

Review

Smart materials: rational design in biosystems via artificial intelligence

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Industry 4.0 encompasses a new industrial revolution in which advanced manufacturing systems are interconnected with information technologies. These sophisticated data-gathering technologies have led to a shift toward smarter manufacturing processes involving the use of smart materials (SMs). The properties of SMs make them highly attractive for numerous biomedical applications. The integration of artificial intelligence (AI) enables them to be effectively used in the design of novel biomedical platforms to overcome shortcomings in the current biotechnology industry. This review summarizes recent advances in AI-assisted SMs for different healthcare products. The current challenges and future perspectives of AI-supported smart biosystems are also discussed, particularly with the regard to their applications in drug design, biosensors, theranostics, and electronic skins.

The pathway to material intelligence

Humankind has sought advances in materials science and engineering for centuries, and the discovery of new materials has sustained civilization and shaped the future. The world has now begun to evolve from traditional materials to the era of smart materials (SMs) with the advent of the Fourth Industrial Revolution (4IR or Industry 4.0). Emerging technological platforms require more sophisticated solutions that involve the use of multifunctional, controllable, sustainable, and reliable substances and material intelligence [1]. To fulfill this demand, SMs have emerged as innovative and self-healing products that promote changes in their physical properties by altering the environmental conditions in which they usually operate [2,3]. Commercialization of these products has been surging, but existing SMs are still far from fulfilling the widespread requirements for compatibility, reversibility, and responsiveness to stimuli. To thoroughly exploit the potential of SMs, a transition from traditional techniques to powerful virtual testing tools is required. State-of-the-art tools such as AI and machine learning (ML) algorithm-driven technologies are playing an increasingly pivotal role in the design and fabrication of more advanced and energy-efficient smart technologies. AI was first devised as a means to design intelligent computer programs and machines as a world-class engineering and science tool [4]. The intriguing aspects of the human mind and function can be embedded in the networks and intelligently simulated via the **Internet of Things (IoT)**, (see [Glossary](#)) to generate an **artificial neural network (ANN)** – a type of AI that can simulate a human brain [5]. Depending on the amount and type of data, massive training of ANNs can be achieved through 'supervised', 'semi-supervised', or the less widely used 'unsupervised' methods [6]. With stepwise algorithms and training data, ML can determine a model by making predictions. The form of input data is also essential for learning because it may be more functional in one format than in others; hence a converting operation – a featurization algorithm – is necessary for standardization.

SMs are key components of manufacturing, healthcare products, transportation units, logistics, robotics, and global economies [7]. Industry needs practical ways to improve their production

Highlights

Smart materials (SMs) can respond to stress, temperature, pressure, light, magnetic or electric stimuli, and their responsive properties make them excellent candidates for use in a myriad of applications.

The scientific and technical evolution of biotechnology will involve increasing use of SMs.

Novel smart biomaterials for use in diagnostic devices, bone regeneration, wound healing, and drug delivery are rapidly advancing.

Artificial intelligence (AI) and machine-learning algorithm-driven technologies play a vital role in the design and fabrication of SM-integrated technologies connected to the Internet of Things.

AI-assisted systems are mainstays in enabling rapid, simple, and autonomous production because of their ability to learn from training datasets without being specifically programmed.

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efficiency; hence, ideal manufacturing methods must be intelligently optimized to predict the desired features of materials. In particular, adopting new strategies, enhancing data collection, designing and studying predictive models, and connecting control processes and factories will be necessary, and policies in terms of smart manufacturing need to be managed strategically [8]. Now that AI 2.0 [9] has emerged, new phases of technologies such as cyberspace, universal sensors, and intensive deep-learning systems have become possible [7]. The creation of new forms, methods, models, and materials can contribute to a more sustainable, autonomous, intelligent, and robotic ecosystem. ANNs have played a vital role in the modeling, manufacturing, and characterization of countless materials since the end of the 20th century [10]. In particular, emerging biophysical and chemical sciences are mainly fed by improvements in mathematical modeling, fabrication technologies, and SMs [11]. The non-linear behaviors of SMs can be exploited to produce robust robotic structures [12]. In particular, revolutionary 4D printing technologies have outstanding potential for the generation of a wide range of dynamic intelligent structures [13]. Biomimicry of living creatures, energy efficiency, viscoelasticity, and low cost are remarkable assets of advanced materials that can be used in biosystem technologies including sensing devices, health monitoring tools, wound dressing, drug design, and pharmacology. Besides biotechnology, the energy-generation, automotive, computer, avionics, and entertainment industries, in addition to military applications, agriculture, and architecture, have exploited the advantages of SMs in the design of more advanced systems [14]. In this context we highlight not only the basics of SMs but also their characteristics and types for robust and well-organized designs that will shape the biotechnology of the future.

