

Current Status and Prospects of Raman Spectroscopy Combined with Deconvolution Algorithms in the Rapid Diagnosis of Complex Infectious Pathogens

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Abstract. With the spread of bacterial resistance and the growing demand for rapid diagnosis of complex infections, traditional pathogen detection methods suffer from long cycles and low efficiency, which can hardly meet the needs of precise clinical diagnosis and treatment. Focusing on Raman spectroscopy combined with deconvolution and artificial intelligence algorithms, this paper systematically reviews the application status of this technology in the rapid identification, drug resistance discrimination and in-situ detection of pathogens causing complex infections. The paper analyzes key challenges of Raman spectroscopy in clinical practice, including spectral overlap, matrix noise interference and weak signals at low pathogen concentrations, and summarizes the improvements of deconvolution, deep learning and other algorithms in spectral denoising, peak shape restoration and feature extraction. The results show that Raman spectroscopy combined with intelligent algorithms can realize rapid identification of drug-resistant bacteria and short-term antimicrobial susceptibility testing, with advantages of non-invasiveness, culture-free detection and single-cell resolution. However, it still faces challenges such as poor model interpretability and insufficient clinical validation. In the future, efforts should be made to advance multi-center database construction and portable equipment development, so as to promote the translational application of this technology in the precise diagnosis of clinical infections.

Keywords: Raman spectroscopy, surface-enhanced Raman scattering (SERS), deconvolution algorithm, multidrug-resistant bacteria, rapid antimicrobial susceptibility testing

1. Introduction

At present, the spread of bacterial resistance and frequent complex infections have become severe challenges to global public health, and there is an urgent clinical demand for rapid, accurate and high-throughput pathogen diagnosis. Currently, common clinical etiological detection methods include traditional culture, automated drug susceptibility systems, polymerase chain reaction (PCR), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and metagenomic next-generation sequencing (mNGS). Although traditional culture and drug susceptibility testing remain the gold standard, they usually take 24–72 h; PCR and mNGS can quickly identify specific genes, but cannot directly reflect the actual drug resistance phenotype;

MALDI-TOF MS enables rapid species identification, but still relies on pure cultured colonies in most cases. Obviously, traditional microbial detection features long cycles and cumbersome operations, which easily leads to antibiotic abuse and aggravates the spread of drug-resistant strains.

Raman spectroscopy records inelastic scattering signals generated by molecular vibrations, and can provide characteristic information of biological macromolecules such as proteins, nucleic acids, lipids and polysaccharides. With the advantages of being label-free, non-destructive, high in single-cell resolution and capable of directly reflecting cell metabolic status, Raman spectroscopy has received extensive attention in medical microbiology in recent years. With the development of surface-enhanced Raman scattering (SERS), stimulated Raman scattering (SRS), optical tweezers Raman spectroscopy, microfluidic Raman technology and Raman flow cytometry, this technology has made remarkable progress in sensitivity, throughput and automation. Relying on the above advantages, Raman spectroscopy has become a research hotspot in pathogen detection and drug susceptibility analysis. The combination of artificial intelligence and laser tweezers Raman spectroscopy can realize accurate microbial identification, providing technical support for clinical sample detection [1].

However, Raman spectral analysis still faces many challenges in complex clinical samples, including fluorescence background interference, characteristic peak overlap, spectral drift and weak signals from low-concentration pathogens. Deconvolution algorithms can separate overlapping peaks and restore real signals through mathematical inversion, which is a basic step to improve the accuracy of spectral resolution. On this basis, machine learning and deep learning further realize high-dimensional feature extraction, pattern recognition and automatic classification, thus significantly improving the performance of pathogen identification and drug resistance prediction.

This paper focuses on the key technical challenges of Raman spectroscopy in the rapid diagnosis of complex infectious pathogens, systematically summarizes the application progress of deconvolution and artificial intelligence algorithms in spectral analysis, and further introduces the latest research status and future development directions of their application in pathogen identification, rapid drug susceptibility testing and clinical translation.

2. Technical challenges of Raman spectroscopy in microbial detection

With its molecular fingerprint recognition property, Raman spectroscopy has prominent advantages in microbial pathogen detection and drug resistance analysis. However, restricted by issues such as complex biological samples, clinical matrix interference and weak signals of low-concentration pathogens, it has low feature extraction accuracy and poor efficiency in identifying drug resistance markers, which can hardly meet the requirements of clinical precise diagnosis. This highlights the necessity and irreplaceability of algorithms in Raman spectroscopy detection.

