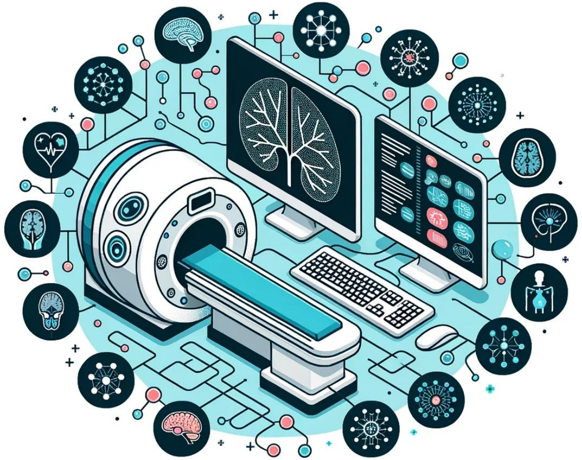
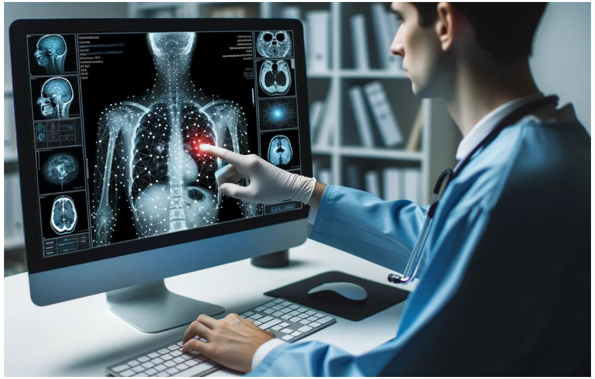
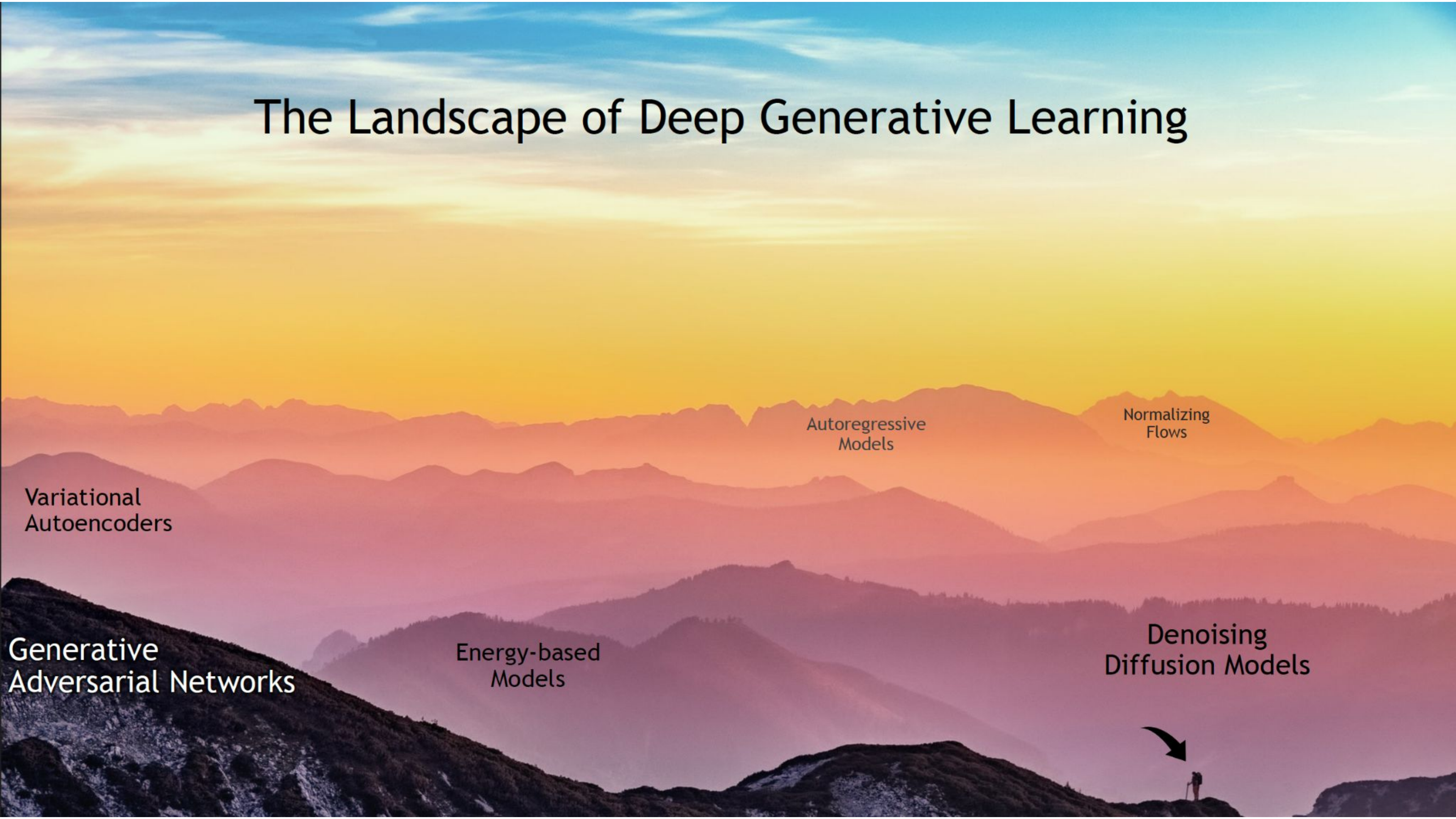
Applied Deep Learning and Generative Models in Healthcare





Session 5: Medical Image Synthesis with Diffusion
Date: Mar 08 2025

Instructor: Mahmoud E. Khani, Ph.D.


