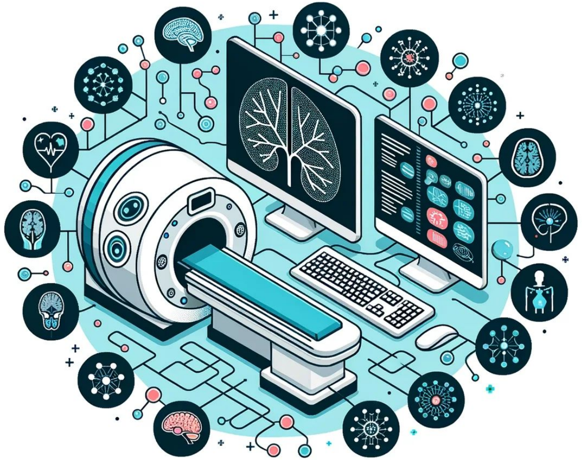
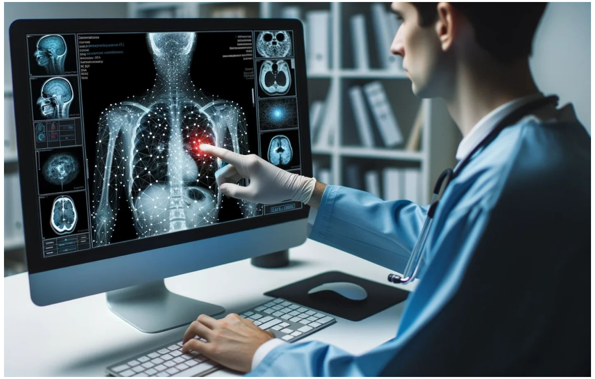
Applied Deep Learning and Generative Models in Healthcare





Session 5: Medical Image Synthesis
Date: Mar 01 2025

Instructor: Mahmoud E. Khani, Ph.D.

Make-up class survey

Attempts: 10 out of 10

How would you prefer to make up the missed class?

Schedule a separate makeup class on another day.	5 respondents	50 %
Start at 12:00 PM instead of 12:30 PM for a few sessions.	2 respondents	20 %
Extend class to 4:30 PM instead of 4:00 PM for a few sessions.	3 respondents	30 %

9	03/08	BREAK – NO CLASSES	
10	03/15	Diffusion Models for Medical Image Generation	Assignment 3 Assigned
11	03/22	Automated Diagnosis with Deep Learning	

Final projects

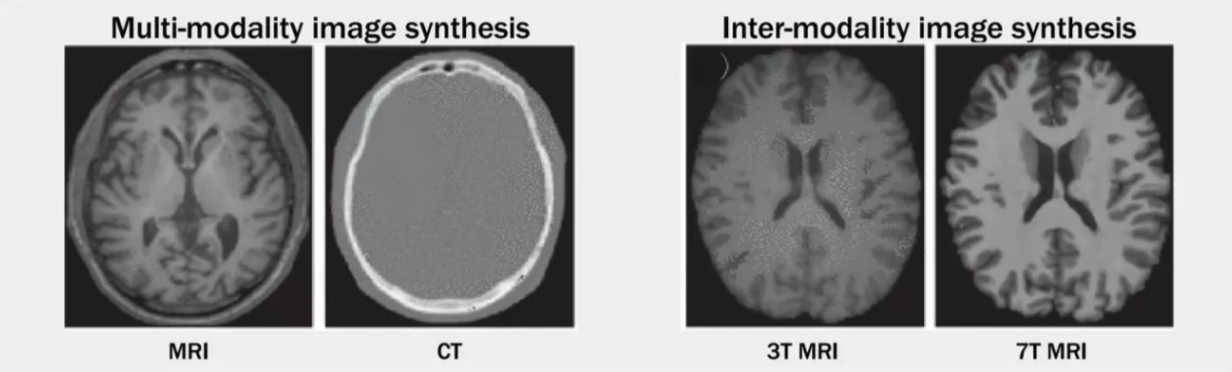
- List of final projects will be published soon!
- If you want to do it by yourself, you need to choose a project and email me by a deadline (will be specified).
- After this deadline, students will be randomly assigned to groups. They will have more time to discuss and choose a project (before another deadline).

Example projects

- **Text-to-Medical-Image Synthesis Using Generative AI**
  - Task: A model that generates medical images based on text descriptions.
  - Example: "brain tumor with contrast enhancement"
  - Dataset: Paired text-image datasets in radiology or pathology reports (e.g., MIMIC-CXR).
  - Extension: Fine-tune the model for specific imaging modalities.
- **AI for Automated Medical Report Generation**
  - Task: A model to generate radiology or pathology reports from medical images.
  - Dataset: MIMIC-CXR for chest X-rays, pathology reports from TCGA.
  - Extension: Study zero-shot generalization to unseen imaging modalities.
- **AI-Powered Diagnosis from Multi-Modal Data**
  - Task: A Multi-modal deep learning model that integrates imaging + genomics + clinical notes to improve disease classification.
  - Dataset: TCGA (imaging + mutation data), MIMIC-III (EHR + imaging).
  - Extension: Implement a clinically explainable AI approach.

