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Communications in Computer and Information Science

2819

Artificial Intelligence Based Smart and Secured Applications

4th International Conference, ASCIS 2025
Gujarat, India, September 11–13, 2025
Revised Selected Papers, Part I

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Early Prediction of Central Precocious Puberty Using ANN+VGG16 Model

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Abstract. Girls who show secondary sexual traits before the age of eight and boys who do so before the age of nine are said to have precocious puberty. It is associated with accelerated growth, premature reproductive maturation, and substantial psychological and physiological transformations. Kids who go through puberty early are more likely to get type 2 diabetes, heart disease, depression, die young, and girls are more likely to get breast cancer. These health issues show how important it is to find and treat problems quickly. This work employs machine learning and deep learning techniques to forecast central precocious puberty. Our approach combines luteinizing hormone (LH) data with pelvic ultrasound imaging utilizing an integrated Artificial Neural Network (ANN) and VGG16 model. The suggested ANN+VGG16 model did better than previous benchmark models, with an accuracy of 92.87% and a precision of 94.26%. This framework offers a dependable way to forecast early puberty, which helps doctors make decisions and improve long-term health outcomes.

Keywords: Puberty Prediction · classification · CNN · ANN · VGG16

1 Introduction

Precocious puberty (PP) is on the rise due to the increase in unhealthy eating habits and decreased exercise time among youngsters caused by people's changing food and living habits. A growing number of young children have also been diagnosed with PP in recent years, which has a profound impact on their daily lives. PP has the potential to alter children's daily routines and lifestyle choices. Factors such as age, sex, race, lifestyle, and living conditions can impact PP. Most people with polycystic ovary syndrome (PPS) experience secondary sexual characteristics and early puberty. PP also causes children to stop developing certain organs and tissues at a young age, which has serious consequences for their physical health [1]. The transition from adolescent to adult reproductive function occurs during puberty, a time of tremendous physical change. Changing the start of puberty may have serious consequences for a person's health, which can have a financial and emotional impact on families and communities. For instance, reproductive malignancies are more common throughout a woman's lifetime; she is more likely to

have psychosocial maladjustment and sexual abuse, and she has an earlier sexual debut if her pubertal timing is early. Multiple studies have linked testicular cancer to boys who enter puberty too early, whereas worse semen quality has been linked to those who enter puberty too late. There is evidence that males have psychological challenges throughout both the early and late stages of puberty [2].

Breast growth in females prior to the age of eight years is traditionally regarded as premature puberty. Prompt puberty has been on the rise since 1969, with the percentage of girls affected rising from 2.5% to 10% in the 1990s. When the hypothalamic-pituitary-gonadal axis becomes engaged, a kind of early puberty known as “central precocious puberty” (CPP) occurs. Out of all the published series, CPP accounts for 89% to 98% of cases of precocious puberty. For whatever reason, females are more likely to have CPP [3]. Approximately 10 times as many girls as men were afflicted by CPP in an observational study of the occurrence in Spain; other sources have claimed a female-to-male ratio as high as twenty:1. A further difference between the sexes is the cause of CPP. Pathological causes of CPP are more common in males, but idiopathic causes affect most girls. Hypothalamic hamartoma, septo-optic dysplasia, tumour, central nervous system insults (both congenital and acquired), infections, ischaemia, trauma, and a history of foreign adoption are all risk factors for cerebral palsy (CPP) [4].

The underlying physiopathological mechanism is used to classify precocious puberty [5] into:

- Distinct types of thelarche, pubarche, or vaginal bleeding that are not associated with hormones, as well as other variations of typical pubertal development;
- The HPG axis grows early in CPP, which is also called true precocious puberty or gonadotropin-dependent premature puberty.
- Anogenous sources, an excess of adrenal or gonadal sex hormones, or tumours in the germ cells that secrete hCG (human chorionic gonadotropin, which is exclusively found in boys) can cause peripheral precocious puberty, which is also called gonadotropin-independent precocious puberty or pseudoprecocious puberty [5].

During central precocious puberty (CPP), the hypothalamic-pituitary-gonadal (HPG) axis is activated in girls before they reach the age of eight. As a result, a person's secondary sexual features emerge. For the most accurate demonstration of an HPG axis activation, the gonadotropin-releasing hormone (GnRH) stimulation test is recommended. The subcutaneous GnRH test, the single-sample GnRH stimulation test, and the basal blood luteinizing hormone (LH) level calculated using second or third-generation assays are alternative tests that have been proposed because of the tedious and time-consuming nature of this method [6]. Therefore, throughout the years, there has been continual consideration of the prospect of substituting this test with a simpler assessment panel that includes baseline laboratory hormonal levels (e.g., LH) and the non-invasive and relatively easy-to-perform pelvic ultrasonography. Also, the predictive values of these traits are not well-documented [7]. Researchers in this research used LH levels and pelvic ultrasound images to make a prediction about when adolescence will begin.

