

HybridMorph: Towards usage of synthetic with real data for medical MR images registration

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Abstract. In biomedical data analysis, the advancement of deep learning techniques faces challenges stemming from the scarcity of ethically sourced datasets and the costs associated with data acquisition. In response to these obstacles, We propose HybridMorph, a novel hybrid model for biomedical image registration, which combines the strengths of synthetic and real data to achieve competitive error rates with state-of-the-art models. It is a pairwise medical image registration model built upon the foundations of VoxelMorph [1] and SynthMorph [2].

Our research showcases the efficacy of transferring knowledge gleaned from Synthmorph models to fine-tune weights for specific tasks, culminating in successful trials of few-shot learning and rapid adaptation capabilities. These methodologies illustrate how hybrid approaches can streamline training processes, mitigate computational resource demands, and alleviate the substantial data prerequisites inherent in contemporary deep learning models. Furthermore, our exploration into transfer learning underscores the potency of such techniques, paving the way for examining meta-learning, multi-task learning, and other avenues to mitigate data dependencies and complexity.

Moreover, we are pleased to offer open access to our code repository at:
<https://github.com/CaffineAddic/HybridMorph>

Keywords: Registration · Transfer learning · Convolution Neural Networks · Hybrid Data Models · MR images

1 Introduction

The emergence of Deep Learning (DL) techniques in the past few decades has resulted in exponential growth in problems being addressed across various disciplines through innovative methods [3]. However, the development of such models in biomedical data faces several challenges, including a lack of large datasets, privacy concerns, high costs of data acquisition, time-consuming and demanding processes of data collection and categorization, and a scarcity of test cases for rare conditions [4].

To address these challenges, various proposals have been made for biomedical Machine Learning (ML) models trained solely on synthetic data that mimics real cases and has shown promising results [2]. However, these methods have limited adaptability as they are solely based on synthetic data, and the model’s generalization depends on how well the synthetic data represents the real-world data distribution.

This study introduces hybrid data models based on voxelmorph that simultaneously incorporate real and synthetic data in training to reduce data requirements and enhance adaptability. We outline the following data-driven models:

1. We trained a Voxelmorph model on a limited sample of Magnetic Resonance (MR) images to evaluate its few-shot registration capabilities and investigate the impact of increasing the training dataset size on registration performance. (Few-shot Learning).
2. Pre-training the models with synthetic images and fine-tuning with a few real MR images (Transfer learning).
3. Pre-training the models with synthetic images and fine-tuning using a hybrid training model with real and synthetic images (Weighted Transfer learning).

Our experimentation with Transfer learning aims to alleviate data scarcity issues by leveraging knowledge from related tasks to enhance performance. We can utilize multi-objective functions by employing transfer learning, facilitating cost-sensitive machine learning. This approach enables us to achieve optimal results with significantly reduced resources and overhead.

2 Related Works

VoxelMorph, as proposed by Balakrishnan et al. [1], deviates from optimizing an objective function for each image pair. Instead, it computes a function that maps an input image pair to a deformation field for aligning these images, parameterized by a Convolutional Neural Network (CNN). This approach leverages both supervised training through auxiliary segmentation and unsupervised training based on image intensity objective functions. In a different vein, Hoffmann et al. introduced SynthMorph [2], which presents a contrast-invariant registration method using synthetic images to render the model agnostic to varying MR image contrasts. They achieve this by training on arbitrary shapes synthesized from a noise distribution, enabling the model to adapt to high variability. Additionally, Yong-xin Li et al. [5] propose enhancements to the original VoxelMorph model by introducing a dual attention architecture. This architecture selectively aggregates features by assigning weights to features at all locations. They also recommend incorporating a bending penalty in the loss function to penalize deformations in the field, thereby enhancing sensitivity and model accuracy.

Alternative techniques, as proposed by F. Maes et al. [6], utilize mutual information (MI) or relative entropy as the matching criteria. These methods operate under the assumption that the MI is maximized at the perfect alignment of image pairs, eliminating the need for any pre-segmentation. Zhang Li et al.

[7] have introduced a framework for registering images with signal fluctuations. Their approach involves an objective function that incorporates local phase features through the autocorrelation of local structures in the monogenic signal. This strategy aims to reduce sensitivity to spatially variant intensity distortions while enhancing the distinctiveness of image features.