2.1. Complexity of biological sample components and spectral overlap

As complex living organisms, the diversity of intracellular biological macromolecules and the overlap of spectral features constitute the primary obstacle for Raman spectroscopy to parse pathogen information, and directly restrict the accurate identification of drug resistance-related characteristic markers in particular. Effective differentiation can no longer be achieved only with original spectral data. Microbial cells contain various biological macromolecules such as proteins, lipids, nucleic acids, polysaccharides and metabolites, and their Raman characteristic peaks are widely distributed in the fingerprint region of 400–1800 cm^{-1} and the high wavenumber region of 2800–3100 cm^{-1} . Since the characteristic peaks of different components are close in position, severe

overlap often occurs. For example, 785 cm^{-1} corresponds to the vibration of nucleic acid pyrimidine rings, 1003 cm^{-1} mainly reflects phenylalanine, 1450 cm^{-1} is related to the CH_2 bending vibration of lipids, and 1655 cm^{-1} corresponds to the amide I band of proteins. The severe peak overlap makes it difficult to directly identify subtle changes related to drug resistance [2].

2.2. Obstacle of narrow peak overlap in the "fingerprint region" to specific drug resistance marker identification

The fingerprint region of Raman spectroscopy ($400\text{--}1800\text{ cm}^{-1}$) contains core molecular information of microorganisms and key signals of drug resistance markers. However, narrow peaks in this region are dense and heavily overlapped, and specific signals are easily masked, making it difficult for traditional methods to achieve accurate identification. This problem severely restricts the differentiation between drug-resistant and sensitive bacteria as well as the identification of drug resistance markers, highlighting the urgency of applying algorithms for spectral unmixing and accurate extraction of characteristic peaks [3].

2.3. Background noise interference from complex clinical matrices

Clinical infection samples are not pure microbial systems. Various biological components in complex matrices such as blood and urine, as well as dynamic changes in the detection microenvironment, will generate strong background noise interference, directly degrade the signal quality of Raman spectroscopy, and further increase the difficulty of extracting pathogen characteristic information.

In the detection of complex clinical infection samples, hemoglobin and albumin in blood, metabolites and inorganic salts in urine, and residual medium components from sample pretreatment will all produce strong spontaneous fluorescence background under laser excitation [4]. The intensity of this fluorescence background is usually much higher than that of Raman scattering signals, which will directly mask the characteristic Raman peaks of pathogens, especially the weak signals corresponding to low-abundance drug resistance markers, making effective information almost unrecognizable in the original spectrum. Even enhanced Raman scattering technology will suffer a significant decline in signal recognition ability when facing clinical samples with high fluorescence background [5]. This problem cannot be completely solved only by hardware optimization, and effective fluorescence background subtraction and signal restoration must be realized with the help of algorithms.

2.4. Spectral drift and broadening caused by microenvironment (pH, humidity)

Raman spectroscopy detection results are highly sensitive to the microenvironment of samples. Fluctuations in pH value and humidity changes of clinical samples will directly alter the intracellular molecular conformation of microorganisms, thereby causing drift and broadening of Raman spectral lines [6]. Spectral drift will make the position of characteristic peaks deviate from the standard reference range, and spectral broadening will further aggravate the overlap of characteristic peaks. The combined effect of the two significantly reduces the specificity and repeatability of spectra. Such microenvironment-induced spectral distortion will lead to different spectral characteristics of the same pathogen under different detection conditions, and even reduce the spectral differentiation between drug-resistant and sensitive bacteria. It brings great interference to subsequent pathogen

identification and drug resistance analysis, and also puts forward higher requirements for the anti-interference and spectral correction capabilities of algorithms.

2.5. Weak signal problem of low-concentration pathogens

In the early stage of complex infection, the concentration of pathogens in clinical samples is extremely low, and the Raman scattering signals they generate are very weak. Coupled with the dual interference of biological components and matrix, the detection of low-concentration pathogens has become another core problem for Raman spectroscopy technology.

