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REVIEW

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Artificial intelligence-assisted design, synthesis and analysis of smart biomaterials

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Abstract

Smart biomaterials that can self-adapt or respond to microenvironmental factors or external signals hold excellent potential for a variety of biomedical applications, from biosensing, drug delivery, and cell therapy to tissue engineering. The complexity of smart biomaterials, including the rational design of their structure and composition, the accurate analysis and prediction of their properties, and the automatic and scale-up synthesis remains a critical challenge but can be addressed by the recent rise of artificial intelligence (AI). To bridge the literature gap, the current mini-review will introduce the background of why marrying AI with smart biomaterials is essential and how biomaterial scientists can integrate machine learning (ML) and AI for the discovery, design, analysis, and synthesis of smart biomaterials. For this purpose, the basic principles of ML and AI will first be introduced so that biomaterial scientists can use ML and AI as a tool for basic research. Next, representative examples of using AI to high throughput screen and establish big data of structure-function relationship of smart biomaterials responding to both chemical, biological, and physical signals. Most importantly, the applications of the AI-designed or AI-discovered biomaterials will be overviewed, with a focus on the field of tissue engineering. Lastly, new directions, such as robot-chemists-assisted fabrication of biomaterials will be highlighted. Taken together, by engaging biomaterial scientists with the most recent updates in AI material science, we expect to observe continuous growth of the field of AI for

science and benefit clinical translation of smart biomaterials for treating a variety of diseases.

KEYWORDS
artificial intelligence, materiomics, smart biomaterials, stem cell, tissue engineering

1 | INTRODUCTION

Smart biomaterials can be broadly defined by their responsiveness to signals existing in biological systems. Signals can originate from physical, chemical, and biological sources and can be amplified by biomaterials via interactions with their structures and compositions.[1–3] The nature of smart biomaterials determines the difficulties in their rational design and synthesis for biological applications, as compared to conventional inert or static biomaterials.[1,4,5] Human tissues contain and can be engineered by smart biomaterials. For example, cell membranes, cytoplasm, extracellular matrix, and even the chromatin in the nucleus are constantly receiving physical (e.g., mechanical, thermal, electrical), chemical (ionic, redox, etc.), and biological (e.g., growth factors) signals, and many of them would respond to these various signals in a real-time manner.[6] This is a convincing example of the complexity of dynamic biomaterial systems that instruct tissue and human intelligence. In parallel, from the viewpoint of therapeutic development, it is crucial to have tailored biomaterials that selectively and accurately respond to one or few stimuli controlled by machines or doctors to interfere with specific biological processes associated with diseases.[3] This further necessitates the advanced design and synthesis of stimuli-responsive biomaterials through compositional or crystal engineering. However, the conventional trial-and-error approaches have often resulted in the low-throughput discovery of biomaterials with tailored dynamics and intelligence, especially in the context of biological systems.[7]

Both the fields of material and biology research have been revolutionized by the increasing power of artificial intelligence (AI).[8,9] At the 2024 Nobel Prize ceremony, scientists specializing in artificial intelligence received awards in both chemistry and physics. This trend further reflects a broader shift in science and biology toward data-driven research. In particular, smart biomaterials have been shaped and characterized by a few milestones built upon the development of machine learning (ML) algorithms and the expansion of existing material databanks.[10,11] These two components further lead to surrogate models that allow predictions of properties and performances based on their structures and compositions. Furthermore, AI has also transformed how a physical laboratory operates by enabling robotics capable of automated synthesis, especially when high throughput screening is needed.[12] Fields such as biomaterials are increasingly using computational modeling, ML, and large datasets to optimize properties that modulate cell behaviors, drug delivery, and tissue regeneration. Incorporating perspectives from high throughput screening, robot chemists, ML, and AI would be a trend to watch for biomaterial design.[13,14] Additionally, integrating multi-omics data, including genomics, transcriptomics, and proteomics into the analysis of the biological outcome from smart biomaterials has become a crucial step for advancing smart biomaterials by providing a comprehensive view of how cells sense and respond to chemical, physical, and biological cues.[15] For example, spatial transcriptomics that constantly reduces the pixel size (currently at 10 μm resolution) would pave the way for resolving this puzzle and facilitate the studies of microstructures of mechanomodulatory biomaterials.[16] However, the continuous expansion of material-omics and multi-omics approaches would lead to a data explosion. Supervised and unsupervised ML tools represent basic models and would not work for higher dimensions and complex data sets.[17] It is thus essential to keep an eye on the development of ML methods for multi-omics data analysis and visualization.

The current review aims to bridge the literature gap by overviewing the most recent updates in the rapidly growing area of artificial intelligence-assisted design, synthesis, and analysis of smart biomaterials (Figure 1). By summarizing the most basic rules and concepts and providing examples, we also hope this review could serve as an entry-level tutorial for scientists working in the area of biomedical engineering materials. In parallel, for those who would like to seek for more in-depth knowledge in AI and smart biomaterials, we encourage them to refer to other excellent reviews detailing the codes, strategies, materiomics, and applications of dynamic biomaterials.[18–22]

2 | BRIEF INTRODUCTION TO ML AND AI

ML and AI are centerpieces of designing next-generation smart biomaterials. There are 2 ML types in general, including unsupervised and supervised ML algorithms

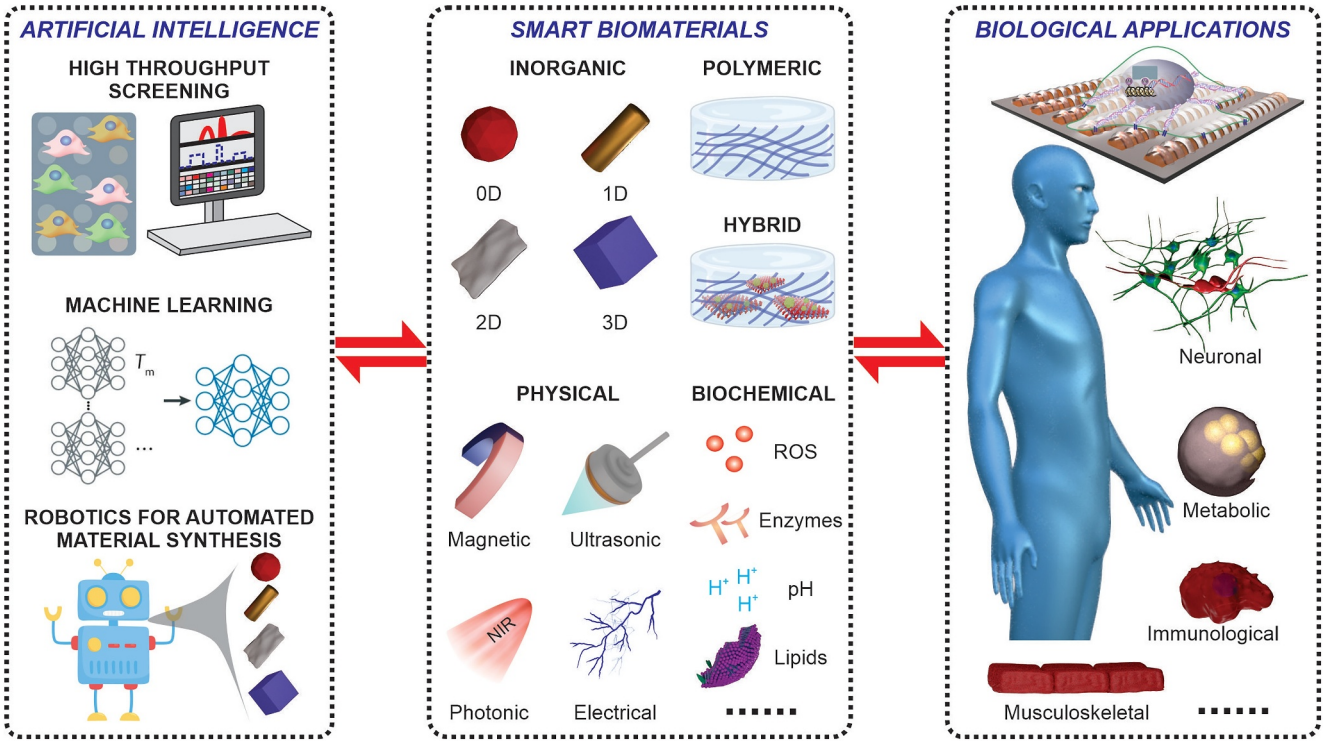

FIGURE 1 Schematic diagram illustrating artificial intelligence-assisted design, synthesis and analysis of smart biomaterials and their potential biological applications.

(Figure 2). Unsupervised ML analyzes data by adapting clustering techniques or reducing dimensionality. Common clustering techniques include fuzzy C-means, agglomerative hierarchical clustering, and k-means, which elucidate data structure by organizing them into groups that share similar characteristics.[23] Clustering techniques are widely used in applications such as compound selection in high-throughput screening (HTS)-based drug discovery and visualizing gene regulatory networks in genomics studies.[24,25] Common clustering strategies include density-based spatial clustering of applications, hierarchical clustering and K-means clustering, which are suitable for analyzing microstructure and cell adhesion. On the other hand, dimensionality reduction-based methods, including diffusion maps (dMaps),[26] independent component analysis (ICA),[27] and principal component analysis (PCA),[28] are suitable for extracting the most notable features and patterns from high-dimensional datasets by identifying low-dimensional parameterization. Dimensionality reduction techniques are particularly useful in identifying key pathways in regulating protein folding, discovering the most significant inhibitors for drug formulation, or elucidating structure-regulated transfection and cellular uptake of nanoparticles used in gene delivery applications. Supervised ML is achieved by combining predictive models with information extracted from unsupervised ML. In general, regression, classification, and ensemble are three common approaches for supervised ML. Regression includes linear regression, gaussian process progression (GP), and K-nearest neighbor, which are mostly used for predicting the properties of biomaterials. Meanwhile, classification can be categorized into support vector machine, decision tree, and random forest. Lastly, the ensemble includes adaptive boosting, extreme gradient boosting, and light gradient boosting machines that are used for enhancing complex material predictions. Among all methods of supervised ML, GP,[29] artificial neural networks (ANNs),[30] and random forests (RFs)[31] models are among the most used training strategies for identifying relationships between input features and output data. The quantitative structure-property relationship (QSPR) model has also been proven valuable for discovering new materials by iterative test cycle training, especially active learning strategies that can most efficiently learn from data in a real-time manner.[32,33] There has also been rapid development of new supervised and unsupervised ML algorithms for material discovery applications. In addition, there are other ML strategies such as semi-supervised learning, reinforcement learning, and self-supervised learning that can be tailored for specific applications. However, tailoring those algorithms for biomaterials requires simultaneous advances in combinatorial screening studies on cell-extracellular matrix

