



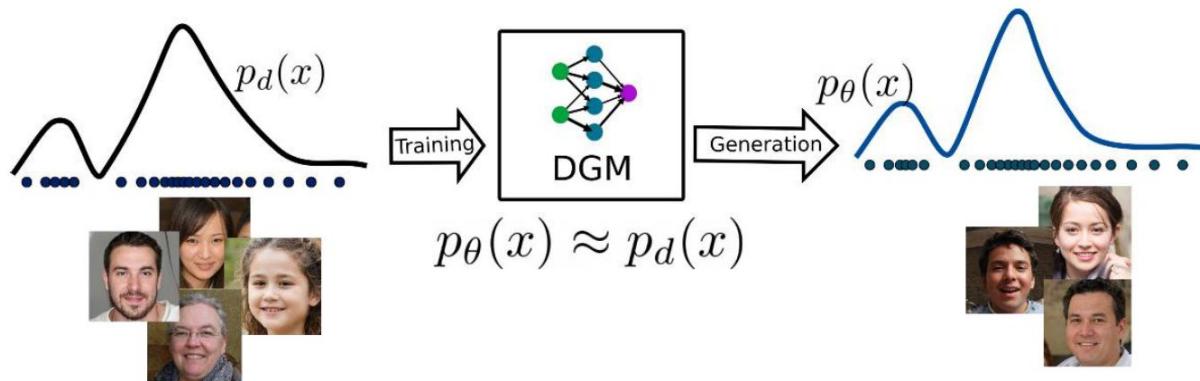
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Diffusion Models

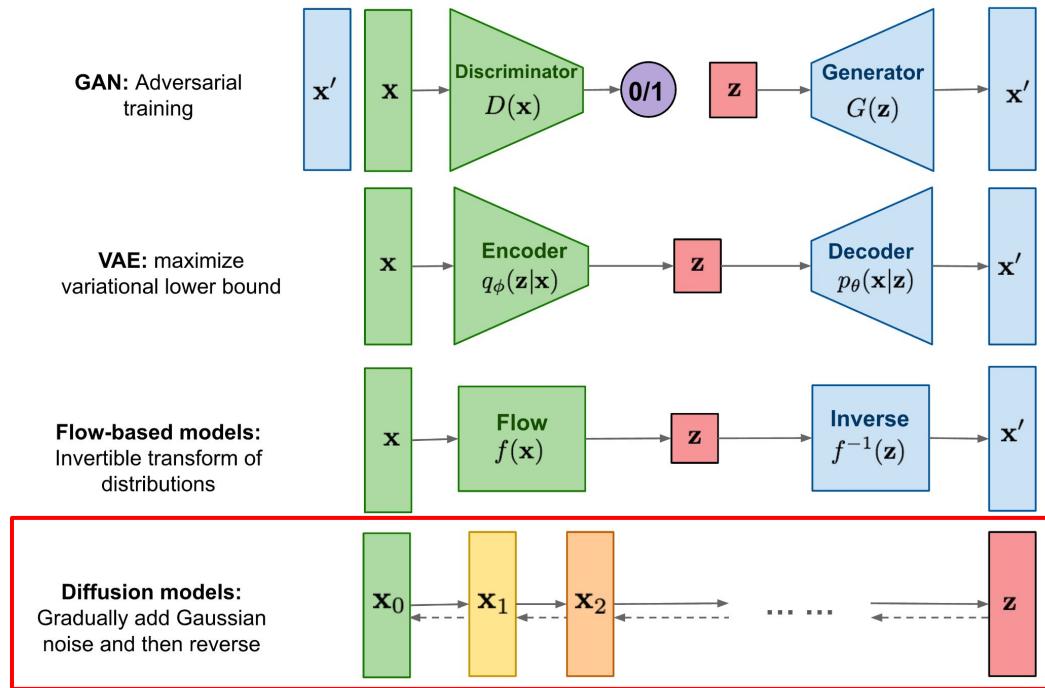
Geometry of Data, Fall 2023

Deep generative modelling

1. Learn a neural network to approximate $p(x)$
2. Sample from learnt $p'(x)$ to generate novel data



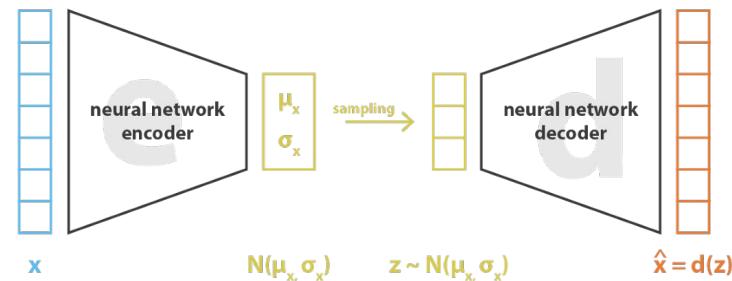
Types of Generative models



Background | Variational Autoencoders (VAE)

The VAE generative process is:

- first, a latent representation z is sampled from the prior distribution $p(z)$
- second, the data x is sampled from the conditional likelihood distribution $p(x|z)$



$$\text{loss} = \|x - \hat{x}\|^2 + \text{KL}[N(\mu_x, \sigma_x), N(0, I)] = \|x - d(z)\|^2 + \text{KL}[N(\mu_x, \sigma_x), N(0, I)]$$

Note that, the *KL-divergence between two gaussians p & q , is defined as follows:*

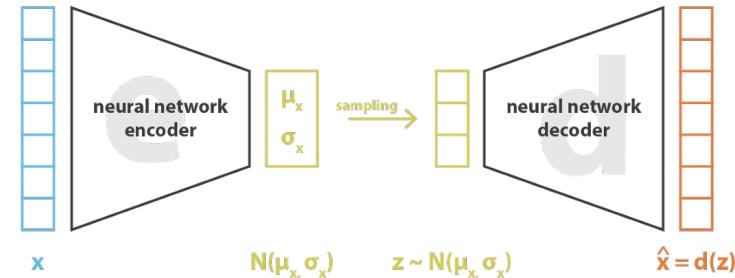
$$D_{KL}(p||q) = \frac{1}{2} \left[\log \frac{|\Sigma_q|}{|\Sigma_p|} - k + (\mu_p - \mu_q)^T \Sigma_q^{-1} (\mu_p - \mu_q) + \text{tr} \{ \Sigma_q^{-1} \Sigma_p \} \right]$$

Background | Variational Autoencoders (VAE)

The “probabilistic decoder” is defined by $p(x|z)$, that describes the distribution of the decoded variable given the encoded one

