Review

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Application of Artificial Intelligence in the Exploration and Optimization of Biomedical Nanomaterials

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Abstract

Nanomaterials play a crucial role in the biomedical field, and with the rise of the digital era, artificial intelligence (AI) has become a valuable tool in all stages of nanomaterial development, spanning from design to synthesis and characterization. In this review, we explore recent advancements in the field of AI-driven nanomaterials. Firstly, we delve into how AI can be leveraged in material design, utilizing vast databases to develop new materials. Secondly, we discuss intelligent synthesis, where AI algorithms are employed to optimize the synthesis process. Subsequently, we explore how to efficiently extract depth information from nanomaterial characterization results using AI-based methods. Lastly, we offer a glimpse into the future of biomedical nanomaterials, highlighting the potential impact of AI in this rapidly evolving field.

Keywords: artificial intelligence (AI); biomedical nanomaterials; nanomaterials design; machine learning; high-throughput

Introduction

Biomedical nanomaterials represent a category of medical materials specifically designed, synthesized, or enhanced at the nanoscale [1, 2]. These nanomaterials possess distinct biological properties and functions, making them valuable for disease detection [3], treatment [4], and prevention [5] at the cellular level. Capable of precisely controlling the structure and characteristics of nanomaterials at the nanoscale, they have great potential applications in biological systems [6]. In experimental research, scientists often gather property data of nanomaterials through extensive experiments and characterizations, continually optimizing parameters to achieve the optimal material state. On the computational side, to gain deeper insights into nanomaterials, key material descriptors are gathered to support the generalizability of the designed computational models [7–9].

Artificial intelligence (AI) is a scientific field dedicated to researching and developing computers capable of simulating and emulating human intelligent behavior. AI algorithms enable computers to perform tasks that traditionally demand human intelligence, such as learning, reasoning, and

problem-solving [10]. The umbrella of artificial intelligence encompasses a wide array of technologies and methods, including machine learning [11], deep learning [12], computer vision [13], natural language processing [14], and more. These sophisticated technologies empower computers to discern patterns through data analysis and make intelligent decisions. In recent years, artificial intelligence has made significant inroads into the field of materials science, emerging as an indispensable tool for its development. The participation of AI reduces the need for trial-and-error experiments required in the design process [15–17], aids in identifying the most suitable synthesis route [18, 19], and extracts in-depth information from the characterization results [20–23]. By quantitatively analyzing the synthesis, characterization and other parameters involved in different stages, AI has played an important role in the fields of design, synthesis, and characterization analysis based on its unique modeling and prediction performance.

In this review, we focus on the recent developments of artificial intelligence in the field of biomedical nanomaterials. As shown in Fig. 1, the review primarily covers three key aspects: material design, intelligent synthesis and characterization analysis. In the materials discovery and design phase, AI algorithms play a vital role in facilitating the design of novel materials with desired properties. By analyzing big databases of material properties and structures [24–26], AI identifies patterns, correlations, and feature descriptors [27], aiding in the creation of optimized materials. During the synthesis stage, artificial intelligence is employed in optimizing and automating the material synthesis process by learning from experimental conditions and parameters [28]. This not only enhances the efficiency of synthesis but also reduces the need for trial and error. In the characterization stage, AI-driven computer vision technology proves invaluable. By analyzing and interpreting data from microscopes and other characterization tools [29], AI helps identify material structures and extracts crucial depth information, offering deeper insights into material properties. These approaches expedite material assessment and selection, aiding in the discovery of materials with superior performance. Moreover, the review delves into how AI can be used to extract information and contribute to materials synthesis within a data-driven context, presenting various real examples at different synthesis stages. Finally, the review concludes with an outlook on the future research directions of AI in the realm of biomedical nanomaterials science. We believe that AI-based algorithms will play a crucial role in propelling nanomaterials science into rapid development within the data-driven era.

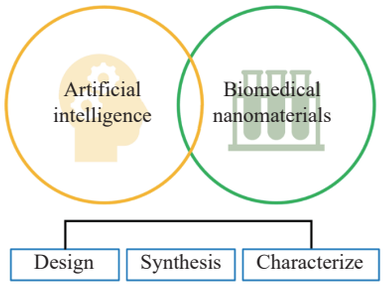

Fig. 1 The application direction of artificial intelligence in biomedical nanomaterials.