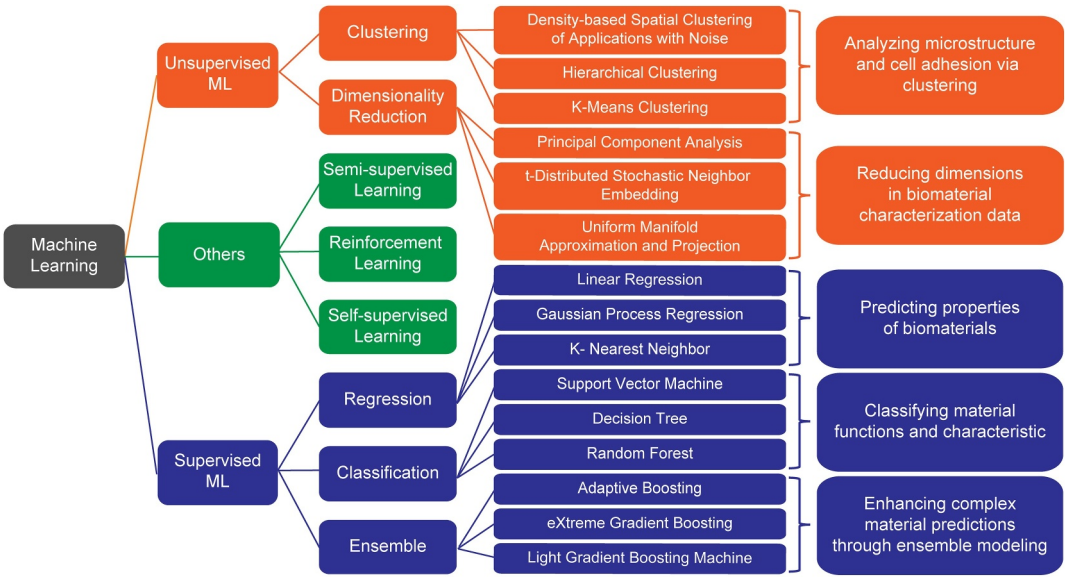

FIGURE 2 Summary of machine learning (ML) types and analysis methods. Machine learning could be categorized into unsupervised and supervised ML. These two have different analysis techniques and algorithms, and each of them has its advantages. There are also some other ML types such as semi-supervised, reinforcement, and self-supervised learning, which are not elucidated in this review.

(ECM) interactions with clear output information from cellular assays.

3 | SMART BIOMATERIALS AND THEIR BIOLOGICAL APPLICATIONS

Smart biomaterials can be broadly defined as materials with dynamic properties that respond to physical or biochemical stimuli with potential biological applications.[6] Smart biomaterials can be categorized based on their composition (inorganic vs. organic) and properties. Based on their responsiveness to stimuli, most commonly seen smart biomaterials include photo-responsive, magnetic-responsive, electric-responsive, ionic-responsive, and self-adaptable biomaterials such as enzyme-responsive biomaterials.[34] X-ray and mechanical force have also been applied as stimuli in smart biomaterial design.[35]

Photonic control over biomaterial functions is the most widely adapted strategy in designing smart tissue engineering applications.[36] The photoresponsive materials are initially built upon photocleavage followed by the release or presentation of biochemical cues that can regulate cell behaviors. Later on, De-Forest et al. and Anseth et al. developed bio-orthogonal chemistry to induce sequential protein inclusion and release via oxime-ligation-based photodeprotection reaction and ortho-nitorbenzyl-based photoscission, respectively.[37–39] Light as a stimulus is advantageous in realizing accurate spatiotemporal control by integrating advanced 3D bioprinting setup. By achieving dynamic 4D protein capture and release, photoresponsive hydrogels can be tailored for recapitulating the 4D microenvironment of healthy and disease (e.g., Alzheimer's diseases, etc) tissue in cell and organoid cultures. In addition, spiropyran, psDronpa dimer, and azobenzene-based photoresponsive ligands that respond to UV or visible light have been tethered to varying polymeric frameworks such as polyethylene glycol, hyaluronic acid, and alginate to induce mechanical changes in hydrogels that can further modulate stem cell fate.[40] Further combination with upconverting nanoparticles has extended the photo-responsive biomaterials to the near-infrared (NIR) light region, which is more permeable to human tissue. Still, the penetration depth is still at the millimeter level, and the in vivo applications are largely restricted.[41]

As compared to light, the magnetic field has a much deeper penetration depth. Magnetic nanoparticles (MNP) tethered to RGD and PEG linker lead to the formation of magnetic responsive hydrogels that can modulate the osteogenesis of mesenchymal stem cells in response to the strength and direction of the external magnetic field through the nuclear translocation of YAP protein.[42,43] In addition to inducing stem cell differentiation, MNPs have been widely applied for the labeling and target-specific delivery of biomacromolecules. Cui et al. developed magnetic nano-islands that mimic the catalytic center of nuclease with varying RGD ligand spacing linked by DNA.[44] Through the magnetic activation, 35 nm spacing was found to be most optimal for the induction of cell mechanotransduction, proliferation, and also the capture

and release of cells. Most importantly, such magnetic responsive biomaterials can be readily translated into in vivo applications, as detailed in previous reviews. Nevertheless, the reliance on external stimuli still compounds the application as the microenvironment dynamics inside the body may not always be periodic and predictable.

In addition to the smart biomaterials responding to physical cues, there are also self-adaptable biomaterials that respond to biochemical cues such as pH, enzyme, and reactive oxygen species (ROS).[34,45] Compared to smart biomaterials responding to external stimuli, self-adaptable biomaterials are advantageous as they can change their biological functions dynamically in accordance with the microenvironmental cues. For example, ROS as a hallmark of many important diseases such as Alzheimer's disease and cancer has been widely adapted into smart biomaterial design. Sun et al. developed a ROS-degradable, PD-1 AAV-encapsulated therapeutic hydrogel using N1-(4-boronobenzyl)-N3-(4-boronophenyl)-N1,N1,N3,N3-tetramethylpropane-1,3-diaminium (TSPBA) and polyvinyl alcohol as building blocks for the immunotherapy-based treatment of glioblastoma.[46] In glioblastoma, the abnormal upregulation of ROS leads to the rapid degradation of TSPBA hydrogel and thus release of AAV and expression of PD-1 to block the PD-1/PD-L1 pathway. This in combination with radiotherapy effectively enhanced the T cell infiltration and activation to suppress the tumor growth. Importantly, the AAV can also be tailored to selectively express PD1 in target cells, which further improves the immunotherapy specificity. Such self-adaptable biomaterials can dynamically modulate cell fate in vivo without requiring external stimuli, thus desirable for clinical translation.

There have been a few smart biomaterial systems that have entered the stage of clinical translation, such as polymer-coated drug-eluting stents, self-assembled peptide amphiphiles, pH-responsive poly(lactic-co-glycolic acid) (PLGA), and glucose-responsive phenylboronic acid (PBA)-based microneedle patch.[47] From the clinicaltrials.gov website, biodegradable drug-eluting polymeric stents have shown improved results for treating cardiovascular diseases. Polymeric drug delivery systems are also under investigation for treating devastating diseases such as Alzheimer's disease. Compared to the bare-metal stent group (EverFlex BMS), the occurrence of chronic total occlusions was reduced in patients treated with Eluvia polymer-coated stents in a clinical study with a patient number of 124.[47] However, in another study comparing the effects of pH-responsive PLGA-coated stents with durable polymer-coated stents on patients with cardiovascular diseases, it was found that key parameters such as major adverse cardiac events (MACE), stent thrombosis (ST), target vessel revascularization (TVR) and target lesion revascularization (TLR) are all non-significantly improved between the two groups at a total patient number of 4255.[48] This strongly suggests the heterogeneity of smart biomaterials in clinical applications, and detailed design and analysis must be performed before their entrance into clinical applications.

Taken together, although the aforementioned systems are mostly based on polymeric and hydrogel-based systems, there are also many excellent examples of inorganic nanomaterials and scaffolds that are stimuli-responsive and have been applied for varying biological applications ranging from tissue engineering, drug delivery to cancer therapies. In the following sections, we will also strengthen the role of AI-based design of both inorganic smart biomaterials and polymeric smart biomaterials given the broader integration of ML and inorganic composites. However, the general design principles could be potentially applicable to the design, synthesis, and analysis of smart biomaterials of any kind.

4 | AI-ASSISTED DESIGN OF BIOMATERIAL COMPOSITIONS AND STRUCTURES

Traditional ways of designing and investigating material properties have often been based upon proposing qualitative theoretical models followed by experimental verification. Recent progress in computational material science and chemistry has significantly improved the accuracy of prediction models for material properties. For instance, ABO3 perovskites as piezoelectrics have greatly benefited from the integration of Bayesian optimization-based ML approaches. By computationally screening 605,000 possible compositions and combining them with 61 experimental tests, over a thousand ML models could be generated by polynomial fits. After further support from linear and radial-based kernel functions and gradient tree boosting, all candidate compositions and their properties could be generated. By iterating this active-learning process for five loops, they could identify an unexpected (Ba0.84Ca0.16)(Ti0.90Zr0.07Sn0.03)O3 composition with an excellent electrostrain of 0.23%, which is more than 50% improvement over the highest known value as shown in the training data. Strikingly, this optimization only took a few weeks of computation time to complete the prediction of 605,000 structures. In contrast, experimental validation of such a high number of compositions and their functions is nearly impossible. This quantitative comparison highlights the huge potential of AI in the discovery and optimization of materials. Using a similar strategy, ML was used to design and

screen the composition and structure of a smart anti-biofouling polymer as an alternative to the current gold standard of poly(ethylene glycol) and zwitterionic polymers for electrochemical biosensor surface coating (Figure 3).[49] First, a combinatorial library of polyacrylamide-based copolymer hydrogels was synthesized and screened with initial anti-biofouling activity. Next, using a random forest model, the molecular features of monomers were delineated from the copolymer library for the estimation of improved formulations of polyacrylamide-based copolymers. Lastly, the improvement in biosensing performance via the enhanced coating was evaluated in blood samples as compared to PEG-based anti-fouling coating.

