ORIGINAL ARTICLE

HivNet: Studying in Depth the Morphology of HIV-1 Virion Using Deep Learning

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Abstract

Purpose: Human Immunodeficiency Virus (HIV) continues to be a disease that kills thousands of individuals each year. The HIV infection is incurable. However, HIV infection has turned into a treatable chronic health condition because of improved access to efficient HIV prevention, diagnosis, treatment, and care. Transmission Electron Microscopy's (TEM) ability to directly visualize virus particles and distinguish ultrastructure morphology at the nanometer scale, makes it useful in HIV-1 research where it is used for assessing the actions of inhibitors that obstruct the maturation and morphogenesis phases of the virus lifecycle. Hence with its use, the disease's serious stage can be avoided by receiving an early diagnosis.

Materials and Methods: Through the dedicated use of computer vision frameworks and machine learning techniques, we have developed an optimized low-computational-cost 8-layer Convolutional Neural Network (CNN) backbone capable of classifying HIV-1 virions at various stages of maturity and morphogenesis. The dataset including TEM images of HIV-1 viral life cycle phases is analysed and augmented through various techniques to make the framework robust in real-time. The CNN layers then extract pertinent disease traits from TEM images and utilise them to provide diagnostic predictions.

Results: It was discovered that the framework performed with an accuracy of 99.76% on the training set, 85.83% on the validation set, and 91.33% on the test set, after being trained on a wide range of micrographs which comprised of different experimental samples and magnifications.

Conclusion: The suggested network's performance was compared to that of other state-of-the-art networks, and it was discovered that the proposed model was undisputed for classifying TEM images of unseen HIV-1 virion and required less time to train and tweak its weights. The framework can operate more effectively than machine learning algorithms that consume a lot of resources and can be deployed with limited computation and memory resource requirements.

Keywords: HIV-1 Virology; Artificial Intelligence; Deep Learning; Computer Vision; Electron Microscopy; Convolutional Neural Networks.

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1. Introduction

One of the biggest public health problems today, especially in low and middle-income nations, is HIV. Its initial symptoms include fever, headache, rash, or sore throat. Other symptoms including enlarged lymph nodes, weight loss, fever, diarrhoea, and cough develop as the virus gradually weakens the immune system. Without medical care, life-threatening conditions, including tuberculosis, cryptococcal meningitis, severe bacterial infections, and cancers can occur. With 40.1 million deaths caused by HIV to date, it is a significant worldwide public health concern. 6,50,000 persons passed away and 1.5 million people acquired HIV in 2021 due to HIV-related causes. At the end of 2021, the number of HIV-positive individuals worldwide was predicted to be 38.4 million, with 25.6 million of these individuals residing in the WHO African Region [1]. According to estimates from the Indian government, there are around 2.40 million HIV-positive people in the country with an adult prevalence of 0.31% (2009). 83% of infections occur in people aged 15 to 49, whereas 3.5% of all infections are in children under the age of 15. 39% (9,30,000) of all HIV infections occur in females [2].

One of the most popular techniques used to diagnose HIV is the antigen/antibody test, which a lab performs on blood drawn from a vein and often finds the virus 18 to 45 days after exposure. There is also a rapid finger-stick antigen/antibody test that is available. Antigen/antibody tests done using blood from a finger stick might take anywhere between 18 to 90 days following exposure.

HIV in India is an epidemic. In India, there is a dearth of medical specialists in rural regions [3]. Access to healthcare in rural areas is severely hampered by this. It is brought on by a lack of knowledge, a lack of medical facilities, and a shortage of expensive laboratories, equipment, physicians, and highly qualified personnel. Moreover, it is tedious to manually examine these tests, which needs clinical professionals. It is also prone to human mistake, which makes it more difficult due to the lack of expertise. As a result, automated diagnosis techniques are needed to find HIV-1 cells by studying microscopic blood cell images. Additionally, in order to stop HIV-1 from progressing to its severe stage, automated methods to classify the various phases of HIV-1 morphology are required.