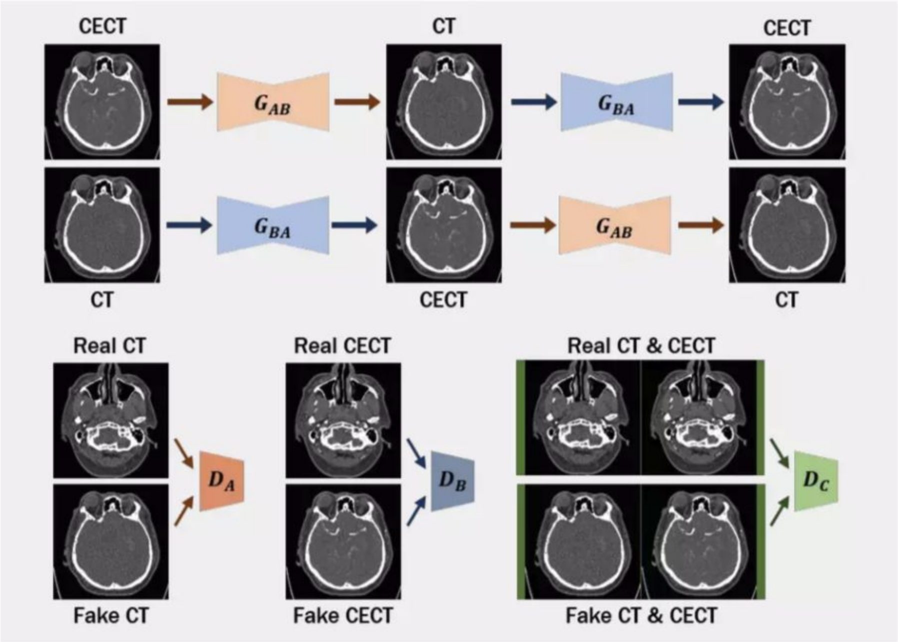
Medical image synthesis

- **An approach to modeling a mapping from given images to unknown images**
- **Necessity**
  - Potential risk of radiation exposure for multiple acquisition of medical images (ec. CT, PET)
  - Not always accessible modalities for every patient
  - Alignment issue on the analysis of multi-images



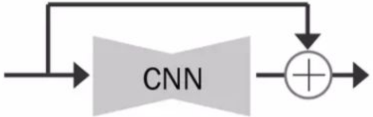
Nie, Dong, et al. "Medical image synthesis with deep convolutional adversarial networks." *IEEE Transactions on Biomedical Engineering*

CycleGAN framework



- Residual learning for generators

  Prevent loss of
  medical information



- **Two Generators**

  G_{AB} : CECT → CT (generate synthetic CT)

  G_{BA} : CT → CECT (generate synthetic CECT)

