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Systematical Analysis of HEp-2 Segmentation and Classification Process

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Abstract: Indirect Immuno fluorescence (IIF) on Human Epithelial-2 (HEp-2) cells is the most recommended approach for diagnosing autoimmune diseases. Yet, the manual analysis of IIF images has some vital limitations including the subjectivity of results, the inconsistency of laboratories, and the low effectiveness of processing a huge count of cell images. To enhance the current situation, automatic as well as reliable cell image classification is needed, which is to be the most active research topic in the present scenario. Recently, more contributions have been made to this topic, particularly during the HEp-2 cell classification competitions. Almost all the methodologies include two stages: feature extraction and classification. This paper makes a brief review of Hep-2 cell classification. For this, 60 papers are reviewed to grant the most spectacular analysis of classification models. The analysis is carried out as follows: initially, the chronological review is made of all the reviewed contributions. The classification and segmentation models from all the papers are subjected in terms of diagrammatic illustration. Further, the performance measures also fall in the review that is tabulated. The maximum performance is also noticed among all the papers, and particularly, the attained accuracy rate is also graphically demonstrated. At last, the clear description of research gaps and challenges is summarised clearly.

Keywords: IIF; Hep-2 Cell; Classification; Performance Analysis; Classification Rate

Nomenclature

Acronym	Description
IIF	INDIRECT Immuno Fluorescence
ANA	Anti-Nuclear Antibody
SIFT	Scale Invariant Feature Transform
LBP	Local Binary Pattern
BoW	Bag of Words
HOG	Histogram of Gradient
k-NN	K Nearest Neighbor
SVM	Support Vector Machine
DSRN	Deep supervised residual network
VHAR	Vector of Hierarchically Aggregated Residuals
SboW	Sparse coding with Bag of Words model
CNNs	Convolutional Neural Networks
cC-GAN	Generative Adversarial Networks
FCN	Fully Convolutional Network
SSID	Spatial Shape Index Descriptor
LOAD	Local Orientation Adaptive Descriptor
SWLDA	Step-Wise Linear Discriminant Analysis
GMM	Gaussian Mixture Model
GSS	Gaussian Scale Space
ET-PRT-IIF	Executable Thematic on Pattern Recognition Techniques for Indirect Immunofluorescence
DCNN	Deep Convolutional Neural Networks
RICWLTP	Rotation Invariant co-occurrence Weber-based Local Ternary Patterns WLTP
TMAs	Tumor Tissue Microarrays
MCC	Matthews Correlation Coefficient
CPM	Cell Pyramid Matching
SAP	Spontaneous Activity Patterns
SN	Stomped Normal
CTD	Connective Tissue Diseases
SLE	Systemic Lupus Erythomatus
CAD	Computer Aided Diagnosis
RIC-LBP	Rotation invariant co-occurrence among adjacent local binary pattern
ADDL	Adaptive Distributed Dictionary Learning
SOM	Self-Organizing map
MCA	Mean classification Accuracy
ACA	Average Classification Accuracy

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1. Introduction

IIF detection modality is particularly utilized to analyze the diagnosis of ANA, which is for autoimmune disease diagnosis as well as treatment. To make the ANA analysis possible, the HEp-2 cell [62] [63] [64] is capable of separating and granting a huge count of antigens. Experts are commonly employing the fluorescence microscope for discriminating the nuclear antibody by visual inspection. Further, the inhomogeneous illumination also leads to large intra-class deviations that make the classification of HEp-2 [65] [66] [67] more complex. To solve this kind of challenge, conventional models have incorporated three phases: feature extraction, feature encoding, as well as classification. Nevertheless, these models particularly concentrate on hand-crafted features that suffer from restricted classification performance rates. To enhance the representation of feature representation abilities to classification enhancement, it is vital to mine more discriminative as well as informative features.

Computer-aided systems aim to do an automated analysis of HEp-2 images [61] [68] [69] [70], which helps doctors to diagnose accurately. Mostly, the conventional system includes three phases. Here, the initial phase includes image pre-processing, intensity normalization as well as removal of noise. The next phase importantly mines features such as SIFT, LBP, HOG, and so on. In some cases, as the local descriptors and their extensions are the usual choices, some approaches also utilize the BoW or Fisher Vector framework for encoding the respective descriptors. In the final phase, classifiers including k-NN, SVM, and naive Bayes are trained by the features that are extracted in the second stage and the respective ground-truth labels. However, the classification rate by all the conventional methods is not even satisfactory, which shows that more enhancements are needed in the future to improve the accuracy rate.

This paper reviews 60 Hep-2 cell classification contributions and hasanalyzed them from different angles. The segmentation and classification models are noticed and viewed in terms of diagrammatic representation. The analyzed performance measures in all the papers are also clearly analyzed and subjected. The attained accuracy rate is also analyzed and represented graphically. The rest of the paper is arranged as follows: Section 2 reviews the selected papers in terms of their contribution. Section 3 shows the study of this Hep-2 segmentation and classification model. Section 4 details the research gaps and challenges. Section 5 concludes the survey.