In parallel, the discovery of novel stimuli-responsive materials often comes from the identification of new compositions and structures, we envision that the rise of computational science will enhance the AI-assisted design of dynamic and intelligent biomaterials. Therefore, the capability of computational material science has been highly valued toward the development of high throughput (HT) material design by marrying quantum mechanics, thermodynamics, and intelligent data mining for target dynamic properties (Table 1).[59] The workflow of such type of HT material design is typically composed of three steps: first, creating databases that contain physical properties of materials expanded from existing ones; second, using data mining techniques for the discovery of key material descriptors for searching and predicting materials with target properties; and last using experimental methods to validate the predicted dynamic materials.[60]

By analyzing the existing datasets of biomaterials, AI and ML algorithms can predict the properties of new biomaterials and create entirely new biomaterials with different compositions and structures to hit the desired functions. To be specific, when screening large-scale biomaterials with varying compositions, it is crucial first to understand the range of compositions that allow the stable formation of target biomaterials, which is closely related to the feasibility of synthesis. For example, in inorganic biomaterials, the key parameter that determines the feasibility of synthesis is the formation enthalpy for the stable phases of the target composition. For effective high-throughput computational screening of inorganic material compositions and structures, codes must incorporate algorithms that can (i) automatically adjust both the structure and composition of candidate inorganic materials and (ii) perform stepwise calculations of formation enthalpy to assess their thermodynamic stability.[61] To make the computation more efficient, the calculated structures must also be built into a standard

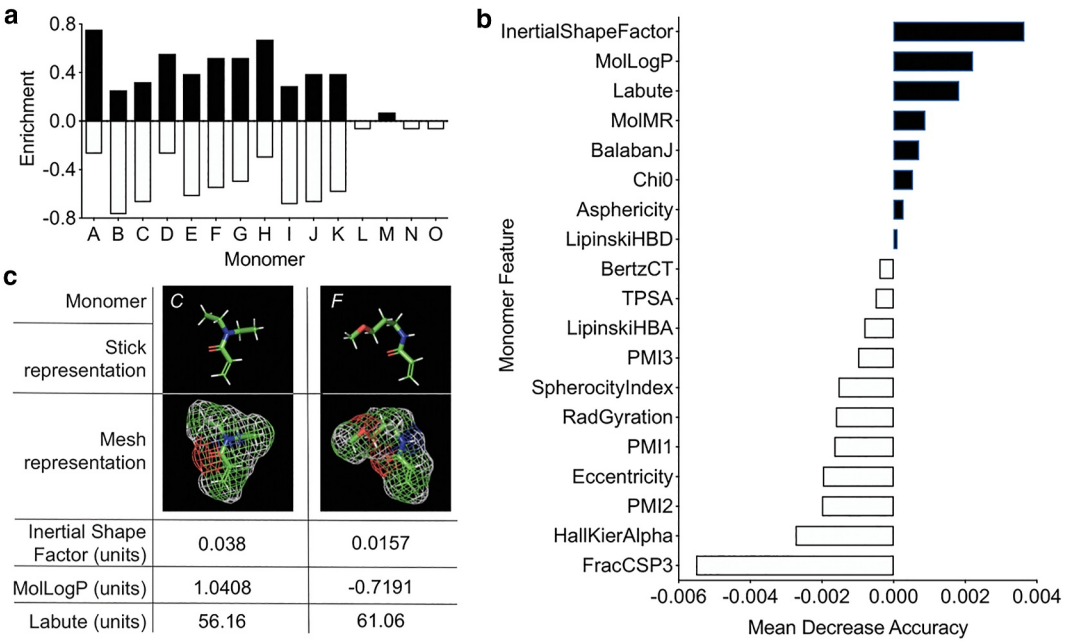

FIGURE 3 ML-assisted prediction of anti-biofouling acrylamide-based copolymer biomaterials. (a) Class enrichment using data from raw platelet adhesion assay indicating the contribution of each monomer to the anti-biofouling outcome. At this stage, only the composition (monomer) is considered. (b) A graph showing mean decrease accuracy summing the significance of features from each monomer. (c) A table summarizing descriptor values based on mean decrease accuracy. The chemical information of each monomer was transformed into descriptors of numerical value for communication with the ML interface. Reproduced with permission.[39] Copyright 2022, Wiley-VCH GmbH.

TABLE 1 Summary of current research using high-throughput experiments to screen and optimize the cell-biomaterial interaction property based on machine learning and artificial intelligence techniques.

Input features	Analyzed method	Through-put	Selection criteria	Result/outcome	Ref
Surface roughness, indentation elastic modulus, surface wettability	Principal component analysis (PCA) and partial least squares (PLS)	496 different arrays	Colony formation frequency of hES cells	Robust self-renewal of fully-dissociated hES and hips cells	[50]
High throughput surface characterization (ToF SIMS, XPS, WCA, AFM)	PLS	576 polymer spots	hES cell adhesion	Secondary ions indicative of the adsorbed fibronectin correlate with increased cell adhesion whereas glycol and other functionalities from the polymers are identified that reduce cell adhesion.	[51]
Different biomaterials ink formulations	Decision tree (DT), Random Forest (RF), Deep Learning (DL)	210 ink formulations	Printing accuracy (PA) and printability index	Generate a model that can predict the printability of different 3D printing biomaterials ink formulations	[52]
3109 structural parameters per molecule by PaDEL-Descriptor	RF, Gradient Boosting machine (GBM), Logistic Regression (LR)	2304 compounds obtained through Ugi reaction	Oscillatory shear modulus (G′ and G″)	Generate a model that can predict the self-assembly behavior of hydrogels	[53]
Polyelectrolyte, MW, Unit_MW, Charge_density, Concentration	K-nearest neighbors (KNN), Naïve Bayes (NB)	50 polymers	Cell viability, NO secretion	The probability of a polymer having anti-inflammatory properties is multiplied by three if it is a polycation	[54]
Concentration of different materials, Quantitative printing conditions	K-means, XGBoost, LightGBM, Gradient Boosting Classifier (GBC)	1171 samples	Cell Response, printability	Generate models that can predict the cell response, print quality, and overall quality of 3D (bio)printed scaffolds	[55]
Biochemical properties and target of drugs and nanoparticles	PTML linear model	Above 5,00,000 Drug Deliver nanoparticles System (DDNS)	Biological activity	Generate a model which is useful for selecting drugs, coating agents, and/or MONPs to be assembled in order to design new DDNS with optimal activity/toxicity profiles.	[56]
The contents of alloying elements and temperatures	Artificial neural network (ANN)	164 + 112 different alloy data	Young's modulus	Generate a model that can assist human to find low-modulus alloys rapidly and at low cost	[57]
RNA-seq data	KNN	132 training samples and 96 testing samples	Marker genes expression level	Develop a robust method to accurately predict the influence of biomaterials on stem cell differentiation, enabling cross-laboratory and material comparisons	[58]

form for convenient calculation with proper relaxation cycles, basis-set energy cutoffs, and k-point grid densities. Typically, for the endpoint of one calculation cycle, one could expect an optimal convergence at the meV level per atom.[62] A good coding process should also take the calculation failures into consideration, especially including scenarios in which hardware resource failures are not related to the structure design itself. The Automatic FLOW (AFLOW) HT framework represents one such HT system that can establish hundreds of materials with varying structures and compositions and output the viable selections of materials based on enthalpy

calculations in an automatic manner.[59] The AFLOW codes typically generate hundreds of different structures/compositions from the initial compound, with the energy and lattice parameters as outputs. Following this, data mining enabled by ML is performed for the cyclic optimization of the structure screening process based on more detailed parameters such as cluster expansion, genetic search on fixed-lattice, evolutionary algorithms (e.g., in off-lattice structures), etc. The Gibbs free-energy landscape would guide the optimization process by identifying minimal energy structures.

Although such a workflow has been relatively well-established for inorganic biomaterials, especially alloys, polymeric systems such as hydrogels that are built upon both covalent and non-covalent assembly mechanisms are much more challenging to predict and screen. So far, the simulation of organic biomaterials including polymer-based systems has been focused on fundamental network architecture properties such as crosslinking dynamics, elastic modulus, relaxation time, and water diffusivity.[63] Some studies have utilized high-throughput methods to map the relationships between cell expansion and biomaterials with varying properties. For example, high-throughput techniques have been employed to analyze how different polymer compositions influence the growth of human pluripotent stem cells. When combined with surface modifications, surface roughness, and elastic properties, methods like Principal Component Analysis (PCA) and Partial Least Squares (PLS) can facilitate the identification of optimal conditions for high colony formation of human embryonic stem (hES) cells. Gormley et al. recently established a research strategy to screen and design polymer-protein hybrids via the synthesis of a library of polymers in combination with Gaussian Process Regression (GPR) machine learning algorithm (Figure 4).[64] Polymer-protein hybrids are important for a variety of tissue engineering applications such as protein delivery. By automating the synthesis, characterization of copolymers assembled from 8 commercially available monomers of hydrophobic (2-diethylamino ethyl methacrylate (DEAMA), hydrophilic (N-(3-(dimethylamino) propyl) methacrylamide (DMAPMA), hydroxypropyl methacrylate (HPMA), butyl methacrylate (BMA), methyl methacrylate (MMA)), poly(ethyleneglycol) (n) monomethyl ether monomethacrylate (PEGMA)), (2-(methacryloyloxy)ethyl) trimethylammonium chloride (TMAEMA)), or ionic (3-sulfopropyl methacrylate potassium (SPMA).[65,66] These 8 monomers covered major copolymer assembly criteria of van der Waals interactions, electrostatic interactions, and hydrogen bonds. They also control the different combinations of hydrophobic, hydrophilic, and ionic functions at varying ratios and also the polymerization degree from 50, 100, to 200.[64] By creating a large library of these copolymers covering a variety of possible combinations, they then used retained enzyme activity (REA) as a key criteria for GPR ML together with a learn-design-build-test cycle. From multiple rounds of selection, 24 copolymers were selected and validated for the most optimal preservation of three proteins/enzymes: horseradish peroxidase (HRP), glucose oxidase (GOx), and lipase (Lip). New polymer composition was also verified in studies on biophysical interactions between polymer and protein complexes. However, the initial assembly unit of 8 monomers is still based upon prior knowledge of their performance in protein delivery, highlighting the importance of future work on a more generalized framework in AI-based prediction of optimal polymer compositions.

To extend these insights to another class of biomaterials, hydrogels have also drawn significant attention for their dynamic and tunable properties. A recent study focused on 3D printing different formulations of biomaterials including not only polymers but also hydrogels, which are favorable and designed for cell adhesion and growth. Most studies continue to focus on optimizing hydrogel composition, but a recent combinatorial approach has explored improving mechanical properties to enhance stem cell proliferation, morphology, and differentiation. Unlike traditional polymers, the design of dynamic hydrogels emphasizes the interplay between diffusion and viscous relaxation. However, their ability to replicate complex biological phenomena remains limited, especially in environments containing cells and macromolecule-rich biological fluids. Viscoelastic hydrogels, in particular, present additional challenges due to their non-Newtonian behaviors. ML and AI could break this limitation. It was reported that the ML has already been applied in the design and prediction of peptide-based hydrogels in elastic and viscous moduli. The predicted hydrogels were synthesized and tested with cells, showing enhanced proliferation, which reinforces the growing role of machine learning in biomedical applications. Additionally, the porosity and degradation mechanism also need to be considered and engineered, which are critical to cell encapsulation and tissue regeneration. However, in terms of stimuli-responsive behaviors, such as photo-, mechano-, temperature-, and enzymatic-responsive properties, the individual bonds could be simulated using quantum mechanics in programs such as Gaussian, but how individual bonds collectively act on the cell behaviors, such as cell deformation and cell mechanotransduction remain elusive in current computational models. The use of Monte Carlo algorithms for semi-empirical calculation of hydrogel systems is thus more common when predicting their bulk properties.[67] In addition to the prediction of the hydrogel property function, AI has also played an important role in the hydrogel formability analysis. For example, Fei et al. starting from 31 monomers including 8