The “probabilistic encoder” is defined by $p(z|x)$, that describes the distribution of the encoded variable given the decoded one

We use Bayes’ theorem to get:



$$\text{loss} = \|x - \hat{x}\|^2 + \text{KL}[N(\mu_x, \sigma_x), N(0, I)] = \|x - d(z)\|^2 + \text{KL}[N(\mu_x, \sigma_x), N(0, I)]$$

$$p(z|x) = \frac{p(x|z)p(z)}{p(x)} = \frac{p(x|z)p(z)}{\int p(x|u)p(u)du}$$

Background | Variational Autoencoders (VAE)

In theory, we know $p(z)$ and $p(x|z)$, we can use the Bayes theorem to compute $p(z|x)$

However, this kind of computation is often **intractable** due to the **integral in the denominator**

Here we are going to approximate $p(z|x)$ by a Gaussian distribution $q_{-x}(z)$ whose mean and covariance are defined by two functions, \mathbf{g} and \mathbf{h} , of the parameter \mathbf{x} .

$$q_x(z) \equiv \mathcal{N}(g(x), h(x)) \quad g \in G \quad h \in H$$

$$\begin{aligned} (g^*, h^*) &= \arg \min_{(g, h) \in G \times H} KL(q_x(z), p(z|x)) \\ &= \arg \min_{(g, h) \in G \times H} \left(\mathbb{E}_{z \sim q_x} (\log q_x(z)) - \mathbb{E}_{z \sim q_x} \left(\log \frac{p(x|z)p(z)}{p(x)} \right) \right) \\ &= \arg \min_{(g, h) \in G \times H} (\mathbb{E}_{z \sim q_x} (\log q_x(z)) - \mathbb{E}_{z \sim q_x} (\log p(z)) - \mathbb{E}_{z \sim q_x} (\log p(x|z)) + \mathbb{E}_{z \sim q_x} (\log p(x))) \\ &= \arg \max_{(g, h) \in G \times H} (\mathbb{E}_{z \sim q_x} (\log p(x|z)) - KL(q_x(z), p(z))) \\ &= \arg \max_{(g, h) \in G \times H} \left(\mathbb{E}_{z \sim q_x} \left(-\frac{\|x - f(z)\|^2}{2c} \right) - KL(q_x(z), p(z)) \right) \end{aligned}$$

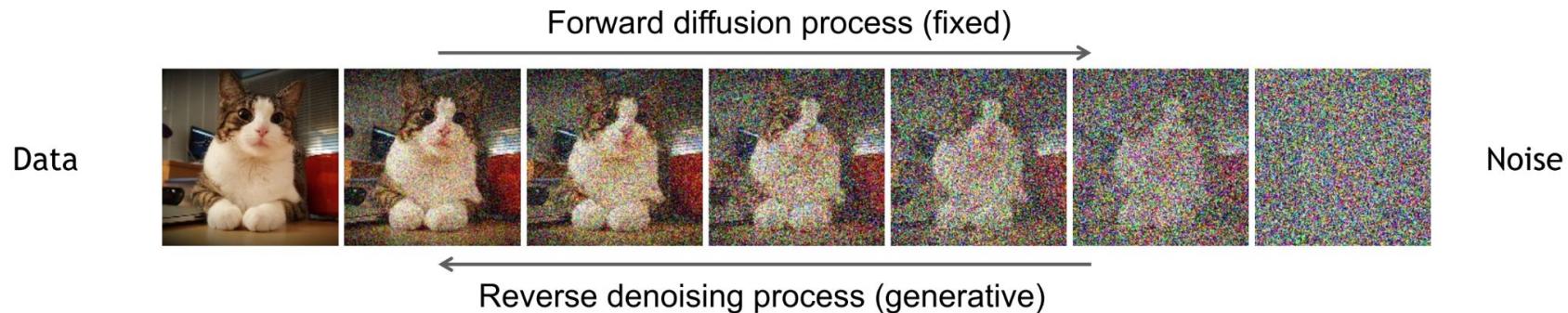
Overall,

$$(f^*, g^*, h^*) = \arg \max_{(f, g, h) \in F \times G \times H} \left(\mathbb{E}_{z \sim q_x} \left(-\frac{\|x - f(z)\|^2}{2c} \right) - KL(q_x(z), p(z)) \right)$$

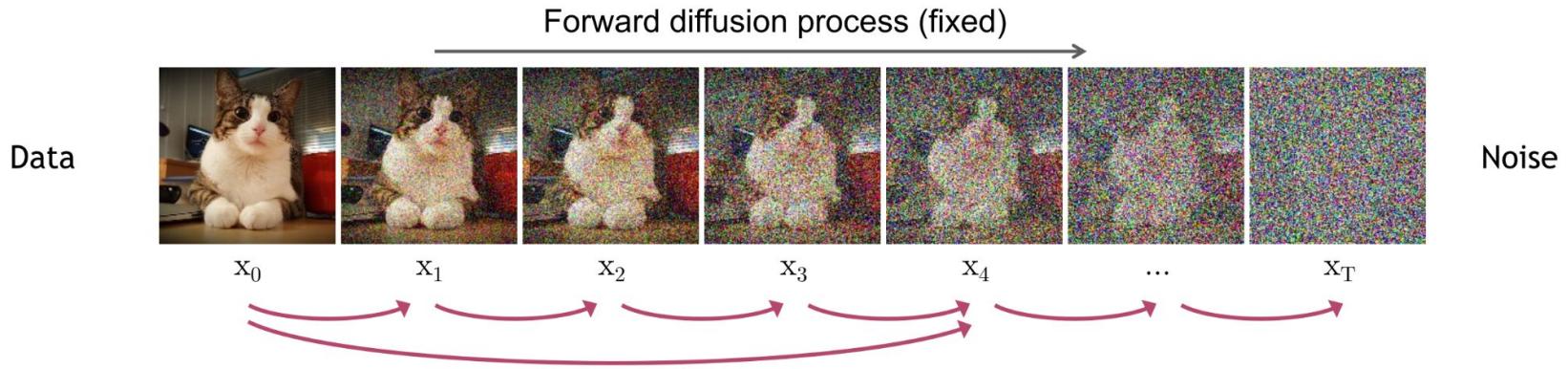
Denoising Diffusion Probabilistic Models (DDPM)

Forward diffusion: Markov chain of diffusion steps to slowly add gaussian noise to data

Reverse diffusion: A model is trained to generate data from noise by iterative denoising