The Landscape of Deep Generative Learning
Autoregressive Models
Normalizing Flows
Variational Autoencoders
Generative Adversarial Networks
Energy-based Models
Denoising Diffusion Models

Denoising Diffusion Models

“Diffusion Models Beat GANs on Image Synthesis”
Dhariwal & Nichol, OpenAI, 2021

“Cascaded Diffusion Models for High Fidelity Image Generation”
Ho et al., Google, 2021

Text-to-Image Generation

DALL·E 2

"a teddy bear on a skateboard in times square"

"Hierarchical Text-Conditional Image Generation with CLIP Latents"
Ramesh et al., 2022

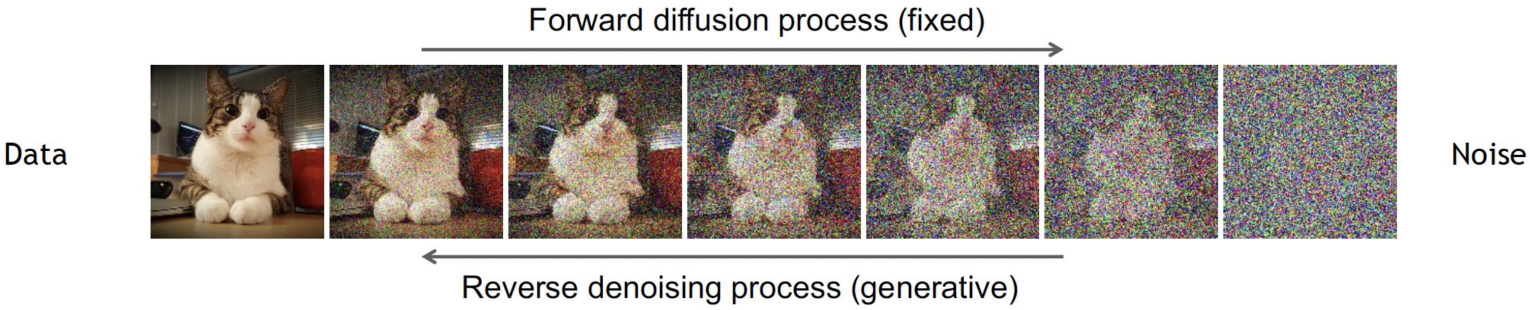
Imagen

A group of teddy bears in suit in a corporate office celebrating the birthday of their friend. There is a pizza cake on the desk.

"Photorealistic Text-to-Image Diffusion Models with Deep Language Understanding", Saharia et al., 2022

Learning to Generate by Denoising

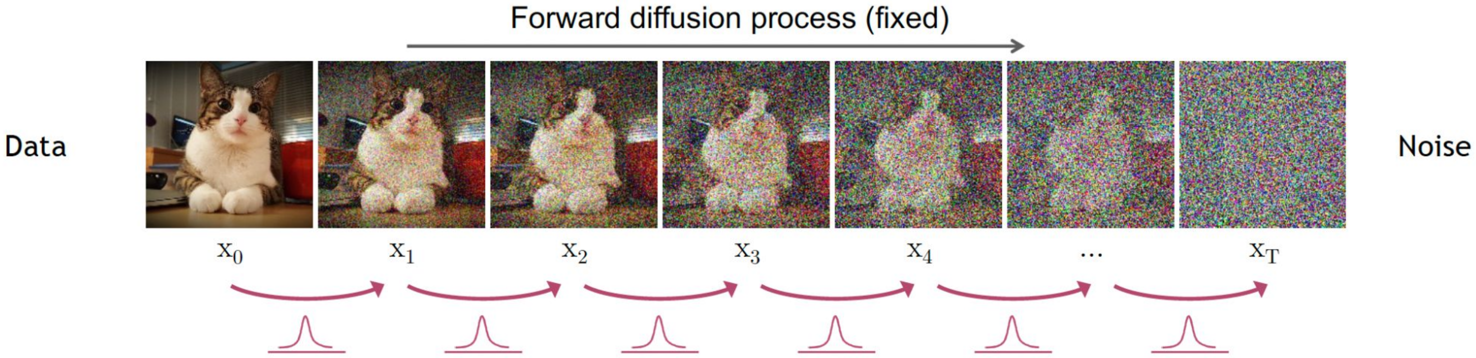
- **Denoising diffusion consists of two processes:**
  - Forward diffusion to gradually add noise to input
  - Reverse denoising that learns to generate data by denoising



Sohl-Dickstein et al., Deep Unsupervised Learning using Nonequilibrium Thermodynamics, ICML 2015
Ho et al., Denoising Diffusion Probabilistic Models, NeurIPS 2020
Song et al., Score-Based Generative Modeling through Stochastic Differential Equations, ICLR 2021

Forward Diffusion Process

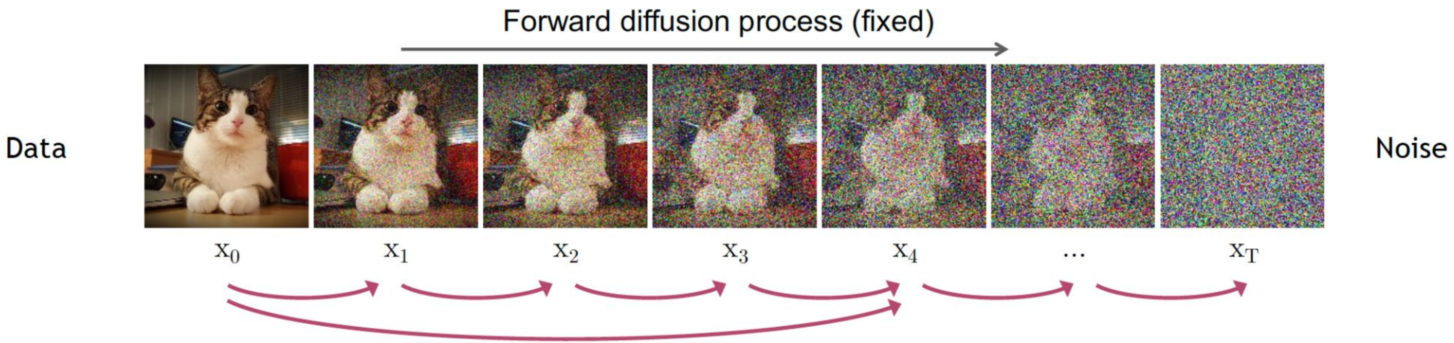
- **The formal definition of the forward process in T steps:**



$$q(\mathbf{x}_t|\mathbf{x}_{t-1}) = \mathcal{N}(\mathbf{x_t}; \sqrt{1-\beta_t}\mathbf{x_{t-1}}, \beta_t\mathbf{I}) \quad \Rightarrow \quad q(\mathbf{x}_{1:T}|\mathbf{x}_0) = \prod_{t=1}^{T} q(\mathbf{x}_t|\mathbf{x}_{t-1})$$

(joint)

