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Review

Review on machine learning application in tissue engineering: What has been done so far? Application areas, challenges, and perspectives

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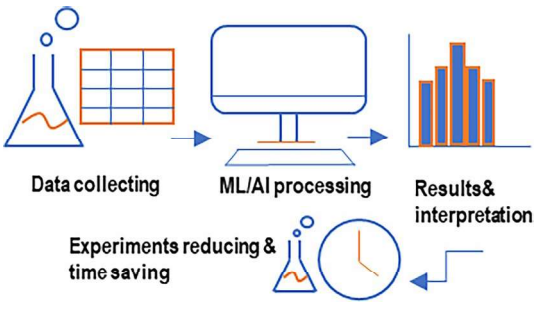
ABSTRACT

Artificial intelligence and machine learning (ML) approaches have recently been getting much of researchers' attention. The growing interest in these methods results from the fast development of machine learning algorithms in the last few years, especially artificial neural networks. In this review, we pay attention to the need and benefits that ML approaches can bring to tissue engineering (TE). We critically evaluate the possibilities of using the ML approaches in the tissue engineering field. We consider various paths of its utility in the TE, such as scaffold design, predicting the biological response to the scaffold, optimizing drug delivery approaches, supporting image analysis, and modeling scaffold in vivo performance. The current status of ML implementation is presented and supported by many study examples. On the other hand, we analyze the present difficulties and challenges in implementing ML approaches to tissue engineering, including the quality of published data, databases and repositories availability, the need for experiment and results publishing standardization, and ethical issues. Additionally, we assess the available natural language processing tools that could support TE research.

GRAPHICAL ABSTRACT



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Introduction

The potential of the human body to regenerate tissue and organs is inherent. However, there are several reasons that the reparative response may be limited and self-healing may not succeed, including infection or a large defect resulting from a serious medical condition. Regeneration solution is important from the perspective of society's aging, the incidence of lifestyle diseases, interest in sports activity and resulting injuries, and patients' expectations for quality of life. Therefore, the utilization of implants and tissue engineering constructs to replace tissue or promote tissue regeneration and healing is necessary [1]. Tissue engineering is a comprehensive and multidisciplinary subject that endeavors to develop biodegradable and bioactive biomaterial constructs, commonly named scaffolds, capable of maintaining or enhancing tissue function. This is a highly evolving discipline that employs a variety of biomaterials, growth factors, manufacturing, and modification methods to stimulate particular biological responses [2–4]. It requires the application of knowledge from a number of cutting-edge disciplines, including materials science, bioengineering, design and manufacturing, medicine, and informatics [5].

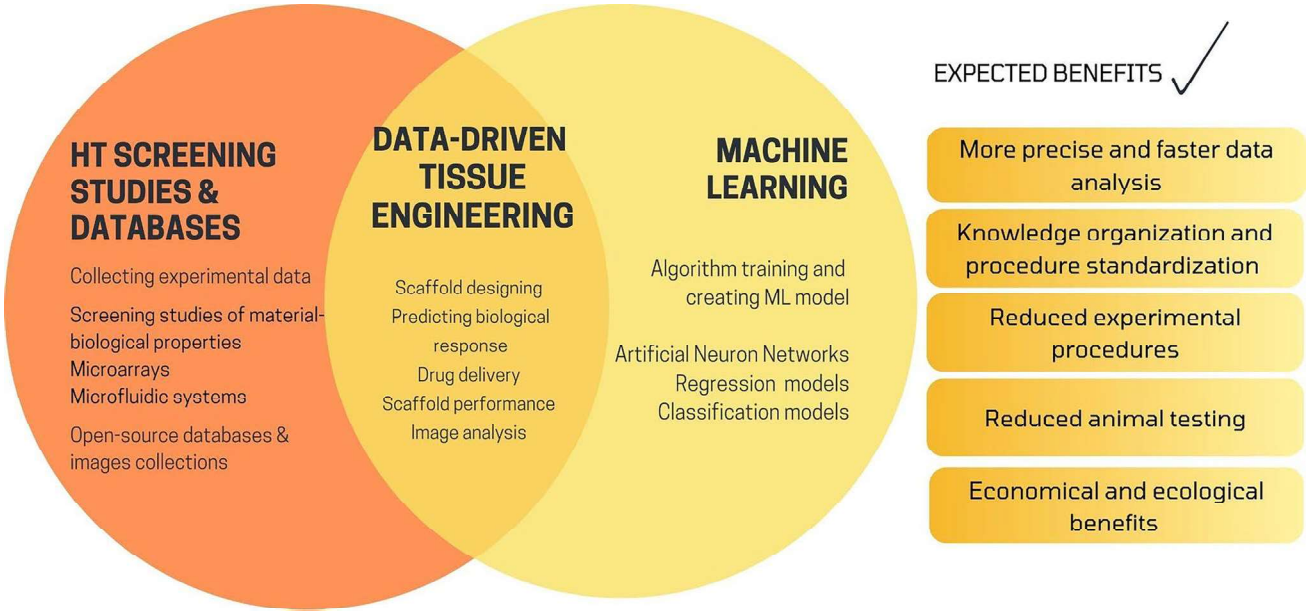
Biomaterial development for tissue engineering applications is a very challenging process. The material to be engineered should have the desired functionality, and it needs to exhibit great biocompatibility in a human physiological environment. From the design of tissue-engineered material to its application, there is a long development process consuming a vast amount of time and resources consisting of prior rational design choices followed by iterative trial-and-error experimentation. Computational materials science offers a variety of material design tools to speed up and lower the cost of developing new materials in line with industry demands. Models based on science and various length scales can determine how designed materials behave at various levels, including the atomistic, microstructural, and product/component scales [6]. The machine learning approach is the new path with the potential to accelerate the progress in tissue engineering.

Machine learning is the subset of artificial intelligence, which uses mathematical algorithms to predict a statistically likely outcome of a defined problem. It aims to process large datasets, find relationships and correlations, and thus improve and fasten the interpretation of data. In the last decade, there has been revolutionary progress in this field, which has pushed forth advanced tools in the financial sector, logistics, motorization, e-commerce, cybersecurity services, and many other areas. ML approaches also influenced the development of many fields of science, such as image analysis in medicine or drug discovery. As it is an extensive and rapidly developing discipline of knowledge, we recommend reading the recent reviews on this topic [7–9]. In the next chapter, we briefly introduce the most important aspects of machine learning that could be helpful for the reader.

Considering the complexity and multitude of factors and dependencies in both scaffold manufacturing and interaction with the human body, machine learning can address a lot of TE needs. ML can accelerate progress in this field, opening new opportunities and solving existing challenges when combined with advanced biomedical technologies (Scheme 1). This review article focuses on the current state of machine learning applications in tissue engineering. As the tissue engineering is a very broad discipline drawing from many fields including bioprinting, drug delivery incorporation, gene&RNA therapies, and many others, we have chosen several important areas of TE in this review. We discuss these areas that are fundamental in TE and currently present many examples of ML/AI implementation, namely optimization of bioprinting and other scaffold design techniques, predicting material-cell interactions, optimizing drug delivery systems, biological structures images analysis, and modeling the in vivo performance of scaffolds. By exploring the latest achievements and critically assessing the possibilities of AI/ML in tissue engineering, this article aims to provide a comprehensive view of the current knowledge and future directions of this dynamically developing field.

Need for AI/ML solutions for the TE field

Currently, the phrase "tissue engineering" generates 89,374 original article results in the *Scopus* database, including 5432 articles published in the year 2023 [10]. So far, huge research work in TE has been done, including, among others, the development of scaffold manufacturing methods, scaffold composition, specific surface modification and enrichment in dedicated biomolecules, as well as the development of analytical methods. Examples of the last 30 years'



Scheme 1 The concept of data-driven tissue engineering and expected benefits.

achievements in the TE field are stimuli-responsive materials [11–13], injectable hydrogels [14], 3D bioprinted constructs [15], 3D-printed scaffolds [16], bioactive coatings [17, 18], release systems of growth factors and drugs [19], various compositions of bioactive glasses [20], and many others.

So far, the development of biomaterials proceeded by intuitive selection and modification of manufacturing procedures together with biological assessment [19]. Material engineering requires a wide knowledge of process–structure–property (PSP) linkages to optimize its design for a specific application. This approach requires initial design decisions, followed by a process of repeated experimentation and refinement. For example, many authors reported methodical studies on the optimization of bioprinting parameters [21, 22]. Webb B. et al. optimized extrusion-based bioprinting to limit the shear stress acting on the bioink thus reducing cell viability, while maintaining maximum geometric quality[23]. Moreover, the problem with a systematic compendium on how material feature affects biological reaction results from a large number of sub-parameters of a given feature, combined effects of material features, and heterogeneity of material structures [1, 19]. For example, Mackay B.S. et al. presented the difficulty and time limitations in conventional analysis of the material feature-cell response on the example of topography and its sub-parameters complexity [1].

For many years, there have been attempts to improve and fasten research in TE using computer modeling (CM) [24, 25], mostly applying the finite element method, which is commonly used to minimize the need for experiments in empirical sciences. For example, CM was used in dental tissue engineering to answer the question of how scaffold-bone compound stiffness is affected by macroporosity, crack density, and resorption/bone formation rates [26]. What is important is that in the CM approach, the given problem is defined by providing relationships between input and output indicators to build devised mathematical models for the simulation of the process. In contrast, in the ML approach, there is no need for prior knowledge of physical, chemical, and biological correlations and mechanisms, which seems to be a big advantage for the investigation of TE systems.

ML is based on building the mathematical model by training on large datasets, which means finding key features and correlations among data based on an enormous amount of examples [27]. The key characteristic of the machine learning approach is the ability to recognize complex patterns in big datasets. Machine learning is based on three components: the input layer including initial data for processing, the

hidden layer meaning computation with mathematical algorithms, and the output layer, which are predicted results. Taking into consideration the characteristics of the training process, three main categories of machine learning can be distinguished: supervised learning, in which the user provides input and accurate output data for training the model; unsupervised learning, in which only input data is provided, and the program itself has to recognize data patterns; and reinforcement learning, in which additionally "punishments and rewards" are defined to make the learning process faster. Examples of commonly used machine learning algorithms are linear regression, logistic regression, support vector machine (SVM), decision trees, K-nearest neighbor (KNN), random forest classifier [9], and artificial neuron networks (ANNs). "Deep learning" is a subcategory of machine learning, that uses ANNs with at least four hidden layers guaranteeing very high computation accuracy, but requiring more computing power and longer training time. It is important to emphasize that different ML algorithms may be more suitable and achieve better results depending on the specific problem and data characteristics.