J. F. Rajotte et al. in [8] have highlighted the emerging trends in synthetic data generation, which offers a promising solution for preserving privacy while providing large, trainable datasets for machine learning applications. By establishing a privacy-utility tradeoff to strike a balance between these two competing factors.

For synthetic data generation, Dahmen et al. in [9] employed a semi-supervised learning approach, leveraging hidden Markov models with regression models initially trained on real data. This approach has been shown to outperform conventional data generation techniques, achieving impressive results while relying on only a limited amount of ground truth information.

To assess data requirements in medical machine learning models, Wang et al. [4] investigated the dataset requirements for patch-based brain MRI segmentation tasks. They proposed a novel method to predict the performance expectations and required training data size using multiple strategies, including the Minor Boundary Adjustment for Threshold by Markov process method and the ROI-based Expanded Patch Selection method. The latter approach standardizes patch selection to maintain randomness while selecting patches.

3 Methodology

3.1 Data-Sets

Synthetic Data Generation: To generate the synthetic images, we utilized the method from SynthMorph [2]. It starts by generating input label maps with random geometric shapes, which are then deformed to create moving and fixed segmentation maps. These maps are used to synthesize gray-scale images, mimicking authentic MRI images. The images are generated by sampling intensities from normal distributions, simulating partial volume effects, and adding spatially varying intensity bias fields. Finally, the images are normalized and contrast-augmented to create the final output. Examples of synthetic images are shown in Fig. 1. The model also applies random transformations to the images, using smooth deformation and spatially varying velocity fields to create realistic variations in the data.

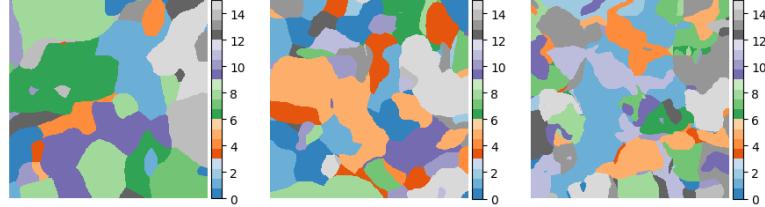


Fig. 1. Random geometric shapes in synthetic images generated from noise distributions.

Real Datasets: The proposed research will utilize weighted T1 images from multiple datasets, each featuring distinct anatomical planes. Specifically, the datasets will include OASIS 1, comprising 414 images with Coronal slices [10]; OASIS 2, consisting of 373 images with Sagittal slices [11]; and BraTS 2021, which contains 391 images with Axial slices [12, 13]. Some exemplary image samples are illustrated in Fig. 2 for reference.

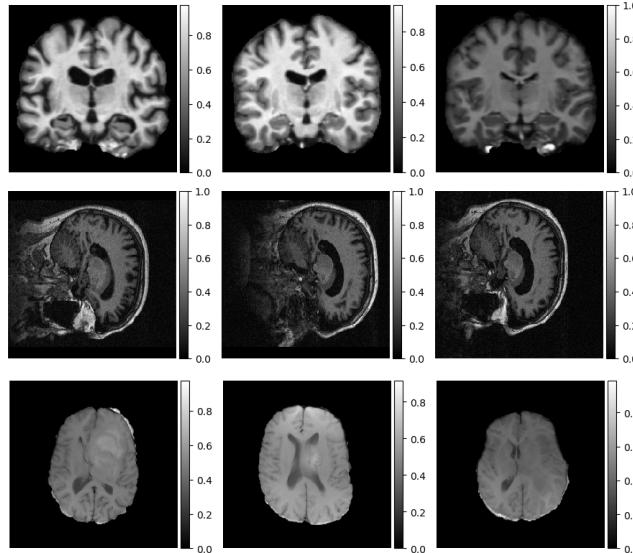


Fig. 2. T1 weighted MR brain images normalized. Top: OASIS 1 dataset (Coronal slices). Center: OASIS 2 dataset (Sagittal slices). Bottom: BraTS 2021 dataset (Axial slices).