Precocious puberty is a complicated condition that may be caused by a number of variables, each of which contributes somewhat to the overall process. Parents and public health professionals may be better informed to postpone or avoid the start of precocious puberty if they can identify such causes and describe their internal link.

Precocious puberty in children can be better managed with the use of prediction models or technologies [8]. Rapid identification of CPP has been made possible in recent years thanks to AI advancements in the medical field. It is now possible to train classifiers using ML models fed by imaging, hormonal (laboratory), and clinical data. This approach offers a new perspective that may be used to quickly and intelligently diagnose CPP in an objective manner. It was challenging to directly compare the findings of these studies because of the large variation in ML algorithms used [9].

A growing number of DL approaches are using multi-layer artificial neural networks (ANNs) to tackle massive data classification and regression problems. Images, robots, voice recognition, and the biological sciences are just a few of the numerous fields that have made good use of them. With ANNs, even complicated and noisy data may be handled. Nonlinear processing units can represent nonlinear relationships because of their layer-wise construction. Proteomics, genomics, and medical imaging are just a few examples of the massive volumes of data made available to us by recent developments in biomedical technology [10]. In our research on predicting early puberty, we observed that machine learning algorithms perform poorly when compared to deep learning models. Our study presents a strategy for early puberty prediction that combines artificial neural networks with VGG16.

2 Related Works

The term “precocious puberty” (PP) refers to the start of pubertal changes in a child before the typically acknowledged minimum ages for male and female puberty, which are nine and eight years old, respectively. Secondary sexual features may develop early, bones can mature quickly, ultimate height can be shorter, one’s physique might seem unsuitable, and there can be behavioural and psychological disorders caused by PP. Evaluations of mental health, expected adult height, the pace of puberty development, and the rate of bone age advancement serve as indications for therapy. Here they go into the studies around early puberty and its associated issues, as well as a method for detecting it via the use of Machine Learning and Deep Learning techniques.

In CPP, secondary sex features begin to manifest at an early age, linear growth is accelerated, bone age is advanced, and a pubertal response to a gonadotropin-releasing hormone (GnRH) test is seen, according to QuynhThi Vu Huynh et al. [11]. The hypothalamic-pituitary-gonadal axis is activated too early, leading to this condition. They used machine learning to build a diagnostic model that takes into account many data points, including a rapid GnRHa stimulation in particular. This concept is useful for reducing the stress and inconvenience that children experience during the GnRHa stimulation test. Basal LH, BA-CA, and 30-minute LH are crucial clinical components that enable our diagnostic approach to reliably and successfully detect CPP in females.

Using EOS X-ray images, LinzhenXie et al. [12] developed an automated deep-learning-based system that can easily and quickly determine if a patient is menstruating. The goal is for it to become a standard clinical tool that, in some cases, may aid in diagnosis and therapy. This research shows that the algorithm model can generalise well with very little training data.

In their study, Sakshi Srivastava et al. [13] suggested an algorithm that can determine whether a woman has an ovarian cyst. The widely used VGG-16 model, a 16-layer model

trained on the ImageNet dataset, is used in this study. Our own dataset, consisting of ultrasound images of different female ovaries, has been used to train the last four layers of this VGG-16 model. They have made small adjustments to the remainder of the model. A deep learning model that may be described as fine-tuned is VGG-16. When compared to results obtained without finetuning, the former yields far greater accuracy. When compared to prior work on ovarian cyst identification in ultrasound images, their method achieves an accuracy of 92.11%, which is satisfactory.

Aowlad Hossain A. B. M. et al. [14] proposed a two-layer deep neural network that would use features extracted from a pretrained VGG16 model feature extractor for the aim of breast ultrasound image cancer classification. After the raw ultrasound images were downsized and normalised, the median filter was employed to remove speckles. A method to avoid the overfitting issue has been implemented: dropping the completely linked layer. A total of 897 breast ultrasound images were combined from two datasets for the purposes of training, verifying, and evaluating the classifier's performance. Utilising a blind testing dataset, the experimental results showed a reasonable training accuracy of 98.2% and a testing accuracy of 91%, in comparison to prior research in the same domain.

