

Development of a Deep Learning Denoising and Super-Resolution Framework for Micro-MRI

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Abstract

Micro-MRI enables high-contrast anatomical imaging in small animal models but often requires a trade-off between spatial resolution, signal-to-noise ratio (SNR), and scan time. This study presents a deep learning framework designed to enhance image quality and reduce acquisition time by combining denoising and super-resolution techniques. Paired T2-weighted scans were acquired for 24 mice using a 7T Bruker Pharmascan system, consisting of low-resolution (1-minute) and high-resolution (12-minute) images. For each mice, scans of multiple regions and along different planes were acquired. After data pre-processing, a convolutional neural network based on a U-Net structure was trained using automated hyperparameter optimization. This process systematically tested combinations of learning rates, optimizers, convolutional filter sizes, upsampling and downsampling strategies, loss and activation functions, batch size, and the inclusion of residual learning to identify the most effective network structure and training configuration. Model performance was evaluated using global and local image quality metrics. Mean squared error (MSE) and structural similarity index (SSIM) quantified overall image accuracy and structural integrity, while contrast-to-noise ratio (CNR) assessed localized contrast improvements, particularly relevant for denoising effectiveness. In addition to the U-Net model, a second denoising framework called the Anchored Path Diffusion Denoising Model (APDDM) was developed. This method adopts a supervised strategy that leverages the real low-quality images as end-points. This allows the forward process to incorporate the empirically estimated noise distribution from the paired image dataset. This model introduces realistic noise during training to improve robustness. Both DL methods demonstrated improved image quality while enabling significantly shorter acquisition times, supporting more efficient imaging workflows in preclinical research.

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Wolf focused on the anchored path diffusion. Fea and Magali focused on the literature study, report and organization. They also give their input to develop the deep learning together with Daan and Darío.

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1 Introduction

Magnetic resonance imaging (MRI) is a non-invasive imaging technique that uses magnetic fields and radio frequency pulses to generate detailed anatomical images. Dedicated micro-MRI systems are available for preclinical imaging that provides excellent soft tissue contrast for anatomical visualization in rodent models. To visualize the animal's anatomy with sufficient details, a high spatial resolution is important. Reducing voxel size improves spatial resolution but also decreases the signal and lowers the signal-to-noise ratio (SNR). On the other hand, increasing acquisition time can enhance signal quality and SNR. However, this increases the risk of artefacts, blurring, and motion-related distortions. Additionally, longer scan times are often impractical in real-life imaging workflows, where efficiency and throughput are essential. A good balance between spatial resolution, acquisition time and SNR is needed. Image processing/restoration tools can be used to improve the quality of the acquired image, but traditional techniques relied on manual tuning or fixed algorithms. More recently, deep learning has emerged, which can learn to restore fine details and reduce noise directly from examples of high and low quality images which has been demonstrated to provide better results. These models address the trade-off between resolution and image quality [1].

2 Data collection

2.1 Infinity lab

This research was conducted at Infinity, the pre-clinical imaging core facility of Ghent University. The lab provides imaging systems of various modalities, including MRI, PET, SPECT. We used a Bruker pharmascan to acquire images for our DL network. To avoid contamination of the lab, the operator must wear a hairnet, face mask, lab coat, latex gloves and shoe covers. Metallic objects can be pulled into the MRI or disrupt the magnetic field, so they should be left outside the MRI room. The Infinity lab also contains X-ray and PET/SPECT systems. While X-ray exposure is monitored with personal dosimeters, the Geiger counter at the lab exit is used to detect possible contamination from radioactive tracers used in PET/SPECT imaging.

2.2 Preparation and calibration

All imaging was performed using a Bruker PharmaScan system operating at 7 Tesla designed for small animal imaging [4]. A dataset of 19 mice was already acquired and provided to us. These made use of the rat brain surface coil. We made

use of the same coil to obtain additional images to maintain uniformity in data acquisition. Before the acquisition sequence began, the mouse needed to be placed inside the scanner properly. Each mouse was scanned in two different fields-of-view; once with the head-thorax in the center of the FOV, and once with the thorax-abdomen region (see Figure 1). Supports and tape were used to fixate the mouse.

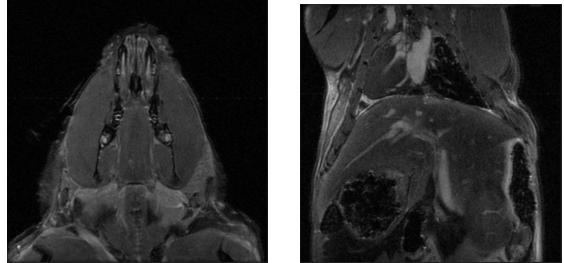


Figure 1: MRI scan regions: head-thorax (left) and thorax-abdomen (right).

The acquisition sequence consisted of multiple steps to fine-tune the system before image acquisition began:

1. svWobble scan: svWobble was only performed at the start of the first scan session. It helps the system determine how much water is present in the coil and fine-tunes the scanner accordingly. This step is especially necessary when switching between different animal species, as the water content in the coil may vary. If the same type of sample (e.g., the same mouse model) is used throughout the experiment, svWobble does not need to be repeated for following scans.
2. Tripilot scan: short, preliminary scan that allows the user to define the field-of-view (FOV) that needs to be acquired. This step generates 3 orthogonal views: axial, sagittal and coronal. A bounding box is then manually defined to encompass the required FOV, ensuring the right structures are within the FOV. Especially important is the phase direction, where the FOV must cover the entire subject.

2.3 Performing the MRI scan

Once the mouse was correctly positioned and the FOV was defined, the process of acquiring 3D MRI data was started. This was done for each mouse for both the head-thorax region and the thorax-abdomen region. To obtain matched high-low resolution data in all directions, the following sequence was performed: axial default, axial fast, coronal default, coronal fast, sagittal

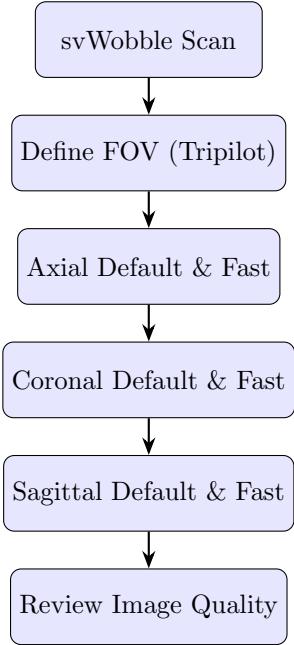


Figure 2: Schematic overview of the MRI acquisition pipeline.

default and lastly sagittal fast. In this case “default” stands for a 12-minute scan and “fast” for a 1-minute scan as can be seen in table 1. After each image sequence is completed, they are reviewed to check for any misalignment, artifacts, or other issues to ensure accuracy and quality.

All scans were acquired using a T2-weighted RARE (rapid acquisition with refocused echoes) sequence. This sequence is often used in pre-clinical imaging because it produces images that have high contrast between different soft tissues. T2-weighted images highlight differences in transverse relaxation time, which reflects how quickly protons lose phase coherence after excitation by a radio frequency pulse. This signal decay changes depending on its interaction within different types of tissues. Shorter T2’s, found in tissues such as muscle and fat, mean that the signal will decay very fast while tissues with a longer T2, for example fluids, retain the signal longer. As a result, in fluids appearing brighter than muscle and fat in the image.

From a technical perspective, the T2-weighted contrast is created by selecting an appropriate echo time (TE) and repetition time (TR). The echo time is the time between the initial radio frequency pulse and the measured MRI signal. A longer TE allows more time for tissues with a short T2 to lose their signal, resulting in them looking darker on the image. Tissues with longer T2 values maintain more signal and will look brighter. Repetition time (TR) refers to the time between successive excitations of the same tissue slice. Specifically for T2-weighted images, a longer TR is used, minimizing the influence of T1 relaxation. For this study a TE of 37.1ms

and TR of 4000ms are used. This provides a strongly T2-weighted image [2] [6].

2.4 Image Datasets

In table 1 the parameters can be found, which were used for the 1-minute low resolution and 12-minute high resolution scans. These values were selected in function of the desired acquisition time, image quality and SNR. The matrix size determines the level of detail in an image with the high-resolution scan (300x300 pixels) capturing finer structures compared to that of the low-resolution scan (150x150 pixels). Other parameters such as repetition time, echo time and thickness remained constant for consistency. The field of view also stays the same at 3 cm x 3 cm to capture the same region of interest. An important difference between the two scans is the in-plane resolution. The lower this value, the higher resolution the visualisation. The 12-minute scan (0,01 cm/pixel) is more precise while the 1-minute scan (0,02 cm/pixel) is faster but has less detail. To significantly enhance SNR by reducing noise, the high-resolution scan uses five averages per slice.

In the summer of 2024 an internship was done by Verhelst Niels and Courtens Joran [8]. The data that they acquired was used in combination with the data acquired in this project. During the internship, 19 mice were scanned. In the project, the data of 5 mice were acquired.

Table 1: Overview of the scan and image parameters used to acquire high- and low-resolution data of mice.

	1 min (low-res)	12 min (high-res)
Number of slices	30	30
Matrix size	150x150	300x300
Repetition time	4000 ms	4000 ms
Field-of-view	3 cm x 3 cm	3 cm x 3 cm
Echo time	37.1 ms	37.1 ms
In-plane resolution	0.02 cm/pixel	0.01 cm/pixel
Slice thickness	0.6 mm	0.6 mm
Averages per slice	1	5

3 Pre-processing and data augmentation

Pre-processing of the slices is a crucial step in preparing the data for the deep learning model. This stage ensures the data is uniform and optimized for training.

3.1 Removal of bad image slices

Some of the obtained images contained artifacts or noise, these could negatively impact the model training. To remove these bad slices from

the data set, a visualization script was used to display the MRI slices allowing for manual inspection. Once bad slices were identified, they were removed from the used dataset (see appendix B: Figure 22). Of the 900 slices acquired, 111 were excluded.

3.2 Cropping of the image slices

Cropping is a commonly used image-manipulation process. The obtained MRI images contained lots of background noise which interferes with the performance of the model. To counter this problem the images were cropped ensuring that our region of interest was intact (see appendix B: Figure 23).

3.3 Zarr arrays

The acquired data were first converted into Zarr arrays to compress the large volume of data while maintaining image quality. Unlike other formats this enables faster access since specific slices can be loaded instead of the entire dataset. The low-resolution image were upsampled using nearest-neighbor interpolation (order=0) with a zoom factor of 2 to match the high-resolution image dimensions.

3.4 Normalization

Mean normalization was performed, each low-resolution image was divided by its mean intensity, and the same mean value was applied as a normalization factor for the corresponding high-resolution image. Both low-resolution and high-resolution images were converted for compatibility with PyTorch models.

