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Review

Application of Machine Learning in Cell Detection

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Abstract: In recent years, machine learning algorithms have seen extensive application in chemical science, especially in cell detection technologies. Machine learning, a branch of artificial intelligence, is designed to automatically discover patterns in data. This review provides an overview of cell detection methods such as bright-field microscopy (BL), dark-field microscopy (DL), surface-enhanced Raman scattering (SERS), and fluorescence detection (FL). We highlight key computational models like support vector machines and convolutional neural networks that significantly enhance the precision and efficiency of automated cell detection. Relevant research applications are discussed, along with future prospects for machine learning in cell analysis.

Keywords: machine learning; cell detection; detection methods

1. Introduction

Machine learning is widely applied across various scientific disciplines, often in tandem with big data analytics and artificial intelligence [1]. It offers exceptional advantages in cellular data processing, with increased flexibility, efficiency, and precision in solving practical problems. In this review, we focus on the evolution of cell detection technology, examining how traditional techniques have transitioned into modern approaches using deep learning models.

Prior to 2012, classical machine learning algorithms, such as the viola jones detector (VJ detector) [2], histogram of oriented gradients (HOG) [3], and deformable part models (DPM) [4], dominated the landscape. However, the introduction of deep learning architectures like AlexNet [5], R-CNN [6], and YOLO [7] after 2012 led to significant advancements in the field. These deep learning models have since been integrated into cell detection technologies, enhancing the intelligence and accuracy of automated detection systems. Traditional detection algorithms primarily relied on feature extraction and image segmentation, using methods based on object region or color. With the advent of deep learning and the growth of cell data, two-stage detection models like R-CNN [8] and single-stage models such as YOLO and SSD [9] have emerged as standard tools. More recently, algorithms based on the Transformer architecture have gained traction, representing the next wave of innovation in object detection [10]. Machine learning in cell detection continues to evolve, with diverse algorithmic approaches improving the accuracy and reliability of detection results. This review explores the trajectory of these advancements and discusses their applications in cell detection.

As a software tool for building models, machine learning is trainable and reliable, which can facilitate researchers in cell analysis. With the advancement of machine learning algorithms and the development of cell detection technology, we can automatically analyze large amounts of data through machine learning models, so as to predict and analyze

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more complex cell behaviors and provide new insights for the treatment of diseases; this is expected to be applied in the fields of chemistry, biology, and medicine and to promote interdisciplinary cooperation.

2. Machine Learning Algorithms for Cell Detection

Early cell detection techniques primarily utilized two types of machine learning algorithms: kernel methods and ensemble methods. Kernel methods address the challenge of mapping non-linear, low-dimensional data into a higher-dimensional space, with support vector machines (SVMs) serving as a classical model. For instance, Svensson et al. achieved an 88% accuracy rate in identifying circulating tumor cells using an SVM coupled with a naive Bayes classifier [11]. This algorithm is reliable and automated and plays a key role in the early diagnosis of diseases. However, the kernel method is often limited to specific types of target models, leading to the development of more generalized ensemble approaches.

Ensemble methods combine multiple machine learning algorithms to transform a series of weak learners into strong predictors. Key examples include the AdaBoost and random forest algorithms [12]. Pereira et al. demonstrated the utility of random forest models in brain tumor segmentation, achieving superior precision and stability compared to earlier segmentation techniques [13]. We believe that the method can be further improved by combining the model with other techniques, resulting in data with higher accuracy and more stable results. Despite these advancements, traditional machine learning algorithms struggle with complex, large-scale cell data, and detection accuracy can be limited by the sample size.

Recent developments in machine learning have introduced deep learning algorithms that simulate the neural networks of the human brain. In particular, a convolutional neural network (R-CNN) is a region-based, two-stage target detection algorithm, which has been shown to be effective in cell detection tasks. Zeune et al. used a CNN combined with visualization techniques to achieve over 96% accuracy in detecting circulating tumor cells, while also identifying novel cell subtypes [14]. This strategy combines a variety of technologies, more in-depth research based on machine learning, and higher accuracy for cell detection. In addition, YOLO is a border-based single-stage target detection algorithm, which has been successfully applied to cervical cancer and breast cancer cell detection [15]. We believe that the single-stage object detection algorithm has lower computational complexity than the two-stage object detection algorithm, so the detection speed is faster. These advancements suggest that deep learning algorithms will continue to play a pivotal role in the future of cell detection technologies.

3. The Application of Machine Learning to Cell Detection Methods

The diversity of machine learning and cell detection methods can help us better understand the similarities and differences in cell data for tasks such as cell data visualization, dimensionality reduction, clustering, and feature selection. In practical applications, it is necessary to select the appropriate cell detection means according to the specific needs, determine the machine learning algorithms and parameters, and evaluate and optimize the results to achieve the best results. Therefore, according to the means of cell detection, we can roughly divide this into four categories: bright-field microscopic detection, dark-field microscopic detection, surface-enhanced Raman scattering, and fluorescence detection.