Biomedical Nanomaterials

As shown in Fig. 2, the research content of biomedical nanomaterials mainly includes medical detection and diagnosis [30–32], therapeutic drugs [33, 34], and functional nanomaterials (such as nanomaterials for imaging [35], antibacterial [36] and drug delivery [37]). Common types of biomedical nanomaterials encompass carbon-based nanomaterials [38–40], inorganic nanomaterials [41–43], organic polymer nanomaterials [44, 45], and nanocomposite [46]. In the field of tissue engineering, biomedical nanomaterials can be used as substrates for cell growth and proliferation, and deliver drugs and biomolecules, eventually creating new tissues or organs under controlled conditions to replace damaged body parts [47–49]. For example, Castro et al. improved the mechanical and osteoconductive properties by adding silica nanoparticles (NPs) to the electrospun poly(ε-caprolactone) (PCL) membrane for guided bone regeneration [50]. Nanomaterials as drug carriers in drug delivery systems allow for more long-term and sustained drug delivery [51–54]. For example, Au NPs are effective nanocarriers for various drugs such as peptides, plasmid deoxynucleic acid (pDNA), proteins, small interfering ribonucleic acids (siRNAs), and chemotherapeutic agents [52]. In addition, nanomaterials can provide high-resolution, high-contrast images for precision medicine and play an important role in bioimaging applications [55, 56]. Among them, iron-based magnetic nanomaterials have the most extensive applications due to their own

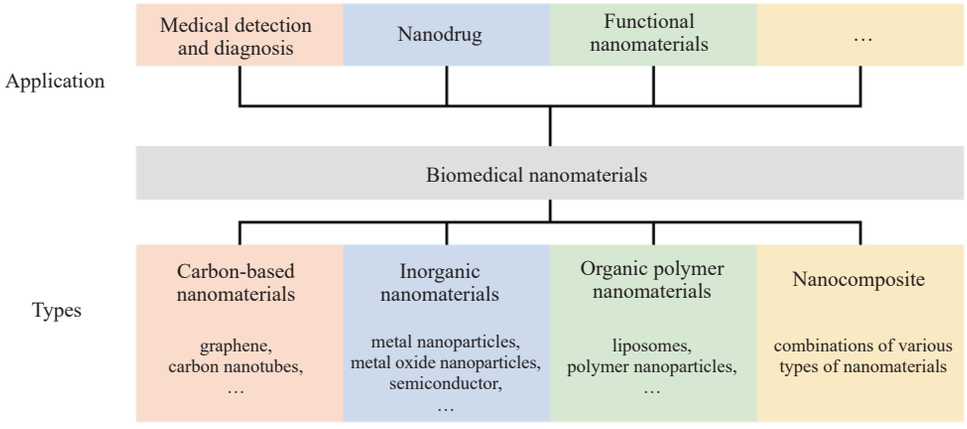

Fig. 2 The significant application and types of biomedical nanomaterials.

imaging effect [57], and can be used in magnetic resonance imaging (MRI) [58] and magnetic particle imaging (MPI) [59]. Leveraging the distinctive physical, chemical, and biological properties, biomedical nanomaterials play a pivotal role in disease treatment and biological research, leading to innovative breakthroughs and advancements in medical science.

To comprehensively evaluate and study the morphology, structure, and properties of nanomaterials, various characterization methods are available at different levels. Microscopic techniques like scanning electron microscope (SEM) and transmission electron microscope (TEM) are utilized to observe the surface and internal structure of materials [60]. X-ray diffraction (XRD) techniques aid in analyzing the crystal structure within materials [61], while Raman spectroscopy and Fourier transform infrared spectroscopy (FTIR) provide valuable chemical information [62]. Thermogravimetric analysis (TGA) [63] and differential scanning calorimetry (DSC) [64] are employed to investigate the thermal properties of materials. The characterization toolbox for nanomaterials includes several other methods as well. In practice, the comprehensive application of these diverse techniques enhances the in-depth understanding of the structure and properties of nanomaterials during the characterization process.