Taking into account the specificity of the tissue engineering field, we pointed out several areas, in which the discipline can benefit from using ML approaches:

- *More rational scaffold design*—understanding the process-structure–property linkage and optimization of process parameters,
- *Predicting biological response to scaffold*—understanding the complex interaction of cell and scaffold interaction,
- *Image analysis*—automatic and more precise image analysis, for example recognizing cell differentiation stages,
- *Modeling biological and mechanical scaffold performance*—using ML algorithms to improve or replace currently used computation methods,
- *More precise and faster data analysis and results interpretation*—improving analysis of big datasets originating from high-throughput screening studies,
- *Knowledge organization and procedure standardization*—implementation of ML approaches can support experimental and results publishing standardization,
- *Reducing animal testing*—modeling biological performance of scaffold can result in less need for in vivo testing,
- *Ecological and economic benefits thanks to experiment limitation*—using well-trained ML algorithms can cause experiment reduction with ecological and economic savings from a further perspective.

Application areas of the AI/ML methods in the TE field

Artificial intelligence (AI) tools and machine learning (ML) have great potential for advancing the overall effectiveness of tissue engineering projects. The key application areas of machine learning in tissue engineering include optimization of bioprinting and other scaffold design techniques, predicting material–cell interactions, optimizing drug delivery systems, supporting image analysis, and modeling the in vivo scaffold performance. Besides, ML approach can widely contribute to analysis of experimental results, such as those originating from FTIR spectroscopy [28].

These components significantly contribute to advancing the field of tissue engineering, creating innovations with the promise for the future of healthcare. Table 1 presents current examples of AI/ML utilization showing wide spectrum of application in tissue engineering. In the following chapters, we analyze the most significant application areas in detail.

Scaffold designing

ML offers the breakthrough potential to improve the scaffold designing in TE by the systematic analysis of linkage between fabrication parameters, material properties and biological response. Currently, ML algorithms are a tool supporting manufacturing optimization, which has potential to limit the conventional trial-and-error experimental approach in the near future. In the first subsection of this chapter we in particular consider bioprinting, which is currently the leading manufacturing technique in TE, and in the second one, we review the other important scaffold designing methods, such as electrospinning, freeze-drying, and self-assembly of peptide hydrogels.

3D bioprinting

3D bioprinting is one of the fundamental techniques in tissue engineering. Bioprinting was defined by Guillemot F. et al. as the use of computer-aided transfer

Table 1 Examples of application areas of AI/ML in biomedical applications

No	Application area of AI/ML	Description	AI/ML model type	Key parameters used in the model	Pros	Cons	References
1	Bone tissue engineering	Utilizing AI in bone tissue engineering and prosthetics involves tailoring implants and scaffolds through various methods such as visualization, real-time monitoring, and predictive modeling for implantation scenarios	Explainable AI (XAI)	Image recognition for acute intracranial hemorrhage (ICH)	Provides more information about model decisions; greater confidence in research results	The complexity of deep learning models	[29–31]
2	Cardiac tissue engineering scaffolds	Machine learning for predicting cell behavior in cardiac tissue engineering	Decision trees; Logistic regression; K-nearest neighbors and others	Materials and their composition, cell lines, and fabrication method	Analysis of the obtained models showed that ML can accurately predict the behavior of cells on CTE scaffolds. Additionally, Voting Classifier and Adaboost Classifier showed the best performance among all 28 ML techniques used	It is necessary to increase the volume of datasets created by including new composite materials, cells and improved manufacturing methods in order to develop more reliable predictive models	[32, 33]
3	Biomaterial properties	Predictive analysis of biomaterials properties. biocompatibility, properties of the implants, analyze cell interactions with biomaterials, predicting their impact on cells and functions in the tissue environment	Artificial neural networks (ANNs)	Material properties, cell proliferation and differentiation	Data-driven learning, adaptability, high prediction of complex patterns in biomaterial properties and bone tissue engineering	Large dataset, complex ANN structures, in some cases overfitting, complex and difficult interpretation	[34–36]

Table 1 continued

No	Application area of AI/ML	Description	AI/ML model type	Key parameters used in the model	Pros	Cons	References
4	Predicting Cellular Behaviors in Dynamic Culture Conditions	Employing artificial intelligence to predict cellular behaviors in dynamic culture conditions, considering changing parameters in the environment	Linear regression (LR), LASSO, Elastic net (EN), K-nearest neighbor (KNN), classification and regression tree (CART) and others	Viable cell density and viability, glucose, lactate and ammonia concentrations, immunoglobulin G1, dissolved oxygen, pH	Accurate prediction of future cell culture profiles; higher efficiency and effectiveness of recombinant therapeutic protein production through proactive decision-making	The choice of model elements and their combination are important, overfitting, extrapolation, and generalization,	[37]
5	3D printing, synthesis of scaffolds	Prediction and optimization of the rheological properties and printability of the bioinks	Generative adversarial networks (GANs)	Material composition, rheological properties	Enables the synthesis of desired scaffold structures and facilitates optimization	Mode breakdown may occur; challenges in creating clinically viable structures	[38, 39]
6	Image analysis of biomaterial	Utilizing artificial intelligence to analyze biomaterial compositions, ensuring the most effective physical and biological properties	3D deep convolutional neural networks (DCNNs)	Digital tomographies, for different 3D CAD models of the designed lattices	Ability to record complex spatial structures in 3D medical images, increases the accuracy of tests	Large image sets require high computational power, large data sets require high computational resources, and possible overfitting if data is limited	[40, 41]
8	Identification of biomaterials	AI utilizes materials classifications	Support vector machines (SVMs)	Structural and mechanical properties of trabecular bone	Evaluation of scaffolding structures, also in the case of a large number of dimensions	Limited parameters for large data sets, sensitive to Kernel parameters	[36]
9	Drug design	AI used to drug design	Reinforcement Learning (RL)	Molecule decomposed into a series of fragments	Advantages in comparison to SMILES-based methods includes simultanous growing of multiple fragments in a molecule scaffold and enforcing chemical rules on valence during whole process which ensures validity of designed molecules	A highly complex environment causes limitations, and difficulties in defining	[42]

Table 1 continued

No	Application area of AI/ML	Description	AI/ML model type	Key parameters used in the model	Pros	Cons	References
10	Biomaterials classification	Identification of the type of biomaterial	Decision trees	Mechanical properties of materials	Easy interpretation of results, suitable for applications with nonlinear relationships between data	There is a risk of too high a degree of matching, reduced precision with even small changes in the data	[35]

processes for patterning and assembling living structures together with non-living materials with a prescribed 2D or 3D organization in order to produce bio-engineered structures serving in regenerative medicine, pharmacokinetic and basic cell biology studies [43]. It should be emphasized that 3D bioprinting cannot be used as the synonym for 3D printing techniques implemented in tissue engineering, which rely on post-fabrication cell seeding [44]. Within 3D bioprinting three most important methodologies can be distinguished: extrusion-based [44], jetting-based [45], and vat-photopolymerization-based bioprinting[46]. Extrusion-based bioprinting relies on the deposition of bioink through a nozzle into the designed 3D constructs thanks to the fine control of computer designing and device processing. The technology of extrusion-based bioprinting gained the greatest popularity with rapid commercialization and the offer of specialized equipment from many companies. This technique allows for using a wide spectrum of hydrogels of various viscosities, obtaining large-scale constructs, and applying high cell densities. However, the resolution of printing is limited to a minimum of 200–1000 μm. Also, the balance between the mechano-rheological properties of bioinks and their biological properties has to be always considered [47]. The second type of most common bioprinting techniques, the jetting-based one, is based on ejecting cell-laden sub-nanoliter droplets of hydrogel on the substrate with high control of its spatial arrangement. In comparison to other bioprinting techniques, it provides a more precise control of cell density[45]. There are several sub-types of this technique including inkjet-, micro-valve-, acoustic-, laser-assisted-, and electrospun/electrohydrodynamic jet printing [48]. The last one, vat-photopolymerization-based bioprinting, known also as stereolithography, relies on using photoactivatable bioresin placed in a vat, which is systematically cured via the light projected by laser (e.g., UV) [49]. This technique can be equipped with a digital micromirror device, which shortens the process time but decreases bioprinting resolution [46]. Advantages of vat-photopolymerization-based bioprinting include high printing resolution (even 10 μm), high process efficiency, and high cell viability thanks to low shear stress and reduced printing time [50].

3D bioprinting requires a suitable combination of rheometric and mechanical properties of printed material and constructs spatial architecture, material composition and degradability, and biological

response to ensure good material processing, appropriate mechanical behavior, and integration and functioning of construct in the organism. Though a lot of effort has been put into printability optimization, including rheological bioinks analyses, mathematical modeling of the flow properties of bioinks, and analysis of the printed scaffold using imaging techniques, researchers still depend heavily on trial-and-error methods for producing bioprinted scaffolds [51]. The picture becomes even more complicated when taking into account cell behavior. There are many studies in the literature on the optimization of shear thinning behavior of bioinks affecting both printability and cell survival after printing [52]. With the existence of big data collection, ML can facilitate adjusting bioprinting parameters to obtain given properties [53]. Moreover, ML can be also used for in-real-time monitoring and tuning of bioprinting parameters when learning to detect defects and errors in bioprinted constructs. Below, we present examples of ML applications in the three most common bioprinting techniques.