- **Three Discriminators**

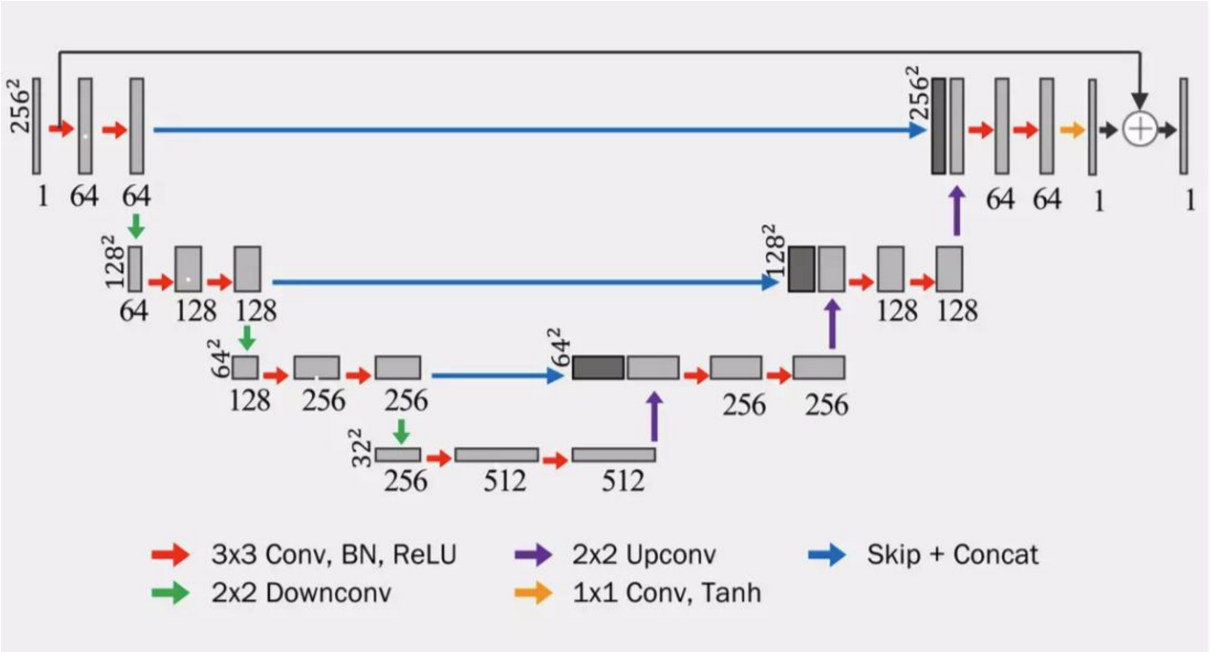
  D_A : Distinguish real and fake CT

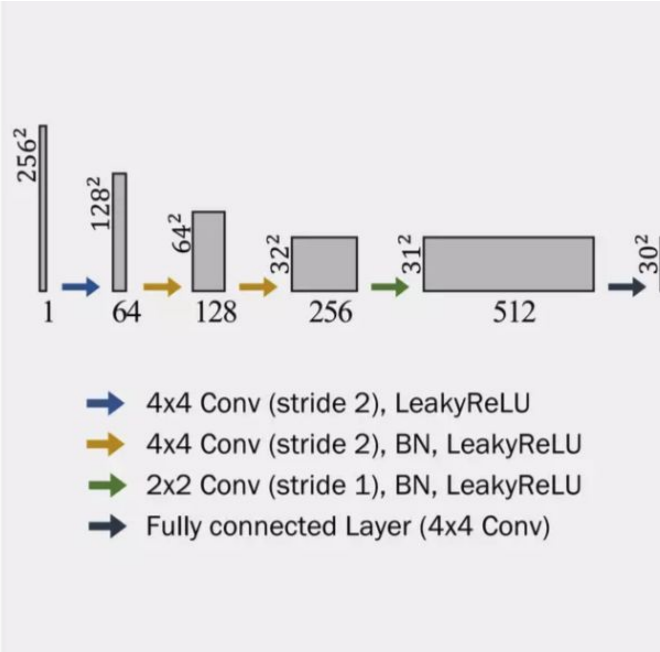
  D_B : Distinguish real and fake CECT

  $\boldsymbol{D_C}$: Distinguish real and fake pair of CT & CECT

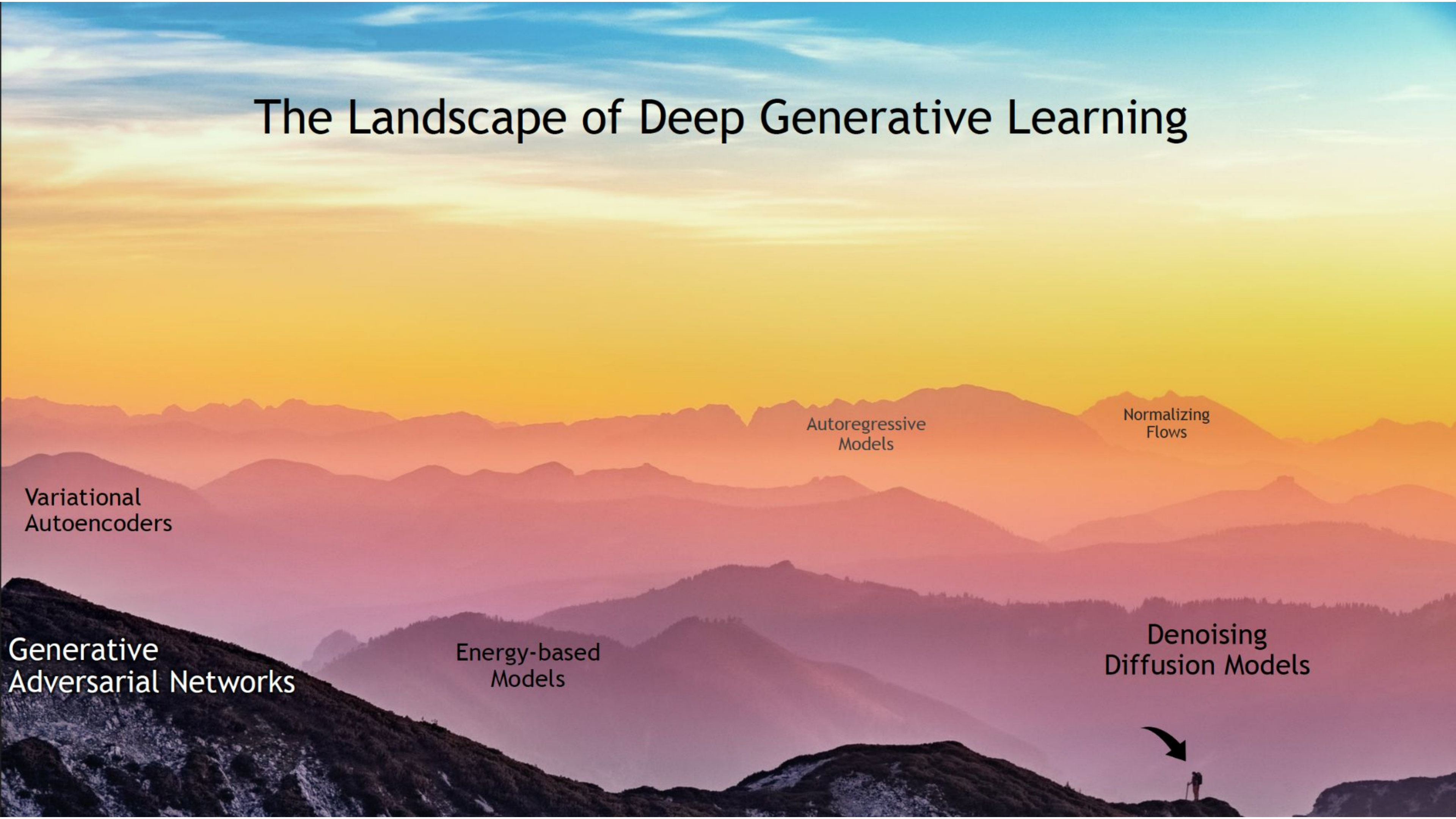
Network architecture

- **Generator (UNet)**
- **Discriminator**





The Landscape of Deep Generative Learning



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]