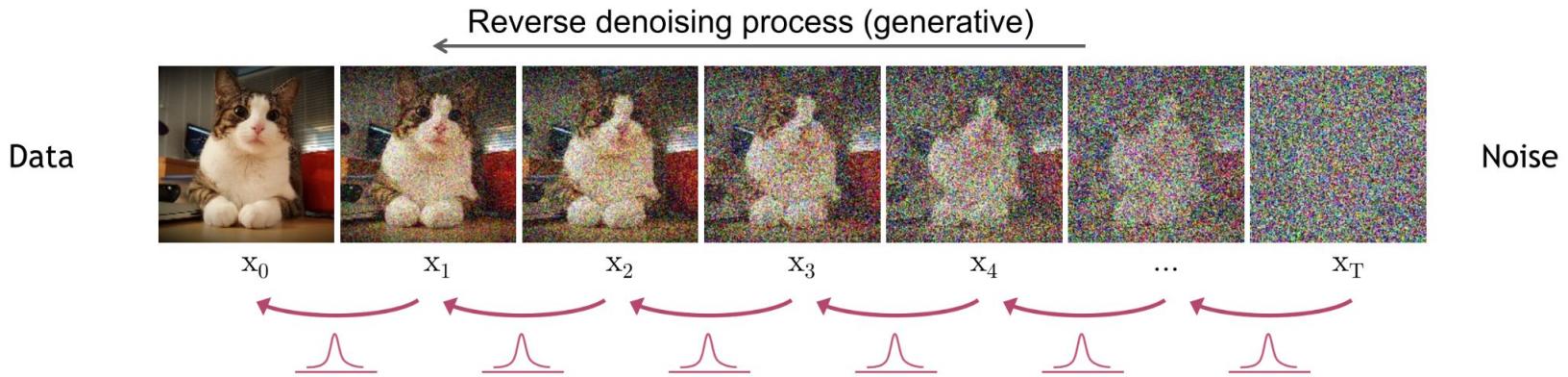
DDPM | Forward diffusion



We add a small amount of gaussian noise to a sample \mathbf{x}_0 in T timesteps to produces noised samples, $\{\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_T\}$. The steps are controlled by the noise schedule as follows:

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

DDPM | Reverse Diffusion



We learn a neural network model (p_θ) to approximate these conditional probabilities $q(x_{(t-1)} | x_t)$ in order to run the reverse diffusion process as follows:

$$p_\theta(\mathbf{x}_{0:T}) = p(\mathbf{x}_T) \prod_{t=1}^T p_\theta(\mathbf{x}_{t-1} | \mathbf{x}_t) \quad p_\theta(\mathbf{x}_{t-1} | \mathbf{x}_t) = \mathcal{N}(\mathbf{x}_{t-1}; \boldsymbol{\mu}_\theta(\mathbf{x}_t, t), \boldsymbol{\Sigma}_\theta(\mathbf{x}_t, t))$$

Training the denoising model

For training, we can form variational upper bound that is commonly used for training variational autoencoders,

$$\mathbb{E}_{q(\mathbf{x}_0)} [-\log p_\theta(\mathbf{x}_0)] \leq \mathbb{E}_{q(\mathbf{x}_0)q(\mathbf{x}_{1:T}|\mathbf{x}_0)} \left[-\log \frac{p_\theta(\mathbf{x}_{0:T})}{q(\mathbf{x}_{1:T}|\mathbf{x}_0)} \right] =: L$$

which simplifies to,

$$L = \mathbb{E}_q \left[\underbrace{D_{\text{KL}}(q(\mathbf{x}_T|\mathbf{x}_0)||p(\mathbf{x}_T))}_{L_T} + \sum_{t>1} \underbrace{D_{\text{KL}}(q(\mathbf{x}_{t-1}|\mathbf{x}_t, \mathbf{x}_0)||p_\theta(\mathbf{x}_{t-1}|\mathbf{x}_t))}_{L_{t-1}} \underbrace{-\log p_\theta(\mathbf{x}_0|\mathbf{x}_1)}_{L_0} \right]$$

and where $q(\mathbf{x}_{(t-1)}|\mathbf{x}_t, \mathbf{x}_0)$ is a tractable posterior:

$$q(\mathbf{x}_{t-1}|\mathbf{x}_t, \mathbf{x}_0) = \mathcal{N}(\mathbf{x}_{t-1}; \tilde{\mu}_t(\mathbf{x}_t, \mathbf{x}_0), \tilde{\beta}_t \mathbf{I}), \quad \text{where } \tilde{\mu}_t(\mathbf{x}_t, \mathbf{x}_0) := \frac{\sqrt{\bar{\alpha}_{t-1}}\beta_t}{1-\bar{\alpha}_t}\mathbf{x}_0 + \frac{\sqrt{1-\beta_t}(1-\bar{\alpha}_{t-1})}{1-\bar{\alpha}_t}\mathbf{x}_t \text{ and } \tilde{\beta}_t := \frac{1-\bar{\alpha}_{t-1}}{1-\bar{\alpha}_t}\beta_t$$

Parameterization of the diffusion model

The model is primarily trained on the term $L_{(t-1)}$ above, which is a KL-divergence of two normal distributions, $q(\mathbf{x}_{(t-1)} | \mathbf{x}_t, \mathbf{x}_0)$ and $p_\theta(\mathbf{x}_{(t-1)} | \mathbf{x}_t)$ and has a simple form:

$$L_{t-1} = D_{\text{KL}}(q(\mathbf{x}_{t-1} | \mathbf{x}_t, \mathbf{x}_0) || p_\theta(\mathbf{x}_{t-1} | \mathbf{x}_t)) = \mathbb{E}_q \left[\frac{1}{2\sigma_t^2} \|\tilde{\mu}_t(\mathbf{x}_t, \mathbf{x}_0) - \mu_\theta(\mathbf{x}_t, t)\|^2 \right] + C$$

In [Ho et al. NeurIPS 2020](#), above is reparameterized to be a noise-prediction network instead of a mean-prediction network,

$$L_{t-1} = \mathbb{E}_{\mathbf{x}_0 \sim q(\mathbf{x}_0), \epsilon \sim \mathcal{N}(\mathbf{0}, \mathbf{I})} \left[\underbrace{\frac{\beta_t^2}{2\sigma_t^2(1 - \beta_t)(1 - \bar{\alpha}_t)}}_{\lambda_t} \|\epsilon - \epsilon_\theta(\underbrace{\sqrt{\bar{\alpha}_t} \mathbf{x}_0 + \sqrt{1 - \bar{\alpha}_t} \epsilon, t)}_{\mathbf{x}_t}\|^2 \right] + C$$

Parameterization of the diffusion model

$$L_{t-1} = \mathbb{E}_{\mathbf{x}_0 \sim q(\mathbf{x}_0), \epsilon \sim \mathcal{N}(\mathbf{0}, \mathbf{I})} \left[\underbrace{\frac{\beta_t^2}{2\sigma_t^2(1 - \beta_t)(1 - \bar{\alpha}_t)}}_{\lambda_t} \|\epsilon - \epsilon_\theta(\underbrace{\sqrt{\bar{\alpha}_t} \mathbf{x}_0 + \sqrt{1 - \bar{\alpha}_t} \epsilon, t)}_{\mathbf{x}_t}\|^2 \right] + C$$

Note that λ_t above is just a time-dependent reweighting parameter.