Artificial intelligence has recently had a significant influence on overcoming issues that arise with the conventional technique and has enabled a manner whereby diagnosis may be carried out automatically without trained personnel [4]. Machine learning is a component of artificial intelligence, a technique for creating smart machines that are capable of performing particular tasks. The major purpose of machine learning algorithms is to identify various illnesses using medical imaging, where disease patterns are retrieved utilizing methods including textural features, visual features, and feature analysis on many aspects [5-7]. The old approaches, however, frequently fall short in their ability to generalize and cover a wide variety of image types when data grows huge or becomes unstructured. Deep learning has a high potential to cope with this issue. It automatically extracts pertinent disease features, which enables massive amounts of data to be trained without the need for feature extractions manually. Only the hyperparameters are being improved in this network, which can be categorised into several different disease categories [8]. Convolutional Neural Networks (CNNs) are frequently the brains behind deep learning models [9, 10]. Small extracellular vesicles (sEVs) may be semantically segmented from TEM micrographs using CNNs [11]. These models have further demonstrated their value in classification, detection, and segmentation tasks across a variety of domains and applications, delivering outcomes on par with those of medical professionals [12]. Because of these powerful qualities of CNNs, there is now considerable interest in their widespread application in medical imaging.

Therefore, in order to diagnose HIV disease, it is advantageous to use these methodologies to create a low-cost, real-time, and accurate prediction system for HIV-1 virion classification. In this way, many researchers used machine learning or deep learning algorithms to create a prediction system.

In order to find prospective HIV-1 entrance inhibitors that target the hydrophobic Phe-43 cavity of gp120, which is crucial for the viral attachment to CD + T cells, Alexander *et al.* [13] created a generative adversarial autoencoder for anti-HIV-1 drug prediction. To handle vast amounts of viral sequences and identify subsets of sequences that were acquired from an ongoing HIV-1 outbreak, Kupperman *et al.* [14] created a deep learning-based approach. With a mean average precision of 80.0%, Juan *et al.* [15] developed a deep learning strategy for the

identification and classification of HIV-1 virion particle morphologies from TEM micrographs. Convolutional neural networks were shown to be the highest-performing design when Steiner *et al.* [16] assessed the performance of three architectures (multilayer perceptron, bidirectional recurrent neural network, and convolutional neural network) for drug resistance classification in HIV-1.

The classification of the HIV-1 virion into its different stages, which is the least explored, is a necessity, which became clear after a review of the reported works utilized for diagnosing HIV disease. A speedier and more accurate diagnosis technique with less computing needs is also lacking, as is one that requires less training time. The relatively high variability and scarcity of training data are the cause of this. This research provides an artificial intelligence-based approach to precisely identify various phases of HIV-1 virion in order to prevent HIV disease, bridging the gap in HIV-1 virion cell classification into its various stages. The proposed architecture also has the benefit of having a low layer count, which means that fewer computational resources would be required for its implementation in practice.

The model, called HivNet, based on deep learning for HIV-1 virion classification in three different categories utilizing TEM images is the primary contribution of the suggested study. For this investigation, a publicly accessible dataset of TEM images of the HIV-1 virion was used. The method is more difficult due to several complex factors such as compact size, cell similarity, and uneven data distribution. Various augmentation approaches are used to equalize pictures in different classes of the training set after the data has been divided into training, validation, and test sets. This is done to reduce the likelihood of overfitting caused by a high sample density in certain classes relative to others. In comparison to other cutting-edge deep learning models, the established architecture of HIV-1 virion classification is less complex and requires less time to train and tweak its weights, making it a better option for usage in the biomedical industry. Fully automated diagnosis can be accomplished using the proposed approach. For early HIV-1 viral identification with its stages at primary healthcare facilities in remote areas, it can confirm medical expert decisions and be managed by non - technical personnel.

Model effectiveness was assessed using a variety of classification metrics, including F1-score, precision, accuracy, and recall. A thorough investigation of the model's performance reveals that HivNet performs well on TEM pictures that have not yet been viewed. To demonstrate the usefulness of HivNet in non-invasive and reliable HIV disease identification in real-time by classifying HIV-1 virion life cycle phases, obtained experimental findings were compared with other state-of-the-art deep learning architectures. Results indicate that when compared to the existing approaches, the suggested method is more accurate.

