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REVIEW/DERLEME

Artificial Intelligence Applications In Clinical Microbiology Laboratory

Klinik Mikrobiyoloji Laboratuvarinda Yapay Zeka Uygulamaları

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Abstract

Artificial intelligence applications are becoming an increasingly important component in clinical microbiology, as in other medical fields. Development of these applications in the microbiology laboratory; has been identified as having the potential to improve the turnaround time, quality and cost of a test. In the laboratory, various technologies are used in artificial intelligence, medical microbiology and diagnostic tests of infectious diseases, image analysis and MALDI-TOF-MS to support decision-making, identification and antimicrobial susceptibility tests. Rapid diagnosis of infections and antimicrobial susceptibility testing applications have entered a rapid development trend with artificial intelligence. Modern artificial intelligence (AI) and machine learning (ML) methods demonstrate comparable performance on an individual (personnel) basis. These applications combine these technologies, including in vitro diagnostics, and help accelerate processes within laboratory medicine more broadly. These technologies are developing rapidly, but there are still issues that need to be improved and supported. We need to further establish best practices and improve our information system and communications infrastructure to promote the application of reliable and advanced machine learning-based technologies. Participation of the clinical microbiology laboratory community is important to ensure that laboratory data are sufficiently accessible and incorporated into robust, safe, and effective ML-supported clinical diagnostics. This process and method will be possible in the modern age with technological advances and widespread digitalization of health information. This review aims to provide information about the subfields of AI and ML in the clinical microbiology laboratories.

Keywords: Microbiology, Artificial intelligence, Machine-learning

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Öz

Yapay zeka uygulamaları, diğer medikal alanlarda olduğu gibi klinik mikrobiyoloji alanında da giderek daha önemli bir bileşen haline gelmektedir. Mikrobiyoloji laboratuvarında bu uygulamaların geliştirilmesi; bir testin geri dönüş süresini, kalitesini ve maliyetini iyileştirme potansiyeline sahip olduğu belirlenmiştir. Laboratuvarda yapay zeka, tıbbi mikrobiyoloji ve enfeksiyon hastalıklarının tanı testlerinde çeşitli teknolojiler, görüntü analizleri ve MALDI-TOF-MS ile karar verme, tanımlama ve antimikrobiyal duyarlılık testlerini desteklemek amacıyla kullanılmaktadır. Enfeksiyonların hızlı tanısı ve antimikrobiyal duyarlılık testi uygulamaları yapay zeka ile hızlı bir gelişme trendine girmiştir. Modern yapay zeka (AI) ve makine öğrenimi (ML) yöntemleri, kişisel (personel) bazda performans özellikleriyle karşılaştırılabilecek performans sergilemektedir. Bu uygulamalar, in vitro teşhisler de dahil olmak üzere bu teknolojileri birleştirir ve daha geniş anlamda laboratuvar tıbbı içerisinde süreçleri hızlandırmaya yardımcı olur. Bu teknolojiler hızlı gelişim göstermektedir, ancak hala iyileştirilmesi ve desteklenmesi gereken konular bulunmaktadır. Güvenilir ve gelişmiş makine öğrenimi tabanlı teknolojilerin uygulanmasını teşvik etmek için en iyi uygulamaları daha fazla oluşturmamız ve bilgi sistemimizi ve iletişim altyapımızı geliştirmemiz gerekiyor. Klinik mikrobiyoloji laboratuvar topluluğunun katılımı, laboratuvar verilerinin yeterince erişilebilir olmasını ve sağlam, güvenli ve etkili ML destekli klinik tanılara dahil edilmesini sağlamak için önemlidir. Bu süreç ve yöntem, modern çağda, teknolojik ilerlemeler ve sağlık bilgilerinin yaygın biçimde dijitalleştirilmesiyle mümkün olacaktır. Bu derlemede, klinik mikrobiyoloji laboratuvarlarında AI ve ML'nin alt alanları hakkında bilgi verilmesi amaçlanmaktadır.