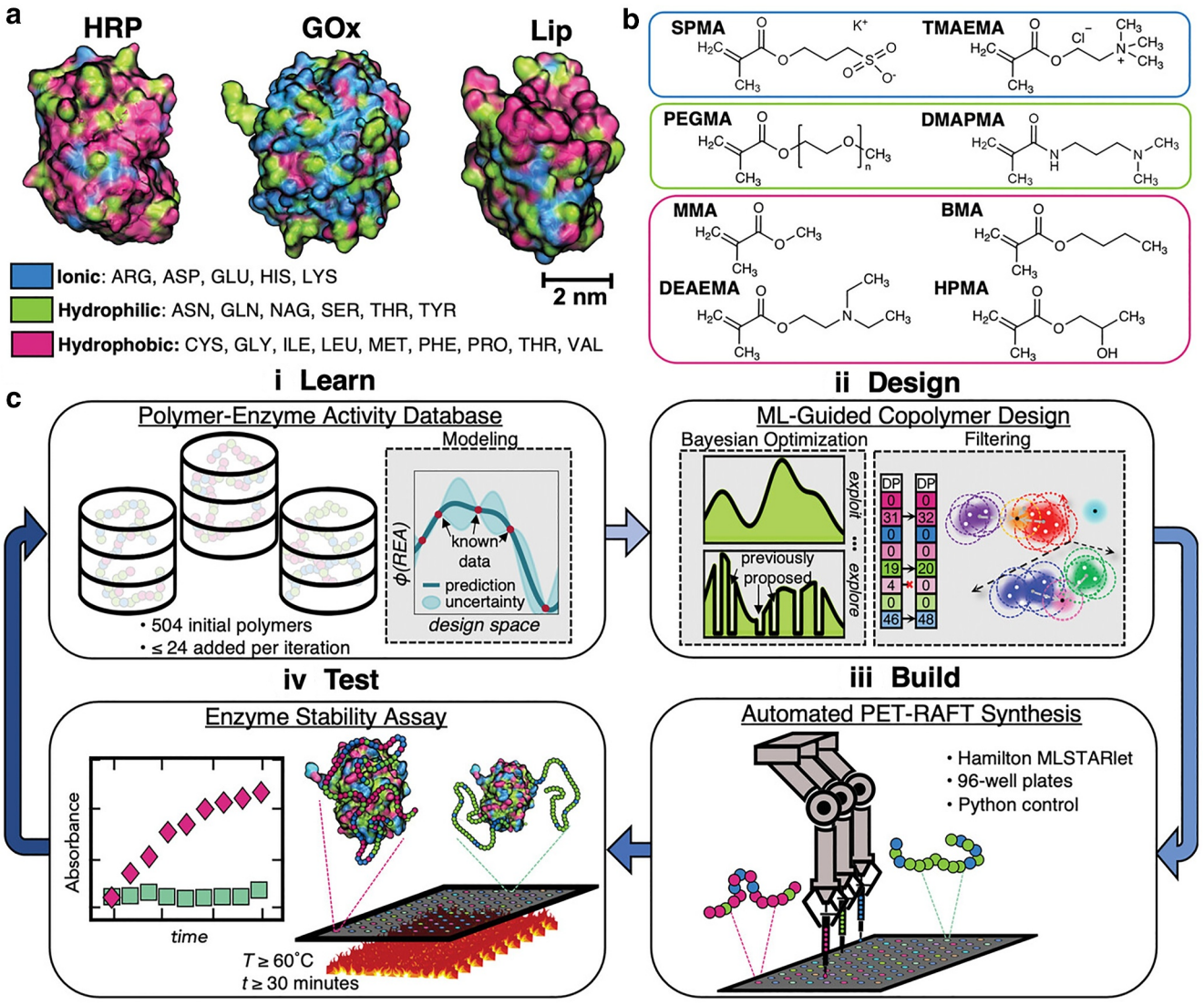

FIGURE 4 Exemplary scheme showing AI-assisted design of biomaterial compositions and structures. (a) The first step for the ML is the working principles of surface chemistry of three representative proteins: horseradish peroxidase, glucose oxidase, and lipase (HRP, GOx, Lip). Building blocks of proteins are colored blue (for ionic structures), green (for hydrophilic domain), and magenta (for hydrophobic domain). (b) Polymer building blocks. (c) Learn-Design-Build-Test discovery process for the ML-guided design of polymer biomaterials. Gaussian process regression (GPR) algorithm was used as the ML algorithm. REA: retained enzyme activity. PPH, polymer-protein hybrid, PET-RAFT, photoinduced electron-energy transfer reversible addition-fragmentation chain transfer polymerization. Reproduced with permission.[64] Copyright 2022, The Authors.

amines, 12 Fmoc-amino acids, 3 isocyanides, and 8 aldehydes/ketones, Ugi methods were adopted to prepare 2304 peptides followed by prediction of 7,163,136 structures with 3109 parameters for each structure using PaDEL-Descriptor. 81 structures were predicted to successfully form the hydrogels out of the two thousand structures.[14] By further applying adaptive synthetic sampling (ADASYN), synthetic minority oversampling technique (SMOTE), and random oversampling (RO), the structure could be further refined. Therefore, given the popularity of developing smart biomaterials including polymeric and hydrogel systems for biomedical applications (Table 1), we envisage the increasing demands on advanced computational models for high throughput predicting and screening of organic biomaterial systems in the next few years.

5 | AI-ASSISTED DESIGN AND PREDICTION OF BIOMATERIAL FUNCTIONS

Besides the analysis of the composition and structure of the biomaterials, intelligent biomaterials could be built upon molecular or crystal structure units that respond to light, heat, magnets, electricity, and other forms of energy

inputs. Thus, AI could enable the design, optimization, and prediction of properties for highly specialized applications such as drug delivery and surface interactions (Figure 5). For light-responsive structures, the most important calculation would be based on the energy bandgap calculation.[68] Earlier computational studies on light-responsive materials have been mostly seen in solar cell and photocatalytic applications, including both organic dyes and solid-state materials. Although their relevance to biomaterials is still vague, it would be beneficial to learn from their approaches to designing smart biomaterials. "Spectroscopic limited maximum efficiency," or SLME is a novel descriptor that integrates the evaluation of bandgap, absorption spectra, and non-radiative energy loss of materials for predicting their performance in response to photonic energy inputs.[69] One of the best examples is the concept of photonic crystals that confine electromagnetic waves within gaps of nanocrystals of noble metals (e.g., gold, silver, and platinum).[70,71] By defining the dielectric constant, nanocrystal size and shapes, as well as the spatial distribution of the nanocrystals (e.g., distance within each two nanocrystals), scientists precisely predict the light responsivity at specific wavelengths using computation such as finite difference time domain (FDTD) methods. The ability to computationally screen hundreds of such spatial layouts aids the rational design of photo-responsive biomaterials for applications ranging from biosensors to cell culture substrates, etc. Furthermore, the photo-amplification units can be coupled with photo-responsive ligands or structure units to input chemical or electrical signals into cells for stimulative applications, thereby enabling dynamic cell control.

Computational tools have also advanced the prediction and screening of other stimuli-responsive materials and processes to achieve the desired response to cells or drugs (Figure 6). For example, the absorption and release of therapeutic molecules on the surface of solid-state materials can be calculated by comparing energy before and after docking of the target molecule to the loading materials. "Parasitic energy" is a term defined in the gas absorption process that might be applicable to stimuli-responsive drug release. In this code, hundreds or even thousands of different structures could be screened for

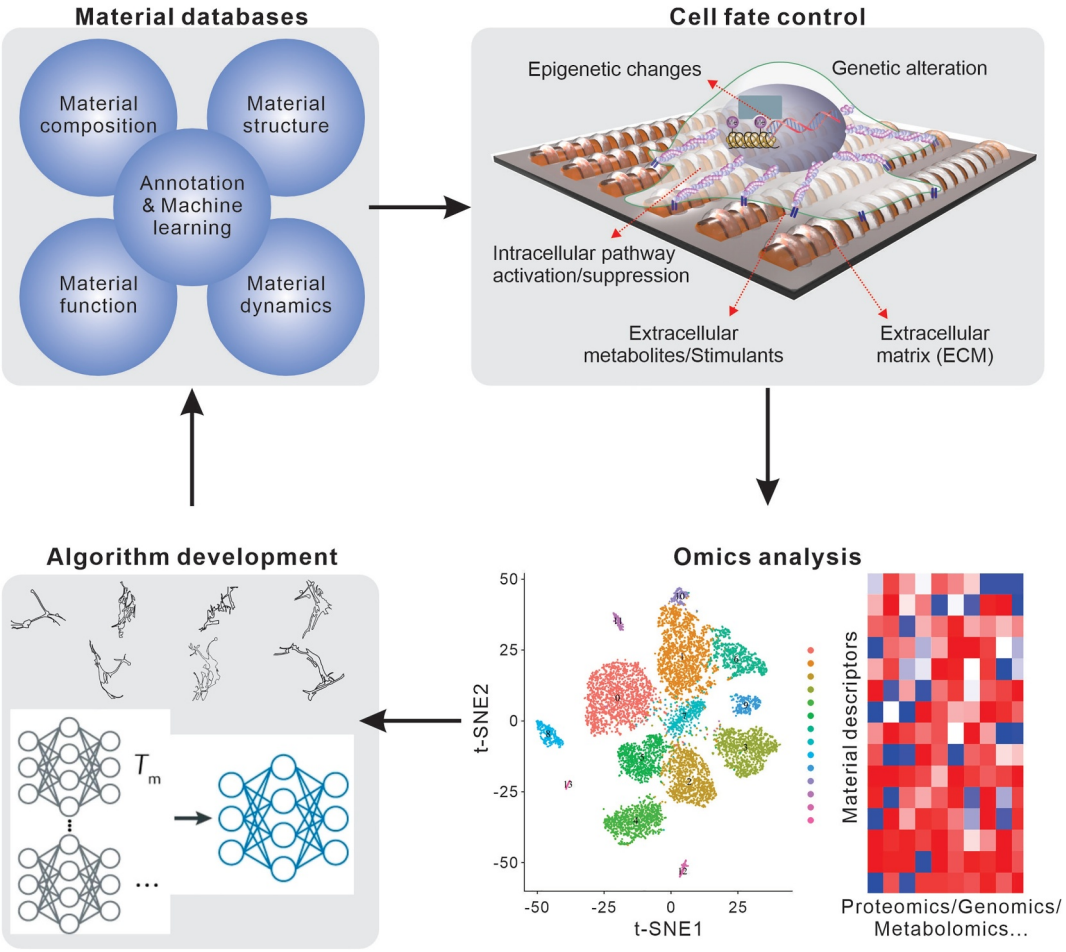

FIGURE 5 Proposed framework for AI-assisted design and analysis of biomaterial functions.