The structure of the paper is as follows. Section 2 presents the data acquisition and neural network architecture, while Section 3 presents the findings of the experiments. In Section 4, the proposed work with a conclusion is presented.

2. Materials and Methods

2.1. Dataset Description

The raw dataset includes 1806 .tif images divided into training (1443 images) and validation (363 images) sets and each of these is divided into eccentric, mature, and immature labeled folders [17]. The classes in the raw dataset were highly imbalanced in terms of the number of images and had grayscale images with low discriminatory features. The raw dataset of .tif images was converted into .png images and then augmented by flipping, zooming, rotating in multiple angles, and changing to black and white images so that there are 2,718 binary images to ensure feature discrimination and the augmented dataset was divided into training (2,061 images), validation (507 images), and test (150 images) sets with an equal number of images in each class. The names of the three classes are - eccentric, mature, and immature. Sample images from the dataset before and after augmentation are shown in Figure 1.

The model is trained for 100 epochs with a batch size of 16, which settles the results and rules out randomness or accuracy loss after a few epochs. Table 1 contains a description of the dataset augmentation that was used and Table 2 shows the distribution of images into training, testing, and validation sets

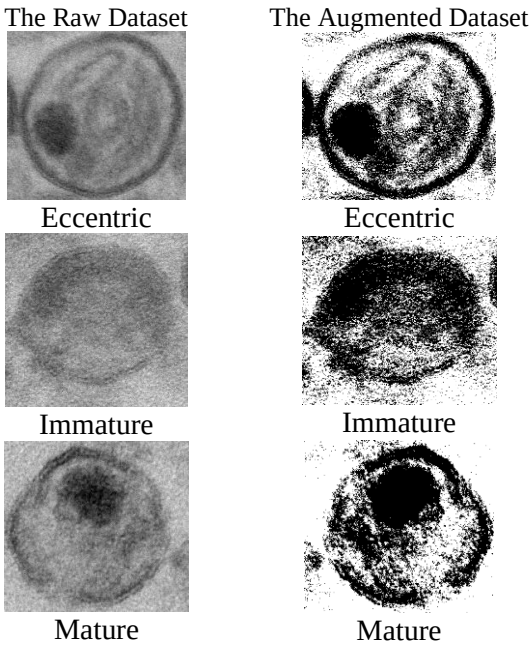

Figure 1. Dataset before and after augmentation

Table 1. Dataset description

Dataset	2718
Image Size	224 X 224
Augmented	flip_left_right (0.5) black_and_white (0.1) rotate (0.3, 10, 10) skew (0.4, 0.5) zoom (probability = 0.2, min_factor = 1.1, max_factor =1.5) rescale = 1. / 255 zoom_range = 0.2 shear_range = 0.2

Table 2. Dataset distribution for training the model

Class	Training Set	Testing Set	Validation Set
Eccentric	687	50	169
Immature	687	50	169
Mature	687	50	169

2.2. Proposed Methodology

A convolutional neural network [18] has been designed to classify images into many categories. A convolutional neural network typically comprises many convolutional layers, max-pooling layers [19], and dropout layers with different activation functions. The suggested model is developed using a convolutional neural network. The block diagram in Figure 2 depicts the presented methodology.

Extraction of pertinent and discriminating characteristics from the provided dataset is the primary strategy of deep learning-based architectures. The proposed work employs a convolutional neural network that receives input TEM pictures that have been scaled to 224 x 224 x 3 in size for each class. Two convolutional layers of kernel size 3 x 3 each with padding size of 1, to recover the picture border information, and one max-pooling layer of size 2 x 2 are used as a pair with a dropout value of 0.1 after every max-pooling layer. While dropout is given to the network to decrease misclassification errors by lowering the likelihood of overfitting in the network, the max-pooling function enables us to choose the highest value among nearby pixels. Only the first pair has a dropout value of 0.15. 16 filters with a 3 x 3 kernel size each make up the input to the first pair of convolutional layers. The next pair of layers includes 32 filters with a kernel size of 3 x 3. The following pair of convolutional layers contains 64 filters with a 3 x 3 kernel size, while the last pair has 128 filters with a 3 × 3 kernel size. In all, eight convolution layers with ReLU activation function and four max-pooling layers were employed.