Nanomaterials Design

The development and research of nanomaterials often involve numerous repetitive experiments or complex molecular dynamics simulations. However, artificial intelligence offers a transformative solution by enabling big data analysis and high-throughput screening. This utilization of AI not only accelerates materials design but also enhances nanomaterial synthesis efficiency and quality. The nanomaterial design process typically involves three steps [65]: Firstly, data preparation is conducted, where materials in the dataset are represented using a set of feature descriptors. Notably, noise in the dataset is eliminated with the aid of domain-specific expertise in materials science [66, 67]. In the second step, a mathematical model is created to establish the mapping between features and targets based on available data, which may include complex neural networks encompassing both linear and nonlinear components [68, 69]. Finally, the designed model is employed for reverse design to create the desired materials, streamlining and optimizing the entire materials design process [70, 71].

In the nanomaterials design stage, high-throughput experimental data play a crucial role in enabling combinatorial synthesis and chemical space exploration. For instance, Chan et al. proposed a reproducible, high-throughput synthesis method for colloidal nanocrystals, offering a systematic approach to efficiently explore multidimensional parameter spaces [72]. This approach empowers researchers to optimize the synthesis process and obtain nanocrystals with desired properties, ensuring reproducibility and scalability. Likewise, Kajita et al. developed an ensemble descriptor approach, combining machine learning with high-throughput screening, to efficiently identify potential superionic conductors from extensive material databases [73]. Despite having a small training dataset of [29], the method maximizes inference capacity. These examples demonstrate the utility of machine learning and high-throughput data in exploring the design of

new materials. The same principle can be applied to high-throughput screening of biomedical nanomaterials, after identifying appropriate and efficient descriptors. For example, Yamankurt et al. identified approximately 1 000 spherical nucleic acids (SNA) candidates based on reasonable ranges of design parameters that could be systematically and independently varied to optimize SNA performance. They developed a high-throughput screening protocol to test the activity of SNA-close nano formulations and used the obtained results to train a machine learning algorithm to predict the activity of new SNA formulations [74].

Defects play a crucial role in the properties of nanomaterials and can be categorized into point defects, line defects, and surface defects. However, analyzing structural defects in materials is often challenging and time-consuming, requiring advanced characterization instruments like high-resolution transmission electron microscopes. Despite the difficulty in detecting defects, nanomaterials with defects may exhibit excellent optical and physical properties, including enhanced redox reaction abilities [75]. To better understand how defects influence the performance of nanomaterials, as shown in Fig. 3, Wu et al. constructed a library of 425 metal–organic frameworks (MOFs) with defects. The decision tree and logistic regression models are trained for using this dataset to gain insights into the impact of defects on MOF materials [76]. In the process of characterizing nanomaterials, deep learning can also realize rapid identification and classification of defects in microscopic images, which will be described in detail later. These works have deepened researchers' understanding of defects and structural transitions in nanomaterials, which are crucial for designing nanomaterials with special functions.

The inverse design method is driving the design of nanomaterials towards being performance-oriented, which involves tailoring the structural parameters of materials to achieve specific functionalities or characteristics. Li et al. introduced a novel approach for inverse design using random forest multi-objective regression, showcasing the ability to predict structural features based on desired properties [77]. By employing algorithms capable of addressing multiple targets simultaneously, they explored the vast design space of multifunctional nanoparticles and identified optimal combinations of structural parameters that meet specific performance criteria. Similarly, Thomas et al. utilized a decision tree algorithm to investigate the immune response of nanoparticles, specifically focusing on how the physicochemical properties of nanomaterials, such as size and zeta potential, can influence the activation of the complement system [78]. Understanding these relationships is crucial for developing safe and biocompatible nanomaterials, as it provides valuable insights into tailoring nanoparticle properties to minimize potential immune responses. Boso et al. used artificial neural networks to predict the number of fluorescent polystyrene nanoparticles attached to the container wall as a function of wall shear rate and nanoparticle diameter. Based on this function, the size of the nanoparticles was reverse engineered. In this