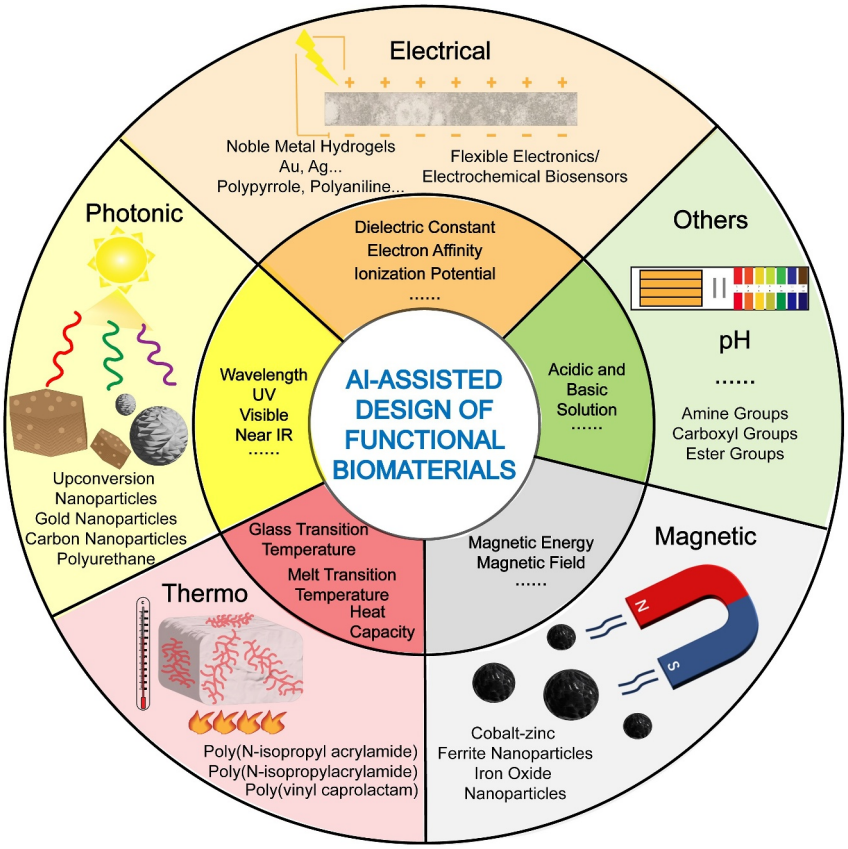

FIGURE 6 An overview of the functional biomaterials designed by artificial intelligence. The current studies of designed functional biomaterials, including but not limited to light-responsive biomaterials, electrically stimulated biomaterials, temperature-sensitive biomaterials, and magnetically controlled biomaterials, etc. are mainly based on the artificial neural networks and machine learning algorithms to optimize the physical, chemical, and biological properties for various treatment outcomes.[72]

binding or releasing the target molecules in porous structures such as metal-organic frameworks (MOFs) or zeolites. The temperature- or light-responsive release of the bound molecules could be simulated by calculating energy states before and after adding the corresponding energy inputs or alteration of the electronic states induced by light, heating, electrical inputs, or other forms of energy inputs. There are a variety of other types of signals similar to the high throughput calculation of light-responsive materials, including piezoelectricity-responsive biomaterials, nuclear energy-responsive biomaterials, thermoelectricity-responsive biomaterials, as well as biocatalytic biomaterials. Some stimuli can excite electronic states of biomaterials but have not yet been applied to biological applications, such as topological insulators, which have also been computationally screened for the smart design of intelligent devices.[73] Additionally, there is a high demand for AI for analyzing and designing multi-stimuli responsive biomaterials combining more than one element for a complex cellular environment. However, similar to the computational screening of biomaterial compositions and structures, most studies on optimizing the physical properties of intelligent materials have not been extended into soft biomaterial systems. There is thus a clear need for computational materials scientists to develop codes and programs capable of automatically generating a diverse array of biomaterials and subsequently screening them for applications in stimuli-responsive mechanical changes, drug delivery, or direct interactions with cells.

6 | AI-ASSISTED ANALYSIS OF SMART BIOMATERIALS IN BIOLOGICAL APPLICATIONS

In contrast to static inorganic biomaterials, soft biomaterials—including polymers, peptides, proteins, nucleic acids, and polysaccharides—possess dynamic mechanical and biochemical properties. These adaptable characteristics are essential for investigating physical, chemical, and biological mechanisms to achieve better therapeutic outcomes. AI has played a tremendous role in propelling this field forward. For example, the recent

popularity of DeepMind's AlphaFold2 and ChatGPT has brought the public to a new wave of interest in ML and AI. The design and optimization of biomaterials involves a highly complex process that integrates multiple material properties, biological interaction, and dynamic remodeling mechanisms. Integration of omics technologies to dissect these complicated processes requires more advanced and accurate data analytical tools. However, to engineer fit-for-purpose soft biomaterials, a better synergy between combinatorial biomaterial screening and ML must be achieved, and this promising area is still in its infancy. Therefore, we also overview the cutting-edge ML- and AI-based design of materials and their implications for the next generation of dynamic and adaptive soft biomaterials.

Among the various biomaterial systems, ECM materials stand out as critical components, offering a dynamic and biologically relevant platform to explore and design advanced therapeutic strategies. The properties of ECM biomaterials, such as polymers, can often be predicted by dividing them into subunits and then calculated based on the interactions among functions from different subunits. For example, peptide and protein scaffolds as ECM material regulate stem cell differentiation largely based on their sequence of amino acids and the secondary structures formed through interactions between different amino acid units.[74] Prediction of properties of synthetic polymers based on the less defined monomers has been proven to be more challenging. However, the development of combinatorial chemistry techniques allows us to survey high-dimensional design spaces of polymers in a more efficient manner. Correspondingly, big data-oriented scientific discovery as the fourth paradigm of science paves a new road for predictable material properties.

Databases are fundamental to AI, especially those mapping the relationships between the structure and function of smart biomaterials in response to chemical, biological, and physical signals. For this purpose, there have been several databases built from these combinatorial screenings, including PoLyInfo,[75] Polymer Property Predictor, CHEMnetBASE-Polymers,[76] and the Polymer Genome.[77] In addition to the database built for different polymeric compositions, there are also different databases under construction for the porous materials. For example, the computational ready experimental (CoRE) metal organic framework (MOF) database contains all MOF structures synthesized so far using the Cambridge Structure Database (CSD) format. These databases are accompanied by in silico simulated parameters, though their methods could be different from each other when different researchers perform their simulations. In addition to databases focusing on compositions and structures, there are also databases focusing on materials with specific properties, such as thermoelectric material databases under the Inorganic Crystal Structure Database (ICSD). Lastly, databases that summarize a collection of biological information, such as genome, transcriptome, proteome, and metabolome, have also been rapidly developed in recent years. However, the integration of biomaterial databases with different focus on composition, structure, function, and their biological outcome is challenging. With the successful integration of different databases and combining with the updated ML, one may expect a bright future of AI-assisted rational design and optimization of smart biomaterials for diverse applications.

In parallel, merging combinatorial studies for ML and AI-based prediction of ECM material properties remains difficult due to a lack of uniformity across different databases. An alternative approach to expand the database for ML and AI-based prediction of ECM material properties would be through molecular dynamics-based simulations. Currently, the Materials Genome Initiative, which emphasizes the simulation of material properties, has successfully generated extensive data and enabled the discovery of numerous novel functional materials. However, the majority of these materials are small molecules or inorganic molecules for which density function theory-based simulations are highly effective.[78] In contrast, for the simulation of polymeric and biomacromolecule-based ECM materials, molecular dynamics (MD) and coarse grain (CG) simulation would be more practical, but they would also require significantly more effort from the theoretical scientists to generate enough data for ML, especially when high accuracy is required. As these tools evolve, they promise to deepen our understanding of biomaterial–cell interactions and accelerate the development of next-generation biomaterials tailored for specific therapeutic applications.

AI-based evaluation of biomaterial functions has also brought great advances in the optimization of smart biomaterials. For example, nanomaterials such as layered double hydroxide (LDH) have shown excellent promise for promoting neurogenesis of neural stem cells (NSCs), with potential applications in treating neural injuries (e.g., spinal cord injury) and neurological disorders (e.g., Alzheimer's diseases) in the treatment of spinal cord injury. However, relying on conventional approaches such as immunostaining and quantitative polymer chain reaction (qRT-PCR) to characterize the effects of smart nanomaterials is not only destructive (e.g., cells need to be fixed or lysed) but also requires tedious procedures and expensive instruments. To address the challenges in the rapid, non-destructive, and real-time monitoring of neurogenesis, Zhu et al. designed an innovative AI-based

platform for the accurate quantification and prediction of LDH biomaterials in LDH-induced neuronal differentiation of NSCs (Figure 7).[79,80] Specifically, they first generated a large amount of experimental data using optimal images of NSC differentiated into different stages of neurons. Using this set of data, they developed an elegant CNN structure to generate a highly reliable and efficient model followed by vigorous verification of the system using unknown data but combining conventional approaches such as immunostaining (e.g., PAX6 and Nestin for neural stem cells, and Tuj1 and MAP 2 for neurons). Retinoic acid as a differentiation inducer was further added to the culture to differentiate NSCs into neurons with varying maturation stages. In parallel, LDH with different compositions was treated to NSCs and their differentiation was monitored as early as Day 1 and Day 3 to provide rapid and timely feedback using the established and verified AI algorithm. The most optimal