Every convolutional layer employs the ReLU activation function [20] to eliminate negative bias. The function will return 0 if a negative value is supplied to it, but it will return the same value if a positive value is passed. The output can therefore be anything between 0 and infinity. The output may be determined using the ReLU function as given in Equation 1 for any value of the input "m":

$$ReLU(m) = \begin{Bmatrix} 0, if\ m \leq 0 \\ m, if\ m > 0 \end{Bmatrix} \quad (1)$$

The extracted 2D feature maps are converted into a vector (i.e. 1D) using a flattened layer. The fully connected layer receives this vector. 12845568 and 1539 parameters are generated by the two fully connected layers, respectively. The proposed model is trained with a 0.001 initial learning rate. Adam optimizer [21] is used in place of classical stochastic gradient descent to update network weights more effectively because Adam uses adaptive learning rates to converge faster. Training of the model was done using a batch size of 16.

When the batch size is set to k, the error gradient will be estimated using k training data points from the total training data points before the model weights are updated. The softmax activation [22] is summarised in Equation 2, where ezi is the standard exponential function for the input vector, k is the number of classes, ezj is the standard

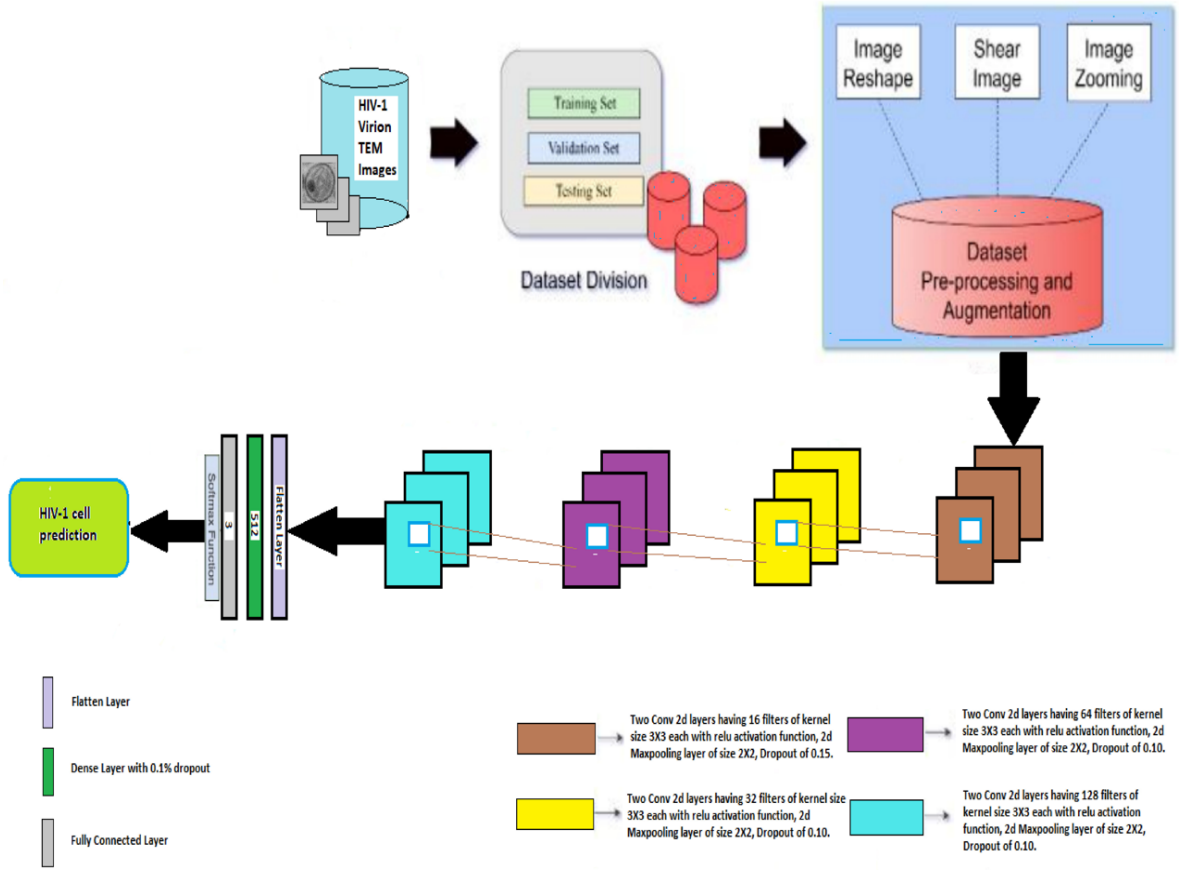

Figure 2. The schematic representation of the presented deep learning-based methodology for classifying HIV-1 virion from TEM images

exponential function for the output vector and $\vec{z}$ is the input vector.

$$Softmax(\vec{z})_i = \frac{e^{z_i}}{\sum_{j=1}^{k} e^{z}j} \quad (2)$$

The last layer of the network uses the softmax activation function to create the network output from the fully connected layers. With its input vector X, weight vector W, bias b, and activation function f, Equation 3 shows a neuron's output in the fully connected layer.

$$Y = f\left(b + \sum_{i=1}^{n} x_i * w_i\right) \quad (3)$$

Table 3 contains information on each layer in detail, including the number of strides, kernel and filter sizes, activation function, number of parameters, and shape of output for each layer. After layer-by-layer implementation, the suggested model predicts the infection stage and groups it into the best category using extracted attributes. The over-fitting issue is solved by the dropout layer. The design specifies 13,140,627 trainable parameters in total. The Table also shows how several layers with diverse features operate.