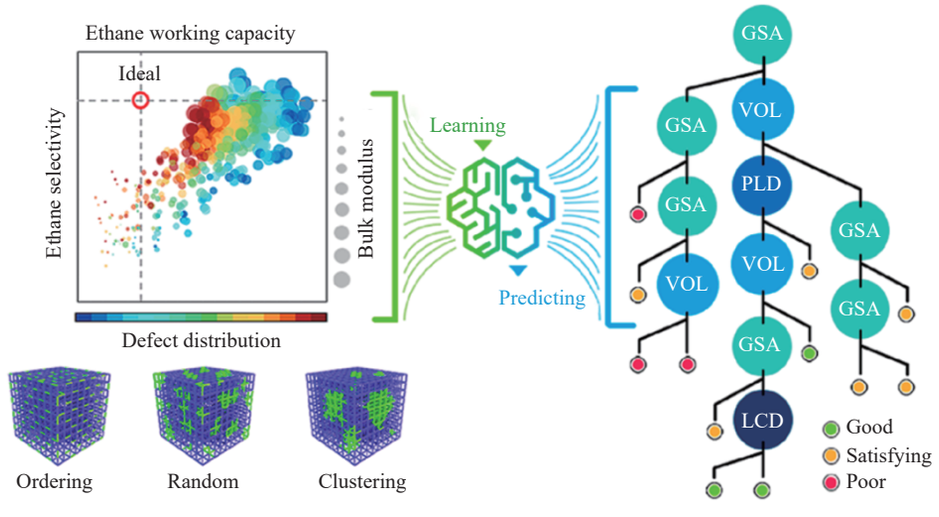

Fig. 3 Flowchart of the method for defect classification in MOFs based on deep learning and decision tree. © 2020 American Chemical Society.

work, it was shown that there is an optimal particle size that maximizes the number of nanoparticles that adhere to the container walls, implying that nanoparticles are able to maximize nanoparticle accumulation at diseased sites [79]. These studies exemplify the power of inverse design and data-driven approaches in advancing nanomaterials research and tailoring nanomaterials for specific applications with enhanced performance and biocompatibility.

Intelligent Synthesis

In the synthesis stage of biomedical nanomaterials, artificial intelligence plays a vital and indispensable role, significantly enhancing the efficiency and intelligence of the synthesis process. The properties and performance of materials are closely tied to the fabrication parameters used during synthesis [80]. Artificial intelligence at this stage is primarily focused on optimizing and designing synthesis parameters. Researchers have leveraged machine learning algorithms to optimize the synthesis of biomedical nanomaterials. Barnard et al. used 14 different machine learning algorithms to describe and optimize 4 000 different synthetic routes for Au NPs using 5 different feature sets [81]. Furthermore, Wilbraham et al. introduced the concept of a chemical processing unit (CPU), a digital platform that integrates and automates various aspects of chemical processes [28]. The CPU enables high-throughput experiments, enabling rapid screening of a large number of reaction conditions to determine the most favorable reaction routes for nanomaterial synthesis. This modular approach to describing chemical reactions represents a novel and efficient method, marking a significant milestone in the mathematization of chemistry. It opens up new possibilities for innovation, efficiency, and reproducibility in chemical research and development.

Microbial synthesis is an eco-friendly and cost-effective method for the synthesis of biomedical nanomaterials [82, 83]. Due to the involvement of various biochemical reactions and biological mechanisms, it is essential to study the biosynthetic capabilities of microorganisms and develop methods to regulate and control the synthesis of nanomaterials to achieve more efficient and controllable outcomes. Conversely, the nanoparticles synthesized by different microorganisms can serve as unique identifiers for distinguishing between different microbial species. Yu et al. demonstrated the application of machine learning techniques to analyze and interpret the biosynthesis patterns of gold nanoparticles produced by various microbial species [84]. By training a machine learning algorithm on a dataset of biosynthesis patterns and associated taxonomic information, the system successfully identified and classified unknown microbial samples based on their gold nanoparticle biosynthesis. This innovative strategy holds great potential for diverse applications, such as environmental monitoring, medical diagnosis, and biotechnology. By harnessing the combined power of microbial synthesis and machine learning, researchers can achieve more precise and efficient microbial identification, contributing to advancements in multiple fields that rely on accurate microbial taxonomy and the synthesis of nanomaterials.