Anahtar Kelimeler: Mikrobiyoloji, Yapay zeka, Makine öğrenimi

INTRODUCTION

Artificial intelligence is a process that involves the combination of various technologies such as machine learning, deep learning, neural networks, natural language processing, reasoning and perception. Machine learning is an artificial intelligence application that makes new interventions and learns new things by comprehensively analyzing defined data. Machine learning methods find systemic problems and produce solutions within the scope of artificial intelligence. Machine learning methods are generally categorized as unsupervised and supervised. Supervised machine learning algorithms can adapt past learning to new data by using labeled examples to predict future events. The analysis starts from a known training dataset and the algorithm is learned to make predictions about the output values. The output can be compared with the correct one, errors can be found. For unsupervised machine learning, the algorithm has no predefined knowledge or experience (1).

The convolutional neural networks (CNNs) are applied to the detection, segmentation and recognition of objects and regions in images. Recent uses of CNNs are traffic sign recognition, the segmentation of biological images,, and the detection of faces, text, pedestrians and human bodies in natural images (2). AlexNet, Clarifai, VGG, and GoogleNet are the most popular CNNs in machine learning applications (3)

In medicine, data-driven technologies can be

applied, especially when the data has a high level of automation and standardization (4). In this sense, significant advances have also been reported in clinical microbiology, but their translation into routine practice remains a long process. various technical and regulatory hurdles. Some of the low hanging fruit for diagnostic scenarios include (i) automated analysis of images such as panels (5,6), (ii) automated analysis of images such as microscopy slides or agar plates. (7,8) and (iii) correlating genome sequences and proteomic profiles with pathogen phenotypes (9). Clinical applications require standardized data formats, ontologies with an interoperable information technology environment (10), infrastructure with sufficient storage and computational capacity, and technical expertise to meet the needs of microbiologists and infectious disease specialists.

Identifying the needs for microbiological digital data will support clinical evaluation of patients, personalization of diagnoses and treatments, improving the quality of digital data and thus reducing healthcare costs. Digital microbiology will also have the potential to impact public health and pathogen surveillance. To improve digitalization, microbiology laboratories need to establish the basic infrastructure that includes perception, knowledge and infrastructure on all aspects of data processing in digital medicine (12,13).

Artificial intelligence applications are generally defined as computer systems that perform tasks such as visual perception, speech recognition and decision-making, and play an important role in diagnosis, treatment and other healthcare industry fields (14,15) . The components of artificial intelligence applications are mainly defined as follows;

1. Machine learning methods

Unsupervised machine learning methods include simple clustering and correlation of samples, and visualization techniques such as heat maps, coordination or networks, that allow patterns in the data to be revealed graphically. Supervised methods include statistical methods, such as multivariate analysis of variance (ANOVA) for direct hypothesis testing of differences between groups, or machine learning classifiers that train models to label groups of samples (random forests or support vector machines) (16). Supervised learning methods are classified as classification and regression. The differences between supervised and unsupervised machine-learning are shown figure.1.

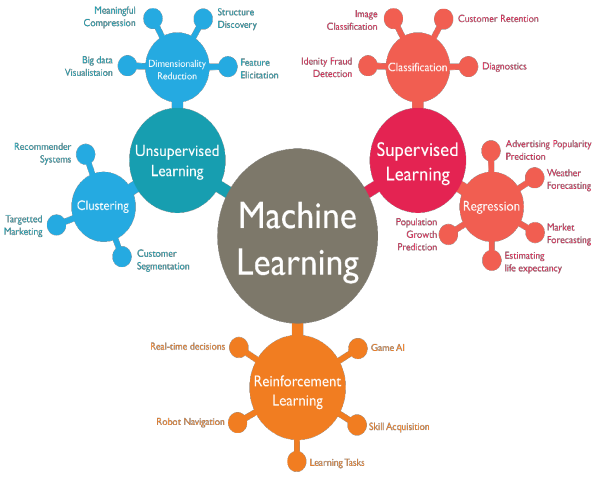

Figure 1. The difference and relationship between machine learning groups. (Alyshai Nadeem, Machine Learning, 2022)

Support vector machines (SVMs), random forests (RFs), Lasso, and Elastic Net (ENet) are examples of systems used as supervised machine learning classifiers for microbiome research. As a supervised machine learning method, support vector machine (SVM)

determines a linear or nonlinear separating surface on a given data set to create the largest distance or margin to the closest training data points of any class. Random forests (RF) is a supervised classification that uses a collection of unpruned decision trees, each built on a bootstrap sample of training data using a randomly selected subset of features. However, the correct feature prediction rate is an important factor for the validation of machine learning methods. For example, similar correct trait prediction rates have been demonstrated for machine learning methods in most microbiome studies (17).