2. Literature Review

2.1 Related Works based on Epithelial type 2 Segmentation and Classification

In 2018, Lei, *et al.* [1] developed a model that was based on DSRN for classifying the cell images of HEp-2. More particularly, they have adopted a residual network that was with 50 layers (ResNet-50), which could mine the rich and discriminative features. They have also imposed deep supervision on the ResNet-based approach for boosting the performance of classification.

In 2018, Linlin *et al.* [2] developed a to classify the HEp-2 cell. Also, they have introduced a cross-connection based residual block for maximizing the flow of information between various network layers. Two benchmark datasets were used for evaluating the model and have proven the results over other models.

In 2018, Divya *et al.* [3] introduced a new model to categorize the HEp-2 cell that could be implanted in the ANA test automation system. They have used the hybrid descriptor that signifies the object's morphological and textural characters with a Binary tree. This was generated through image decomposition into binary images via upper and lower thresholds. Finally, the obtained outcomes have reviewed the effective performance in terms of accuracy.

In 2017, Dimitris *et al.* [4] focused on the classification of HEp-2 cells and introduced a new model for local feature encoding, which has allowed for generalizing the concept of residual encoding. Particularly, the developed model has hierarchically aggregated the sparse representation of feature vectors that led to a VHAR. Finally, it was revealed that the model attains a high classification accuracy rate.

In 2017, Shahab *et al.* [5] presented an automatic classification model, which has exploited the visual features' SBoW. Particularly, they have integrated features like SIFT and so on for working in a complementary fashion. Finally, they performed the investigation by considering the publicly available datasets, and the outcomes have shown that the developed model could outperform other conventional models at specimen and cell levels.

In 2017, Gao *et al.* [6] developed a strategy for the task of classification by utilizing the deep CNNs. Additionally, the authors have elaborated on various interesting observations and the findings attained through the work. The outcomes have revealed that the developed model has attained better results in terms of data augmentation.

In 2018, Li *et al.* [7] developed a new transfer-learning model by cC-GAN to make the robust segmentation of various HEp-2 datasets. The model also can resolve the issue of overfitting and that could enhance the transfer capacity. Moreover, they have developed an enhanced U-net, namely Residual U-net (RU-net) for working as the generator of the cC-GAN approach.

In 2017, Qi *et al.* [8] developed an effective model for automated HEp-2 cell classification through the combination of large regional shape information and multi-resolution co-occurrence texture. More specifically, they have developed for proposing three major factors and the developed method has attained comparable performance.

In 2017, Li *et al.* [9] developed an automatic pattern recognition system by FCN for addressing the issue of segmentation along with the classification of HEp-2 specimen images. Moreover, they have developed a sand-clock shape residual module for enhancing the FCRN performance in terms of accuracy rate.

In 2016, Qi *et al.* [10] implemented SSID for capturing the 2nd order structures' spatial layout data and utilized a LOAD for the task of Hep-2 cell classification. This has been initially designed for classifying the texture. the method has also proven its superior performance on a new dataset.

In 2016, Loris *et al.* [11] used an automated classification model through the fusion of several texture descriptors with the SVM ensembles. The model was evaluated over other conventional methods and has proven its superiority.

In 2016, Shahab *et al.* [12] implemented a classification model of Hep-2 that was based on super pixel. The model was performed by evaluating the image patches' sparse codes that were prepared intelligently. Particularly, while doing the neighboring pixel aggregation of similar patterns, the superpixelmodel has guided the definition of the right image patches. Finally, they evaluated the work on two datasets and attained a high accuracy rate of classification over other models.

In 2014, Masoud *et al.* [13] extended the existing bag of word approaches from the Euclidean space to non-Euclidean Riemannian manifolds, which were utilized for classifying the HEp-2cells. Initially, they have discussed an intrinsic bag of Riemannian words approach and subsequently, they have Fisher tensorsthat could in turnencode further data related to the signatures' distribution in a bag of word approach.

In 2016, Omid *et al.* [14] introduced a system for automated classification of cellpatternsin immunofluorescence imaging. The classification of HEp-2 was done by SWLDA and GMM. Initially, the authors normalized the images and then they extracted the intensity, binary, spectral, statistical, wavelet-based, Haralick, CLBP, and Gabor features from the respective normalized images. With the aid of SWLDA, they have chosen the best features, and the GMM model was utilized for classification purposes. The examination was carried out for the method and has proven its superiority.

In 2016, Qi *et al.* [15] analyzed the significance of pre-processingand also investigated the role of GSS theory for the task of HEp-2cell classification. They have validated the GSS pre-processing under the models like LBP and the BoW. In this BoW model, the developed pre-processing model aided single LOAD has attained better performance on ET-PRT-IIF image analysis.

In 2016, Han *et al.* [16] introduced a model that is based on the fact that human perception of the distinguished pattern. To do the integration of spatial as well as orientation context data, the authors have further used a RICWLTP model that was more discriminant to represent the image. Finally, the method has proven its betterment in enhancing recognition.