Diffusion Kernel



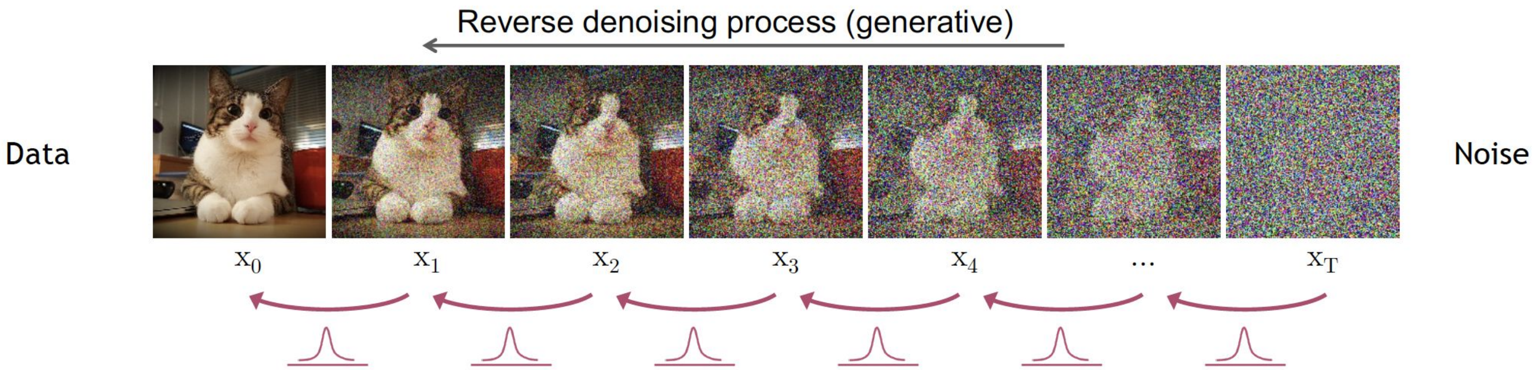
Define $\bar{\alpha}_t = \prod_{s=1}^{t}(1-\beta_s)$ $\Rightarrow$ $q(\mathbf{x}_t|\mathbf{x}_0) = \mathcal{N}(\mathbf{x}_t; \sqrt{\bar{\alpha}_t}\mathbf{x}_0, (1-\bar{\alpha}_t)\mathbf{I}))$ (Diffusion Kernel)

For sampling: $\mathbf{x}_t = \sqrt{\bar{\alpha}_t}\,\mathbf{x}_0 + \sqrt{(1-\bar{\alpha}_t)}\,\epsilon$ where $\epsilon \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$

β_t values schedule (i.e., the noise schedule) is designed such that $\bar{\alpha}_T \to 0$ and $q(\mathbf{x}_T|\mathbf{x}_0) \approx \mathcal{N}(\mathbf{x}_T; \mathbf{0}, \mathbf{I}))$

Reverse Denoising Process

- **Formal definition of reverse process in T steps:**



$$p(\mathbf{x}_T) = \mathcal{N}(\mathbf{x}_T; \mathbf{0}, \mathbf{I})$$

$$p_\theta(\mathbf{x}_{t-1}|\mathbf{x}_t) = \mathcal{N}(\mathbf{x}_{t-1}; \underbrace{\mu_\theta(\mathbf{x}_t, t)}_{\substack{\text{Trainable network} \\ \text{(U-net, Denoising Autoencoder)}}}, \sigma_t^2\mathbf{I})$$

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

Training and Sampling Algorithms

Algorithm 1 Training

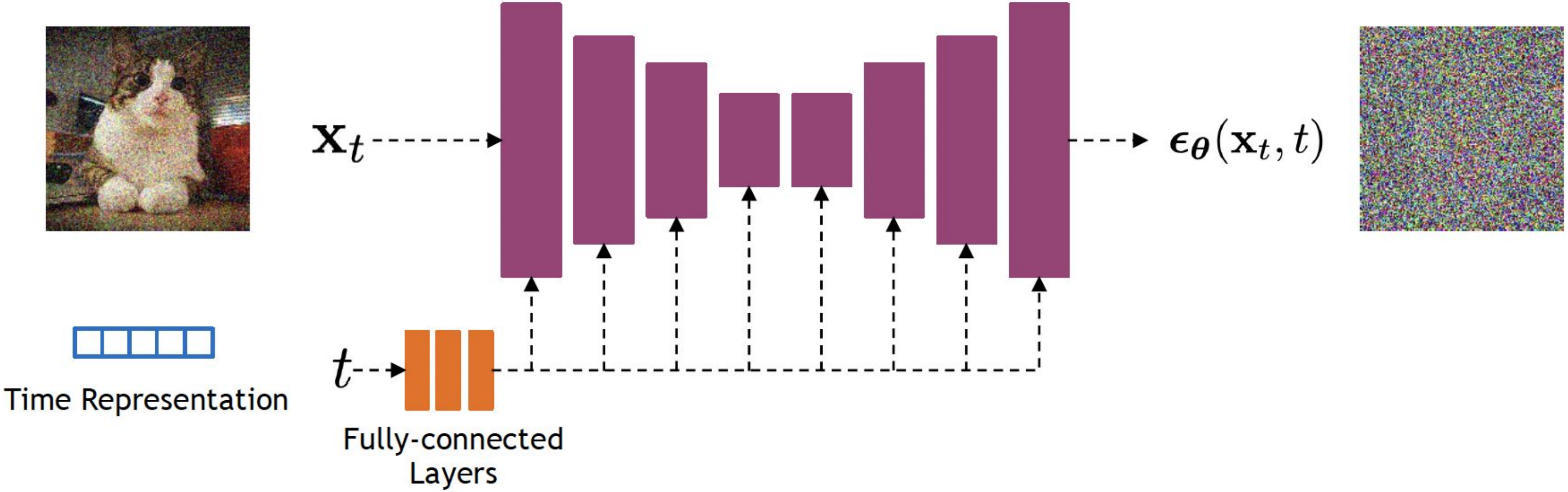
repeat
  $\mathbf{x}_0 \sim q(\mathbf{x}_0)$
  $t \sim \mathrm{Uniform}(\{1, \ldots, T\})$
  $\boldsymbol{\epsilon} \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$
  Take gradient descent step on
  $$\nabla_\theta \left\| \boldsymbol{\epsilon} - \boldsymbol{\epsilon}_\theta(\boxed{\sqrt{\bar{\alpha}_t}\mathbf{x}_0 + \sqrt{1-\bar{\alpha}_t}\boldsymbol{\epsilon}}, t) \right\|^2$$
until converged

Algorithm 2 Sampling

$\mathbf{x}_T \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$
for $t = T, \ldots, 1$ **do**
  $\mathbf{z} \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$
  $$\mathbf{x}_{t-1} = \boxed{\frac{1}{\sqrt{\alpha_t}}\left(\mathbf{x}_t - \frac{1-\alpha_t}{\sqrt{1-\bar{\alpha}_t}}\boldsymbol{\epsilon}_\theta(\mathbf{x}_t, t)\right)} + \sigma_t \mathbf{z}$$
end for
return $\mathbf{x}_0$

Network Architectures

- **Diffusion models often use U-Net architectures with ResNet blocks and self-attention layers**



Time representation: sinusoidal positional embeddings or random Fourier features.

