlight the anomalous regions of the image [69, 70, 71]. Generative models have dramatically shaped queries on anomaly detection in recent years and have shown promising results. Accordingly, we explore diffusion models as dominant generative models in anomaly detection in the following section.

Wolleb et al. [28] introduce a weakly supervised learning method based on Denoising Diffusion Implicit Models (DDIMs) [72] for medical anomaly detection. Given an input image of a healthy or diseased subject, image-to-image translation first performs such that the objective is to translate the input image into the healthy one. Then, the anomaly regions are identified by subtracting the output image from the input. This process begins by encoding an input image into a noisy image with reversed DDIM sampling. Then, the denoising process is guided through a binary classifier trained beforehand on the healthy and diseased images to produce the healthy image. Finally, the anomaly map is calculated by taking the difference between the output and input. Results on BRATS2020 [73, 74, 75] and CheXpert [76] datasets demonstrate the superiority of the proposed approach compared to both VAE [77] and GAN [78] models.

Wyatt et al. [53] in AnoDDPM train a DDPM only on healthy medical samples. The anomaly image is then rendered by computing the difference between the output and input images. They also show that leveraging Simplex noise over Gaussian noise significantly enhances the performance.

In contrast, CDPM [54] demonstrates that training the diffusion probabilistic models only on healthy data generates poor segmentation performance. Thus, CDPM presents a counterfactual diffusion probabilistic model for generating healthy counterfactuals from factual input images. As illustrated in Figure 6, the input image is initially encoded into a latent space by iteratively applying diffusion models using an unconditional model. Then, the decoding step is accomplished by reversing the diffusion process. Using implicit guidance [79], the latent is decoded into a counterfactual by conditioning it on a healthy state and \emptyset . Inspired by [80, 81, 82], Sanchez et al. [54] then enhance the conditioning process by incorporating conditional attention into the U-Net backbone. As a final step, a dynamic normalization technique is applied during inference to avoid saturation in latent space pixels, caused by the guided iterative process that may change the image statistics. Eventually, the location of abnormality is determined by subtracting the input image from the generated healthy counterfactual.

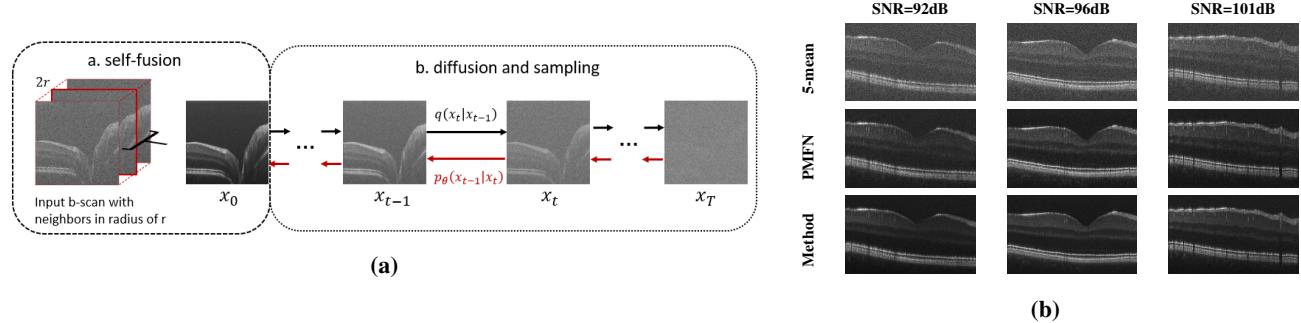


Figure 7: (Left) General pipeline of DenoOCT-DDPM [47]. To feed the diffusion model more low-noise reference images, DenoOCT-DDPM applies a self-fusion [86] on the red canvas b-scan in (a) with neighboring b-scans for higher SNR b-scan. (b) indicates a straightforward DDPM scheme in an unsupervised manner to learn speckle noise distribution in the red arrow sampling stream. (Right) Ultimate visual comparison of DenoOCT-DDPM [47] for denoising b-scans of volumetric OCT images demolished by speckle noise. DenoOCT-DDPM compared itself with PMFN [87] and the average of 5 successive b-scans as the ground truth. PMFN results in good feature preservation in diverse retinal layers, but it can easily over-smooth small vessel regions. In contrast, the DenoOCT-DDPM retinal layers are more homogenous than PMFN in diverse acquisition SNRs.

3.2 Denoising

The major challenge in medical imaging is obtaining an image without losing important information. The images obtained may be corrupted by noise or artifacts during the acquisition and/or further processing stages [83, 84]. Noise reduces the image quality and is especially significant when the imaged objects are small and have relatively low contrast [85]. Due to the nature of generative models, diffusion models are convenient for diverse denoising problems. In this section, we will explore the contribution of diffusion models to this field.

Hu et al. [47] utilized a DDPM [22] to despeckle Optical Coherence Tomography (OCT) volumetric retina data in an unsupervised manner, denoted as DenoOCT-DDPM. OCT imaging utility suffers from limited spatial-frequency bandwidth, which leads to the resulting images containing speckle noise. Speckle noise hinders the ophthalmologist's diagnosis and can severely affect the visibility of the tissue. The classic methods, such as averaging multiple b-scans at the same location, have extreme drawbacks, such as prolonged acquisition time and registration artifacts. Due to the multiplicative properties of speckle noise, these methods enrich rather than reduce the noise. Deep-based models perform outstandingly. This performance, however, depends on the availability of noise-free images, which is a rare and costly process to acquire. To this end, DenoOCT-DDPM [47] utilizes DDPM's feasibility in noise patterns rather than real-data pattern. Therefore, they use a self-fusion [86] as a preprocessing step to feed the DDPM with a clear reference image and train the parameterized Markov chain (see Figure 7a). Their investigation demonstrated the SOTA results over the Pseudo-Modality Fusion Network (PMFN) [87], which uses information from the single-frame noisy b-scan and a pseudo-modality that is created with the aid of the self-fusion [86] method, regarding Signal-to-Noise Ratio (SNR) metric. The qualitative results over PMFN depicted in Figure 7b (represented in multiple acquisition SNRs) endorse the ability of diffusion models in removing the speckle noise while preserving the fine-grained features like small vessels.

Positron Emission Tomography (PET) is a non-invasive imaging utility that plays a crucial role in cancer screening and diagnosis. However, as with OCT devices, PETs suffer from low SNR and resolution due to the low beam count radiation to patients. Deep learning methods over PET image denoising have advanced, but over-smoothing is a prominent drawback of CNN-based approaches. Therefore, Conditional Generative Adversarial Networks (CGANs) [88, 89] neutralize the mentioned deficiency but still depend on training and test sets distributions. Gong et al. [46] proposed the DDPM-based framework for PET denoising in collaboration with an assistive modality embedding as prior information to DDPM formulation, namely PET-DDPM. Gong et al. used ^{18}F -FDG and ^{18}F -MK-6240 datasets for PET and MR modalities, respectively. PET-DDM is a multi-disciplinary study investigating the excessive modalities of collaboration in learning noise distribution through PET images. This intuition follows the original paper in a generative paradigm [23] with a guided classifier to converge the learned distribution to desired distribution. PET-DDM produced SOTA results compared with U-Net [90] based denoising network in terms of Peak Signal-to-Noise Ratio (PSNR) and Structural Similarity Index Measure (SSIM).