3.5 Padding and random flipping

The images were randomly flipped horizontally and vertically with a 50% probability, to introduce variations. This is done during network training. This improves the model generalization. Since input may have varying dimensions, the images were padded to match the largest width and height within each batch, ensuring uniform sizes for batch processing.

4 Neural Network and Training Process

4.1 Model architecture

For the denoising deep learning model, a convolutional neural network based on the U-Net architecture was used. U-Net is a form of autoencoder, consisting of two main parts: an encoder and a decoder (see Figure 3) [3].

The input to the network is a low-resolution (150×150 pixels), which is first upsampled via interpolation to match the high-resolution target size (300×300 pixels). The network then processes this input to produce a denoised output with a higher signal-to-noise ratio (SNR).

The encoder comprises a series of convolutional layers followed by downsampling steps (e.g., pooling or strided convolutions). These layers extract hierarchical features while reducing spatial resolution and increasing the number of feature channels.

The decoder mirrors the encoder structure and consists of upsampling layers (e.g., transposed convolutions or interpolation followed by convolution) that reconstruct the spatial resolution of the input. To preserve spatial information and enhance feature propagation, **skip connections** are added between corresponding layers of the encoder and decoder. These allow the decoder to directly access feature maps from earlier stages in the encoder, improving the model’s ability to recover fine details.

In this implementation, residual learning is optionally used—not between intermediate layers, but globally between the input and output of the network. This means the model learns to predict the residual (i.e., the noise component), which is then added back to the input to reconstruct the denoised image. This technique can lead to faster convergence and improved stability, as the network focuses on learning the difference rather than the full image content.

The rationale behind using this U-Net structure is that the encoder condenses and abstracts the relevant features of the input image, while the decoder reconstructs an enhanced version by combining this condensed representation with spatially detailed information from the skip connections.

4.2 Encoder-Decoder Model: Hyperparameter Optimization

To get the best results for the deep learning model for micro MRI image denoising and super-resolution, the hyperparameters need to be fine-tuned. Given the number of components and interactions within the model, manual tuning would be inefficient and inconsistent. Therefore, an open-source optimization software, such as Optuna, was used [35].

Each trial corresponds to the training of the model with a specific set of hyperparameters. The performance metrics are recorded after each trial, for example a validation loss. These metrics are used as a guide for the search. A built-in sampler selects new parameter values to explore, while a pruner stops trials early if the model is clearly not improving. This combination is especially helpful to reduce the number of trainings

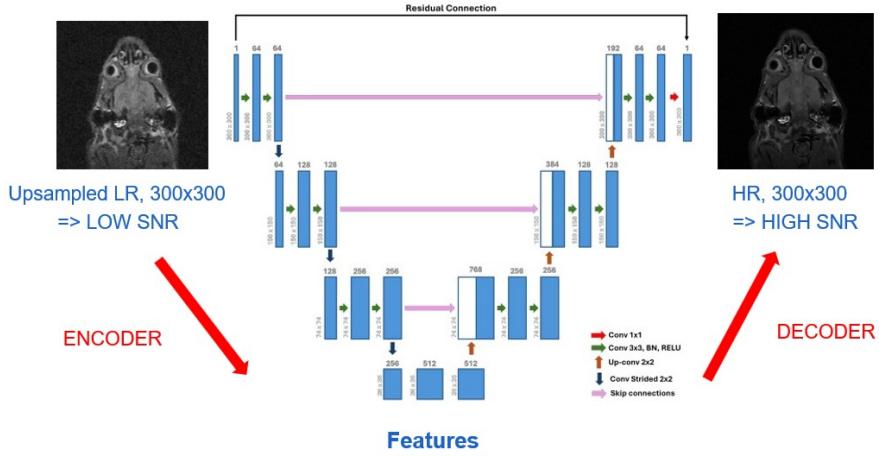


Figure 3: U-Net architecture.

that need to be run, this saves computational resources.

One of the advantages of Optuna is its define-by-run approach [9]. This means that instead of predefining the entire parameter space before the optimization, the search space is defined dynamically while being executed. This gives more flexibility especially in cases where certain parameters are only relevant under specific conditions. Instead of testing all combinations blindly, Optuna can selectively explore subsets of the parameter space based on earlier decisions within the same trial. The avoidance of meaningless testing makes the optimizations process more efficient.

Overall Optuna played a key role in helping reach a well-performing model more efficiently, and ensured that our final configuration was based on data-driven search rather than trial and error.

In summary, the hyperparameter optimization explored a wide variety of configurations for the network structure. However, to ensure a fully optimized model, it is equally important to fine-tune the training process itself. Section 4.2.2 extends the optimization to parameters such as learning rate, scheduler strategies, optimizers, loss functions, and training routines. This combined approach ensures that both the network architecture and its learning dynamics are tailored to get the best denoising performance.

4.2.1 Hyperparameters of the Network Structure

Features main and features skip To determine the number of main features, different powers of 2 were explored. Each component of the `features_main` list was assigned a different power of 2, and subsequent elements followed incrementally higher powers. The number of elements in this list determines both the depth

of the network and the number of feature channels at each layer. While sometimes overlooked, these are in fact fundamental architectural hyperparameters, as they define the model’s capacity and depth. Therefore, they were explicitly included in the optimization process to assess their impact on performance.

For the `features_skip`, the same values as in `features_main` were used, but with the last element removed. These values define how many filters are used in each layer of the encoder and decoder. The skip connections pass feature maps from the encoder to the decoder at corresponding levels, helping the model retain spatial information during reconstruction.

To test different configurations, one value was selected from each of three predefined categories. Specifically, `features_main_1` was chosen from [32, 64, 128], `features_main_2` from [64, 128, 256], and `features_main_3` from [128, 256, 512]. This setup allowed us to systematically explore various combinations of feature sizes and evaluate their influence on model performance.

Downsampling method The downsampling method is an important aspect of the encoder and determines how the images will be reduced. Different methods were considered such as maxpooling, meanpooling and strided convolution. Maxpooling selects the maximum value from each patch in the feature map, preserving the most prominent features while reducing spatial dimensions. This concept can be observed in Figure 4 [14]. Another approach is Meanpooling. Instead of taking the prominent feature, this method averages the values within a patch, offering a smoother downsampling method. In Figure 5 the concept of meanpool can be seen. The last method, is strided convolution. The principle can be seen in Figure 6. In this approach, the convolution is applied with a larger stride, which determines how far the filter moves across the feature map during the convolution

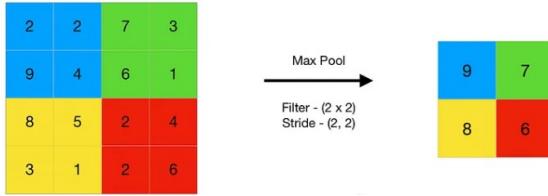


Figure 4: Downsampling - Maxpool



Figure 5: Downsampling - Meanpool

process. When the stride is greater than 1, the convolution operation skips some of the pixel, which results in an effective method to reduce the size of the feature map [15]. Each of these methods reduce the size of the feature map but with different strategies.

Upsampling The upsampling method is the process in the decoder by which the resolution of an image is increased while minimizing the loss in image quality. The goal is to increase the number of rows and/or columns of the image. Several methods are available, including nearest neighbor, linear, bilinear, trilinear, and bicubic interpolation, as implemented in PyTorch’s interpolation modes.

The nearest neighbor interpolation is the simplest approach. Each pixel of the upsampled image is assigned the value of its nearest neighbor in the original image. This method is fast and simple, but might produce pixelated images.

The linear interpolation calculates the new pixel value by taking a weighted average of the two nearest pixels along a single axis. The bilinear interpolation calculates a weighted average of the four nearest neighbors’ pixel values in the original image. It uses linear functions and a 2×2 pixel grid.

The trilinear interpolation is used in 3D images. The interpolation is first performed linearly along one axis, followed by linear inter-

polation along the second and third axes. The linear, bilinear, and trilinear methods result in smoother images than the nearest neighbor method.

Bicubic interpolation is more advanced. This method first identifies the nearest 4×4 grid of pixels surrounding the point that needs to be interpolated. Then, it calculates the cubic polynomials that best fit the pixel values in the grid. After that, the pixel intensity is estimated at the target position. It is an effective method for high-quality upscaling because it preserves details and reduces artifacts [18] [19].

Activation function Activation functions introduce a non-linearity into the network. This allows complex mapping between inputs and outputs. Without an activation function, the network would behave like a linear system and would not be able to model intricate relationships such as edges and contrast. Different options were tested such as ReLU, LeakyReLU, ELU and PReLU. Each of these options come with their own set of advantages and difficulties. ReLU (Rectified Linear Unit) is most commonly used as an activation function because of its simplicity and computational efficiency. This function 1 returns the positive inputs directly and zero if negative. One of the limitations is a phenomenon called ‘dying neurons’, if a neuron only receives negative inputs, it will always output zero and stop learning. LeakyReLU addresses this problem by allowing small negative outputs. This function 2 helps keeps neurons active and keeping them active. This technique keeps the simplicity of ReLU while improving stability. ELU is similar to LeakyReLU in sense that negative outputs are generated, but in this case with a smooth exponential curve 3 instead of a constant curve. Finally, PReLU (Parametric ReLU) also starts from LeakyReLU but in this case the negative slope is a learnable parameter and not a fixed value. This lets the model adapt the activation function in training leading to potentially better performance. However it does introduce an extra parameter increasing computational cost [23].

$$f(x)_{ReLU} = \max(0, x) \quad (1)$$

$$f(x)_{LeakyReLU} = \begin{cases} x & \text{if } x \geq 0 \\ \beta x & \text{if } x < 0 \end{cases} \quad (2)$$

$$f(x)_{ELU} = \begin{cases} x & \text{if } x \geq 0 \\ \alpha(e^x - 1) & \text{if } x < 0 \end{cases} \quad (3)$$

$$f(x)_{PReLU} = \begin{cases} x & \text{if } x \geq 0 \\ ax & \text{if } x < 0 \end{cases} \quad (4)$$

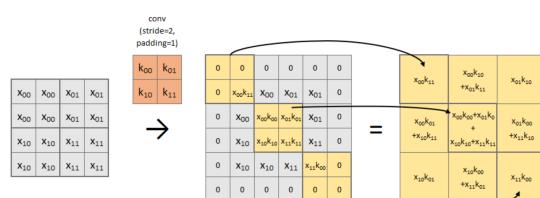


Figure 6: Downsampling - convStrided

Residual learning With residual learning instead of predicting the final high-resolution images the model learns the difference between the low- and high-resolution, this is called the residual. After training, the residual is added back onto the input image to produce the final image. This method has its advantages. Learning the missing information is often faster and easier than predicting the entire image. This can lead to faster and better convergence. In this project residual learning is an optional feature, which can be set True or False. Optuna was used to explore if enabling led to better performance.