2. Artificial neural network (ANN) and Deep learning (DL):

Artificial neural networks (ANN) are an algorithmic system that works similar to biological neurons. It includes an input vector of numerical values multiplied by weights (like dendrites in a neuron), an activation function applied to the sum of weighted input vectors (like a cell body), and an output-generating function (like an axon). To solve a complex problem, multiple hidden layers are added to the neural network model (18).

The data size can be expanded or reduced, the data size can be expanded or reduced by increasing or decreasing the number of nodes in the middle layers (hidden layers). Thus, classification analysis can be performed on big data. Deep learning (DL) is the application of a neural network modeling technique consisting of many layers.

There are important points to consider when collecting and sharing data; Data developers must ensure that patients are well informed and their consent is obtained, and must take into account various national and international laws that protect the privacy of health information (20).

3. Laboratory automation, informatics, and artificial intelligence

In clinical microbiology, the term «Total Laboratory Automation» (TLA) is used to describe the automation of the entire diagnostic workflow: inoculation of agar plates, incubation, reading of culture results, identification (ID), and antimicrobial susceptibility testing (AST). All these steps in a traditional laboratory are usually performed manually with a sample-centric approach. Two laboratory automation (LA) systems are currently available: the BD Kiestra™ system (Becton Dickinson, Sparks, MD) and the WASPLab system (Copan Diagnostics, Murrieta, CA) (21). AI applications in healthcare and correlations between fields are shown in figure 2.

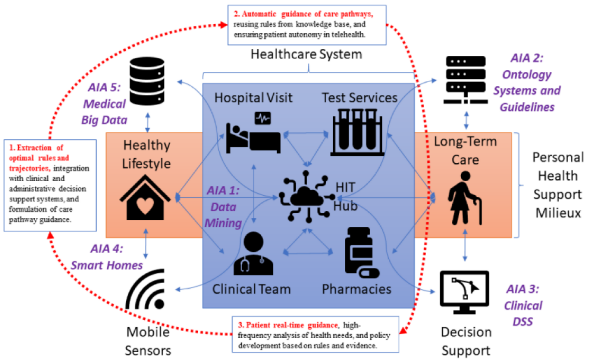

Figure 2. Patient-centric framework for healthcare artificial intelligence and analytics (AIA). (Source: Inspired by (Barr, V.; Robinson, S. Hosp. Q. 2003, 7, 73–82), based on (Wagner, E.H.; Austin, B.T. Improving Chronic Illness Care: Translating Evidence Into Action. Health Aff. 2001, 20, 64–78))

Advanced, sophisticated technologies such as mass spectrometry and molecular diagnostics allow rapid diagnosis of infections (22), but they need to be viewed as complementary to traditional growth-based diagnostics. Applications for

laboratory automation and intelligent use of informatics also have a transformative effect on microbiology diagnostics. These tools have the potential to accelerate clinical decision-making and positively impact the management of infections, improve patient outcomes, and facilitate diagnostic and antimicrobial stewardship (ED) programs (23). However, these technologies require modification of well-established workflow practices. Additionally, these techniques will have an impact on patient and hospital management, as well as automation and informatics (Figure 3) (24).