In 2016, Xu *et al.* [17] presented a feature learning model that was based on DCNN. This was for the automated segmentation and classification process of EP and ST regions from digitized TMAs. The models were based on the representation of handcraft features including texture, color, and LBP for classifying two regions. At last, the proposed method has been proven in terms of accuracy rate, MCC, and so on. In 2014, Arnold *et al.* [18] proposed a new automatic cell image classification approach namely CPM that was composed of regional histograms of visual words tied with the Multiple Kernel Learning model. They have presented a study of different deviations in producing histograms and have shown the system efficiency on two datasets.

In 2014, Yan *et al.* [19] gave a biologically inspired solution for addressing the issues through the utilization of SAP. Moreover, the spontaneous activity patterns that were associated with the activities of spontaneous neural through the brain's chemical release; were found as the classic stimuli for the development of newborn animals. For the Hep-2 classification, the authors have used a model SAP as the set of image patches that have arbitrarily placed Gaussian spots.

In 2014, Kong *et al.* [20] presented a discriminative dictionary learning model (supervised), which was particularly designed to classify the patterns. Further, the developed model was the extension work of the renowned K-SVD algorithm. In the training phase, the dictionary atoms' discriminative power was considered and minimized the reconstruction error at every update. At the same time, they were also concerned about the inter-class reconstruction impact. Finally, the developed algorithm has proven its learning ability to do classification.

In 2014, Shen *et al.* [21] developed a model via gradient feature and bag of words that were based on intensity order pooling to do the classification process. Further, the pooled feature was rotationally invariant without having any orientation assessment. They have tested the developed model by using the SZU and ICPR datasets, and have proved its betterment over others.

In 2014, Ilias *et al.* [22] developed an automatic classification system for classifying the staining patterns on HEp-2 images. The model has utilized two descriptors for encoding the textural as well as gradient characteristics of represented patterns. With the SIFT features distribution, the authors have proposed a novel GoC-LBP descriptor that was based on co-occurrences of uniform Local Binary Patterns. In the 2nd stage, the fusion of descriptors was carried out while generating the images' dissimilarity representation. They have incorporated a powerful classification approach that has utilized a discriminative sparse representation-based model to do the classification process.

In 2011, Rigon *et al.* [23] presented the SLIM system, which has supported the two phases of IIF test classification purpose. This was based on two systems: the first system labeled the fluorescence intensity, while the next system recognized the staining pattern of positive wells. The dataset with 600 images was used. The authors have assessed the error rate as per the eight-fold cross-validation approach. They have also reported the test results.

In 2013, Linnea *et al.* [24] combined Raman imaging with a multivariate classification for quantifying the spatial distribution of oxide nanoparticles inside the living lung epithelial cells (A549). At different incubation times, the cells were exposed to a-FeO(OH) (goethite) and TiO2 (titania) nanoparticles. With the utilization of hyperspectral Raman data along partial least-squares distinguish analysis, they have reviewed the surprisingly large spectra fraction, which was classified to the cell nucleus, and that has shown the relation among Raman bands and nanoparticles. At last, the framework has proven its betterment over other models.

In 2010, Xi *et al.* [25] developed a model for addressing an intrinsic regulation by a new model for genome-wide identification, which was derived from paired mRNA profiles and microRNA. They have used 2 publicly available datasets that have included microRNA expression and the profile of gene expression. Resultant of this, microRNA expression could grant the best classifiers of epithelial cancers over normal epithelial tissue. They have identified the best accuracy rate of the method over other models.

In 2011, Muthu *et al.* [26] fixed a major aim of providing a segmentation algorithm that was on the texture basis to do better delineation of the epithelial layer in histological images. The authors have evaluated the Gabor-based texture gradient followed by the preprocessing stage. Similarly, they obtained the images' color gradients in the transformed Lab color space. The outcomes have proven the superior performance of the texture-based segmentation when compared to other segmentation approaches regarding the misclassification error.

In 2015, Tonti *et al.* [27] implemented a solution for one of the most demanding steps of the segmentation process, and the Hep-2 cell segmentation was done through the adaptive marker-controlled watershed model. The model could automatically conform the marker selection pipeline for the weird input image characteristics. Thus, the model could cope with various fluorescent intensities and staining patterns even under no knowledge.

In 2016, Abhirup *et al.* [28] presented a clustering algorithm, named rough-probabilistic clustering that has integrated the merits of the sensibly rough set and an SN distribution. The representation of class intensity distribution was done by SN distribution, in which every class includes probabilistic boundary region and crisp lower approximation. They modeled the image's intensity distribution as a mixture of finite SN distributions. They used the expectation-maximization algorithm for assessing the class's parameters. The performance of the model was evaluated over other conventional methods.

In 2011, Carolien*et al.* [29] stated that because of the drawbacks of manual testing, the process of classification requires an automated system. The authors developed an unsupervised segmentation model for developing the CAD system for digital support iIFT testing.

