Supplementary Material: A Morphology Focused Diffusion Probabilistic Model for Synthesis of Histopathology Images

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1. Supplementary Materials

This section provides additional information that we could not include in the paper itself because of space limitations.

1.1. Color Normalization in Detail

Let $I_s \in \mathbb{R}^{m\times n_s}$ be the source image, and let $I_t \in \mathbb{R}^{m\times n_t}$ be the target image, where m indicates the number of channels, and n_s and n_t are the number of pixels in the source and target images, respectively. Also, $H \in \mathbb{R}^{r\times n}$ is the stain density map for r stains. The objective is to normalize the colors of the source images into similar color domain of the target, and find the transferred source image denoted as I_s^{norm}. Vahadane et al. [2] showed that for both I_s and I_t, we can estimate the normalized source patch (I_s^{norm}) as:

$$H_s^{norm}(j,:) = \frac{H_s(j,:)}{RM(H_s(j,:))}RM(H_t(j,:)),\;\; j\,=\,1,...,r,$$
$$V_s^{norm} = W_t H_s^{norm},$$
$$I_s^{norm} = I_0 \exp\left(-V_s^{norm}\right),$$

where RM denotes the robust maximum of a vector.

1.2. Forward Diffusion in Detail

This diffusion process q is a Markov chain and produces latents x_{1,g_m} through x_{T,g_m} as follows [1]:

$$q(x_{1,g_m},\ldots,x_{T,g_m}|x_{0,g_m}) = \prod_{t=1}^{T} q(x_{t,g_m}|x_{t-1,g_m}), \tag{1}$$

$$q(x_{t,g_m}|x_{t-1,g_m}) = \mathcal{N}\left(x_{t,g_m}; \left(\sqrt{1-\beta_t}\right)x_{t-1,g_m}, \beta_t I\right), \tag{2}$$

and by using reparameterization, latent x_{t,g_m} can be derived directly from x_{0,g_m} as below:

$$x_{t,g_m} = \sqrt{\alpha_t}x_{0,g_m} + \sqrt{1-\alpha_t}\varepsilon, \tag{3}$$

$0 < \beta_1, \beta_2, ..., \beta_T < 1$ are fixed noise scales for each time step t and $\alpha_t := \prod_{s=1}^{t}(1-\beta_s)$. Also, the distribution of theε is as $\varepsilon \sim \mathcal{N}(0,I)$

1.3. Model Implementation and Training

We trained our model using PyTorch with 1000 diffusion steps using a workstation with an NVIDIA V100 GPU. The rest of the parameters are available at Table 1.

Parameter	Value
Image size	128
Weighting scheme	P2
Diffusion steps	1000
Maximum Patches	100
Channels	64
Heads	4
Heads channels	64
Attention resolution	32,16,8
BigGAN up/downsample	yes
Num Resblocks	2
Learning rate	1e-4

Table 1: Hyperparameters for diffusion models used in this paper.

1.4. Samples of Real Patches

Table 2 provides the breakdown of the extracted patches based on genomic subtypes and Figure 1 shows samples of real extracted patches after applying the the color normalization module to them.

	IDHC	IDHNC	IDHWT	Total
Patches	12,139	16,975	4,663	33,777
IDH Status	Mutant	Mutant	Wildtype	-
1p19q Status	Codeletion	Retained	-	-

Table 2: Breakdown of extracted patches per subtype

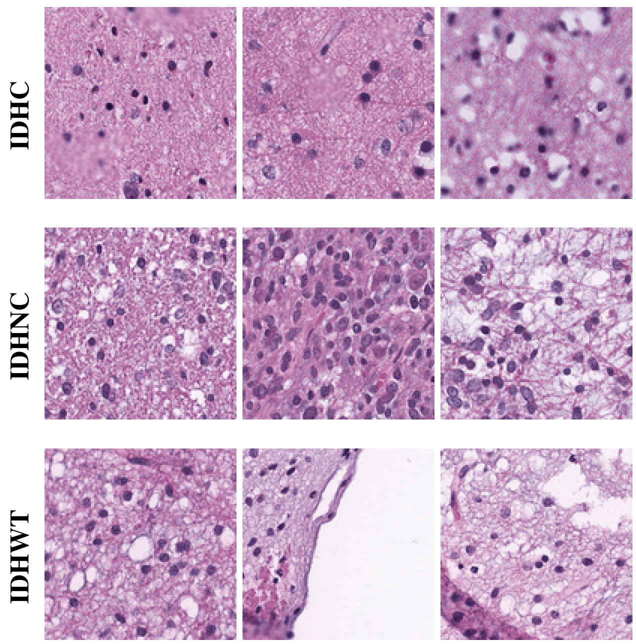

Figure 1: Selection of patches with size =128x128 pixels extracted from the WSI. Each row represents a different genotypes.