Wang J. used the ML approach to investigate the printability of alginate/methylcellulose hydrogel as the bioink in extrusion bioprinting. The study was divided into two screening steps and the total dataset included: alginate concentration in two variants, methylcellulose concentration in four variants, temperature in two variants, nozzle shape in two variants, nozzle size in two variants, printing speed in two variants, and printing pressure in twenty variants. The filament spreading ratio (FSR) parameter calculated as the width of the printed filament divided by the diameter of the nozzle tip was established to assess the bioink printability. 1–5 values were assigned as printable and "0" and "above 5" values as unprintable due to failure in filament extrusion or filament breaking, and poor printing resolution, respectively. Firstly, ML binary classification models were used to recognize the parameter combinations resulting in printable inks. Then, eight ML regression models were applied to quantitatively assess the printability of bioink. The results indicated XGBoost model as performing the best with the R^2 value of 0.783, whereas the DNN model has the lowest prediction accuracy with the R^2 value of 0.464. The study proved the feasibility of predicting hydrogel printability by applying a systematic approach [54].

Huang X. et al. predicted the number of printed cells in an inkjet-based bioprinting process based on droplet velocity profile [55]. They measured and collected the reduction in droplet velocity between two points along the distance from the nozzle to the substrate. The testing set included 5–40 droplets with 20 droplets-set chosen for the comparison of five ML algorithms: linear regression (LR), support vector regression (SVR), decision tree regressor (DTR), random forest regression (RFR), and extra tree regression (ETR). The best accuracy with a mean error of 17% was achieved for ETR. Further, the performances of algorithms were as follows: SVR with a mean error of 19%, DTR with a mean error of 20%, RFR with a mean error of 22%, and LR with the lowest accuracy at a mean error of 31%.

Xu H. et al. employed the ML approach to predict cell viability in dynamic optical projection stereolithography-based bioprinting as the existing physics-based models are not able to forecast cell viability with suitable accuracy due to the complexity of biological systems [56]. They collected input experimental data including four crucial process parameters: UV intensity, UV exposure time, GelMA concentration, and layer thickness. Output cell viability was investigated with fluorescence assays and calculated as the ratio of the living (green) cells over the total number of cells. Neural networks, ridge regression, K-nearest neighbors, and random forest (RF) were combined in an ensemble learning algorithm. Three training sets containing 70%, 80%, and 90% of the total data were used with the remaining data for the validating set. The best results were observed in the case of a 90%-training set, for which the ensemble algorithm performed with R^2 equal to 0.953, RE—0.013, and RMSE—0.015. Also, it was presented that an ensemble learning model achieves higher prediction accuracy than its individual constituents in all training set cases. Moreover, Bao Y. stated that the machine learning approach could facilitate the selection of the most suitable photoinitiators for vat-photopolymerization-based bioprinting, especially tricomponent systems, based on the reported data with a reduction of experimental work [57].

Rafieyan et al. created an open-access dataset related to bioprinted and 3d-printed scaffolds including 60 materials, crosslinkers, enzymes, etc., 49 cell lines, cell densities, and different printing conditions with the total amount of data records equal to 1171, whereas cell response was assigned only for bioprinted constructs. Data were collected from papers and datasets available in the literature. Over 40 machine learning and deep learning algorithms were tested in predicting cell response, printability,

and scaffold quality. Neural networks performed with accuracy values equal to 0.804, 0.934, and 0.794 for qualitatively assessed features of scaffold quality, printability, and cell response, respectively [58]. This shows the high potential of currently existing data, which should encourage researchers to unify data collection and sharing.

The fine control of 3D bioprinting process parameters with the involvement of computer design creates suitable conditions for machine learning applications. The current state of the art includes mostly applying ML to optimize the printability of bioinks, predicting cell response and scaffold quality. On the basis of the literature, it can be said that researchers see great potential in machine learning as a new paradigm in bioprinting [59–61]. Overall, the use of ML in bioprinting is still in its early development phase. The attention of researchers should be paid to the choice of the type of ML algorithm model or considering an ensemble learning approach. As it was shown in many studies the prediction accuracy can differ a lot depending on the model. There are also other directions that so far are less commonly investigated such as scaffold vascularization or shape designing. Moreover, there is no doubt about the need for an open-source platform for data sharing in bioprinting, especially taking into account the promising results of ML implementation on literature data. We discuss the topic of data collection and database existence in tissue engineering in more detail in chapters 4. and 5.

Other scaffold designing methods

In this chapter, we present the application of the ML approach in other common fabricating methods in tissue engineering, such as 3D printing, electrospinning, freeze-drying, and self-assembly of peptide hydrogels.

Bayesian optimization was applied to obtain the best structural and biomechanical properties of 3D-printed PCL/magnesium nanocomposite scaffolds [62]. The goal was to optimize printing parameters including air pressure, printing speed, and nozzle temperature to achieve accurate printability and print resolution. Using machine learning techniques, the authors create a predictive model that is then used in the Bayesian optimization process. The results suggest that using the Bayesian optimization technique can effectively improve the adjusting process evidenced by limiting the experiment number to 11 iterations for each target width. It was proved that the introduction of magnesium into the PCL structure has a positive effect on the mechanical properties and biocompatibility of the scaffolds. This research illustrates the potential of combining modern 3D printing techniques, nanocomposites, ML approach, and Bayesian optimization to improve structures used in advanced biomedical applications.

In the study of Nair M. et al., random forest regression was applied to investigate the impact of freeze-drying parameters on pore size, percolation diameter, and median interconnection diameter of collagen sponges [63]. Eleven input features were taken into consideration, namely drying pressure, temperatures, choice of solvent, presence of additives, collagen concentration, whether dialysis was performed, minimum and maximum spectral intensity from circular dichroism dataset, pH, and solute content. The authors assessed the feature importance via analysis in two variants: mean impurity decrease-based importance and permutation importance. For the first one, collagen concentration or pH was indicated as the most important feature influencing three structural parameters, and for the second one—collagen concentration was pointed as the most important in all cases. The RMSE values were equal to 14%, 7%, and 18% for pore size, percolation diameter, and median interconnection diameter, respectively.

López-Flores et al. [64] predicted the production or not of aligned nanofibers by binary classification methods together with the orientation, angle, and diameter of the nanofibers by regression models and ANNs. ANNs performed with very high accuracy equal to 0.94 in binary classification and accuracy equal to 0.90 for the validation test. In the literature, there are other examples of the utilization of ML models in designing electrospun scaffolds [65, 66]. Carotenuto et al. [67] carried out a rational methodology based on the DOE for electrospun scaffolds, obtaining heuristic models that capture the relationships between process parameters (Xs) and scaffold properties (Ys). Five polycaprolactone scaffolds were fabricated according to a 22-factor combinatorial scheme in which the two X's, i.e., flow rate and applied voltage, vary between two given levels plus the midpoint. The scaffolds were characterized to measure a set of properties (Ys), i.e., fiber diameter distribution, porosity, wettability, Young's modulus, and adhesion of mouse C1C12 myoblast cells. The results of this study confirm that the implementation of statistical mapping of electrospinning processes is

possible and that the resulting statistical models can be useful for the development of TE scaffolds. Thus, electrospinning technique has a great potential for the wide usage of ML approach.

In the work of Li et al., machine learning was employed to predict the formation of self-assembled peptide hydrogels [68]. The authors created a library of 2304 compounds synthesized by Ugi reaction from 31 monomers, including 8 amines, 8 aldehydes/ketones, 12 Fmoc-amino acids, and 3 isocyanides as a training set for machine learning. The precisions of 54%, 57%, and 62% for the random forest, logistic regression, and gradient boosting, respectively were achieved. These indicators probably could be higher when increasing the quality of the dataset. The authors drew attention to the fact that data were highly imbalanced (less than 4% of cases corresponding to hydrogel-forming), thus data resampling was applied. What's more, feature importance calculation indicated the top 20 molecular descriptors for gel-forming prediction, whereas the most important were the presence of Fmoc-amino acids, the largest absolute of Burden modified eigenvalue, and the smallest absolute of Burden modified eigenvalue.

So far, the ML approach is most commonly used in 3D bioprinting and 3D printing due to the highest level of fine control of process parameters, process replicability, and feasibility to create high-quality datasets. There is no doubt that the ML approach has the potential to enhance the statistical design of experiments (DOE) in other fabrication methods as it was presented in examples of ML application in this chapter. Nevertheless, the ML approach is much less popular in some techniques. For example, we did not find a study on using ML methods in the thermally induced phase separation technique. We are convinced that in that case ML implementation could help adjust the key process parameters, such as polymer concentration, solvent type, temperatures, or cooling rate to obtain the desired scaffold structure. The above studies show that the ML approach is a crucial step toward developing advanced technologies, where data-driven methodology supports and improves the fabrication process.

Predicting the biological response to the scaffold

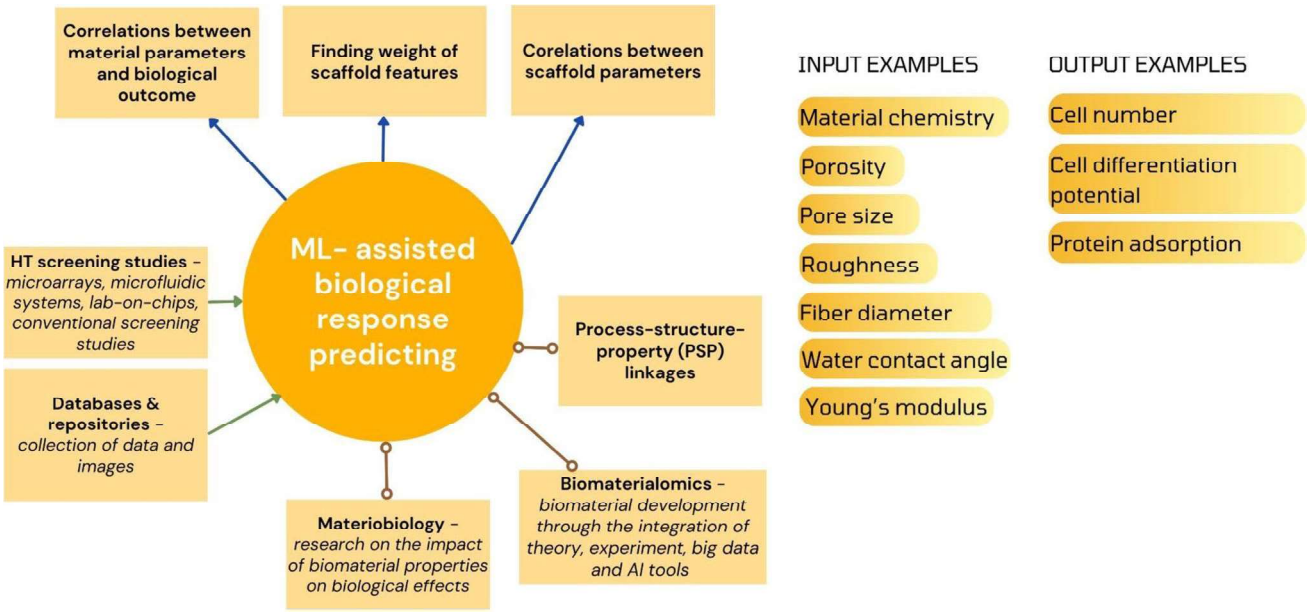
There is a belief that the machine learning approach can give new insight into the biological response to scaffold by identifying correlations between material parameters and biological outcomes, finding the weight of scaffold characteristics, and correlations between scaffold parameters. TE researchers have to face challenges regarding the high complexity of mimicking the tissue structures and the very dynamic nature of the biomaterial and human body interaction. Once a biomaterial is introduced into the organism, it initiates a series of reactions within the surrounding tissues and at the interface with the biomaterial. Interaction between scaffold and organism is dependent on the multiplicity of physicochemical factors from the scaffold side and the very intricate matter of biochemical signaling pathways [69]. In vitro tests are aimed to investigate cell response to given scaffold parameters and sub-parameters [70]. However, despite commonly performed *in vitro* studies picture of cell–scaffold interaction is still very complex. Based on the work of Roy et al. [71], we propose a mathematical expression of the correlation between scaffold parameters and biological response:

$$\text{Biological response} = f\ (\text{physicochemical or mechanical property}),$$

$$Y = a_0 + a_1X_1 + a_2X_2 + \cdots + a_nX_n,$$

where Y is the dependent variable denoting the biological response (e.g., protein adsorption, cell metabolic activity), X_1, X_2,…, X_n are the independent variables representing scaffold features (topography, porosity, pore size, surface stiffness, surface charge, wettability, surface chemistry, fiber diameter etc.), and the a_1, a_2, …, a_n are the contributions of given feature to the response with a_0 being a constant.

However, there are also internal correlations between scaffold properties, which have to be taken into account. For example, it is known that the roughness of electrospun fiber is correlated with its diameter [72]. The existence of these correlations makes it very difficult to distinguish the impact of a given characteristic and predict the biological result of a given system. Moreover, it has to be taken into consideration that the specific biological reactions to scaffold indicators are different depending on the cell type. For example, a rough surface was found as be more favorable for osteoblast-like cell adhesion in comparison to a smoother one, and the reverse dependence was observed for the fibroblast cells [70]. So it's not surprising that currently, the matter of



Scheme 2 The concept of the ML-assisted prediction of biological response to scaffold with the associated components and examples of input and output items.

cell-biomaterial interactions is the area of very active research in the TE sub-field known as Materiobiology [73]. Going forward, the *Biomaterialomics* concept was established recently based on the development of the data science paradigm [19]. *Biomaterialomics* aims to integrate process–structure–property (PSP) linkages of the biomaterials with biological science and data science approaches. Scheme 2 presents the concept of the ML-assisted prediction of biological response to scaffold with the associated components and examples of input and output items.

Table 2 presents currently available examples on using machine learning to predict the biological response to scaffolds/biomaterials. In the paper of Sujeen L.Y. et al., physicochemical characteristics of nanofibrous scaffolds for skin tissue engineering were correlated with their in vitro performance [74]. The authors used thirteen scaffold families consisting of various polymers, and in some cases, also of nanosilica, and produced at least four blend compositions for each family. The dataset of 182 in-house observations included four features of nanofibrous scaffold (pore diameter, fiber diameter, water contact angle, and Young's modulus) and the MTT test result as the number of cells after 7-day culture. 80% of the data was used for training the algorithms and 20% for testing the cross-validated model and evaluating the prediction accuracy. Six regression methods were used as machine learning algorithms: linear regression, support vector regression (SVR), lasso regression, random forest regression, decision tree regression, and k-NN regression. Pearson correlation matrix showed that none of the four scaffold features are correlated. Feature importance graphs computed using the random forest regression algorithm indicated the fiber diameter and pore diameter as the most significant features for the performance of the model. The models performed accuracy from 53.91% to 62.74% being the highest for random forest regression. It shows that analysis requires more data points or methodology modification to perform better.

In the work of Le et al. [75], two machine learning methods were applied: multiple linear regression with expectation maximization (MLREM) and nonlinear Bayesian regularized artificial neural networks (BRANNs). The study aimed to find the quantitative relationships between the surface chemistry of the SAMs and protein adsorption. 176 data points concerning the percentage protein monolayer coverage on mixed SAMs were collected from the work of Ostuni et al. [76] Lysozyme and fibrinogen were used as model proteins and exposure times of 3 and 30 min were taken into consideration. Firstly, MLREM results indicated positive and negative contributors to protein adsorption. Hydrophilicity and the presence of hydrogen bond-accepting functional groups were

Table 2 ML-based studies on predicting the biological response to biomaterial

Scaffold/biomaterial form	Input	Output	No. of data points	Source of the data	Model type	References
Electrospun nanofibrous scaffold	Fiber diameter Pore diameter Water contact angle Young's modulus	Number of cells as determined from MTT assay	182	Original research	Regression methods: linear, SVR, lasso, random forest, decision tree, k-NN	[74]
Hydrogels, (micro)plates, 3D-printed structures, electrospun mats, patches, and sponges	Material composition, cell line, and fabrication method	Cell viability, growth, proliferation, and differentiation on the scaffold rated on a scale of 0–3	99	Literature collected data	Decision trees, logistic regression, K-nearest neighbor (KNN), XGBoost, CatBoost, multi-layer perceptron (MLP), support vector machine (SVM), deep learning and ensemble learning	[32]
PCL nanofiber scaffolds and spin-coated films	Fiber density in nanofiber scaffolds, day 1 cell morphology measurments	Human bone marrow stromal cell osteogenic differentiation potential	n/a	Original research	SVM/supercell method	[80]
Self-assembled monolayers (SAMs)	Molecular descriptors related to protein structure, partial charges, existence of particular molecular fragments or functional groups, the molecular graph, and atomic mass, type of protein (lysozyme or fibrinogen), exposure time (3 and 30 min), total number of descriptors: 67	Percentage protein monolayer coverage on a mixed SAM	176	Literature collected data (data extracted from another study)	Multiple linear regression with expectation maximization (MLREM) and nonlinear Bayesian regularized artificial neural networks with Bayesian prior (BRANNGP)	[75]
Microarrays of 496 polyacrylate	Wettability, surface topography, surface chemistry and indentation elastic modulus	Human embryonic stem cell response	496	Original research	Multivariate PLS regression	[81]
SAMs	Chemical composition and structure descriptors	Water contact angle, protein adsorption	145	Literature collected data	ANN	[82]

identified as having the most negative impact on protein adsorption and a larger number of hydrogen bond donor groups promoted greater protein adsorption. Further, a combined method of MLREM and nonlinear BRANNGP and BRANNLP (Bayesian regularized artificial neural network with Laplacian prior) was employed to quantitatively connect protein adsorption with 67 descriptors. The most negative effect on protein adsorption on studied SAMs was associated with the molar refractivity representing ligand size and polarizability, and the most positive one with a higher ratio of aromatic groups.

In the other study, the authors were concerned with predicting cell behavior on cardiac tissue engineering scaffolds based on data collected from the literature [32]. Three features were included in the analysis: material composition, cell line, and fabrication method. Cellular response to the scaffold was evaluated according to the 4-value scale. The dataset included 33 different materials, 16 different cell lines, and 6 different fabrication methods and is available in open-access repository [77]. Twenty-eight algorithms were compared in the study, namely decision trees, logistic regression, K-nearest neighbor (KNN), XGBoost, CatBoost, multi-layer perceptron (MLP), support vector machine (SVM), deep learning, and ensemble learning. The highest accuracy of 87% was achieved in the case of the XGBoost algorithm. Furthermore, the ensemble learning approach of 5 algorithms increased accuracy to 93%. However, it must be considered that both material and biological data have been greatly simplified in this study. The authors granted online access to the final model together with a step-by-step guide.

In the literature, there are also examples of studies on nanoparticles (NPs) toxicity and their in vivo performance. Here, we briefly mention it as the great number of biomaterial scaffolds contain NPs.

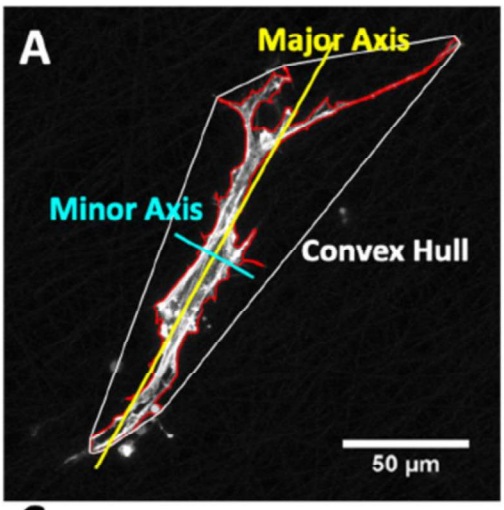
In the work of Desai et al. [78], the authors built decision tree (DT) and random forest (RF) models to predict the toxicity of silver NPs based on literature data. They collected 1315 data points from 40 articles with NPs physicochemical indicators as the input data and MTT assay results as the output. Various normal and cancer cell lines were included in their analysis. The comparison of regression metrics R^2 (0.97 for DT and 0.87 for RF) and RMSE (4.22 for DT and 9.75 for RF) showed that Decision Tree prediction was more precise and accurate in cell response prediction, however performances of both algorithms are very promising. In another study, the authors compared five classifier algorithms (decision tree, random forest, support vector machine, Naïve Bayes, and artificial neural network) in prediction of nanoparticle toxicity [79]. The training data included NPs' physicochemical properties, exposure conditions, and cellular responses of different cell lines. The random forest model demonstrated the highest accuracy among studied algorithms on the given data.