In 2002, Perner *et al.* [30] presented the results under classification and analysis by image analysis along with the models of data mining. They have also developed a feature extraction algorithm. Further, they had also been assessed by cross-validation. The work has shown the feasibility of the work.

In 2008, Huang *et al.* [31] used a classification model, which has assessed 2573 cells along 6 individual fluorescence patterns from 45 images. Finally, the outcomes have proven that the developed approach could find cell outlines via manual sketched. This kind of model could grant robust as well as speedy HEp-2 fluorescent patterns segmentation in the testing of ANA.

In 2015, Jiang *et al.* [32] developed a new model for HEp-2 cell segmentation, which was based on multi-threshold probing. The model generated cell hypotheses through binarization by the verification process. Moreover, the developed approach had the property of joining adaptive local thresholding along with the incorporation of high-level knowledge.

In 2012, Soda *et al.* [33] developed an approach to segment the cell in HEp-2 images, which addressed and overcame the major drawbacks of the conventional models. Further, the developed model adopted the reconstruction of the image to do the segmentation process. Further, it employed a sort of dilation that was classifier-controlled to get the best determination of cell structure.

In 2008, Chung *et al.* [34] developed a new multi-staged segmentation model to make the automated detection of outlines of fluorescence cells in IIF images. The similarity-based watershed model has proven its betterment over other conventional methods.

In 2014, Sriram *et al.* [35] developed a system, which was based on hierarchical classification that intakes discriminative features to do the process of classification. They have also implemented a texture descriptor that was based on a change of curvature. They have also developed a model adaptation approach by non-linear transformation functions to make the classification process more accurate.

In 2014, Gragnaniello *et al.* [36] dealt with the designing of a classification approach to extract the cells from IIF images. Particularly, the authors developed a model for using the dense local descriptor invariant for classifying the patterns' six categories. Further, the descriptor could grant the compact as well as the representation of discriminative and also combined a log-polar sampling along spatially-varying Gaussian smoothing, which was applied on the gradients images with particular directions. Further, they have used Bag of Words for performing the classification process and the experimental outcomes have proven the better performance.

In 2015, Hobson *et al.* [37] developed a benchmarking outcome of HEp-2 classification approaches on a huge dataset. The authors applied a much immune fluorescence approach for identifying the connective tissue diseases including Sjögren's syndrome and systemic lupuserythematosus. Nevertheless, the approach suffered from some problems like consumption of time and labor intensive. This motivated the authors to develop an automated CAD system that classifies the cell images.

In 2016, Peter *et al.* [38] stated that the ANA test via HEp-2 cells has been the gold standard for identifying the existence of CTD-like SLE. Since the ANA test was time-consuming, subjective, and labor-intensive, there had been an ongoing effort to develop image-based CAD systems. The authors have discussed the working process and the drawbacks of the area, which also stated that the field needs more attention.

In 2016, Peter *et al.* [39] updated the conventional model on HEp-2 cells and also the classification process of specimens, which analyzed the attained performance through participation in the contest on Performance Evaluation of IIF Image Analysis Systems.

In 2010, Foggia *et al.* [40] developed a heterogeneous feature set that was utilized for describing the mitotic cell peculiarities and also tested 5 classifiers, which belonged to various paradigms of classification. Further, the developed model was subjected to the assessment of performance rate on an annotated dataset that has mitotic cells and has attained promising performance.

In 2014, Ryusuke and Kazuhiro [41] developed a new approach to classify six pattern categories of HEp-2cell (fluorescence staining). The developed approach was developed as the combination of the RIC-LBP image feature along with the linear SVM. It was obtained that the RIC-LBP could grant the greatest descriptive capability and robustness over local rotations of images.

In 2014, Gao *et al.* [42] developed a model for classifying the HEp-2 cells by utilizing deep CNNs. Along with the designed network model as well as optimized parameters, the network model has hierarchically extracted the raw pixel features and has performed the process of classification.

In 2015, Bayramoglu *et al.* [43] have devised a model of Hep-2 classification by CNN. A more conventional model has shown a classification accuracy rate of 75.6% under the benchmark dataset. They also conducted various schemes to enhance, augment, and process the training data in the CNN model to do the classification.

In 2014, Larsen *et al.* [44] developed an approach to the automated classification of HEp-2 cell images into various staining pattern classes. The model was based on a texture measure named shape index histograms, which has captured 2nd order image structure at various scales. Furthermore, they have introduced a spatial decomposition approach that was radically suitable as well as symmetric for cell images. The model was superior to other models with minimal complexity.

In 2014, Kastaniotis *et al.* [45] have presented an automated classification approach for staining patterns. They also designed a full pipeline of processes such as preprocessing, feature extraction as well as classification for overcoming distinctive difficulties of data. Morphological features as extracted by multi-level thresholding. The model had proven its performance over other models.