2.6. Challenge of detection limit for bacterial metabolites in early infection samples

In the early stage of infection, there are a small number of pathogens in clinical samples, and the concentration of drug resistance-related metabolites secreted by them is far below the conventional detection limit of Raman spectroscopy. These metabolites are an important basis for judging the drug resistance phenotype of pathogens, but due to their extremely low signal intensity, they are easily submerged by noise in the complex spectral background, making accurate detection difficult. Even single-cell Raman spectroscopy technology can hardly break through the detection limit when facing the weak metabolic signals of a small number of pathogens in early infection samples [7], and cannot capture early molecular changes related to drug resistance in time. This has also become a key bottleneck for the application of Raman spectroscopy in early infection diagnosis.

2.7. Contradiction between improving signal-to-noise ratio (SNR) and maintaining spectral feature integrity

To address the weak signal of low-concentration pathogens, conventional methods usually improve the spectral SNR by extending detection time, increasing laser power or adopting signal enhancement algorithms, but all these methods have obvious limitations. Extending detection time and increasing laser power may damage microbial cells, alter their molecular structure and destroy the integrity of spectral features; while traditional signal enhancement algorithms tend to over-smooth the spectrum while improving SNR, resulting in the loss or distortion of characteristic peaks related to drug resistance markers [8]. This contradiction between improving SNR and maintaining spectral feature integrity puts Raman spectral analysis of low-concentration pathogens in a dilemma. Only through high-precision algorithm design can we effectively improve SNR while maximally retaining the original characteristic information of the spectrum.

3. Applications of deconvolution and artificial intelligence algorithms in spectral analysis

In complex infection samples, Raman spectra are often affected by fluorescence background, random noise, peak overlap and instrument drift at the same time, resulting in the masking of effective information in original spectra. Especially in complex matrices such as blood, urine and sputum, drug resistance-related signals often manifest as weak peak shifts or intensity changes, which are difficult to stably identify only by manual observation. Therefore, in recent years, researchers have gradually established a complete calculation workflow of "deconvolution preprocessing – feature extraction – pattern recognition – interpretable analysis", so as to improve the analytical accuracy and clinical applicability of Raman spectra from complex samples.

3.1. Deconvolution algorithms

Commonly used deconvolution methods include Fourier deconvolution, Wiener deconvolution, Richardson–Lucy (RL) iterative algorithm, blind deconvolution, and peak fitting methods based on Gaussian, Lorentzian or Voigt functions. Fourier deconvolution has fast calculation speed and is suitable for batch spectral processing; the Wiener algorithm achieves a good balance between denoising performance and stability; the RL algorithm can effectively restore narrow peak details through iterative optimization; blind deconvolution does not require preset peak shape parameters, and is more suitable for samples with complex components and insufficient prior information such as microorganisms; Voigt fitting can accurately calculate peak area, full width at half maximum and peak position changes [5].

The Fourier-space deconvolution method proposed by Wahab et al. outperforms traditional manual fitting methods in noise suppression, peak shape fidelity and artifact control. For microbial Raman spectra, this type of algorithm can effectively separate nucleic acid-related peaks (785 cm^{-1}), phenylalanine peaks (1003 cm^{-1}), lipid CH_2 bending vibration peaks (1450 cm^{-1}) and protein amide I peaks (1655 cm^{-1}), significantly improving the detectability of subtle spectral changes related to drug resistance. Therefore, deconvolution is not only a spectral preprocessing step, but also determines the quality of information available for subsequent machine learning models, serving as the foundation of the entire analysis workflow.

3.2. Traditional machine learning

After baseline correction, normalization and deconvolution, traditional machine learning methods can be used for dimensionality reduction, feature selection and classification of high-dimensional Raman spectra. Due to the common problems of limited sample size, high variable dimension and class imbalance in microbial Raman research, traditional machine learning is still the most widely used and stable analytical method at present.

Principal component analysis (PCA) extracts the main variance information in data through linear transformation, which can effectively reduce dimensions and eliminate redundant variables. Linear discriminant analysis (LDA) achieves classification by maximizing inter-class differences. Support vector machine (SVM) is suitable for small-sample high-dimensional data, and shows high accuracy and good generalization ability when dealing with nonlinear boundaries. Random Forest improves robustness through ensemble learning of multiple decision trees, and can screen key spectral regions according to feature importance. Gradient boosting models such as XGBoost have also been widely used in pathogen identification and drug resistance prediction in recent years.