Diffusion Parameters

- **The noise schedule**

$$q(\mathbf{x}_t|\mathbf{x}_{t-1}) = \mathcal{N}(\mathbf{x_t}; \sqrt{1-\beta_t}\mathbf{x_{t-1}}, \beta_t\mathbf{I})$$

Data

Noise

$$p_\theta(\mathbf{x}_{t-1}|\mathbf{x}_t) = \mathcal{N}(\mathbf{x}_{t-1}; \mu_\theta(\mathbf{x}_t, t), \sigma_t^2\mathbf{I})$$

Above, β_t and σ_t^2 control the variance of the forward diffusion and reverse denoising processes respectively.

Often a linear schedule is used for β_t, and σ_t^2 is set equal to β_t.

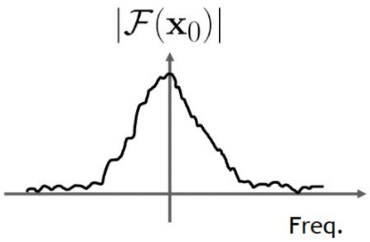
Fourier Analysis of the Forward Process

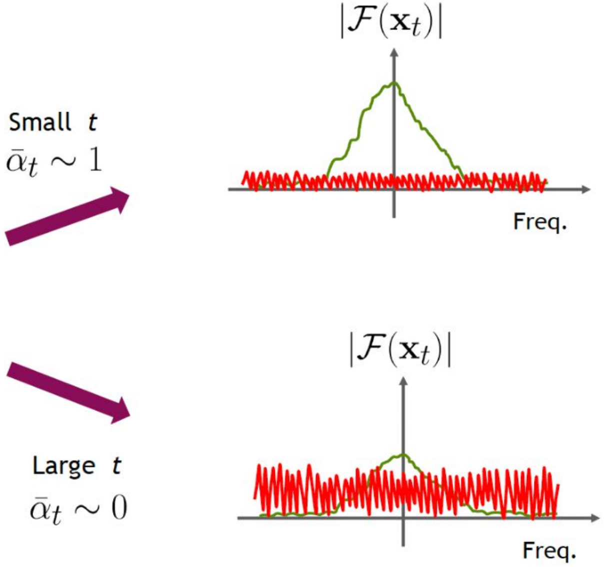
Recall that sampling from $q(\mathbf{x}_t|\mathbf{x}_0)$ is done using $\mathbf{x}_t = \sqrt{\bar{\alpha}_t}\ \mathbf{x}_0 + \sqrt{(1-\bar{\alpha}_t)}\ \epsilon$ where $\epsilon \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$

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

$$\Big\downarrow \text{ Fourier Transform}$$

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

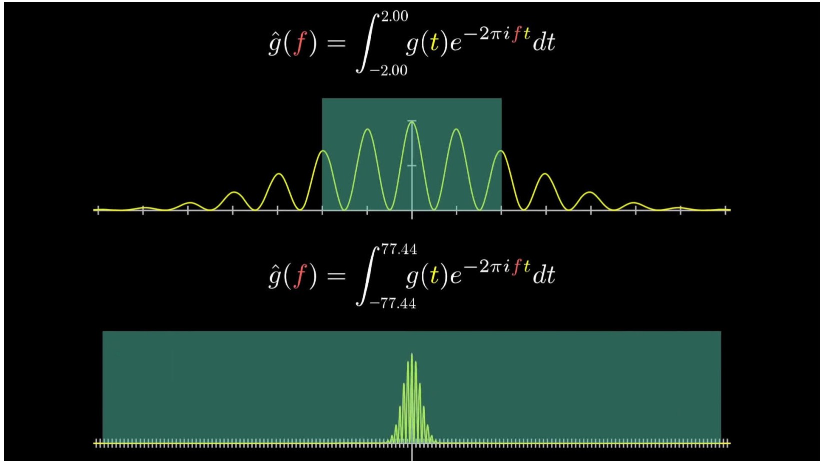


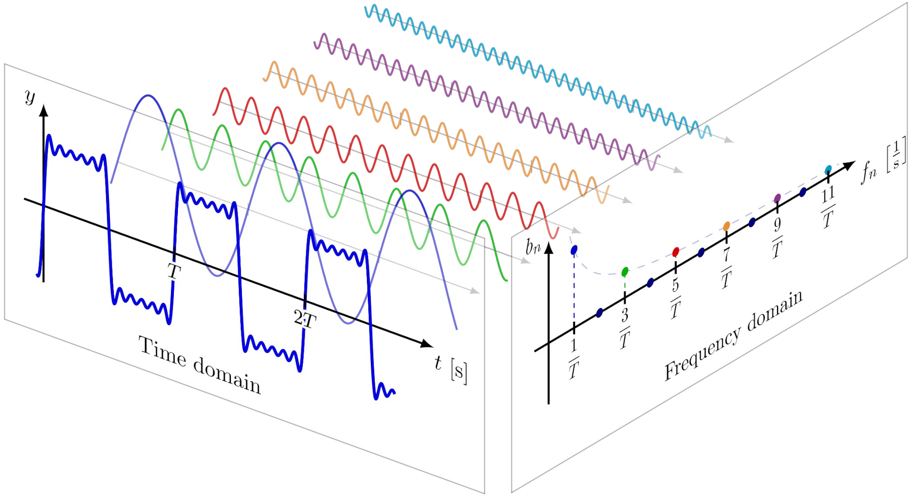


In the forward diffusion, the high frequency content is perturbed faster.