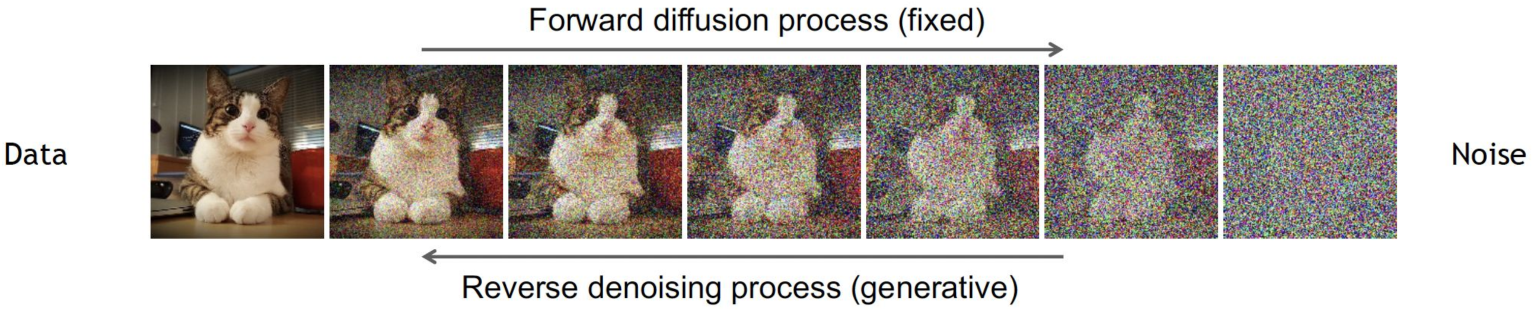
Imagen

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

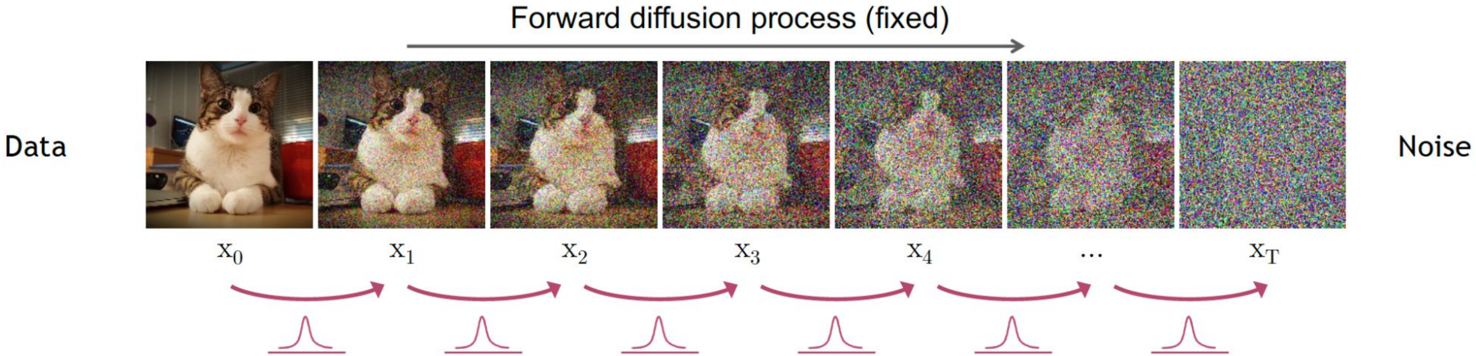
- **Denoising diffusion consists of two processes:**
  - Forward diffusion to gradually add noise to input
  - Reverse denoising that learns to generate data by denoising



[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

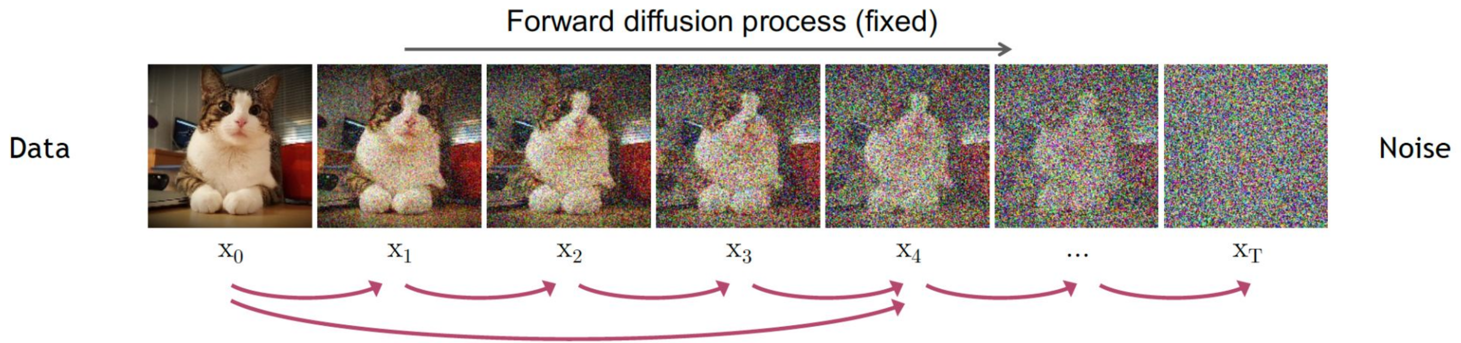
- **The formal definition of the forward process in T steps:**



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

(joint)

Diffusion Kernel



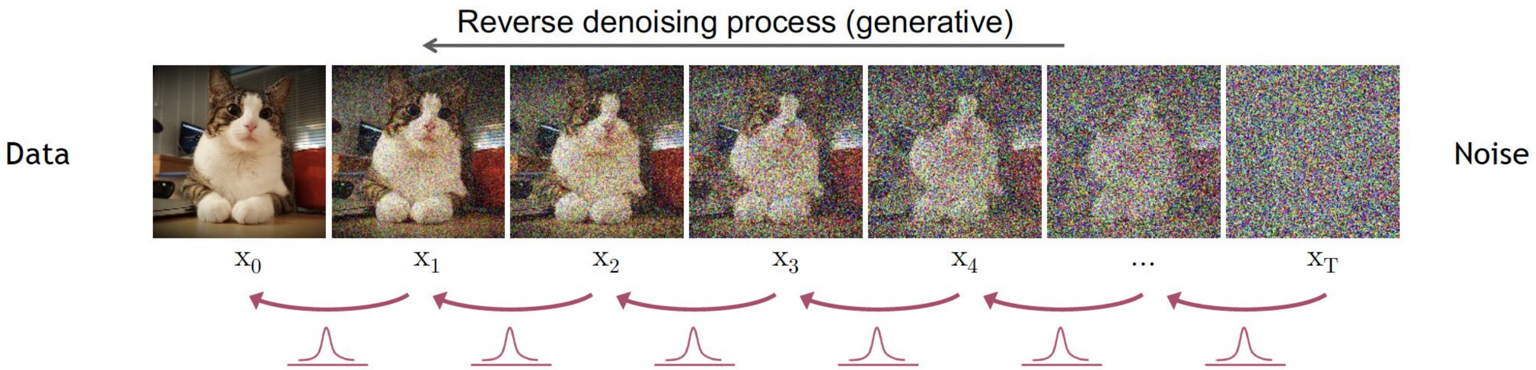
Define $\bar{\alpha}_t = \prod_{s=1}^{t}(1-\beta_s)$ ➡ $q(\mathbf{x}_t|\mathbf{x}_0) = \mathcal{N}(\mathbf{x}_t; \sqrt{\bar{\alpha}_t}\mathbf{x}_0, (1-\bar{\alpha}_t)\mathbf{I}))$ (Diffusion Kernel)

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 $\bar{\alpha}_T \rightarrow 0$ 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