SMs are rapidly evolving to achieve superior properties

SMs, also defined as intelligent or advanced materials, can respond to stress, temperature, light, pressure, magnetic or electric stimuli. They are capable of passively or actively altering their self-organization in response to specific stimuli under specialized conditions. Passive SMs only sense the external stimulus and do not have the inherent capability to transduce the received signal. They are therefore usually used as sensors, and not as transducers or actuators [15]. To give an example, fiber optic materials can transfer electromagnetic waves without any alterations in their structure [16].

By contrast, active SMs can alter their properties in response to applied stimuli. These are mainly divided into two subtypes. The first can alter only a limited number of properties; for example, photochromic glasses can only change their color when exposed to sunlight [17]. The latter subtype of active SMs can convert one type of energy into another, as observed in piezoelectric crystals that generate a current when exposed to stress or change their shape when subjected to a potential difference [16,18,19]. Moreover, classifying SMs depends on the types of response to different stimuli, including magnetic fields (magnetostrictive materials and magneto-rheological fluids), electric fields (electrostrictive and electro-rheological fluids), pressure and electricity (piezoelectric), stress or thermal effect (shape-memory alloys), pH or humidity (pH-responsive or moisture-sensitive materials), and lastly strain and light (optical fibers and materials) [16,20–22]. Most commonly, the properties of SMs rely on their method of synthesis, which is usually through conventional processes. Despite a huge demand for advanced technology to meet the needs of affordable, easy-to-produce, controllable, and consistent manufacturing, there are significant obstacles that must be faced when translating smart products from the laboratory bench to industry [23,24]. To overcome these challenges, an AI-assisted perspective has many advantages because SMs have diverse applications across different disciplines. For example, AI has been used in the production of piezoelectric materials, carbon fiber-based materials, and shape-memory polymers/alloys that are also used as the basis of aerospace hardware [25]. In another example, the near-IR and visible spectrum of sunlight suits the powerful spectral response of crystalline silicon or GaAs-based solar cells; however the solar cells employed as outdoor

Glossary

Artificial neural network (ANN): a computing system that mimics animal brains by using a set of artificial neurons. The neuronal system detects a signal, then processes it, and the final output is computed by a myriad of nonlinear functions.

Biovitals™ analytics engine: an engine that computes a time series of the Biovital™ Index, alerting providers to changes in the vital signs of a patient such that the clinician can take the necessary steps to change the trajectory of a disease.

Convolutional neural network (CNN): a type of ANN that contains convolutional filters and kernels to analyze and process images, videos, and recommender systems.

Cyber-physical system: a computer system in which a system is monitored or controlled by a set of algorithms operating at different temporal and spatial scales.

Deep neural network (DNN): an ANN that contains multiple layers between the input and output layers. It represents the type of machine learning (ML) in which the system utilizes several layers of nodes to derive high-level functions using input information.

Density functional theory (DFT): a computational system for quantum mechanical modeling of electronic structures by utilizing functionals that are dependent on electron density.

Ensemble of regression trees: an ensemble method that combines several regression trees one by one and sums the individual trees sequentially.

Fuzzy inference system (FIS): a method of mapping inputs to output space by using fuzzy set theory.

Information and communication technologies (ICTs): the convergence of unified communications and telephone networks with computer networks through a single link or cabling system.

Internet of things (IoT): physical objects that are embedded with software, processing ability, sensors, and other technologies in a network that connects and exchanges data with other systems.