3.1. Bright-Field Microscopic Detection

Bright-field microscopy, a cost-effective optical method, allows for the analysis of cell shape, size, and morphology [16]. By applying machine learning algorithms to bright-field

images, researchers can rapidly and accurately identify cellular characteristics, improving detection and analysis outcomes.

The early diagnosis and evaluation of cancer are crucial to the treatment of patients with the disease. Chemotherapy is an important method used in the treatment of leukemia, but cancer cells of different patients have different resistances to the treatment effect [17]. Uelu et al. used the computer vision algorithm to quantitatively detect the immunomagnetic beads and leukemia cells by using the cell images collected by the high-power objective lens under the bright-field microscope (Figure 1a), and the accuracy reached 91.6% under the 40-fold objective lens [18]. This method provides convenience for the realization of on-site cell analysis.

Circulating tumor cells (CTCs) are an important biomarker of cancer, and their count can predict the survival of patients, but their identification is difficult [19]. Wang et al. used convolutional neural networks to detect CTCs in blood under a bright-field microscope (Figure 1b) and counted the CTCs simply and quickly through cell images with high detection accuracy [20]. This method is smart and could be used to detect rare cells in the future.

Due to the low contrast of images obtained under bright-field microscopy and the possibility of cell overlap, automatic segmentation cannot be performed, and manual acquisition is time-consuming and complicated [21]. Asha et al. developed a remarkable and spherically driven U-shaped network (SBU-net), which can accurately segment cells in bright-field microscopic images (Figure 1c) and obtain cell structure information [22]. This model has strong cell segmentation performance and greatly promotes the development of the automatic segmentation of microscopic images.

Mesenchymal stem cells (MSCs) are a kind of stem cell with diverse differentiation abilities, widely used in the research of immune diseases. The aging of MSCs will cause adverse reactions to the human body, so the count of senescent cells in MSCs is very important [23,24]. Celebi et al. used the model combined with self-supervised learning and mask R-CNNs to automatically segment and count senescent cells in bright-field microscopy images (Figure 1d), with an accuracy of more than 80% [25]. The model can be further applied to the detection of other cell types.

3.2. Dark-Field Microscopic Detection

Because of the low contrast that is characteristic of bright-field images, the performance of the segmentation algorithm is affected to some extent, and there are some limitations to cell detection. With a dark-field microscope, the condenser collects diffracted light by passing light through the aperture of the lens so that the background of the image is black but the cells are bright, and a high-contrast image is obtained [26]. The combination of machine learning and dark-field microscopy has improved the accuracy of cell detection due to the enhanced performance of the algorithm.

In cell detection studies, the growth state of cells is extremely important, among which cell density and activity are the most important [27]. Wei et al. developed a probe based on the support vector machine model (SVM), which was used to analyze yeast cell images under dark-field microscopy (Figure 2a), so as to separate living and dead cells and detect cell density and activity with high precision [28]. This method has high precision, good stability, and good application prospects in distinguishing living cells from dead cells.