The same dataset was trained with several pre-trained, state-of-the-art CNN architectures, including VGG-16 [23], VGG-19 [23], ResNet50 [24], Inception V3 [25], and Xception [26], after the suggested CNN Architecture was implemented. In order to draw a conclusion from the study and provide a response to the research question, the outcomes of the pre-trained models were compared to the outcomes of the suggested CNN model.

3. Results

The technical specifications of the system used had 8 GB DDR4 RAM, a Ryzen 5 Hexa Core 4600H processor, and Windows 11 as the operating system for designing and training the suggested framework. It used Nvidia Geforce GTX 1650 graphics card (4 GB). All programmes are built up on the training model using Google Colab on a Python interface using Keras, Tensorflow, and other relevant libraries.

Table 3. Layer architecture of the proposed convolutional neural network

Layers	No. of filters	Strides	Activation function	Size of the kernel	Shape of the output	No. of parameters
Input image	-	-	-	-	(224, 224, 3)	-
Conv2d (Conv2D)	16	1	ReLU	3 x 3	(None, 224, 224, 16)	448
Conv2d_1 (Conv2D)	16	1	ReLU	3 x 3	(None, 224, 224, 16)	2320
Max_Pooling2d (MaxPooling2D)	-	2	-	2 x 2	(None, 112, 112, 16)	0
Dropout (Dropout)	-	-	-	-	(None, 112, 112, 16)	0
Conv2d_2 (Conv2D)	32	1	ReLU	3 x 3	(None, 112, 112, 32)	4640
Conv2d_3 (Conv2D)	32	1	ReLU	3 x 3	(None, 112, 112, 32)	9248
Max_Pooling2d_1 (MaxPooling2D)	-	2	-	2 x 2	(None, 56, 56, 32)	0
Dropout_1 (Dropout)	-	-	-	-	(None, 56, 56, 32)	0
Conv2d_4 (Conv2D)	64	1	ReLU	3 x 3	(None, 56, 56, 64)	18496
Conv2d_5 (Conv2D)	64	1	ReLU	3 x 3	(None, 56, 56, 64)	36928
Max_Pooling2d_2 (MaxPooling2D)	-	2	-	2 x 2	(None, 28, 28, 64)	0
Dropout_2 (Dropout)	-	-	-	-	(None, 28, 28, 64)	0
Conv2d_6 (Conv2D)	128	1	ReLU	3 x 3	(None, 28, 28, 128)	73856
Conv2d_7 (Conv2D)	128	1	ReLU	3 x 3	(None, 28, 28, 128)	147584
Max_Pooling2d_3 (MaxPooling2D)	-	2	-	2 x 2	(None, 14, 14, 128)	0
Dropout_3 (Dropout)	-	-	-	-	(None, 14, 14, 128)	0
Flatten (Flatten)	-	-	-	-	(None, 25088)	0
Fully Connected Layer	512	-	ReLU	-	(None, 512)	12845568
dropout_4 (Dropout)	-	-	-	-	(None, 512)	0
Fully Connected Layer	3	-	Softmax	-	(None, 3)	1539