4.2.2 Hyperparameters of the Training Process

Learning Rate Strategies The scheduler adjusts the learning rate during training according to a predefined strategy. The following schedulers were tested: exponential learning rate (`ExponentialLR`), step learning rate (`StepLR`), and reduce learning rate on plateau (`ReduceLROnPlateau`).

The `ExponentialLR` divides the learning rate every epoch by the same factor Γ . As a result, the learning rate decreases quickly during the first epochs and then gradually stabilizes, approaching zero over time. `StepLR` is similar to `ExponentialLR`. It also decays the learning rate by gamma. However, the key difference is that this decay occurs only every N epochs. This leads to more gradual and less frequent reductions in the learning rate compared to `ExponentialLR`. Their respective formulas 5 and 6 are given below.

Another scheduler is `ReduceLROnPlateau`. Unlike the others, it adapts the learning rate based on the performance of a specified metric. This algorithm decreases the learning rate when the specified metric stops improving for longer than allowed. So, the learning rate is kept constant as long as the metric improves. When the learning rate is reduced, the results stagnate [17] [16].

These schedulers make use of a learning rate decay value, which determines how much the learning rate is reduced at each step. The learning rate decay decreases the learning rate as training progresses and becomes more stable. It is used in the scheduler algorithms as the step size. Here, the learning rate decay values of 0.1, 0.3, and 0.5 were tested.

In addition to scheduling and decay, selecting an appropriate initial learning rate is also crucial. The pace in which the weights are updated during training depends on the learning rate. A learning rate value which is too high can lead to instability and poor convergence, while a value that is too low might slow down the training of the model, as shown in Figure 7, or even cause

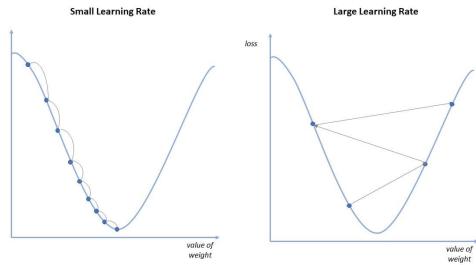


Figure 7: Comparison of different learning rates

the model to get stuck in a local minimum [20]. Optuna was used to search across a continuous range of values $[10^{-2}, 10^{-6}]$ to find the optimal balance between convergence and stability.

$$lr_{\text{epoch}} \text{ExponentialLR} = \Gamma \times lr_{\text{epoch}-1} \quad (5)$$

$$lr_{\text{epoch}} = \begin{cases} \Gamma \times lr_{\text{epoch}-1}, & \text{if epoch mod step_size} = 0 \\ lr_{\text{epoch}-1}, & \text{otherwise} \end{cases} \quad (6)$$

Optimizer The optimizer plays a crucial role in fine-tuning the model’s weights during training to minimize the loss function. Different methods are available, each with its own advantages and disadvantages. In this project, four different optimizers will be tested: Adam, AdamW, SGD and RMSprop. One of its limitations is the way it incorporates L2 regularization directly into the gradient update, which can sometimes negatively affect the performance. Stochastic gradient descent(SGD) updates the model’s parameters based on the gradient loss function. Unlike Adam, it uses a fixed learning rate and does not estimate moments of the gradients. In contrast, AdamW decouples weight decay from the gradient update, applying it separately after the parameter update, which provides a more effective approach [13]. RMSprop, also known as root mean square propagation, is another gradient-based optimization algorithm. It uses a moving average of the squared gradients to adapt the learning rate for each parameter. This means it does not rely solely on the current gradient, but also incorporates information from previous updates. By “remembering” the magnitude of recent gradients, RMSprop smooths out noisy updates and helps stabilize the training process. This leads to faster and more reliable convergence, particularly in settings with sparse gradients or noisy data, functioning similarly to momentum-based methods. It uses an adaptive learning rate instead of treating the learning rate as a hyperparameter, which results in a change of learning rate over time. This can result in faster convergence [12].

Loss function The loss function defines how well our model is performing by evaluating the prediction against the target images. It guides the process by providing a measure of error which then can be minimized during training. 3 loss functions were tested: Mean Squared Error (MSE) , Mean Absolute Error (MAE) and a hybrid loss. MSE penalizes the squared difference between the predicted and true pixel values. This loss function penalizes large errors more severely because the errors are squared. This method is effective for achieving high numerical accuracy but can lead to overly smooth outputs with less fine structural detail. MAE computes the average of the absolute differences between predicted and true pixel values. This method preserves edges and sharper transitions better than MSE but it is less sensitive to small errors and can converge more slowly [21]. The last option, the hybrid loss, is a custom-defined loss which combines mean squared error (MSE) and structural similarity index (SSIM).

$$\mathcal{L}_{\text{hybrid}} = \alpha \cdot \mathcal{L}_{\text{MSE}} + (1 - \alpha) \cdot (1 - \text{SSIM}) \quad (7)$$

- $\alpha \in [0, 1]$ controls the balance between the two components,
- \mathcal{L}_{MSE} measures the average pixel-wise error between the predicted and ground truth images,
- SSIM evaluates perceptual similarity.

The Structural Similarity Index Measure (SSIM) is used to evaluate the perceptual similarity between two images. Unlike MSE or MAE, which focus on absolute pixel-wise differences, SSIM compares structural information by considering changes in luminance, contrast, and structure. This makes it particularly suitable for applications like medical imaging, where preserving anatomical detail is important.

$$\text{SSIM}(A, B) = \frac{(2 \cdot \mu_A \cdot \mu_B + c_1)(2 \cdot \sigma_{AB} + c_2)}{(\mu_A^2 + \mu_B^2 + c_1)(\sigma_A^2 + \sigma_B^2 + c_2)} \quad (8)$$

- μ_a, μ_b : mean intensities of images A and B
- σ_A^2, σ_B^2 : variances
- σ_{AB} : covariances
- c_1, c_2 : 2 variables which stabilize the division (both are typically small values)

MSE helps preserve pixel-wise fidelity while SSIM ensures structural integrity of the image, which is crucial in medical contexts. Optuna was used to choose the type of loss function to apply and, in the case of the hybrid loss, to optimize the value of alpha. This allowed the model to adaptively prioritize pixel accuracy versus perceptual quality.

Others Several training-related settings were applied to control the model optimization process, including early stopping, batch size, and the number of training epochs. While these are not traditional hyperparameters in the architectural sense, they significantly influence model performance and training efficiency.

Early stopping was used to prevent excessive training and potential overfitting. The criterion is based on a ‘no improvement’ threshold, where training stops if validation performance does not improve for a set number of epochs. In this project, training was stopped if no improvement was observed after 6 consecutive epochs, with a minimum of 10 epochs always run to ensure sufficient learning.

Batch size determines how many training samples are processed before updating the model weights. Larger batch sizes provide more stable gradient estimates, which can speed up training but require more memory and may generalize worse. Smaller batches introduce more noise into gradient updates, which can help escape local minima but may lead to slower convergence.

Number of epochs refers to how many times the model sees the entire training dataset. Although not a direct hyperparameter, it plays a key role in controlling learning. Too few epochs can result in underfitting, while too many may lead to overfitting, especially when early stopping is not properly configured.

4.3 Anchored Path Diffusion Denoising Model (APDDM)

To complement the direct image-to-image denoising approach, discussed in the previous section, a second model was implemented, the Anchored Path Diffusion Denoising Model (APDDM). This model is a diffusion based framework based on the original DDPM by Ho et al. (2020) [22]. It is designed specifically for paired high and low SNR images, in this case the high-resolution (12-minute) scans and the low-resolution (1-minute) scan. Unlike conventional denoising diffusion models that add noise to the HNR images until the endpoint is complete Gaussian noise, APDDM uses the actual low SNR image as the endpoint, allowing the model to incorporate real noise from the dataset into the forward process.

4.3.1 Forward Diffusion Process

The forward process defines a stochastic path that gradually transforms the clean image x_0 into a noisy version x_t , with the endpoint distribution anchored around the real noisy scan x_T^* . This is achieved using a Markov chain defined by:

$$x_t = q(x_{t-1}) = x_{t-1} + \frac{1}{T} \cdot R + f(t) \cdot \hat{\epsilon} \quad (9)$$

$$t = 1, 2, \dots, T$$

- $R = x_T^* - x_0$: the residual between 2 paired images
- $\hat{\epsilon}$: noise sampled from empirical residuals
- $f(t) = 4 \cdot \frac{t}{T} \cdot (1 - \frac{t}{T})$: noise schedule function (this can be defined in multiple ways, but a certain choice is made)
- T : the total number of diffusion steps

The approach guarantees that the endpoint of the forward diffusion x_T is close to the true low-SNR image x_T^* . By anchoring the path to x_T^* , the model maintains connected to the real noise present in the dataset. This concept is illustrated in Figure 8. The forward diffusion path (indicated in orange) gradually moves from the high-SNR image x_0 toward a distribution centered around the noise image x_T^* , with each step adding increasing amount of noise.

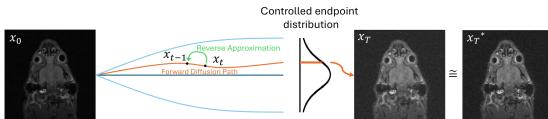


Figure 8: forward diffusion APDDM.

4.3.2 Reverse Process and Training

To reconstruct x_0 from any intermediate x_t , a U-Net model r_θ is trained to predict the added noise. The predicted noise is then subtracted to obtain an estimate of \hat{x}_0 , and training is performed using mean squared error loss:

$$\hat{x}_0 = x_t - f(t) \cdot r_\theta(x_t, \frac{t}{T}) \quad (10)$$

$$\mathcal{L} = \|x_0 - \hat{x}_0\|^2 \quad (11)$$

The network does not need to generate high-quality images from scratch but only needs to estimate the noise added from the forward process. Figure 9 shows the training strategy. The clean image x_0 is transformed into x_t via forward diffusion and the network is trained to reverse this transformation by removing predicted noise and minimizing the loss. This setup allows the network to focus on denoising realistic degraded images, guided by noise from the data.

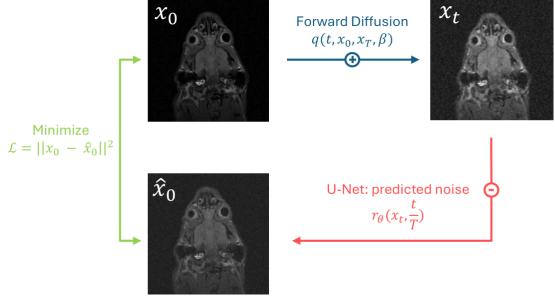


Figure 9: training overview of APDDM.