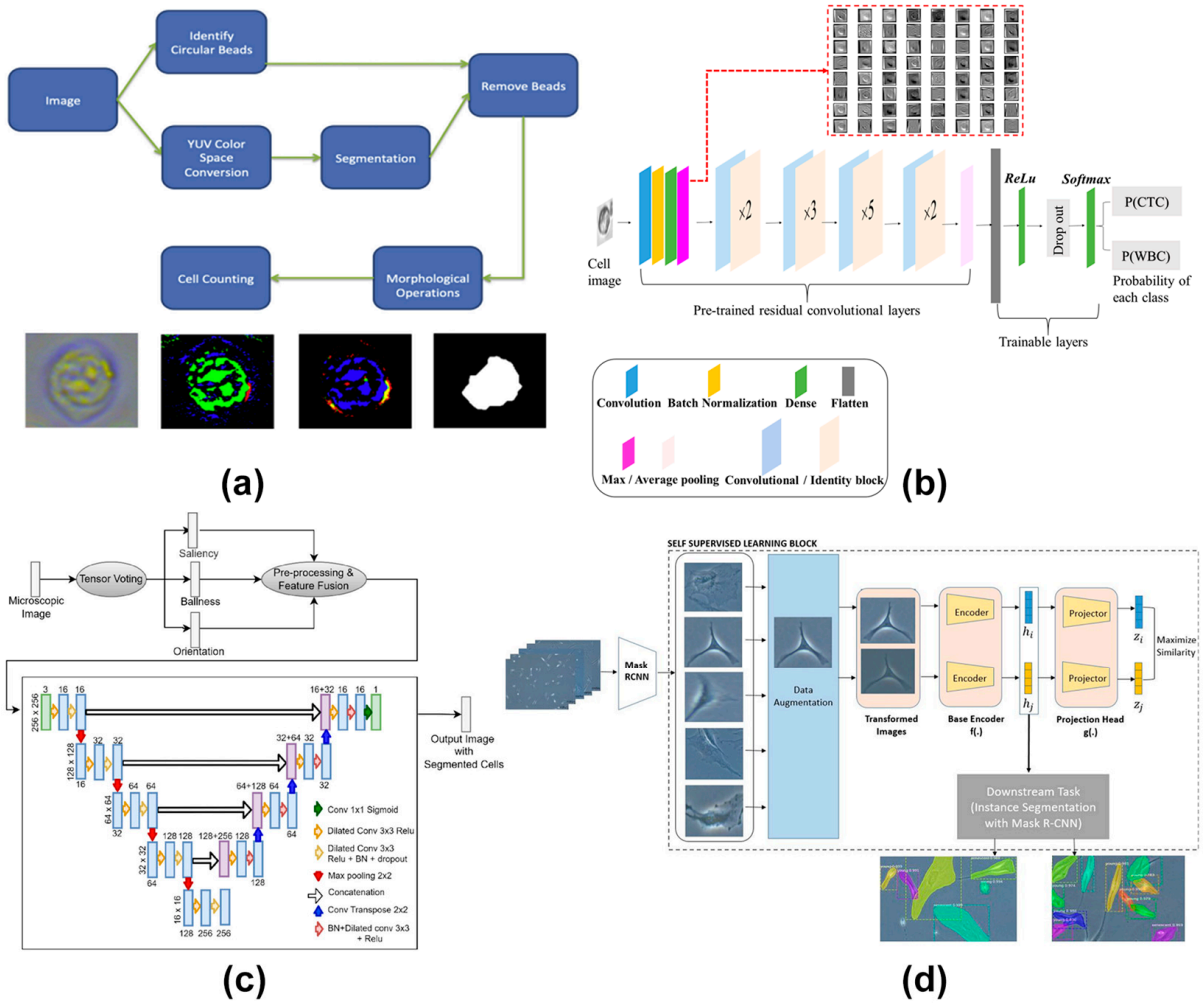

Figure 1. Application of machine learning in bright-field microscopic detection of cells. (**a**) Quantitative detection of immunomagnetic beads and leukemia cells using visual algorithms and bright-field microscopy. Reproduced from Ref. [18] with the permission of Elsevier. (**b**) Using CNN algorithm and bright-field microscope to detect CTCs in blood. Reproduced from Ref. [20] with the permission of Nature. (**c**) Accurate segmentation of cells in bright-field microscopic images using SBU-net. Reproduced from Ref. [22] with the permission of Elsevier. (**d**) Automatic segmentation of senescent cells in bright-field microscopic images using self-supervised learning. Reproduced from Ref. [25] with the permission of Wiley Online Library.

In the process of cell culture, cells are easily affected by the external environment and so are easy to be contaminated, and it is important to develop non-staining and non-harmful cell analysis methods. Based on SVMs in machine learning, Burgemeister et al. proposed a CellViCAM system (Figure 2b), which can estimate the animal cell density and cell differentiation degree without adding any marks when processing dark-field microscopic images [29]. This strategy can better distinguish cell differentiation states such as live cells, necrotic cells, and apoptotic cells.

The change in blood value will lead to the occurrence of many diseases. The count of blood cells includes red blood cells, white blood cells, platelets, and other quantitative indicators [30]. The collection of human blood is conducive to the screening of diseases, in which the morphologic study of red blood cells can know whether anemia is present [31]. Using Mi scattering and machine learning, Chen et al. obtained cell morphological information (Figure 2c) by imaging in the dark field, including the volume, concentration, and distribution range of red blood cells, with high accuracy [32]. This method has a good advantage in detecting anemia.

Gold nanoparticles (AuNPs) have high stability, good biocompatibility, and strong molecular signals, which can provide good imaging [33]. Based on the scattering properties of AuNPs, researchers can construct functional nanosensors [34,35]. However, conventional methods for detecting nanoparticle scattering in living cells are time-consuming and complex. Huang et al. developed U-Net convolutional deep learning neural network technology (Figure 2d), which can identify the scattered light signal of nanoparticles in living cells with high accuracy under complex environments with background interference by using dark-field microscopic imaging technology [36]. This method provides a new idea for the imaging analysis of living cells in the field of chemistry.

In addition to intracellular, we can also detect the degree of AuNPs' aggregation in different saline solutions. Wang et al. used dark-field microscopic imaging to build an AlexNet model of machine learning, which could accurately predict the AuNP aggregation degree in solution (Figure 2e) with an accuracy higher than 96% [37]. This strategy is useful for the predictive analysis of dark-field imaging, and it has potential biological applications.

