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Drug Delivery System Tailoring via Metal-organic Framework Property Prediction using Machine Learning: A Disregarded Approach

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Article title: Drug Delivery System Tailoring via Metal-organic Framework Property Prediction using Machine Learning: A Disregarded Approach

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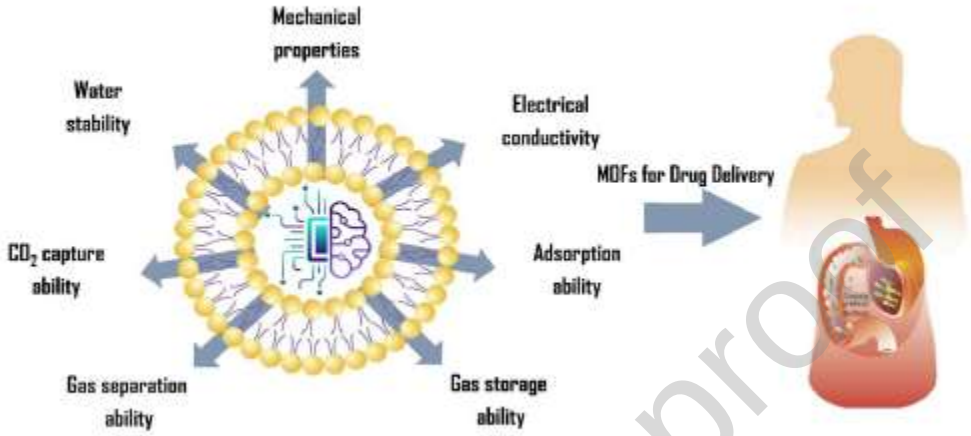
Abstract

Metal-organic frameworks (MOFs) have demonstrated exclusive features, including high porosity, high surface area, favorable biodegradability, and biocompatibility. Due to these unique properties, MOFs could be used extensively in several applications, including gas storage, catalyst, separation, and biomedical applications. Also, multiple types of MOFs with various features have been identified and used in many applications. Due to the diversity in the characteristics and capabilities of MOFs, their experimental examination is complex, costly, and time-consuming. Machine learning (ML), as an artificial intelligence tool, is an alternative for accurately predicting MOF characteristics. MOFs can benefit from integrating ML techniques for the design and development of them in various fields. This review summarizes ML tools that can be applied to predict MOF properties in designing drug delivery systems (DDSs). To this end, various ML classifiers were introduced first, and then related studies of ML methods for predicting MOF properties and capabilities were presented. ML exhibited a unique role in MOF research to predict the properties of MOFs with less cost and time. Finally, the potential application of ML in developing optimum MOF-based drug carriers is presented as a route to *in silico* DDS tailoring.

Graphical abstract



Keywords: artificial intelligence, machine learning, metal-organic framework, property determination, biomedical application, drug delivery system

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1. Introduction

Metal-organic frameworks (MOFs) encompass a category of crystalline and porous substances that find numerous applications across various fields, including nanomedicine, catalysis, gas storage, and sensing. These materials consist of metal ions/clusters and organic linkers, resulting in a significant surface area for interaction. The properties exhibited by MOF structures are contingent upon the specific constituents employed, the length of the organic linker, the presence of functional groups within the structure, and the availability of open metal sites, among other factors [1–4].

Understanding MOF features is pivotal for choosing the best MOF for the given purpose; for example, a nano-sized MOF with high surface area, magnetic resonance imaging (MRI) capabilities, and small pore diameters might be desirable in the field of theranostics, while a MOF with high void fraction, large pore volume, and low density is beneficial for hydrogen storage [5–8]. Predicting these properties is not always easy. Experimental studies can be tiresome and unfruitful in MOF investigations. Bearing this in mind, the utilization of trial and error in MOF

synthesis and characterization is not of much interest because this method is time-consuming, low-yield, and has a high cost [9].

The Cambridge Structural Database (CSD), managed by the Cambridge Crystallographic Data Centre (CCDC), provides a comprehensive collection of small crystal structures showcasing the distinct properties of different Metal-Organic Frameworks (MOFs). The expansive CSD MOF database presently encompasses over 100,000 MOF structures, of which over 12,000 are accessible for unrestricted utilization at no cost [10]. Another MOF database is computation-ready experimental MOF (CoRE MOF). CoRE MOF and CSD are among the MOF databases that contain already synthesized (real) MOFs. However, many MOF data banks only include hypothetical MOFs (hMOFs) [5]. MOF datasets can be applied with Monte Carlo (MC) simulations and molecular dynamics (MD) to anticipate new MOF structures via computer science, statistics, and probability. Predicting MOF characteristics with such models can happen after inspecting traits like gas storage, separation, or surface adsorption [11–13]. Software packages such as topologically-based crystal constructors (ToBaCCo) provide another toolset for the construction of hMOFs. This software attaches MOF construction units using the data input from comprehensive databases [14].

A conventional method for screening various datasets to find the MOF with desired features can be high-throughput computational screening (HTCS). This screening method is often accompanied by techniques like density functional theory (DFT) or grand canonical Monte Carlo (GCMC) to identify MOF candidates with promising capabilities. Even while applying such techniques, HTCS takes much time and is costly and inefficient [15,16].

Artificial intelligence (AI), and more specifically, machine learning (ML), may be the fast route to quick and high-yield anticipation of MOF attributes [17]. ML is the application of algorithms or technologies that make trend identification and decision-making achievable for systems. ML can be utilized in data classification, genomics, biomedicine, etc. Discovering patterns for the synthesis of numerous materials, such as MOFs, is feasible through ML as proper material prediction happens faster in this method compared to HTCS. ML also improves material performance by establishing connections between molecular chemistry, structure, and performance [18–20].

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The input for AI algorithms may be data regarding the material, such as geometrical, chemical, and spatial properties. This data can be employed to train and form the model that predicts versatile MOF functions as the output. Properties range from conductivity and mechanical attributes to surface adsorption and gas capture [21,22].

Various machine learning (ML) algorithms can be employed for this objective, which can be categorized into four distinct groups: 1. Supervised learning, encompassing support vector machines (SVM) and k-nearest neighbor (KNN); 2. Unsupervised learning involving Gaussian mixture model and sparse autoencoder; 3. Semi-supervised learning, incorporating semi-supervised SVM and graph theory method; 4. Reinforcement learning, specifically Q-learning.[23–25].

One of the recently growing fields of MOF implementation is drug delivery owing to the biocompatibility and biodegradability of these nanostructures and their great capacity for drug loading [26]. The prediction of critical characteristics in MOFs, including pore dimensions, surface area, and polarity, can provide valuable insights into the functionality of these compounds as drug nanocarriers. It can predict their capacity to incorporate drugs, cellular absorption, and safety profile. Nevertheless, to the best of the authors' knowledge, there is currently no available literature documenting the utilization of this approach. Therefore, highlighting the importance of this application holds significant relevance. [27–30].

The current DDSs suffer from a lack of biodegradability in most carriers, the danger of dose dumping, fast elimination by immune system cells and organs such as the liver and kidneys, and unpredictable pharmacokinetic parameters [31,32].

This article reviews the literature on the prediction of different drug delivery-related MOF properties using ML algorithms. First, ML techniques are introduced, then MOF properties are described, and the prediction of these attributes via ML tools and their relation to DDSs is discussed.