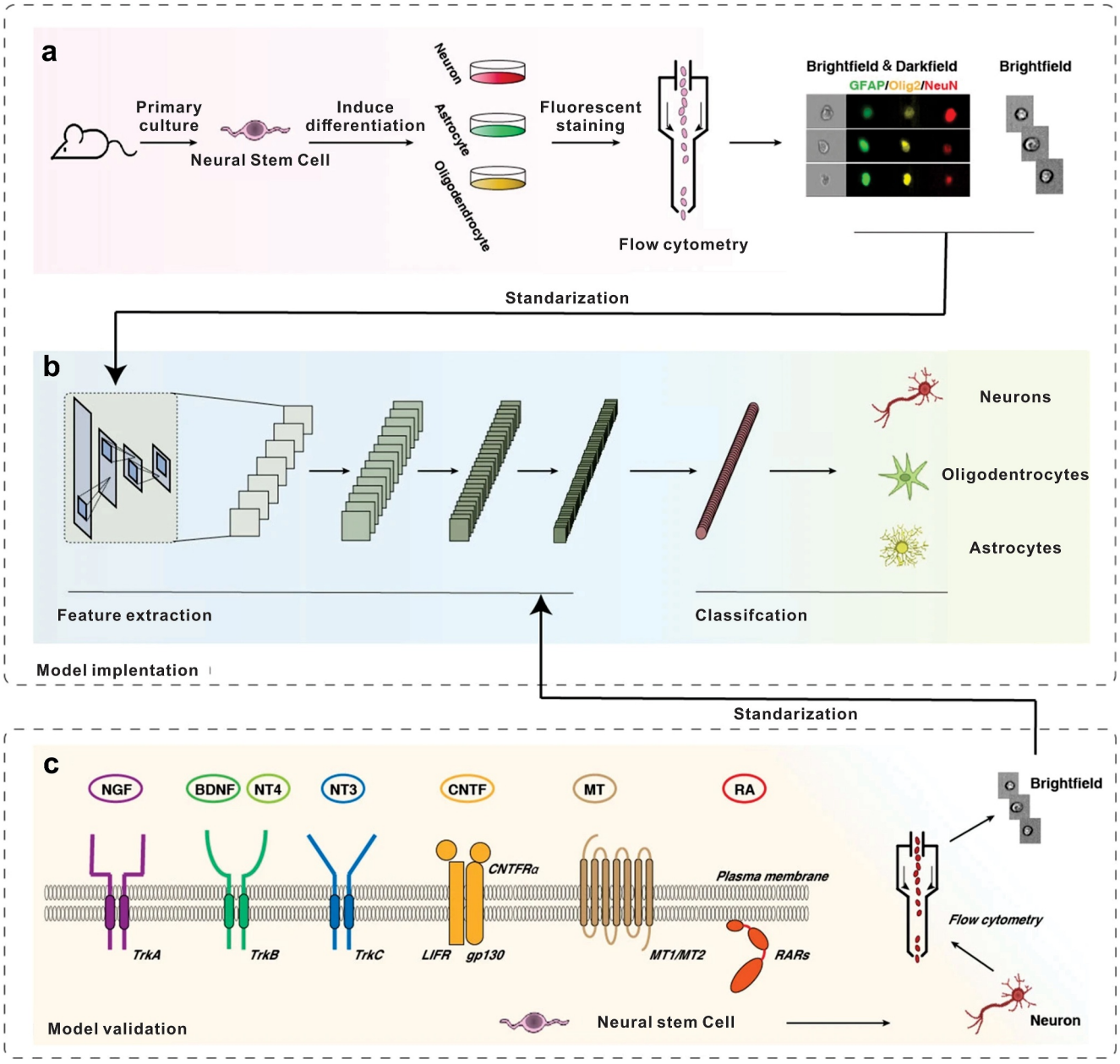

FIGURE 7 ML-based analysis of LDH nanomaterial-induced neurogenesis of NSCs. (a) The differentiation of NSCs and immunostaining with NeuN (red, neurons), GFAP (green, astrocytes), Oligo2 (yellow, oligodendrocytes) followed by flow cytometry characterization. (b) ML model implementation based on bright field images of NSCs differentiated at varying conditions using CNN. (c) LDH and other neurogenesis inducers treated to NSCs and their prediction of capability of neuronal differentiation by deep network model. Reproduced with permission under the Creative Commons CC BY license.[68] Copyright 2021, The Author(s).

composition of LDH for inducing neurogenesis was identified at an early stage and then verified later after Day 7. Mechanistic studies also supported the optimal role of LDH in promoting neurogenesis via the leukaemia inhibitory factor receptor β (LIFRβ)-associated pathways. This serves as an excellent example using AI for both the prediction and optimization of smart biomaterials and guide the design of their composition.

As mentioned above, ML can significantly reduce the time and cost associated with designing smart materials by analyzing their structure and property-based scales. Smart materials often comprise multiple components (e.g., natural polymers, synthetic polymers, and growth factors) interacting through hydrogen bonding, and electrostatic interactions. Therefore, it is essential to leverage ML for assisting the analysis of material-material interactions at a higher complexity. Such multi-material interactions are more challenging to predict and simulate, making the ML difficult. For example, protein-based smart biomaterials often demonstrate high variations in terms of compositions and structures. Therefore, there has been lacking effective ways to study their biological responsiveness in silico. For this purpose, Ruan et al. proposed a method to add protein sequences encoding intermolecular interactions into the known protein framework.[81] This strategy could be extended to other heteropolymer systems to predict their biological properties. First, starting from natural protein libraries and previous designs on heteropolymer ensembles representing mixtures of folded, partially folded, and disordered proteins, they extract the sequence arrangement and composition properties following the major protein chain with different segments. In this way, they could high throughput screen diverse protein combinations to form cytosol-like biofluids by taking into account the electrostatic and hydrogen interactions. Molecular simulation could then be further incorporated to specifically analyze intermolecular interactions with a quantitative description of diversity and spatiotemporal availability. Thus, such a framework innovates principles for realizing protein function simulation and ML of biomaterials and helps with the understanding of matter-to-life transformation.

7 | AI-ASSISTED SYNTHESIS OF BIOMATERIALS

Beyond applications in simulating and analyzing material dynamics, ML integrated with sensing (e.g., computer vision), or CV and motor (e.g., robotic arms) units that further enable AI-based creation of biomaterials is another trend to watch. For example, cell competition as a process regulated by mechanical forces from surrounding cells plays an important role in human tissue development and self-cell sorting.[82] However, it is extremely difficult to track many events of cell movement in real-time, which limits the current study of the cell competition phenomenon. Lowe et al. approach this imaging issue by first inventing τ-VAE, a deep learning algorithm that can couple with an imaging system to predict cell fates in the epithelium and then identify the key physical origins driving cell movement.[83] Similarly, AI-based fabrication of 3D devices for mechanically modulating stem cells is also under development. By advancing AI-based real-time sensing, adaptation, and prediction of the printing environment, biological inks can be 3D-printed into functional organs (e.g., spinal cord) from stem cells in a more accurate manner.[84] This is an area that has emerged in the past few years, with many challenges and opportunities remaining to be explored. For example, conventional robots can only perform relatively simple tasks when optimizing biomaterials with a wide spectrum of physical and biological properties. Training robots with the capability to automatically search for target compounds for regulating stem cell behaviors is far beyond the reality that needs joint efforts from not only biologists and material scientists but also computational scientists.

As a step further, 4D printing that aims to generate devices with time-varying properties using additive manufacturing has also attracted significant attention in recent years. Traditional approaches to design 4D printing procedures have been mostly based on trial-and-error, but involving AI to tailor the printing program could be a promising approach to speed up the device innovation.[85] For example, the conformal-flattening method previously commonly seen in computational geometric design could be exploited for programming the dynamic shape change of soft devices made by 4D printing.[86] The logic behind lies in setting curved surfaces as targets and 2D meshes within the surface as an active element with printable biomaterial with specific expansion/contraction constants in response to external stimuli (e.g., heat or light). Upon exposure to external stimuli, the soft device could then transform into the desirable curved surfaces. This could be further extended into a multi-stimuli-responsive system with an improved ML algorithm. For instance, by selecting two printable biomaterials responsive to two orthogonal external stimuli, and designing two target shapes via similar 2D mesh-based approaches, we could then achieve a shape-shifting path by properly increasing the stimulus level. Although the area of 4D printing research is still at the early stage of translation, leveraging AI to continuously expand the complexity of 4D printed biomaterials highlights its excellent potential in theragnostic applications.

Recently, there has been a milestone development of a mobile robot that can autonomously operate for over a week to synthesize 688 experiments at the complexity of a ten-variable level (Figure 8).[87] To empower this robot, a batched Bayesian search algorithm was integrated. Using this robot, a photoresponsive material was identified for converting water into oxygen at an efficiency six times higher than the initial input formulation with excellent reproducibility. Earlier versions of such robot-based synthesis of biomaterial libraries are microscale synthesis of combinatorial arrays of polymers using an automatic sampler with programmable reaction parameters such as temperature and stirring speeds, followed by ML-based analysis of optimal reaction conditions. These studies, despite being at an early stage of this emerging field, serve as excellent examples of how ML and AI can be incorporated into the screening, investigating, imaging, and microfabrication of intelligent materials. The convergence of AI, robotics, and biomaterials science may tackle complex challenges in biomaterial design and synthesis. As these tools evolve, they promise to revolutionize the field by enabling high-throughput experimentation and the development of next-generation biomaterials with tailored properties.

The idea of AI-assisted synthesis of biomaterials is closely related to "self-driven labs (SDLs)." SDL contains broader concepts beyond biomaterial synthesis and refers to automated experimental workflows including experimental planning to implementation. There have been a few excellent reviews providing in-depth analysis of different aspects of SDL technologies with diverse applications from material science, drug discovery to genomics, with discussions on software and hardware infrastructure.[88] For smart biomaterial synthesis, the most relevant example could be a self-driving autonomous machine for protein landscape exploration (SAMPLE) platform built by Rapp et al, which successfully guided the engineering of a glycoside hydrolase family 1 (GH1) enzyme with improved thermal stability.[89,90] Briefly, a GH1 combinatorial sequence space was composed from elements of natural GH1 family proteins using Rosetta. Using the 1352 GH1 sequences from the design space, a constrained selection-based sampling strategy was customed to predict the subset of active sequences. Afterwards, SAMPLE leverages the Golden Gate method to combine pre-synthesized DNA fragments to generate the target gene, which could be further translated into a protein with quality control by colorimetric or

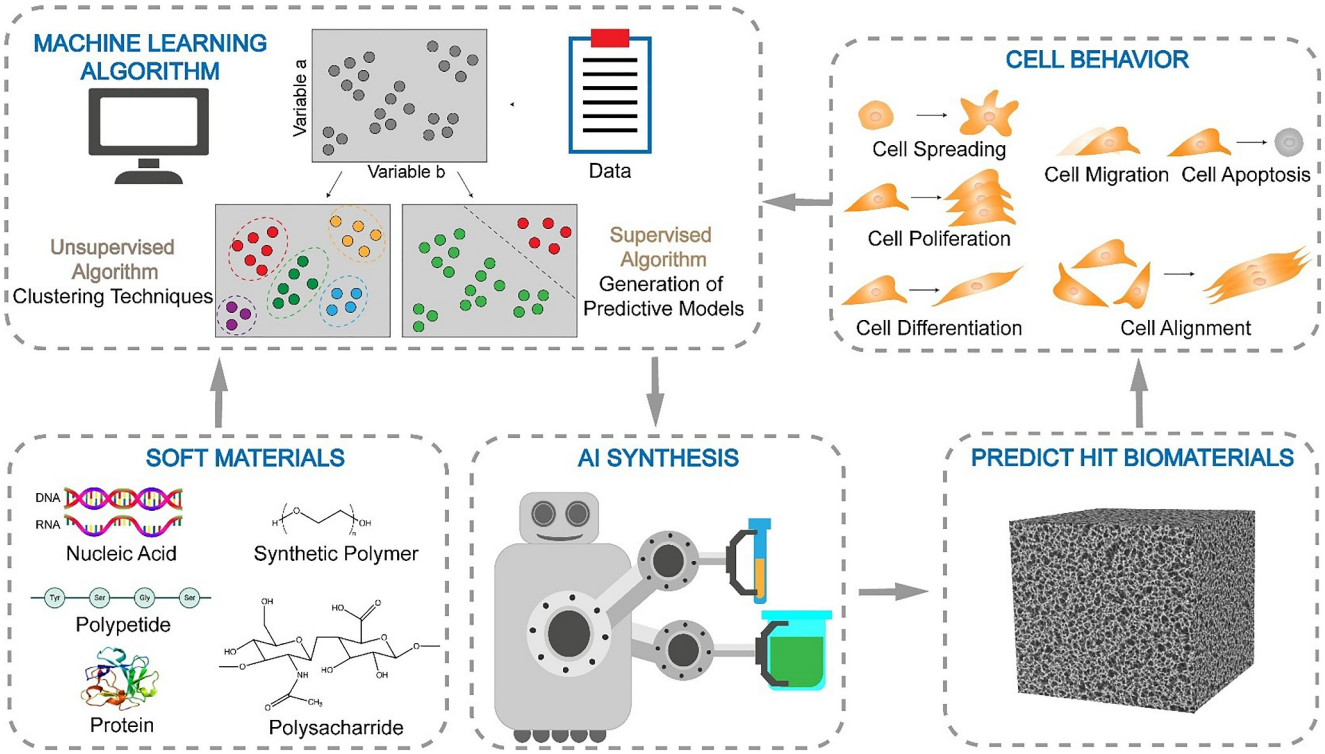

FIGURE 8 AI-assisted design and synthesis of intelligent biomaterials. Design of soft biomaterials could be achieved by first segmentation of targets into different functional groups followed by calculation of converging properties from individual units. Automated handlers or robotics for mixing and controlling reaction conditions during synthesis enable high throughput and automated synthesis of soft biomaterials. The synthesized biomaterials can also be analyzed with AI-guided biological assays followed by ML for quantifying cell responses to the extracellular biomaterials. The whole process creates a feedback loop in designing and synthesizing intelligent polymers for guiding cell differentiation.

fluorescent assays under varying temperatures. This finally guides the discovery of an enzyme highly stable across a wide range of temperatures. Meanwhile, as the whole procedure is fully automated and can be performed on the Strateos Cloud Lab, high throughput, excellent reproducibility, and also higher efficiency are achieved in discovering smart protein-based biomaterials. Given the essential role of AI, we envisage the continuous growth of the field of "AI-enabled self-driven labs" for a variety of other applications in discovering and optimizing smart biomaterials.