1.5. Samples of Generated Images by Our Diffusion Probabilistic Model

Figure 2 presents the 10 synthetic images produced by diffusion model, which are significantly close to real images.

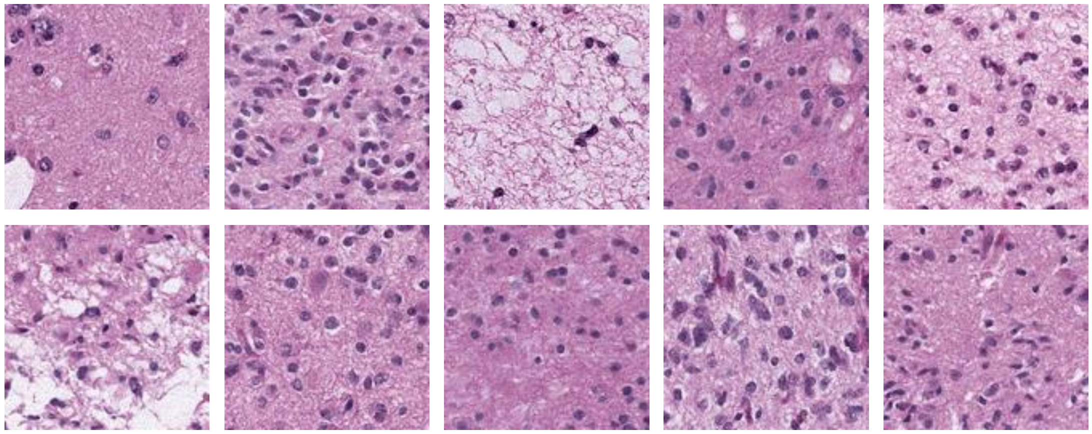

Figure 2: Top 10 generated images by our diffusion model.

1.6. Survey Visualization

Figure 3 shows a sample section of the web-form that the pathologists completed. Figure 4 is the detailed illustration of each expert opinion about each real or synthetic image. Green and yellow colours depict synthetic and real images, respectively. Also, brown presents a synthetic images that classified as real by pathologists and red corresponds to a real images identified as synthetic. Purple shows medium confidence answers.

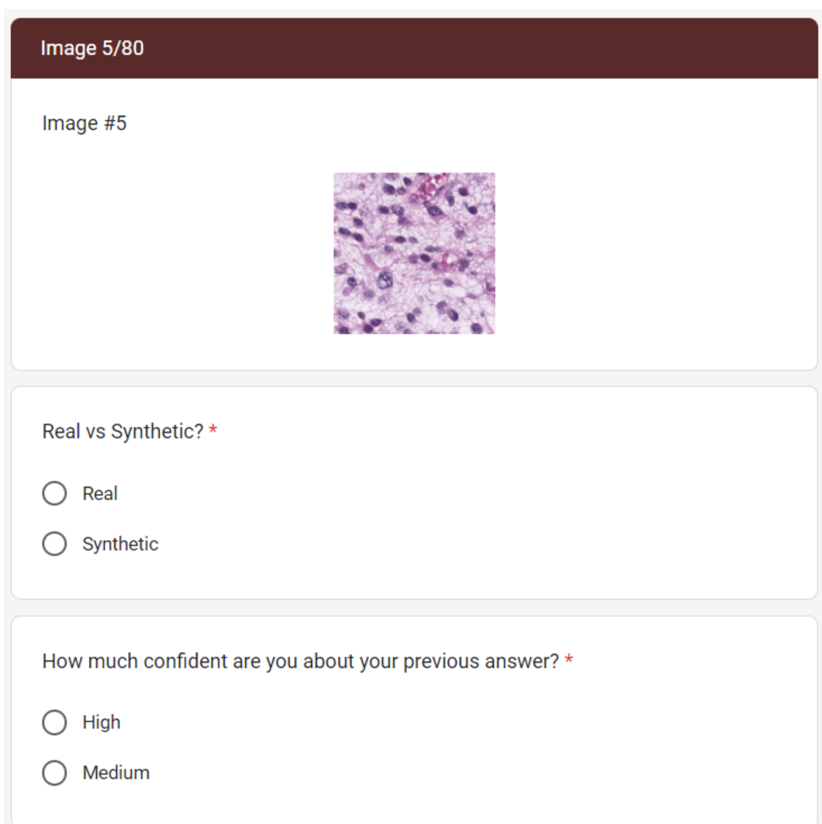

Figure 3: The web form for subjective study

References

[1] Jonathan Ho, Ajay Jain, and Pieter Abbeel. Denoising diffusion probabilistic models. *Advances in Neural Information Processing Systems*, 33:6840–6851, 2020.