4.3.3 Integration

APDDM is particularly well suited for our micro-MRI dataset, where paired scans with varying SNR levels are available. By using real residuals between the paired images as noise sample, the forward process creates realistic, data-driven noisy versions of the high-resolution images. This ensures that the denoising task is meaningful and well-aligned with the expected variation in practice. Furthermore, the ability to modulate noise strength and variance offers great control over training difficulty. As an example, increasing noise allows for more challenging samples, improving the model’s robustness to varying noise levels in unseen data. Overall, APDDM offers a highly customizable framework for modeling noise in paired data and provides a strong foundation for future extensions. The mathematical derivations that support this model can be found in Appendix C

5 Model performance evaluation

In this section, the used validation methods are described. All the methods check the performance of the model.

5.1 Visual comparison

A visual inspection can also be done to evaluate the quality of the reconstructed images. The visual comparison will compare the residuals of high-resolution and low-resolution images to the residuals of high-resolution and deep-learning images. Ideally the residual of high-resolution and deep-learning images should be close to zero in most regions, indicating an accurate reconstruction.

5.2 Mean squared error

The mean squared error (MSE) measures the amount of error in statistical models by taking the average squared difference between the observed and predicted values. If there is no error,

the MSE will become zero. Formula 12 can be used to calculate the MSE:

$$\text{MSE} = \frac{1}{x \cdot y} \sum_{i=0}^{x-1} \sum_{j=0}^{y-1} (S(i, j) - \hat{S}(i, j))^2 \quad (12)$$

Here, $S(i, j)$ is the observed value, and $\hat{S}(i, j)$ is the corresponding predicted value. X represents the number of pixels in a row and y denotes the number of pixels in a column. [24]

The MSE was calculated for the high resolution and the result of the deep learning model. After these calculations the ratio is taken of these two.

5.3 Structural similarity index measure

As previously introduced in section 4.2.2, the Structural Similarity Index Measure (SSIM) is also used independently as an evaluation metric in this study. While it forms part of the hybrid loss function, SSIM is valuable on its own for assessing perceptual image quality, as it accounts for luminance, contrast, and structural consistency. In this context, SSIM is used to compare the predicted images to the high-resolution reference scans. This is particularly relevant in medical imaging, where preserving structural details is critical. The SSIM score ranges from 0 to 1, with values closer to 1 indicating higher structural similarity and visual fidelity [25].

5.4 Contrast-to-noise ratio

Contrast-to-noise ratio (CNR) is a metric that evaluates the quality of an image by measuring how well a region of interest (for example, liver) can be distinguished from the surrounding background.

$$\text{CNR} = \frac{\mu_{ROI} - \mu_b}{\sigma_b} \quad (13)$$

μ_{ROI} is the mean of the region of interest, μ_b is the mean of the background and σ_b is the noise in the background. A higher CNR value indicates better differentiation of the region of interest from its background. To obtain the CNR the program Amide is used.

6 Results

6.1 First results

First the model was run on the hpc to check whether all components were implemented correctly. With this first run, the pre-processing steps could be verified and the first results could be observed. The training was done on the acelgor cluster. The 11th epoch was the best, as



Figure 10: Visual representation of the loss function over different epochs. geen assen!!!

can be observed in Figure 10. In the best epoch the loss of the training is equal to 0.481, while the one of the validation equals 0.426.

In this script the training, validation and test mice were defined. A detailed overview can be found in Table 2. The hyperparameters were chosen based on knowledge and guessing what the best one would be. They were chosen as followed:

- 64 filters in the first layer
- 128 filters in the second layer
- 256 filters in the third layer
- meanpooling for downsampling
- upconv upsampling
- residual connections
- learning rate of 0.0001
- RMSprop optimizer
- ReduceLROnPlateau scheduler

The model was trained with a batch size of 32 and training was conducted over 200 epochs. MSE was employed as the loss function and ReLU was the activation function.

In Figure 11, Figure 12 and Figure 13 the results can be observed, where each is an example of the training mice. Since the output gave not all images back, Figure 13 is a result of the 13th epoch. Each image depicts another plane of the mouse. Also, images of the test mice can be found in Appendix D.1

	Training	Validation	Testing
Mouse	1, 2, 3, 4, 5, 8 9, 11, 12, 13, 14, 15 17, 18, 19, 20, 21, 23	6, 10	7, 16, 22

Table 2: Mouse distribution across training, validation, and testing sets.

Mouse01_Sagittal_16_epoch_10

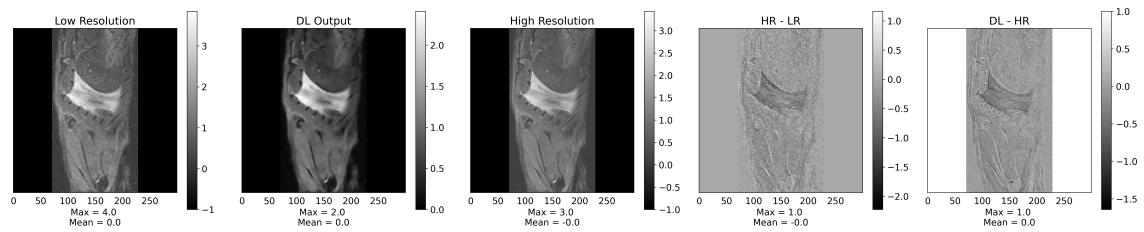


Figure 11: First results of abdomen of training mouse.

Mouse23_Transax_27_epoch_10

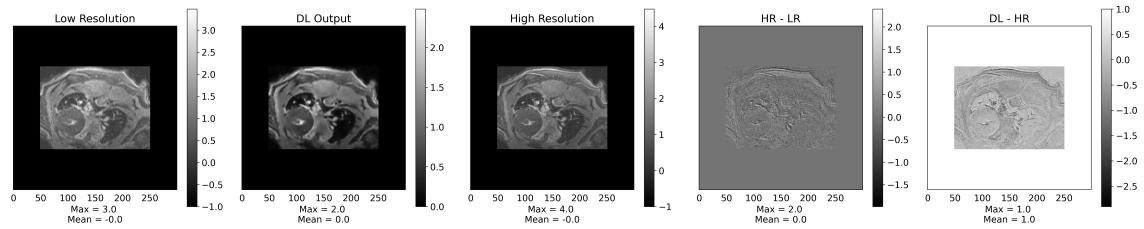


Figure 12: First results of abdomen of training mouse.

Mouse23_Coronal_19_epoch_12

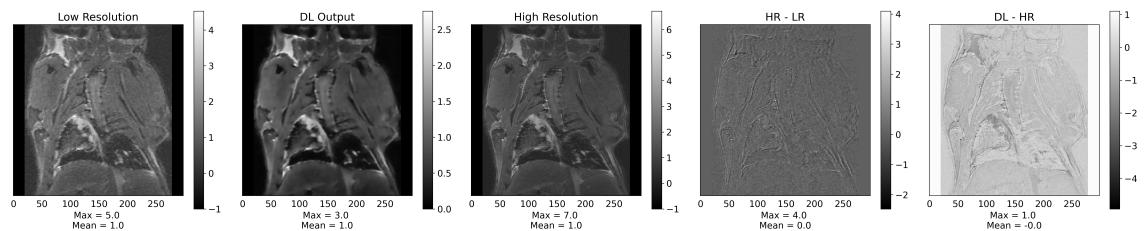


Figure 13: First results of abdomen of training mouse.

6.2 Trained hyperparameters

To improve the performance of the model, hyperparameter tuning was done using Optuna’s framework. The MSE was used as the validation metric. The search space included the number of filters in each layer, the downsampling, upsampling, presence of residual connections, learning rate, optimizer and the learning rate scheduler. The best-performing configuration achieved a validation MSE of 0.03034 and this optimal network used:

- 128 filters in the first layer
- 128 filters in the second layer
- 64 filters in the third layer
- strided convolution for downsampling
- bilinear upsampling
- no residual connections
- learning rate of 0.0003139
- Adam optimizer
- step-wise learning rate scheduler

In addition to these hyperparameters, the activation function and loss function were fixed as ReLU and MSE, respectively. These choices were guided by prior literature and informed by earlier tuning, during which alternative activations such as LeakyReLU and PReLU, and loss functions including SSIM-based objectives, were preliminarily evaluated but did not yield consistent improvements. ReLU demonstrated stable convergence behavior and compatibility with the U-Net architecture, while MSE remained the most reliable objective for optimizing pixel-wise accuracy during supervised training. As such, both were retained as fixed components throughout the main hyperparameter optimization process.

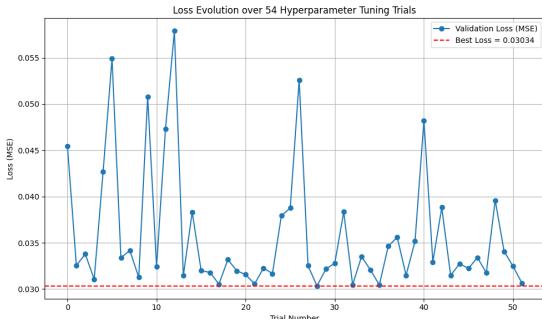


Figure 14: Visual representation of the loss function over trials in hyperparameter tuning

Figure 14 illustrates the evolution of the validation MSE over all tuning trials. Several other trials achieved losses close to the best-achieving

one (e.g. trial 18). These well-performing trials shared nearly identical architectures, differing in learning rate. This consistency supports the robustness of the design.

6.3 Results after hyperparameter training

After hyperparameter tuning, the model was run again. Hereby, the parameters of section 7.2 were used. As in the part of the first results, the images of the training mice can be found in this section. Figure 15, Figure 16 and Figure 17 represent the different planes. Images of the test mice can be found in Appendix D.2. The same division of mice was used, as in indicated in Table 2.

6.4 APDDM

6.5 Validation

6.5.1 Visual comparison

Figure 18 shows a sagittal view of the mouse spine and surrounding anatomy. The yellow box highlights the lower thoracic to lumbar spine, an area where fine bone structure is particularly important. The LR input of the spine and organ boundaries is quite noisy. The DL output is somewhat sharper for example, the white spine column and rib edges within the yellow-highlighted region are brighter and better defined than in LR. However, the DL image still lacks the crisp detail of the HR reference. Subtle textures, especially within and around the spine, are smoothed out.