Researchers in the field of nanomaterial synthesis often conduct extensive characterization of synthesized materials to understand their properties before attempting to improve the experimental synthesis process. AI has emerged as a powerful tool to optimize synthesis parameters by analyzing and characterizing the results obtained from various experiments. Yao et al. developed an automated analysis workflow that utilizes nanomorphology to link synthetic conditions to properties by quantifying information in TEM image datasets [85]. They employed convolutional neural networks and unsupervised learning models to quantify and classify nanomorphology in three different systems. This approach revealed the synthesis-nanomorphology relationship, identifying both the diversity and similarity of nanomaterials under different synthesis conditions. This work sheds light on how synthesis parameters influence the development of nanomorphs, opening the possibility for AI to enhance nanomaterial synthesis and better understand and control complex nanomorphologies. Jiang et al. proposed a fully autonomous chemical synthesis robot capable of exploring the multi-step synthesis of gold nanoparticles via online ultraviolet–visible (UV–Vis) characterization [18]. By using a mass diversity algorithm, three interrelated chemical spaces were explored, and gold nanoparticles with diverse characteristics were discovered, including spheres,

rods, spherical, stars and so on. Au NPs are an important class of functional nanomaterials in biomedical applications [86]. In this work, the synthesis process is output in a common format using a chemical description language and analytical data to generate unique digital signatures, enabling reproducibility of design synthesis.

The reproducibility of nanomaterial synthesis is indeed a critical challenge in the transition of biomedical nanomaterials from the laboratory to the market. To address this issue, researchers have been exploring various controllable synthesis approaches, with microfluidic platforms being one of the prominent methods [87, 88]. Guda et al. conducted systematic investigations on the controllable synthesis of gold nanoparticles with specific sizes and shapes [89]. They studied the effects of different gold precursors, reducing agents, and surfactants on the formation of gold nanoparticles. By employing modified Latin hypercube sampling, they selected experimental points in the response parameter space and varied the variables of $HAuCl_4 \cdot 4H_2O$, ascorbic acid, and hexadecyltrimethylammonium bromide (CTAB). This approach enabled the preparation of gold nanoparticles in spherical or elongated shapes, and the in-situ reactions were monitored using UV–Vis spectroscopy. This study helps researchers gain a deeper understanding of the complex interactions among reaction parameters, enabling the rational tailoring of the synthesis process to achieve desired properties and achieve controllable synthesis. As shown in Fig. 4, Ferreira et al. developed an impedance millifluidic sensor based on machine learning data processing to monitor the 24-hour synthesis of silica nanoparticles [90]. By continuously monitoring the reaction, they obtained detailed information on the kinetics of formation, particle size distribution, and other key parameters that influence the properties of the resulting silica nanoparticles. This real-time monitoring approach provides researchers with valuable insights into the synthesis process, enabling them to more precisely control nanoparticle synthesis and develop high-quality and reproducible nanoparticles with desired properties. These innovative approaches demonstrate how controllable synthesis methods and real-time monitoring techniques, driven by artificial intelligence and machine learning, can help overcome the challenge of reproducibility in nanomaterial synthesis.

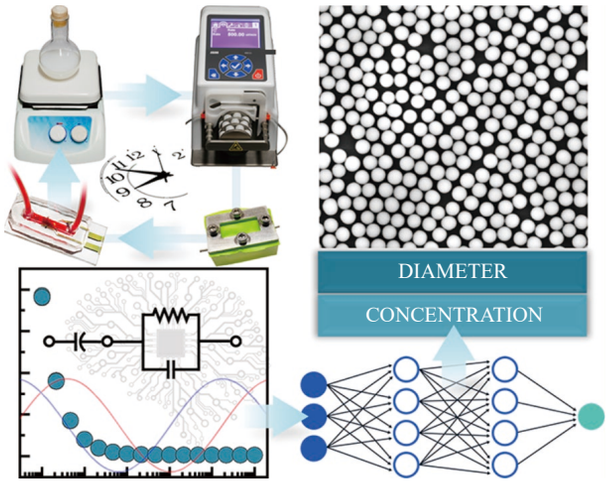

Fig. 4 The impedance millifluidic sensor based on machine learning data. © 2022 American Chemical Society.

