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Early Diagnosis of Alzheimer's Disease using Multiscale and Multipath Convolutional Neural Network

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***Abstract*—Early diagnosis of Alzheimer's disease is inevitably essential to prevent the progression of the disease to its final stage. It helps the patient to be aware of the severity of the disease and can take necessary therapeutic and medication to prevent the progression. An MRI is a good biomarker to detect the disease at an early stage, known as Mild Cognitive Impairment(MCI). This work aims at performing a ternary classification using 2D MRI images to simultaneously diagnose MCI, AD and Normal in a single algorithm. Due to the subtle nature of the atrophy regions, discriminating between the classes is cumbersome, so here we propose a multiscale and multipath convolution neural network to learn discriminating features for proper classification among the three categories. The shallow and deep layers features are concatenated using multipath mode for better feature learning and avoiding vanishing gradient problems. In multi-scale, low-rank convolutional kernels in parallel extract multiscale features, which enhances the feature extraction property of the network.The proposed model is trained and tested on ADNI dataset comprising 900 subjects to give an accuracy of 95.19% with ten-fold cross-validation. The multiscale and multipath method significantly reduces the number of learnable parameters.**

***Index Terms*— Mild Cognitive Impairment, Multipath and Multiscale, 2D Convolutional Neural Networks, Gradient-Weighted Class Activation Mapping.**

I. INTRODUCTION

Alzheimer's disease(AD) is a progressive neurodegenerative disease that occurs in late life. An AD individual will have memory loss and cognitive impairment due to abnormal protein accumulation. One of the proteins, Amyloid beta, gets deposited as plaques, and another protein, tau, accumulates as tangles around the brain. The statistics are sobering; around 26.6 million people were affected by AD in 2006 and among which 56% were in the early stage, and it is anticipated to rise by 106.8% million by 2050 [1]. AD diagnosis was considered a difficult clinical task because the mental test evaluation is challenging when consciousness is impaired. MCI is regarded as an early stage of AD with minor memory loss and cognitive impairment, which does not affect their daily life, but there is a high risk of progression towards AD. So diagnosing AD at the MCI stage is crucial and of the same interest among the researchers as it is beneficial for clinical trials. MRI is one of the well-recognized biomarkers for the early detection of AD. Structural MRI gives clearly the atrophy regions related to the disease

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conditions. But identifying MCI from AD and Normal is challenging because only subtle changes exist between the classes. Ternary classification plays a vital role in such situations to place AD, MCI and Normal using a single algorithm. In three-way classification, the same algorithm is trained with AD, MCI and NC, which gives an added advantage of learning better features common for AD and MCI and different from Normal.
In [2] T1 weighted MRI and Amyloid PET are fused using CNN to classify between AD and healthy people. The paper talks about using amyloid PET, an early indicator of disease but does not consider the detection of MCI subjects. An end to end learning is proposed in[3] performing Binary classifications of AD vs MCI, pMCI vs NC, sMCI vs Normal and pMCI vs sMCI and mapping the brain affected region using a gradient-based method. Convolution autoencoder is used for pretraining to initialise weights. Further finetuning is done using supervised training, but the accuracy for detecting MCI is less, which can be solved using ternary-based classification. A multimodal approach to classify AD, MCI and CN using intermediate features level, feature level and decision level of MRI Image, genetic data and clinical is performed in the [4]. A comparison study is done to analyse the performance of SVM, decision trees, Random forest, KNN and deep models. Among these, deep models perform well. A fusion-based method is proposed in [5] in which MRI and PET images are combined to form the GM-PET image and use the multiscale 3DCNN method to classify AD, MCI and CN. This work utilises metabolic and structural information of the brain to perform classification. Even though the accuracy is higher, some instability exists in the specificity and sensitivity measures. 3D DenseNet based method is proposed in [6] diagnose AD. Dense connections are introduced to solve limited training data, solve vanishing gradient problems, and lessen the number of parameters. An extensive study is conducted with different hyperparameters and optimization algorithms to suit optimum parameters for DenseNet. In [7] patch-based method is used to classify AD, MCI and NC. 27 patches extracted from brain MRI are fed into cascaded 3DCNN architectures to learn global features corresponding to all patches and finally classified using an SVM. Gradcam is used to highlight the areas of the brain affected region. In [8] a cascaded 3DCNN architecture is used to extract features relevant to disease conditions and multilayered perceptron to classify AD, MCI and NC. It gave a 97.1% accuracy and used Gradcam to find brain affected regions. Classification of AD versus MCI was performed in [9] by using features extracted from gray matter and CSF of brain MRI images. Image segmentation was done using a novel meta-heuristic Markov random field-based method considering spatial properties. The classification was performed using a two-layered neural network. The disadvantage is Image segmentation is time-consuming, and feature extraction requires domain expertise. Patch-based, region-based and voxel-based methods are combined to form a unified framework in [10] to detect AD and MCI. A deep neural network is trained to learn multilevel nonlinear relationships among voxels and regional output abnormality. Regional abnormalities are averaged and integrated using SVM to classify. In [11] LSTM based method is proposed to predict the progression of AD. Designed a one layer size of 256 to train and evaluate progression. Finally were able to predict the clinical status, ventricular volume and ADAS-cog13 score.
From the literature, we understand that Conventional methods require segmentation and feature extraction, which is time-consuming and requires domain expertise. 3DCNN based method automates the feature extraction and uses the whole brain information. However, due to high computational resources and complexity, it is not applicable in most clinical settings. So we propose a 2DCNN based method using the 2D MRI images extracted from the most prominent atrophy region of AD, Mid temporal part of the brain that covers the whole hippocampus area. This method assures less computational resources and ease of use in clinical settings. The main contributions of the proposed method are described below :.