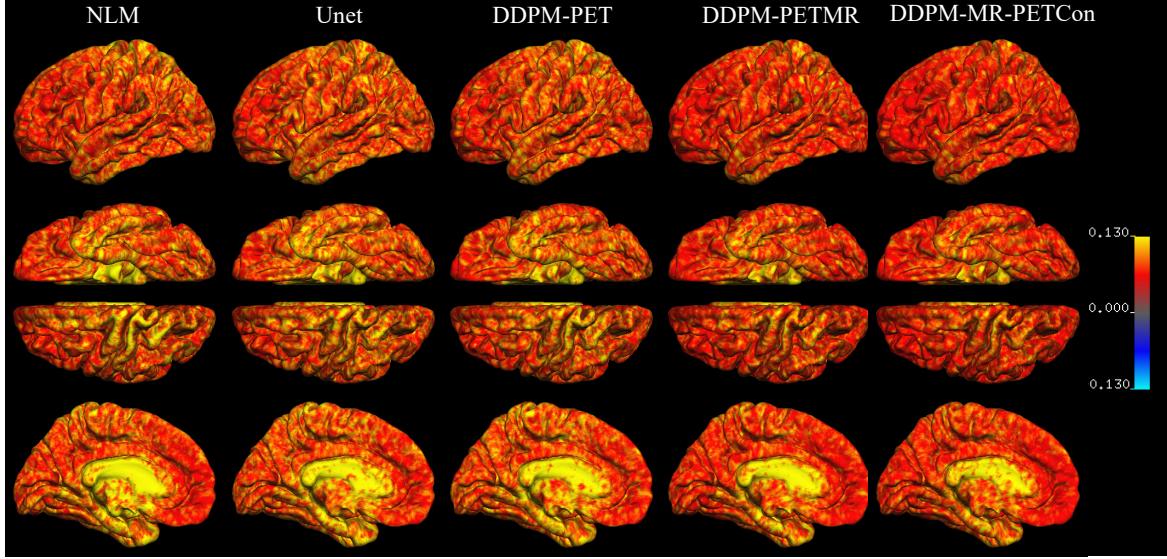


Figure 8: Comparison by different methods of surface error mapping of the left hemisphere from 20 ^{18}F -MK-6240 test dataset. The results confirm that DDPM-MR-PETCon has the lowest error, followed by the DDPM-PETMR method. DDPM-MR-PETCon is short for using the MR image as network input while using the PET image as a data consistency item, and DDPM-PETMR denotes that PET and MR images are used as network input.

3.3 Reconstruction

Medical imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are the most popular imaging tools in medicine. However, due to their functionality, they can harm patients; therefore, their radiation exposure is reduced from the standard dose, or the imaging process is done in an under-sampled or sparse-view manner [91, 92, 93, 94]. To diminish these drawbacks, e.g., low Signal-to-Noise Ratio (SNR) and Contrast-to-Noise Ratio (CNR), medical image reconstruction must overcome the challenges mentioned and solve this ill-posed inversion problem [95]. This section overviews the diffusion-based paradigms for medical image reconstruction and enhancement.

Magnetic Resonance Imaging (MRI) is a popular non-invasive imaging utility in medical diagnosis treatment, but due to its innate physics, it is a time-consuming process of imaging sessions in which the movement of patients results in various artifacts in images. Therefore, to decrease bedtime and to accelerate the reverse problem-solving from the spatial domain (or k -space) to image level, miscellaneous solutions are provided in the supervised-learning concept. However, these methods are not robust to distribution changes or drifts in their train/test sets. Jalal et al. [96] proposed the first study in the MRI reconstruction domain via Compressed Sensing with Generative Models (CSGM). To this end, CSGM trains the score-based generative models [67] on MRI images to utilize as prior information for the inversion pathway in reconstructing realistic MRI data from under-sampled MRI in posterior sampling scheme with Langevin dynamics [97]. CSGM [96] demonstrated its better performance over fastMRI [98] and Stanford MRI [99] datasets with Structural Similarity Index Measure (SSIM) and PSNR metrics in comparison with end-to-end supervised-learning paradigms.

Cheng et al. [37] propose a score-based diffusion framework that solves the inverse problem for image reconstruction from accelerated MRI scans, as depicted in Figure 9. In the first step, a single continuous time-dependent score function with denoising score matching is trained only with magnitude images. Then, in the reverse SDE process, the Variance Exploding (VE)-SDE [62] is exploited to sample from the pretrained score model distribution, conditioned on the measurement. Afterward, the image is first split into real and imaginary components at each step. Each part is fed into the predictor, followed by data consistency mapping to reconstruct the image. The obtained image is split again, and the correcter and the data consistency mapping are applied to each part to compensate for errors during the diffusion and reconstruct the improved image, respectively. Results demonstrate that the proposed model outperforms the previous SOTA methods [100, 101, 98] and can even reconstruct the data, which is considerably outside the training distribution with high fidelity, e.g., reconstructing anatomy not seen during training. In addition, the proposed framework has shown to be very effective for reconstructing the image when multiple coils exist. For the aforementioned problem, they present two approaches: (1) they reconstruct each coil image in parallel; (2) they take into account the correlation between the coil images by injecting the dependency between them at each given step during reverse SDE. Then, the final image is acquired by taking the sum-of-root-sum-of-squares (SSoS) [102] of each reconstructed coil image. Although these two techniques have shown great results qualitatively and practically, they are time-consuming.

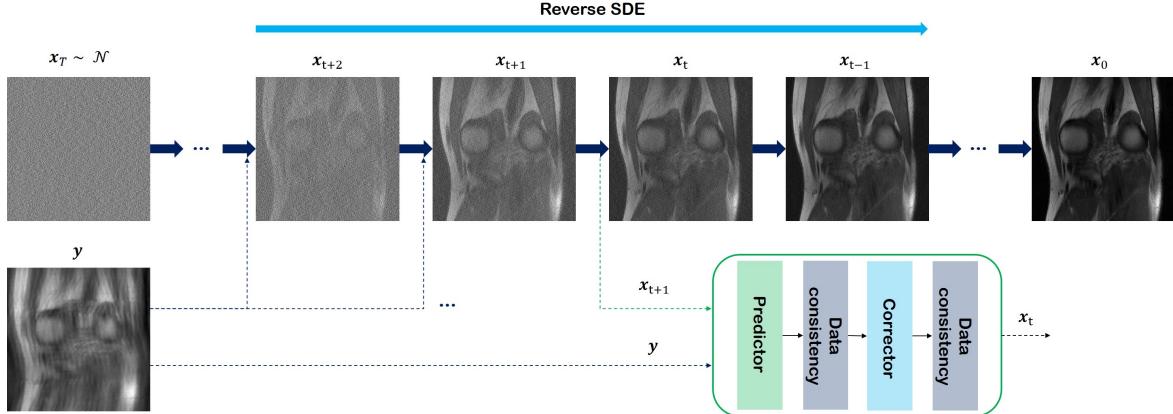


Figure 9: An overview of Score-MRI [54]. x_T is derived from the pre-trained prior distribution, and x_0 is retrieved by sequentially applying the predictor, data consistency, corrector, and data consistency steps, given the measurement through the reverse SDE procedure.