In Figure 19, the coronal view shows the spine vertically at the center and organs. The yellow box at the top highlights a region of upper thoracic anatomy. In the LR image, this area is extremely grainy, it’s difficult to distinguish between noise and actual anatomical detail. However, in the DL output, this region appears less noisy, making the underlying structures slightly more recognizable. The noise reduction improves the clarity of texture, helping to separate anatomy from background artifacts. While still not as crisp as the HR reference, this DL improvement aids interpretability. The green circle marks the kidney and mid-abdominal area. Here, too, the DL output reduces noise and enhances structure visibility. For example, the kidney outlines and the vertebral column (centerline) appear a bit clearer than in LR. Contrast along bone boundaries and organ edges is higher in DL, particularly within these highlighted areas, but still not as sharp as HR. The HR-LR residuals highlight the kidneys and spine quite strongly, whereas DL-HR shows weaker residuals that still trace those same shapes. In conclusion,

Mouse01_Sagittal_THORAX-ABDOMEN_26_epoch_0

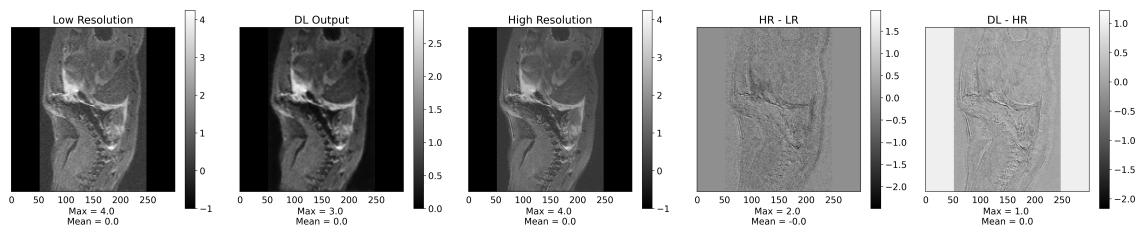


Figure 15: Results after hyperparameter tuning of abdomen of training mouse.

Mouse01_Transax_THORAX-ABDOMEN_27_epoch_0

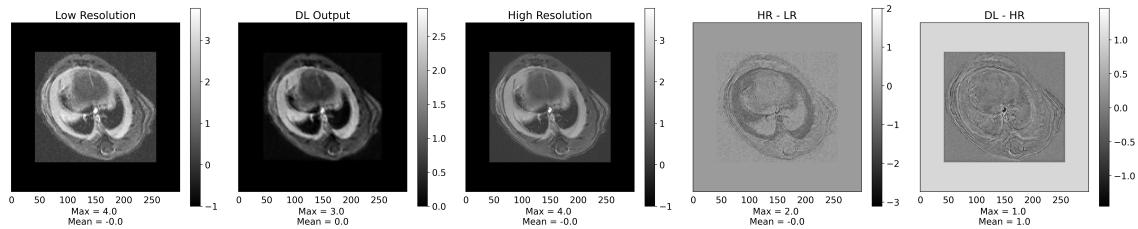


Figure 16: Results after hyperparameter tuning of abdomen of training mouse.

Mouse01_Coronal_THORAX-ABDOMEN_20_epoch_2

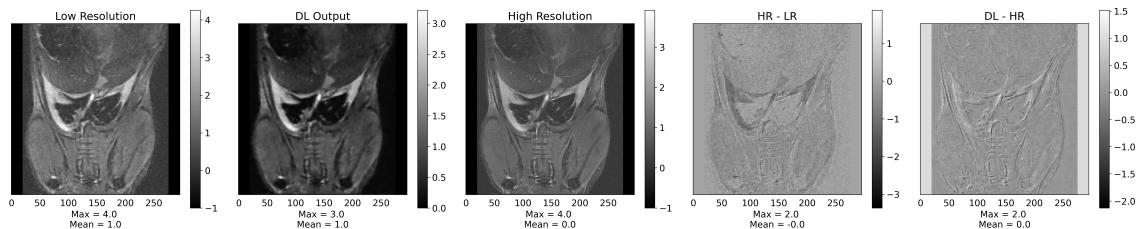


Figure 17: Results after hyperparameter tuning of abdomen of training mouse.

Mouse01_Sagittal_THORAX-ABDOMEN_26_epoch_0

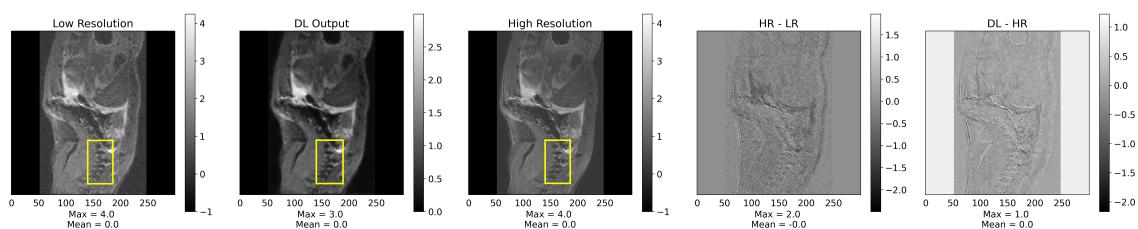


Figure 18: Sagittal view of the mouse thorax-abdomen region (Mouse01)

DL recovers some large-scale anatomy from LR but smears over finer details.

Figure 20 shows the spinal column (bright vertebrae, highlighted by the yellow rectangle) and pelvic region below, with thoracic soft tissues above (highlighted by the green circle). In the LR image, the green-circled region is dominated by noise, making it hard to distinguish anatomical content from background variation. In the DL output, this area shows reduced noise, which improves the visibility of the underlying structures, though fine detail remains limited. The noise suppression makes it easier to infer the presence of soft tissue textures that are otherwise obscured in the LR input. DL gains some edge clarity over LR, especially around the vertebral column (yellow rectangle), but this improvement is still modest. The vertebral outlines are only faintly improved. In the HR-LR difference map, the vertebral bone and joint edges stand out strongly, reflecting the detail missing in LR. The DL-HR residual still traces those same locations, though with reduced amplitude, indicating partial recovery of anatomical edges. This pattern is evident throughout both highlighted areas: the network removes large-scale blur and suppresses noise but leaves behind residual contours at anatomical edges. Overall, DL improves global sharpness and interpretability over LR, especially in noisy regions like the top soft tissue (green circle), but continues to blur finer anatomical features.

6.5.2 MSE and SSIM

Table 3 shows the obtained values for MSE and SSIM. The SSIM values are in the range 0.0272–0.0675, and the MSE values span 0.01–0.059. These low SSIM scores indicate that the network is currently unable to reconstruct the fine anatomical details and texture present in the high resolution target. The MSE values indicate low average pixel difference.

6.5.3 Contrast-to-noise ratio

I (Fea) am still busy working with amide to get the CNR. This table is an indication of how I will represent the results. I will also add a detailed table with the calculations in the appendices.

6.5.4 LEGO phantom test

For extra validation the model was tested on a 1 min scan of a LEGO brick and compared to its 12 min scan target. The results can be seen in Figure 21. The DL output has suppressed some echo artifacts that are present in the LR image between the black pins. The residuals show that the sharper edges and rectangular shapes are closer to the HR image in the LR image. A

more in depth quantitative and qualitative discussion follows in ??.

7 Discussion

7.1 First results

After obtaining the first results, a visual validation was made. At first sight, the results were very promising. Figure 11, Figure 12 and Figure 13 shows that the deep learning (DL) image has clearly higher quality and sharper details compared to the low resolution (LR) image at the left side. The DL image approaches the high resolution (HR), but still has noise and structures that are not totally visible. Also, some parts are depicted more black than in the HR. The maximum intensity of the DL image is always lower than the one of the HR and the one of the LR. This indicates small intensity bias or scaling difference. This is also due to the background that is cropped in the original images but depicted at the edges and not depicted in the DL output. Looking at the edges of the mice in the DL images, it shows that these are generally more smeared out and less sharp than in the HR images. The noise of the LR is reduced with minimal loss of important structural information. The same observations can be made when looking at the validation mice (see Appendix D.1). As said, the results are very promising but there is also room for improvement. The first step in this process is training the hyperparameters.

7.2 Trained hyperparameters

The results of the hyperparameter optimization provide insights into the performance of the model. Several key hyperparameter choices reflect current best practices in deep learning for medical image restoration, while others diverge in notable ways

The feature dimensions were set to 128, 128, 64, showing that the moderately deep but not excessively wide networks achieved optimal performance. This allows the network to capture a sufficient range of spatial features while avoiding overfitting, which is a risk in smaller-scale datasets such as micro-MRI.

Strided convolution (convStrided) was preferred over pooling for downsampling. This aligns with expectations from common CNN practice. Strided convolution allows the model to practice how to compress feature maps instead of relying on fixed operations such as meanpooling. This learnability likely helped preserve critical structural details [31]. For upsampling, bilinear interpolation was favored over learned transposed convolutions. Unlike transposed convolutions, which introduce additional

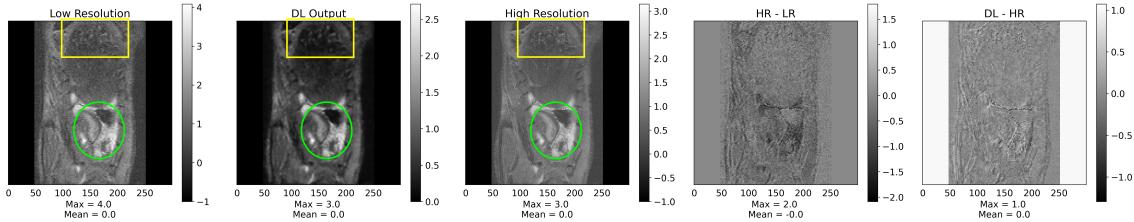


Figure 19: Coronal view of the thorax-abdomen (Mouse06).

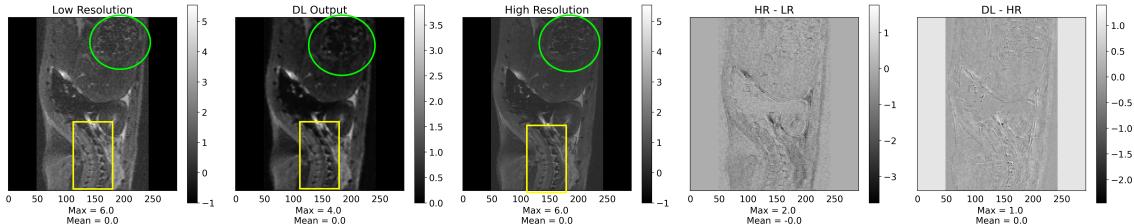


Figure 20: Sagittal view of the spine and pelvic region (Mouse10).

parameters and are prone to artifacts, bilinear upsampling provides a smooth and stable to restore spatial dimensions. This upsampling method does not learn to add high-frequency details [33]. The consistent selection of bilinear upsampling in high-performing trials suggests that its simplicity and robustness were well-suited for this task.

Residual connections were disabled which is an unexpected result which contrasts with many image restoration models that benefit from residual learning. In this case the low-resolution and high-resolution images were relatively similar in structure and intensity, making transformations less complex. This reduces the benefit of residual modeling. The U-Net's skip connections inherently serve a similar role to residuals, which likely compensated for this. This allows effective feature reuse and reduces the need for a global residual link [32].

The learning rate was consistently selected in the lower range, supporting gradual and stable learning. The chosen scheduler, step learning rate, reduces the learning rate at fixed intervals. This allows the network to learn quickly during early epochs and refine weights more delicately later in training. This balance is preferred for restoring subtle textures in high-resolution data.