3.2 Network Definition

HybridMorph is a pairwise medical image registration model that builds upon the foundations of VoxelMorph [1]. VoxelMorph is a deep learning-based approach for 3D image registration, which learns a registration field between two image volumes using a convolutional neural network (CNN). The method takes two 3D image volumes, f and m , as input and outputs a displacement field u that aligns the moving volume m with the fixed volume f . The registration field is modeled using a CNN, $g_\theta(f, m) = u$, where θ are the network parameters.

Network Architecture The CNN architecture is based on a UNet structure, consisting of encoder and decoder sections with skip connections. The network takes a 2D image as input, formed by concatenating m and f . The encoder section uses strided convolutions to reduce the spatial dimensions, with a feature map size of [32, 32, 32, 32]. The decoder section uses upsampling and convolutional layers to generate the registration field, with a feature map size of [32, 32, 32, 32, 16].

Loss Functions Two loss functions are proposed: an unsupervised loss function L_{us} and an auxiliary loss function L_a . L_{us} consists of two components: L_{sim} , which penalizes differences in appearance between f and $m \circ \phi$, and L_{smooth} , which encourages a smooth displacement field ϕ . A Mean Squared Error (MSE) loss metric is used to measure the difference between the predicted and ground-truth registration fields. L_a leverages anatomical segmentations at training time.

Spatial Transformation Function A spatial transformation function calculates $m \circ \phi$ from m and ϕ . This function is based on spatial transformer networks and uses linear interpolation to compute the values at subpixel locations.

Weighted Training Function The input distribution can be thought of as a mixture distribution, where the real images are sampled from $P_{real}(x)$ with probability α and the synthetic images are sampled from $P_{synth}(x)$ with probability $1 - \alpha$. Let X be the input random variable, then:

$$X \sim \begin{cases} P_{real}(x) & \text{with probability } \alpha \\ P_{synth}(x) & \text{with probability } 1 - \alpha \end{cases} \quad (1)$$

The expected output of the VXM model can be written as:

$$\mathbb{E}[Y] = \alpha \cdot \mathbb{E}_{x \sim P_{real}(x)}[f(x)] + (1 - \alpha) \cdot \mathbb{E}_{x \sim P_{synth}(x)}[f(x)] \quad (2)$$

where Y is the target output random variable, and $f(x)$ is the transformation learned by the VXM model.

The loss function can be written as:

$$L(f(x), y) = \alpha \cdot L(f(x), y) + (1 - \alpha) \cdot L(f(x), y) \quad (3)$$

where L is the loss function.

The optimization objective of the VXM model can be written as:

$$\min_f \mathbb{E}_{x \sim P_{real}(x)} [L(f(x), y)] + \frac{1 - \alpha}{\alpha} \cdot \mathbb{E}_{x \sim P_{synth}(x)} [L(f(x), y)] \quad (4)$$

The value of α controls the trade-off between the real and synthetic images in the optimization objective. When α is close to 1, the model is optimized more towards the real images, and when α is close to 0, the model is optimized more towards the synthetic images.

In terms of the batch size, the number of real images in a batch is $\alpha \cdot \text{batch_size}$, and the number of synthetic images in a batch is $(1 - \alpha) \cdot \text{batch_size}$. The value of α can be adjusted to control the proportion of real and synthetic images in the training data.

3.3 Process Flow

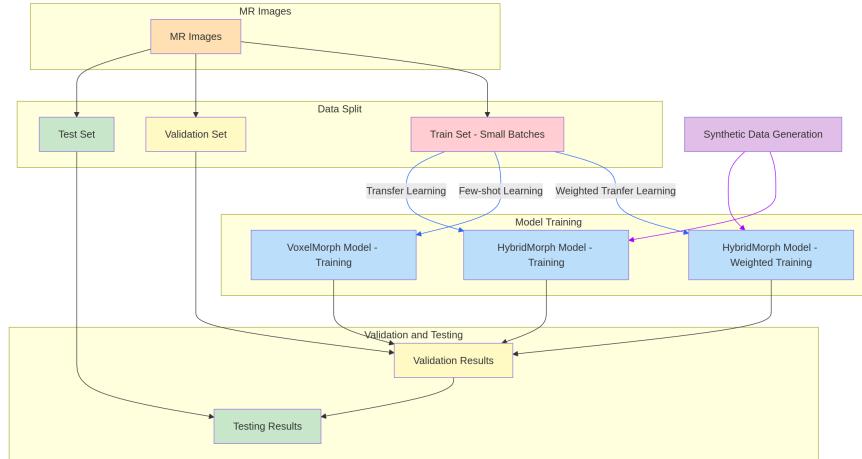


Fig. 3. Block diagram explaining the modeling paradigms.