3.4 Segmentation

Image segmentation is a vital task in computer vision, which investigates simplifying the complexity of the image by decomposing an image into multiple meaningful image segments [103, 104]. Specifically, it facilitates medical analysis by providing beneficial information about anatomy-related areas. However, deep learning models often require vast amounts of diverse pixel-annotated training data in order to produce generalizable results [105, 106]. Nonetheless, the number of images and labels accessible for medical image segmentation is restricted due to the time, cost, and expertise required [107, 108, 109]. To this end, diffusion models have been propelled to the forefront in investigations of image segmentation by synthesizing the labeled data and obviating the necessity for pixel-annotated data.

brainSPADE [43] proposes a generative model for synthesizing labeled brain MRI images that can be used for training segmentation models. brainSPADE is composed of a label generator and an image generator sub-model. The former is responsible for creating synthetic segmentation maps, and the latter for synthesizing images based on generated labels. In the label generator, the input segmentation map is first encoded during training using a spatial VAE encoder and builds a latent space. The compressed latent code is then diffused and denoised via LDMs [82] and produces an efficient latent space in which imperceptible details are ignored, and semantic information is highlighted more. A spatial VAE decoder then constructs the artificial segmentation map via the latent space. In the image generator, Fernandez et al. [43] take advantage of SPADE [110], a VAE-GAN model, to build a style latent space from the input arbitrary style and use it with the artificial segmentation map to decode the output image. nnU-Net [111] was leveraged to examine the performance. Findings show that the model achieves comparable results when trained on synthetic data compared to that trained on factual data, and their combination significantly improves the model result.

Kim et al. [44] propose a novel diffusion adversarial representation learning (DARL) model for self-supervised vessel segmentation, aiming to diagnose vascular diseases. There are two main modules in the proposed DARL model: a diffusion module, which learns background image distribution, and a generation module, which generates vessel segmentation masks or synthetic angiograms using a switchable SPADE algorithm [110]. Figure 10 illustrates two ways in which this method can be applied. In path (A), a real noisy angiography image $x_{t_a}^a$ is input into the model to produce a segmentation mask \hat{s}^v , and the SPADE switch is off. In path (B), a real noisy background image $x_{t_b}^b$ is fed into the model, and the SPADE becomes active and receives a vessel-like fractal mask, generating a synthetic angiography image \hat{x}^a . Then, by giving the generated synthetic angiography images into the path (A), a cycle is formed, which helps in learning the vessel information. In addition, during inference, path (A) is performed at one step, where the model produces the mask by only inputting the noisy angiography image into the model. Results verify the generalization, robustness, and superiority of the proposed method compared to SOTA un/self-supervised learning approaches.

3.5 Image-to-Image Translation

Acquiring multi-modality images for diagnosis and therapy is often crucial. Also, we may miss modalities in some conditions. Diffusion models have shown favorable results for generating missing modalities utilizing cross-modalities and producing ones using other modality types, e.g., translating from MRI to CT.

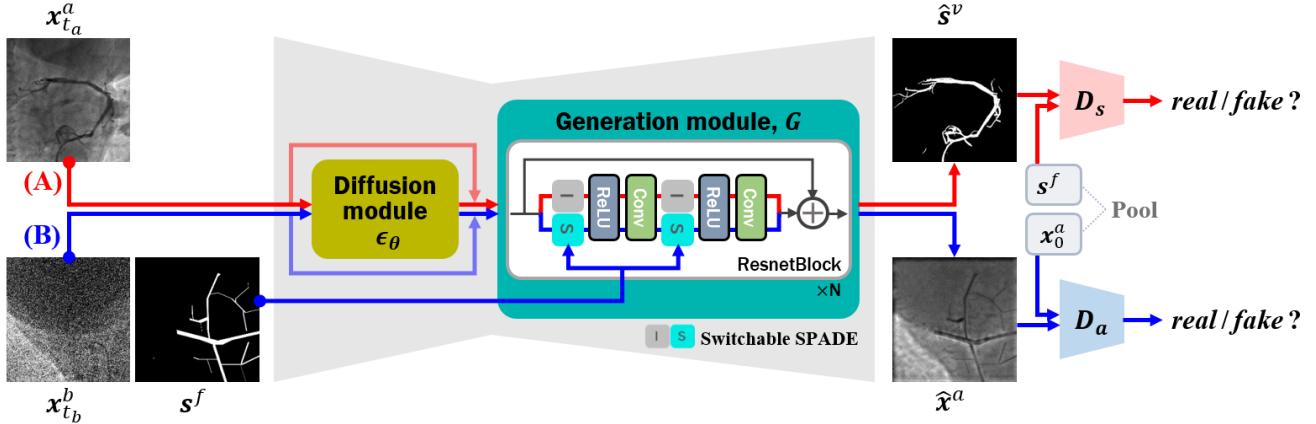


Figure 10: An overview of DARN [44]. Path (A) involves feeding a real noisy angiography image through the model to generate a segmentation map. Path (B) incorporates passing a noisy background image alongside a vessel-like fractal mask through the model to synthesize a synthetic angiography image.