In 2016, Qi *et al.* [46] analyzed the significance of the pre-processing phase and investigated the role of GSS theory, which also acted as the pre-processing model of the classification task. They also validated the GSS pre-processing on LBP as well as BoW models. The analysis results have also been evaluated finally.

In 2015, Bayramoglu *et al.* [47] have presented a model of Hep-2 classification by CNNs. They also conducted an exploration of various strategies to improve and training process. The model had given significant enhancement over other models in terms of accuracy rate.

In 2016, Divya et al. [48] introduced a new algorithm for pattern recognition of HEp-2 cells that could be embedded into the CAD system. First, the HEp-2 cell Classification system differentiated both intermediate as well as positive cells before the process of preprocessing, which was also processed to classify attaining high accuracy.

In 2016, Divya *et al.* [49] developed a binary decision tree model to do the cell classification (HEp-2) process that could be embedded in a CAD system for detecting the ANA. The model relied on texture descriptors that were proven to be efficient differentiators. The investigational outcomes proved the performance of the work over others.

In 2014, Akbar *et al.* [50] described a pattern recognition system to classify the immunofluorescence images into 6 classes nuclear, homogeneous, centromere, Golgi, speckled, as well as nuclear membrane. They also utilized the locality-constrained linear coding for encoding the multiple local features along with the two-level cell pyramids for capturing the cell's spatial structure.

In 2016, Monajemi *et al* [51] implemented an ADDL approach, in which the evaluation of dictionary learning was done. Along with the model, they had also built an automated and robust model, which could efficiently handle the issue's difficulty for computational cost and memory.

In 2013, Kastaniotis *et al.* [52] developed a classification staining pattern system, which was inspired by the recently developed approach to aggregate the local image (SIFT) features. Particularly, they also presented a new model, where the aggregated features were mapped into feature vectors. The betterment of the developed model was also proven over other models.

In 2014, Roman *et al.* [53] dealt with the designing and enhancement of the HEp-2 cells classifier. The classifier could categorize the pre-segmented images into various classes and the core of the engine has included some of the descriptors like Local Binary Patterns, Haralick features, surface description, and SIFT as well as the granulometry-based descriptor. Vectors were formed to determine the metric spaces. Extensive evaluation sets were done and compared to other conventional models.

In 2016, Manivannan *et al.* [54] presented a system for recognizing the patterns, at both specimen and cellular levels, in HEp-2 cells. They had trained the SVM Ensembles for classifying cells into six classes, which was based on texture feature's sparse encoding along cell pyramids, capturing spatial, and so on. Similarly, they also classified the specimens into various classes.

In 2012, Kastaniotis *et al.* [55] used an automated system of staining patterns classification under single-cell fluorescence images. The model utilized the morphological features. Further, the incorporation of modified Uniform Local Binary Patterns descriptor was happened for capturing the local textural information. SVM classifier was used to do the classification process. The outcome had been proven over other conventional methods.

In 2014, Ensafi *et al.* [56] developed an automated HEp-2 cell image classification model, which exploited various spatial scaled representations of images and both SIFT and SURFs sparse coding. Further, the developed approach was applied to the ICIP2013 dataset. Experimental outcomes proved its superiority over other state-of-the-art models.

In 2014, Ensafi *et al.* [57] presented an automated HEp-2 cell image classification model, which exploited various spatial scaled image representations along with the SIFT feature's sparse coding. Further, the authors have used spatial max pooling at various scales to boost the performance of classification. The testing was carried out and has proved the outperformance performance over other conventional models.

In 2012, Chu *et al.* [58] developed an automated model for identifying the HEp-2 cell's fluorescence patterns in IIF images. They used the SOM neural network for the classification process of patterns. The evaluation was done over more datasets and has proven the performance rate with a high accuracy rate.

In 2014, Gennady *et al.* [59] presented a fully automated approach to recognize the immune fluorescent image type that was generated through the ANAHEp-2 medical test. Further, the developed model makes use of variance in terms of the number, size, shape, and localization of cell regions, which were targeted through antinuclear antibodies. The model extracted the morphological properties by combining the thresholding-based as well as thresholding-less models.

In 2003, sack *et al.* [60] presented a CAD system to do the classification process of immunofluorescence patterns (inter-phase HEp-2), which was an automated process. Representative patterns were obtained through the operator in a digital microscope camera, which was also transferred to a PC as well. Machine learning models were also used to extract the features and classification. Results proved the best performance of the developed approach over other approaches.

In 2023, Khamael Al-Dulaimi *et al.* [71] introduced an activation function called Softmax and a perceptron technique. Initially, the cells were segmented using a Geometric Active Contours (GACs) technique to find information from shoddy simple microscope pictures. Secondly, in three steps, feature

extraction was carried out. Finally, the adapted multi-class and multilayer perceptron technique and Softmax activation function were used to calculate higher-order spectral features and to classify them into six classes. Moreover, it addresses problems such as over fitting, staining, and large-scale data volumes while achieving high accuracy (90% with augmentation). It also outperforms existing techniques when compared to results obtained using Task 1 datasets from the ICPR2014 and 2016 competitions.