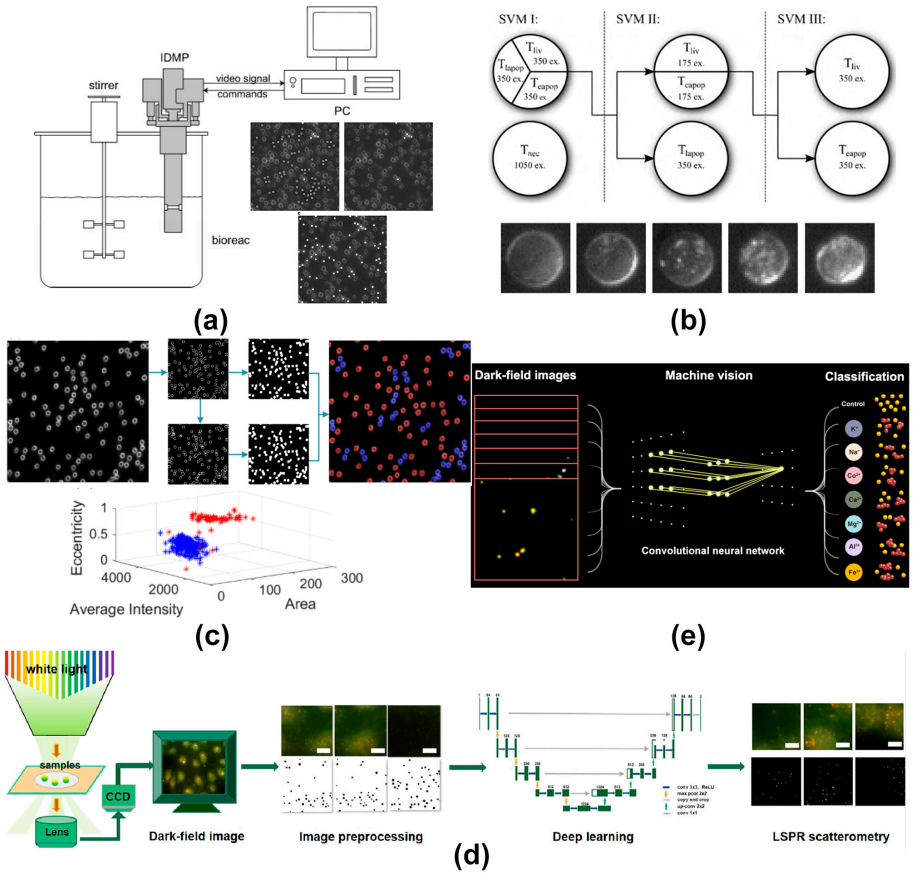

Figure 2. Application of machine learning in dark-field microscopic detection of cells. (**a**) A probe developed based on SVMs for the analysis of yeast cells under dark-field microscopic images. Reproduced from Ref. [28] with the permission of Wiley Analytical Science. (**b**) Cell density in dark-field microscopic images was estimated based on the CellViCAM system. Reproduced from Ref. [29] with the permission of Elsevier. (**c**) The morphologic information of red blood cells was obtained by using machine learning imaging under dark-field microscopy. Red represents single cells and blue represents multiple cells. Reproduced from Ref. [32] with the permission of Optica Publishing Group. (**d**) Detection of nanoparticle scattering in living cells using U-Net convolutional deep learning neural network technology and dark-field microscopic imaging. Reproduced from Ref. [36] with the permission of American Chemical Society. (**e**) Dark-field microscopy and an AlexNet model were used to predict AuNPs aggregation in salt solution. Reproduced from Ref. [37] with the permission of American Chemical Society.

3.3. Surface-Enhanced Raman Scattering

Nowadays, surface-enhanced Raman scattering (SERS) technology is used to study the spectrum of biomolecules in cells. The Raman effect is caused by the vibration of the molecule, and this technique can identify differences in the composition of the sample by the characteristic peak location and intensity. This method has high detection speed, high accuracy, and no sample pretreatment, so it has been more and more widely used in cell detection [38]. Different cells have different feature types, and the collected Raman spectral data are different. Machine learning can be used to quickly analyze the structure and composition of different feature peaks from a large number of Raman spectral data, so as to find the best feature data and obtain effective information faster. Therefore, after the introduction of machine learning technology, the detection effect of cells is better, the accuracy is higher, and the research value is very meaningful.

Ulcerative colitis (UC) is a chronic inflammatory disease, and evaluating the severity of UC is crucial for the treatment of the disease, but the biomolecular information related to UC cannot be found by conventional methods [39]. Kirchberger-Tolstik et al. used Raman spectroscopy to construct a 1D CNN model (Figure 3a) for predicting the Mayo endoscopic score in biopsies of patients with colonic inflammation [40]. The results show that many molecular changes, such as proteins, DNA, and lipids, occur during inflammation, and this work also has important implications for the diagnosis of other types of diseases.