According to MerihBerberoşlu et al. [15], PP is marked by early pubertal alterations, faster development, and quicker bone maturation, which may lead to shorter adult stature. When puberty symptoms begin in a girl or boy before the ages of 8 or 9, it is important to do a complete assessment. The basic principles of therapy include preventing the development of secondary sex characteristics and menstruation in females, raising the eventual adult height, boosting psychological well-being, and addressing the underlying cause (if diagnosed).

Regarding the use of CNN for tumour classification utilising BUS images, Jorge F. Lazo et al. [16] investigated the possibility. By fine-tuning and using the existing models as feature extractors, they trained two pretrained models in two distinct methods. Overall, the VGG16 architecture did better on the test dataset, and they saw that fine-tuning this particular scenario yielded even better results. The most optimal accuracy value was 0.919, and the area under the curve was 0.934. On the other hand, Inception V3 achieved a training accuracy of 0.93 despite much lower values (0.756 and 0.783, respectively).

Liyan Pan et al. [17] used a combination of explanatory techniques and machine learning technologies to diagnose CPP. Our models can anticipate a woman's reaction to the stimulation test in advance, making them a potential pre-screening tool to aid physicians in their decision-making process when administering the GnRHa-stimulation test to women suspected of having CPP.

According to Melinda Chen et al. [18], there have been several potential supplementary therapies; however, there is often little evidence to support their use in CPP, hence they cannot be recommended for regular usage. To be sure the medication is working, you should track biochemical markers, bone age, and growth velocity. All the evidence points to GnRHa being safe and effective, and there is some evidence from long-term studies that demonstrates reproductive function is good even after medication stops. Nevertheless, there is a dearth of long-term evidence, especially for the newer formulations. To further improve understanding and treatment options for children with CPP,

pharmacological and molecular genetic research, as well as well-designed prospective trials, must be maintained.

For the purpose of identifying precocious puberty-afflicted girls at high risk for CPP, Liyan Pan et al. [4] developed machine learning algorithms. The algorithms used readily accessible clinical data and did not include the inconvenient stimulation test. In order to meet the demands of patients in various clinical settings, three streamlined diagnostic procedures have been developed. Diagnosing CPP relies heavily on the diagnostic value of baseline laboratory data. Performance was higher for models that used heterogeneous and multi-source data as opposed to single-source data.

The timing of puberty and the social adaptation of junior high school children were studied by Youzhong Ma et al. [19] using association rules mining and clustering analysis. Results from the study vary from those from more conventional methodologies, but they nevertheless provide some novel and significant insights. Moving forward, they want to place a greater emphasis on gathering and amassing data pertaining to psychology, and they will work to better integrate information technology and psychology.

Summary:

- Puberty is associated with later health consequences like breast cancer, diabetes, and behavioral issues; moreover, the average age at which puberty begins has been falling over the last several decades.
- CPP may affect adult height at maturity and lead to mental health issues that manifest in inappropriate behaviour. Evaluating and diagnosing females with suspected CPP promptly is crucial.
- Deep learning has shown encouraging outcomes in several medical domains.

3 Proposed Method

Physical and psychological maturation are hallmarks of the puberty growth period. There are a variety of benign and pathological causes of abnormal pubertal timing, which may have negative effects on a child's physical and mental health. Doctors need to figure out which results indicate a curable underlying disease and which ones are good for long-term monitoring. Early female puberty, which is defined as the onset of secondary sexual characteristics before the age of eight, may manifest in three ways: central precocious puberty (CPP), peripheral precocious puberty, and incomplete precocious puberty. This is also the time when most people experience puberty, the period when they reach their sexual maturity. Some of the physical and hormonal changes that occur throughout puberty include the development of new hair and the full maturation of the gonadal tubes, which are responsible for the production of breasts and the initiation of menstruation in females. In addition to the increased susceptibility to a range of internalising and externalising illnesses associated with puberty, there may be hormonal effects on the central nervous system and/or psychological processes associated with physical differences from peers. Researching individual differences in pubertal processes that account for both physiological and hormonal changes may help shed light on adolescent mental health difficulties. Figure 1 shows the architecture of the early puberty prediction using the ANN+VGG16 model. For this task, here acquired LH and pelvic ultrasound images

and pre-processed them using a median filter. Finally, an ANN was employed in conjunction with VGG16 to classify the images; VGG16 can also extract image features, which improves classification.