Characterization Analysis

Information extraction from nanomaterials' characterization results is a valuable tool that enables researchers to gain a deeper understanding of materials and uncover hidden patterns and features within them. Nanomaterials' characterization data comes in various forms [91], such as images from TEM or curves from UV–Vis absorption spectroscopy. Artificial intelligence plays a pivotal role in automatically identifying and classifying nanostructures, crystal structures, and morphology information in the samples. This intelligent characterization method assists in the interpretation of experimental results, making it easier for researchers to analyze complex data and extract meaningful insights.

The information about the size, shape, surface, and other characteristics of nanoparticles is crucial for understanding materials and is typically obtained through microscopy. Different microscopes have varying resolutions, which affects the level of information that can be obtained. For instance, optical microscopes can provide size and shape information, while high-resolution TEM can capture crystallographic details of materials [92]. Recent advancements in AI methods have been applied to automate and expedite the analysis of microscopic images. For example, Xu et al. established a machine learning model using images acquired by a defocused scanning optical microscope on a traditional optical microscope to accurately determine the size of silver nanoparticles [93]. Their method achieves an estimation error of less than 5% for individual

particles, enabling accurate visualization of particle size distributions, even for complex samples with broad size variations. Due to the higher resolution of TEM, it is more widely used in nanomaterial characterization due to its capability to provide more depth information, such as defects [94] and space groups [95]. Groschner et al. have designed automatic analysis methods, like combining U-net [96] and random forest models [97], to segment nanoparticles in high resolution TEM (HRTEM) images and predictively classify different defect types in the particles [98]. Additionally, our group have developed automatic frequency domain information analysis systems based on the U-net model, successfully analyzing lattice fringe information in HRTEM images through information calibration and Fourier transform calculation [99]. This method has been effectively applied to iron oxide nanomaterials.

SEM is a valuable tool for obtaining high-resolution surface morphology and topological information of nanomaterials, enabling researchers to study their structure, shape, and size [100]. As the volume of SEM data increases with the continuous development of technology, the analysis capabilities need to be enhanced accordingly. Researchers have leveraged deep learning models to automate and improve the analysis of SEM images. Aversa et al. annotated a large dataset of 22 000 SEM images and used a deep learning model to classify them into ten categories, such as 0D particles, 1D nanowires, 2D films, and 3D devices [101]. Similarly, Dahy et al. proposed an intelligent classification model based on the VGG-19 deep network [102] and a support vector machine model [103] to classify the shape types of nanoparticles in SEM images, achieving an impressive overall accuracy of 97% [104]. Furthermore, researchers have gone beyond shape classification and extracted more comprehensive information from SEM images using machine learning. Kim et al. developed a computer vision algorithm based on machine learning (Fig. 5) to quantitatively extract particle size, size distribution, shape, and core-shell structure information from SEM images [105]. This method offers automated and high-throughput measurements, even when dealing with overlapping nanoparticles, rods, or core-shell nanostructures.

In fact, for the characterization results of images such as TEM and SEM, the model design process can be unified into four steps: data set construction, training set calibration, model training, and model verification. By combining artificial intelligence algorithms to extract information from images, the analysis results are made faster and more accurate, especially reducing the analysis errors between different analysts. The use of artificial intelligence in nanomaterial characterization can enable more efficient and reliable data analysis, leading to a deeper understanding of materials and advancing the field of nanotechnology.