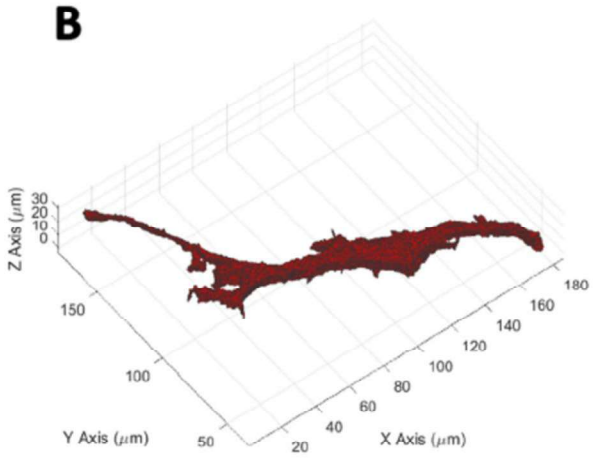
Figure 1 presents 2-D and 3-D single-cell morphology quantification and metrics used for early time-point human bone marrow stromal cell morphology classifiers reported in the work of Chen D. et al. inluded in Table 2 [80].

Drug delivery

Following the advancements of TE as both in vitro and in vivo approaches, the modern drug delivery field has also evolved rapidly in biomedical applications. The simplest approach for delivering medication to diseased tissue is through local administration, but this method can only be used on easily accessible organs due to the physiological and anatomical barriers in the local tissues. Over the past years, many studies have focused on developing advanced biomaterial systems to address the challenges in the controlled and efficient release of therapeutic agents to the target site. Biomaterial systems intended to tissue engineering often provide functionality of drug delivery with the advantages including local and targeted delivery, controlled degradation, and advanced biocompatibility [83].

Designing of innovative drug delivery systems including smart drug delivery, implantable microchips, and nanomaterials as drug reservoirs with a variety of geometries capable of delivery of multiple drugs for targeted delivery, sustained release, efficient therapy with minimum side effects has been the focus of intense research in recent years [84, 85]. Currently, there is a need for improved comprehension of how drug delivery materials interact with the drugs and the extracellular matrix in the target tissue and along the route in order to overcome biological barriers and hence achieve efficient delivery at the targeted tissue and cellular levels [86–88]. ML possesses the potential to establish strong and complex relationships between release kinetics and formulation parameters, optimize drug delivery system performance, and predict in vivo





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Metric	Metric Type	Metric	Metric Type	Metric	Metric Type
Area	2-D	L_1	3-D (L_1)	L_1 Circularity	3-D (L_1)
Perimeter	2-D	L_1 Depth	3-D	L_2 Circularity	3-D
Mean Distance	2-D	L_2 Depth	3-D (L_1)	L_3 Circularity	3-D
Max Distance	2-D	L_3 Depth	3-D (L_1)	L_1 Aspect Ratio	3-D (L_1)
Circularity	2-D	z Depth	3-D	L_2 Aspect Ratio	3-D
Mean Negative Curvature	2-D	Surface Area	3-D	L_3 Aspect Ratio	3-D
Normalized Number of Troughs	2-D	Volume	3-D	$(L_3/L_1)^{0.5}$	3-D
Tortuosity	2-D	Surface to Volume Ratio	3-D	$(L_3/L_2)^{0.5}$	3-D (L_1)
Major Axis Length	2-D	L_1 Perimeter	3-D (L_1)	$(L_2/L_1)^{0.5}$	3-D
Minor Axis Length	2-D	L_2 Perimeter	3-D	Radius of Gyration	3-D
Solidity	2-D	L_3 Perimeter	3-D	Asphericity	3-D
Aspect Ratio	2-D	L_1 Area	3-D (L_1)	Acylindricity	3-D
L_1	3-D	L_2 Area	3-D	Anistropy	3-D
L_2	3-D (L_1)	L_3 Area	3-D		

Figure 1 2-D and 3-D single-cell morphology quantification and metrics used for early time-point human bone marrow stromal cell morphology classifiers. Adapted with permission from reference [80]. Copyright [2021], [Elsevier].

response of material/pharmaceutics and suitable dosage [89]. It can be strong candidate as an effective tool advancing research and development for new pharmaceuticals, predicting efficacy and reducing failure in clinical trials, and fostering automation in high workflows. Scientists can assess different situations and improve drug delivery systems without conducting plenty of laboratory tests by modeling the drug formulation and distribution processes. This significantly reduces the time and cost compared to traditional lab-based approaches and improves efficiency. There are many different tools and algorithms developed for different applications including novel drug discovery, dosage form designs, pharmacokinetics, and drug delivery [90].

One of the most up-to-date and real-life examples for the AI power in healthcare sector stood out during COVID 19 pandemic. For example, Pfizer effectively used AI to manage vaccination trials and accelerate distribution. On the other hand, it made use of AI throughout the COVID-19 vaccine development process to make sure that all necessities were addressed [91]. It helped to accelerate to costly and long process of vaccine development. In addition, Moderna and Astra-Zeneca were the other leading companies using AI technologies for the development and streamline processes[92].

Due to these and more such compelling healthcare-related instances, scientists conducting research in a variety of fields are finding it increasingly crucial to employ such powerful tools and benefit from their

advantages. Here, we explored it more specifically in the field of drug delivery from the point of tissue engineering applications. So far, AI and ML implementation in this field is promising with various application examples but still, there is a long way to go in practical applications. Also, more effort toward the development of such novel delivery approaches for controlled and efficient delivery of therapeutics at the cellular level within the target tissue is required.

In a few works, artificial neural networks (ANNs) have been applied to predict the physicochemical properties of nanomaterials, and analyze complex relationships between the drug delivery carriers and release profiles from the particular carriers [89, 93]. For example, an ANN model has been applied to identify the factors influencing the nanoparticle size of PLA-PEG-PLA copolymer prepared as a drug carrier [94]. Three-layer feed-forward backpropagation ANN was used to model the process of producing nanoparticles and the concentration of the polymer was found to have the greatest influence among the processing parameters((Fig. 2A). Practical experiments also confirmed the accuracy of the predictions made by machine learning systems. Results suggested that such developed algorithms appear to hold promise for gaining a better understanding of the process of production associated with developing drug carriers with controlled diameter and size distributions, which is crucial from the point of application areas. In another study, the ANN model was used to optimize the formulation of polymer-lipid nanoparticles for pharmaceutical delivery [95]. Multi-objective optimization was performed by applying validated ANN models and continuous genetic algorithms. As a result, the generated nanoparticles showed favorable characteristics as a drug carrier such as a drug loading efficiency of 92%. Another study suggests the regularized least squares classifier as an efficient way to predict drug-target interactions among supervised learning systems [96]. As a different application approach, ANNs were applied to find a quantitative correlation between the release pattern of loaded anti-infective agent and the formulation and physiological factors of female intravaginal mucoadhesive barrier device [97]. ANNs were applied to assess diffusion coefficient, affecting release profile mostly for such system forms, under different physiological and formulation conditions employing generated datasets. It was found that effect of physiological conditions of the target area on the release pattern was more significantly over formulation variables. It has been claimed that this could lead to the development of parameter-specific prevention methods for diseases associated with sexually transmitted infections. In another research, ANNs were applied to predict optimum formulation parameters providing desired drug release profiles from cochlear implant coatings to avoid post-surgical problems after implantation [98]. The predictions made by ANN modeling closely matched the experimentally obtained outcomes showing the model efficacy. This study demonstrated how artificial neural networks could help reduce the period needed to produce formulations and the associated expenses with aimed outcomes. In another recent work, ANNs were applied to optimize physicochemical properties for the formulation of a self-nanoemulsifying system containing rosuvastatin (Ros) (Fig. 2B [99]. The experimentally prepared Ros samples, predicted by the ANN approach, possessed physicochemical properties that satisfied the optimization requirements including droplet size ≤ 100 nm,, polydispersity index ≤ 0.3, and Ros entrapment ≥ 90% providing high solubility of the drug and compatibility with rosuvastatin. It was reported that the application of ANNs for the formulation shortened time and reduced research costs.

AI is also able to evaluate massive data sets and model the behavior of 3D-printed pharmaceutical ingredient carriers by utilizing machine learning and computational modeling. This enables rapid prototype development and optimization of dosage strengths, geometries, and drug release profiles [100, 101]. In a recent research study, key components of the 3D printing formulation process and in vitro dissolving characteristics were predicted using literature data including 968 different formulations to create AI machine learning models [93]. The machine learning methods investigated could learn from and deliver 93% accuracy for the data. Furthermore, an artificial neural network produced the best forecast, with a mean error of ± 24.29 min in predicting the drug release times of a formulation. It is worth noting that use of AI in 3D-printed dosage forms provides promising opportunities to advance personalized medicine and enhance patient outcomes.

There are lots of different approaches in AI-driven predictive modeling for particular applications and this facilitates the optimization of drug formulations and dosage regimens, fostering advancements toward