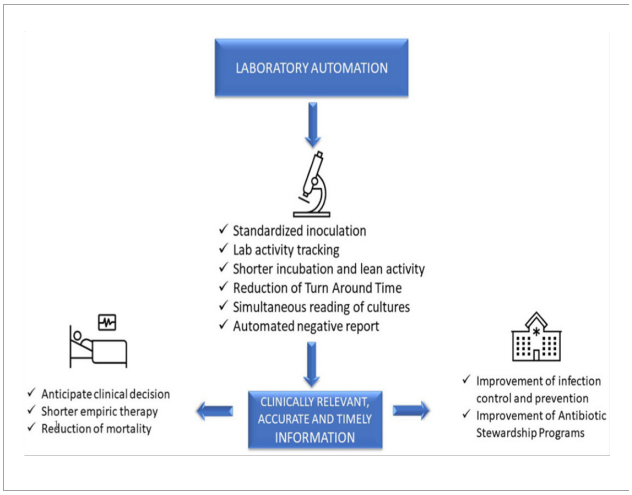

Figure 3. Impact of automation on laboratory, patient and hospital management (Mencacci A, De Socio GV, Pirelli E, Bondi P, Cenci E. Laboratory automation, informatics, and artificial intelligence: current and future perspectives in clinical microbiology. Front Cell Infect Microbiol. 2023 Jun 27;13:1188684. doi: 10.3389/fcimb.2023.1188684. PMID: 37441239; PMCID: PMC10333692).

4. Artificial Intelligence (AI) and its basic implementations in microbiology laboratories

4.1. Artificial Intelligence (AI) in Infection Disease Diagnosis and Disease Preventation

Artificial intelligence supports clinicians in clinical decision-making processes. Using data collected from electronic health records (EHRs), it can be predicted which hematological patients with febrile neutropenia will have multidrug-resistant Gram-negative bacillus (MDR-GNB) infections. Advantages of EHRs; Central storage of all patient data and faster access to patient care and test results. The risk of contracting a multidrug-resistant infection is associated with several factors, such as history of antibiotic use, hospital environment, and the patient›s microbiota status (26). Artificial intelligence programs for early detection of infectious diseases

They have been accepted as important systems and have become one of the basic systems in the management of infectious diseases, as seen in Figure 4. (Source: Kaur, İ., Behl, T., Aleya, L. et al. Artificial intelligence as a fundamental tool in the management of infectious diseases and its current application in the COVID-19 pandemic. Environ Sci Pollut Res 28, 40515–40532 (2021) .-021-13823-8)

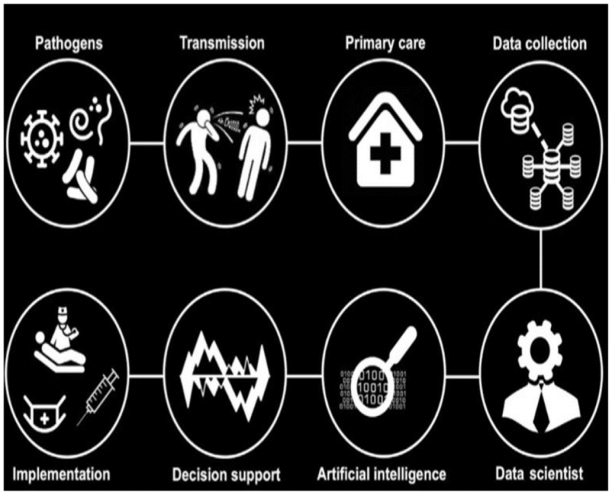

Figure 4. AI and infectious diseases management.

4.2. Role of Artificial Intelligence (AI) For Fighting With Covid-19 Disease Outbreak

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China, in December 2019 and declared a pandemic by the World Health Organization (WHO) has been made in March, 11 2020 (27). Human-to-human transmission of SARS-CoV-2 occurs primarily through droplets, respiratory secretions, and direct contact (7). Rapid diagnosis of patients with COVID-19 disease is important in terms of rapid implementation of disease treatment and patient isolation. Virus-specific reverse transcriptase polymerase chain reaction (RT-PCR) test is routinely used in the diagnosis of COVID-19 Disease. Unfortunately, the 6-48 hour turnaround time and false negative results can cause a delay in treatment and increase the risk of person-to-person transmission of the disease (28). Recently, artificial intelligence algorithms have begun to be used for the early detection of SARS-CoV-2 (29).