Certain parameters were fixed prior to tuning, based on theoretical justification and preliminary experiments. The activation function was set to ReLU, chosen over alternatives such as LeakyReLU, PReLU, or ELU. Although ReLU is susceptible to the "dying neuron" problem, it remains a robust default in convolutional archi-

tectures due to its simplicity, computational efficiency, and effective gradient propagation. Initial exploratory tests showed no instability or gradient vanishing that would necessitate more complex activations. The network's stable convergence confirmed that ReLU was a suitable choice for this task.

The loss function was fixed as mean squared error (MSE), a standard objective for pixel-wise regression tasks. MSE offers a simple, differentiable, and interpretable loss landscape that aligns well with the goal of minimizing reconstruction error. While alternative loss functions, such as SSIM or perceptual loss, were considered, MSE was retained due to its stability and its compatibility with the validation metric used during tuning.

The optimization process solely relied on MSE for validation. This choice was made due to MSE's simplicity, ease of interpretation, and its direct compatibility with the pixel-wise loss functions used during training. This decision may introduce some form of metric bias. MSE disproportionately penalizes large pixel errors, which often lead to overly smooth outputs. In denoising tasks, this can result in models that reduce noise effectively in terms of pixel accuracy but at the cost of signal preservation, leading to a lower signal-to-noise (SNR) in practice. MSE is also sensitive to outliers and intensity shifts, while being oblivious to perceptual structure and contrast consistency [29]. Future work could benefit from using alternative validation metrics, such as SNR or perceptual similarity measures, to better guide model selection and

Mouse	Plane	Slice	MSE	SSIM
1	Sagittal	3	0.046	0.027
		26	0.033	0.039
	Transaxial	7	0.010	0.061
		17	0.027	0.034
		25	0.026	0.039
		27	0.031	0.038
6	Coronal	12	0.029	0.035
		7	0.026	0.048
	Sagittal	23	0.020	0.068
		12	0.023	0.045
		22	0.018	0.044
10	Transaxial	8	0.017	0.048
		5	0.016	0.045
	Coronal	19	0.018	0.056
		16	0.029	0.044
23	Transaxial	19	0.059	0.034

Table 3: Overview of the mice, slices and planes used to obtain MSE and SSIM.

ensure outputs are both quantitatively accurate and visually informative [6]. Metrics such as LPIPS (Learned Perceptual Image Patch Similarity) offer a promising alternative by leveraging deep features that align more closely with human perception and quality [30].

7.3 Results after hyperparameter training

When looking at the results after hyperparameter, it can be seen that the model is still working quite good. The DL image in Figure 15, Figure 16 and Figure 17 shows again sharper details and higher quality compared to the LR image. The DL image is still more black than the HR image. The maximum intensity of the DL image is again lower than the ones of the LR and HR image, but the difference is only 1. In the first results, this difference was much higher. This means the intensity bias and scaling difference are better than previously. The background also needs to be taken into account, which can also leads to other maximum intensities. Compared to Figure 11, Figure 12 and Figure 13, the images after hyperparameter tuning have sharper edges. The edges are less smeared out and a bit sharper. The loss of structural information is still present, but less than previously.

7.4 APDDM

7.5 Validation

7.5.1 Visual comparison

In all cases the DL output appears to be smoother than the HR reference. This over-smoothing is a known effect of using MSE loss. This is due to the network learning to average high-frequency patterns which results on blurred textures. The residuals of DL-HR consistently have lower amplitudes than the HR-LR, this means the network shrinks the differences but is unable to restore all fine details [34]. MSE encourages finding pixel-wise averages of solutions, producing overly-smooth results. Our visual inspection confirms this.

7.5.2 LEGO brick phantom

As an extra validation step, an MRI scan of a LEGO brick with a 1-minute scan time was given as input to the trained model and compared with its 12-minute scan time counterpart. This can show whether the model is overtrained and whether it could potentially be used to denoise and improve shorter scan time images of objects other than mice. The images discussed here can be seen in Figure 21.

Visually, the model produces an output that

	Mouse	Plane	Slice	Region	LR CNR	DL CNR	HR CNR
1	1	Transaxial	3	TA			
			26	TA			
			7	HT			
			17	TA			
			25	TA			
			27	TA			
6	6	Coronal	12	TA			
			7	TA			
			23	HT			
			12	TA			
			22	HT			
10	10	Sagittal	8	TA			
			5	HT			
			19	TA			
			16	HT			
	23	Transaxial	19	TA			

Table 4: Overview of the mice, slices and planes used to obtain CNR in LR, DL and HR images. TA stands for thorax-abdomen, while HT is used for head-thorax.

strongly resembles both the LR and HR images. The model removes noise in the grey regions from the LR image, as well as echo artifacts that can be seen, for example, between the black LEGO pins at the top. The rectangular shapes are preserved, although the training data of mice did not contain many such shapes.

However, comparing the residuals shows that the LR image is closer to the HR image in terms of the rectangles than the DL image. This could be due to the fact that the model was trained on mouse scans, which, as mentioned, do not contain the sharp edges characteristic of a LEGO brick, and that the model used MSE as the loss function during training. MSE penalizes large pixel errors, so the model tends to smooth out sharp changes.

The MSE between the DL and HR images is 0.1269, and between the LR and HR images is 0.0737 (an increase of 72% from the LR to the DL image). This means that if we only consider the pixel-wise error, the LR image remains a better approximation of the HR image than the DL image.

Another indicator of image quality is the Structural Similarity Index Measure (SSIM), as discussed in section 5.3. The DL and HR images have an SSIM of 0.4548, while the LR and HR images have one of 0.4624. So the SSIMs differ by only 1.6%, indicating that according to SSIM, neither the LR nor the DL image is clearly a better approximation of the HR image. Very similar conclusions regarding MSE and SSIM can be drawn from examining other slices of the LEGO phantom.

It is important to note that MSE and SSIM are purely quantitative metrics and should be considered as supplementary to qualitative visual assessment. Despite the DL image having

a slightly higher MSE and lower SSIM than the LR image, it remains a strong approximation of the HR image due to its effective denoising and artifact suppression capabilities, also for objects different from mice.

8 Conclusion

LEGO Phatom Test

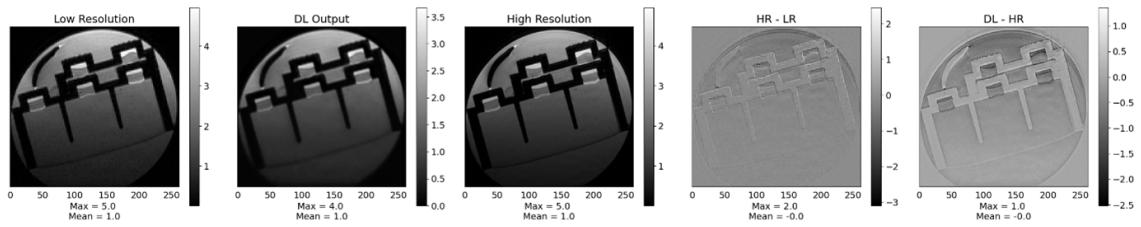


Figure 21: Results after hyperparameter tuning of LEGO phantom.

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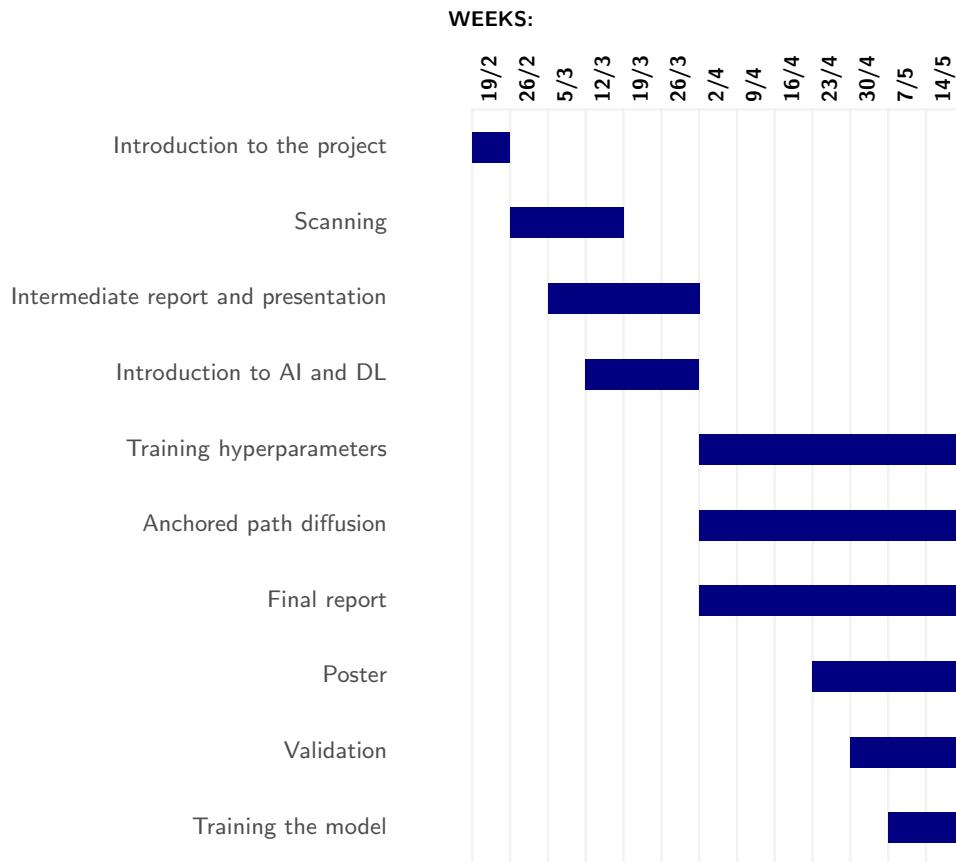
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Appendices

A Appendix: Gantt chart



B Appendix: Figures Preprocessing

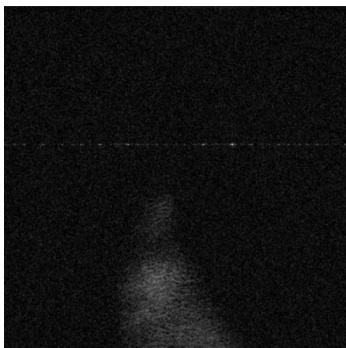


Figure 22: Example of a bad slice.

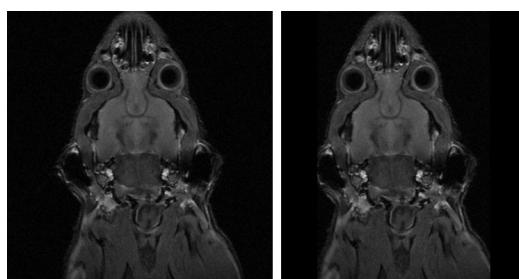


Figure 23: The left figure shows the original slice, while the right figure is the cropped slice.