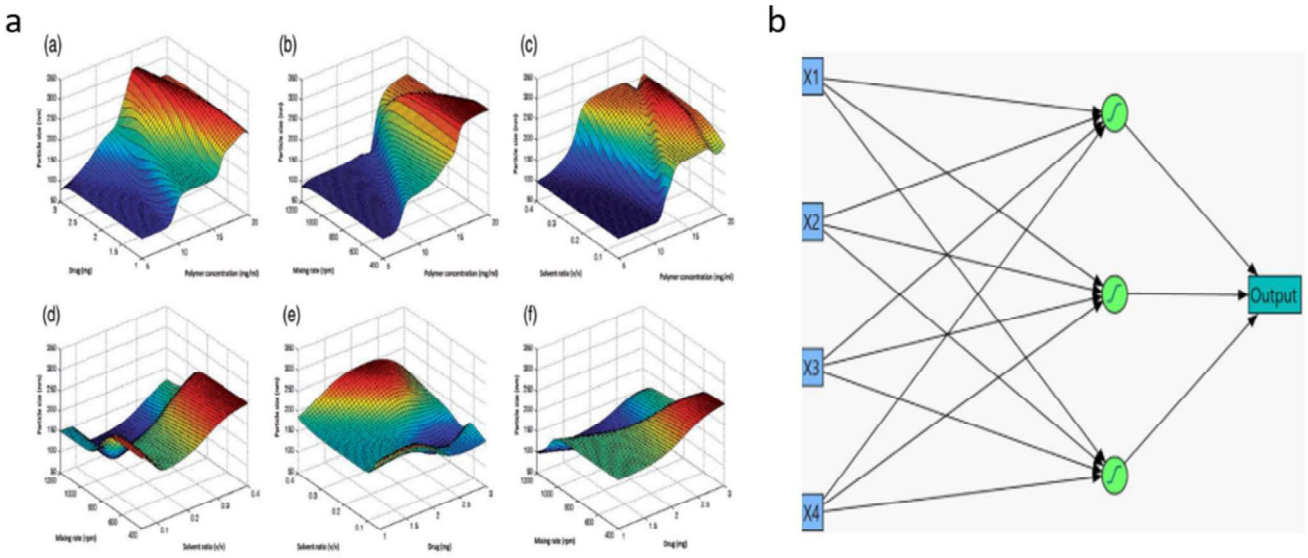

Figure 2 **A** The 3-D plot of particle size (nm) predicted by the ANN model for (a) polymer concentration and drug, (b) polymer concentration and mixing rate, (c) polymer concentration and solvent ratio, (d) solvent ratio and mixing rate, (e) drug and solvent ratio and (f) drug and mixing rate. In each figure, the effect of variation of two input factors is shown against the particle size (output). Reprinted from ref. [94] with the permission from Taylor & Francis, Copyright 2011. **B** Diagram of ANN where the output variables were separately trained by a three-node one-hidden layer neural network. X1 represents the percentage of drug molecules, while X2, X3, and X4 represent the proportion of surfactant, oil, and cosurfactant, respectively. Adapted with permission from reference [99]. Copyright [2020], [Open Science Publishers LLP].

personalized medicine in tissue engineering applications. To fully realize the potential of AI in drug delivery, further efforts are needed to enhance interpretability, define machine learning models, as well as improve the quality of the data gathered [86].

Support for image analysis

Artificial intelligence can greatly improve and automize image analysis in tissue engineering. Thanks to its classification and recognition possibilities, it can help in the evaluation of cell morphology, cell differentiation states or analysis of histological images. Moreover, considering the growing applications of related cutting-edge technologies such as 3D tissue models or organ-on-a-chip, the use of medical imaging tools and AI for analysis could be the mainstream methodologies soon [111]. It is worth noticing since conventional light microscopy cannot penetrate deeply into the tissue, medical imaging techniques are extensively utilized and hold great significance in tissue engineering technologies. The development trend of the number of publications bringing together tissue engineering and different medical imaging techniques is depicted in Fig. 3 for the years 2013–2023.

Deep learning has gained importance in particularly classification [113], and resolution enhancement [114] in microscopy images. SEM is one of the most common instruments used in nanotechnology and material science to explore the materials' structure. Since it is often employed, each user in each field of application produces an enormous amount of images. Considering the massive data stored, its long-term use and reproducibility are required to employ new approaches to have the ability to identify and recognize specific features in many numbers of images [115]. In this context, Modarres et al104 employed neural networks for SEM image recognition and automatic categorization. They proposed a comprehensive method for automatically categorizing SEM images using deep convolutional neural networks for feature extraction and transfer learning techniques. The approach would enable the user to automatically make a first selection of the most pertinent cases from a significant number of SEM images.

Additionally, image recognition algorithms could be used to do a more thorough investigation on the

chosen images. There have been many studies working on several different deep learning techniques for similar goals [116, 117]. For example, ANNs were applied by using recognition imaging for cellular identification in images from scanning probe microscopy [118]. In another study, it was demonstrated that pre-trained CNNs were effective for feature extraction from micrographs of dendrites [119]. Such cases demonstrate the effectiveness of a well-trained and built network at categorizing physical properties across large amounts of data [120]. An automatic classification based on predefined criteria saves time and allows for high-throughput analysis of large datasets. Moreover, as it makes it possible to quickly and thoroughly analyze experimental data, tissue engineering research can advance more quickly. Discovery and development procedures become more efficient as a result of researchers' ability to promptly decide on interesting materials or configurations for further investigation. In another case, deep learning is applied for image quality enhancement. In a study, the results of the investigations using deep learning for resolution enhancement demonstrated that the trained model could double the resolution of SEM pictures while maintaining their quality [114]. Trained CNNs provided enhanced resolution of lower magnification of SEM images which were highly matched with higher magnification of SEM images of the same samples (Fig. 4). Such an approach may provide advantages in decreasing sample charging and beam damage through enabling the implementation of a lower magnification scan across a greater field of view without losing image quality. Researchers may be able to observe the composition, characteristics, and behavior of the materials employed in tissue engineering with greater clarity because of this improved visualization.

Recently, deep CNNs were applied for identifying and quantifying vascular metrics in an angiogenesis model for vascular tissue engineering [121]. High-throughput vascular density measurements of fluorescent or phase contrast images were achieved by a newly developed machine learning detection tool. The method achieved highest accuracies for high magnification fluorescent images in which accuracy percentages ranged from 82.79 to 98.74% and from 56.4 to 98.48% for phase contrast images at the same magnification. It has been reported that it can quickly and precisely measuring vascular characteristics from microscopic images saving huge amounts of time where periodic evaluation may be necessary for fabricated tissue structures.

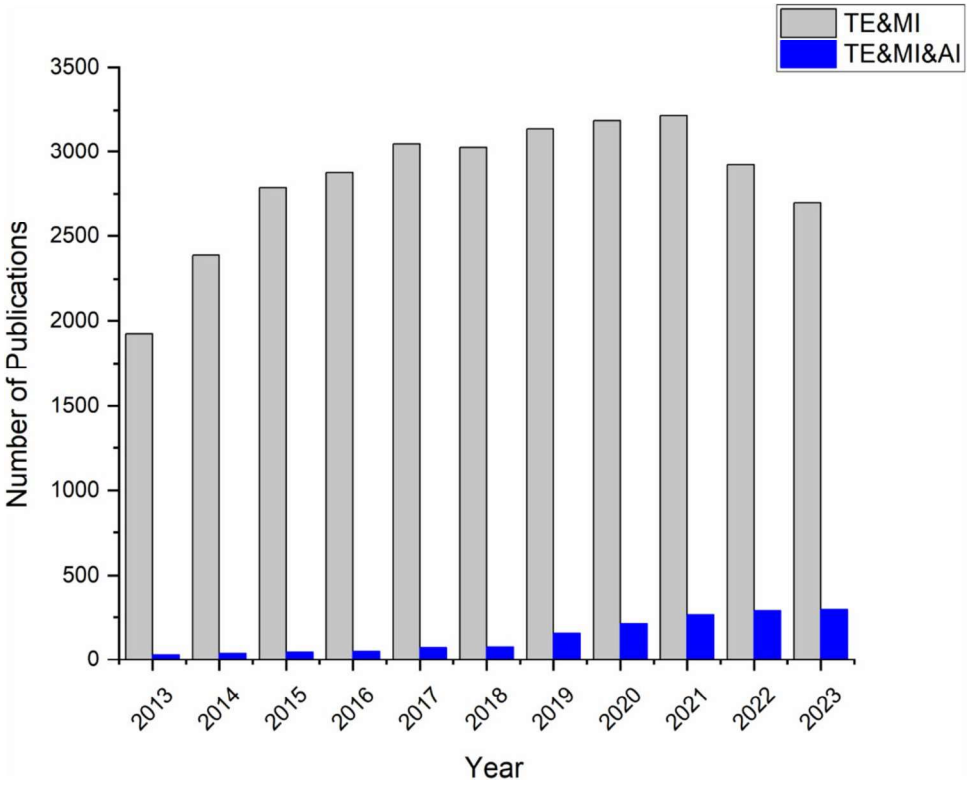

Figure 3 Number of publications in PubMed from 2013 to 2023. Gray bars represent a search for combining tissue engineering and medical imaging keywords (TE&MI). Blue bars represent a search for combining tissue engineering, medical imaging, and artificial intelligence (TE&MI&AI). (National Library of Medicine, https://pubmed.ncbi.nlm.nih.gov/ [112]. Accessed January 27, 2024).

In another study [122], CNNs were employed for exploiting the information in bright-field single-cell images for prospective identification of neural stem cell differentiation even at the early stages of the cell culture. Such a well-architected image classification may improve the understanding of differentiation outcomes and pave the way for more effective cell-based therapies. In the thesis of MacKay, B. S., cell density on glass substrates was approximated based on the brightness of the original, unprocessed fluorescent image of cells as a part of neural networks training to predict cell behaviors to topographical cues [123]. Chen D. et al. used support vector machines (SVMs) to evaluate the response of human bone marrow stromal cells (hBMSCs) to fibrous vs flat microenvironments [124]. The authors used the SVM/supercell paradigm, meaning considering cell shape phenotypes of small groups of cells, so-called "supercells", to avoid disorders resulting from the single-cell heterogeneity (Fig. 5). Analysis showed that a minimum of 57 cell cases are required for processing the phenotyping. Minor axis length, solidity, and mean negative curvature of the cell were the most important indicators of the hBMSCs response.

CNNs as a deep learning method are also a promising tool in the applications for bone tissue engineering. In research in the field, it has been found that 3D CNNs, trained using layered 2D images obtained by digital tomographies, are an effective tool for predicting the mechanical characteristics of designed scaffolds [41]. In another recently reported study [125], CNNs were utilized for recognizing complex processes of composite material design and prediction of morphological and functional properties, e.g., porosity and stiffness of engineered bone scaffolds. It was claimed that smart manufacturing scaffolds may be made possible by approach. Overall, such approaches by deep learning tools can facilitate accurate measurement of factors including cell dispersion, scaffold form, and porosity—all important for determining if a material is suitable for tissue engineering applications (Table 3).