The methodology employed in this study is illustrated in the flowchart depicted in Figure 3. The process commences with the acquisition of Magnetic Resonance

(MR) images, which are subsequently divided into three distinct sets: training, validation, and testing.

The training set is utilized to facilitate few-shot learning, enabling the model to learn from a limited dataset. Concurrently, the training set is used in conjunction with synthetic data to train two models: one using transfer learning and the other using weighted transfer learning. This hybrid approach combines the strengths of real and synthetic data to enhance the model’s performance and adaptability.

The validation set is utilized to evaluate the model’s performance, with the resultant outcomes informing refinements to the training process. The testing set is subsequently employed to assess the model’s registration performance.

3.4 Training paradigms

Few-shot Learning We trained a Voxelmorph model on a limited sample of MR images to evaluate its few-shot registration capabilities, and investigated the impact of increasing the training dataset size on registration performance. This approach enables us to assess the model’s ability to generalize to unseen data with limited training examples, which is crucial in medical imaging where annotated data is scarce and data augmentation techniques may not be sufficient to capture the variability of real-world data. By evaluating the effect of increasing the training dataset size, we can determine the optimal amount of data required to achieve satisfactory registration performance, and analyze the trade-off between model capacity and overfitting.

Transfer Learning Pre-training the models with synthetic images and fine-tuning with a few real MR images (Transfer learning) leverages the abundance of synthetic data to learn generalizable features, which can then be adapted to real MR images with minimal additional training data. The advantage of transfer learning is that it can reduce the need for large amounts of annotated real data, making it a more efficient and cost-effective approach. Additionally, pre-training with synthetic data can help improve the model’s robustness to variations in real-world data, such as differences in image acquisition protocols or scanner manufacturers.

Weighted Training Pre-training the models with synthetic images and fine-tuning using a hybrid training model with both real and synthetic images (Weighted Transfer learning) combines the benefits of transfer learning with the ability to incorporate real-world data into the training process. By weighting the importance of real and synthetic data during fine-tuning, we can balance the model’s ability to generalize to unseen data with its ability to adapt to the specific characteristics of real MR images. The advantage of weighted transfer learning is that it can provide a more nuanced and accurate registration performance, especially in cases where real data is limited or noisy, and can help mitigate the effects of domain shift between synthetic and real data.

4 Experiments

All datasets were split into training, validation, and testing sets in a ratio of 60:20:20 to ensure a robust evaluation of the model’s performance. The training was performed with 100 steps per epoch using the Adam optimizer [14] and a learning rate of 1×10^{-4} . This allowed us to assess the model’s convergence and stability. Also, the model loss was evaluated using batches with 1000 steps.

4.1 Few-shot Learning

We trained the VoxelMorph model with varying training dataset sizes, comprising 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 images, each configuration running for 1000 epochs. This experiment was repeated for all datasets to assess the model’s performance under different data scarcity scenarios, including limited training data and class imbalance. Figure 4 shows, in black, the performance of the few-shot learning. The dotted blue line consists of the performance of Synthmorph, and the dotted red line consists of the performance of VoxelMorph with all available data.

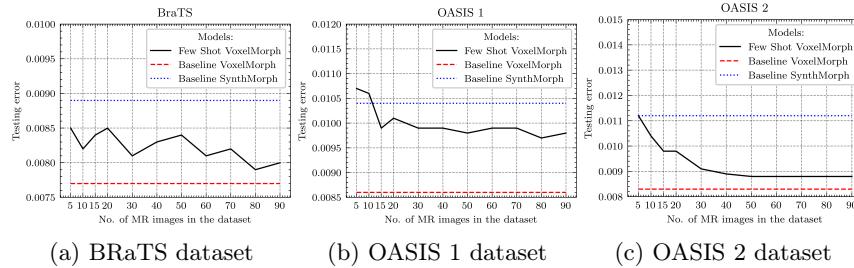


Fig. 4. Testing loss on VoxelMorph with few-shot data, demonstrating the model’s performance under varying training dataset sizes.