C Appendix: Mathematics APDDM

C.1 Ansatz: linear interpolation between image pair

Some definitions:

\mathbf{x}_0 = high-SNR image

\mathbf{x}_T^* = low-SNR image (* denotes that this is the ground truth endpoint, the reason for this differentiation will be clear later)

T = total amount of steps that will be taken

t = current timestep in the diffusion path

$\alpha_t = \frac{t}{T}$, notation for the fraction of the diffusion path at the current timestep

$\mathbf{R} = \mathbf{x}_T^* - \mathbf{x}_0$, the residual

Note: \mathbf{x}_0 and \mathbf{x}_T^* should be normalized images:

$$\mathbf{x} \leftarrow \frac{\mathbf{x} - \frac{1}{i,j} \sum_{ij} \mathbf{x}_{ij}}{\sqrt{\frac{1}{ij} \sum_{ij} \mathbf{x}_{ij}^2}} \quad (14)$$

and \mathbf{x}_T^* should be interpolated to match the size of \mathbf{x}_0 .

We will start by first defining a procedure, where we linearly interpolate between \mathbf{x}_0 and \mathbf{x}_T^* , and add a not yet specified noise term:

$$x_t = (1 - \alpha_t) \cdot \mathbf{x}_0 + \alpha_t \cdot \mathbf{x}_T^* + \text{noise}(t) \quad (15)$$

C.2 Proposition of the Markovian process

We will now transform this into a Markovian process, by allowing the endpoint to not be exactly \mathbf{x}_T , but rather let the endpoint \mathbf{x}_T be \mathbf{x}_T^* in expected value.

If we subtract \mathbf{x}_t by \mathbf{x}_{t-1} , we get:

$$\mathbf{x}_t - \mathbf{x}_{t-1} = \alpha_t (\mathbf{x}_T^* - \mathbf{x}_0) - \alpha_{t-1} (\mathbf{x}_T^* - \mathbf{x}_0) + \text{noise} \quad (16)$$

\Leftrightarrow

$$\mathbf{x}_t - \mathbf{x}_{t-1} = (\alpha_t - \alpha_{t-1}) \mathbf{R} + \text{noise} \quad (17)$$

\Leftrightarrow

$$\mathbf{x}_t = \mathbf{x}_{t-1} + \frac{1}{T} \mathbf{R} + \text{noise} \quad (18)$$

By using a Markov process, we create a natural diffusion path from \mathbf{x}_0 to \mathbf{x}_t , where each step builds up on the previous one. We now define our final Markov process as:

$$\boxed{\mathbf{x}_t = q(\mathbf{x}_{t-1}) = \mathbf{x}_{t-1} + \frac{1}{T} \mathbf{R} + f(t) \hat{\epsilon}; \quad t = 1, 2, \dots, T} \quad (19)$$

Where we define $f(\alpha_t)$ to be a function that is zero for arguments 0 and 1, and reaches a maximum of 1 somewhere in the range $[0, 1]$. This is the noise schedule function. Let:

$$f(t) = 4\alpha_t(1 - \alpha_t) = 4\frac{t}{T}(1 - \frac{t}{T}) \quad (20)$$

This choice of function is arbitrary, but in this way, the noise term is gradually introduced and attenuated again so the course of the diffusion path has a natural way of going from starting point to endpoint. Below, the course of the variance throughout the path will be shown, where it will be clear why such a choice of attenuating noise schedule function is favorable.

The noise term ϵ should be distributed according to the real noise in our data:

$$\epsilon \sim P[\text{noise}] \quad (21)$$

We will approximate this empirically by sampling from all the observed residuals in our dataset:

$$\epsilon \approx \hat{\epsilon} \stackrel{i.i.d.}{\sim} \mathcal{E}_{\text{dataset}} \quad (22)$$

This sampling of the noise residual can be done by i.i.d sampling residual bank $\mathcal{E}_{\text{dataset}}$. These are then rotated at random over 0° , 90° , 180° and 270° as an augmentation technique so coherent edge artifacts won't accumulate (see Fig. 24 for an example of such artifacts).

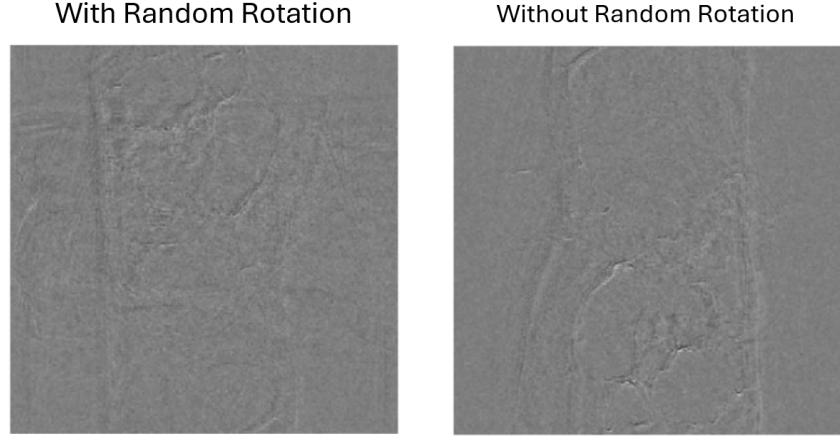


Figure 24: Demonstration of coherent edge artifact accumulation when no rotation is applied.

C.3 Expected value of the endpoint

Note that generally: $\mathbf{x}_T \neq \mathbf{x}_T^*$. It will now be shown that the expected value $\mathbb{E}[\mathbf{x}_T]$ still is \mathbf{x}_T^* :

We apply a Markov chain T times to the input \mathbf{x}_0 :

$$\mathbb{E}[\mathbf{x}_T] = \mathbb{E}[q(q(\dots q(\mathbf{x}_0) \dots))] = \mathbb{E}[\mathbf{x}_0 + \frac{T}{T} \mathbf{R} + \sum_{t=1}^T f(t) \cdot \hat{\epsilon}_t] \quad (23)$$

Because $\mathbf{R} = \mathbf{x}_T^* - \mathbf{x}_0$:

$$\mathbb{E}[\mathbf{x}_T] = \mathbb{E}[\mathbf{x}_T^* + \sum_{t=1}^T f(t) \cdot \hat{\epsilon}_t] = \mathbf{x}_T^* + \sum_{t=1}^T f(t) \cdot \mathbb{E}[\hat{\epsilon}_t] \quad (24)$$

If we assume $\mathbb{E}[\hat{\epsilon}] = 0$:

$$\boxed{\mathbb{E}[\mathbf{x}_T] = \mathbf{x}_T^*} \quad (25)$$

C.4 Variance of the endpoint

We will now derive the expression for the variance on our endpoint \mathbf{x}_T :

$$\begin{aligned} \text{Var}[\mathbf{x}_T] &= \text{Var}[q(q(\dots q(\mathbf{x}_0) \dots))] = \text{Var}[\mathbf{x}_0 + \mathbf{R} + \sum_{t=1}^T f(t) \cdot \hat{\epsilon}_t] = \text{Var}[\sum_{t=1}^T f(t) \cdot \hat{\epsilon}_t] \\ &= \sum_{t=1}^T f(t)^2 \text{Var}[\hat{\epsilon}_t] + \sum_{i \neq j}^T f(i)f(j) \text{Cov}[\hat{\epsilon}_i, \hat{\epsilon}_j] = \sum_{t=1}^T f(t)^2 \text{Var}[\hat{\epsilon}_t] \end{aligned} \quad (26)$$

Where we used $\text{Cov}[\hat{\epsilon}_i, \hat{\epsilon}_j] = 0$ because the noise samples are independent.

Now using the notation: $\text{Var}[\hat{\epsilon}_t] = \sigma_\epsilon^2$, and substituting (19), we get:

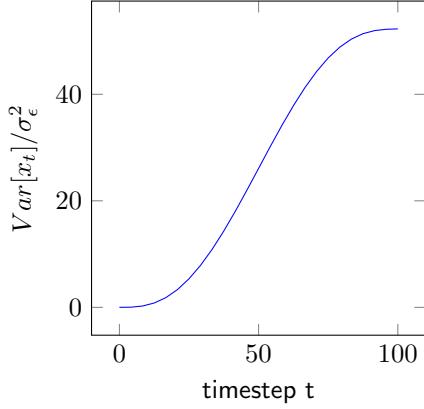
$$\boxed{\text{Var}[\mathbf{x}_T] = \sigma_\epsilon^2 \cdot \sum_{t=1}^T f(t)^2 = \frac{8}{15} \frac{T^4 - 1}{T^3} \cdot \sigma_\epsilon^2} \quad (27)$$

Note that for $\lim_{T \rightarrow +\infty} \text{Var}[\mathbf{x}_T] \sim \frac{8}{15} T$.

We can also derive the general variance throughout the whole path (not just at the endpoint):

$$\text{Var}[\mathbf{x}_T] = \sigma_\epsilon^2 \cdot \sum_{\tau=1}^T f(\tau)^2 = \sigma_\epsilon^2 \cdot \frac{8}{15} \frac{1}{T^4} t(t+1)[6t^3 - 15t^2T + 9t^2 + 10tT^2 - 15tT + t + 5T^2 - 1] \quad (28)$$

Example Variance for T=100 timesteps



This exact course of the variance has also been confirmed by numerical simulation.

We can observe that the variance increases slowly in the beginning, and before the endpoint, it slows down and stabilizes again. This is the reason for the particular choice of the noise schedule function $f(t)$ discussed previously. **However, a lot of noise schedule choices can be made and should be investigated.**

C.5 Controlling the variance

I will now propose a method of controlling the variance of this path. This way, we can have the variance of the endpoint as a variable parameter, and even optimize the model in function of this parameter. Thus the “degree of noise” can be controlled. First, we will normalize the sampled residual $\hat{\epsilon}$, so we know the variance of the noise is 1:

$$\hat{\epsilon}' = \hat{\epsilon}/s_{n,\epsilon} \quad (29)$$

($s_{n,\epsilon}$ = population variance of $\mathcal{E}_{\text{dataset}}$)

Additional note: we assume that an empirical noise distribution has an expected value of 0.

We will then control the variance by adding a parameter σ :

$$\boxed{\mathbf{x}_t = q(\mathbf{x}_{t-1}) = \mathbf{x}_{t-1} + \frac{1}{T} \mathbf{R} + \sigma f(t) \hat{\epsilon}'; \quad t = 1, 2, \dots, T} \quad (30)$$

Where:

$$\sigma = \sqrt{\frac{15}{8} * \frac{T^3}{T^4 - 1} * \beta} \quad (31)$$

Now, the variance of our endpoint is:

$$Var[\mathbf{x}_T] = \beta^2 \quad (32)$$

We now have full control over the variance of the endpoint, with exception to the stability criterion as described in the following section.

C.6 MSE stability

Important to note is that there are some constraints on this parameter beta (and thus the variance of the noise term), if we want the diffusion path to converge to \mathbf{X}_T^* . We will measure this in the form of the MSE between \mathbf{x}_T and \mathbf{x}_T^* , which should not be exceedingly large.