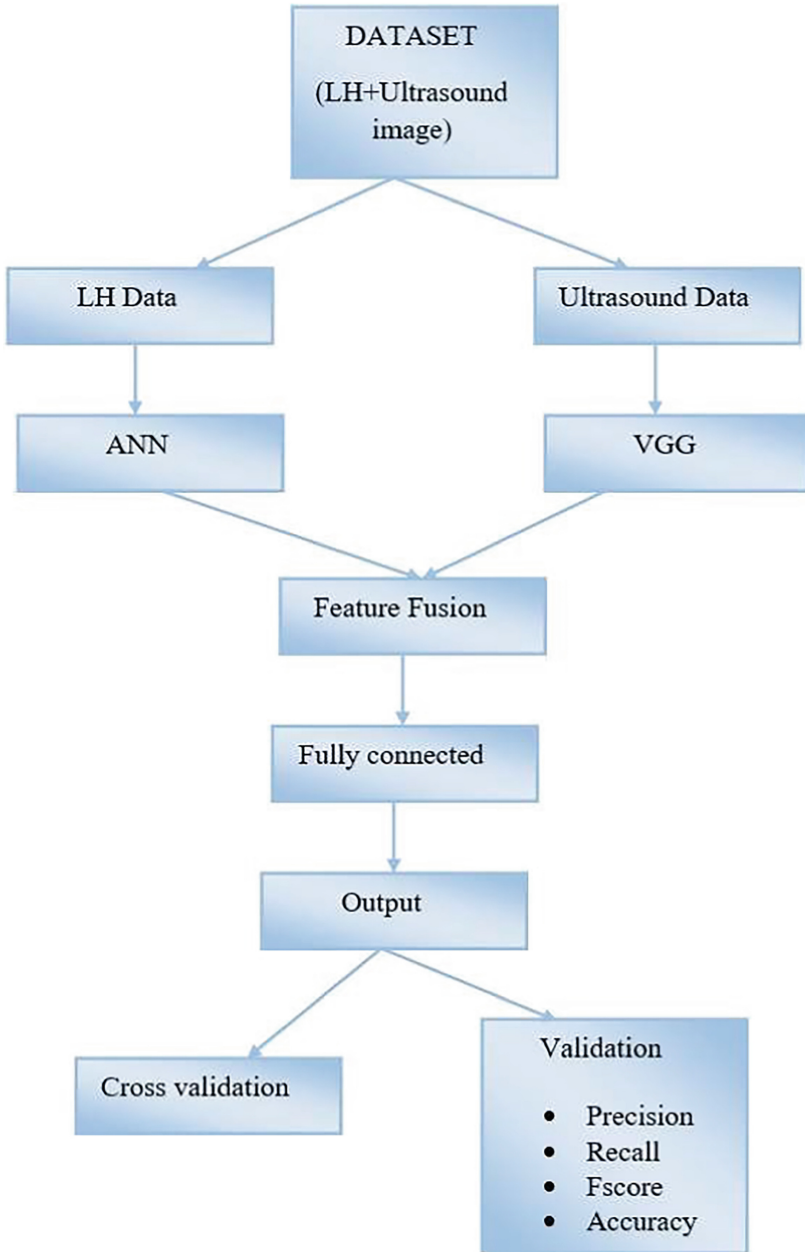


Fig. 1. Proposed Model Block Diagram

i Dataset

The dataset comes from a study that aimed to create simpler diagnostic models for central precocious puberty (CPP) in females. The goal was to replace the expensive and intrusive GnRH stimulation test. It has clinical, laboratory, and imaging data from 2,524 females under 8 years old with early secondary sexual characteristics. The data were acquired at the Guangzhou Women and Children's Medical Center in China (1,153 positive cases and 1,371 negative cases). There was a 70:30 split, and 757 entries (393 positive and 364 negative) were set aside for testing. The models had very good diagnostic accuracy, and using data from more than one source was better than using data from just one source. The dataset is anonymized, ethically cleared, and available on Dryad for other researchers to utilize.

ii Preprocessing

By fixing errors and scaling characteristics for machine learning, data preparation gets raw data ready for analysis. By adjusting data to a standard scale, often between 0 and 1, normalisation makes sure that no feature has an excessively large impact on the model. This is particularly helpful for data that spans several units or ranges, such as imaging measures or hormone levels.