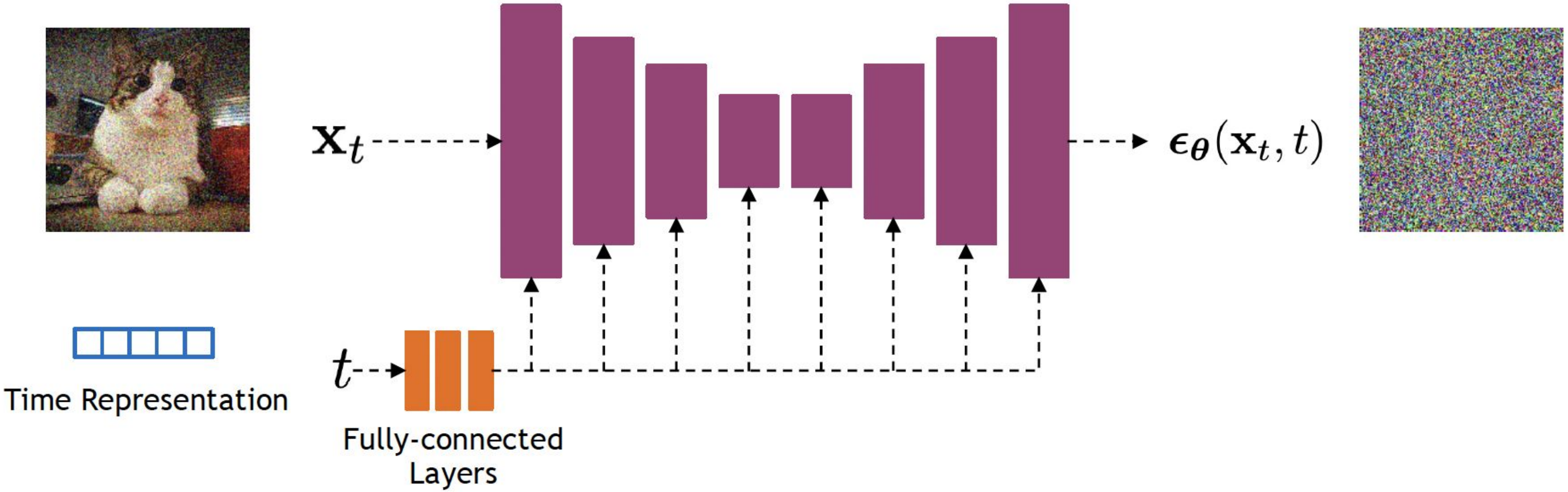
repeat
  $\mathbf{x}_0 \sim q(\mathbf{x}_0)$
  $t \sim \mathrm{Uniform}(\{1, \ldots, T\})$
  $\boldsymbol{\epsilon} \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$
  Take gradient descent step on
$$\nabla_\theta \left\| \boldsymbol{\epsilon} - \boldsymbol{\epsilon}_\theta(\boxed{\sqrt{\bar{\alpha}_t}\mathbf{x}_0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

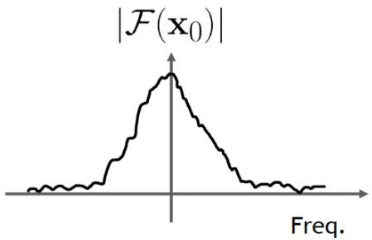
Fourier Analysis of the Forward Process

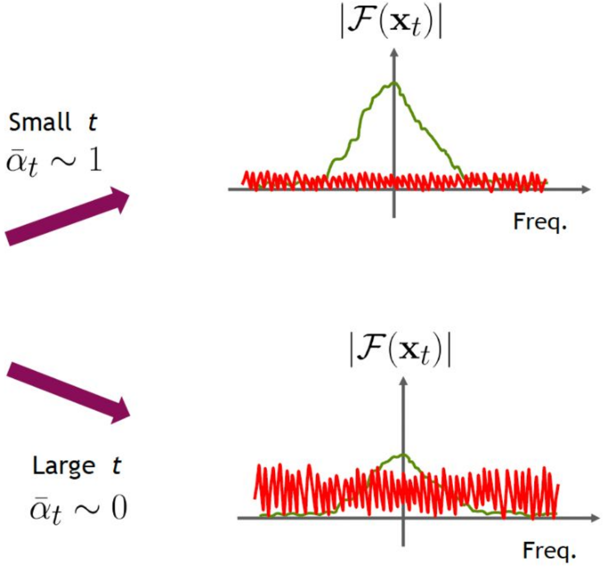
Recall that sampling from $q(\mathbf{x}_t|\mathbf{x}_0)$ is done using $\mathbf{x}_t = \sqrt{\bar{\alpha}_t}\ \mathbf{x}_0 + \sqrt{(1-\bar{\alpha}_t)}\ \epsilon$ where $\epsilon \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$