Least-squares support vector machine (LS-SVM): a group of associated supervised learning systems that analyze data and identify patterns by

technologies become insufficient between 400 and 650 nm spectral region. In this manner, ML models can be the key to hurdle this limitation [130]. Moreover, AI-based techniques have been initiated to utilize SMs in healthcare applications [26]; for instance, AI-assisted systems are the key to combating the COVID-19 pandemic [27]. AI-assisted next-generation trends in standardization, design, and fabrication are summarized in Box 1.

AI is a powerful tool for the rational design of SMs to revolutionize future biotechnology

Industry 4.0 has garnered significant attention for manufacturing SMs because conventional methods are challenging as a result of limitations in construction platform dimensions, inaccurate manufacturing methods, lack of adaptation to different industrial fields, limited reproducibility, restricted production scale, limited interlayer communication, inconvenience, poor data management, and non-sustainability.

Box 1. The path towards smart design and material fabrication

The first step in the creation of SMs is the selection of material type and its composition, which can be an organic/inorganic, biological, and composite [127], and the identification of a suitable fabrication method such as microfabricating and nanofabricating (e.g., laser cutting, chemical etching, and photolithography) to obtain different structures, geometries, and shapes. The final pathway is to functionalize the material with physical and chemical modifications that affect the properties of stimulus-sensitive SMs (Figure 1). Both the degree of 'smartness' and the 'adaptivity' of the material make the SM distinguishable from other materials in terms of transiency (responsiveness to different stimuli), immediacy (instantaneous response to stimuli), self-actuation (the ability to alter shape), selectivity, and directness of action/reaction [128]. Smart design comprises five key components: (1) (tactile sensing) data acquisition – the collection of raw input data; (2) (sensory nerve) data transmission – the transport of the raw data; (3) (brain) command and control unit – controlling, analyzing, and managing the data to achieve an output; (4) (motor nerve) data instruction – transmitting the output decision; and (5) (muscle) action devices: taking action by activating a control unit [129].

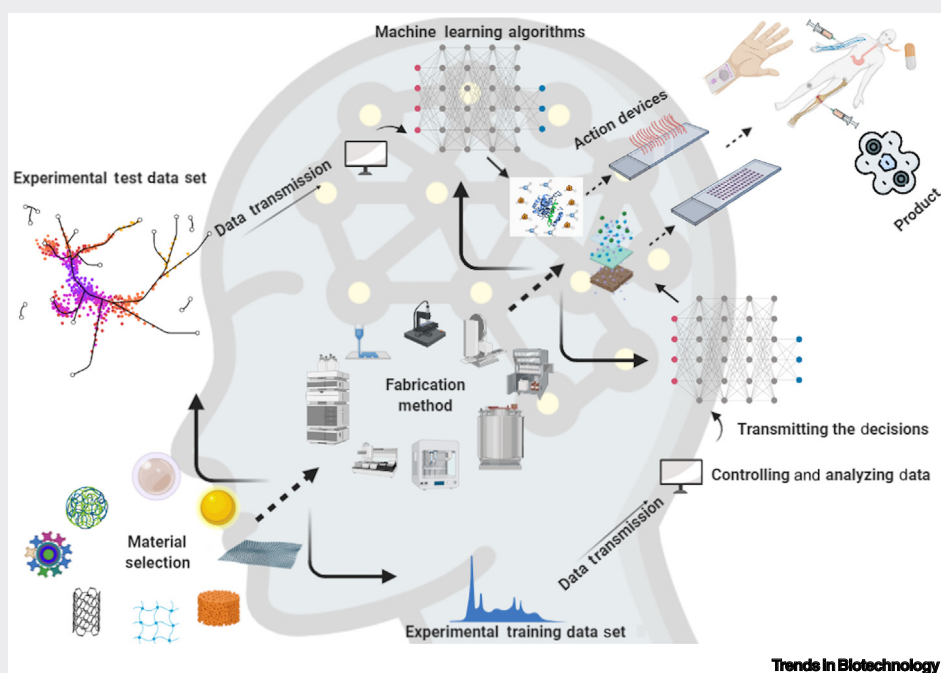


Figure 1. The overall process of SM fabrication integrated with AI and machine learning. Figure constructed with BioRender.com.

solving linear equations for classification and regression investigation.

Levenberg–Marquardt algorithm

(LM): a technique which is used to solve non-linear least-squares problems.