8 | AI IN BIOMATERIAL MULTIOMICS

Building on these capabilities, the integration of multiomics technologies with AI offers an unprecedented opportunity to comprehensively analyze biomaterial–cell interactions. By leveraging AI-driven insights into genomics, proteomics, and metabolomics, researchers can dissect the complex biological processes underlying biomaterial performance and further refine their design for enhanced therapeutic efficacy. For instance, a major challenge in developing next-generation biomaterials for the regulation of stem cell fates lies in their constantly increasing functionality and complexity of the ECM. The stiffness, viscoelasticity, nanotopography, and porosity can all impact cellular mechanotransduction through varying mechanisms, including integrin clustering, cytoskeletal remodeling, force transmission to linker of nucleoskeleton and cytoskeleton (LINC), followed by the relocation of YAP/TAZ, disruption of Lamin A complex, and epigenetic modifications that lead to altered protein and gene expression. In addition, the biomaterial-mediated magnetic, photonic, thermal, chemical, and electrical signals can also induce the alteration of stem cell fates in 3D and 4D, further compounding the dissection of mechanotransduction mechanisms. How to balance the need for systematically elucidating the cell-biomaterial interactions with varying biomaterial properties is thus urgently needed for tissue engineering applications. Developing new strategies for identifying simple yet translatable principles to design biomaterials represents a promising means. Omic technologies have been revolutionizing the fields of biology and medicine in the past decades and are also rapidly emerging as a promising strategy that allows biomaterial scientists to evaluate cell-matrix interactions and their downstream pathways in a high throughput manner. As a result, these high throughput screening and omic analyses direct scientists to discover new dimensions of biomaterial parameters to instruct the stem cell fates, leading to a further increase in biomaterial complexity.[91] To deal with the data explosion associated with biomaterial complexity and omics data sets, it is equally important to integrate machine learning algorithms or artificial intelligence that can automatically summarize key rules from big data in a non-biased manner.

These advancements have also influenced the design and optimization of biomaterials, such as polymers used as extracellular matrices (ECM) for stem cell culture. Using polymers as ECM for stem cell culture requires systematically optimizing the compositions, structures, degradation rates, and tethering to the cell-binding motif. For this purpose, Langer and Anderson 's group performed the pioneering work in developing combinatorial microarrays that contain polymers with different compositions, degradation rates, and cell binding affinities.[92] These have led to the prediction and discovery of new polymeric scaffold systems for drug/gene delivery, as well as stem cell engineering. In these arrays, polymers often share the same backbone, while the grafting of biologically relevant functional groups renders the polymer with different material properties. The output is based on fluorescence- or radiation-based cell assays. Elisseeff's group also adapted the approach for screening natural ECM macromolecules derived from 11 different porcine tissues. This study thoroughly explored their interactions with stem cells by integrating genomic, proteomic, and transcriptomic research.[93] They also compared 2D and 3D microarrays regarding the induction of stem cell differentiation from diverse ECM protein compositions. Additionally, screening of ECM with varying stiffness for inducing stem cell chondrogenesis, or the maintenance of embryonic stem cell fate has also been realized by the conventional microarray system, or through the generation of stiffness gradient across a wide range of hydrogel stiffness. However, one current limitation is that although various ECM materials and their parameters have been screened and studied, conclusions are often drawn based on individual polymer backbones. How much we can apply conclusions drawn from one study to another remains unclear. In parallel, we could expect an overwhelming data explosion if we optimize and screen all key polymer parameters for each type of polymeric system. This would certainly necessitate the biomaterial community to join their efforts on the most promising material backbones but expand studies on their diverse material properties and effects on stem cell differentiation through varying omics technologies rather than focusing on the synthesis of new biomaterial systems.

Recent interest in biomaterial multiomics technologies also underscores the need to address another critical challenge in stem cell engineering: the high-throughput screening of micro- and nanostructures in mechanomodulatory materials (Figure 9). High throughput screening

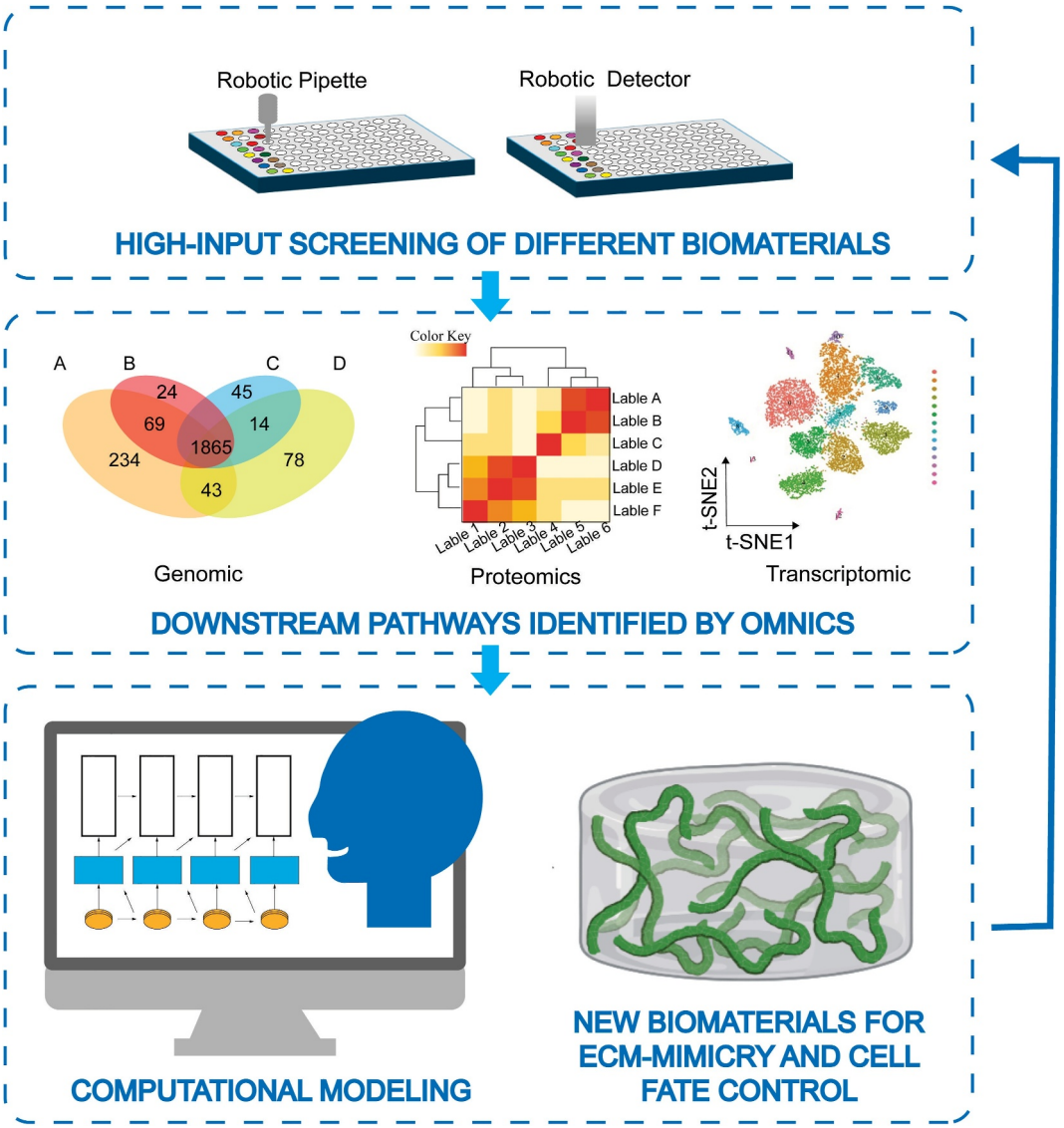

FIGURE 9 Current and future perspectives on how materiomics revolutionize biomaterial discovery and optimization for ECM-mimicry in the cell fates. The high throughput screening on the chemical, physical, and biological properties of biomaterials interacting with cells provides enough information for computational modeling to establish and process. Based on this machine learning, the cell interaction will use new biomaterials created to hit the desired outcome.

of micro and nanostructures of ECM biomaterials has brought out another critical barrier for stem cell engineering. Unlike the screening of compositions, stiffness, degradation rates, and cell adhesive ligand tethering, which are often described and evaluated as bulk material properties, the micro and nanostructures are much more difficult to characterize and screen at a large scale. First, nanostructures of biomaterials are extremely diverse in nature. For example, collagen fibrils have varying diameters from sub-10 nm to hundreds of microns. Fibrils can entangle with each other to form different orientations of hierarchical networks. When screening such diverse nanotopographical cues for stem cell differentiation, from the perspective of nanofabrication, it is a formidable task to cover a wide range of sizes, shapes, and orientations, especially when complex (e.g., hierarchical) structures are of interest during the screening. It is equally challenging to characterize thousands of complex nanostructures at a large scale (centimeter scale and above). Therefore, current screening strategies for designing nanotopographies for stem cell fate regulation or reprogramming have been largely compromised. For example, by focusing on simpler structures such as line patterns, one can screen the most optimal size of aligned fibers for specific stem cell differentiation and axonal alignment applications. Attempts have been made to use e-beam nanolithography to generate hierarchical structures and investigate their effects on stem cell

differentiation.[94] However, the high cost and low throughput of e-beam nanolithography have restricted the number of complex nanostructures generated at a large scale containing thousands of different nanostructure arrays. Similar issues exist in other cutting-edge nanofabrication techniques, such as dip-pen nanolithography and soft lithography, while conventional photolithography lacks the necessary precision to create complex nanostructures. Therefore, the barrier in screening ECM nanostructure-mediated passive mechanomodulation of stem cells is clear.