Fourier Analysis

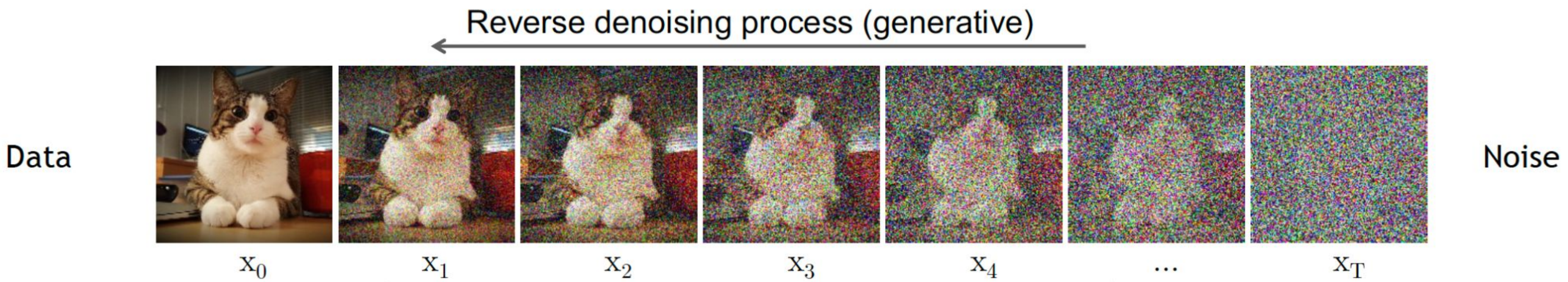
- **Decomposition of signal into frequency components**





https://dibsmethodsmeetings.github.io/fourier-transforms/

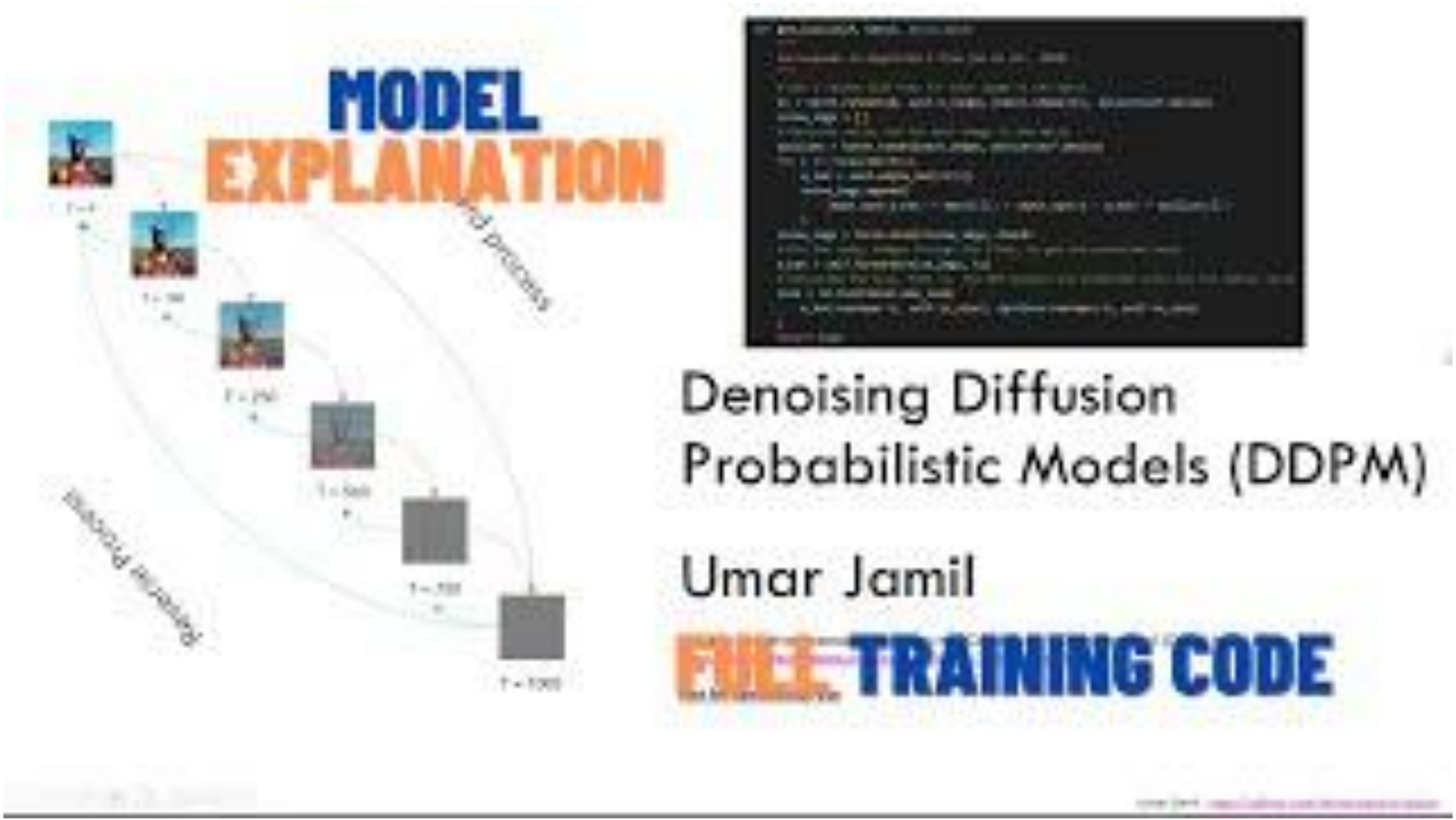
Content-Detail Tradeoff



The denoising model is specialized for generating the high-frequency content (i.e., low-level details)

The denoising model is specialized for generating the low-frequency content (i.e., coarse content)

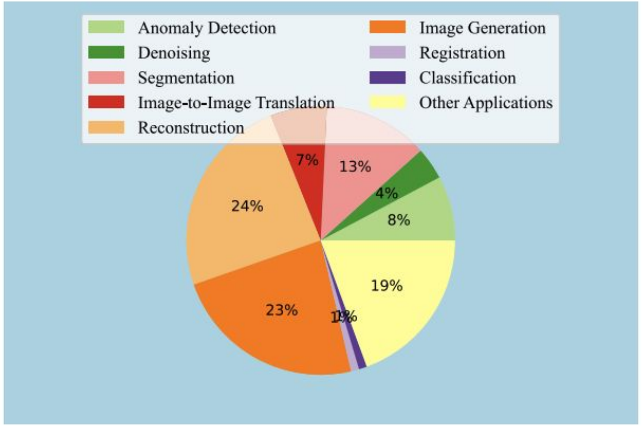
The weighting of the training objective for different timesteps is important!