ML-based modeling of the scaffold in vivo performance

Machine learning algorithms are currently tested in supporting or replacing conventional methods for modeling the mechanical and biological performance of scaffolds. Wu C. et al. demonstrated for the first time a ML-based multiscale modeling and remodeling approach to predict bone formation in ceramic scaffolds as an alternative to the conventional multilevel finite element (FE^2) method [126]. The both in silico predictions were compared with previously obtained in vivo data. The authors randomly generated 40,000 representative volume elements (RVE) samples and another 55,992 sequentially generated RVE samples at the microscopic level to train and evaluate the model. A fully connected NNs with a single layer with nine independent material parameters was used for ML modeling. The model predicted the homogenized elastic tensors and unit strain energy density (SED) components to simulate bone remodeling. The outcome of the ML modeling was in agreement with the FE^2 method with linear regression values being equal to 0.99721 for homogenized

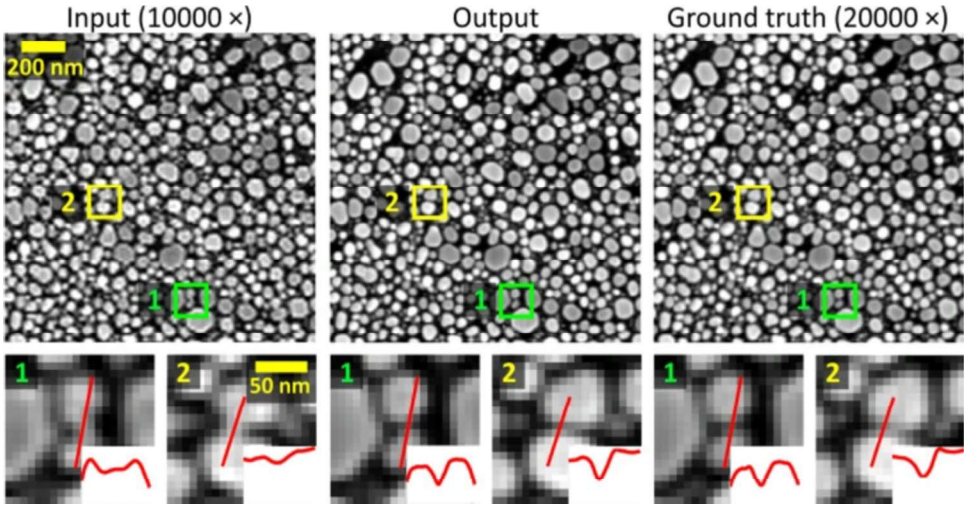

Figure 4 Comparison of input images which are processed by neural networks with their output images and corresponding higher magnification SEM images. A spatial feature with considerable resolution enhancement is displayed. Adapted with permission from reference [114]. Copyright [2019], [Springer Nature].

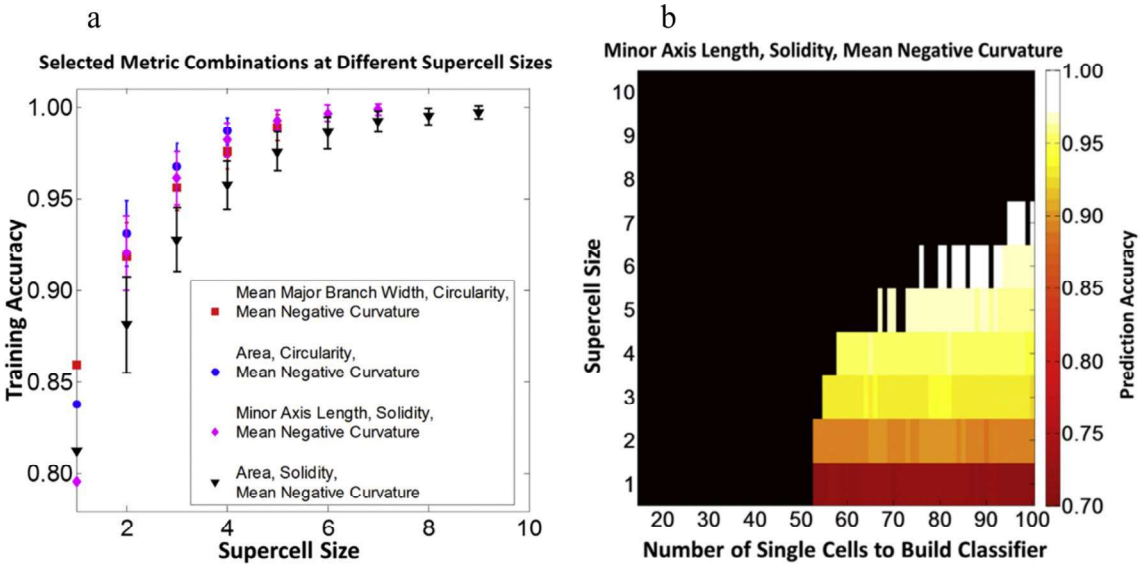

Figure 5 Correlation between **a** supercell size with selected metric combinations and training accuracy, **b** number of single cells to build classifier, supercell size and prediction accuracy of support vector machines classifier. Adapted with permission from reference [124]. Copyright [2016], [Elsevier].

elastic tensors and 0.97237 for SEDs. Moreover, the ML-based approach was much more effective taking 32 h for training and 300 s to perform prediction vs 150 h for FE^2 analysis.

Horikawa S. et al. used Gaussian mixture regression to build two models estimating bone-forming ability of porous hydroxyapatite ceramics [127]. The first model was used to predict material properties based on fabrication conditions, and the second one for predicting the rate of bone formation from material properties and conditions of in vivo procedure. The study indicates material crystalline structure as the most influential on bone-forming ability. The four values of FWHMs of XRD peaks of the HAp and β-TCP turned out to be the most important material features in the analysis. The authors obtained good agreement in predicted bone formation rates and in vivo outcomes with a standard deviation of error between estimated values and actual ones being ± 12.93%.

Entekhabi E. et al. used artificial neural networks and kernel ridge regression (KRR) to predict the degradation rate of genipin crosslinked gelatin scaffolds [128]. In the analysis, they included fifteen samples with seven input parameters: gelatin percentage, genipin percentage, swelling ratio, pore size, ultimate tensile strength, elongation, and degree of crosslinking. The mean-squared error (MSE) being the measure of model accuracy was equal to 2.68% for ANN and 4.78% for KRR. Interestingly, it was shown that excluding the degree of crosslinking from the analysis has very low significance on accuracy due to the correlation of other input parameters with this indicator.

Methods for big data gathering in tissue engineering

The basis for the relevant application of machine learning in any area is the existence of high-quality big data, which provides algorithms with the appropriate dose of information on a specific issue. Currently, good examples of the successful usage of ML methods can be found for example in financial analysis, production optimization, e-commerce, and drug design, which can be clearly associated with the availability of big datasets in these areas.

In tissue engineering, data for machine learning processes can originate from two sources—can be self-produced or can be gathered from existing experimental studies. Good-quality dataset for machine learning approaches can be provided from high-throughput screening studies. Examples of such screening methods are microarrays, which are studied in the biomaterial structure–properties correlation and

Table 3 Studies on application of AI/ML approach with an indication of drug delivery application, model and outcome

Application	ML model type	Outcome	References
Prediction of the formulation impact and process parameters involving the release of prednisone through a multi-unit pellet method	Multiple layer perceptron trained—back-propagated ANN model	In vitro release profile of prednisone was significantly impacted by microcrystalline cellulose concentration. The production process parameters had minimal impact on prednisone release but had a significant impact on extrudate and pellet quality	[102]
Comparison of two different modeling for prediction of the drug dissolution of the designed matrices	ANN	Point-to-point modeling was significantly better than kinetic parameter-based models. It provided greater reliability and consistency with observed experimental results	[103]
Development of 3D printed drug distribution scaffold using polymer-variable concentration optimization	ANN using a feed-forward backpropagation	As a controlled release platform, the ANN-optimized 3D bioprinted scaffold demonstrated drug release over a 20-day period, exhibiting remarkable properties	[104]
Modeling and controlling the particle size and release behavior of polymeric nanoparticles	Multi-objective based genetic algorithm approach	Optimum particle size and uniform particle distribution for controlled initial burst release were achieved and obtained results were validated through the experimental studies	[105]
Estimation of the nonlinear correlation between drug loading formulation and release profile from a polymeric implant system	Comparison of three types of feed-forward neural networks	Multilayer perceptron model based ANN was significantly efficient on finding drug release profiles over radial basis function network, and generalized regression neural network	[106]
Designing and screening graphene based drug delivery system	Genetic algorithm based method	A promising novel computational platform was developed to identify formulation parameters including binding parameters between graphene and drug	[107]
Prediction of experimental drug release profiles from long-acting hydrogels	Several ML algorithms including, Multiple linear regression, decision tree, random forests, support vector regressor, neural networks, and light gradient boosting machine (lightGBM) have been trained	The lightGBM model performed the best out of all of them, accurately predicting fractional drug release. The results were very promising to reduce cost and time in drug formulation development	[108]
Accelerating the screening of poly-beta-amino-esters as drug delivery vehicles for cartilage tissue treatment to identify the optimal candidate	Bagged multivariate adaptive regression splines model was optimized as the optimum model in a variety of ML models	The research made it possible to identify the ideal candidate that was expected to increase drug uptake by more than 20 times compared to standard clinical treatment; this uptake improvement was also verified through experimental work.	[109]

Table 3 continued

Application	ML model type	Outcome	References
Prediction of nanoparticle based drug release systems to design the new systems based on their components' properties	Perturbation theory-machine learning algorithm (PTML)	The first multi-label PTML model developed that can be applied to the design of new drug delivery nanoparticle systems with the best activity/toxicity profiles by choosing pharmaceuticals, coating agents, and metal or metal-oxide nanoparticles to be formed	[110]

biomaterial–cell interactions [129, 130], and microfluidic systems, which are used in the development of hydrogels for TE applications [131].

Literature collected experimental data, which are the second potential source of data are generally narrow and tend to be conflicting with each other because of variations in data analysis techniques or experimental methodologies, especially in biological assessment. This makes the collecting process difficult and demands a lot of specific experimental knowledge. However, even if the current usage of literature data and ML approach is very challenging, we believe published data should be analyzed in systematic meta-analysis. This could indicate the direction for further standardization of experimental procedures and results publishing.

There is no doubt about the necessity of an easily accessible, reliable data source to extend ML techniques for the development of biomaterials, choosing additives, and identifying processes to be applied to tissue engineering applications. Although thousands of polymers can be found in online databases along with some of their structural properties, images, and other identification techniques [132, 133], this doesn't allow for predicting the properties of fabricated polymers. These types of chemical structure databases are well implemented in the synthesis of small molecules in chemistry and drug discovery [134, 135]. However, in tissue engineering, the number of variables is much greater including different materials, fabrication methods, modification techniques, etc., which makes building such a database much more difficult and requires sharing the data in a standardized way.