In 2023, Xie *et al.* [72] introduced a watershed segmentation algorithm and the Otsu thresholding method to separate cells through IIF tests. Initially, Otsu thresholding and watershed transformation performed the segmentation of IIF pictures. Then, To get dual patterns they used Local Binary Pattern (LBP), Scale-Invariant Feature Transform (SIFT), and also Cooccurrence among Adjacent LBPs (CoALBP), which were utilized for image classification purposes. Further, the K-Nearest Neighbour Algorithm (KNN), Random Forest, and support vector machine (SVM) were traditional machine learning approaches that combined an Ensemble Classifier with soft voting rules to classify cell images. In the end, Inception ResNet V2 was employed via deep learning techniques. Finally, Inception ResNet V2 provided higher accuracy than other schemes.

In 2022, Andrade *et al.* [73] have practiced the immunofluorescence assay. A laboratory test that detects autoantibodies in blood samples can be used to diagnose early systemic autoimmune diseases they were Juvenile Idiopathic Arthritis (JIA), Systemic Lupus Erythematosus (SLE), Primary Biliary Cholangitis (PBC), Auto Immunity Hepatitis (AIH). It worked by searching antibodies against the antigens that are found in the nucleus, cytoplasm, or mitotic machinery of human epithelial type 2 cells, which were artificially produced for this purpose. Indicators of an optimistic HEp-2 IFA test included a variety of morphological patterns connected to particular autoantibody specificities relevant to JIA, PBC, SLE, and AIH.

2.2 Chronological Review

This section explains the chronological review and the percentage of contributions under respective years. The graphical representation of a chronological review is given in Fig 1. The survey is worked on by analyzing various papers from different years. Here, it is observed that 5% of papers are taken from the years 2018, 2012, and 2011 respectively. 10% of papers are reviewed from the year 2017. 25% of total papers are reviewed from the year 2016, 28.33% of total papers are reviewed from the year 2014. Further, 3.33% of the total analysis is done on the papers that were published in the years 2013, 2010, and 2008, respectively. Only 1.66% of total papers are taken from the year 2003 and 2002, respectively.

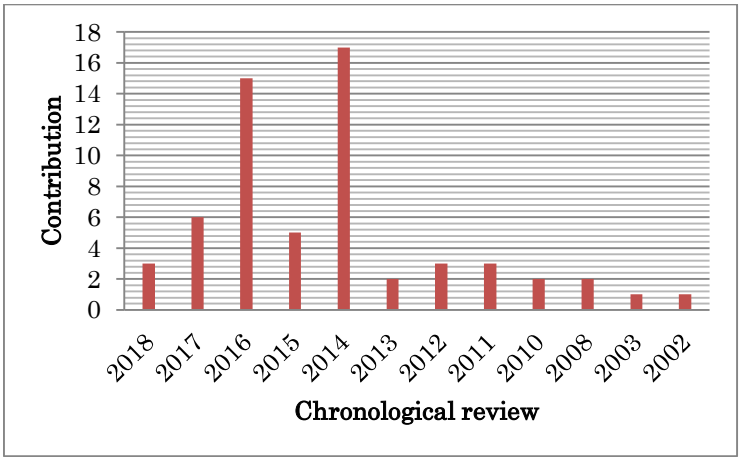

Fig. 1. *Bar chart illustrating chronological review*

3. Study on HEp-2 Segmentation and Classification

3.1 Analysis of Classification Algorithms

This section analyzes various classification models that are used in the review papers. From the analysis, the classification models are categorized into certain forms including Deep learning network system-based classification, CNN classifier, and BoW algorithm-based classification. SVM-based classification, NN-based classification, Gaussian Scale-Space theory-based classification, and some other classification models as well. More particularly, the papers [1] and [2] have used the deep learning network system. BoW is acted as the classifier in [5] [21] and [56]. The authors in [6] [9] [17] [39] [42] [43] and [47] have used the CNN classifier. SVM is the classifier of [41] [51] [56] [57] and [59]. Then, the Gaussian scale

space theory is applied in [15] and [46] as a classifier to classify the Hep-2 cells. Similarly, NN-based classification is used in [58] [53] and [48]. Other classification models are there that are used in the rest of the contributed works, and some of the models are dictionary learning model, Penalized Local Regression (PLR) algorithm, binary decision tree model, fisher tensor, dense sampling descriptors, and so on. The diagrammatic representation of this analysis is given in Fig 2.