An important condition that must be met, is that \mathbf{x}_t becomes more similar to \mathbf{x}_T^* each step.

This condition will not be met if the noise term overpowers the term $\frac{1}{T} \mathbf{R}$ at a certain step. In other words, the residual term magnitude should be larger than the noise term magnitude in each step, so that the diffusion path still mostly converges towards \mathbf{x}_T^* . We will make an estimation of the size of the subsequent terms based on their Mean Square value $\frac{1}{i,j} \sum_{i,j} X_{i,j}^2$ (MS value). We will also let $f(t) = 1$, to have a conservative estimation.

The diffusion path will converge if for all steps:

$$\mathbb{E}[MS(\hat{\epsilon})] \lesssim MS\left(\frac{1}{T} \mathbf{R}\right) \quad (33)$$

$$\begin{aligned}
&\Leftrightarrow \sigma^2 \cdot MS(\mathbb{E}[\hat{\epsilon}']) \lesssim \frac{1}{T^2} MS(\mathbf{R}) \\
&\Leftrightarrow \boxed{\sigma \lesssim \frac{1}{T} RMS(\mathbf{R}) = \sigma_{crit}}
\end{aligned}
\tag{34}
\tag{35}$$

This last expression is a conservative MSE convergence condition. Substituting (31), we get the criterion in terms of β :

$$\beta \lesssim \sqrt{\frac{8}{15} \frac{T^4 - 1}{T^5}} RMS(\mathbf{R}) = \beta_{crit} \tag{36}$$

This result can be demonstrated by a simulation where beta is varied and the mean square error between x_T and x_T^* is computed over N diffusion path samples (Fig. 25). We indeed observe that if β is within the order of magnitude of β_{crit} , the diffusion process won't converge towards x_T^* anymore, which manifests itself in an increase in the MSE.

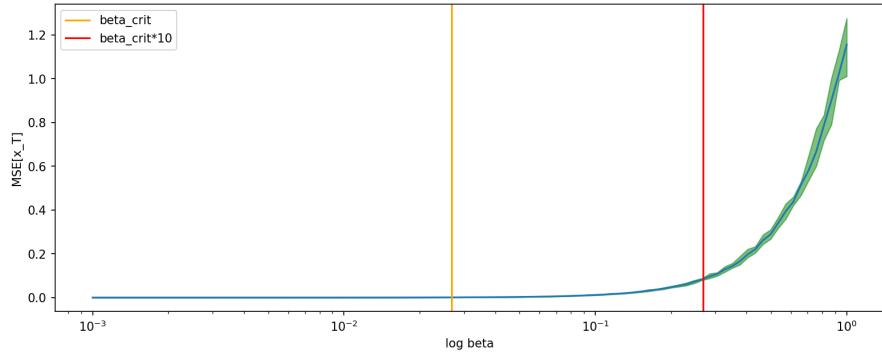


Figure 25: Plot of $MSE(x_T, x_T^*)$ against β .

D Appendix: Figures Results

D.1 Appendix: first results

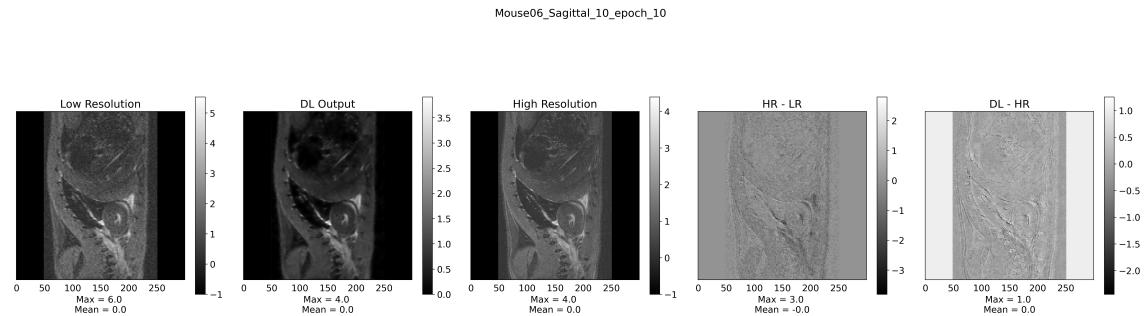


Figure 26: First results of abdomen of test mouse.

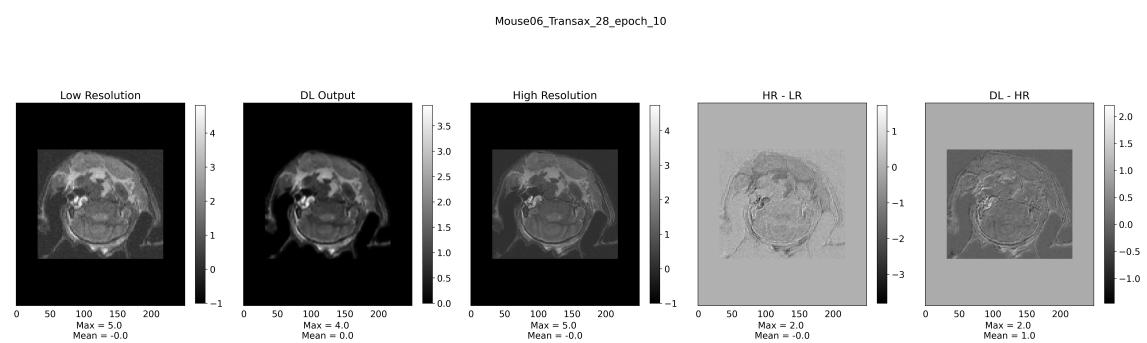


Figure 27: First results of abdomen of test mouse.

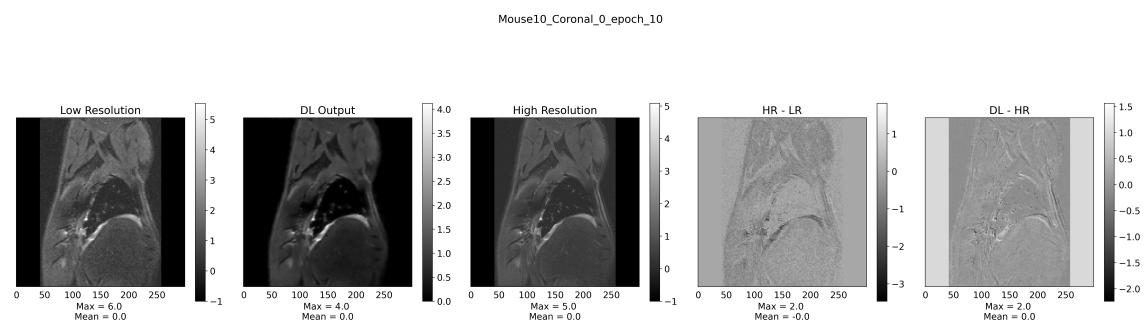


Figure 28: First results of abdomen of test mouse.

D.2 Appendix: results after hyperparameter tuning

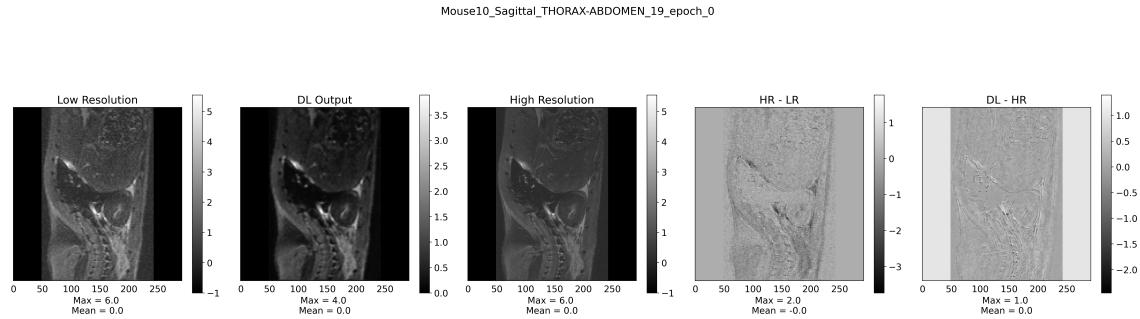


Figure 29: Results after hyperparameter tuning of abdomen of test mouse.

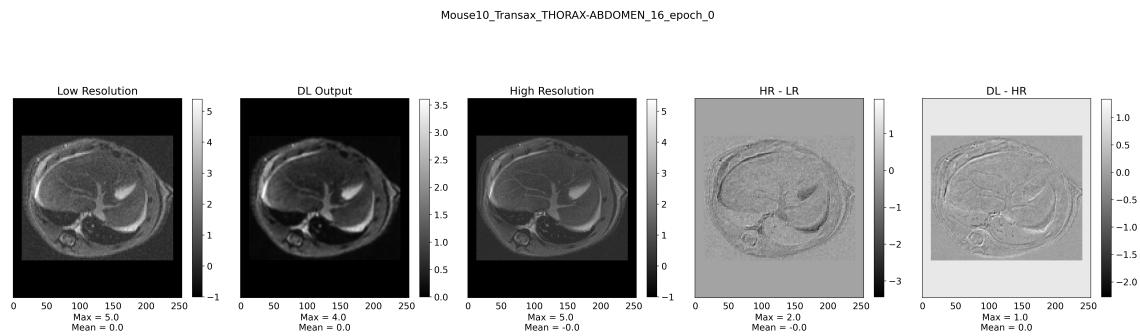


Figure 30: Results after hyperparameter tuning of abdomen of test mouse.

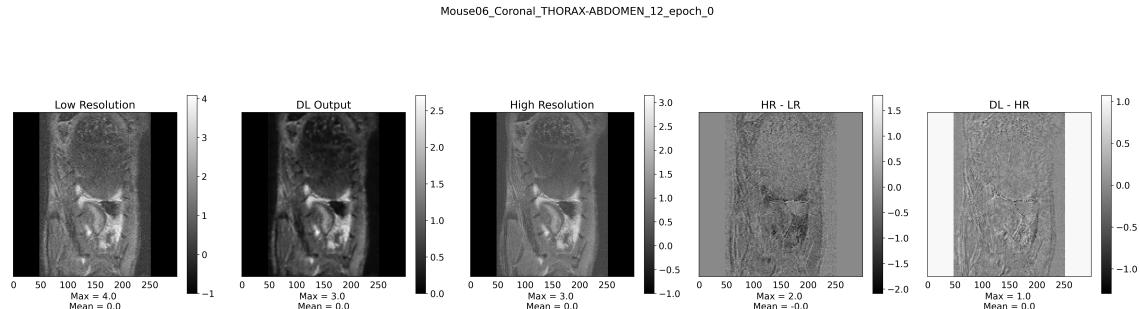


Figure 31: Results after hyperparameter tuning of abdomen of test mouse.