1. Multiscale and Multipath based network learns good feature representation for disease conditions with fewer parameters and few layers.
2. Grad Cam enables visualisation of AD and MCI's atrophy regions, thus helping the doctor confirm the areas for the early detection.
3. The proposed work has achieved a high accuracy with less computational load, thus increasing the speed and reducing computation cost.

II. Materials and Methods

A. Materials

The proposed work is trained and tested using the ADNI dataset. A total of 900 subject MRI image scans were downloaded, out of which 300 were AD, 300 were MCI and 300 were CN. The following preprocessing steps were conducted using freesurfer software: Motion correction, Non-uniform intensity normalization, Tailairach Transformation, Intensity Normalization, and Skull Stripping. Further, we found that all images don't lie in the

same orientation. So non-linear registration was performed using FSL software to orient with the MNI152 template and obtained an image size of 182 x 218 x 182.

B. Experiment

This work proposes multipath and multiscale based CNN architecture to classify AD, MCI and NC using T1 weighted MRI 2D coronal slices. There are several advantages of using 2D images over 3D images, even though 3D images have more information. As 3D images consist of huge dimensionality, it is required to build deep layers to learn good representation for efficient classification. Still, it is infeasible due to the computational complexity, limited availability of computational resources and GPU memory. The processing time requirement and computational resources for 2D images are less and can be used in most clinical settings. Another advantage is such images are widely applicable in clinical settings rather than 3D images, which may not be available. And also, the availability of numerous standard public datasets like ImageNet, CIFAR and classic architecture like GoogleNet, ResNet etc., aids 2D based methods to be used for diagnosis. We use 2D coronal slices of the Medial Temporal Lobe (MTL) area. The algorithm will learn the Medial Temporal lobe Atrophy scale, used as a standard clinical measure for AD-related neurodegenerative diseases. As per National Institute on Aging and Alzheimer's Association research guidelines [12] this scale is used as evidence for AD-related neurodegenerative disease. Medial temporal lobe based detection is commonly used and more specific to AD diagnosis, even though other areas also give information. The other atrophy areas indicate inter-subject variability [13] and are not consistent with AD. The algorithm learned with such patterns may result in confusion and lead to a decrease in accuracy. We extracted 30 slices of coronal views from the Medial Temporal Lobe starting from the hippocampus corpus area(from the level of anterior pons). We can cover the entire hippocampus area, the most useful information. The slices were converted to 224 X 224 X 3 standard image size by stacking the same slice three times and using zero padding.