For ML implementation in image analysis, it is necessary to have a great number of items to train the algorithm. ML-assisted analysis has been widely developed and implemented on a high level in detection of cancer tumors in ultrasound images [136]. There are a few publicly available datasets collecting tumor images, which were launched thanks to the efforts of the cancer research community. An example of such a database is *The Cancer Imaging Archive* operating within *The Cancer Genome Atlas (TCGA) Database* [137]. So far, this type of image repository is not available in the tissue engineering field.

There is a promising, recently launched data-sharing platform called *Community Resource for Innovation in Polymer Technology (CRIPT)* [138]. CRIPT's data model is aimed to have all kinds of data including polymer synthesis, material processing/characterization,

and raw experimental data which provides descriptive and comprehensive information. The aim is to address the high level of complexity involved in defining a polymer structure and the complexities of characterizing material properties. This scalable polymer informatics solution intends a community-driven polymer science data ecosystem supported by FAIR (findable, accessible, interoperable, and reusable data concept) and open-source principles [139]. For the implementation of the data, a Python tool called CRIPT Python Software Development Kit (SDK) has recently been launched [140]. It aims to enable the manipulation of the CRIPT data using the Python programming language and can assist with automating the data uploading to CRIPT.

Another example of a big data initiative is an EU-funded project named *BIOMATDB*, which aims to create a database providing detailed information on chemico-physical, biological, and toxicological properties of biomaterials [141]. It is designed to support researchers and user groups in searching information about biomaterials together with making it easier for companies to offer their products. The base will include several AI-assisted data analysis and visualization tools to support the search process. Such approaches to provide well-organized data would give rise to new ideas and make it possible for the scientific community to share information and discoveries more quickly.

Difficulties, challenges, and perspective

In this section, we will indicate the most important difficulties in the implementation of ML in tissue engineering that should gain the attention of the scientific community together with giving the perspective that emerged after the literature review.

There is no doubt that high-quality open databases would support the wide implementation of ML methods in tissue engineering, which was discussed in the previous chapter. The difficulty in creating such datasets in tissue engineering results from the heterogeneity of data including different materials, fabrication methods, modification methods, analytical methods, cell lines, and medical application sites. In particular, biological assessment is challenging to compare due to the variability of experiment conditions. Moreover, it was reported that scaffold material and architecture can affect the performance of biological tests. For example, it has been shown that nanofibrous materials can influence the reaction of cytotoxicity assays, probably, because of dye sorption and the possibility of reducing tetrazolium salt to formazan by [142]. The authors of this study also demonstrated incompatibility between MTT, XTT, CCK-8, alamarBlue, PrestoBlue, and Live/Dead assays used to evaluate cell proliferation. They proposed that the minimum incubation time of cell culture in direct contact with nanofibrous materials should be equal to 72 h and recommended Live/Dead assay as the most accurate method.

Predicting biological phenomena and the production of materials by advanced data analytics has been the focus of recent efforts. Therefore, standardized data collection, cross-disciplinary cooperation, and robust safety and validation protocols are essential to enhance the processing of enormous datasets by machine learning algorithms [143]. Data mining is a valuable method for collecting data to train models and inform future designs by using decades of publicly available research. However, challenges arise from incomplete datasets and inconsistent reporting in the literature. To address these issues, automated algorithms are being developed to extract and standardize data from scientific papers, although this remains a complex process[144]. Criteria for data supporting open science were formulated and published in *Nature Scientific Data* in 2016 [145]. According to this source, data should be findable, accessible, interoperable, and reusable (FAIR). Such a standardization requires the joint effort of community representatives. These days, several publications demand that all raw data be submitted in the supporting documentation or on openly accessible database platforms such as the Materials Data Facility (MDF), Polymer Genome, Polymer Property Predictor and Database, caNanoLab, and the Community Resource for Innovation in Polymer Technology (CRIPT) [144, 146].

In the past and now, there are examples of extensive, international projects engaging many researchers for particularly complex and important matters like *The Human Genome Project* generating the first sequence of the human genome, *Global Genome Initiative*, the goal of which is to capture and understand the Earth's genomic biodiversity, or *Material Genome Initiative* being US federal multi-agency initiative to discover, manufacture, and deploy advanced materials [147]. These examples would be a good inspiration to develop and promote such an initiative among the TE

scientific community. Moreover, in the literature, there are a few systematic reviews and meta-analyses for example on the topic of materiobiology and preclinical and clinical studies of TE scaffolds, which could indicate a direction for the standardization of research planning and results publishing in tissue engineering [148, 149]. Furthermore, we believe high-throughput studies should gain more attention from the TE community as these screening studies can provide good-quality data for machine learning approaches.

In addition, there are many ML frameworks such as the TensorFlow, and Pytorch, which are incompatible with each other. Therefore, it is also critical to establish a unified ML framework to make it easier for researchers to share ML models [150]. Furthermore, such data-driven ML techniques including deep learning trained by large data sets might be computationally expensive and time-consuming. To avoid these, it is important to choose the correct method depending on the problem to be solved, the size of the dataset, and computational resources.

After all of the above, the incorporation of AI/ML technology into useful biological applications requires the resolution of ethical and regulatory concerns. Regulatory concerns from the point of application of such technologies might arise from standardized input data, data bias in large datasets, data protection legislation, and privacy issues while gathering vast amounts of data for model training [151]. Those matters and more must be addressed by regulators to maintain the principles of medical ethics and integrate AI-driven technologies.

A unified regulatory framework for biomedical applications can be formed by combining many crucial European regulatory acts, such as those related to clinical trials, data protection, and medical devices. Moreover, to further address the concerns associated with the widespread implementation of AI, the European Commission recently introduced the Artificial Intelligence Act [152]. This proposed act requires that high-risk AI systems have to go through pre-deployment compliance examinations and post-market monitoring to make sure they comply with all of the act's provisions for the responsible deployment of the AI technologies [153].

Ethical concerns arise from possible data bias, efficacy, lack of transparency and accountability, and moreover safety for clinical trials. In current applications, transparency and accountability are the fundamental problems [34]. Understanding the decision-making process underlying ML-driven material design requires ensuring the transparency of the ML model. When a machine learning system makes a decision that has unanticipated consequences, accountability and liability issues arise especially if it harms people or the environment. In particular, if the guidance directly impacts human health, researchers must be aware of the rationale behind an AI system's recommendation for a given material or design [154]. In order to apply AI-driven biomaterial research to biomedical technologies, including tissue engineering applications, research on improving the practicability of AI in biomaterials must be forcefully pursued. The intention of ethical principles is to improve the design and application of these technologies by providing guidance to developers, users, and regulators. Recently, a comprehensive guideline of fundamental ethical principles including accountability, transparency, explainability, safety, and autonomy associated with the development and implementation of AI technologies was established by WHO in 2021[155]. Following these ethical guidelines will be essential to the appropriate and successful integration of AI, as it will promote innovation while preserving public confidence and safety in biomedical applications.

Despite the above-mentioned challenges, we believe machine learning will be an important tool in tissue engineering research in the coming years. There are many benefits that ML approaches can bring to tissue engineering including high analysis accuracy, cost- and time savings, limitation of harmful laboratory experiments, and animal testing. At this moment, ML is tested in many areas of TE research including scaffold design, predicting the biological response to the scaffold, optimization of drug delivery, support for the image analysis, and modeling of the scaffold *in vivo* performance. There is no doubt that in comparison to other areas, the nature of TE requires greater effort from researchers so that ML can be implemented into it.

Natural language processing tools supporting the research

With the development of artificial intelligence, many tools supporting the research work have been created. Here, we briefly present chosen AI-assisted software that can improve and fasten the process of paper review and information finding.

Elicit, available on elicit.com, is projected to immediately get a response to research questions, for example, "What are the methods of scaffold surface modification?" or "How does aminolysis reaction affect material surface properties?". In the basic mode, the response is referenced to four scientific articles. The second functionality is extracting data from uploaded papers. There is the possibility to choose from many proposed items, such as summary, main findings, hypotheses tested, limitations, etc.

AskyourPDF, available on askyourpdf.com, allows users to upload research papers and ask very precise and specific questions about the documents. In the example of our recent paper, the accuracy of the responses was evaluated as very high.

Scispace available on typeset.io is an advanced tool that enables literature review, asking questions on pdf documents, and extracting data. Similarly, the results of our exemplary paper analysis were highly accurate.

ChatGPT 4.0 version with an accurate plugin such as ScholarAI can analyze scientific literature in a very detailed way.

There is no doubt about the supportive role of these tools, however, ethical regulations have to be formulated before their wider implementation in research.

Summary

Machine learning approaches are currently supporting numerous scientific disciplines. The applications of ML in tissue engineering are vast and promising, from scaffold design to predicting biological responses, optimizing drug delivery, supporting image analysis, and modeling scaffold in vivo performance. This review presents a range of impressive examples of ML applications in these areas and gives an overview on the potential of this approach in the TE field.

There is no doubt that great ML-assisted progress can be achieved in bioprinting optimization, cell image analysis, and modeling of the scaffold performance. However, in some fields of tissue engineering, such as predicting cell response, using ML algorithms is still challenging due to data quantity and quality. Nevertheless, even if satisfactory status in this particular area is not currently possible, it is essential to popularize the standardization of the experiments and results publishing for the future development of ML-assisted approaches.

Employing large datasets is key to achieving high identification and prediction precision. Having solid data collection methodologies and standardizing data to qualify as reliable datasets has become increasingly critical as novel materials and processes are published in the literature. Standardized data collection and processing would ensure efficient data sharing and promote engagement within science.

It is important to emphasize that the nature of the TE field requires much greater effort from scientists to implement ML approaches. There is no doubt that the application of machine learning approaches in tissue engineering is still at the very beginning stage. The question of whether machine learning will revolutionize the TE discipline or whether it will be the tool of evolution remains open.

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Data and code availability

Not applicable.

Declarations

Competing interests Not applicable.

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