Xu et al. used the PCA-SVM model to analyze single-cell Raman spectra and realized rapid identification of various bacteria, with classification accuracy significantly higher than that of traditional statistical methods. Random Forest is often used to screen characteristic wavenumbers closely related to drug resistance phenotypes, helping researchers locate potential biological markers. Compared with deep learning, traditional machine learning has lower requirements for data scale, fast model training and good interpretability, so it still has important application value in small and medium-sized clinical studies.

3.3. Deep learning

Traditional machine learning usually relies on manually designed features, while deep learning can automatically extract multi-level nonlinear features directly from original spectra, showing

significant advantages in dealing with complex backgrounds and weak differential signals.

Convolutional neural network (CNN) identifies peak structures through local convolution kernels, and is currently the most widely used model in Raman spectral analysis. Residual Network (ResNet) alleviates the training difficulty of deep networks through skip connections, and is suitable for complex pattern recognition [9]. Autoencoders can realize unsupervised denoising and feature compression. Generative adversarial networks (GAN) and diffusion models can be used for data augmentation and spectral reconstruction to alleviate the problem of insufficient sample size. In recent years, the Transformer architecture has also been applied to Raman spectral analysis, which can capture the correlation between distant spectral regions.

The super-resolution generative adversarial network (SRGAN) constructed by Ma et al. can shorten the acquisition time of single-cell Raman spectra by 10 times while maintaining a classification accuracy of 94.9%. The deep learning-based reconstruction method proposed by Zhou et al. significantly improves SNR while retaining key peak shape details. Compared with traditional methods, deep learning has stronger adaptability in scenarios with complex matrix interference, low SNR and large-scale data analysis. However, it has higher requirements for training data scale and computing resources, and the decision-making mechanism of the model is usually not transparent enough.

3.4. Multi-algorithm fusion

To further break through the limitations of single algorithms, the multi-algorithm hybrid fusion framework has become a research hotspot in spectral analysis in recent years. Through complementary advantages of different technologies, the overall performance of spectral analysis is comprehensively improved. Single deconvolution can only complete spectral preprocessing, and both traditional machine learning and single deep learning have the problem of single-dimensional feature extraction, which cannot take into account multi-dimensional information in both time and frequency domains. The multi-algorithm hybrid model combines Fourier transform, temporal networks and convolutional network structures, simultaneously mines temporal changes and frequency domain features of Raman spectra, and performs multi-dimensional information fusion analysis, which greatly improves the recognition accuracy of complex systems [10]. The multi-model fusion idea is also applicable to clinical pathogen detection. Combining convolutional neural networks with feature weight analysis can directionally screen drug resistance-related specific spectral intervals and enhance the recognition efficiency of key markers, which has good application effects in spectral diagnosis of clinical samples [11]. The hybrid model effectively balances the demands of denoising, unmixing, feature mining and intelligent classification, providing complete algorithm system support for accurate detection of infectious pathogens.

4. Current status of clinical applications

4.1. Rapid species identification of multidrug-resistant bacteria

Surface-enhanced Raman scattering technology provides an ultra-high-sensitivity solution for drug-resistant bacteria identification. The combination of CRISPR-based specific gene recognition and SERS signal enhancement enables direct detection of multidrug-resistant pathogens without nucleic acid purification and PCR amplification. Combined with magnetic nanoparticle separation, on-site capture and in-situ detection of multidrug-resistant bacteria can be realized [12].

The core principle of using SERS to detect carbapenemase-producing strains is that carbapenemase produces identifiable unique spectral fingerprint changes when catalyzing the hydrolysis of carbapenems, and accurate detection of drug-resistant strains can be achieved by capturing this change [13]. Portable Raman spectrometers can quickly record the development of drug resistance in *Salmonella typhimurium* under cefotaxime exposure. Studies have found that the relative Raman intensity of I-990/I-1348 has a very strong positive linear correlation with the minimum inhibitory concentration (MIC) value ($R^2=0.9962$), which can be used for quantitative evaluation of drug resistance [14].

4.2. Paradigm innovation in phenotypic antimicrobial susceptibility testing

Stimulated Raman scattering imaging combined with heavy water metabolic labeling is an important breakthrough in rapid drug susceptibility testing. By using stimulated Raman scattering imaging to track the metabolic incorporation of D₂O in bacteria, the metabolic signal of a single bacterium can be detected in only 10 minutes, and results can be obtained within ≤ 2.5 hours in total. It can be directly applied to complex clinical samples such as urine and whole blood [15]. The study proposed and measured the single-cell metabolic inhibitory concentration, which is highly consistent with the clinical standard MIC [16].