2. Machine learning algorithms

Different ML algorithms could be used for the prediction of various parameters. These ML algorithms include four categories: Supervised learning (e.g., support vector machines, k-nearest

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neighbor), Unsupervised learning (e.g., Gaussian mixture model, sparse autoencoder), Semi-supervised learning (e.g., semi-supervised SVM, graph theory method), and Reinforcement learning (e.g., Q-learning) [23–25].

2.1.Supervised learning

Supervised learning is a category of machine learning methodologies that involve training models using input and target features extracted from a provided dataset. The model identifies the relationship or mapping between the input and target features. Subsequently, the trained model can utilize this mapping to classify unseen samples (classification) or predict numerical values for the target feature (regression). Prominent examples of supervised learning models encompass artificial neural networks (ANN), Naïve Bayes, Support Vector Machine (SVM), Decision trees, Random Forest (RF), and K-nearest neighbor (KNN).[33,34].

2.2.Unsupervised learning

In this category of techniques, the data is given to the model without any labels. The model should cluster the data based on the similarities of the records. In these techniques, the records with high similarities are assigned to the same cluster. Clustering, Association rule mining, principal component analysis (PCA), and self-encoding algorithms are samples of this category [33,34].

2.3.Semi-supervised learning

In this category of techniques, the input data contains labeled and unlabeled data. Moreover, the models of this category try to extract as much information as possible to learn the patterns from this mixture of input data. This category combines the two categories mentioned above mentioned earlier [33,34].

2.4.Reinforcement learning

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This category of techniques deals with those who try to learn by trial and error, maximize their reward, and minimize their punishment signal. Q-learning and Temporal differential learning fall into this category [33,34].

3. Machine learning tasks

In the previous section, machine learning algorithms were categorized based on their ability to solve various tasks, including classification, regression, and clustering [35]. Classification is employed when assigning an input to a predefined category, such as determining whether an MOF is electrically conductive or not. Regression is used to predict a numerical label based on input features, like estimating the gas absorption ability of an MOF given its features. Clustering involves grouping samples based on their input features without knowledge of the output for each sample. For instance, MOF materials can be grouped based on their feature set, with the assumption that MOFs within the same group likely possess similar properties.

4. Machine learning datasets

A machine learning dataset encompasses several aspects. One such aspect is the dataset size, which plays a significant role. A larger dataset, consisting of samples from a wide range of combinations of input features, tends to have higher quality. Another aspect to consider is the dataset type. It can vary, including records, signals, images, or a combination of these data types [36].

5. Feature selection

Feature selection is a valuable approach to effectively prepare data, especially when working with high-dimensional datasets, for a variety of machine learning tasks. It involves selecting the most important features from a dataset to achieve several objectives: simplifying models, improving data mining performance, and ensuring the preparation of clean and comprehensible data [37].

6. Machine learning evaluation

To select the optimal machine learning model based on performance, various metrics can be employed. In classification tasks, commonly used metrics derived from the confusion matrix include Accuracy, Classification Error, and Cohen's Kappa coefficient. For regression tasks, metrics such as Mean Absolute Error (MAE), Root Mean Squared Error (RMSE), Relative Absolute Error (RAE), and Root Relative Squared Error (RRSE) are

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often utilized. These metrics provide valuable insights into the model's performance and enable comparison between different machine learning models [38].

7. Properties of MOFs

Like other materials, MOFs exhibited different characteristics, including physicochemical properties and their different characteristics from the point of view of their different applications. Since sometimes determining their characteristics and predicting their efficiency in various applications is experimentally tricky, challenging, and costly, AI methods could be helpful and promising for predicting MOF properties. Some of the characteristics of MOFs have been predicted by ML methods, which are stated in the following sections [39].

MOFs have porosity and high surface area properties, making them great options in various fields like catalysis or drug delivery [40]. Conventional drug delivery suffers from different problems. The drug molecules can be distributed in the whole body, causing adverse effects. Nano-sized delivery can be useful in ensuring better drug disposition and fewer side effects in diseases from cancer to inflammatory ailments. Such diseases show great vascular fenestration in the affected sites, enhancing nanocarrier permeability and retention (EPR). Targeting ligands can also be applied on the surface of the drug carriers for active targeting and, therefore, a more precise drug treatment [41,42]. Different carriers have been applied over the years, like liposomes, dendrimers, polymeric micelles, etc [43,44]. MOF drug carriers can be synthesized with the nano-sized scale and have high encapsulation efficiency and drug loading. They can also be tailored using different metal clusters and organic ligands with various synthesis methods that make these nanoparticles promising for medical applications like imaging and theranostics [27].

8. DDS tailoring: a promising opportunity for MOF property determination via ML tools

ML algorithms can determine MOF structures with decent quality and easy synthesis procedures [45]. MOF nanoparticles are promising in biomedical applications such as drug delivery and imaging [46]. However, much time and effort is wasted in the lab due to clinically inappropriate MOF carrier synthesis that can only be detected after cellular testing or in vivo evaluation. Another

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possible source of unproductive laboratory work occurs due to low encapsulation efficiency and drug loading of the synthesized MOF nanoparticles or labor-intensive efforts that result in micronized MOF molecules, particles that bear few applications as drug delivery systems owing to fast clearance via the reticuloendothelial system and other parts of the immune system [47–50].

Instead of checking all the possible formulations in the lab, it is useful to generate ML algorithms to ensure greater precision in designing DDSs and novel nanocarriers such as MOFs [39,51].

A possible answer to such lab difficulties is the application of ML algorithms to anticipate such properties *in silico* before entering the experimental phase [52].

The process of using ML in MOF property prediction initiates with data collection, which can happen either using the literature or lab data. For MOFs, this data (input) consists of basic MOF traits such as ligand, metal cluster, size, zeta potential, etc. In supervised learning, output data (label) is also set for each sample as an aid in training that, in this case, are the MOF characteristics that need prediction (such as, while in unsupervised training, the algorithm is able to find a meaningful relationship between the inputs without knowing the labels. One of the methods for gathering lab data in ML training is applying experimental design to perform relevant laboratory experiments. After data collection, pre-processing is essential as the data might not be enough for algorithm training, which necessitates the application of methods such as data augmentation. Outlier removal is another important pre-processing step. Also, data normalization is vital for distance-sensitive algorithms like logistic regression and k-nearest neighbor, while this might not be the fact for ML algorithms that are not sensitive to distance, such as decision trees or random forests [53].

Then, the data is separated into training, validation, and test sets to be presented to the model. Then, the accuracy and sensitivity results (along with other factors for model evaluation such as f1 score or cross-validation results) are inspected in order to set the model hyperparameters for better response optimally. Using the properly trained algorithm, labels related to new inputs can be predicted [54].

As far as the authors are concerned, there have not been many reports on this subject. Therefore, suggestions may be of benefit to commence this new era in molecular prediction via ML. Using the characterization data of biomedical MOF nanoparticles as inputs to teach ML models can be a

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decent way to start this path [55]. Many levels would be of benefit in MOF nanocarrier synthesis: (a) drug loading, (b) drug release, (c) carrier safety, (d) biostability, (e) biodistribution and pharmacokinetics, (f) antibacterial and photodynamic properties. Diagram 1 presents MOF molecular properties against drug cargo properties and shows that predicting each molecular characteristic results in understanding which drug cargo attributes.