It was thought that robotics could be used to control epidemics. Robots will play an important role in diagnosing, treating and preventing the transmission of Covid-19 disease in hospitals, workplaces and streets, as they do not need masks and do not get sick. (30). As an example of an application for this situation, the drawing of the artificial intelligence-based diagnostic aid system proposed for simultaneous recording, detection and classification of cough features using fuzzy logic methods is shown in figure 5 (Source: Ön Med., March 31, 2021 Department Infectious Diseases - Surveillance, Prevention and Treatment, Volume 8-2021 https://doi.org/10.3389/fmed.2021.585578).

As examples of other robot systems; Robots developed by UBTech Robotics can remind people to wash their hands and wear a mask. AIMBOT, on the other hand, provides support for body temperature monitoring, crowd density monitoring, information broadcasting and environmental disinfection (31). Lifeline robotics developed the fully automatic swabbed robot. This robot uses computer vision and machine learning to identify the perfect target spot on a person›s throat. A long-rod robotic arm moves to collect the sample without person-to-person contact (32).

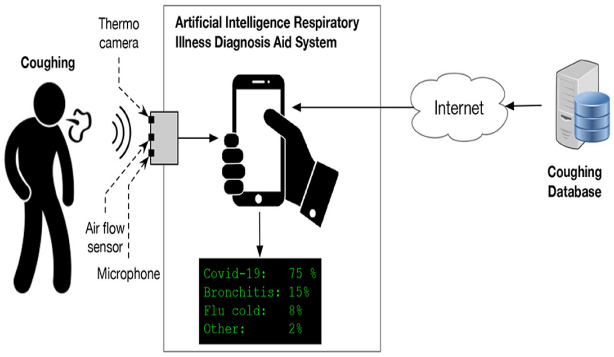

Figure 5. Illustration of the proposed AI-based diagnosis aid system for simultaneously recording, detecting, and classifying cough characteristics using fuzzy logic methods.

5. Machine Learning in Clinical Microbiology Laboratory and Applications used for Microbial Identification

Bacterial infections are often the leading cause of death. Rapid diagnosis is important for early treatment of these infections. MS (Mass spectrometry)-based techniques used to identify microorganisms are: Matrix-assisted laser desorption ionization time-off light mass spectrometry (MALDI-TOF MS) and Vitek-MS (33).

MALDI-TOF MS is a rapid and cost-effective method to refine the identification of microorganisms in clinical samples. The basis of the MALDI-TOF MS method is to analyze ribosomal proteins that are characteristic of a particular organism, family, genus,

species and strain. This technology was first developed in the 1980s. Until the last few years, it could not be introduced into routine microbiology laboratories due to the lack of adequate databases covering all pathogenic species and the differences and similarities in mass spectral patterns not being fully consistent with established taxonomy (34). The advent of new technologies such as matrix-assisted laser desorption time of flight mass spectrometry (MALDI-TOF MS) has provided faster and more reliable results in analyzing and identifying microorganisms (Figure 6). (Source: Han, S.-S.; Jeong, Y.-S.; Choi, S.-K. Current Scenario and Challenges in Direct Identification of Microorganisms Using MALDI-TOF MS. Microorganisms 2021, 9, 1917. https: //doi .org/10.3390/ microorganisms9091917)

The resulting mass spectra are characteristic for a particular type of microorganism, called a fingerprint. The MALDI-TOF MS system also allows analysis of peak intensity, quantification, and peak correlation and comparison of mass spectra of a particular living organism with spectra in an existing mass spectral database. The number of peaks is specific that are characteristic for the genus and/or species of microorganisms (35).

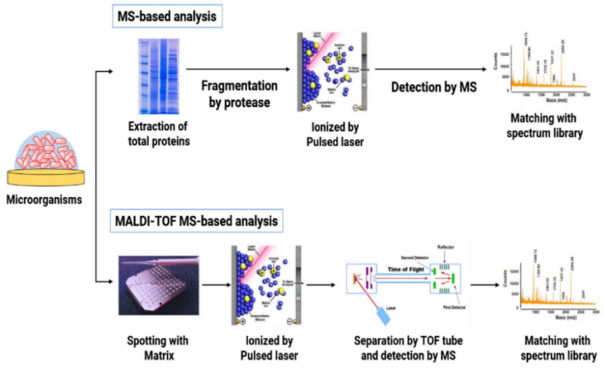

Figure 6. The roles of MALDI TOF-MS and MS operation in microorganisms identification.