It is observed that for training the model, it is **helpful** if we set $\lambda_t = 1$.

Making the objective even simpler,

$$L_{\text{simple}} = \mathbb{E}_{\mathbf{x}_0 \sim q(\mathbf{x}_0), \epsilon \sim \mathcal{N}(\mathbf{0}, \mathbf{I}), t \sim \mathcal{U}(1, T)} \left[\|\epsilon - \epsilon_\theta(\underbrace{\sqrt{\bar{\alpha}_t} \mathbf{x}_0 + \sqrt{1 - \bar{\alpha}_t} \epsilon, t)}_{\mathbf{x}_t}\|^2 \right]$$

Overall algorithm (like we see it!)

Algorithm 1 Training

```
1: repeat
2:    $\mathbf{x}_0 \sim q(\mathbf{x}_0)$ 
3:    $t \sim \text{Uniform}(\{1, \dots, T\})$ 
4:    $\boldsymbol{\epsilon} \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$ 
5:   Take gradient descent step on
      
$$\nabla_{\theta} \|\boldsymbol{\epsilon} - \boldsymbol{\epsilon}_{\theta}(\sqrt{\bar{\alpha}_t} \mathbf{x}_0 + \sqrt{1 - \bar{\alpha}_t} \boldsymbol{\epsilon}, t)\|^2$$

6: until converged
```

Algorithm 2 Sampling

```
1:  $\mathbf{x}_T \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$ 
2: for  $t = T, \dots, 1$  do
3:    $\mathbf{z} \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$ 
4:   
$$\mathbf{x}_{t-1} = \frac{1}{\sqrt{\bar{\alpha}_t}} \left( \mathbf{x}_t - \frac{1 - \bar{\alpha}_t}{\sqrt{1 - \bar{\alpha}_t}} \boldsymbol{\epsilon}_{\theta}(\mathbf{x}_t, t) \right) + \sigma_t \mathbf{z}$$

5: end for
6: return  $\mathbf{x}_0$ 
```

Conditional diffusion models

In conditional diffusion models, an additional input, y (eg. a class label or a text sequence) is available and we try to model the conditional distribution $p(x | y)$ instead.

This allows us to generate data given the conditioning signal.

Some examples generated from Google's Imagen [1], and OpenAI's Dalle-2 [2] on the right.



A medieval painting of the wifi not working



A still of Homer Simpson in Psycho (1960)



An Alpaca is smiling and underwater in the pool



A tulip pushing a baby carriage

[1] Saharia, Chitwan, et al. "Photorealistic Text-to-Image Diffusion Models with Deep Language Understanding." *arXiv preprint arXiv:2205.11487* (2022).

[2] Ramesh, Aditya, et al. "Hierarchical text-conditional image generation with clip latents." *arXiv preprint arXiv:2204.06125* (2022).

Conditional diffusion models

In practice, the denoising model $p(\mathbf{x}_{t-1} | \mathbf{x}_t, \mathbf{y})$ is also conditioned on ' \mathbf{y} ' in addition to the image from the previous timestep, \mathbf{x}_t

Reverse process: $p_\theta(\mathbf{x}_{0:T} | \mathbf{c}) = p(\mathbf{x}_T) \prod_{t=1}^T p_\theta(\mathbf{x}_{t-1} | \mathbf{x}_t, \mathbf{c}), \quad p_\theta(\mathbf{x}_{t-1} | \mathbf{x}_t, \mathbf{c}) = \mathcal{N}(\mathbf{x}_{t-1}; \boldsymbol{\mu}_\theta(\mathbf{x}_t, t, \mathbf{c}), \boldsymbol{\Sigma}_\theta(\mathbf{x}_t, t, \mathbf{c}))$

Variational upper bound: $L_\theta(\mathbf{x}_0 | \mathbf{c}) = \mathbb{E}_q \left[L_T(\mathbf{x}_0) + \sum_{t>1} D_{\text{KL}}(q(\mathbf{x}_{t-1} | \mathbf{x}_t, \mathbf{x}_0) \| p_\theta(\mathbf{x}_{t-1} | \mathbf{x}_t, \mathbf{c})) - \log p_\theta(\mathbf{x}_0 | \mathbf{x}_1, \mathbf{c}) \right].$

Practical considerations

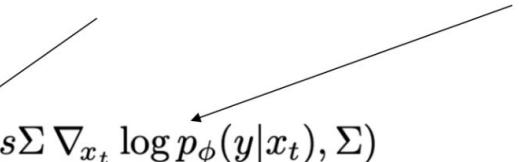
- **Scalar conditioning:** encode scalar as a vector embedding, simple spatial addition or adaptive group normalization layers.
- **Image conditioning:** channel-wise concatenation of the conditional image.
- **Text conditioning:** single vector embedding – spatial addition or adaptive group norm / a seq of vector embeddings – cross-attention.

Score-model based guidance

Using the gradient of an independently pre-trained score model as guidance
Given a conditional model $p(x_t | y)$, we use gradients from an extra score model $p(y | x_t)$ during sampling.

Algorithm 1 Classifier guided diffusion sampling, given a diffusion model $(\mu_\theta(x_t), \Sigma_\theta(x_t))$, classifier $p_\phi(y|x_t)$, and gradient scale s .

```
Input: class label  $y$ , gradient scale  $s$ 
 $x_T \leftarrow$  sample from  $\mathcal{N}(0, \mathbf{I})$ 
for all  $t$  from  $T$  to 1 do
     $\mu, \Sigma \leftarrow \mu_\theta(x_t), \Sigma_\theta(x_t)$ 
     $x_{t-1} \leftarrow$  sample from  $\mathcal{N}(\mu + s\Sigma \nabla_{x_t} \log p_\phi(y|x_t), \Sigma)$ 
end for
return  $x_0$ 
```