To address this challenge, we have pioneered a novel dynamic interference lithography technique that can generate thousands of distinctively different micro/nanostructure arrays with varying complexity as a novel biomaterial omic platform (Figure 10).[95,96] We named this platform as combinatorial biophysical cue (CBC) array. Using the CBC array, we first demonstrated the cell

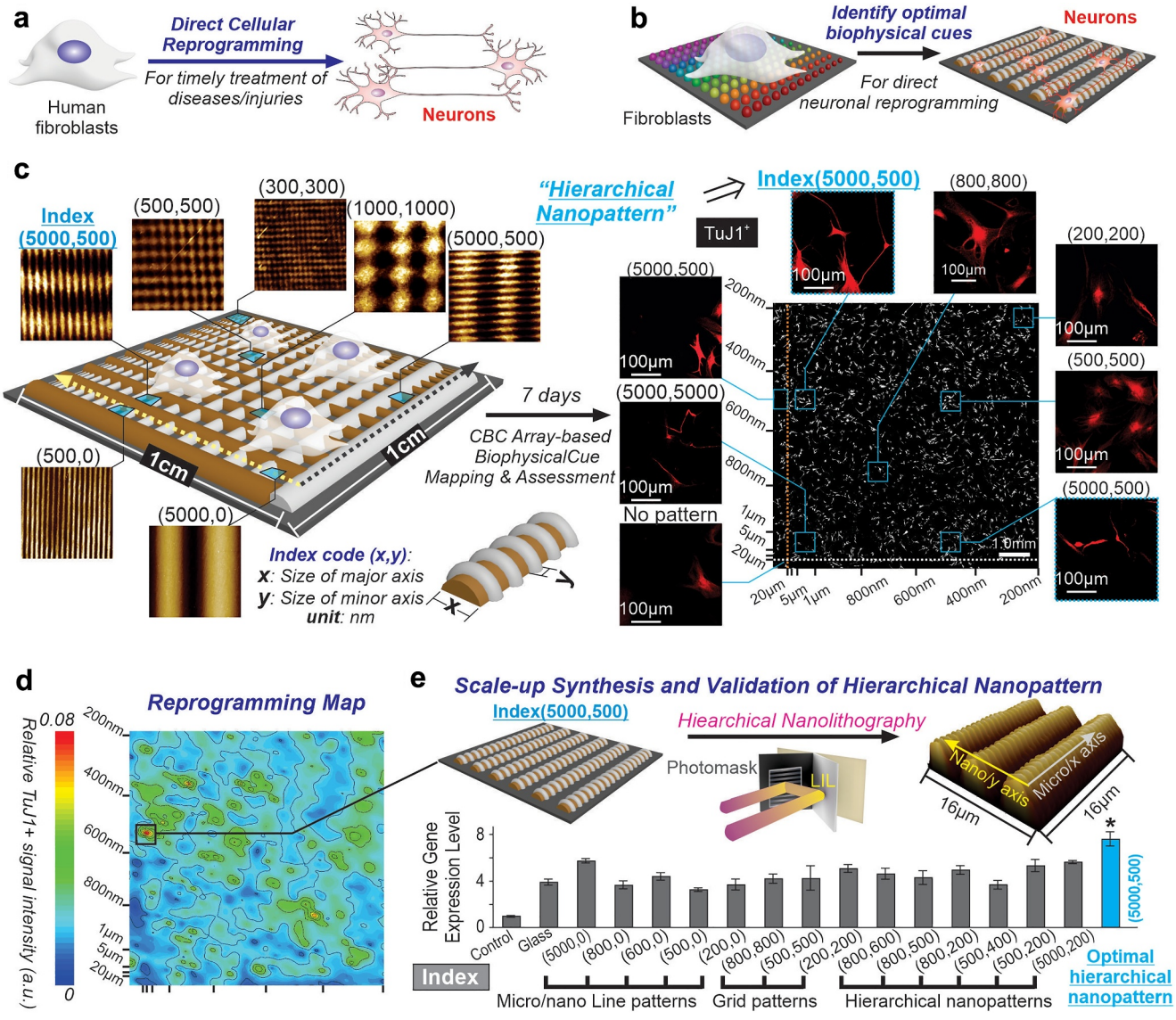

FIGURE 10 Biophysical cue-induced cell reprogramming using CBC array-based high-throughput screening. (a–c) Schematic diagrams illustrate how material database analysis laid the groundwork for designing the CBC array-based high-throughput screening process, which identified optimal biophysical cues for direct neuronal reprogramming of human fibroblasts. The schematic diagrams shown in (a) and (b) demonstrate the neuronal reprogramming of somatic (foreskin fibroblast) cells. Panel c shows the screening of reprogramming via the combinatorial nanoarrays. (d–e) These findings were scaled up using a hierarchical nanolithography technique to develop a biophysical cue-based neuronal reprogramming map, enabling the continuous refinement and optimization of material composition, structure, function, and dynamics in interaction with cells. LIL indicates laser interference lithography reproduced (Adapted) with permission.[95, 96] Copyright 2022, Elsevier Ltd.

type-specific design of nanotopographies for the mechanomodulation of stem cells.[97] Specifically, adult neural stem cells (ReNcell), human iPSC-derived neural stem cells (hiPSC-NSCs), and Rett syndrome patient-derived hiPSC-NSCs (hiPSC-NSC-Q83X) differentiated on the CBC array were analyzed with neuronal marker expression, then corresponded with the thousands of different nanostructures underneath. However, due to the existence of areas without any neurons, the default output of zero value leads to the generation of a stochastic heatmap as a function of position (x, y) and neuronal marker expression (z). We thus further adapted a Gaussian process regression (GPR) machine learning algorithm in MatLab®, which automatically learned from the trend of existent spots where neuronal marker expression is nonzero and generated a more accurate heatmap reflecting the real trend of nanotopography-regulated neuronal differentiation in a cell-type specific manner. This further facilitated the cell-type specific design of nanofiber biomaterials, which are of clinical relevance in neural stem cell therapy. Using the same platform, we have also performed high throughput screening of nanotopography-mediated neuronal reprogramming of somatic (fibroblast) cells.[95] The screening directly generated a neuronal reprogramming heatmap that led to the discovery of a novel hierarchical structure with 500 nm-sized nanolines vertically carved on 5 μm-sized microline arrays. This serves as one of the first systematic screening of highly complex micro/nanostructures for guiding neuronal reprogramming. Preliminary mechanistic studies revealed that changes in epigenetic (H3K4Me3) landscape induced by the synergized force generation from the micro and nanoline features could be responsible for the rapid reprogramming of fibroblasts into mature neurons. In general, the CBC array-based platform provides an example on how advanced fabrication could facilitate novel biomaterial multiomics in varying biological applications.

Despite the aforementioned progress made in developing high-throughput assays and materiomics approaches, significant barriers remain in systematically understanding and optimizing the regulation of cell fate in the context of detailed biological applications. For instance, it is crucial yet challenging to develop omic technologies and analytical approaches to develop 3D materiomic technologies for high throughput screens of diverse ECM biomaterials in 3D cell culture systems. Using cutting-edge 3D printing and other microfabrication technologies is promising, yet how to make injectable dynamic micro/nanostructure niches is crucial for their translation into clinical applications. Also, to deal with the data explosion associated with materiomic studies, developing accurate and smart data analysis would be essential, and machine learning would be the future for synergizing with materiomic to elucidate mechanotransduction mechanisms and mechanotherapies.

9 | CONCLUSIONS

Biomaterials, cells, and soluble factors are the three essential components of tissue engineering. With the increasing need for precision therapy for human health, the past 2 decades have witnessed the rapid growth of interest in smart biomaterials that self-adapt to tissue microenvironmental factors such as pH, enzymes, ions, or external signals such as light, electricity, or magnetic field. The complexity of smart biomaterials can be advantageous for realizing precise control over the disease microenvironment but becomes a challenge when translation into in vivo or clinical applications where predictable, accurate, and reproducible treatment is essential. Additionally, the continuous evolution of smart biomaterials necessitates higher throughput strategies to design biomaterials in silico, screen and analyze biomaterials in vitro, and synthesize biomaterials in sterile reproducible laboratories in robots.

Addressing these challenges, ML and AI have undoubtedly transformed the way of biomaterial research. We first discussed 2 ML types, including unsupervised, including dMAPs, ICA, and PCA, as well as supervised ML algorithms, such as GP, ANN, and RFs. AI has helped the design of biomaterials, both in terms of structure and composition. By simulating a large number of biomaterials and establishing structure-function or composition-function relationships based on experimental parameters, AI could guide the discovery of new biomaterial formulations tailored for specific applications. For example, the PoLyInfo, Polymer Property Predictor, CHEMnetBASE-Polymers, the Polymer Genome, and Automatic FLOW (AFLOW) HT framework represent one such HT system for the design and optimization of polymer-based smart biomaterial systems. For hydrogels, Monte Carlo algorithms for semi-empirical calculation are more popular. Among physical cues that trigger the responses in smart biomaterials, spectroscopic limited maximum efficiency, or SLME is a novel descriptor that integrates the evaluation of bandgap, absorption spectra, and non-radiative energy loss of materials for predicting their performance in responses to photonic energy inputs. Besides, AI has played a tremendous role in propelling this field forward. For example, the recent popularity of DeepMind's AlphaFold2 and ChatGPT has brought the public to a new wave of interest in machine learning and AI.

Although the importance of AI in biomaterial synthesis has been increasingly recognized in recent years, there are a few challenges and trends to watch. First, biomaterial scientists must understand that AI is not just a cool term but is intrinsically associated with the ability to generate large amounts of data. Biology is still less quantitative and more empirical than math, physics, and chemistry, which means the amount of data required to train algorithms for accurate prediction would be significantly higher. A key step to bridge this gap lies in the continuous expansion of the datasets related to smart biomaterials and bridging the current individual database of biomaterials, biology, and engineering. The continuous expansion of the complexity of a data bank would also require the simultaneous development of advanced algorithms. Additionally, the descriptors in designing smart biomaterials can be even more complex, given the dynamic features of smart biomaterials. Unifying descriptors and definitions in the field of biomaterial and tissue engineering research is an important step but would require significant efforts from leadership in different academic associations. Also, most of the training datasets on smart biomaterials are still from in vitro assays. However, the properties of biomaterials can vary significantly in vivo and in humans. Integrating organ-on-chip systems and improving data curation and collection from in vivo systems would be essential to bridge this gap. Furthermore, when biomaterial complexity is integrated with transcriptomics, genomics, proteomics, and metabolomics commonly seen in biology studies, data analysis becomes a major challenge that must be addressed by collaboration with data scientists. Moreover, new directions, such as self-driven labs, robot-chemists-assisted fabrication of biomaterials, and 4D printing are expected to fly, but how biomaterial scientists can take advantage of these state-of-the-art technologies remains vague. However, the continuous development of AI, robotics, biotechnologies, and their synergy with smart biomaterials is set to address challenges in disease treatment by offering personalized, accurate, and safe tissue engineering with higher efficacy.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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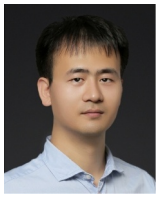

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