Cyanobacteria are important microorganisms in photosynthesis, and the selection of mutant cells from them is of great significance in biogenetic studies [41]. Gao et al. used surface-enhanced Raman scattering technology to establish a support vector analyzer (SVC) model (Figure 3b) to distinguish wild-type and mutant cyanobacteria cells with an accuracy of 97% [42]. This high-throughput selection approach provides innovative strategies for genetic and cellular detection in biology.

Changes in cell secretions affect cell death, so the classification of cancer cells is beneficial for cancer treatment, but conventional methods are time-consuming and easily destroy cells [43,44]. Plou et al. used marker-free SERS to combine microfluidic and machine learning to quickly identify cell secretions under different conditions (Figure 3c), with an accuracy of 95% [45]. This scheme lays a good foundation for high-throughput cell detection.

Exosomes are extracellular vesicles with abundant cellular body fluids, which contain a lot of molecular information and are an important biomarker for cancer [46,47]. However, it is difficult to find comprehensive molecular information when detecting exosomes [48]. By using machine learning and SERS, Diao et al. used AuNPs as a basis to accurately detect exosomes in samples with high sensitivity (Figure 3d), and the prediction accuracy of cancer reached 91.1% [49]. This method has a wide application prospect for the diagnosis of cancer and even other diseases in the future.

Dopamine (DA), as a neurotransmitter, plays an important role in functional regulation [50]. However, it is difficult to determine the content of DA in exosomes secreted by cells. Lv et al. built an XGBoost model that can accurately identify exosome signals secreted by different cells (Figure 3e) and used nanotubes as an auxiliary method to accurately measure the DA content in exosomes by using continuous pulse current [51]. This strategy uses the continuous pulse current signal and can obtain a single dimension spectrum similar to the Raman spectrum. The spectrum with signal peaks can also be analyzed by it, which provides a new idea for chemical research.