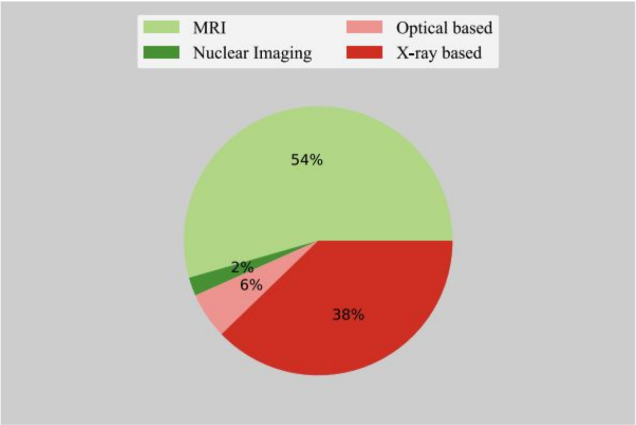


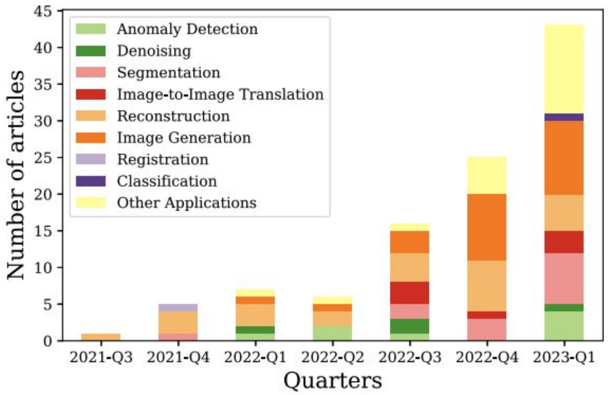
https://youtu.be/I1sPXkm2NH4?si=8wMzGKPii936tvlU

Diffusion Models in Medical Imaging

- **Diffusion models have emerged as powerful generative models in medical imaging**
  - improved sample quality, mode coverage, and versatility across various applications.