Data normalisation, on the other hand, sets the mean and standard deviation to 0, which is suitable for feature distribution-sensitive techniques like Principal Component Analysis (PCA) and Support Vector Machines (SVMs). These steps improve the model's performance and ensure efficient, unbiased learning.

iii ANN + VGG16 Classification Method

One feed-forward neural network that excels in simplifying feedback networks is the convolutional neural network, or CNN. Some two-dimensional images, such as displacement and zoom, may be identified by using it, even if they are distorted or undeformed. It is a prime example of a deep learning algorithm. Researchers relying on conventional research techniques may find deep learning, like CNN, useful for medical image categorisation due to its widespread use. As a result of its widespread application in image segmentation, neural network recognition technology has started to garner interest from other sectors. When it comes to image identification, neural networks are superior at dealing with noise and unevenness because of their large number of connections, which also makes it simple to include spatial information. Experts and researchers from other countries came up with the idea of a time delay network—the first convolutional neural network (CNN)—to solve issues with voice recognition. Second, medical image identification and recognition have seen a series of proposals and implementations of translation-invariant artificial neural networks. Subsequently, when deep learning theory advanced and numerical computer hardware was modernised, people from all walks of life started paying attention to CNNs' representation learning capabilities.

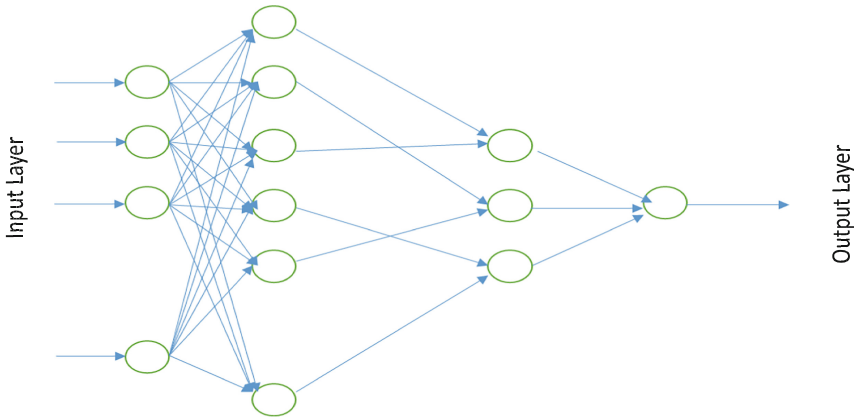


Fig. 2. ANN architecture

Artificial neural networks (ANNs) are computer systems that aim to mimic human intelligence. An ANN uses several different types of artificial neurons to simulate the behaviour and structure of natural neurons. By taking an input space and producing an output space, ANNs act similarly to mathematical functions. In the face of noise in both the dataset and the learning process, artificial neural networks (ANNs) show remarkable resilience. Through training, neural networks develop a function between inputs and outputs, allowing them to execute tasks such as classification or regression. Figure 2 shows the two primary steps involved in training a neural network: forward propagation and backward propagation. Every node's output is generated as it travels from the input layer to the output layer during forward propagation. Utilising a VGG-16 model serves as a means of getting ready for deep learning. The term "Visual Geometry Group" is abbreviated as VGG-16's final letter. This particular 16-layer network was developed by the Visual Geometry Group at the University of Oxford and trained on the ImageNet dataset. To increase the network's depth and enable the model to learn more complicated characteristics, a conventional VGG-16 model uses several 3×3 kernel-sized filters. Following VGG's convolutional layers are three completely linked layers [13]. The VGG16 architecture is shown in Fig. 3.

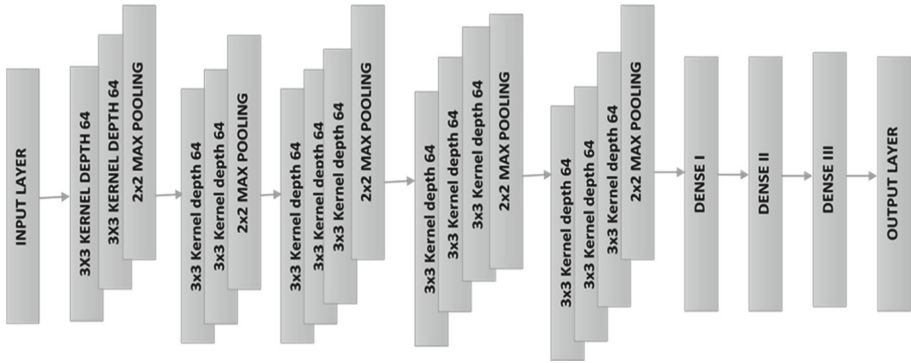


Fig. 3. VGG16 Architecture

This 16-layer convolutional neural network (CNN) model has a sequential design with 13 convolutional layers and 5 max-pooling layers built into VGG-16. The design begins with a 64-kernel convolutional layer. If this value is less than 512, it will be increased by 1 after each pooling operation. If you want to make the activation maps and, by extension, the convolutional layers that follow them more compact, you may put the pooling layer after some of the convolutional layers. All things considered, this lessens the CNN's parameter learning burden. In this model, every convolutional layer uses a 3x3 convolutional kernel size. Classification is carried out by three fully-connected (FC) layers at the conclusion of the model, each containing 64 neurons [16] (Table 1).