[2] Abhishek Vahadane, Tingying Peng, Amit Sethi, Shadi Albarqouni, Lichao Wang, Maximilian Baust, Katja Steiger, Anna Melissa Schlitter, Irene Esposito, and Nassir Navab. Structure-preserving color normalization and sparse stain separation for histological images. *IEEE Transactions on Medical Imaging*, 35(8):1962–1971, 2016.

Image Number	Label	P1		P2	
1	Synthetic	Real	High	Synthetic	High
2	Synthetic	Real	High	Real	High
3	Real	Real	High	Real	High
4	Synthetic	Synthetic	Medium	Real	Medium
5	Real	Real	High	Synthetic	Medium
6	Synthetic	Synthetic	High	Synthetic	Medium
7	Synthetic	Real	High	Real	Medium
8	Synthetic	Real	High	Synthetic	Medium
9	Real	Real	High	Synthetic	Medium
10	Synthetic	Real	High	Real	Medium
11	Real	Real	High	Synthetic	High
12	Real	Real	High	Real	High
13	Real	Real	High	Synthetic	High
14	Synthetic	Synthetic	Medium	Synthetic	Medium
15	Real	Real	High	Real	High
16	Synthetic	Real	High	Synthetic	Medium
17	Synthetic	Real	High	Real	Medium
18	Synthetic	Real	High	Real	Medium
19	Real	Real	High	Real	High
20	Real	Real	High	Synthetic	High
21	Synthetic	Synthetic	High	Synthetic	High
22	Real	Real	High	Real	High
23	Synthetic	Real	High	Synthetic	High
24	Synthetic	Real	High	Synthetic	Medium
25	Real	Real	High	Real	Medium
26	Real	Real	High	Synthetic	Medium
27	Real	Real	High	Real	Medium
28	Real	Real	High	Real	Medium
29	Real	Real	High	Synthetic	High
30	Real	Synthetic	Medium	Real	Medium
31	Synthetic	Real	High	Synthetic	Medium
32	Real	Real	High	Real	High
33	Synthetic	Real	Medium	Real	High
34	Real	Real	High	Synthetic	Medium
35	Synthetic	Real	High	Synthetic	High
36	Synthetic	Real	High	Synthetic	High
37	Real	Real	High	Synthetic	High
38	Synthetic	Real	High	Real	High
39	Real	Synthetic	Medium	Synthetic	Medium
40	Real	Real	Medium	Synthetic	High
41	Synthetic	Real	High	Real	Medium
42	Synthetic	Real	High	Real	High
43	Synthetic	Real	High	Real	High
44	Real	Synthetic	Medium	Real	Medium
45	Synthetic	Real	High	Real	High
46	Synthetic	Real	High	Real	High
47	Real	Synthetic	Medium	Synthetic	Medium
48	Real	Real	High	Real	High
49	Synthetic	Real	High	Real	High
50	Synthetic	Synthetic	Medium	Synthetic	High
51	Real	Real	High	Synthetic	High
52	Synthetic	Real	High	Synthetic	High
53	Real	Synthetic	Medium	Synthetic	High
54	Synthetic	Real	High	Real	Medium
55	Real	Synthetic	Medium	Synthetic	High
56	Real	Synthetic	High	Synthetic	High
57	Real	Real	High	Synthetic	Medium
58	Synthetic	Real	High	Real	Medium
59	Real	Real	High	Real	Medium
60	Real	Real	High	Real	High
61	Synthetic	Real	High	Real	High
62	Real	Real	High	Synthetic	High
63	Synthetic	Real	High	Real	High
64	Real	Real	High	Real	Medium
65	Real	Real	High	Real	Medium
66	Real	Real	High	Synthetic	High
67	Synthetic	Synthetic	Medium	Real	High
68	Synthetic	Real	High	Real	High
69	Synthetic	Real	High	Real	High
70	Real	Synthetic	Medium	Synthetic	High
71	Real	Real	High	Real	High
72	Synthetic	Synthetic	Medium	Synthetic	High
73	Real	Real	Medium	Synthetic	Medium
74	Real	Real	High	Synthetic	Medium
75	Synthetic	Real	Medium	Synthetic	Medium
76	Real	Real	High	Synthetic	Medium
77	Synthetic	Real	High	Synthetic	Medium
78	Synthetic	Real	High	Synthetic	High
79	Synthetic	Real	High	Real	Medium
80	Synthetic	Real	High	Real	Medium

Figure 4: Illustration of each pathologist's opinion. Green: synthetic image, yellow: real one. Brown: synthetic images that classified as real by pathologists. Red: real image diagnosed as synthetic image. Purple: medium confidant answers.