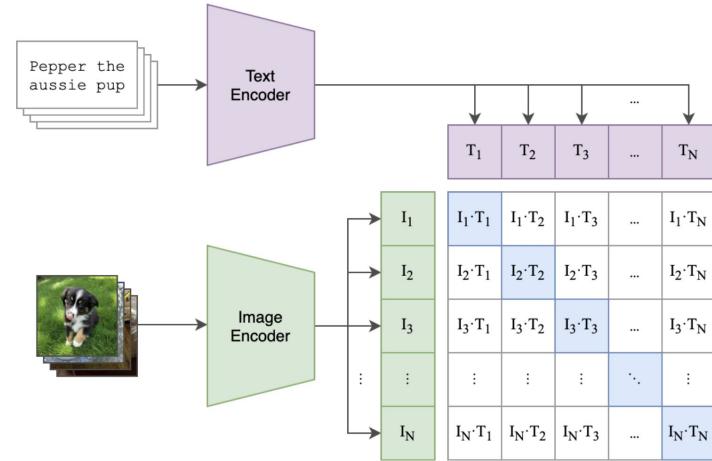


CLIP guidance

Given an image x and a prompt y , a CLIP model computes the alignment $\text{cos_sim}(x, y)$ which indicates how similar the image and the prompt are.

To use this signal for guidance, we assume that the CLIP similarity score is a good estimation of the function $p(y|x)$

The gradient of this score wrt the noised image, x_t at timestep t is used as the guidance gradient



*Note that this requires the CLIP model to compute score for **noised-images** at intermediate timesteps, hence a noised-CLIP model is trained for guidance*

Classifier-free guidance

Given both a conditional and an unconditional diffusion model, we can design an “implicit” classifier as follows:

$$p(\mathbf{c}|\mathbf{x}_t) \propto p(\mathbf{x}_t|\mathbf{c})/p(\mathbf{x}_t)$$

Conditional diffusion model Unconditional diffusion model

In practice, $p(\mathbf{x}|\mathbf{c})$ and $p(\mathbf{x})$ are trained together by randomly dropping the conditioning signal with a certain probability during training.

Using above, the score-gradient becomes:

$$\begin{aligned}\nabla_{\mathbf{x}_t} [\log p(\mathbf{x}_t|\mathbf{c}) + \omega \log p(\mathbf{c}|\mathbf{x}_t)] &= \nabla_{\mathbf{x}_t} [\log p(\mathbf{x}_t|\mathbf{c}) + \omega (\log p(\mathbf{x}_t|\mathbf{c}) - \log p(\mathbf{x}_t))] \\ &= \nabla_{\mathbf{x}_t} [(1 + \omega) \log p(\mathbf{x}_t|\mathbf{c}) - \omega \log p(\mathbf{x}_t)]\end{aligned}$$

GLIDE | OpenAI

- A 64x64 base diffusion model
- A 64 -> 256 conditional super-resolution model
- Evaluates both classifier-free and **CLIP guidance**

CLIP guidance: Use the CLIP alignment score $p(x, y)$ as a estimation of $p(y | x)$



“a boat in the canals of venice”



“a painting of a fox in the style of starry night”



“a crayon drawing of a space elevator”



“a futuristic city in synthwave style”

DALL.E 2 | OpenAI

- 1kx1k text-conditioned image generation
- Uses a **prior** to produce CLIP embeddings conditioned on the text-caption
- Uses a **decoder** to produce images conditioned on the CLIP embeddings



a shiba inu wearing a beret and black turtleneck



a close up of a handpalm with leaves growing from it



panda mad scientist mixing sparkling chemicals, artstation

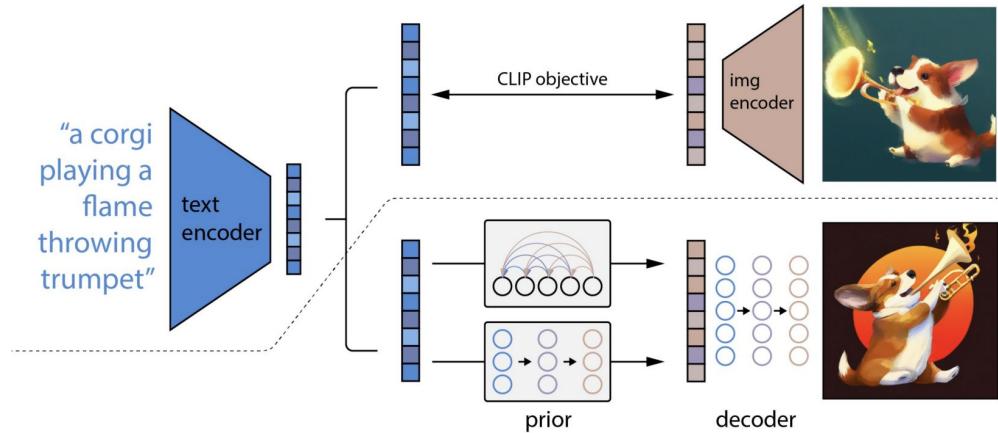


a corgi's head depicted as an explosion of a nebula

DALL.E 2 | Open AI

Conditioning on CLIP-embeddings

- Helps capture multimodal representations
- The bi-partite latent enables several text-controlled image manipulation tasks



DALL.E 2 | Open AI

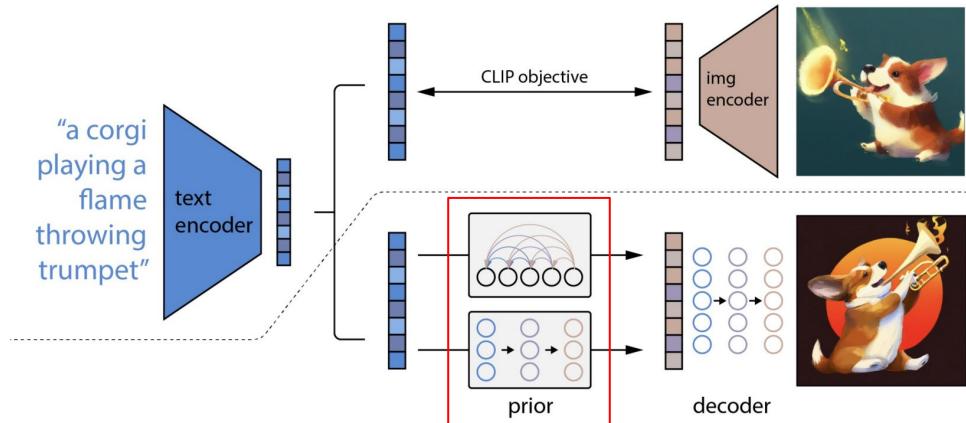
Proposes 2 types of priors:

1. Autoregressive prior

Quantize image embeds into a sequence of discrete codes and predict them autoregressively