Conventional image processing usually uses handcrafted features for classification, which requires more time and human expertise. Feature extraction and feature selection methods used in such a process always result in the throwaway of some features due to dimensionality problems and result in less accurate results. Convolutional Neural Networks(CNN) have solved this issue by automating feature extraction and classification. Deep layer CNN can learn generic features specific to the disease-related conditions and provide high interclass and low intraclass variance. 2D CNN is mainly used in many applications, like object detection and classification, medical diagnosis, facial recognition, etc. There are many standard architectures and standard public datasets available. Even though 2DCNN has come a long way, it is still challenging to develop architectures for medical applications due to the limited dataset availability. Here we propose Multiscale and Multipath based architecture for three-way classification of Alzheimer's disease from MRI scans. Most of the CNN require high parameters, more computational load, and huge deep layers to achieve the desired output, limiting further applications. Here we use the concatenation of shallow and deep layers in multipath, which helps avoid the vanishing gradient problem and fuse multi-layer features. The network also consists of Low-rank kernels used at multiscale levels to increase the feature extraction capability of the network. Also, the use of low-rank kernels compresses the network with less number of parameters and space [14]. The proposed architecture as shown in Fig. 2 uses a 224 x 224 x 3 size image as input. It has two paths to incorporate multiscale and multipath computation; the primary path includes two single scale convolutions (SSL) followed by one multiscale convolution and then a SSL convolution, and finally converting to a one dimensional vector by averaging the feature maps for ternary classification. The other path includes a single scale convolution whose features are concatenated with the multiscale features at the primary path, which helps to learn both local as well as global features [15]. The multipath also helps to avoid the vanishing gradient problem that may occur in the primary path while going through many layers.

First, a single scale convolution(SSL) is performed in the main path by a 3x3 size eight filters to give eight feature maps. The second SSL provides 16 feature maps using 3x3 size 16 filters. Subsequent low-rank kernels are used to extract features at multiple scales using 1x1, 3x3 and 5x5 with 32 filters each to give 96 feature maps at the output. A parallel path is formed from the output of first SSL layer in the primary feedforward network using a 9x9 size 32 filters which generates 32 feature maps. The output of multipath output is merged with the multiscale output in the primary path to produce 128 feature maps. The shortcut connection leads to the combination of early features and late features resulting in the extraction of local as well as global structures from the data. Next, the combined features pass through an SSL layer to give 128 feature maps. Global average pooling is applied to average all feature maps from the previous layer to provide a single feature vector of size 128. Finally, AD, MCI and NC classification is done using a softmax. The average of 30 slices for each subject is considered while taking the output.

Relu is the activation function used after each convolution process. It suppresses all the negative values to zero and passes the positive values. Relu increases the speed and accuracy of the computation compared to other activation function and exhibits more gradient shift . Average Pooling layer is included after each convolutional layer to cut short the spatial dimension by retaining the most important features. The multipath connected from first SSL layer to the output of multiscale layer helps to compensate for the loss of global features incurred while moving through a single path convolution layers. There is a possibility of focusing more on the hippocampus region alone in a brain MRI image since the anatomical boundaries of hippocampus are distinct in T1 weighted MRI images. It may lead to the loss of information from other regions of MRI which is critical for the detection of AD that is MCI. Inorder to elevate the problem of learning local patterns alone and shrinking to very particular region while going deep in a single path convolution layer, multipath enables to provide the features learned at the early part of layers. Thus increasing the learning capability of the architecture.