Our results show that the VoxelMorph model achieves competitive performance even with limited training data, highlighting its robustness to data scarcity. Furthermore, we observe that the model’s performance improves as the training dataset size increases, indicating the importance of sufficient training data for achieving optimal results.

In this experiment, we evaluate the performance of the Few-shot model in a few-shot learning scenario, where only a limited number of real brain images are available for training. We observe that the HybridMorph model is able to achieve competitive error rates with the VoxelMorph model, even when only a small number of real brain images are available.

4.2 Transfer Learning

To leverage the benefits of transfer learning, we pre-trained a SynthMorph model on a large dataset of synthetic images for 900 epochs. Subsequently, we fine-tuned the model on real images from the respective datasets for an additional 100 epochs. We also investigated the impact of varying the number of training images, comprising 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 images, on the model’s performance to determine the optimal number of images required for effective transfer learning and mitigate the overfitting risk. Figure 5 shows, in black, the performance of the transfer learning approach. The dotted blue line consists of the performance of Synthmorph, and the dotted red line consists of the performance of VoxelMorph with all available data.

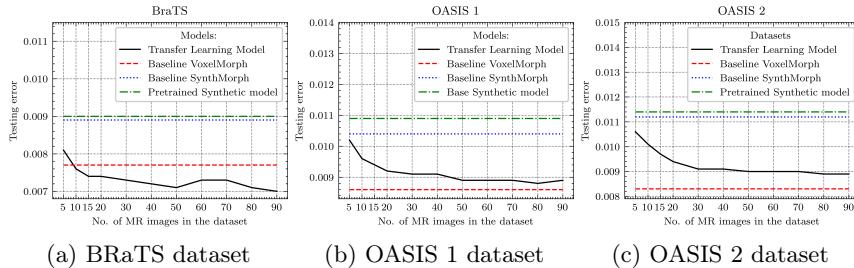


Fig. 5. Testing loss on SynthMorph with transfer learning, demonstrating the model’s performance under varying numbers of training images.

Our results show that the SynthMorph model achieves improved performance with transfer learning, particularly when fine-tuned with a larger number of real images. This highlights the effectiveness of transfer learning in adapting the model to new datasets and mitigating the risk of overfitting.

Our second experiment evaluates the performance of the HybridMorph model in a transfer learning scenario, where the model is pre-trained on synthetic data and fine-tuned on real brain images. We observe that the HybridMorph model is able to achieve better error rates than the SynthMorph model, even when the number of real brain images is limited. Furthermore, we find that the transfer learning model is also robust to changes in image type and intensity, demonstrating its versatility and reliability.

4.3 Weighted Transfer

To further investigate the effectiveness of weighted transfer learning, we conducted experiments with varying numbers of real images. We adjusted the parameter α , which controls the weight (importance) of the real images. Specifically, we first pre-trained the SynthMorph model on synthetic data for 900 epochs. Then, we fine-tuned it on real images from the respective datasets with

5, 10, and 15 images, respectively, across all datasets. Additionally, we adjusted α from 0.5 to 0.9 in increments of 0.1 to evaluate the impact of increasing the importance of real images on registration performance. This allowed us to identify the optimal balance between real and synthetic data for achieving the best results, and to assess the model’s robustness to varying levels of domain shift.

Our results show that the HybridMorph model achieves improved performance with weighted transfer learning, particularly when the importance of real images is increased. This highlights the effectiveness of weighted transfer learning in adapting the model to new datasets and achieving optimal results.

Our third experiment evaluates the performance of the HybridMorph model, which combines the strengths of synthetic and real data. We observe that the HybridMorph model is able to achieve better error rates than both the VoxelMorph and SynthMorph models, while also exhibiting robustness and invariance to image type. This suggests that the HybridMorph model is a promising approach for biomedical image registration tasks, particularly in scenarios where real data is scarce.