Multilayer feed-forward neural network (MLFFNN):

a type of ANN containing multiple layer interconnections between the nodes.

Poly(*N*-isopropylacrylamide) [poly (NIPAAm)]:

a thermosensitive polymer that is insoluble at body temperature but the phase changes reversibly at room temperature.

Radiomic analysis: a technique to extract a large number of features from a medical image using data-characterization algorithms.

Regression tree: a type of decision tree containing one or multiple input variables and a single output variable to design approximate real-value functions instead of classification methods.

Response surface methodology

(RSM): an analytical methodology that investigates the relationships between one or more response variables and several explanatory variables.

Support vector regression (SVR):

ML models that examine data for classification and regression analysis.

ing hydrogels, nanomaterials, nanofibers, bioconjugates, and shape-memory materials can be used in AI-based beacon technology, basic sciences, **cyber-physical systems**, big-data-driven frameworks, blockchains, and additive manufacturing that include – but are not limited to – cloud, digital twin, robot-assisted, improved reality, and IoT visualization systems. They are mainstays in enabling rapid, simple, and autonomous production before prototyping, tooling, and printing smart devices [28]. For instance, smart pillbox, temperature-responsive wearable devices, eyeglasses, biodegradable drug-delivery agents, and light-sensitive smart gels can be fabricated via IoT-assisted 4D printers [29,30], incorporating additive manufacturing for building time-varying systems. In particular, hydrogels – polymeric 3D materials – are strong candidates as printable biomaterials because they are biocompatible, adhesive, and viscoelastic polymers {e.g., **poly(*N*-isopropylacrylamide)**, **[poly(NIPAAm)]** [31]} that can interface with organs and soft tissues in bioelectronics and tissue-engineering applications [32–34]. Moreover, soluble smart biopolymers can be conjugated with proteins, cells, peptides, carbohydrates, lipids, RNA or DNA to adjust their self-assembly behavior, bioactivity profile, and stability for bioseparations, drug delivery, microneedles, and molecular-switching technologies [35–37]. Nevertheless, the synthesis of well-defined bioconjugates remains challenging owing to the complexity of their functional group interactions and molecular constituents [38].

SMs are at the forefront of novel biomedical applications. For example, wearable devices for health monitoring can directly detect analytes and trigger a response to inform users. These can be designed in different forms such as watches, wristbands, shirts, headbands, shoes, necklaces, and eyeglasses [39]. The sensing devices generally contain a combination of SMs that interact with analytes, and the sensing materials are mainly classified as electric, capacitive or resistive. For instance, a touchpad was demonstrated as a calculator on a thin polyethylene terephthalate (PET) substrate containing a triboelectricity-based self-powered nanogenerator array through pretraining using a **convolutional neural network (CNN)** [40]. Furthermore, smart nanofibers can be used to reproduce tissue architecture owing to their high adhesivity, high porosity, 1D morphology, high contact surface area, surface charge density, and high surface-to-volume ratio. They can be integrated with piezoelectric materials to enhance nanogenerator power generation at human–machine interfaces (Figure 1) [41]. However, advanced interfaces are hampered by structural complexity and the requirement for a convenient power source; these systems therefore need to be modulated in a programmable manner with non-linear neural interfaces [42]. For example, neural activities can be collected via thermal, electrical, optical, and pharmacological methods, and the dynamic responses of the body can be tracked by multimodal flexible sensing using implantable devices for health monitoring [43]. Thanks to its ability to store energy and its mechanical strength, one of the most used components in the flexible system is graphene – an excitable 2D shape-memory biomaterial with a very long periodic carbon honeycomb chain in the horizontal plane, but 1–3 atoms in the vertical plane [44–46]. Moreover, graphene has a high Young's modulus and improved dielectric characteristics, yet does not have a band-gap. Graphene quantum dots (GQDs) are, on the other hand, quantum-confined materials and contain a band-gap owing to their size and edge effects. Conventional quantum dots (QDs) are potential SMs that could provide precise responses to stimuli such as pH, light, temperature, and pressure [47]. Their fabrication is mainly classified into top-down and bottom-up models, and the production and characterization of QDs can be managed by either ANN- or ML-derived algorithms (Table 1) [48].