Optical absorption spectroscopy is an important characterization method for analyzing the interaction of light with materials and further extracting information about electronic and molecular properties. However, for nanomaterials, due to their complexity, the optical absorption peaks in the spectrum are difficult to be identified. It is difficult to identify chemical constituents from absorption spectra unless special control measures such as size focusing [106] or high-resolution separation [107] are employed. By applying a machine learning model based on a one-dimensional convolutional neural network, Chen et al. took the UV–Vis absorption spectrum of metal nanoclusters as a demonstration, and achieved a good match between the predicted results and the experimental results and a low mean

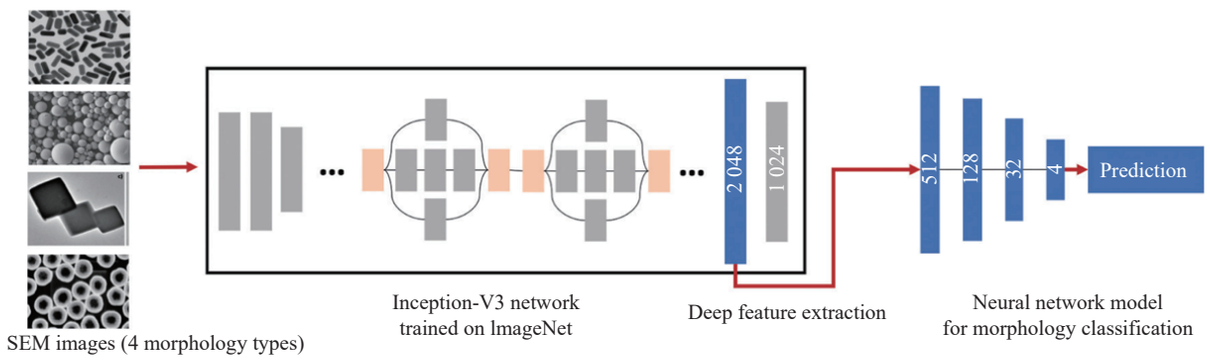

Fig. 5 Deep convolutional neural network-based morphology classification of SEM images. © 2022 Royal Society of Chemistry.

absolute error value [108]. This work opens the door to the identification of nanomaterials from their optical properties with molecular precision, providing the methodological basis for rapid, high-throughput characterization.

Future Prospects

In the realm of biomedical nanomaterials, artificial intelligence has proven to be highly advantageous and versatile. Its applications span across material design, intelligent synthesis, and characterization result analysis, and these algorithms can be adapted for most nanomaterials. However, how to effectively apply the algorithm to the actual scene and reduce the cost and time of the experiment is also an important problem that needs to be solved. First, in the material design stage, building large biomedical nanomaterials databases and specific descriptors is key to improve algorithm performance. Second, in the material synthesis stage, improving the efficiency and versatility of the algorithm is the key issue, which will enable artificial intelligence to more effectively support and guide the process of experimental synthesis. Third, at the stage of material characterization analysis, it is suggested to design an algorithm that can comprehensively analyze various characterization results and design a visual interface for the algorithm. By making these improvements, AI can become more accessible and valuable as an effective auxiliary tool for researchers in the biomedical domain, fostering its wider adoption and enhancing its potential impact.

Conclusion

Artificial intelligence has brought significant advancements and opportunities to the optimization and exploration of biomedical nanomaterials. Researchers can now obtain information more rapidly, thanks to the superior efficiency of AI-assisted methods compared to traditional manual analysis. The use of large databases and high-throughput screening for nanomaterial design has drastically reduced the reliance on trial-and-error experiments, enabling more efficient development and design of new materials based on desired performance. In the material synthesis stage, artificial intelligence plays a crucial role in making the process more intelligent and efficient by designing synthesis reaction parameters. Moreover, AI-driven methods for analyzing nanomaterial characterization results aid in quantifying and extracting valuable information. Overall, the integration of artificial intelligence in biomedical nanomaterials development is driving the field towards greater intelligence and automation. As artificial intelligence continues to contribute to transformative advances in the field, the rapid development of nanomaterials research and applications has brought new breakthroughs and possibilities to the field of biomedicine.

CRediT Author Statement

Xiaoyang Zhu: Data curation, writing–original draft, writing–review, and editing. **Yan Li:** Conceptualization, writing–review, and editing. **Ning Gu:** Conceptualization, resources, writing–review and editing.

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Conflict of Interests

The authors declare that no competing interest exists.

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