While MALDI-TOF MS has been applied to bacterial colonies growing on culture plates, recent advances in this technology have enabled direct analysis of clinical samples without the need for existing culture or subculture. On the other hand, rapid identification of bacteria by MALDI-TOF MS in positive blood culture bottles allowed rapid inclusion of relevant diagnosis and treatment for patients (36). Because blood culture bottle media contains a variety of nonbacterial proteins that can lead to misinterpretation of bacterial proteome profiles, pretreatment (through purification of bacterial pellets and short-term subcultures (microcolonies)) is necessary for accurate identification of pathogenic microorganisms. Commercially available protocols to extract host proteins and blood cells: Sepsityper® kit (Bruker Daltonics), VITEK® MS blood culture kit (bioMérieux), and rapid BACpro® II kit (Nittobo Medical Co., Tokyo, Japan) also concentrate microorganisms. It can be used for successful identification (37).

6. Applications used for Antibiotic Susceptibility Testing (AST)

Current international AST reference methods are broth microdilution (BMD), which can be used to obtain the minimum inhibitory concentration (MIC) of antibiotics for individual microorganisms. BMD takes 18-24 hours after primary isolation of bacteria from clinical specimen culture. Application of the ensemble machine learning algorithm to PIC (predictive inhibitor concentration) results generated with FAST (Flow Cytometry Method of Antimicrobial Susceptibility Testing) data on the same business day. MALDI-TOF MS combined with FCM (Flow cytometry) is applied to

quickly identify the pathogen and antibiotic susceptibility testing. With the MALDI-TOF MS method, bacterial identification time can be reduced to one hour and AST time to two hours (total report time up to 3 hours from 36-72 hours or more). The FAST method is not currently available in routine microbiology laboratories. However, after having comprehensive data or adapting PICs to MICs, this work will be in the laboratory. AI applications combine original algorithms using machine learning (ML) and image processing with a rule-based expert system for automatic AST analysis (Figure 7).

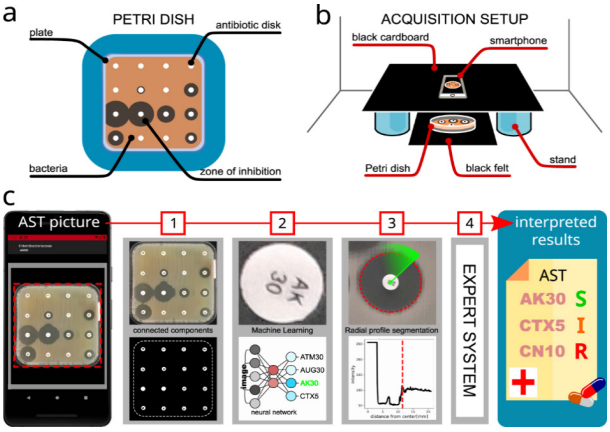

Figure 7. A prepared and incubated Petri dish (a) is positioned in a simple image acquisition setup made of cardboard (b), the researchers used two containers available in the laboratory as stands. A picture of the plate is taken with a smartphone and the analysis follows the workflow described in (c): the Petri dish image is cropped and the antibiotic disks are found (c1); the image of each antibiotic disk is fed to a ML model that identifies the antibiotic (c2); the diameter of the inhibition zone is measured (c3) with an original algorithm. After all, the Expert System uses the diameters to output interpreted results (c4). (Pascucci, M., Royer, G., Adamek, J. *et al.* AI-based mobile application to fight antibiotic resistance. *Nat Commun* 12, 1173 (2021). https://doi.org/10.1038/s41467-021-21187-3)

Recently, a direct-on-target microdroplet growth assay (DOT-MGA) has been proposed as a rapid universal phenotypic AST method. This method is easy to implement and perform by incubating the microbial suspension as microdroplets directly MALDI targets with and without antibiotics. After measurement, the results are evaluated by a software with simple algorithm. The method is resistance mechanism independent and close to the CLSI and ISO broth microdilution standards and can be extended to further applications, such as susceptibility determination directly from clinical specimens (for blood culture bottles) and simultaneous testing of multiple antibiotics. It also has the automation capability to allow high-throughput testing (39).