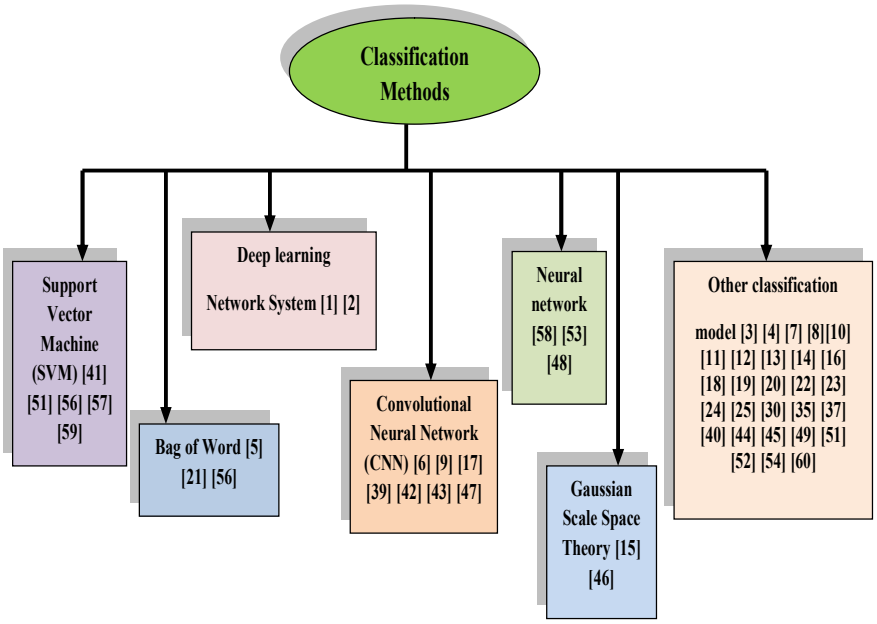

Fig. 2. *Analysis of HEp-2 Cell Classification Models*

3.2 Analysis of Segmentation Models

Fig 3 shows the analytical review of segmentation models in various reviewed papers. Here, the segmentation models are grouped into two: network Systems and other models. algorithms like Fully Convolutional Network and CNN are used in [9] and [17]. Some of the other algorithms used in the review papers are the transfer-learning framework using cC -GAN [8], Sobel filter algorithm [12], Texture segmentation [26], Adaptive marker-controlled watershed approach [27], Hidden Markov random field model [28], Adaptive edged based segmentation method [31], Verification based multi-threshold probing model [32] and Watershed algorithm [34].

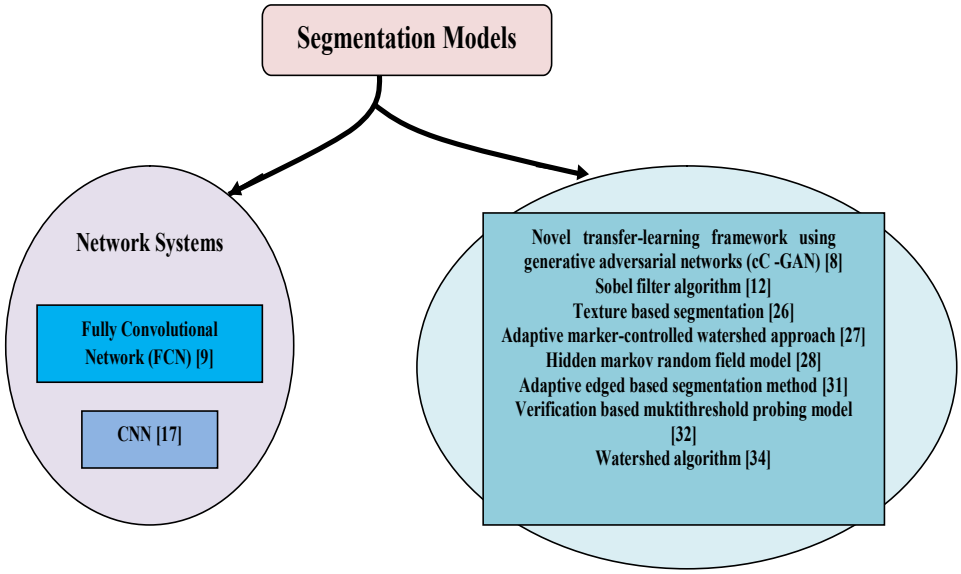

Fig. 3. *Analytical Review on HEp-2 Segmentation Models*

3.3 Analysis of Performance Measure

Table I shows the analysis of used performance measures from all the reviewed papers. It is observed that the performance analysis of different classification models. Some of the commonly used performance measures are accuracy, precision, recall, F1 Score, false positive, false negative, true positive, true negative, MCA, ACA, Computational Time, Sensitivity, Specificity, etc. Table I shows that the Accuracy measure is almost used in all the papers. Particularly, 75% of total papers have measured the accuracy rate. The precision measure is used in various papers, which is 11.66% of the total contribution. Only 8.33% of the total contribution has used the recall measure to analyze the performance. F1Score and specificity are used in various papers, which is 5% of the total contribution. MCA is the measure that is used by 16.66% of total contribution. ACA is the measure that is used by 3.33% of total contribution. Computational time and sensitivity are also analyzed in different papers, which is 6.66% of the total contribution. false positive and False Negative are also measured in 6.66% and 5% of total contribution.