CT and MRI are two of the most prevalent imaging types. CT, however, is limited in displaying the intricacies of the images for soft tissue injuries. Hence, a subsequent MRI may be needed for a conclusive diagnosis after receiving the initial CT results. Nevertheless, in addition to being time-consuming and costly, this process may also cause misalignment between MRI and CT images. To this end, Lyu et al. [32] take advantage of the recently introduced DDPMs [112, 22] and score-based diffusion models [62] in solving the translation problem between two modalities, i.e., from MRI to CT. In particular, they present conditional DDPM and conditional SDE, in which their reverse process is conditioned on T2w MRI images and conducts comprehensive experiments. The authors adopt the DDPM and SDE with three different sampling methods and compare them with the existing GAN-based [113] and CNN-based [90] methods. These three methods, which aim to solve the reverse-time SDE Equation (12), can be summarized as follows:

1. **Euler-Maruyama (EM) method:** Using a simple discretization technique in which dt is replaced with Δt and $d\bar{w}$ with Gaussian noise $z \sim \mathcal{N}(0, \Delta t \cdot I)$, Equation (12) can be solved.
2. **Prediction-Correction (PC) method:** In this method, the prediction and correction process takes place in a nested loop, in which the prior data is first predicted and then corrected in several steps. The predictor can be solved using EM. Since the corrector can be any score-based Markov Chain Monte Carlo (MCMC) method, including annealed Langevin dynamics, it can be solved utilizing Langevin dynamics in Equation (10).
3. **Probability flow ODE method:** SDE equations in Equation (11) can be written as ODE equations as follows:

$$d\mathbf{x} = \left[\mathbf{f}(\mathbf{x}, t) - \frac{1}{2} g^2(t) \nabla_x \log p_t(x) \right] dt \quad (14)$$

Hence, by solving the ODE problem, x_0 can be found. However, while ODE is a quick solver, it lacks a stochastic term to correct errors, resulting in slightly diminished performance.

Their extensive experiments on the Gold Atlas male pelvis dataset [114] demonstrate that diffusion models outperform both CNN and GAN-based methods in terms of SSIM and PNSR. Additionally, they employ the Monte Carlo (MC) method to investigate the uncertainties of diffusion models; in this technique, the model outputs ten times, and the average yields the final result. Qualitative results are depicted in Figure 11.

To cope with the missing modality issue, Meng et al. [33] propose a unified multi-modal conditional score-based generative approach (UMM-CSGM), which synthesizes the missing modality based on all remaining modalities as conditions. The proposed model is a conditional format of SDE [62], in which it employs only a score-based network to learn different cross-modal conditional distributions. Experiments on the BraTS19 dataset [73, 74, 75], which contains four MRI modalities for each subject, show that the UMM-CSGM is capable of generating missing-modality images with higher fidelity and structural information of the brain tissue compared to SOTA methods [115, 116, 117, 118, 119].

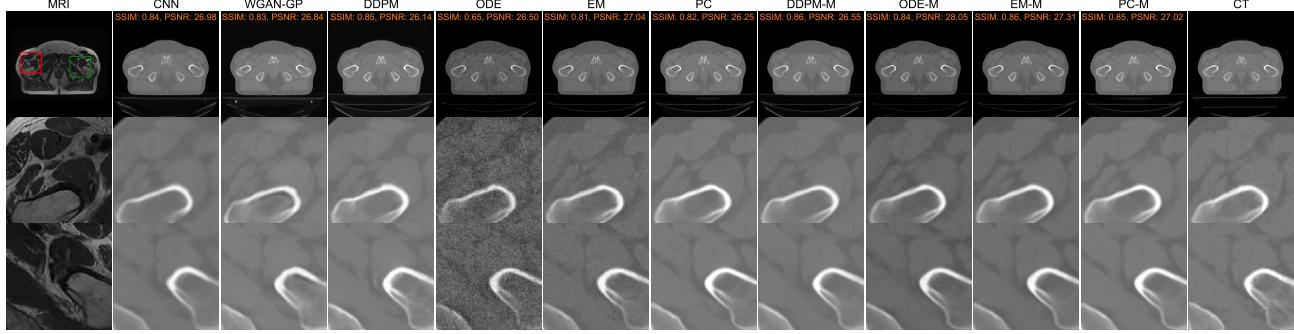


Figure 11: Visual and quantitative comparison of different methods of translating an MR image to a CT image conducted by [32]. The second and third rows indicate zoomed regions in the original image, delineated by red and green boxes. Results after applying the Monte Carlo method (taking an average from ten outputs) using DDPM, ODE, EM, and ODE sampling methods are displayed with DDPM-M, ODE-M, EM-M, and PC-M, respectively.

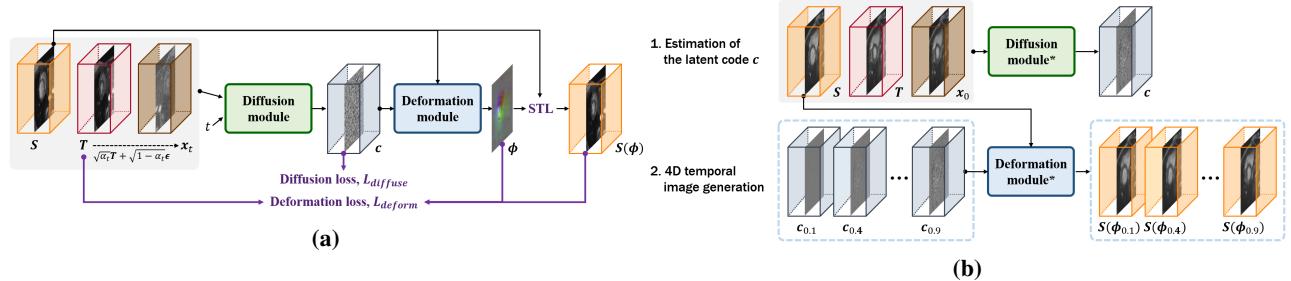


Figure 12: (a) demonstrates the DDM [52] training phase and (b) the inference phase.

3.6 Image Generation

Image generation is one of the primary objectives of diffusion models, which has been widely applied in a variety of styles, including generating synthetic 2D/3D medical images [48, 49, 51, 52], reconstructing 3D cell from 2D cell images [50], etc. This section will outline the diffusion-based approaches for medical image generation.

Using 4D imaging to follow anatomical changes is one of the methods used in medicine to track 3D volumes over time to detect anomalies and disease progression. Such 4D images are primarily obtained with MRI, but this is a relatively time-consuming process. Kim et al. [52] recently proposed the Diffusion Deformable Model (DDM), which takes source and target images and generates intermediate temporal frames along the continuous trajectory. This approach comprises two main modules: (i) a denoising diffusion probabilistic model (DDPM) module and (ii) a deformation module. In the DDPM module, a latent code is constructed by learning the source and target images, and in the deformation module, the acquired latent code and the source image are used to render the deformed image. In the training phase, as shown in Figure 12a, the diffusion model, derived from [22], takes source, target, and perturbed target images and outputs a latent code. The learned latent code along the source image is fed into the deformation module, adopted from [120], and creates deformation fields. Then, the spatial transformation layer (STL) [121], with tri-linear interpolation, is employed to warp the source volume using the deformation fields in order to build the deformed source image. Afterward, inference begins with the diffusion module providing the latent code, which contains spatial information from the source toward the target (see Figure 12b). Then, deformed intermediate frames are generated using the deformation module by scaling the latent code with a factor, which is an element of $[0, 1]$.