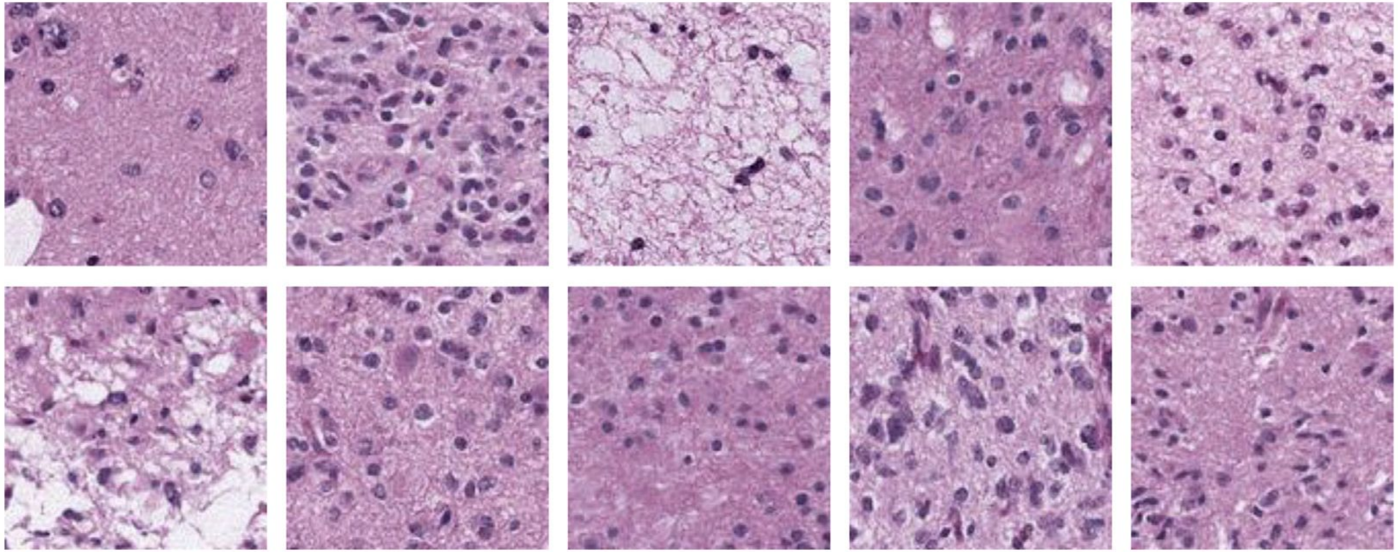




https://www.sciencedirect.com/science/article/pii/S1361841523001068

Applications in medical image generation

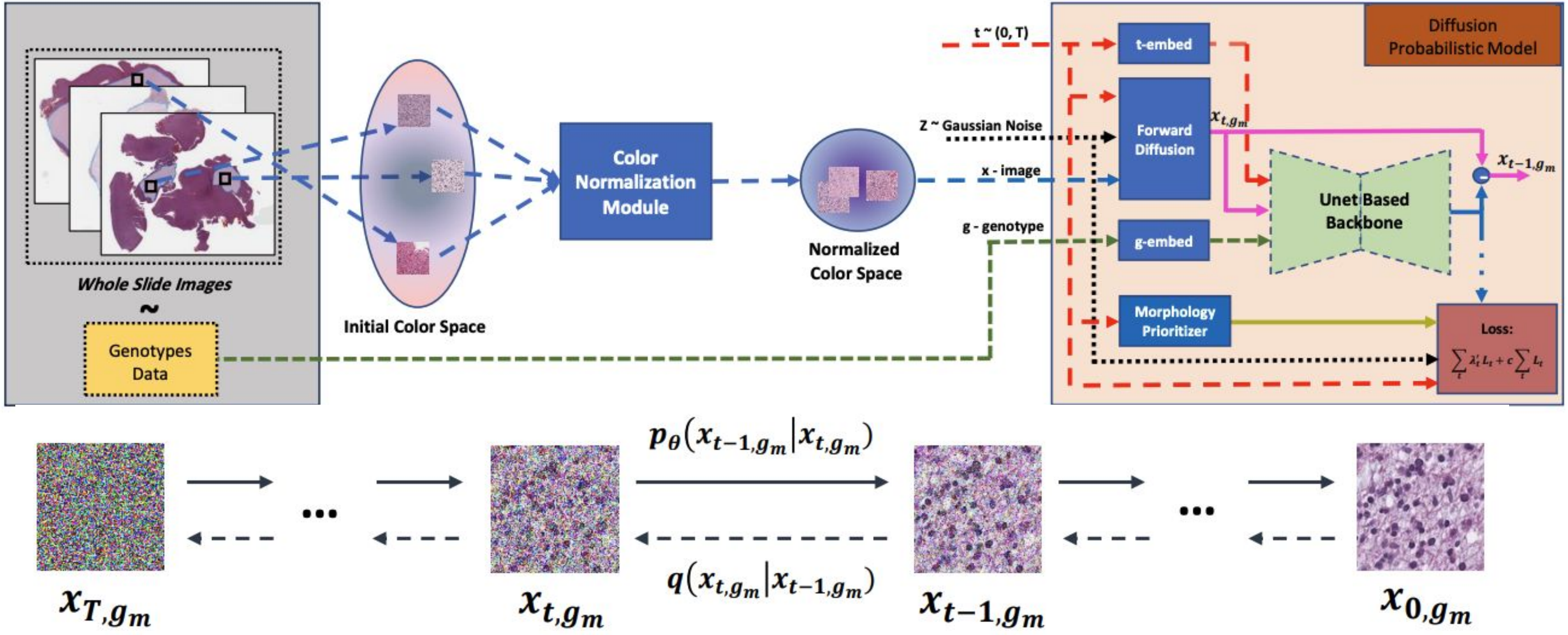
- **Diffusion models have remarkable performance in generating synthetic medical images**
    - aiding data augmentation and rare disease representation



https://arxiv.org/abs/2209.13167

Applications in medical image generation

- Generating histopathology images with genotype guidance



Genotype-conditioned Image Generation

How Are IDH Mutation and 1p/19q Co-Deletion Extracted for Training Data?

The training data for the diffusion model includes **paired histopathology images and genotype information**. The genotype labels (IDH mutation status and 1p/19q co-deletion) are extracted through **molecular and genetic tests**, including:

1. IDH Mutation Detection

- **Immunohistochemistry (IHC)**: Uses **antibodies** to detect **mutant IDH1 protein** in tumor samples.
- **Next-Generation Sequencing (NGS)**: Directly sequences the **IDH1/IDH2 genes** to detect mutations.

2. 1p/19q Co-Deletion Detection

- **Fluorescence In Situ Hybridization (FISH)**: A cytogenetic test that detects the **loss of chromosome arms 1p and 19q** in tumor cells.
- **Comparative Genomic Hybridization (CGH)**: Identifies chromosomal deletions.
- **PCR-based methods**: Detects loss of heterozygosity (LOH) in 1p and 19q regions.

Once the genetic data is obtained, it is **paired with corresponding histopathology images** to create a **genotype-labeled dataset** for training.

Genotype-conditioned Image Generation

- **What is an IDH Mutation?**
  - IDH (Isocitrate Dehydrogenase) Mutation refers to genetic alterations in the IDH1 or IDH2 genes.
  - These mutations are commonly found in gliomas (brain tumors) and are important for tumor classification, prognosis, and treatment decisions.
  - IDH-mutant gliomas tend to have better survival rates compared to IDH-wildtype gliomas, which are more aggressive.
- **What is 1p/19q Co-Deletion?**
  - The 1p/19q co-deletion is a chromosomal alteration where parts of chromosomes 1p (short arm of chromosome 1) and 19q (long arm of chromosome 19) are missing.
  - This is a key molecular marker used to classify gliomas.
  - Gliomas with 1p/19q co-deletion are almost always oligodendrogliomas, which respond well to chemotherapy and radiation therapy.
  - If a glioma has IDH mutation but no 1p/19q co-deletion, it is classified as an astrocytoma instead of an oligodendroglioma.

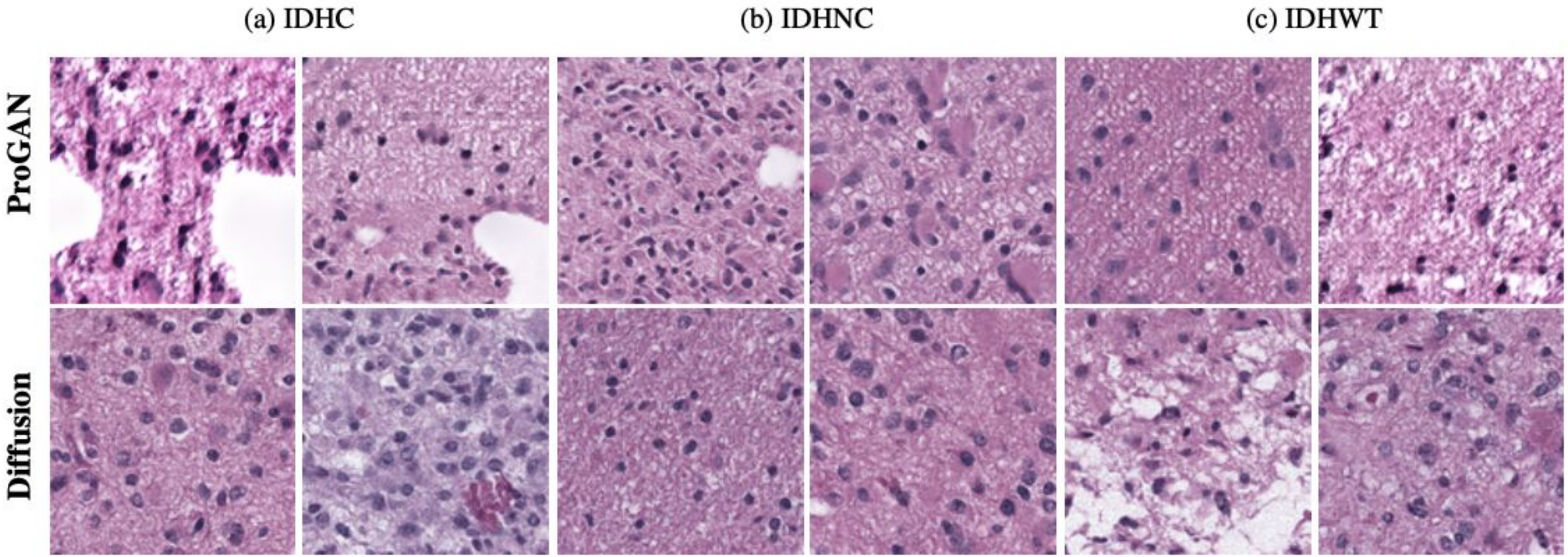
Inception score

What it measures: The **quality** and **diversity** of generated images.