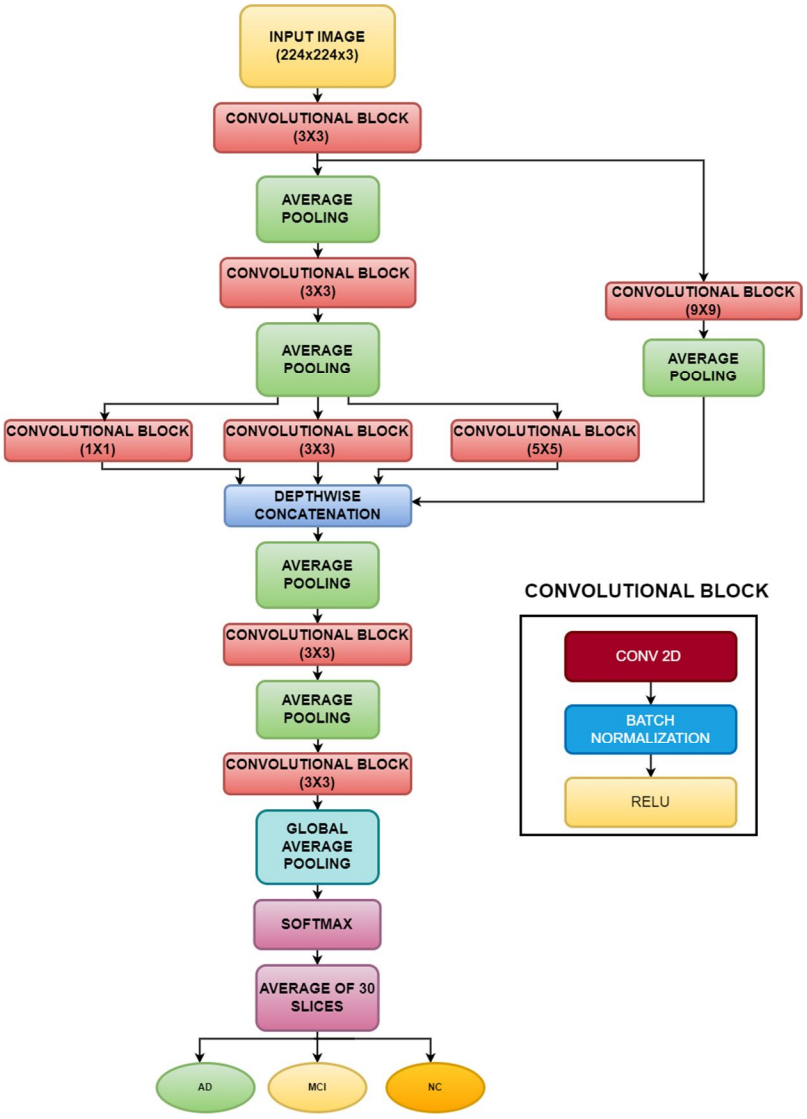

Figure 1. Schematic of Multiscale and Multipath Architecture

Big kernel size 9×9 is chosen for the multipath to extract global structures pertaining to early detection of AD. Another advantage of parallel path is to reduce vanishing gradient, which is always a problem for deep learning architectures. There will be no gradient changes towards the deeper layers and resulting in poor training of the architecture. Parallel path connections go through less number of nonlinear activations reducing the squashing of the derivatives and lead to improvement of the derivative of overall architecture. Learning features at different scales enables the architecture to explore local patterns at different dimensions. The Alzheimer's brain MRI

image have different atrophy regions of various sizes and structures throughout the image. So it is very difficult for single scale convolution kernel alone to extract this kind of complex features pertaining to early detection of the AD. So in the proposed architecture we have included multiscale convolutional layer to focus on sparse local atrophy regions pertaining to the disease conditions. We use three different filter sizes for the purpose. First 1× 1 filter size enables channel wise pooling to increase the feature maps from 16 to 32 without any loss of dimensions. Next 3 × 3 size filter learns larger local patterns related to disease. Finally, expanded 5 × 5 size filter can learn even more larger local structures. The feature maps obtained in all three filters are concatenated in a Depth-wise manner. Inorder to maintain the same ouput dimension for all the feature maps zero padding is applied. Totally 128 feature maps of different scales are obtained through this operation which leads to learning various local structures and is very useful for MCI detection.The parameter utilization efficiency is attained by applying an Adam optimizer to train the network. It uses adaptive learning rate mechanism in which learning rate is adjusted based on the performance of the model during training. Categorical cross-entropy is used to find the loss value corresponding to three classes. With a Mini batch size of 16, the network was trained to 23 epochs. The number of filters and filter size were optimized using the grid search method. The method has 0.188 million learnable parameters.