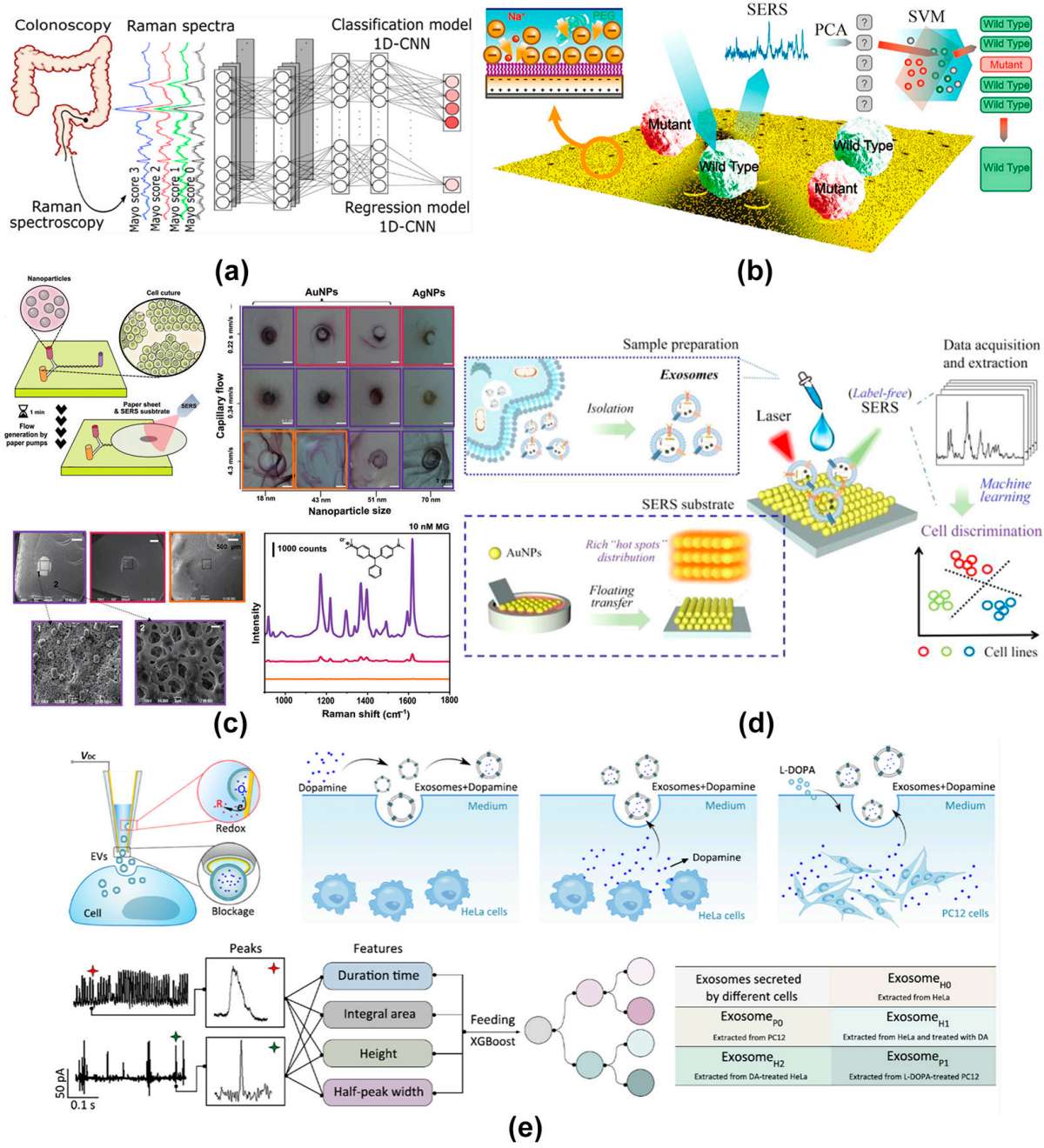

Figure 3. Application of machine learning to cell detection with surface-enhanced Raman scattering technique. (**a**) Raman spectrum and CNN model were used to classify the severity of UC. Reproduced from Ref. [40] with the permission of American Chemical Society. (**b**) SVC model and SERS were used to identify mutant cyanobacteria cells. Reproduced from Ref. [42] with the permission of American Chemical Society. (**c**) Rapid identification of cell secretions using marker-free SERS and machine learning. Reproduced from Ref. [45] with the permission of Wiley Online Library. (**d**) Highly sensitive detection of cellular exosomes using machine learning and SERS. Reproduced from Ref. [49] with the permission of American Chemical Society. (**e**) XGBoost model and continuous pulse current were used to determine the DA content in exosomes. Reproduced from Ref. [51] with the permission of American Chemical Society.

3.4. Fluorescence Detection

For cell detection, the fluorescent probe is also a good detection method, which has good specificity, high sensitivity, and strong tissue penetration [52]. However, it is sometimes limited by the high complexity of the sample, and the establishment of an

algorithm model through machine learning can break through this limitation, so as to obtain a fluorescence probe with higher sensitivity and specificity, which makes the cell detection more accurate, allowing it to be widely used in the detection of various biological cells. In addition, fluorescent labeling methods based on optical imaging can make specific cells show fluorescent signals in order to clearly observe the behavior of cells. By using machine learning algorithms, fluorescent images can be automatically analyzed, specific objects can be identified after multiple training, quantitative information can be collected, and reliable data can be obtained quickly, which is conducive to cell analysis.

Non-melanoma skin cancer (NMSC) is a type of skin lesion, and its early diagnosis is crucial for the treatment of the disease [53]. NMSC is divided into various types, and it is difficult to evaluate the growth status of the cells [54]. Chen et al. used the stained cell sections for fluorescence imaging and built a linear support vector machine model (LSVM), which could accurately obtain different characteristics of skin cancer (Figure 4a), so as to detect cancerous cells with high sensitivity [55]. This strategy has great potential for the diagnosis of skin diseases.

Myelin is a lipid on the outside of neurons, and damage to it by heredity and external environments can lead to multiple sclerosis disease [56,57]. Drug treatments that regenerate myelin are urgently needed, so its detection is crucial [58]. Based on machine learning, Yeti et al. proposed a method for detecting myelin in fluorescence microscopic images (Figure 4b), which could extract feature data. In different machine learning technologies, the detection accuracies of the Boosted Trees model and CNN model were up to more than 98% [59]. This method facilitates the rapid screening of drugs for myelin regeneration.

Muscle stem cells (MuSCs) play an important role in the growth of skeletal muscle and contribute to the repair of damaged tissues; that is, they have strong regenerative capacity [60,61]. Therefore, the dynamic regulation of MuSCs contributes to the regeneration of skeletal muscle. Togninalli et al., using machine learning strategies, invented a microscope method for Dual-FLIT imaging (Figure 4c), which can track the dynamic growth of single cells at high resolution, thus regulating the dynamics of MuSCs [62]. This strategy helps us better understand the mechanisms of tissue cell regeneration.

Bladder cancer is a malignant tumor with a high incidence, and the detection of bladder cancer cells is helpful for early diagnosis and treatment [63]. Based on the SVM model in the machine algorithm, Zhang et al. developed a double-fluorescence micro-image flow cytometer (μ-FCM) for the high-throughput detection of bladder cancer cells (Figure 4d) and effectively reduced the overlap of different cells [64]. The system provides a new method for the detection of bladder cancer cells and the diagnosis of the disease.