Histopathology involves the study of tissues and cells at the microscopic level in order to diagnose diseases and cancer [123]. Histology images, however, are rare for some cancer subtypes, thereby increasing the significance of generative models to fill the void. To this end, Moghadam et al. [49] investigate adopting DDPMs for generating histopathology images for the first time. Specifically, they exploit the DDPMs with genotype guidance to synthesize images containing various morphological and genomic information. To tackle this data consistency problem and enforce the model to focus more on morphological patterns, they first feed input images into a color normalization module [124] to unify the domain of all images. In addition, they apply a morphology levels prioritization module [125] that designates higher weight values to the loss at earlier levels to emphasize perceptual information and lower weights to the loss at later levels, resulting in higher

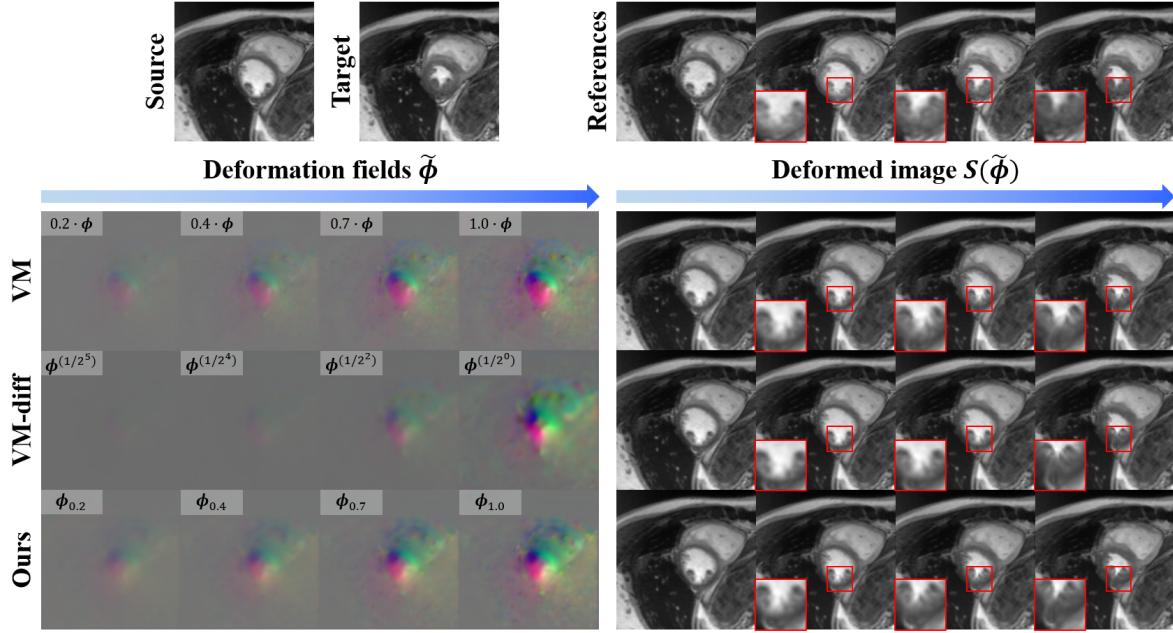


Figure 13: Visual comparison of DDM [52], VM [120], and VM-Diff [122] for generating temporal cardiac images. The deformed intermediate frames $S(\tilde{\phi})$ (right) are constructed using the source and target, and produced the deformation fields $\tilde{\phi}$ (left).

fidelity samples. Experiments on the Cancer Genome Atlas (TCGA) dataset [126] exhibit the superiority of the proposed method compared to GAN-based approaches [127].

3.7 Other Applications and Multi-tasks

Based on Figure 4, there are still studies that could not be assigned to a particular category, and the use of diffusion is not limited to those six categories. Multi-scale DDAM [56] utilizes DDPM [22] for designing a neutralizing concept for adversarial attacks by Gaussian noise. Diffusion models are not limited to vision-related tasks in the medical domain and can be an innovation in biology. The platforms presented in [57, 128] can be used for designing drugs and vaccines. In the following paragraphs, we explore some of the recent diffusion-based approaches used in multi-task learning and distinctive uses in the medical domain.

Un/self-supervised learning is an ideal alternate approach in medical image denoising, where accessing paired clean and noisy images is difficult to achieve [129, 130]. Conventional deep-based networks utilize Minimum Mean Square Error (MMSE) estimates, which lead to unsatisfactory and blurred images due to the distribution change in train/test data or the preliminary assumption of Gaussian noise is at odds with the data's actual distribution. Chung et al. [58] proposed a multi-successive paradigm for MRI image denoising and super-resolution, namely R2D2+, with the SDE [62] algorithm to tackle the mentioned deficiencies. Diffusion generative models are robust to any distribution change over the data and produce more realistic data [23]. Despite the advantages of diffusion models, they are very time-consuming. To this end, Chung et al. [58] do not start the reverse diffusion process from the pure noise but start from the initial noisy image. R2D2+ [58] solves a reverse time SDE procedure with a non-parametric estimation method based on eigenvalue analysis of covariance matrix rather than the conventional numerical methods [62]. To restrain structure alleviation through the process, R2D2+ uses a low-frequency regularization to hamper any change in the low-frequency counterparts of the image. R2D2+ utilizes the same network for the super-resolution task after the denoising step. The overall results over the single coiled fastMRI [98] knee dataset and private liver MRI dataset indicate the superiority of this approach over conventional SOTA un/self-supervised learning schemes in terms of SNR and Contrast-to-Noise Ratio (CNR) metrics.

Pinaya et al. [59] propose a fast DDPM-based approach for detecting and segmenting anomalous regions in the brain MR images (see Figure 14). This method follows the strategy of generating a healthy sample and delineating the anomaly segmentation map by subtracting it from the input image. To this end, VQ-VAE [131] is first adopted following [82], which encodes the input images into a compact latent representation and provides the quantized latent representation from input images utilizing a codebook. The DDPM then uses the acquired latent space and learns the distribution of the latent representation of the healthy samples. A binary mask indicating the location of the anomaly is constructed by applying a

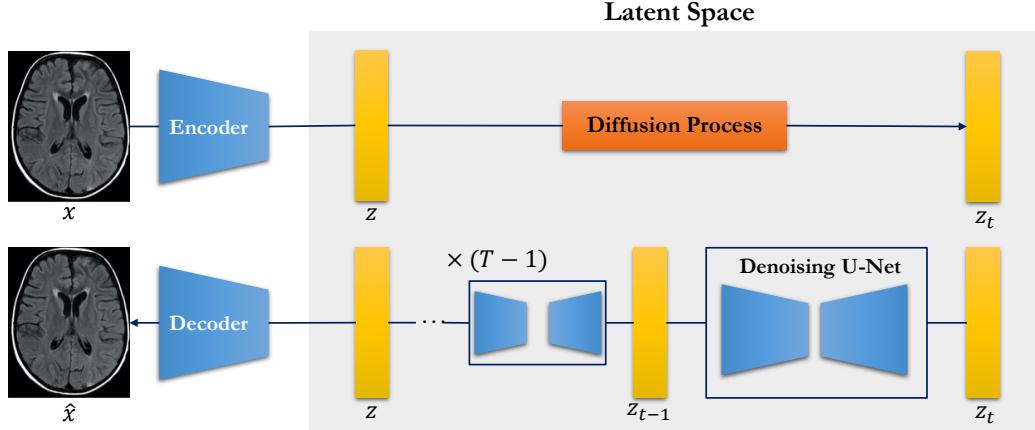


Figure 14: An overview of BAoDDPM [59]. An autoencoder compresses the input image into a latent code, further enhanced by applying diffusion and reverse processes, and decodes into the pixel space.

pre-calculated threshold on the average of intermediate samples of the reverse process, which contain less noisy and more distinct values. Using the middle step as the starting point for the reverse process, they denoise the anomalous areas of the image and preserve the rest using the obtained mask, thereby removing the lesion from the sample. Eventually, upon decoding the sample, a healthy image is produced.