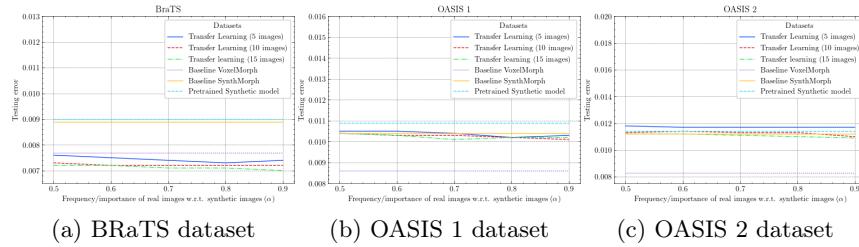


Fig. 6. Testing loss on HybridMorph model with varying values of α , demonstrating the model’s performance under different weighting of real and synthetic images.

5 Observation

Our experimental results, as presented in Figures 4, 5, and 6, offer several key insights into the performance of the HybridMorph model.

Firstly, we observe that the VoxelMorph model, which relies solely on real data, achieves the lowest error rates across all three datasets (BRaTS, OASIS 1, and OASIS 2). This suggests that real data is essential for achieving high accuracy in biomedical image registration tasks.

However, we also observe that the SynthMorph model, which is trained solely on synthetic data, is able to achieve competitive error rates when combined with a small number of real brain images. This indicates that synthetic data can be a useful supplement to real data, particularly in scenarios where real data is limited.

Furthermore, our results demonstrate that the HybridMorph model, which combines the strengths of synthetic and real data, is able to achieve error rates that are comparable to or even better than VoxelMorph. This suggests that the HybridMorph model is a promising approach for biomedical image registration tasks, particularly in scenarios where real data is scarce.

In addition, we observe that the HybridMorph model exhibits robustness and invariance to image type, which is a critical advantage in biomedical image registration tasks where image types can vary significantly. By combining synthetic and real data, the HybridMorph model is able to generalize well across different image types, achieving better accuracy than the SynthMorph model while maintaining robustness.

Moreover, our results show that the HybridMorph model is able to leverage the strengths of both synthetic and real data to achieve better accuracy than the SynthMorph model, while also being more robust to changes in image type and intensity. This suggests that the HybridMorph model is a more reliable and versatile approach for biomedical image registration tasks, particularly in scenarios where image types and intensities can vary.

Finally, we observe that the value of α has a smaller impact on the error rates of the HybridMorph model, suggesting that the model is relatively robust to changes in the weighting of synthetic and real data.

6 Conclusion and Discussion

In conclusion, our experimental results demonstrate the effectiveness of the HybridMorph model in biomedical image registration tasks, particularly in scenarios where real data is limited. By combining the strengths of synthetic and real data, the HybridMorph model is able to achieve competitive error rates with state-of-the-art models while exhibiting robustness and invariance to image type. Our results suggest that the HybridMorph model is a promising approach for biomedical image registration tasks, offering a reliable and versatile solution for scenarios where image types and intensities can vary.

The implications of our findings are significant, as they highlight the potential of hybrid models to overcome the limitations of traditional approaches that rely solely on real or synthetic data. Furthermore, our results demonstrate the importance of considering the role of synthetic data in biomedical image registration tasks, particularly in scenarios where real data is scarce. Future work could explore the application of hybrid models to other biomedical image analysis tasks, as well as the development of new synthetic data generation techniques to further improve the performance of hybrid models.

7 Future Scope

The promising results of the HybridMorph model in biomedical image registration tasks open up several avenues for future research and development. One

potential direction is to explore the application of hybrid models to other biomedical image analysis tasks, such as image segmentation, object detection, and disease diagnosis. Additionally, the development of new synthetic data generation techniques could further improve the performance of hybrid models, enabling them to tackle even more complex and challenging biomedical image analysis tasks.

Another area of future research could involve investigating the use of hybrid models in multi-task learning and meta-learning scenarios, where the model is trained on multiple tasks or datasets simultaneously. This could enable the model to learn more generalizable representations and improve its performance on unseen tasks or datasets.

Furthermore, the HybridMorph model's ability to leverage synthetic data could be particularly useful in scenarios where real data is scarce or difficult to obtain, such as in rare disease diagnosis or personalized medicine. Future research could focus on developing hybrid models that can operate effectively in these scenarios, potentially leading to breakthroughs in healthcare and medicine.

Finally, the open-sourcing of the HybridMorph model's code repository provides an opportunity for the research community to build upon and extend this work, potentially leading to further innovations and advancements in the field of biomedical image analysis.

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