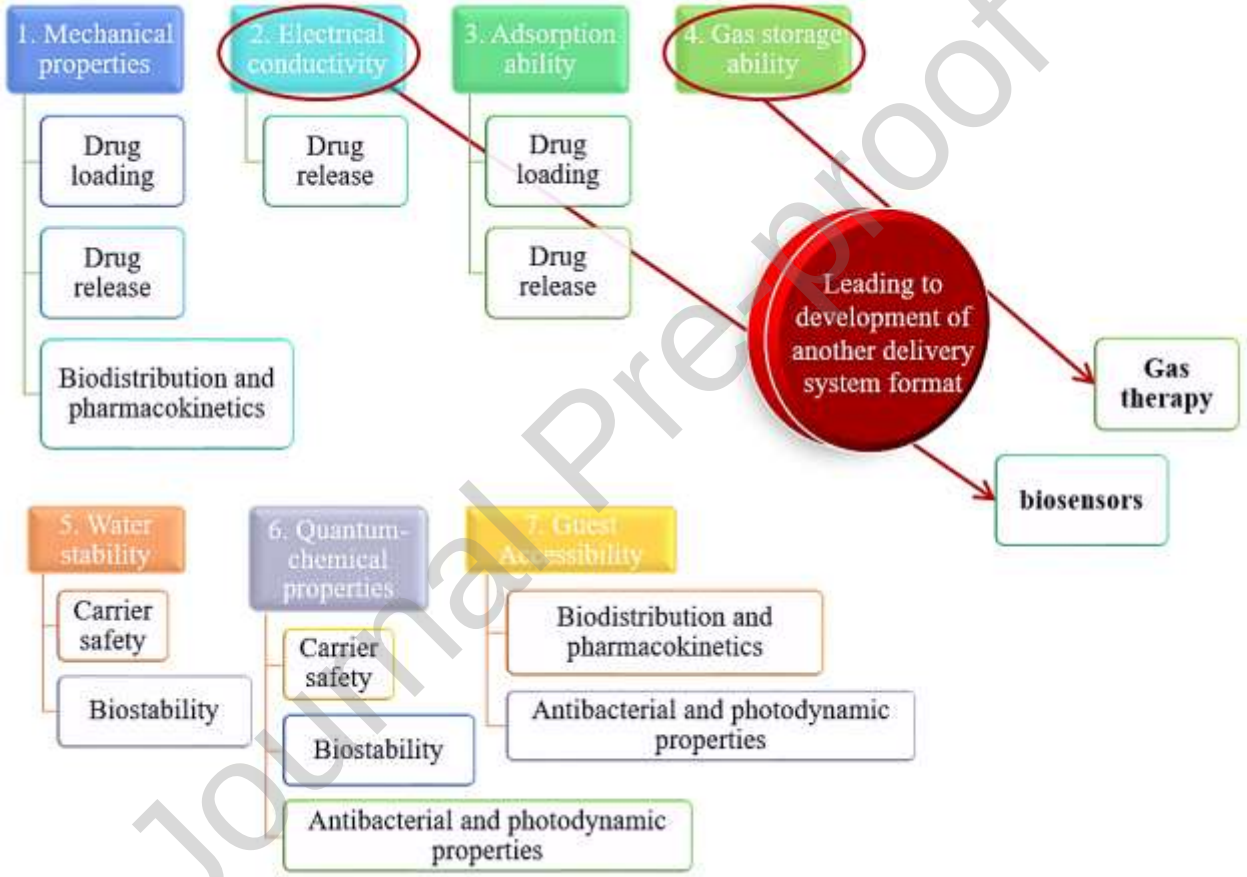

Diagram 1. MOF molecular attributes leading to the development of new drug delivery systems or predicting MOF characteristics

(a) Surface adsorption and MOF pore sizes (figure 1) [51] determine the amount of drug that can be loaded. Pore sizes must be larger than the drug molecule for the MOF molecule to load the drug efficiently. However, if in situ synthesis methods are to be applied, large pore sizes are unnecessary for cargo loading and high encapsulation efficiency. MOF nanoparticles with high surface areas

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(resulting from the Brunauer, Emmett, and Teller (BET) test) are most probably subjects to high-loading outcomes [56–58].

In a recent article, 40 different MOFs were gathered from literature, providing support vector regression (SVR), categorical boosting (CatBoost), adaptive boosting (AdaBoost), and random forest (RF) algorithms with 5 inputs (surface area, functional groups, ligand and metal type, size and pore volume) to predict loading capacity of ibuprofen in MOFs. CatBoost proved to be the superior predictor with R^2 of 0.76 [59]. This study, although the only one regarding MOF drug delivery using ML approaches, lacked some aspects: MOF nanoparticles are diverse when it comes to ligands and ion clusters; therefore, predicting loading capacity using various MOFs can diminish accuracy. Also, 40 samples don't seem to be enough to cover the diversity explained. The better approach could have been to utilize a single type of MOF molecule, such as ZIF-8, and come up with different lab data instead of relying only on the literature.

(b) Large pore sizes can also guarantee faster drug release. Therefore, it is advised for cargoes that need to be released in a controlled or slow manner to be loaded into MOF molecules with smaller pore sizes in situ. The nanocarriers in question are best responsive (e.g., pH-sensitive for inflammatory or tumor-based diseases) to focus the release process in the affected area. It is also possible to predict the existing functional groups on the MOF surface so that ligands mostly beneficial in targeted therapy can be attached to the functional groups [60,61].

Prediction of polymeric nanoparticle drug release with neural network using release modeling happened in 2022. The polymers were surface eroding, and different inputs were synthesized in the laboratory to obtain 22 release curves. The inputs were related to the drug, the applied polymer, loading content, and pH. High Pearson's coefficient values demonstrated successful training and modeling [62]. Such studies can also be of benefit for distinguishing release mechanisms in different MOF nanoparticles to fulfill the potentials of this molecule in responsive drug delivery.

(c) Considering the atoms of MOF molecules or compiling the cell toxicity endpoints of in vitro cellular studies might help foretell MOF toxicity before performing complex cellular and animal toxicity studies. The nanocarrier's polarity and size can also determine how the carrier is possibly distributed in animals and which organs bear the highest risk of being intoxicated [63–65].

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The safety of quantum dots and metal oxide nanoparticles was evaluated with ML. The model was trained with the nanomaterial properties, the attributes of the biological environment, and the characteristics of the experiment. Toxicological endpoints such as half maximal inhibitory concentration (IC_{50}) were considered as outputs, while the performance of the algorithm was inspected using root-mean square error (RMSE) and R^2. This study represents the benefits of ML methods for other nanoparticles that can also be used in MOFs [66].

(d) The biostability of MOF nanoparticles depends on the metal clusters and organic ligands used and is significantly related to how the two parts come together and produce MOF structures [67,68].

It is widely known that ZIF-8 MOF nanoparticles are acid-labile, making them suitable for responsive and triggered release drug delivery in diseases such as cancer or some inflammatory problems like rheumatoid arthritis [69,70]. Another stability issue raised with ZIF-8, one of the most famous and easily synthesized MOF structures, is the ability to interact with phosphate-buffered saline (PBS) to produce zinc phosphate crystals [71,72]. This issue might be problematic in several ways as this buffer is frequently used in biological research for being iso-osmolar and with the same concentration of ions as the human body, urging researchers to coat this structure with other materials such as folic acid or hyaluronic acid for better results [73,74]. The prediction of this biostability issue in the first place could have avoided the time-consuming processes of synthesis and testing, bringing up the coating option or changing the MOF structure before further studies.