3.8 Comparative Overview

Table 1 comprehensively categorizes the reviewed diffusion model papers according to which algorithm they directly used or inspired: (1) DDPMs, (2) NCSNs, and (3) SDEs. In addition, **Table 1** highlights the key concepts and objectives of each algorithm and represents the practical use cases that can be investigated and utilized in future research based on reviewed papers.

It is evident that conditioning the reverse diffusion process is one of the most studied methods for obtaining the desired output. This guiding process can be done using different constraint types. In [32, 36, 50], they control the reverse process by applying conditions using images; in particular, Lyu et al. [32] condition the DDPM and SDE utilizing T2w MR images to obtain CT images, Xie et al. [36] propose measurement-conditioned DDPM constituted for under-sampled medical image reconstruction, and Waibel et al. [50] constrain the 3D model using 2D microscopy images for generating 3D single cell shapes. Moreover, BrainGen [39] produces realistic examples of brain scans, which are conditioned on meta-data such as age, gender, ventricular volume, and brain volume relative to intracranial volume. In addition, the use of a classifier and implicit guidance methods in [28] and [54] have been investigated thoroughly. In this way, the distribution is shifted in a manner that is more likely to reach the expected outcome.

Some of the primary concerns and limitations of diffusion models are their slow speed and required computational cost. Several methods have been developed to address these drawbacks. Training-free Denoising Diffusion Implicit Model (DDIM) [72] is one of the advancements designed to accelerate the sampling process. DDIM extends the DDPM by substituting the Markovian process with the non-Markovian one, resulting in a faster sampling procedure with negligible quality degradation. [132, 133] propose a suitable initialization instead of a random Gaussian noise in the reverse process, causing a significant acceleration. Specifically, Chung et al. [133] prove that, based on stochastic contraction theory, beginning the reversion, for example, after one step prediction of the pre-trained neural network, fastens the reverse diffusion and reduces the number of reverse samplings. Dar et al. [39] also verify that adversarial learning can boost reverse diffusion speed by two orders of magnitude.

Several methods have also been worked on to enhance the output quality of diffusion models. AnoDDPM [53] substantiates that generalization to other types of noise distributions can enhance task-specific quality. They ascertain that in the case of anomaly detection, Simplex noise shows superiority over Gaussian noise. Furthermore, Cao et al. [132] corroborate that operating the diffusion process only in the high-frequency part of the image improves the stability and quality of the MRI reconstruction.

With their remarkable results, diffusion models have proven that they can be a powerful competitor against other generative models, as an examination of [Figure 15](#) reveals the promising future of this field in the academic environment.

Table 1: Overview of the reviewed diffusion models for medical image analysis based on their algorithm choice presented in our taxonomy, [Figure 4](#). The symbol * indicates that the mentioned paper explores both DDPM and SDE algorithms.

| Algorithm | Networks | Core Ideas | Practical Use Cases |
|--|--|---|---|
| Denoising Diffusion Probabilistic Models (DDPMs) | ¹ AnoDDPM [53] ² CDPM [54] ³ IITM-Diffusion [55] ⁴ AnoDDIM [28] ⁵ PET-DDPM [46] ⁶ DenoOCT-DDPM [47] ⁷ brainSPADE [43] ⁸ DARL [52] ⁹ IISE [45] ¹⁰ *MT-Diffusion [32] ¹¹ SynDiff [34] ¹² MC-DDPM [36] ¹³ DiffuseRecon [38] ¹⁴ AdaDiff [48] ¹⁵ BrainGen [39] ¹⁶ MFDDPM [49] ¹⁷ DISPR [50] ¹⁸ 3D-DDPM [51] ¹⁹ DDM [52] ²⁰ Multi-scale DDAM [56] ²¹ SMCDiff [57] ²² BAanoDDPM [59] ²³ DiffuseMorph [134] ²⁴ 20x-DenoDDPM [135] | In DDPMs [22], the forward diffusion process is represented as a Markov chain in which Gaussian noise is gradually added to the data. Data generation is then accomplished using the attained pure random noise and begins iterative denoising through a parametrized reverse process. Unlike VAE, where both the encoder and decoder are trained, only a single network is trained during the reverse process, and the forward process is considered fixed. An objective function of DDPMs is to simulate noise, which means that given a noisy input image, the neural network will produce the distribution modeled as normal distribution and indicate where the noise originates. | <ul style="list-style-type: none"> Generalization to other types of noise distributions [53] Facilitating diffusion process via implicit guidance [54] Acceleration improvement using training-free DDIM sampling [55, 28] Guiding diffusion process via classifier guidance [28] Conditional DDPMs [46, 32, 36, 50, 135, 57] Generating synthetic segmentation datasets [43, 44] Cross-modality translation [34] Multi-modal conversion [32, 34] Exploiting K-space parameter-free guidance [38] Accelerate MC sampling using coarse-to-fine sampling [38] Adversarial learning in the reverse diffusion process [39, 34] 3D reconstruction from 2D images [50] Conditioning on medical meta-data [48] Using LDM to enhance the training and sampling efficiency [48, 59] DDPMs for histopathology images [49] 3D medical image generation [51] Using deformation fields for medical image generation [134, 52] DDPMs in skin image adversarial attacks [56] |
| Noise Conditioned Score Networks (NCSNs) | ¹ CSGM-MRI-Langevin [96] ² Self-Score [41] | In this algorithm [61], creating samples requires solving the Langevin dynamics equation. However, this equation mandates the solution of the gradient of the log density w.r.t. the input, $\nabla_x \log p(x)$, which is unknown and intractable. NCSN formulates the forward diffusion process by disturbing the data with Gaussian noise at different scales. Through this approach, this equation can be solved by training a single score network conditioned on the noise level and modeling the scores at all noise levels. Therefore, using the annealed Langevin dynamics algorithm and estimated score function at each scale, data can be generated. | <ul style="list-style-type: none"> Using Langevin dynamics with different random initializations to get multiple reconstructions [96] Using conditioned Langevin Markov chain Monte Carlo (MCMC) sampling [41] Utilizing K-space data [41] |
| Stochastic Differential Equations (SDEs) | ¹ *MT-Diffusion [32] ² UMM-CSGM [33] ³ SIM-SGM [35] ⁴ Score-MRI [37] ⁵ MRI-DDMC [40] ⁶ MCG [42] ⁷ HFS-SDE [132] ⁸ Diffuse-Faster [133] ⁹ HKGM [136] ¹⁰ WKGM [137] ¹¹ R2D2+ [58] | <p>As in the cases of DDPMs and NCSNs, SDEs [62] follow a similar approach in the forward diffusion process, in which the input data is perturbed consecutively utilizing Gaussian noise. In contrast, previous probabilistic models can be viewed as discretizations of score-based models by extending the number of noise scales to infinity and treating them as continuous.</p> <p>Having operated backward in time, the reverted SDE Process solves the reverse-time Stochastic Differential Equation and recovers the data. Even so, each time step of this process requires the score function of the density. SDEs are, therefore, intended to learn the actual score function via a neural network and construct samples using numerical SDE solvers.</p> <p>Any numerical method can be adopted to solve the reverse-time SDE equation. In particular, three notable sampling methods are named and described in Section 3.5: Euler-Maruyama (EM) method, Prediction-Correction (PC), and Probability Flow ODE. EM follows a simple strategy, PC generates more high-fidelity samples, and Probability Flow ODE is fast and efficient.</p> | <ul style="list-style-type: none"> SDEs achieve better results in multi-modal conversion [32] Cross-modality translation [33] Conditional SDEs [33, 38, 42] Solving linear inverse problems [35] Using K-space data [136, 137] Using manifold constraints [42] Good initialization in the reverse process instead of random Gaussian noise leads to a faster convergence [133, 132] Diffusion only in high-frequency space increases the stability and quality [132] |