3.5. Other Methods

The combination of machine learning and cell detection technology is diverse, and in addition to the combination method mentioned above, the research has more directions. Islam et al. developed a multi-head attention-based transformer model for finding plasmodium parasites from blood cell data using the gradient-weighted class activation graph technique with high test accuracy [65]. Karimzadeh et al. developed a multi-task generating artificial intelligence model for analyzing orphan non-coding RNA from patients with non-small cell lung cancer, which can detect early cancer with high sensitivity. Due to the large amount of blood sample data required in the experiment, this study can promote interdisciplinary cooperation in chemistry and medicine [66]. Pastuszak et al. developed a tree-based machine learning model for screening circulating tumor cells by analyzing single-cell RNA sequencing data [67].

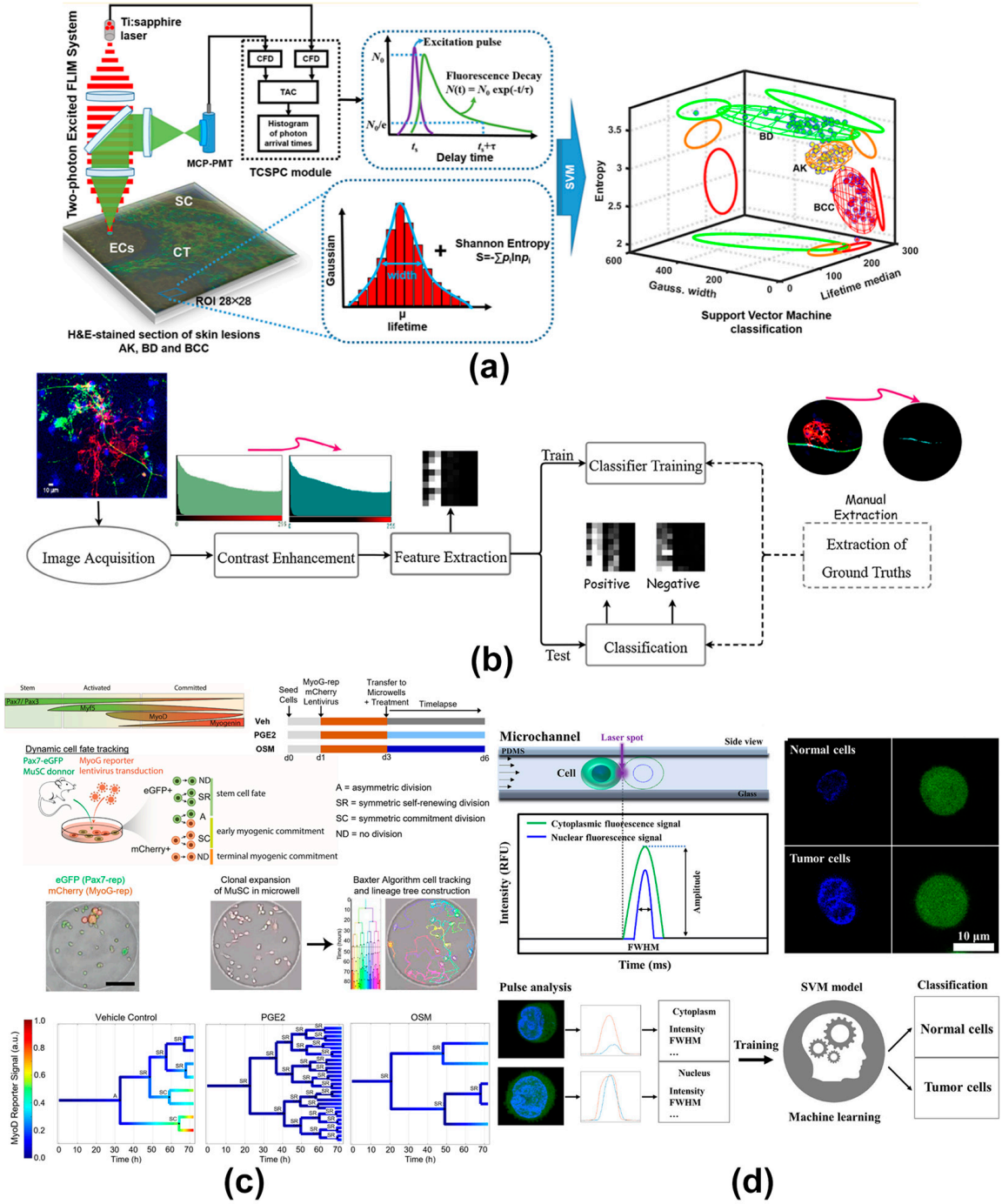

Figure 4. Application of machine learning to fluorescence detection of cells. (**a**) LSVM and fluorescence imaging were used to obtain characteristic information about different skin cancer cells. In the figure on the right, green represents Bowen's disease (BD), yellow represents actinic keratosis (AK) and red represents basal cell carcinoma (BCC). Reproduced from Ref. [55] with the permission of American Chemical Society. (**b**) Detection of myelin using machine learning models and fluorescence. Reproduced from Ref. [59] with the permission of Elsevier. (**c**) Dynamic regulation of MuSC using machine learning and Dual-FLIT. Reproduced from Ref. [62] with the permission of Nature. (**d**) SVM and μ-FCM were used to detect bladder cancer cells. Reproduced from Ref. [64] with the permission of Elsevier.