This method covers 8 bacterial species and 14 antibiotics, with strong clinical representativeness [17]. By combining SRS metabolic imaging with bacterial morphological changes, the dual-index joint judgment achieves a classification consistency rate of 93.2% for 103 *Escherichia coli* strains, improving the accuracy and robustness of drug susceptibility testing [18].

4.3. In-depth analysis of drug resistance mechanisms

The combination of SERS and artificial intelligence provides a new tool for drug resistance mechanism research. Through spectral feature extraction and artificial intelligence model training, drug resistance phenotypes or genotypes can be efficiently identified, providing a basis for clinical precise medication [19].

4.4. Case analysis of in-situ detection for clinical samples

Table 1 compares the clinical application performance of different detection methods. The CRISPR-SERS combined technology does not require nucleic acid purification or PCR amplification, and can directly detect original clinical samples [12]. The SRS-D₂O metabolic imaging technology realizes rapid drug susceptibility testing within 2.5 hours at the single-cell level, and is suitable for complex matrices such as urine and whole blood. The liquid core optical fiber enhancement technology can effectively solve the problem of weak signals. The SRGAN-enhanced Raman technology shortens the acquisition time by 10 times through deep learning, and the recognition accuracy reaches 94.9% [7].

Table 1. Comparison of clinical application of different detection methods

Method	Detection Time	Key Performance	Sample Type	Main Advantages
Traditional culture + drug susceptibility testing	24-72h	Gold standard	Pure colonies	Reliable results

Table 1. (continued)

CRISPR-SERS combination	1-2h [12]	High sensitivity	Original clinical samples	No nucleic acid purification, no PCR amplification
SRS-D ₂ O metabolic imaging	≤2.5h [15]	Consistent with MIC	Urine, whole blood	Single-cell level, direct detection
Liquid core optical fiber enhanced Raman	Rapid [5]	SNR increased by 15.3 times [5]	Synovial fluid and other body fluids	Solves the problem of weak signals
SRGAN-enhanced Raman	Acquisition time shortened by 10 times [7]	94.9% accuracy [7]	Single cell	Deep learning improves performance
Microfluidic-Raman combination	Rapid [20]	High sensitivity, high throughput, non-destructive	Biological samples, cells, clinical samples	Integrates microfluidic automatic manipulation and SERS high sensitivity
Raman flow cytometry	Stable operation for about 10h [21]	Throughput ≈ 600 cells/min, accuracy > 90% [21]	Microbial suspension, single cell	Label-free, high throughput, live cell sorting, activity retention

5. Conclusion and prospects

Artificial intelligence-enhanced Raman spectroscopy is ushering in a new era of medical microbiology. By capturing the complete biochemical profile of microbial cells, this label-free, non-destructive and culture-free technology can realize species identification, drug susceptibility testing and phenotypic characterization at single-cell resolution.

In terms of technical breakthroughs, liquid core optical fiber enhancement solves the problem of weak signals, deep learning algorithms realize rapid spectral restoration and enhancement, and blind deconvolution methods provide tools for component analysis of complex biological samples. In terms of clinical application, the CRISPR-SERS combined technology realizes in-situ capture and detection of drug-resistant bacteria, and SRS-D₂O metabolic imaging shortens drug susceptibility testing time to less than 2.5 hours, providing a feasible solution for clinical precise medication.

Current research still faces three major challenges: first, overfitting risk. When models are trained on single-center or small-sample datasets, they may learn non-biological features rather than generalized drug resistance patterns [19]; second, the "black box" problem. Although most machine learning models can accurately predict drug resistance phenotypes, their decision-making process is difficult to interpret; third, the lack of multi-center, large-sample clinical validation studies.

Future development directions should focus on building large-scale multi-center Raman spectral databases and carrying out prospective clinical validation; developing interpretable algorithms to associate spectral features with specific biochemical signals; promoting the R&D and integration of portable Raman devices to realize point-of-care testing in resource-limited settings. With the continuous integration of photonic technology and artificial intelligence, Raman spectroscopy is expected to become a transformative tool for decoding microbial complexity and provide new solutions for addressing the global crisis of drug-resistant bacteria.

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