4 Future Direction and Open Challenges

Diffusion models are becoming a popular topic in medical vision and medical-biology fields; evidence shows an upward trend in [Figure 3](#). Due to the lack of such data in this field, diffusion processes do not need a pair of labeled or not labeled data, making them a strong candidate in medical image analysis. This paper gathered the latest medical-related papers and investigated numerous of them based on the taxonomy proposed in [Figure 4](#) to demonstrate the power of diffusion models. We hope this review sheds light on the emergence of diffusion models in the medical field and serves as a guide for readers. Thus, in this section, we highlight the open directions for future investigations. In addition, due to the nature of diffusion models, they are a strong candidate for denoising medical images in diverse modalities. Still, a limited number of studies address this concern (see [Section 3.2](#)), rendering it suitable for further research. For clarification, sonography uses a high frequency to view inside a body, thus the transmitted ultrasound beams weaken as they penetrate the tissue. Moreover, Radio-Frequency (RF) data contains an additive Gaussian noise which is brought about by the acquisition card and the sensor noise [139]. Therefore, diffusion models could compensate for the drawbacks of sonography imaging technology

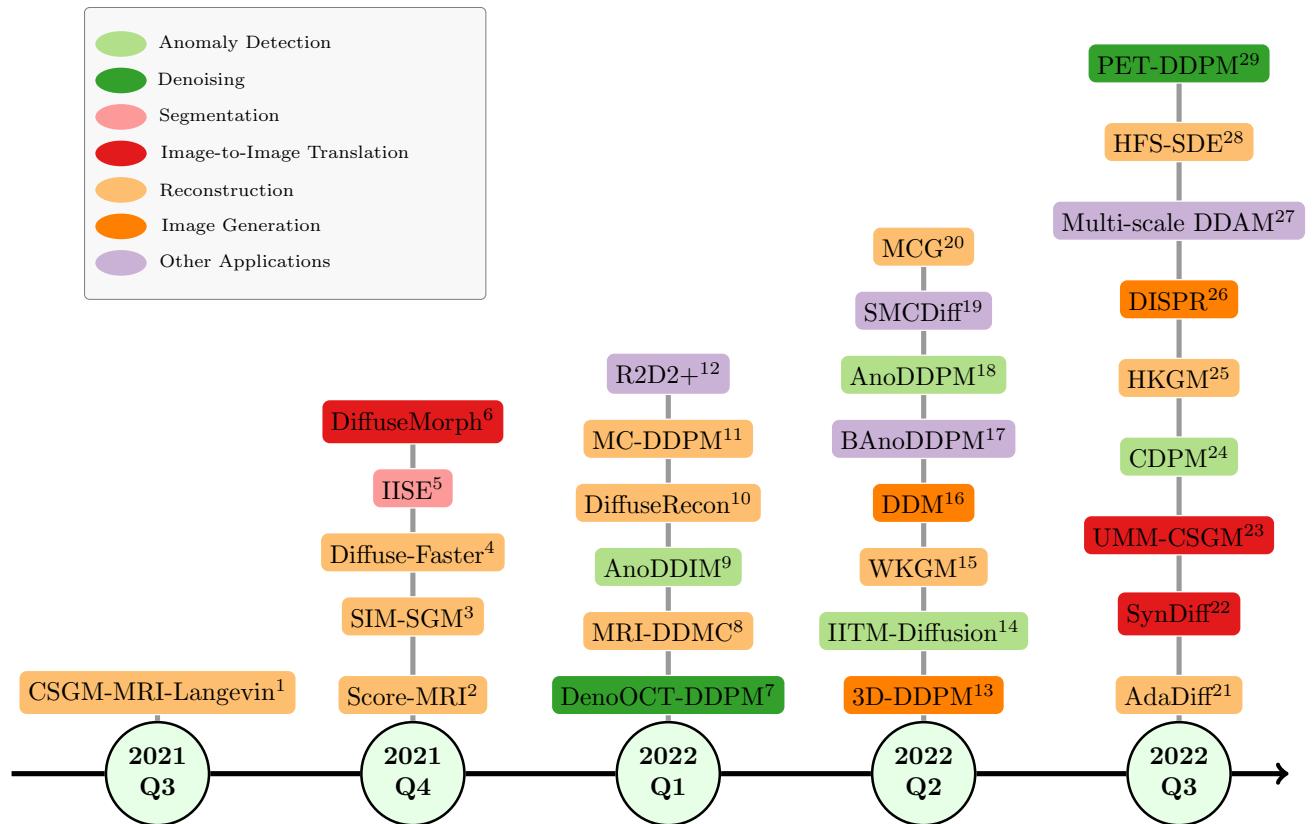


Figure 15: Diffusion models timeline from 2021 to 2022-Q3 through the first paper in the medical field. The superscripts in ascending order represent 1.[96], 2.[37], 3.[35], 4.[133], 5.[45], 6.[134], 7.[47], 8.[40], 9.[28], 10.[38], 11.[36], 12.[58], 13.[51], 14.[55], 15.[137], 16.[52], 17.[59], 18.[53], 19.[57], 20.[42], 21.[39], 22.[34], 23.[33], 24.[54], 25.[136], 26.[50], 27.[56], 28.[132], 29.[46], respectively.

practically instead of utilizing the conventional methods, e.g., increasing the power of transmitted beams that control by safety threshold, averaging successive frames to hinder the noise effect that causes a low frame rate and decreasing the transmitting frequency that slumps the spatial resolution.