Bond-type embedded crystal graph convolutional neural network (BE-CGCNN) has proven to be effective in demonstrating the electrochemical stability of metallic nanoparticles. This ML method was more effective than plain CGCNN or DFT-generating surface Pourbaix diagrams for stability prediction [75]. Similar approaches could also be applied in forecasting the stability of MOFs.

Interaction between nanomaterials and biological media can also be predicted, which might assist in biostability foretelling in nano-molecules such as MOFs. Convolutional neural network models were utilized in 2020 to convert pictures of 147 nanoparticles into information about physicochemical attributes along with cellular uptake and adsorption of proteins on the surface of nanomaterials [76].

Journal Pre-proof

(e) MOF structures have different attributes regarding their biodistribution and pharmacokinetics due to different metal and organic sections that can be used with various surface potentials, sizes, and functional groups [27,77].

MIL-100 (Fe) is a MOF made of iron clusters and benzene-1,3,5-tricarboxylic acid. This nanocluster was loaded with gemcitabine in a 2019 study that resulted in nanoparticles with approximate hydrodynamic diameters of around 200 nm and zeta potentials of around -30 mV. Pharmacokinetic studies using rats showed higher elimination half-life after the encapsulation of gemcitabine in MIL-100 (Fe) nanoparticles, and the biodistribution results showed that gemcitabine in its free form was highly distributed in the animal body. In contrast, in the encapsulated form, the drug was primarily confined in blood and less distributed in various organs. The drug was detected using HPLC (high-performance liquid chromatography). The loaded drug was detected mostly in the liver after blood [78].

Another study used ZIF-8 nanoparticles radiolabeled with technetium-99 m to evaluate biodistribution and pharmacokinetics, which mostly detected ZIF-8 nanoparticles in the lungs. Attachment of pertechnetate to ZIF-8 MOFs increased the area under the plasma concentration-time curve (AUC), mean residence time (MRT), and elimination half-life compared to the free radiolabel while decreasing its clearance and volume of distribution [79].

Since large particles tend to enter the lungs, these results show a possibility of nanoparticle aggregation. Using a coating around ZIF-8 MOFs such as PEG (polyethylene glycol) can be considered if there is a need for the MOFs to avoid lung accumulation [80].

The application of ML and other predictive devices could be vital in determining the biodistribution results and finding suggestions for using more desirable materials for MOF preparation or coating.

Physiologically-based pharmacokinetic model was applied along with 5 ML models to anticipate tumor delivery of nanoparticles *in vivo*. Training occurred using the "nano-tumor database" in which 200 studies were accumulated. 21 variables were used for model training, which resulted in a novel tool for early cancer drug screening that could end up in less animal use [81,82]. A problem with the database presented was that the nanomaterials used were of different groups, and some groups had more members than others (like the high frequency of gold nanoparticles compared to

Journal Pre-proof

nanocrystals), which could make the algorithm biased and more trained on specific nanomaterials. A concordant outlook would be advantageous for different MOFs and for diseases other than cancer, as none of the diverse nanoparticles of this article were MOFs.

(f) Determination of antibacterial properties in MOFs greatly affects delivery systems applied in wound healing or infections [83].

Photodynamic MOFs such as ZIF-8 and porphyrin-based particles can produce reactive oxygen species (ROS) to terminate nearby cells (bacterial or cancer cells). Meanwhile, copper and silver-based MOFs show inherent antibacterial properties without light irradiation [84,85].

These effects could have been predicted in the early stages of developing a wound healing agent to establish the necessity of adding an extra antibacterial or photodynamic agent or the self-sufficiency of the synthesized MOF regarding this property.

After training 5 ML models with input data from 60 articles, RF was chosen to be the best algorithm for predicting the antibacterial properties of nanostructures. The important features were bacteria type, nanoparticle size, and dose. The high R^2 value showed the good performance of this model [86].

Likewise, a 2023 study demonstrated responses of normal and tumor tissues following photodynamic therapy-associated gold nanoparticle delivery. The application of ML estimated such responses and presented the superiority of the utilized nanoparticles against tumor cells along with recoverable toxicity against normal tissue [87].

Such perspectives could also be put into application for MOFs in order to foresee antibacterial or photodynamic effects.

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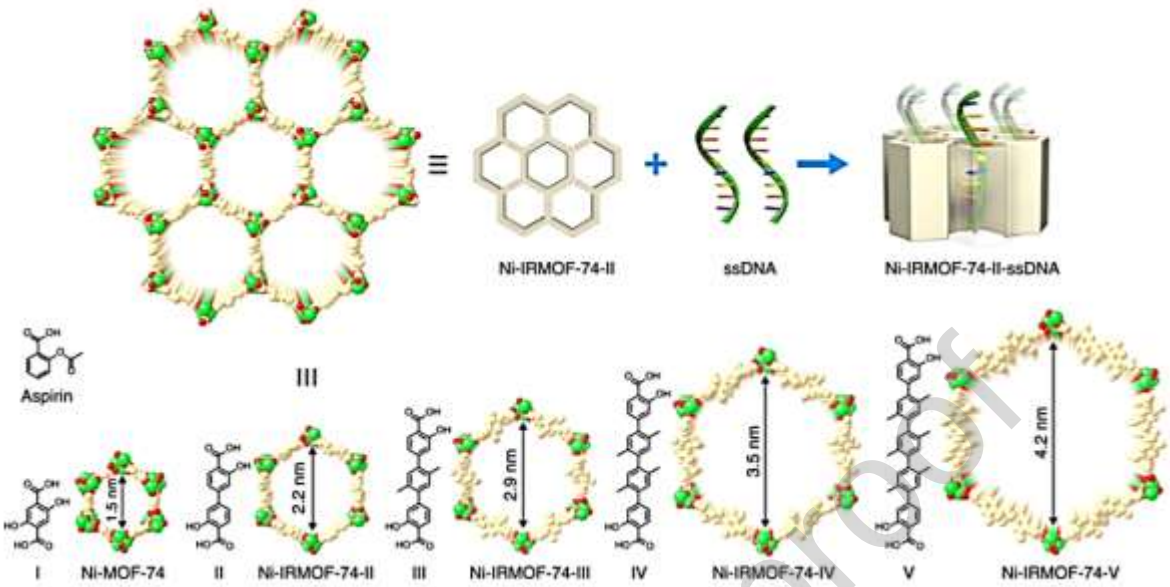

Fig. 1. Tailoring of MOF ligands for better DNA loading due to pore size optimization "Adapted with permission from [88] " .

9. Prediction of MOF properties using machine learning

As mentioned earlier, the experimental analysis of material properties can take a long time, ranging from several hours to several months, depending on conditions, availability of materials, and applied methods. Therefore, various AI methods have been developed for predicting various material characteristics. The timescale of experimental analysis could be reduced from days to minutes or hours using AI methods. Furthermore, these techniques provide a platform for large-scale material monitoring and screening, such as MOFs. Among different AI techniques, ML approaches could accelerate materials analysis and extend the data from a smaller dataset to a more extensive search space of MOF materials [89].

The selection and preparation of input and output data in ML models are essential for property prediction. In the case of MOFs, researchers usually have used input data, including geometrical chemical and energy-based descriptors, that could be calculated using the computational tools and output data, including large-scale computational outcomes, which present an adequate number of data points [90]. There are several studies in which ML has been utilized for the property prediction of MOFs, which will be described in the following sections. The benefits of these properties for designing various DDSs are also presented accordingly.