2. Diffusion prior

Model continuous image embeddings by diffusion models conditioned on caption

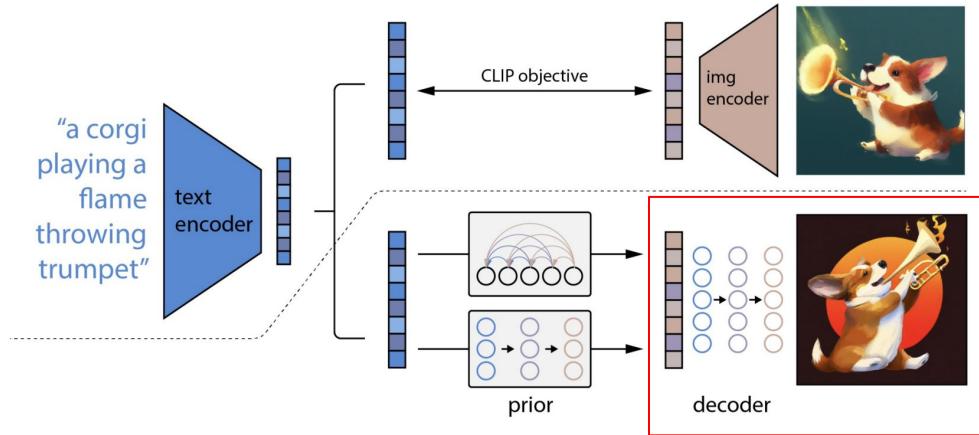


DALL.E 2 | Open AI

Decoder: produces images conditioned on CLIP image embeddings (and text caption)

The model is trained as cascaded diffusion models 64->256->1024

It is observed that classifier-free guidance works better for sample quality here.



DALL.E 2 | Open AI



Interpolate CLIP embeddings to generate different interpolation trajectories

DALL.E 2 | Open AI



a photo of a cat → an anime drawing of a super saiyan cat, artstation



a photo of a victorian house → a photo of a modern house



a photo of an adult lion → a photo of lion cub

Change the image CLIP embedding towards the difference of the text CLIP embeddings of two prompts. Note that decoder latent is kept as a constant.

Imagen | Google Research

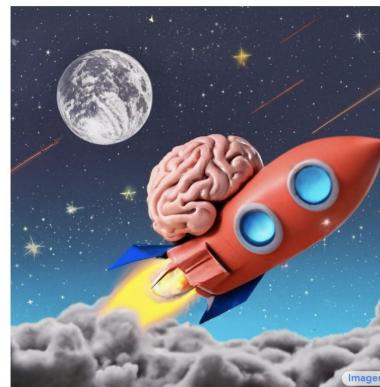
- Generates 1kx1k images
- Exceptional photo-realism
- Extremely simple parameterization
- SOTA on quantitative and qualitative benchmarks
- Proposes a new qualitative benchmark (drawbench)



Teddy bears swimming at the Olympics 400m Butterfly event.



A cute corgi lives in a house made out of sushi.



A brain riding a rocketship heading towards the moon.



A dragon fruit wearing karate belt in the snow.

Imagen | Google Research

Model details

- Cascaded diffusion models
64 -> 256 -> 1024
- Classifier-free guidance and dynamic thresholding
- Frozen large pretrained language models as text encoders (T5-XXL)

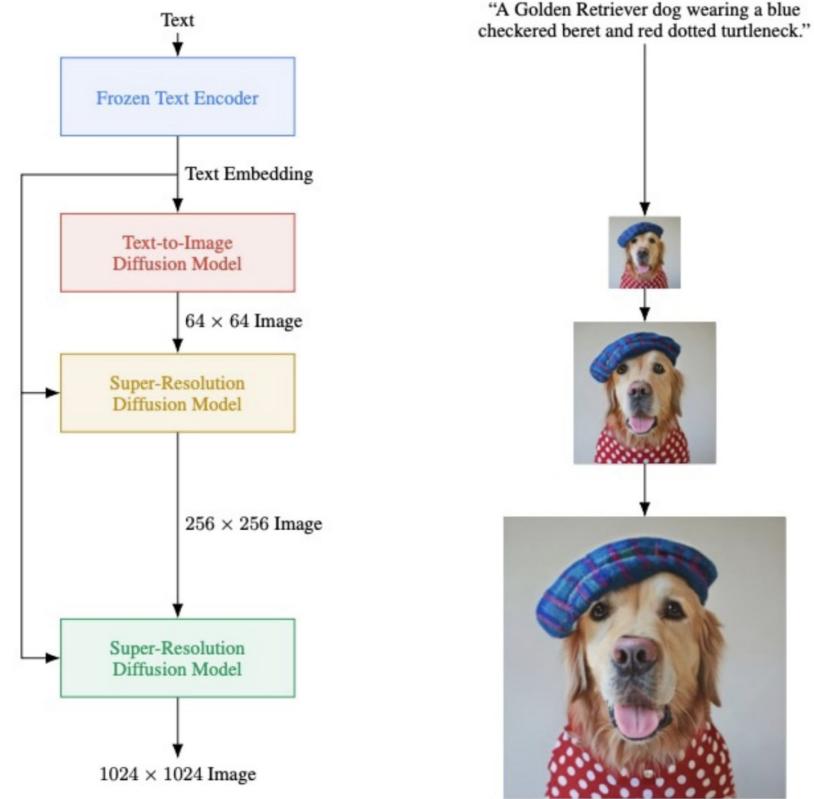


Imagen | Google Research

Main discoveries

- Better text-conditioning signal is important, i.e. large frozen text-encoders are used, eg. T5-XXL
- Stronger classifier-free guidance leads to better text-alignment but worse image quality