Combined with the detailed analysis of the latest progress, the machine learning model and detection means are diversified, and the detection means and machine learning model are selected according to the specific detection target. To improve detection accuracy,

researchers often improve on the original machine learning model to develop new models that are conducive to cell detection. This type of research uses a variety of analytical chemical assays, cell, and blood sample data, so it can greatly facilitate interdisciplinary collaboration. The applications of machine learning models in chemistry and medicine are promising, but they also pose ethical challenges. The privacy of patient data is the most critical issue, with the risk of data breach or misuse in research. As we analyze data and develop machine learning models, we also need to ensure that patient confidentiality is maintained, either by encrypting or anonymizing the data. In short, the application of machine learning in cell detection has broad prospects and unlimited potential.

4. Discussion

The combination of machine learning and various cell detection methods, including bright-field, dark-field, SERS, and fluorescence techniques, has significantly improved the accuracy and efficiency of cell analysis. While traditional cell analysis methods cannot analyze the heterogeneity between cells, machine learning can analyze the data of individual cells to provide information at the single-cell level. In the single-cell analysis of tumor tissue, machine learning can excavate the function and interaction relationship of different cell groups through cluster analysis, providing new ideas and methods for tumor precision treatment. Machine learning is capable of processing and analyzing complex datasets, thus improving research efficiency and potentially revealing relationships at the cellular and molecular level that cannot be observed with traditional methods. Combined with cell analysis and machine learning, new biological phenomena and laws can be discovered to promote the further development of life science research. However, challenges remain. The performance of machine learning models is highly dependent on the quality and type of training data, and mislabeled or incomplete data can hinder model performance. Additionally, complex machine learning models often lack interpretability, making it difficult to balance accuracy with transparency.

To improve the reliability of machine learning models in cell detection, ensuring high-quality, diverse, and accurately annotated datasets is critical, as it enhances model generalizability and reduces bias. Techniques such as data augmentation and synthetic data generation can further expand dataset variety and prevent overfitting. Employing robust validation strategies like stratified k-fold cross-validation and leveraging ensemble learning can mitigate individual model weaknesses and improve overall robustness. Incorporating transfer learning from pre-trained models accelerates learning while enhancing performance on smaller datasets. For better data interpretation, explainable AI (XAI) techniques can be utilized to visualize and understand model decisions, while feature attribution methods, such as SHAP or Grad-CAM, help link model predictions to meaningful biological insights. Together, these approaches ensure both reliable performance and improved interpretability in cell detection tasks.

The future of machine learning in cell detection holds immense promise in terms of advancements in computational methods, imaging technologies, and biological research converge. Enhanced algorithms, including deep learning techniques like transformers, will improve the accuracy and speed of cell detection, enabling the real-time analysis and more precise identification of cell types and abnormalities. The integration of multimodal data from imaging techniques, genomics, proteomics, and transcriptomics will facilitate holistic cell profiling, linking cellular morphology with molecular states and behaviors. Machine learning will also play a vital role in personalized medicine by analyzing single-cell heterogeneity and predicting cellular responses to therapies, thus accelerating drug discovery and enabling tailored treatments. Automated, high-throughput systems powered by machine learning will handle large-scale cell imaging datasets, while edge comput-

ing and IoT devices will decentralize and democratize cell detection across laboratories worldwide. Additionally, machine learning models will improve the detection of rare cell types and complex interactions, providing critical insights into tissue organization, immune responses, and disease progression. Explainable AI (XAI) will enhance the transparency of these models, fostering trust in clinical applications and aiding researchers in uncovering new biological insights. Emerging technologies like quantum computing and neuromorphic chips will further revolutionize machine learning applications by increasing processing speed and energy efficiency. Ethical considerations, such as bias-free models and data privacy, alongside the proliferation of open-source tools and interdisciplinary education, will democratize access to machine learning in cell detection, ensuring global adoption. These advancements will transform not only basic research but also clinical diagnostics, drug development, and personalized medicine, driving novel therapeutic approaches and deeper insights into cellular mechanisms.

5. Conclusions

This review highlights the growing role of machine learning in cell detection technologies, focusing on four primary methods: bright-field, dark-field, SERS, and fluorescence detection. By leveraging advanced algorithms, researchers can now perform rapid, accurate, and high-throughput cell analysis. As artificial intelligence continues to evolve, its integration into cell detection technologies will likely yield new breakthroughs in both scientific research and clinical practice.

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