7. Using Artificial Intelligence (AI) To Study Host-Pathogen interactions

The human microbiome plays an important role in maintaining human health and associated with many clinical conditions such as inflammatory bowel disease, metabolic syndrome and obesity, antibiotic associated diarrhoea, pregnancy, neurological disorders, cardiovascular disease and cancer (40). Currently, there are high-throughput technologies that enable genus and species level sequencing and classification of microorganisms living in the human body (genomic sequencing of bacterial 16S ribosomal RNA (rRNA), shotgun sequencing, internal transcription separator and the IS-pro technique). These approaches enable ideally genomic analyzes of all microbes in a sample, whether culturable or nonculturable (41). Shotgun sequencing is used to profile taxonomic composition and functional potential of microbial communities and to recover whole genome sequences whereas 16S rRNA gene sequencing profile selected organisms or single marker genes. Determining which microorganisms are metabolically active and which microbial genes are actively

expressed is called as metatranscriptomics. The analysis of proteins and metabolites is referred to as metaproteomics and metabolomics, respectively (42).

Some researchers have focused on five tasks to understand vector-host-pathogen interactions when assessing the strengths and weakness of machine learning applications. These tasks include: (1) prediction-to assess the continuous trends or deterministic responses in each relationship; (2) classification-to identify meaningful classes governing the interactions and the responses of each component in the relationship; (3) clustering–to detect functional patterns interesting to the interaction ecosystem; (4) association rules mining / hypothesis generation to provide formal validation of existing hypotheses, propose new ones, and evaluate their pertinence regarding the vector-host-pathogen relationship; and (5) deep learning-to provide a multi-level organization of different dataset modalities involved in the vector-host-pathogen systemic relationship (Fig. 8). (Source: Diing D.M. Agany, Jose E. Pietri, Etienne Z. Gnimpieba, Assessment of vector-host-pathogen relationships using data mining and machine learning, Computational and Structural Biotechnology Journal,Volume 18,2020, Pages 1704-1721, ISSN 2001-0370, https://doi.org/10.1016/j.csbj.2020.06.031.)

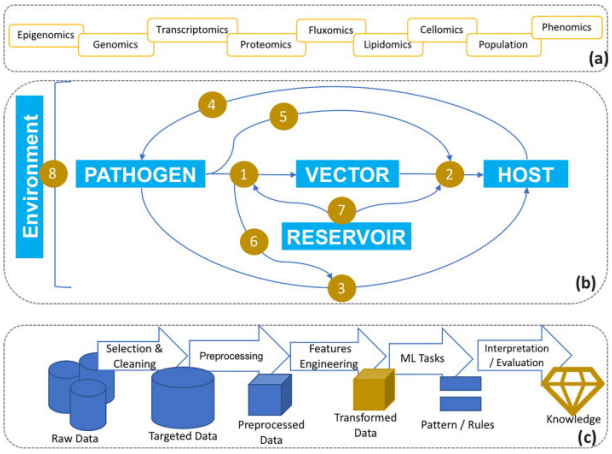

Figure 8. Overview of Systems Bioscience (a) of vector-host-pathogen relationships (b) of Data Mining and Machine Learning processes (c) emphasizing the information flow and interwinding nature of the subject matter in relationship to tools used in the review papers.

Diagnosing diseases with machine learning (ML) methods is rapidly being adopted in microbiome studies. Where traditional statistical approaches are useful for identifying cases in which a single organism is associated with a disease, ML methods can include the structure of the microbial communities as a whole and identify relationships between community structure and disease status. Unfortunately, ML models have not yet been fully adopted because of microbiome data are complex, and traditional ML methods are limited by the representation ability of the models and can not learn complex patterns from the data (43). However, it is worth mentioning that, there are Human Microbiome important resources for algorithm developers such as The project, the ENCODE project consortium (44). The NIH Human Microbiome Project analyzed microbiome and host activities in longitudinal studies of disease-specific cohorts as follows: creating multi-omic

datasets (45). Here, multivariate statistics and machine learning are used as post-processing tools.