How it works:

- Uses a pre-trained **Inception network** (e.g., Inception v3) to classify generated images.
- Measures:
  - **Quality**: If a generated image is highly classifiable (i.e., strong class predictions).
  - **Diversity**: If the generated images cover multiple classes.
- Requires a **well-trained classifier on medical data**, unlike natural images (e.g., CIFAR, ImageNet).

Applications in medical image generation

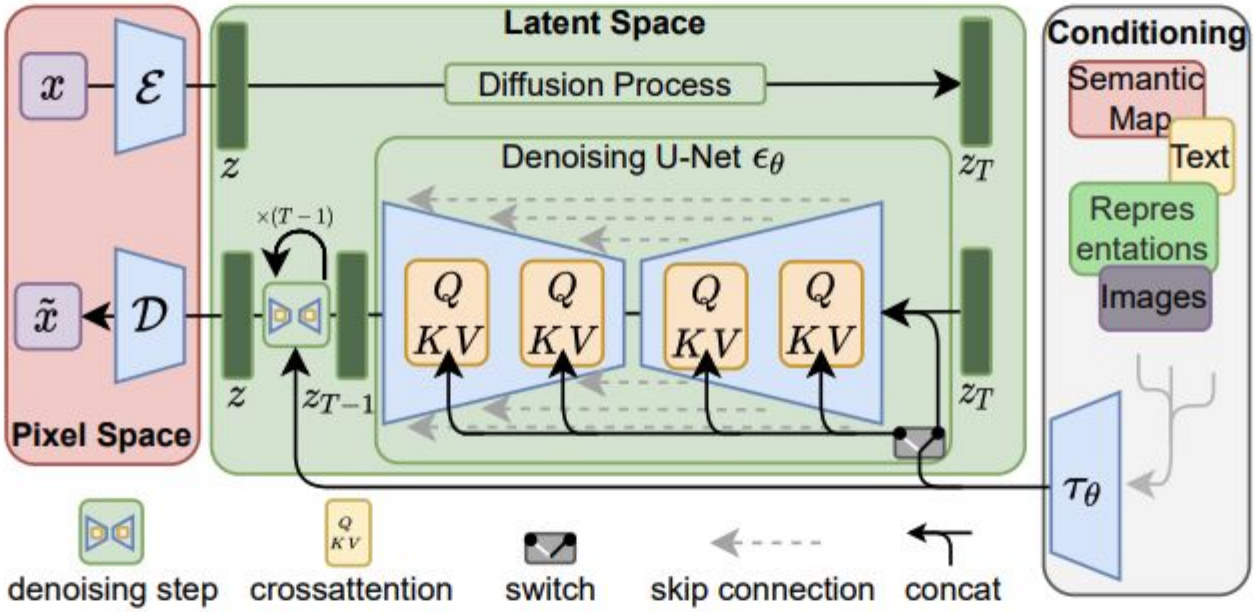


	ProGAN	Diffusion Model
Improved Recall	0.4816	**0.8528**
Improved Precision	0.0078	**0.2573**

	ProGAN	Diffusion Model
Inception Score	1.67	**2.08**
FID	53.85	**20.11**
sFID	24.37	**6.32**

https://youtu.be/US9CzPrT2H8?si=RrIt7CYwKE55rd5H

Conditional Diffusion



https://arxiv.org/abs/2112.10752

Self-Attention Module

- **Purpose:** Captures long-range dependencies within feature maps.

  Mechanism:
  - Flattens spatial dimensions into “tokens.”
  - Applies multi-head self-attention (along with layer normalization and a feedforward network) to let every part of the feature map attend to every other part.
- **Role in Diffusion:** Helps preserve global structure during the denoising process.

Self-attention vs Cross-attention

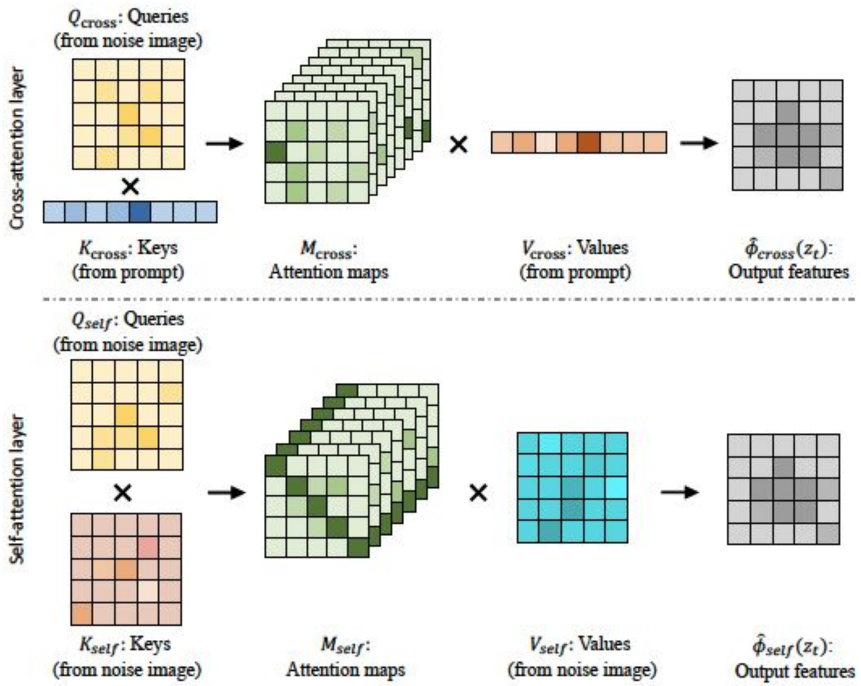


Figure 2. Cross and self-attention layers in Stable Diffusion.

https://arxiv.org/abs/2403.03431