In addition to graphene, SMs include shape-memory alloys, composites, ceramics, and polymers that show unique characteristics including pseudo-elasticity (PE) and shape-memory effects in response to external stimuli [49,50]. To exemplify, polyurethane (PU) with a polycaprolactone (PCL) switching segment, poly[ethylene-co-(vinyl acetate)], poly(NIPAAm), poly(propylene

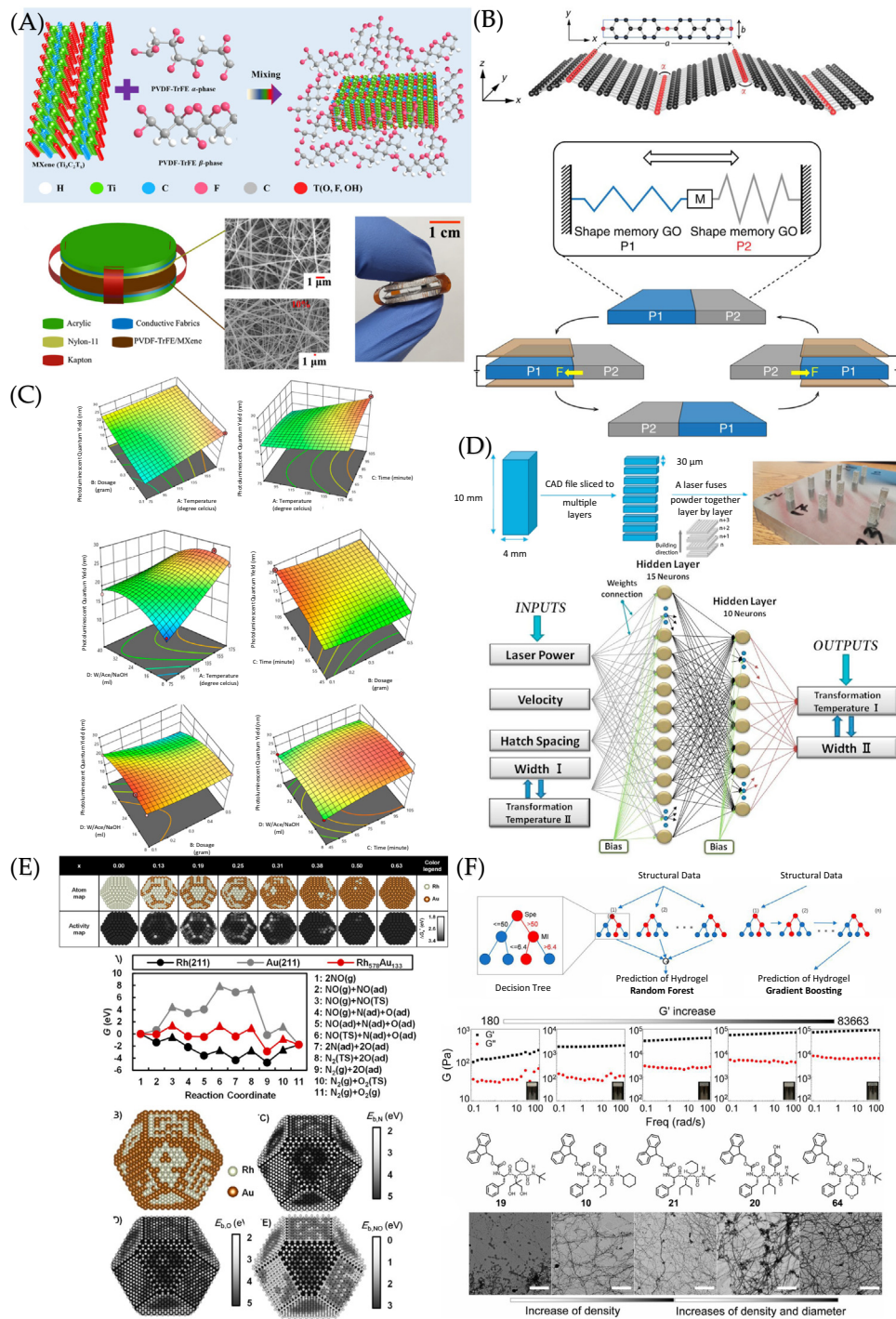


Figure 1. Diverse biomaterials have been synthesized and characterized via artificial intelligence (AI) and machine learning (ML) methods for use in the field of biotechnology. (A) A composite electrospun fiber-based nanosheet consisting of MXene (2D inorganic compound), polyvinylidene fluoride (PVDF), and trifluoroethylene (TrFE) for use as a triboelectric nanogenerator. Reproduced, with permission, from [111]. (B) Lattice constant and crystal structure