DISCUSSION

The main reason to for automating in a laboratory is to increase productivity and minimized to face limited budgets and personnel shortages. However, implementation of LA may represent an exceptional opportunity to change laboratory organization, improve quality, and reduce TTR, with a potential positive impact on laboratory, patient, and hospital management (46).

One of the LA's most interesting innovations concerns the read phase, which offers the possibility to simultaneously read all inoculated plaques from one of more samples from the same patient. Moreover, taking advantage of informatics, it is also possible to display patient's microbiological, hematological, and even clinical and therapeutic data by using informatics while reading the plates. This patient-oriented approach provides meaningful clinical interpretation of results and decision-making (47).

By constantly monitoring all the analytical steps, LA lets that the microbiologist knows the work to be done in real time. This concept entirely dependent fully on the so-called "lean" organization, which is increasingly applied to healthcare processes originally envisioned for industry (48). "Lean" means doing only valuable activities, without any delay, avoiding "waste" or unnecessary work. This represents, shifting from sample-only laboratory work to a more clinically oriented activity, shortening TTR and prioritizing diagnosis of time-dependent infections. With routinely workflow optimization, approximately 24 h reduction in TTR was observed for positive BC processed by LA, with a significant reduction in empirical treatment time and mortality (49). Similar results were observed for urines (50) and nasal MRSA surveillance (51) and all specimens types (52).

An AI algorithm to interpreteting culture results is another important tool that applies to LA: Automatic reporting of negative samples can be done without delay and without further human assistance, so clinicians can get results earlier to rule out MDRO colonization or a urinary tract infection and reduce the need for patient isolation or antibiotic therapy (24).

Beside LA, a various revolutionizing technologies are used in clinical microbiology. These include MALDI-TOF MS (53), time-lapse microscopy for ID and phenotypic AST (54), molecular diagnostic tests and syndromic panels (55) and next-generation sequencing (56). All of them can significantly improve the diagnosis and treatment of infections, but as noted above, primarily complementary to culture (57). Therefore, in an advanced laboratory, the goal would be to apply all these technologies in a coordinated and timely diagnostic program (DS). For example, both molecular and culture methods should be available in the laboratory for active surveillance of MDRO (58). Indeed, active surveillance of carbapenem-resistant Enterobacteriaceae can limit and prevent their spread and infections, which is crucially relevant to LAS (Laboratory automation system) (59). In high-risk patients, rapid molecular methods are more appropriate, but cannot

replace culture-based methods, because the latter can detect all strains of carbapenem-resistant organisms, perform phenotypic susceptibility testing, and collect and store the isolates (60)

Information from the microbiology laboratory is essential for the control and management of infections in a hospital. In particular, timely and accurate data on the antibiotic susceptibility profiles and and MDRO colonization/ infection for pathogens isolated from different wards provide the basis for establishing hospital infection control and AS programs, that may ultimately affect patient outcome.

Unfortunately, laboratories are not always able to provide timely whole information due to lack of dedicated expertise, personnel, user-friendly software, and optimized workflow applications. The application of LA and informatics can support integration into routine practice monitoring specimens' quality, isolation of specific pathogens, alert reports for infection control practitioners, and real-time collection of laboratory specific data, all essential for the prevention and control of infections and epidemiological studies.

Consequently, timely, accurate, and clinically relevant information forms is the basis for prevention and treatment of infections. LA and informatics can greatly improve the accuracy of diagnostic procedures, TTR, and laboratory workflow. However, to take advantage of these technologies for the benefit of the patients, clinical microbiologists will need to work more closely with clinical staff to shift the way they work and think, towards a lean workflow and a patient-centered approach.

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Authorship Contributions: Concept – E.Y.; Design – E.Y.; Supervision – E.Y.; Funding – E.Y.; Materials – E.Y.; Data collection &/or processing – E.Y.; Analysis and/or interpretation – E.Y.; Literature search – E.Y.; Writing – E.Y.; Critical review – E.Y.

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