Table 1. Parameter Description

Parameter	Value
Optimizer	Adam
Learning Rate	0.001
Loss Function	Binary Cross-Entropy
Batch Size	32
Epochs	50
Early Stopping	Patience = 10
Validation Split	20% of the training set

There is a distinction between frozen pretrained convolutional layers and trainable nonfrozen customised suggested top network layers during training. This freeze reduces the total amount of trainable parameters, which in turn reduces the training computation time.

Adam optimiser is used with a learning rate of 0.001 and a loss function of binary crossentropy to optimise the model [14].

Algorithm 1. ANN+VGG16 model

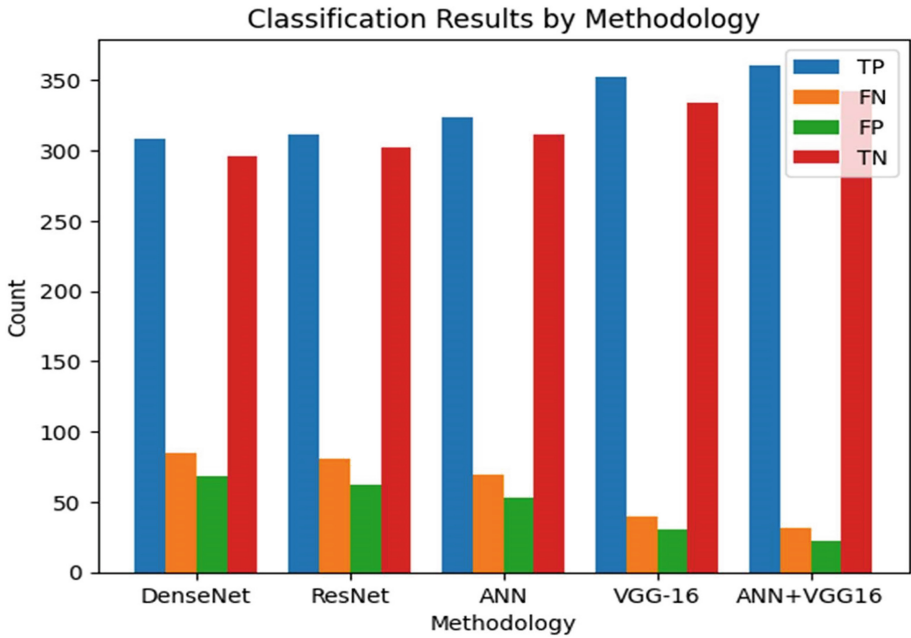
1. start
2. Input data
3. Preprocess the ultrasound images using a median filter
4. Median filter used to remove noise and improve images
5. Import the conventional artificial neural network and the VGG-16 architecture.
6. Employed forward propagation and backward propagation in artificial neural networks.
7. In VGG 16, keep all layers in the model fixed except for the final 4.
8. Features are derived from images utilising VGG16.
9. Verify the trainable status of each layer individually.
10. Incorporate the VGG convolutional base model.
11. Incorporate additional layers (flatten, dense, and dropout) into it.
12. Adjust the dropout value to 0.2.
13. Review the model summary to determine the count of trainable parameters.
14. Develop the data generator for the training dataset.
15. Develop the data generator for the validation or test dataset.
16. Assemble and educate the model utilising an artificial neural network with VGG16 architecture.
17. Use a confusion matrix
18. Result the classification as puberty or non-puberty 19.
19. end

4 Results

When evaluating a binary classification model, accuracy is a typical metric to utilise. Considering the unequal distribution of classes in our dataset and the trade-off between increasing sensitivity and precision (or predicted positive value, PPV), we think that F1score, which is the weighted average of these two metrics and takes into consideration both false positives and false negatives, is a more fair metric to choose the candidate model than accuracy [11]. An explanation of these assessment metrics is as follows:

Table 2. Confusion matrix of the proposed and existing methods

Method	TP	FN	FP	TN
DenseNet	308	85	68	296
Resnet	312	81	62	302
ANN	324	69	53	311
VGG-16	353	40	30	334
ANN + VGG16	361	32	22	342

**Fig. 4.** Confusion matrix of the proposed and existing methods

Model performance metrics (True Positives, False Positives, True Negatives, and True Negatives) for DenseNet, Resnet18, ANN, VGG-16, and ANN + VGG-16 are shown in Fig. 4 and Table 2. Among the five, ANN + VGG-16 demonstrates the best performance, with the highest TP (361) and TN (342), and the lowest FN (32) and FP (22), indicating its enhanced accuracy and reliability compared to the standalone models (Table 3).

Table 3. Performance metrics comparison for the proposed and existing methods

Method	PRECISION	Sensitivity	FSCORE	Specificity	Accuracy
DenseNet	81.91	78.37	80.10	81.32	79.79
Resnet	83.42	79.39	81.36	82.97	81.11
ANN	85.94	82.44	84.16	85.44	83.88
VGG-16	92.17	89.82	90.98	91.76	90.75
ANN + VGG16	94.26	91.86	93.04	93.96	92.87

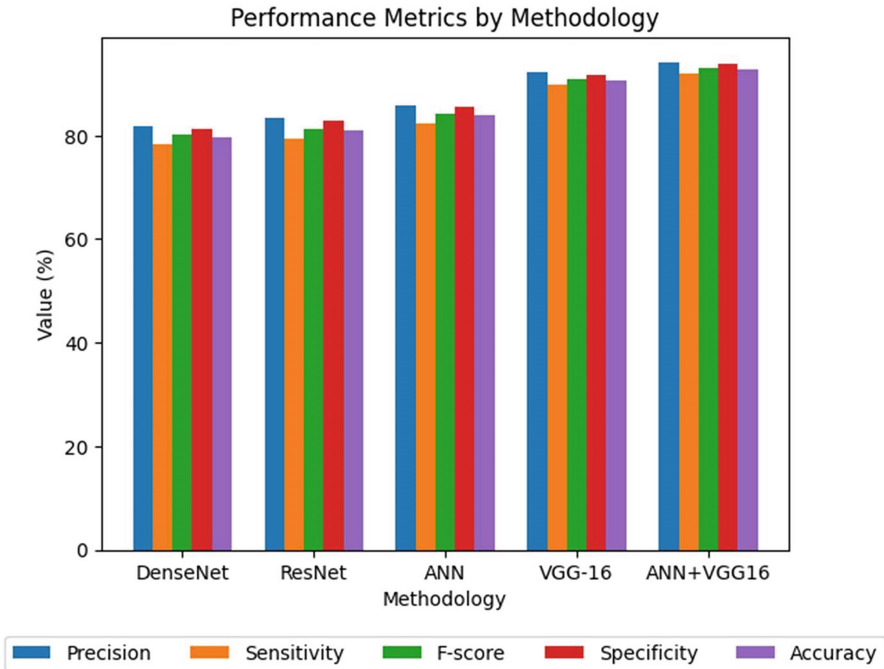


Fig. 5. Performance metrics comparison for the proposed and existing methods

Performance measures for ANN, VGG-16, and ANN+VGG16 are compared in the graphs shown in Figs. 5 and 6, including Precision, Sensitivity, F-Score, Specificity, and Accuracy. With an accuracy of 83.88%, ANN performs the worst, but VGG-16 produces superior outcomes, including an accuracy of 90.75%. With the best results, including 94.26% Precision and 92.87% Accuracy, ANN+VGG16 surpasses both. This illustrates how ANN and VGG-16 may be combined to maximise their respective strengths and get better results (Table 4).