Total params: 13,140,627
Trainable params: 13,140,627
Non-Trainable params: 0

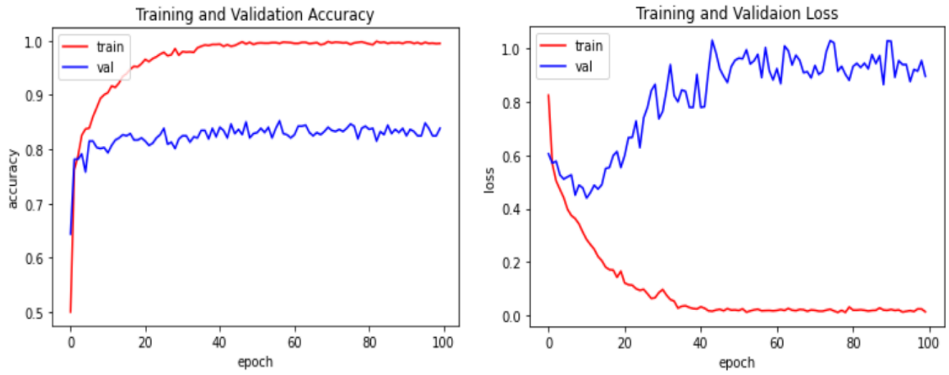

Figure 3. Accuracy and loss curve obtained from the training of the proposed model

The loss function of the model was categorical cross-entropy, and the model was run with a batch size of 16 and trained on the training dataset. The validation set helps to train the model and improve its accuracy by tuning its parameters. The dataset is trained over 100 epochs for increased accuracy and less saturation loss. The validation accuracy of the training model was 85.83%, while the training accuracy was 99.76%. For the training set and validation set, respectively, the consequent loss on the dataset was determined to be 0.012 and 1.029. The obtained findings attest to the suggested architecture's effectiveness and reliability. The training and validation accuracies and the training and validation losses are shown in Figure 3.

In order to calculate the true positive value of the images using a confusion matrix, the model employed a test set that had 150 images altogether, distributed

equally across the three classes. Figure 4 displays the confusion matrix that was acquired when the trained model was put to test on a different test set. The results of several classification model performance matrices used to assess the proposed architecture are summarized in Table 4. The test set's weighted average is obtained as 92%.

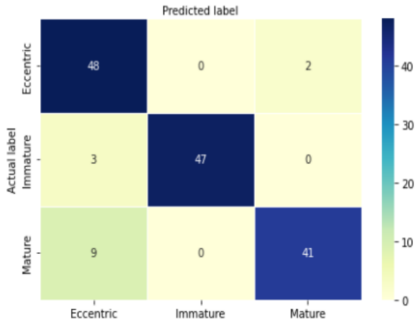

Figure 4. Confusion matrix

Table 4. Proposed convolution neural network model performance matrices

	Precision	Recall	F1 Score
Eccentric	0.80	0.96	0.87
Immature	1.00	0.94	0.97
Mature	0.95	0.82	0.88
Weighted average	0.92	0.91	0.91

The proposed CNN architecture and the other state-of-the-art architectures are trained by tuning with different settings of hyperparameters. The details of the hyperparameters used are described with the help of Table 5. In contrast to other pre-trained models, the model under examination is quite lightweight, which is the basis for the method adopted. In the experiments, pre-trained versions of the VGG16, VGG19, ResNet50, InceptionV3, and Xception models were employed. In Table 6, the outcomes of the suggested architecture were contrasted with those obtained from the pre-trained models. In contrast to all the previous pre-trained models used in this study, the suggested model requires less training time.