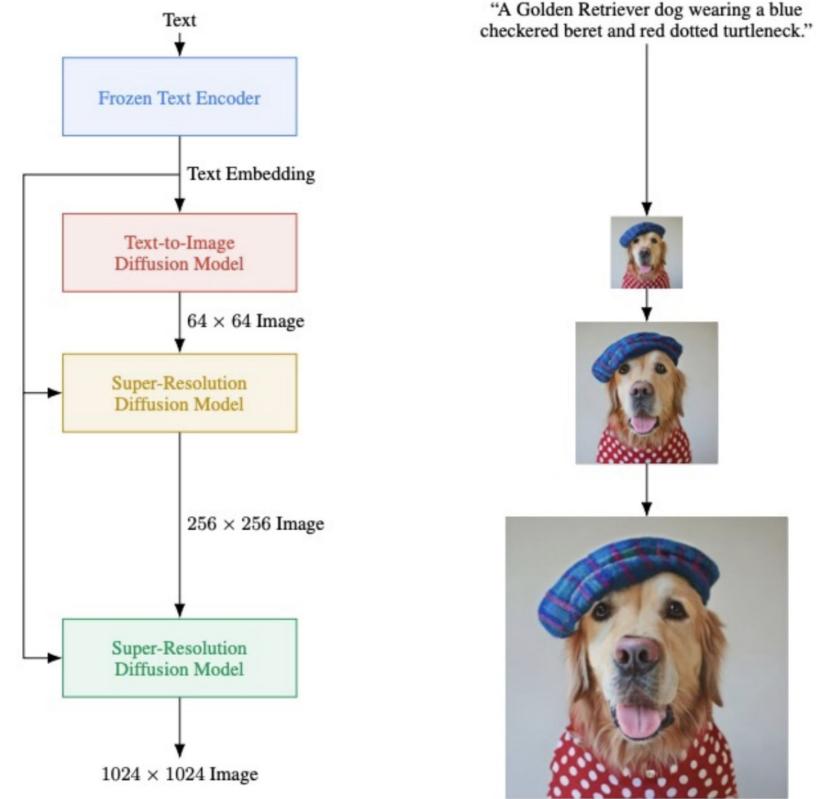


Imagen | Google Research

The paper also proposes a new benchmark called the “drawbench”

- Collection of 200 prompts that test semantic understanding and image diversity.



A brown bird and a blue bear.



One cat and two dogs sitting on the grass.



A sign that says 'NeurIPS'.



A small blue book sitting on a large red book.



A blue coloured pizza.



A wine glass on top of a dog.



A pear cut into seven pieces arranged in a ring.



A photo of a confused grizzly bear in calculus class.



A small vessel propelled on water by oars, sails, or an engine.

Imagen | Google Research

Model	FID-30K	Zero-shot FID-30K
AttnGAN [76]	35.49	
DM-GAN [83]	32.64	
DF-GAN [69]	21.42	
DM-GAN + CL [78]	20.79	
XMC-GAN [81]	9.33	
LAFITE [82]	8.12	
Make-A-Scene [22]	7.55	
DALL-E [53]		17.89
LAFITE [82]		26.94
GLIDE [41]		12.24
DALL-E 2 [54]		10.39
Imagen (Our Work)		7.27

Imagen achieves SOTA using auto-evaluation scores on COCO dataset

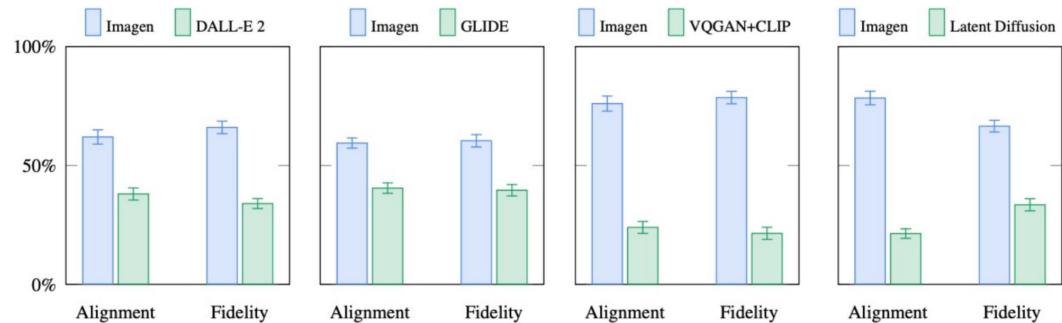


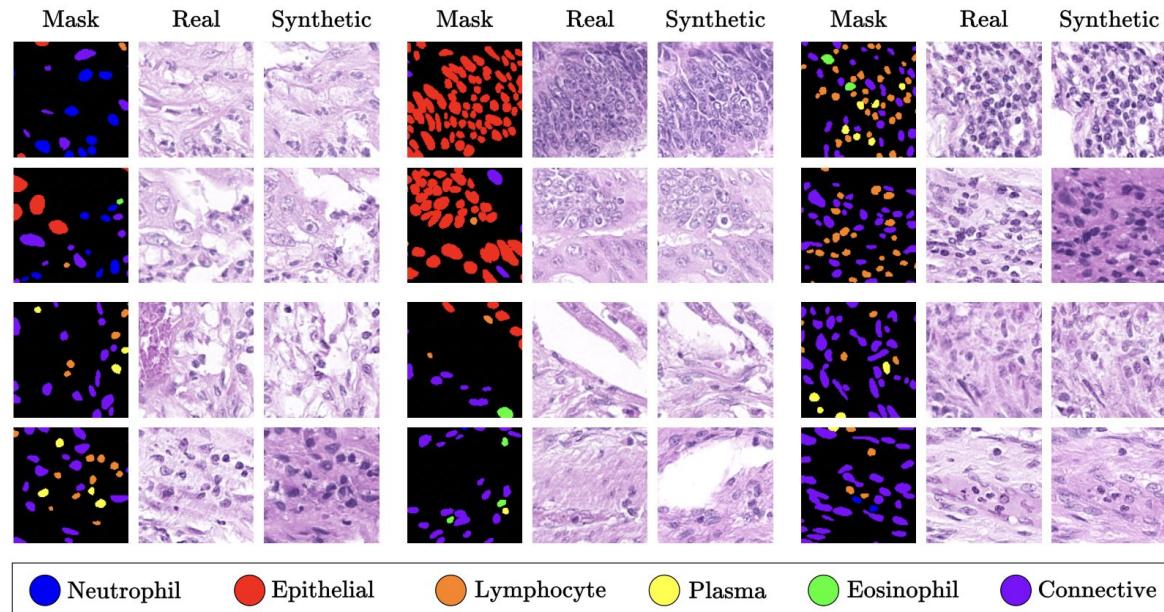
Imagen is preferred over recent work by human raters in sample quality & image-text alignment on DrawBench

NASDM: Nuclei-Aware Semantic Histopathology Image Generation Using Diffusion Models

Accepted at MICCAI 2023

Overview

The diffusion model can generate realistic histopathological patches conditioned on the semantic locations of six different types of nuclei.