Journal Pre-proof

9.1. Mechanical properties

Mechanical properties, as physical properties, could affect the performance of MOFs in different applications [4]. There are some studies in which MOF behavior has been investigated under mechanical stress. MOFs' mechanical stability and flexibility are essential parameters that should be considered in the field of interest. At a larger scale, some MOFs, such as MIL-53, and MIL-88, could display mechanical flexibility [91–94], which could be applied to increase MOF performance in different applications. Thus, predicting and regulating the MOF mechanical properties is a crucial phase for effective implementation [95]. Mechanical properties such as pore volume or surface area are important in drug delivery applications, especially loading and release [67,96]. Also, the mechanical flexibility of such nanoparticles can assist in various matters of carrier design. Compared to rigid structures, flexible nanoparticles can have more blood circulation and endocytosis [96].

In addition to experimental analysis, computational methods could also assist in understanding the mechanism of the deformation process under mechanical stress [97]. However, computational analysis of MOF mechanical properties, especially on a large scale, is not economical. Therefore, ML techniques could provide a promising alternative for evaluating mechanical properties.

In this context, Moghadam et al. [98] analyzed the mechanical properties of MOFs on 3385 hypothetical MOFs with different topologies using a multiscale modeling approach. In this regard, firstly, high-throughput screening was performed using classic simulations to estimate G and K for the MOFs in the data bank. In the outcomes, fascinating relationships appeared, particularly how the linker length, pore volume, surface area, and maximum coordination number (MCN) affect the elastic modulus of materials. The elastic moduli of MOFs were predicted using an artificial neural network (ANN) based on 13 judiciously selected.

Two distinct ANN models, one with topology information and another without topology information, incorporated as descriptors, were constructed to reveal the topology effect on the MOF mechanical properties. The prediction accuracies of the two ANN models exhibited prominent differences. The model with descriptors exposed $R^2 = 0.98$, whereas another model (without descriptors) showed $R^2 = 0.70$. These findings reveal a crucial correlation between topology and mechanical properties of MOFs. A deeper assessment showed that ANN with topology descriptors reserved accuracy in all modulus, while ANN model without descriptors showed a worse result in the prediction for MOFs with greater bulk modulus. After ML-based analysis, MD simulation, as a type of molecular simulation, was performed on a series

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of specific structures, in which force field parameters were obtained using the ab initio method. The results obtained from MD analysis validate the previously observed patterns inferred from ANN modeling and extensive screening.

Specifically, a consistent decrease in bulk modulus with increasing equilibrium cell length (approximately proportional to the length of the liquid crystal display (LCD) or interface) was confirmed. Additionally, MD simulations assessed the pressure at which a lack of crystallinity may be detected, revealing a significant linear relationship between this pressure and the bulk modulus. In summary, ML models offer potential advantages in assessing the mechanical characteristics of MOFs. However, further investigation is required to determine the impact of these properties on drug delivery.

9.2. Electrical conductivity

Large pores and electrically inactive parts, such as carboxylate linkers in the MOF structure, make them electrical insulators. However, researchers achieved electrically conductive structures by rationally designing MOFs while maintaining porosity. Dinca et al. demonstrated that MOFs could become electrically conductive through a rational design and permanently maintain their porosity [99].

Subsequently, several other studies designed electrically conductive MOFs, which experimentally discovered MOF conductivity up to 1580 S/cm [100–103]. This type of MOF could be used in various applications, such as transistors [104], sensors [105], and supercapacitors [106].

Applications of electrical conductivity in DDSs are diverse. The conductive MOFs can form biosensors to evaluate the effectiveness of drug delivery or might be applied for the triggered release of cargo using electrical waves [107,108].

The increased contact between the molecules of interest and the conductive pathways due to the intrinsic porosity of MOFs results in capable conductive MOFs. Since a limited number of these MOFs are known, AI techniques such as ML can lead to the detection of new conductive MOFs and the prediction of MOF conductivity. In this regard, He et al. used ML methods to predict the electrical conductivity of MOFs for the first time. MOFs' large units and chemical diversity lead to a greater need for computation. The transfer learning method was applied in their study to overcome these limitations (Figure 2). Initially, ML models (Logistic Regression, Support Vector Classifier, Neural Network, and Random Forest) were trained using data from various but related classes of inorganic materials from a database (Open Quantum Materials Database). Logistic

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Regression (LR) involves constructing a model to determine the probability of a specific outcome occurring based on an input variable [109]. The Support Vector Classifier (SVC) is utilized to classify input data that is provided and processed as a group [110]. Subsequently, the trained models were utilized to predict electrical conductivity, employing techniques from ML. The performance of these models was evaluated, revealing accuracies ranging from 88% for the LR model to 97% for the RF model. Prior to predicting the electrical conductivity of MOFs, a method called t-distributed stochastic neighbor embedding (t-SNE) was employed to compare the distribution of MOFs with that of the inorganic materials used to train the models. The significant overlap observed in the distributions indicated that ML models developed for inorganic materials could be effectively applied to predict electrical conductivity in MOFs.

Furthermore, a multivoting scheme was applied for the transfer learning method, and outcomes were obtained from all four models. A CoRE MOF database containing 2932 MOFs was analyzed, and ML models could detect metallic MOFs from multivoting results [111]. If it is of concern to produce MOFs with electrical properties for triggered drug delivery or biosensor formation, the presence of such attributes can be evaluated before synthesis using AI models.

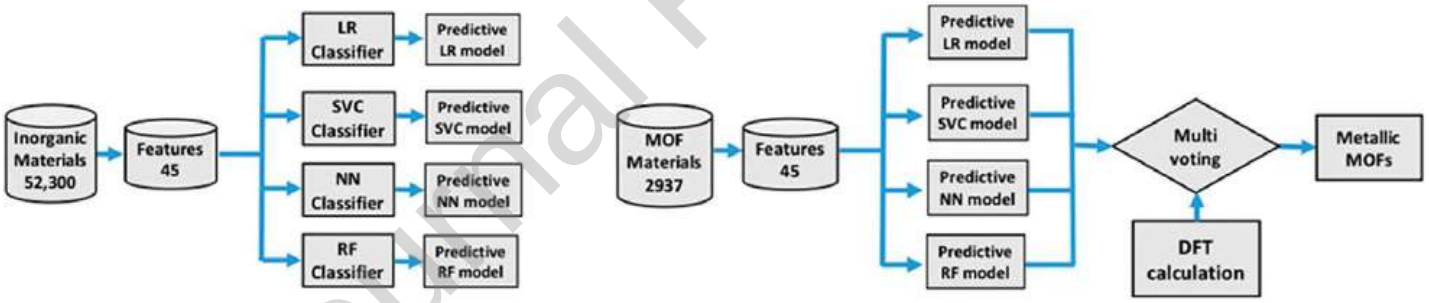

Fig. 2. Transfer learning approach used to predict MOF electrical conductivity "Adapted with permission from [111]. Copyright {2018} American Chemical Society"

9.3. Adsorption ability

One of the abilities of MOF structures is adsorption. Adsorption via MOF structures has been reported in many articles [112–116]; however, researchers have only recently shifted the focus toward ML modeling of this MOF characteristic.