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fumarate), poly[ethyleneterephthalate-co-(ethylene oxide)] and their combinations are examples of shape-memory polymers [51].

Nickel–titanium (NiTi) alloys have been used in cardiovascular surgery, orthodontics, and orthopedics owing to their biocompatibility and superelasticity enabled by austenite-to-martensite phase transformation. On the other hand, NiTi is vulnerable to corrosion, and it can extensively release Ni ions into the bloodstream, possibly inducing toxicity [52]. To overcome this drawback, the optimum chemical structure, manufacturing method, and physical properties of NiTi were investigated with a myriad of AI-assisted models, such as **multilayer feed-forward neural network (MLFFNN)**, **fuzzy inference system (FIS)**, and ANNs [53–56].

In terms of biochemistry, quantum mechanics has enabled models based on fundamental physics that can predict the behavior of molecules [57], and simulations allow the properties of a chemical compound to be predicted with high accuracy. Designing a workflow via computational chemistry requires extensive data collection, representation, assisted learning, and model selection [6]. In particular, data collections may require smoothing because of error propagation, and cheminformatics-based applications compare molecular similarities and fingerprints via data fusion to improve the accuracy of data collection [58]. For instance, by means of SMs, nanoparticles (NPs) and their assemblies can be used in dozens of areas such as chemical and bioanalyte sensing, diagnostics, pharmaceuticals, and catalysis [59,60]. During the synthesis of NPs, physical properties including size, shape, surface chemistry, isotropy, and polydispersity should be controlled to provide the desired features. Owing to the increasing amount of experimental data, several ML models have been deployed to build stimulus-sensitive molecules. One example is the **density functional theory (DFT)**-assisted ML algorithm for predicting the catalytic activity of rhodium/gold (RhAu) NPs through kinetic information analysis of single-crystal surfaces – the representation of a solid-state lattice via ML can theoretically be achieved in an infinite number of ways because of the fractional coordinates and translation vectors of the atoms [61].

AI-assisted materials can be embedded into a broad range of biosystems

Bioinspired polymers with stimulus-responsive properties

Stimulus-responsive materials are able to modify their chemical and physical features in response to external stimuli in adaptive, interactive, and self-regulating modes [62–65]. However, many obstacles remain in terms of scalability, reproducibility, and robustness in altering, transferring, and converting stimuli [66]. AI-inspired methods are crucial in overcoming these challenges. For instance, biomaterials such as hydrogels are widely used as contact lenses [67] and in wound dressing [68], but better understanding their swelling–deswelling behavior would be possible using AI techniques because numerous parameters must be investigated simultaneously. AI-based analysis of a combinatorial hydrogel library of thousands of diverse chemical structures can accelerate the design of new hydrogels [69]. ML systems can effectively link the molecular skeleton and the properties of stimulus-responsive materials by calculating the molecular descriptors and fingerprints of a large library of different chemical structures in conjunction with millions of parameters [70]. After resampling of these parameters, three ML algorithms (random

of shape-memory graphene oxide (C₆O) consisting of a P1 phase transition to P2 when an electric field is applied, or vice versa. Reproduced, with permission, from [45]. (C) Versatile experimental factors affecting the fluorescence of architectural neural network (ANN)-assisted carbon dots. Reproduced, with permission, from [112]. (D) Selective laser melting and ANN model for shape-memory NiTiHf alloys. Reproduced, with permission, from [55]. (E) Different local activation energy diagrams of RhAu nanoparticles (NPs) according to rhodium and gold allocations, the disintegration of NO at 500 K, and the binding energies of N, O, and NO to various atomic distributions. Reproduced, with permission, from [61]. (F) Random forest and gradient-boosting ML algorithms for the rational design of the chemical and physical structure of hydrogels according to shear rheology. Reproduced, with permission, from [70].