As inferred from the results of the CNN Models, the proposed architecture performs well in the classification of HIV-1 virion cell images. On the test set of unseen images, the proposed model performs better than the other state-of-the-art architectures. Due to numerous parameters connected with their architecture, pre-trained models have larger sizes than the proposed model, which therefore makes our model more appropriate for this purpose requiring little computational work. The outcomes prove that the suggested method for automated accurate HIV-1 virus cell classification is more precise and effective.

Table 5. Hyperparameter tuning for training the models

Hyperparameters	Values
Epochs	100
Optimizer	Adam
Learning Rate	0.001
Batch Size	16
Input Size	224 X 224
Loss Function	Categorical Crossentropy

Table 6. Results for the trained models

Models	Training Accuracy (%)	Validation Accuracy (%)	Testing Accuracy (%)	Approx. Training Time
Vgg16	94.61	82.68	85.33	3 hours 20 min
Vgg19	99.42	80.12	86.67	3 hours 40 min
Resnet50	89.22	75.39	84.67	1 hour 25 min
InceptionV3	84.42	78.35	87.33	1 hour 30 min
Xception	87.77	73.04	83.33	1 hour 35 min
Proposed Model	**99.76**	**85.83**	**91.33**	**1 hour 18 min**

4. Discussion and Conclusion

A key component of the HIV treatment regime is early diagnosis. Early and precise identification is crucial for these treatment regimens to be effective. However, in nations with a lack of medical infrastructure and qualified medical personnel, it is difficult to do manual diagnosis for HIV patients. Additionally, virus analysis is a difficult and time-consuming process that calls for in-depth investigation and cutting-edge computational

resources. The uneven dataset and the disparate lighting conditions under which the images were taken make it difficult to create a deep learning-based architecture. This makes the dataset challenging to handle, necessitating the need for a strong deep-learning model. The suggested architecture uses deep learning for HIV-1 virus classification to address these problems. The suggested model successfully classifies HIV-1 virion cells on unseen images with a testing accuracy of 91.33%. To evaluate the robustness, the new model is compared to a number of pre-trained models.

The suggested design has the benefit of having a low layer count, which means that implementing it in practice would need fewer computer resources. Better pre-processing methods can be used in subsequent work to refine the model and change the planned design. The effectiveness and generalizability of the model will also be enhanced by adding more images and a category for HIV-2 to the dataset.

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References

1- (2022). HIV. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/hiv-aids.

2- (2012). HIV/AIDS in India. [Online]. Available: https://www.worldbank.org/en/news/feature/2012/07/10/hiv-aids-india.

3- Mathummal Cherumanalil Jeeja Jayakrishnan Thayyil, "Issues of Creating a new Cadre of Doctors for Rural India." *International Journal of Medicine and Public Health*, Review Article Vol. 3pp. 8-11, (2013).

4- A. Alexander, A. Jiang, C. Ferreira, and D. Zurkiya, "An Intelligent Future for Medical Imaging: A Market Outlook on Artificial Intelligence for Medical Imaging." (in eng), *J Am Coll Radiol*, Vol. 17 (No. 1 Pt B), pp. 165-70, Jan (2020).

5- Ibrahim Mahmood and Adnan Mohsin Abdulazeez, "The Role of Machine Learning Algorithms for Diagnosing Diseases." *Journal of Applied Science and Technology Trends*, Vol. 203/19 (2021).

6- Chinmay Chakraborty, "Computational approach for chronic wound tissue characterization." *Informatics in Medicine Unlocked*, Vol. 17p. 100162, 2019/01/01/ (2019).

7- Q. Wang, J. Wang, M. Zhou, Q. Li, and Y. Wang, "Spectral-spatial feature-based neural network method for acute lymphoblastic leukemia cell identification via microscopic hyperspectral imaging technology." (in eng), *Biomed Opt Express*, Vol. 8 (No. 6), pp. 3017-28, Jun 1 (2017).

8- Xiaoxuan Liu *et al.*, "A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: a systematic review and meta-analysis." *The Lancet Digital Health*, Vol. 1 (No. 6), pp. e271-e97, (2019).