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

Fourier Transform

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

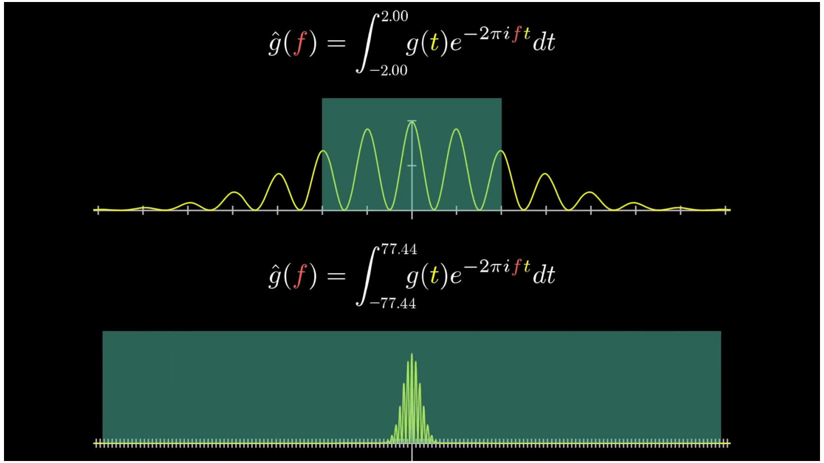


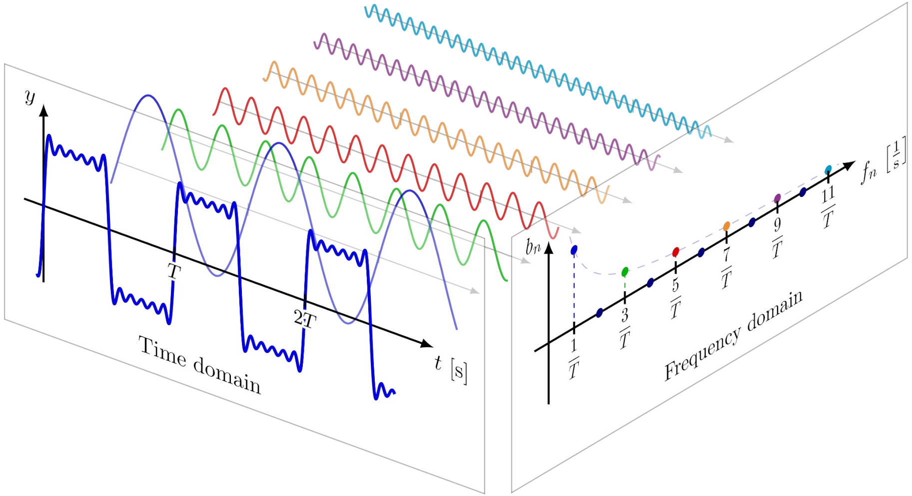


In the forward diffusion, the high frequency content is perturbed faster.

Fourier Analysis

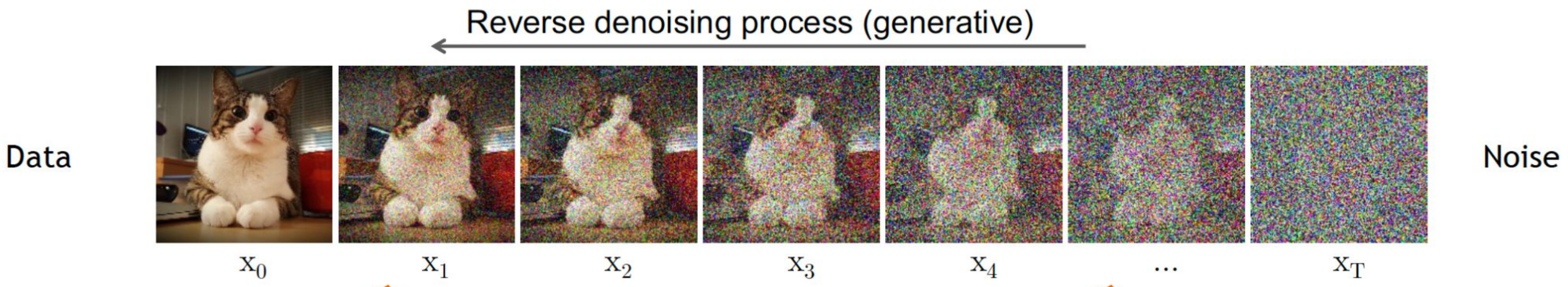
- **Decomposition of signal into frequency components**





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

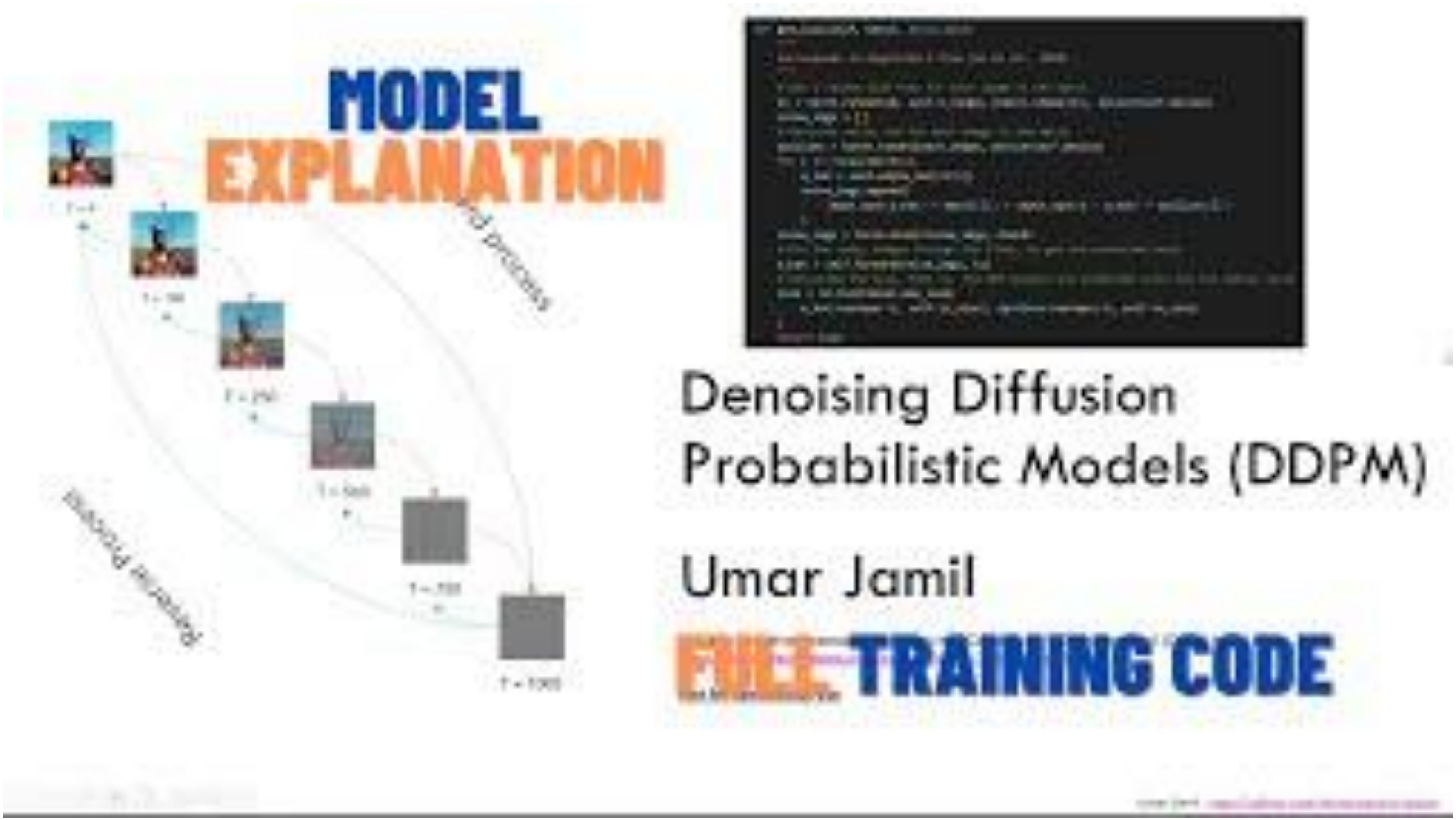
Content-Detail Tradeoff



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)