Diffusion models generally suffer from deficiencies that are probably transferred to early-stage medical-based studies. First, diffusion models are time-consuming processes that originate from performing iterative steps at inference time to generate a sample. Second, most of the works paid attention to Gaussian noise distribution through the diffusion models and neglected other perturbations, e.g., Poisson noise which is the most probable distribution in imaging modalities such as PET [140]. Efforts in facilitating the mentioned limitations could be a direction of research in the medical domain with diffusion models.

Due to privacy concerns in medical imaging, which limit data integration, diffusion models along with federated learning can create a profound and robust learning platform in the medical domain. In addition, due to the same privacy concerns, diffusion models can consolidate their steps in generating synthetic medical data for educational purposes. The inverse problem-solving of the diffusion models could be performed by the reinforcement learning paradigm to estimate the best inversion path rather than solid mathematical solutions. Diffusion models become a cornerstone in text-to-image tasks [80, 141]. However, the reverse problem, image-to-text, is still in its early stages [142], which is a promising direction for research to produce comprehensive texts such as transcripts from medical images as assistive information for physicians. Exploiting conditional diffusion models for using meta-data like CT images in the analysis of MRI, and PET could be another deviation of the diffusion research in the medical field. Finally, due to the wide use of diffusion models in diverse medical tasks (as we studied during this survey), it would be remarkable to create software ecosystems that contain diffusion models for these tasks analogous to primitive studies such as nnU-Net [111] and Ivadomed [143]. In Figure 16, we depict the simple proposal ecosystem on a small scale within a specific healthcare establishment, i.e., a hospital. The first step of this pipeline starts with data acquisition within the diverse imaging systems in the organization. Afterward, by applying preprocessing steps, the data is stored in the data centers to share with diffusion-based software for desired purposes.

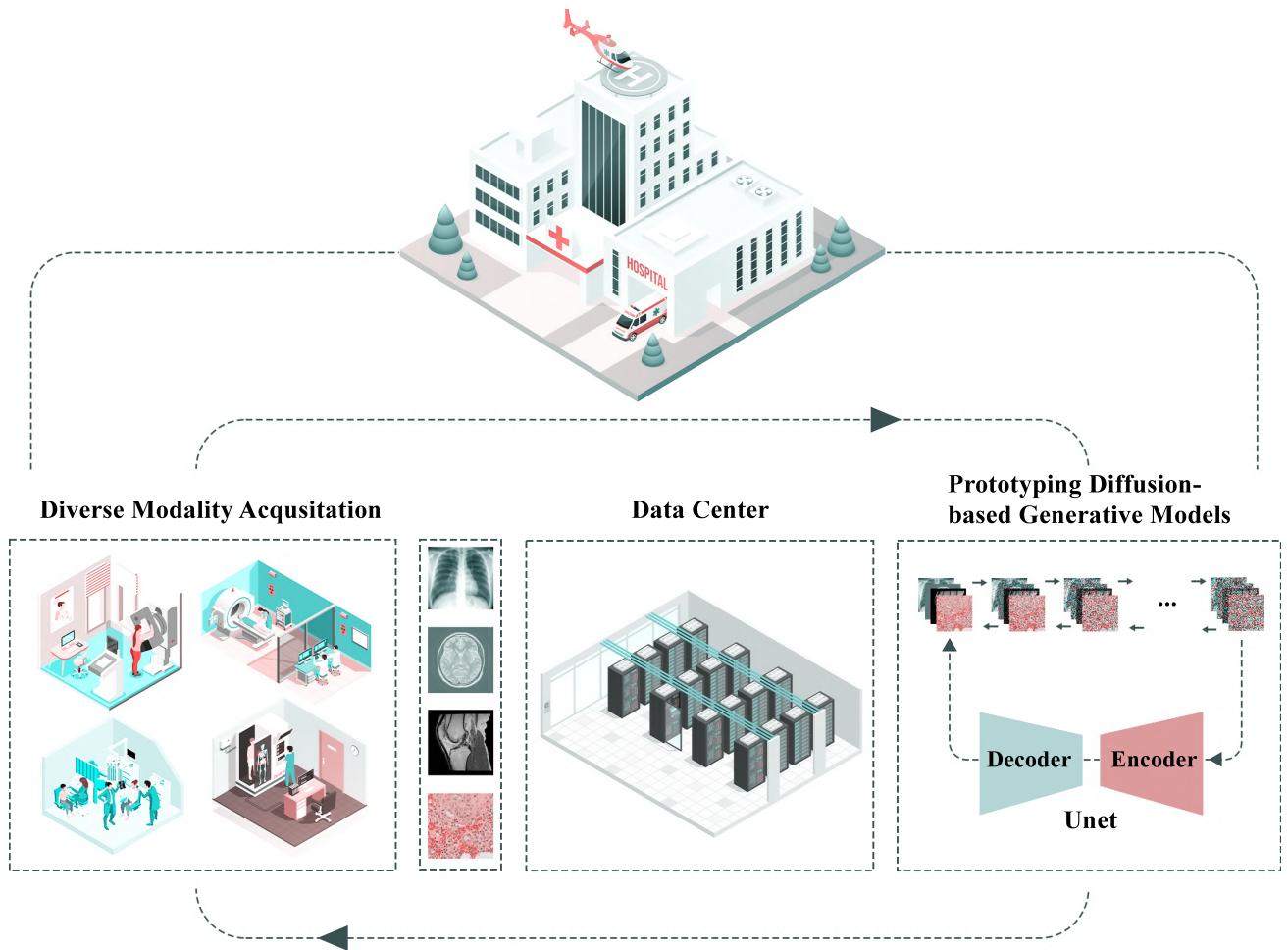


Figure 16: Simple diffusion-based ecosystem in the medical domain. Some of the image elements are designed by Freepik® [138].

5 Conclusion

In this paper, we provided a survey of the literature on diffusion models with a focus on applications in the medical imaging field. Specifically, we investigated the applications of diffusers in anomaly detection, medical image segmentation, denoising, classification, reconstruction, synthesis, generation, and other tasks. In particular, for each of these applications, we provided a taxonomy and high-level abstraction of the core techniques from various angles. Moreover, we characterized the existing models based on techniques where we identified three primary formulations of diffusion modeling based on: DDPMs, NCSNs, and SDEs. Finally, we outlined possible avenues for future research.

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