9- Ian Goodfellow, Yoshua Bengio, and Aaron Courville, Deep learning. *MIT press*, (2016).

10- Zhuang Liu, Hanzi Mao, Chao-Yuan Wu, Christoph Feichtenhofer, Trevor Darrell, and Saining Xie, "A convnet for the 2020s." in *Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition*, (2022), pp. 11976-86.

11- I. Nikishin, R. Dulimov, G. Skryabin, S. Galetsky, E. Tchevkina, and D. Bagrov, "ScanEV - A neural network-based tool for the automated detection of extracellular vesicles in TEM images." (in eng), *Micron*, Vol. 145p. 103044, Jun (2021).

12- F. Xing, Y. Xie, H. Su, F. Liu, and L. Yang, "Deep Learning in Microscopy Image Analysis: A Survey." *IEEE Transactions on Neural Networks and Learning Systems*, Vol. 29 (No. 10), pp. 4550-68, (2018).

13- A. M. Andrianov, G. I. Nikolaev, N. A. Shuldov, I. P. Bosko, A. I. Anischenko, and A. V. Tuzikov, "Application of deep learning and molecular modeling to identify small drug-like compounds as potential HIV-1 entry inhibitors." (in eng), *J Biomol Struct Dyn*, Vol. 40 (No. 16), pp. 7555-73, Oct (2022).

14- Michael D. Kupperman, Thomas Leitner, and Ruian Ke, "A deep learning approach to real-time HIV outbreak detection using genetic data." *PLOS Computational Biology*, Vol. 18 (No. 10), p. e1010598, (2022).

15- J. S. Rey *et al.*, "Deep-learning in situ classification of HIV-1 virion morphology." (in eng), *Comput Struct Biotechnol J*, Vol. 19pp. 5688-700, (2021).

16- M. C. Steiner, K. M. Gibson, and K. A. Crandall, "Drug Resistance Prediction Using Deep Learning Techniques on HIV-1 Sequence Data." (in eng), *Viruses*, Vol. 12 (No. 5), May 19 (2020).

17- Juan S.; Li Rey, Wen; Bryer, Alexander J.; Beatson, Hagan; Lantz, Christian; Engelman, Alan N.; Perilla, Juan R., "Dataset for deep-learning in-situ classification of HIV-1 virion morphology." (2021).

18- Y. Lecun, L. Bottou, Y. Bengio, and P. Haffner, "Gradient-based learning applied to document recognition." *Proceedings of the IEEE*, Vol. 86 (No. 11), pp. 2278-324, (1998).

19- Hossein Gholamalinezhad and Hossein Khosravi, "Pooling Methods in Deep Neural Networks, a Review." *ArXiv*, Vol. abs/2009.07485(2020).

20- Vinod Nair and Geoffrey Hinton, Rectified Linear Units Improve Restricted Boltzmann Machines Vinod Nair. (2010), pp. 807-14.

21- Diederik P. Kingma and Jimmy Ba, "Adam: A Method for Stochastic Optimization." *CoRR*, Vol. abs/1412.6980(2015).

22- John S. Bridle, "Training Stochastic Model Recognition Algorithms as Networks Can Lead to Maximum Mutual Information Estimation of Parameters." in *Proceedings of the 2nd International Conference on Neural Information Processing Systems*, (1989) (No. 7): *MIT Press*, pp. 211-17.

23- Karen Simonyan and Andrew Zisserman, "Very Deep Convolutional Networks for Large-Scale Image Recognition." *CoRR*, Vol. abs/1409.1556(2015).

24- K. He, X. Zhang, S. Ren, and J. Sun, "Deep Residual Learning for Image Recognition." in *2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR)*, (2016), pp. 770-78.

25- C. Szegedy, V. Vanhoucke, S. Ioffe, J. Shlens, and Z. Wojna, "Rethinking the Inception Architecture for Computer Vision." in *2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR)*, (2016), pp. 2818-26.

26- François Chollet, "Xception: Deep Learning with Depthwise Separable Convolutions." *2017 IEEE Conference on Computer Vision and Pattern Recognition (CVPR)*, pp. 1800-07, (2017).