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Although this approach has not been tested in drug carrier tailoring, the adsorption of drug molecules can ensure high loading capacity and encapsulation efficiency, resulting in a high yield and cost-effective treatment using MOF molecules [117].

Acetylene (C_2H_2) is one of the essential alkynes and is hard to store due to the risk of explosion in high pressures [118]. A recent study presented a method to predict MOF adsorption in less than one minute [119]. MOFs with Cu open metal sites (Cu-OMSs) proved to have the best acetylene adsorption capacity compared to other MOFs. 7855 Cu-OMS MOFs were synthesized via ToBaCCo software based on 877 Cu-OMS MOFs gathered from CSD. Among the synthesized MOFs, only structures with aperture diameters less than C_2H_2 kinetic diameter were selected (8681 structures). Decision Tree (DT) modeling showed that Cu-OMS, pore volume (PV), and gravimetric surface area (GSA) are adequate to determine high MOF adsorption. Gradient Boosting Decision Tree (GBDT) was the best modeling algorithm to relate C_2H_2 adsorption to MOF attributes. The prediction accuracy via GBDT was high, with an R^2 of 0.93, proving this method to be time-saving and precise.

Adsorption of harmful metals from natural media like water using MOFs is essential for solving environmental issues and wastewater treatment [120]. A UiO-66-(Zr) MOF structure grown on layered double hydroxide sheets was simulated via ANN in 2022 to adsorb Pb(II) and Cd(II) from water [121]. The adsorption capacity and metal concentration in aqueous media showed a positive correlation owing to the change in the pace of the mass transfer and the process driving force. Due to the strong interaction between Cd(II) and MOF structure, Cd(II) sorption was more on the nanocomposite compared to Pb(II). The R^2 value greater than 0.99 presented high accuracy during the algorithm's training and validation.

Another example of metal absorption from aqueous media happened in a 2022 study about Arsenic absorption [122]. A total of 13 distinct MOF structures were investigated under a range of experimental conditions encompassing temperature, pH, and the surface area of the adsorbent. The study employed several machine learning algorithms, namely Random Forest (RF), Extreme Gradient Boosting (XGBoost) [123], GBDT, and Light Gradient Boosting Machine (LightGBM), to analyze the data. LightGBM exhibited superior performance among these models, exhibiting the lowest average absolute percent relative error (AAPRE) at 2.88% and the smallest standard deviation of errors (STD) at 0.0628.

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These examples may hold great promise in applying the prediction of this property for the design of DDSs in the future.

9.4. Gas storage ability

Gases are important energy sources, and gas storage is one of the most efficient ways of providing green energy. It also prevents toxic gasses from entering the atmosphere, controlling the greenhouse effect [124,125].

Gas therapy is considered a new perspective in treating various diseases, from cancer to infectious and cardiovascular problems [126]. The labile properties of most gases make them hard to deliver, urging researchers to think of novel gas storage and delivery methods [68]. Co-delivery of gases and drugs is also helpful for gaining synergistic and additive effects from both elements [127].

One of the best approaches to storing gases is via MOF nanostructures due to their porous structure, high surface area, tunable apertures, and easy functionalization [128–130].

Hydrogen (H_2) can be used as a fuel; however, storing H_2 in fuel cells is difficult but possible with MOFs [131,132]. Prediction of proper MOF structures to be applied as a storing structure for H_2 is applicable via ML [133,134]. Extremely randomized tree (ERT) was the model used in 2021 for the uptake of hydrogen (Figure 3) [5]. 24,674 MOFs were utilized for training the algorithm, resulting in accurate predictions made upon 820,039 structures in seven crystallographic aspects, among which pore volume and void fraction proved more efficient for gravimetric and volumetric capacities, respectively. The ML model could determine suitable MOFs for pressure swing and appropriate structures for temperature-pressure swing. The high R^2 and accurate modeling resulted in a website (HyMarc) entailing the model used in the article for MOF prediction.

Gradient boosting regressor (GBR) was used in 2022 to predict five MOF features, temperature, and temperature-pressure swing to be applied in the process of gasification with liquefied natural gas (LNG), which was coupled with adsorbed natural gas (ANG) charging method [135]. LNG–ANG could be of use in methane storage and delivery. The resulting data were used to synthesize two MOF compounds (one with cobalt and the other with copper metal core) for LNG–ANG methane storage. The Cu-MOF was the more stable structure after multiple methane adsorption-desorption, which was predictable with MD data.

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Foretelling gas storage abilities via MOF structures might establish better nanoparticles for gas therapy and delivery, especially gases such as nitric oxide, hydrogen sulfide, and carbon monoxide, specifically considered in various treatments [136].

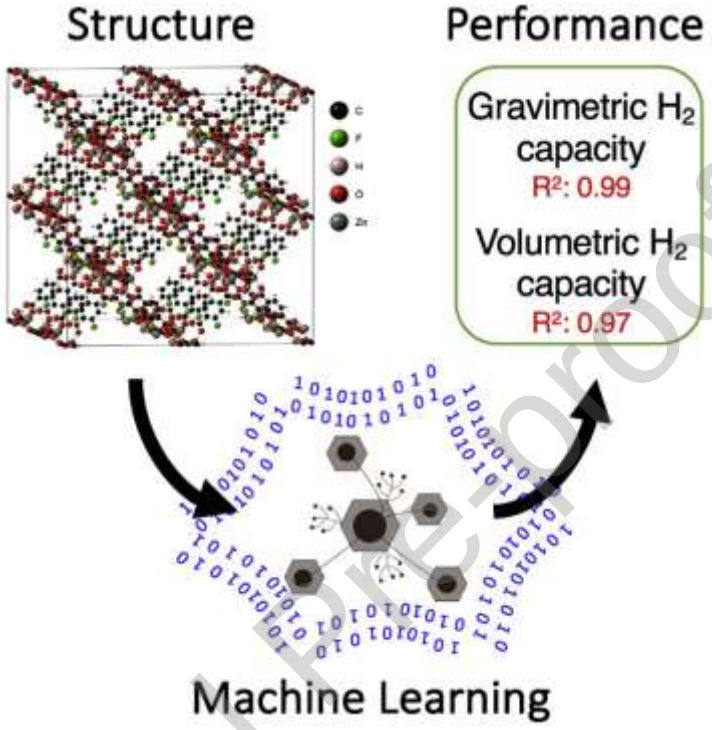

Fig. 3. H_2 storage prediction of MOF structures via ML "Adapted with permission from [5]".

9.5. Water stability

Water purification ensures proper environmental balance and safe drinking water [137]. MOFs are of use in water treatment, removing contaminants from this medium. Therefore, water stability is a feature that needs to be checked in these MOFs [138,139]. Also, some other MOF applications (e.g., adsorption) may be conducted in humid conditions, which urges water-stable MOFs [140]. ML is beneficial in classifying MOFs in groups based on water stability or predicting their stability based on structure [141].

MOFs that degrade easily in water cannot be trusted for drug delivery due to easy degradation in biological fluids and cargo release in mediums other than the targeted organ. Therefore, MOFs used in drug transportation must be stable in water for the duration of acting as a carrier [140]. However, degradation has to occur in the site of action (e.g., tumor environment) to guarantee drug

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release, which calls for some sensitivities in the MOF structure, such as low-pH sensitivity [142]. Hopefully, ML algorithms can forecast such delicacies in molecular formation and prevent the usage of confounding factors such as multiple layers and coatings that might change the surface properties and nanoparticle size [143].