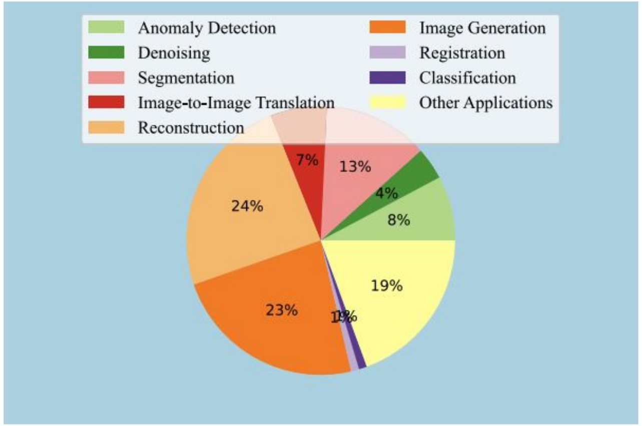
The weighting of the training objective for different timesteps is important!

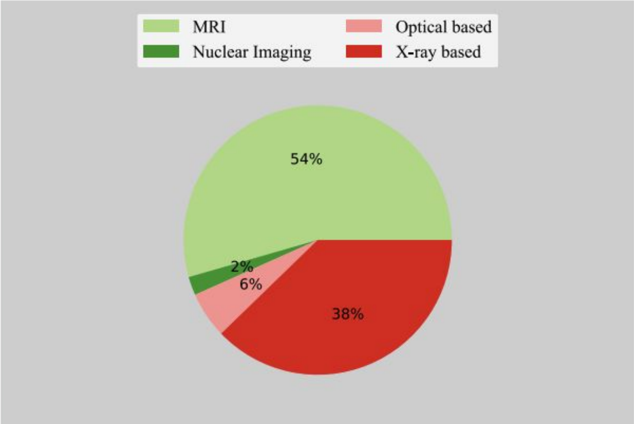


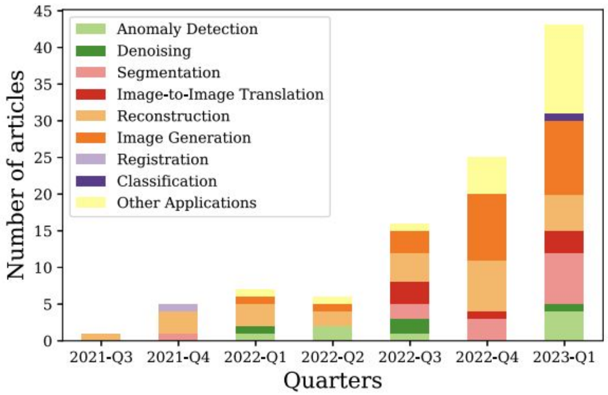
https://youtu.be/I1sPXkm2NH4?si=8wMzGKPii936tvlU

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.