III. RESULTS

A multipath and multiscale architecture with less learnable parameters and low computational load is proposed to classify AD, MCI and NC. The algorithm's performance is evaluated using the ADNI dataset by a 10-fold cross-validation method. A total of 900 subject MRI scans are used for training and testing, out of which 300 AD, 300 MCI and 300 CN. 30 coronal slices from the mid temporal lobe of each subject are extracted and resized into 224 x 224 x 3. So there are, in total, 27000 images. Each slice is labelled as AD, MCI or NC; it is averaged for each subject while obtaining results. The binary cross-entropy loss is shown in the (1)

$$L(w)= -\frac{1}{M}\sum_{K=1}^{M}[y_k^i \log\left(f\left(x_k^i;w\right)\right) + \left(1-y_k^i\right)\log\left(1-f\left(x_k^i;w\right)\right)] \quad (1)$$

Where x_i is the coronal slices of an MRI brain x and y_i is the true label of the slice. M corresponds to the total number of samples of each batch, and w is the weight parameter. During testing and validation process the average probability of all slices of each subject (x_1, x_2, x_3, …., x_{30}) is taken into consideration for diagnosing AD and MCI. We validated the algorithm's performance using Average weighted Accuracy obtained after ten-fold cross-validation. The Accuracy is computed by

$$Accuracy = \frac{TP+TN}{TP+TN+FP+FN} \quad (2)$$

We achieved an Average accuracy of 95.19 % with only 0.6 million learnable parameters, which outperforms most of the other existing works. Other evaluation metrics used are precision, recall and F1 score, as given below. Table I gives the class wise performance of the proposed work, in which Precision, Recall and F1 score comes to be high values for every classes indicating that the proposed model can be used for early detection that is MCI stage and diagnose AD correctly.

$$Precision = \frac{TP}{TP+FP} \quad (3)$$

$$Recall = \frac{TP}{TP+FN} \quad (4)$$

$$F1score = 2* \frac{Precision*Recall}{Precision+Recall} \quad (5)$$

Table I. Class Wise Performance Metrics of the Proposed Model

Class Label	Precision	Recall	F1-Score
AD	0.95	0.964	0.957
MCI	0.953	0.934	0.943
CN	0.953	0.956	0.954

IV. DISCUSSION

The proposed work utilizes multiscale and multipath features to classify AD, MCI and NC efficiently. The architecture provides 95.19 % accuracy with high sensitivity, specificity and F1 score. The feature extraction ability of multiscale and fusing of multilayer features using multipath mode helps to learn local and global features relevant to disease [16]. The vanishing gradient problem is also solved using multipath mode. Low-rank 1 X 1, 3 x 3 and 5 x 5 kernels replaces the use of large rank kernel computations with lesser parameters. A comparison is made in Table II with existing standard architectures. Each model pretrained with ImageNet dataset is used to train with MRI dataset. The table shows that the proposed model performs better than any other standard architecture because of multiscale and multipath techniques. It is challenging to train big architectures and get efficient output with a limited dataset. The multiscale feature extraction and multipath fusing of early features enable the model to perform well with fewer parameters and without going into much deeper layers. It is fast and easy to train the architecture from scratch and takes only 25 epochs to converge to optimum global value. Table II shows the comparison with some of the existing works which tells that our model perform better than any other methods with respect to metric accuracy.

TABLE II. COMPARISON OF PROPOSED MODEL WITH EXISTING STANDARD NETWORKS

Methods	Precision	Recall	F1-Score	Accuracy	Parameters (Millions)	No. of Flops (BFLOPS)
Proposed model	**0.952**	**0.951**	**0.951**	**0.9519**	**0.138**	**0.0233**
VGG 16 [18]	0.884	0.874	0.894	0.877	15.04	15.50
Xception [19]	0.815	0.815	0.815	0.813	21.9	11
ResNet50 [20]	0.88	0.87	0.876	0.873	24.7	3.8
NASNetMobile [21]	0.756	0.742	0.751	0.746	4.87	0.749
EfficientNetB0 [22]	0.933	0.926	0.926	0.926	4.7	0.3066
DensNet121 [23]	0.83	0.82	0.82	0.821	7.03	0.0567

TABLE III.COMPARISON WITH EXISTING WORKS

Methods	**Accuracy**	**Modality**	**Techniques used**
Janani et.al [3]	79	MRI, Genetic and clinic	3DCNN and Autoencoder
Juan Song et.al. [5]	74.54	MRI+PET	Fusion with 3DCNN multiscale
Karasawa et.al. [24]	87	MRI	3DCNN with 39 layers
Hossseini –Asl E [25]	89.1	MRI	3DCNN with 3DCAE
Adrien Payan [26]	85.53	MRI	2DCNN
H. Lei. Et.al [27]	85.30	MRI	Multitask sparse low rank learning
Proposed Method	**95.19**	**MRI**	**Multiscale and Multipath using 2DCNN**