A model trained with approximately 200 MOFs used metal nodes, organic linkers, and metal-to-ligand ratios for water stability prediction [144]. A two-class model (to distinguish stable MOFs from unstable) and a three-class model (to distinguish kinetically and thermodynamically stable MOFs from unstable) were applied. Water stability was associated with more atomic radius and less potential for ionization of metal centers, along with ligands having fewer 6-atom rings and more cyclic bivalent junctions. SVM, RF, and GB were the applied algorithms of this study. The accuracy of this model was tested by predicting data from 10 already known MOFs, and it was also used on new MOFs as a means of their water stability analysis.

In the gas storage section, previous discussions have highlighted the potential of MOF materials in this particular process. Nevertheless, a significant obstacle to overcome in CO_2 adsorption is achieving effective carbon capture when water vapor is present [145,146]. To address this challenge, researchers have employed the Monte Carlo tree search (MCTS)29 and recurrent neural network (RNN) techniques to evaluate the capacity of MOFs to capture CO_2 under humid conditions. (Figure 4) [147]. Low Henry coefficient and hydrophobic nature were traits that led to water vapor stability. Synthesizability and high adsorption capability were characteristics leading to better CO_2 capture. The structure-property relationship showed that an intermediate value was suitable for pore size (14.18 Å), and the optimal surface area was 1750 m^2/g because specificity in adsorption favored smaller pore sizes while higher adsorption needed larger values of this factor. Designing promising hydrophobic MOFs for CO_2 capture in the pressure swing adsorption was achieved by benefiting from the algorithm applied in this study.

Water stability prediction algorithms can also pave the way for anticipating stability in other media, such as blood or metabolizing organs like the liver. It might even facilitate the production of oral MOF formulations by recommending structures stable in the gastrointestinal fluids [148,149].

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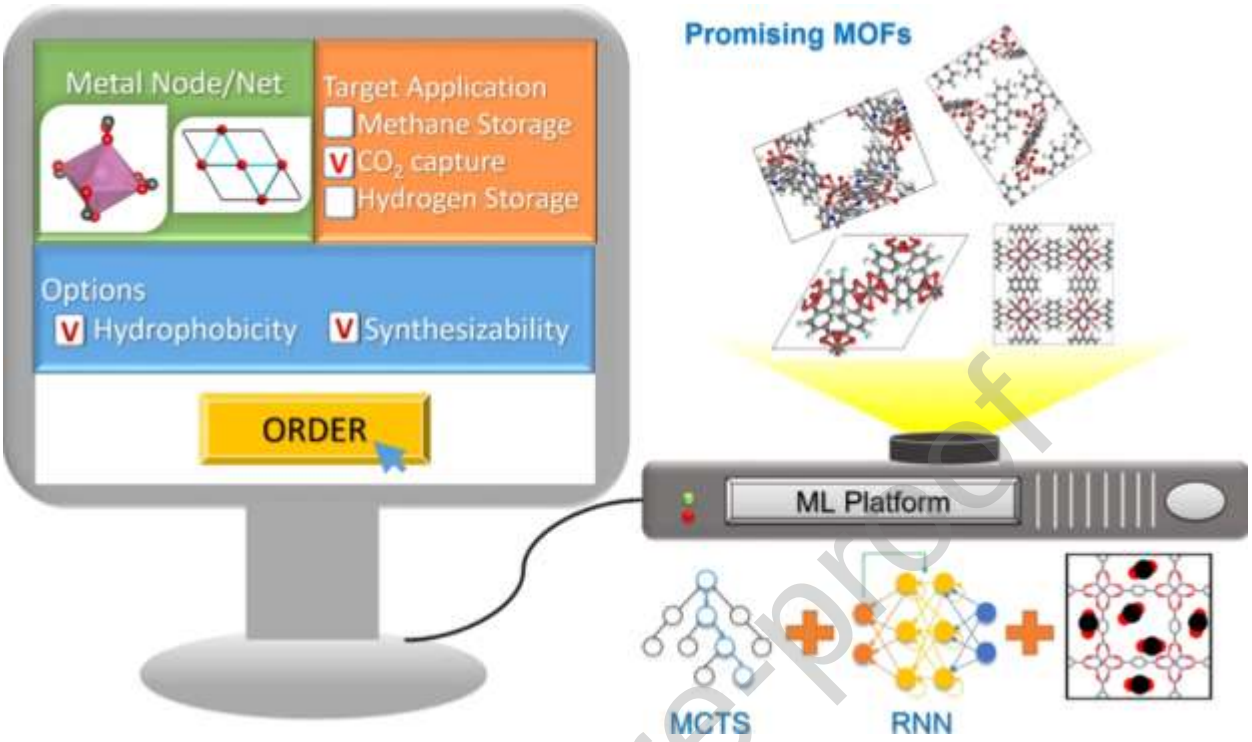

Fig. 4. ML modeling of MOF CO_2 capture in humid conditions "Adapted with permission from [147]".

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9.6. Quantum-chemical properties

Different quantum-chemical characteristics of MOFs can also be evaluated and used as classification elements. Characteristics include charge, spin and state densities, partial charges, and optimized geometrics. Computational models could be applied to anticipate some features of hMOFs. Models can be arranged into two classes: (A) quantum-based electronic structural techniques and (B) classical methods (e.g., MD and MC simulations). Wave function theory (WFT) and DFT are two routes to solving the Schrödinger equation, a major tactic in characterizing various quantum-chemical attributes [150,151].

DDSs are used toward various ends. As quantum-chemical properties may show interactions happening at molecular levels, predicting such characteristics in drug carriers could show whether they are increasing the solubility of the loaded drug (such as the circumstances in which ABRAXANE® was first created) or if the carrier can contain multiple drugs without the fear of their possible interactions [152–155]. This outlook may seem far-fetched for the moment; regardless, such predictions have occurred for MOFs, although not yet in drug delivery with all

the delicate interactions between the body and the drug, the carrier and the drug, the carrier and food, etc. [156].

A Quantum MOF database was introduced with the quantum-chemical characteristics of about 14,000 MOFs (Figure 5) [152,157]. DFT was employed in combination with various ML models. Among these models, the crystal graph convolutional neural network (CGCNN) [158] and the smooth overlap of atomic positions (SOAP) [159] exhibited the most favorable performance metrics. The mean absolute error, coefficient of determination (R^2), and Spearman rank-order correlation coefficient for CGCNN were determined to be 0.274 ± 0.008, 0.876 ± 0.011, and 0.932 ± 0.005, respectively. Conversely, the corresponding SOAP values were 0.357 ± 0.008, 0.822 ± 0.010, and 0.910 ± 0.003. This model anticipated different quantum properties, concentrating on band gap prediction to identify conductive MOF structures based on materials presenting low band gaps. Although not as precise as CGCNN in regression, SOAP and composition-based attributes (examples of tested ML models in the study with composition-based features were Stoichiometric-45 and Stoichiometric-120) can be applied along with unsupervised dimensionality reduction methods for uncovering structure–property relationship in the designed database. Identification of some newly explored iron-based MOFs was among the many outcomes of the 2021 article, which gives hope in proposing such predictions in drug formulations within MOF structures.