Table 1. *Analysis of Performance Measure of HEp-2 Segmentation and Classification Models*

Citation	Accuracy	Precision	Recall	F1 score	MCA	ACA	Computation-al Time	Sensitivity	Specificit-y	True Positive	True Negative	False positive	False negative	Others
[1]	✓	✓	✓	✓										
[2]					✓	✓								
[3]					✓									
[4]	✓						✓							
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3.4 Attained Maximum Measure

The attained best performance from all the reviewed papers is given in Table II. From this, it is observed that the maximum attained accuracy rate is 97.14, the maximum achieved precision value is 97.42, the maximum MCA performance is 97.5, s the attained best ACA is 89.04, the computational time is also measured in many contributions and the attained best computational time is 114 sec. Further, the sensitivity measure is also measured in different papers and the best value is 98.5%

Table 2. *Attained Maximum Performance Measures from the Reviewed Models*

Measures	Attained Results
Accuracy	97.14
Precision	97.42
MCA	97.5
ACA	89.04
Computational time	114 sec
Sensitivity	98.5%

3.5 Analysis of Accuracy Rate

Fig 4 shows the analysis of the accuracy rate. Here, 10% of the total contribution has attained an accuracy rate that is in the range of 60% to 70%. 21.66% of total contributions have attained the classification accuracy of 70% to 80% and 80% to 90%. Further, 20% of total contributions have attained an accuracy rate that is in the range of 90% to 100%.

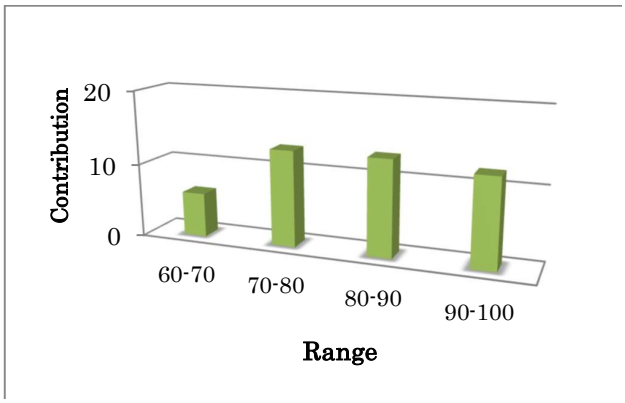

Fig. 4. *Bar diagram of Accuracy Analysis on HEp-2 Classification Models*

4. Research gaps and challenges

Even though the conventional HEp-2 classification process shows its positive side, still the methods are lagging with some of the most prompt challenges, which has to be considered in future work. The most important problem with some of the classification processes is that because of the deep representation with minimal labelled medical images, there occurs over overfitting problem. To address this problem, more investigation is needed under the transfer learning approach that too in an efficient manner. Further, to get more satisfactory results, the obtained IIF image by ANA test is required to be investigated by a minimum of two scientists under the microscope. For staining pattern classification, it falls to 76.0%, which is due to the lack of quantitative data supplied to the physicians and the used optical system in the test. In some cases, the authors have evaluated the performance of the organizers of "Performance Evaluation of Indirect Immunofluo rescence Image Analysis Systems", and suggested that better outcomes can be attained by fusing the top approaches, which should be focused on in the future. More often, problems may arise with the dataset used for the classification process. One of the challenges with the ICPR2012 dataset is the two classes' classification of fine as well as coarse speckled since the patterns are closer to one another. Here, the performance on specimen-level classification is not as reliable since there are only a few specimen images. Further, the ICIP2013 dataset has richer and more specimen images but most of the provided cell masks of the images are tangled with noise. Hence, the dataset for better classification needs to be more probable.

On the other hand, more cell masks are associated with one another creating the problem in the phase of classification. In recent years, the use of CNN has become more common, but there needs so many enhancements to the model to address the problem of biomedical image segmentation. Further,

there is a trade-off between window size and segmentation performance of the CNN model, i.e. larger window size minimizes the accuracy rate of segmentation. All the mentioned problems might focus the research to deal with new advanced strategies in both Hep-2 image segmentation and classification process.

5. Conclusion

This survey has reviewed different Hep-2 segmentation and classification models. This has been attained by revising 60 papers on this topic. The analysis was carried out in certain scenarios that are given below:

- Initially, all 60 papers were reviewed to describe the research work in terms of classification and segmentation models.
- A detailed chronological review has been made and has been represented in terms of a bar chart.
- A diagrammatic representation was given to explain the methods for the classification and segmentation.
- The performance measures were reviewed from all the papers and have made a subjective analysis.
- From all the papers, the maximum attained measures are tabulated with the attained value.
- Further, the classification rate from all the reviewed papers wasanalyzed, and a bar diagram.
- Finally, the most important research gaps in this topic have been justified, which aids in working on future contributions.

Compliance with Ethical Standards

Conflicts of interest: Authors declared that they have no conflict of interest.

Human participants: The conducted research follows the ethical standards and the authors ensured that they have not conducted any studies with human participants or animals.

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