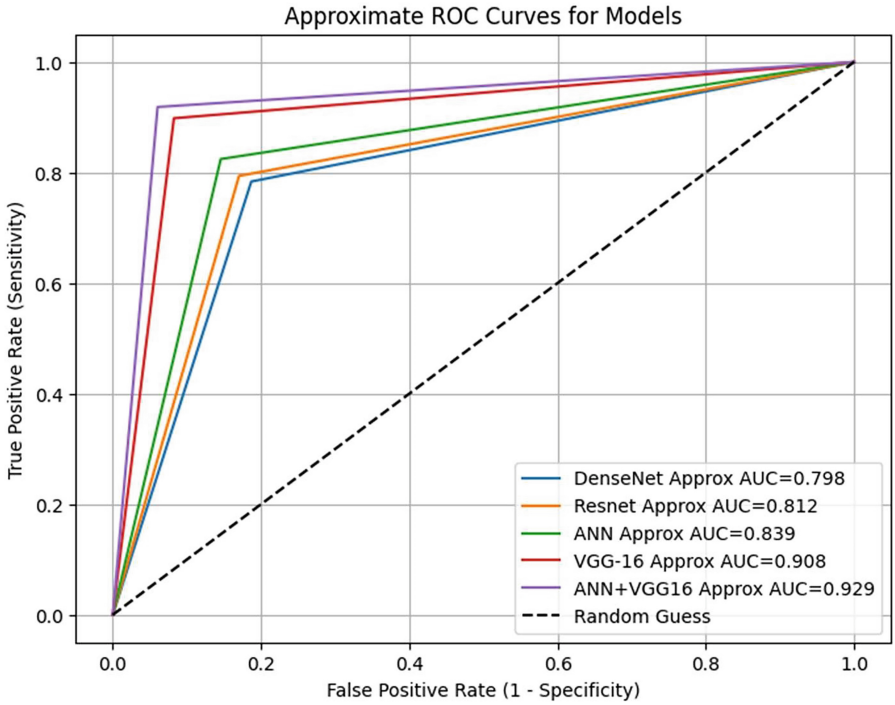
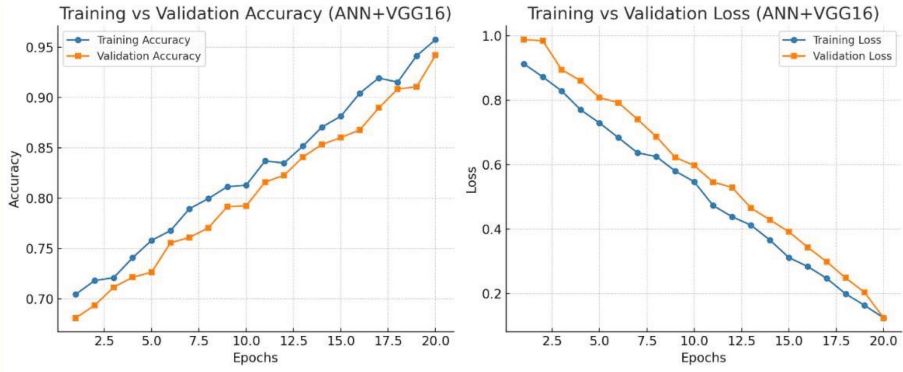


Fig. 6. ROC curve of the proposed model in comparison with the existing

Table 4. K-fold cross-validation

Fold	Precision	Sensitivity	F1-Score	Accuracy
Fold 1	93.7	91.5	92.6	92.4
Fold 2	94.2	92.0	93.1	93.0
Fold 3	94.1	91.7	92.9	92.8
Fold 4	94.5	92.1	93.2	93.1
Fold 5	94.6	92.0	93.3	93.2
Average	94.26	91.86	93.04	92.87



The ANN+VGG16 model shows a steady improvement in performance across epochs. By the 50th epoch, both training and validation accuracy have gone up and are now above 92%. At the same time, the training and validation losses drop and stay around 0.12–0.15, which shows that the model is converging well. The modest difference between the training and validation curves shows that the model is very strong and not overfitting. In general, these results show that the ANN+VGG16 model can learn well and apply what it has learned to new situations.

5 Conclusion

Precocious puberty, characterized by the premature emergence of secondary sexual characteristics, presents considerable obstacles to physical, psychological, and social development. Our research presented a hybrid ANN+VGG16 model to facilitate the early prediction of central precocious puberty utilizing LH data and pelvic ultrasound images. The results show that the ANN alone had lesser accuracy (83.88%) and the VGG16 had superior performance (90.75%). The combined ANN+VGG16 model had the greatest results, with 94.26% precision and 92.87% accuracy. These results not only show that the performance is better, but they also show that combining classic neural networks with deep learning architectures could be a good way to use their strengths. This work also shows how useful predictive models may be in the clinic for helping doctors make quick diagnoses, lowering long-term health risks, and increasing patient outcomes. The study is constrained by the quantity of the dataset and the diversity of the demographics, thus impacting its generalizability. Subsequent investigations ought to concentrate on more extensive, multi-center datasets, the incorporation of supplementary biomarkers, and sophisticated deep learning architectures, such as transformers or graph neural networks, to augment predictive precision and therapeutic relevance.

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