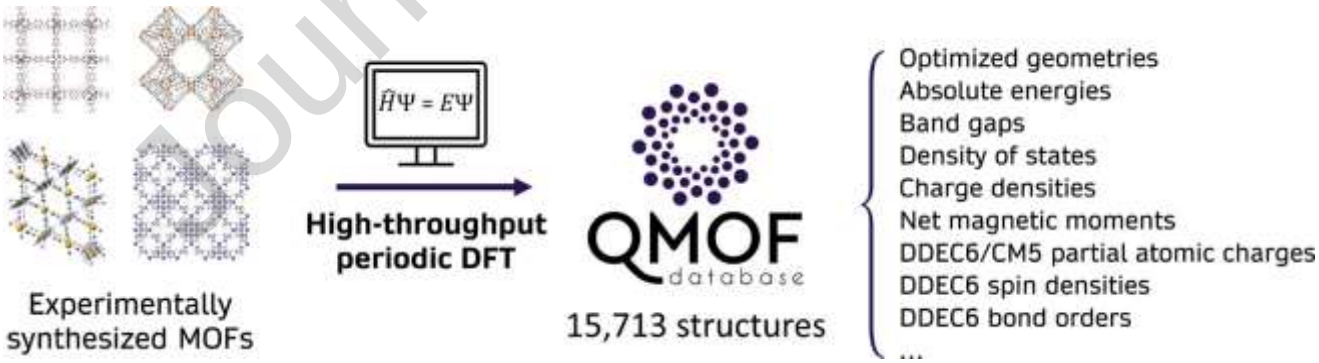

Fig. 5. Schematic of quantum MOF database "Adapted with permission from [152,157]".

9.7. Guest Accessibility

Adsorption, separation, and other applications of MOF materials are relative to the accessibility of its structure. Whether or not guest molecules can access MOF structure determines the MOF's

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ability to fulfill its functions. ML can relate structural or chemical MOF features to guest accessibility using various algorithms [160–163].

The flexibility of MOF structure and its capability to interact with cells or cell receptors can be predicted using guest-accessibility properties that can be of major significance in DDSs [164,165]. Many carriers are attached to ligands to internalize via cell receptors in inflamed or cancerous tissues [166]. The ability of MOFs to be attached to such ligands (from antibodies to small molecules) could be measured beforehand with ML models, preventing blind laboratory efforts and the waste of materials [167].

Chemical characteristics of metals and organic ligands were investigated in a 2021 article to predict guest accessibility of MOFs based on these factors via ML algorithms (Figure 6) [164]. A dataset of 3D MOFs was collected from CSD, and RF was applied as the best ML algorithm to correlate metal-ligand mixtures with corresponding guest accessibility, defined as pore size larger than 2.4 Å. 14,296 MOFs were selected as 1M1L3D dataset that contained one linker and one metal. ML model was trained based on different metals, linkers, and target accessibility regarding pore size. The metal descriptors were atomic weight, number, radius, polarizability, electronegativity, and affinity for electrons. Then, a second model was developed based on whether the MOF pore sizes were small (between 2.4 and 4.4 Å) or medium and large (more than 4.4 Å), and a third model for determining if the pores were medium (between 4.4 and 5.9 Å) or large (more than 5.9 Å). The three models' accuracy was 80.5%, 76.4%, and 68.5%. The results of this study could be used in absorption, separation, and catalysis fields.

Awareness of such important molecular traits would enlighten drug carrier design and synthesis, preventing problems after development and during in vitro and in vivo testing.

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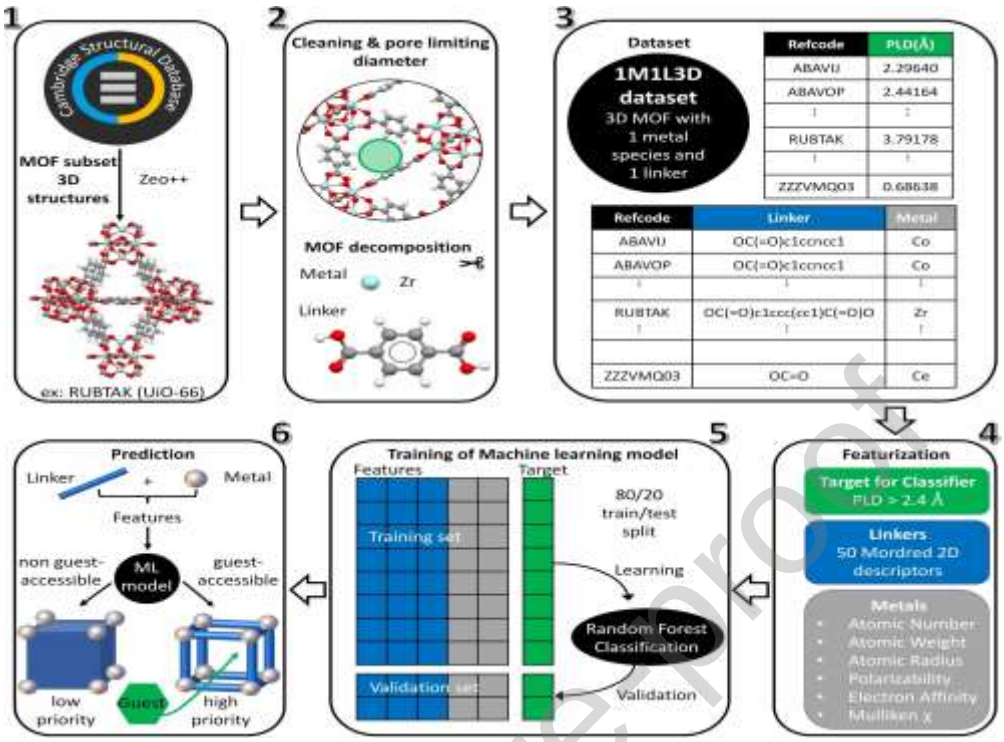

Fig. 6. MOF guest accessibility ML modeling "Adapted with permission from [164]".

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Conclusion

Machine learning (ML) has appeared as a new tool providing a platform for predicting material properties that are not easy to determine using conventional methods. In this review, various ML procedures were introduced to predict the properties and capabilities of MOFs in drug delivery systems (DDSs). As observed in the studies presented in this review, it is clear that ML models greatly impact MOF investigations. ML techniques have been successfully applied to predict mechanical characteristics, electrical conductivity, adsorption, gas storage, gas separation, CO_2 capture abilities, water stability, and guest accessibility of MOFs. However, little work has been done to predict MOF properties in biomedical applications, especially drug delivery. Although notable advancement has been made, ML applications on MOFs are in the early stages and require more studies. Predictably, there will be a substantial surge in the number of such investigations in the near future aimed at predicting the characteristics of MOFs. Coupling ML methods with the efforts in the lab to synthesize MOFs for drug delivery purposes might be the key to faster drug carrier development soon.

Declarations of interest

The authors declare no conflict of interest.

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CRediT author statement

Niki Pouyanfar: Visualization, Conceptualization, Writing- Original draft. **Mahnaz Ahmadi:** Visualization, Writing- Original draft. **Seyed Mohammad Ayyoubzadeh:** Writing- Original draft. **Fatemeh Ghorbani-Bidkorpeh:** Supervision, Project administration, Writing- Review & Editing.

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Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Metal-organic frameworks have shown exclusive properties and many applications
- The use of metal-organic frameworks is of great importance in drug delivery
- Experimental examination of these materials is complex, costly, and time-consuming
- Machine learning is an alternative for accurately predicting such characteristics
- Predicting properties of drug cargos with machine learning is highly effective

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