Method

We condition the diffusion model on the **7-channel semantic mask** comprising of 6 individual nuclei semantics and an additional edge mask highlighting the nuclei instances overall

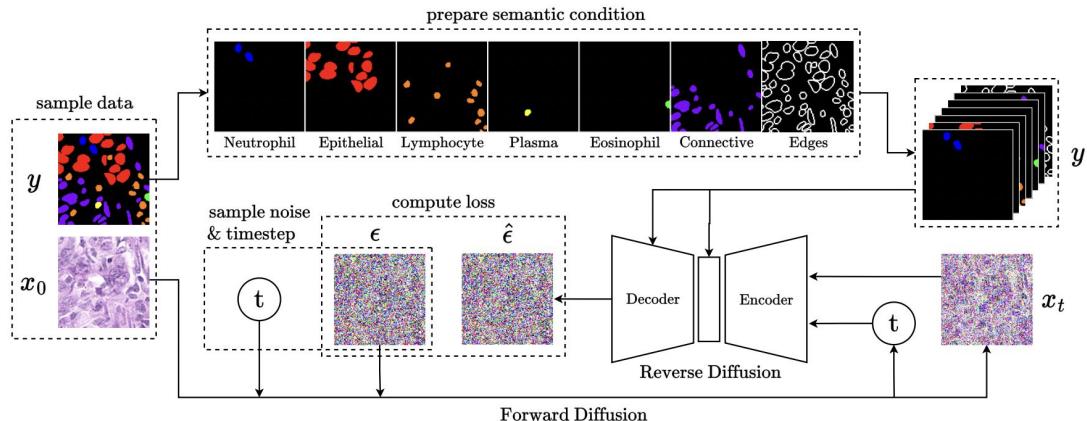


Fig. 1. NASDM training framework: Given a real image x_0 and semantic mask y , we construct the conditioning signal by expanding the mask and adding an instance edge map. We sample timestep t and noise ϵ to perform forward diffusion and generate the noised input x_t . The corrupted image x_t , timestep t , and semantic condition y are then fed into the denoising model which predicts $\hat{\epsilon}$ as the amount of noise added to the model. Original noise ϵ and prediction $\hat{\epsilon}$ are used to compute the loss in (4).

Results

We train the model on the lizard dataset at 20× magnification split into 128 × 128 pixels patches

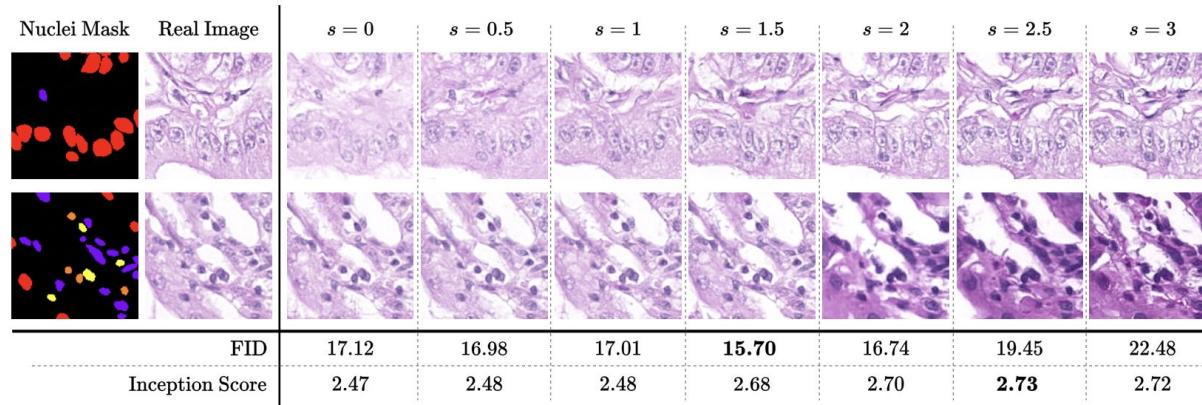
For training, we extract a total of 54,735 patches for training and 4,991 patches as a held-out set

Table 1. Quantitative Assesment: We report the performance of our method using standard generative metrics Fréchet Inception Distance (FID) metrics and Inception Score (IS) with the metrics reported in existing works. (-) denotes that the corresponding information was not reported in the original work.

Method	Tissue type	Conditioning	FID(\downarrow)	IS(\uparrow)
BigGAN [2]	bladder	none	158.4	-
AttributeGAN [32]	bladder	attributes	53.6	-
ProGAN [11]	glioma	morphology	53.8	1.7
Morph-Diffusion [18]	glioma	morphology	20.1	2.1
NASDM (Ours)	colon	semantic mask	15.7	2.7

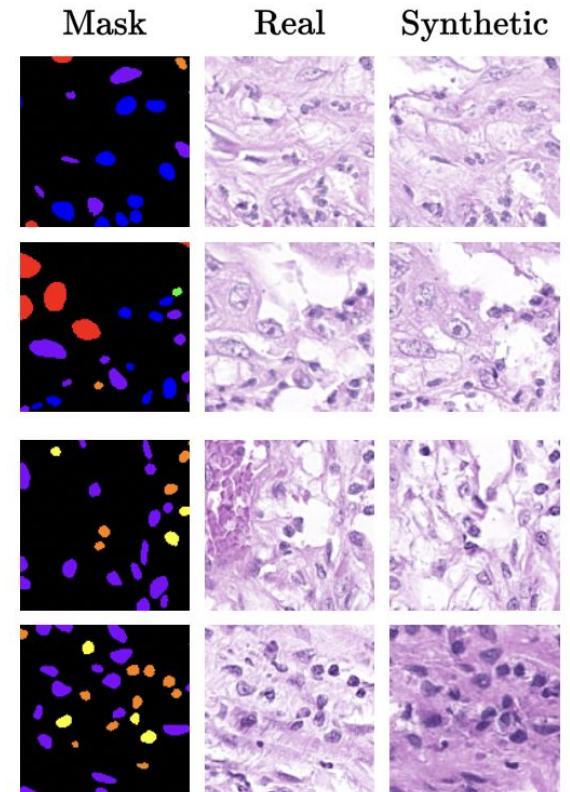
Key insights

1. Diffusion models are extremely powerful and **can generate hyper-realistic images** which are hard to distinguish from real ones
2. The model already **achieves state-of-the-art performance quantitatively**
3. The model **can effectively process the semantic conditioning information and generate images consistent with the mask**



Future directions

1. Train a model to generate the masks as well to design a truly end-to-end tissue generation framework that can **from scratch generate a tissue patch and a corresponding nuclei mask**
2. **Extend the generation to other types of organ tissue i.e. illial, glioma, breast, bladder, liver etc.**
 - a. Ideally the model should be able to take this information as a conditioning signal
3. **Study if a nuclei segmentation model can be improved by addition of synthetic annotated images in the training dataset**
4. Design a model to generate patches conditioned on neighbouring patches to **enable generation of an entire synthetic whole slide image**



● Neutrophil

● Epithelial

● Lymphocyte

● Plasma

● Eosinophil

● Connective

Questions?