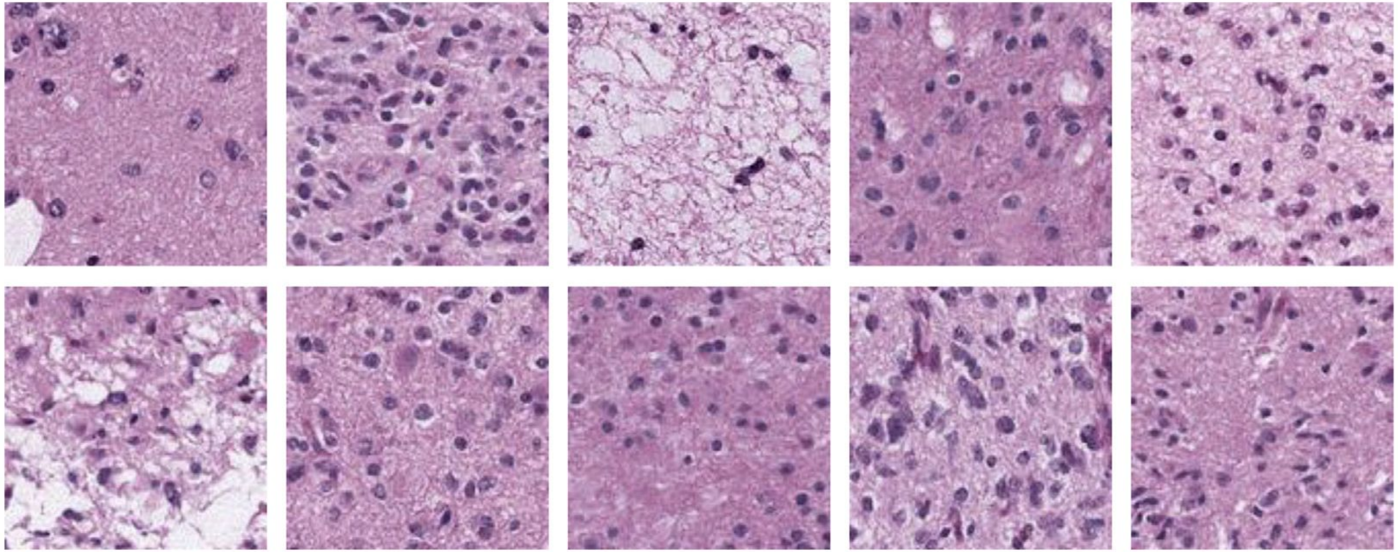




https://www.sciencedirect.com/science/article/pii/S1361841523001068

Applications in medical image generation

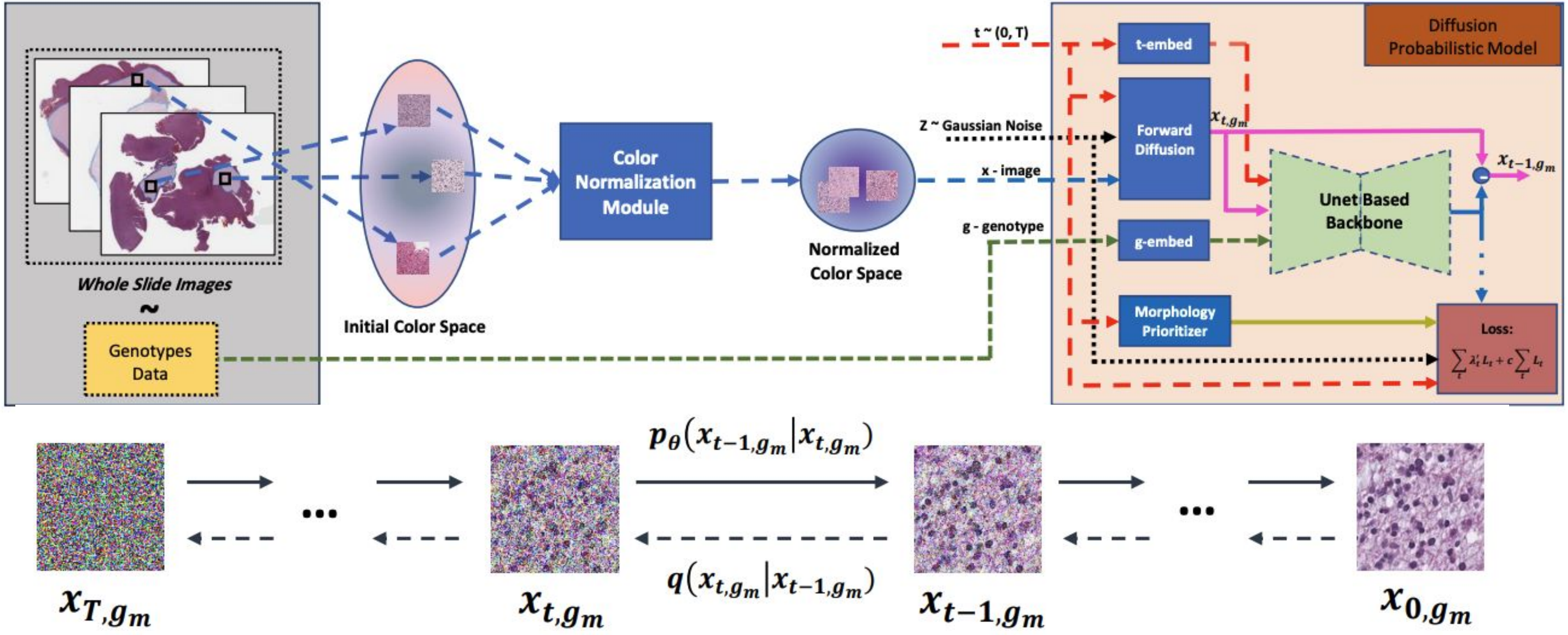
- **Diffusion models have remarkable performance in generating synthetic medical images**
  - aiding data augmentation and rare disease representation



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.

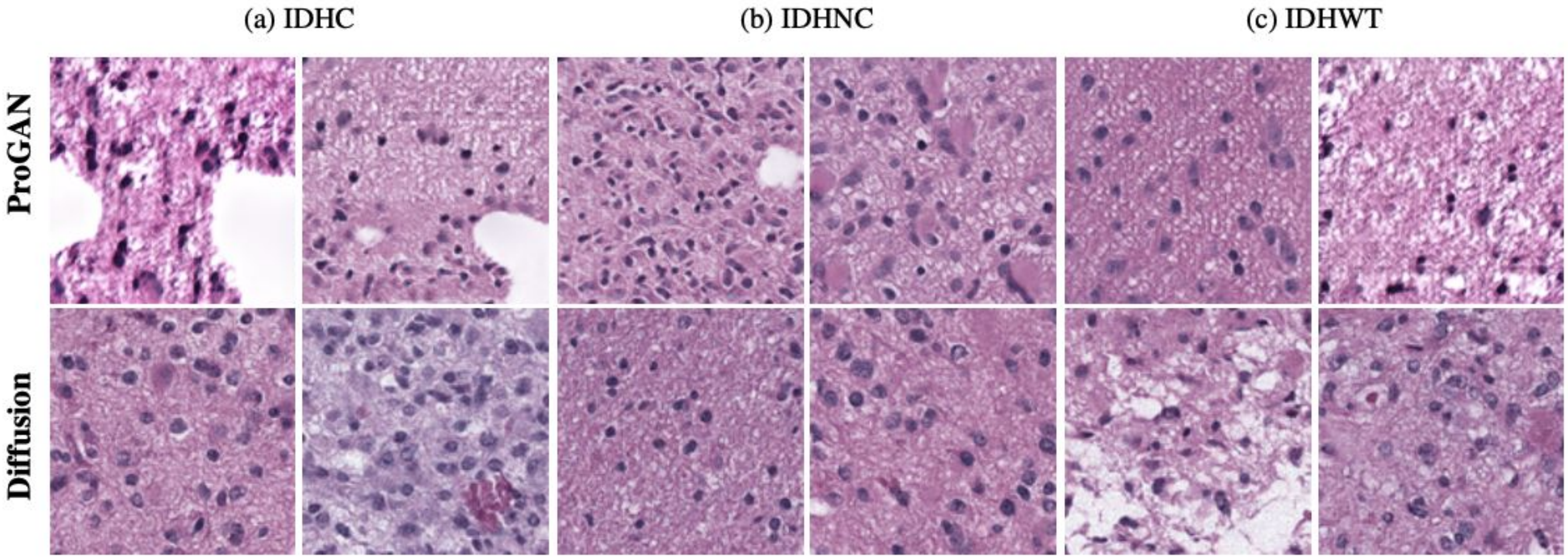
Inception score

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