Gradient-weighted Class Activation Mapping (Grad-CAM) describes an internal architecture of the proposed architecture model by attention weights visualization to localize relevant image regions in the feature maps [7],[8]. Fig. 2 and Fig.3 represents the visualization of Grad-CAM for the qualitative evaluation. The highlighted areas of heat map for AD and MCI shows that 2D coronal slice helps to easily discriminate early stage from the late stage thus early diagnosis is possible with 2D images of MRI. In the case of MCI, we can see that most of the sample coronal slices have the lateral ventricular region highlighted. This confirms with the existing references of AD diagnosis that the enlargement of the lateral ventricular region increases more while progressing to AD than a normal individual [7]. It plays a vital role in discriminating MCI from AD and Normal individuals. Atrophy of the Amygdala and parahippocampus region, as highlighted in the slices, also plays a vital role in determining the MCI. Amygdala is affected in the early stage, due to which neuropsychiatric problems are prevalent in the mild stage of AD [3]. The last slice in MCI shows the temporal horn region of the lateral ventricle as one of the discriminating features not found in any AD samples. In AD, the most discriminative region is the hippocampus, highlighted in the coronal slices in Figure 3. The volume of the hippocampus region decreases by 10-15 % than a Normal individual for MCI and by 15-30 % for AD [17]. Since there is a drastic

change in the volume and thickness of the hippocampus region, it is the central affected region highlighted in the AD coronal slices. The hippocampus structure are easier for automated algorithms to identify than the amygdala, entorhinal cortex or parahippocampal gyrus, as the anatomical boundaries of the hippocampus are distinct on T1 weighted MRI. Amygdala and entorhinal cortex also help in the discrimination of AD from MCI and Normal. The comparison table with existing works shows that 2DCNN based method can achieve higher accuracy than a 3DCNN based method because medial temporal lobe atrophy contributes to a significant portion of AD, and hippocampal atrophy is validated to be the best marker for AD patients. So the best way to assess the atrophy of the medial temporal lobe is by taking coronal slices of T1 weighted MRI [17]. Also, 2D images are more applicable in clinical settings than 3D images due to its more availability. This justifies using 2D images of the brain for doing this work.

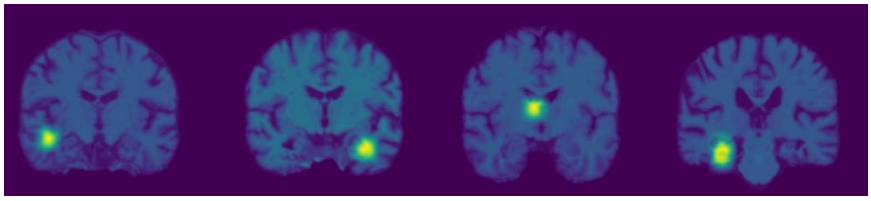

Figure 2. Grad-CAM visualization of Coronal slices of AD

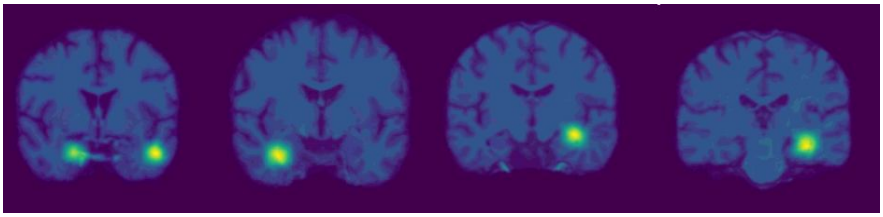

Figure 3. Grad-CAM visualization of Coronal slices of MCI

V. Conclusion

This study proposed a novel architecture for ternary classification of AD, MCI and NC using 2D MRI images. A multiscale and multipath architecture is proposed to increase the feature extraction ability, prevent vanishing gradient problems and lessen the computation load. The main path has the multiscale features extracted, and the parallel path fuses the early features with multiscale features to learn local and global features. The heat map generated confirms the hippocampus area as the main affected region for an AD patient, whereas for MCI is the lateral ventricles, temporal horn and amygdala.

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