Table 1. Conventional and AI-assisted fabrication and characterization techniques for smart biomaterials based on statistics and mathematics

Group	Material type	Input and modified variables	Conventional	AI-assisted		Disadvantages	Refs
				Systems	Advantages		
Nanoparticles (NPs)	Graphene/carbon quantum dots	Temperature, pH, time, dosage, and solvent ratio	Top-down: acidic oxidation; electrochemical; ultrasound-based synthesis; ultraviolet (UV) or electron beam (E-beam) irradiation; chemical exfoliation Bottom-up: hydrothermal; solvothermal	ANN-based design parameters comparison: response surface methodology (RSM) for data acquisition; Levenberg-Marquardt backpropagation (LMBP) for photoluminescence (PL) characteristics	A myriad of experimental data can be rapidly analyzed to build smart materials, compositions, and properties	Optimization of the input variables and reaction conditions is challenging because there are many input variables	[48,112,113]
				ML-based PL analysis: k-means; partial least-squares analysis (PLS); principal component analysis (PCA); hierarchical cluster analysis (HCA); multivariate curve resolution (MCR-ALS); non-negative matrix factorization (NMF)	Designing and performing more controllable experimental conditions for high rate production	The choice of an ML algorithm to optimize the experimental setup is challenging	
Hydrogels	Gold nanoparticles (AuNP-s)	pH; salt ratio; scanning velocity; intensity; reaction molecules and agents	Surfactant-mediated growth (Murphy, El-Sayed)	Prediction of localized surface plasmon resonance (LSPR) signal via matching the fabrication parameters-size of AuNPs with an ANN model	Desired properties and physical structures of AuNPs can be modeled easily	The projected experimental strategies can be demanding because of optimization challenges such as shape, physical properties, and surface plasmon signals	[114–117]
			Direct reduction of Au ions (Frens, Turkevich)	Graph convolutional neural network (GCNN) + Siamese neural networks (SNN) models for investigating the relationship between molecular properties, final monodispersity, and reaction conditions for gold nanocluster fabrication			
Hydrogels	Poly (N-isopropylacrylamide) [poly(NIPAAm)]	Temperature, pH, initiator concentrations; monomer and substrate type; quantity of hydrogen bond acceptors and donors;	Surfactant-free emulsion polymerization	A type of binary genetic algorithm (GA) method inspired by the process of natural selection for synthesizing versatile sizes of AuNPs	The AI-assisted system can be used to estimate the deswelling, mechanical strength, and	Simulation and model development are demanding because of the effects of various parameters on the	[31,32,70,118]
			Membrane emulsification	Quantitative method hydrogel structure-property			

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Table 1. (continued)

Group	Material type	Input and modified variables	Conventional	AI-assisted			Refs
				Systems	Advantages	Disadvantages	
		polymerization time	tunable/dynamic/isothermal volume-phase transition kinetics Plasma-induced pore-filling graft polymerization Atom-transfer radical polymerization (ATRP) Free-radical polymerization	investigation via a binary classification ML algorithm Least-square support vector machine (LS-SVM) and ANN method for analyzing the deswelling behavior of NIPAAm and acrylic acid (AAc) copolymer	phase transition behaviors of hydrogels	swelling/deswelling behaviors of hydrogels	
Bioconjugates	Amphiphilic polymer bioconjugates	Experimental scattering intensity profiles; dimension and shape versatility of specimen; polymer chemistry and design; wavevector function	Site-specific polymer conjugation of biomaterials Radical polymerization for polymer bioconjugation; ATRP; reversible addition-fragmentation chain transfer polymerization (RAFT) Protein cages, denatured proteins, self-assembling peptides for protein-polymer conjugate Nucleic acid-patterned and DNA-programmed synthesis of precision polymers Carbohydrate and lipid biotemplate-based polymer conjugates	ANN-based, two step (GA)-(MD) reverse engineering method for analyzing the structural properties of self-assembled polymers	The computational methods allow the identification of the most efficient model for amphiphilic polymers	The number of scatters may increase the cost of the computational process	[38,119]
Shape-memory materials	Graphene and graphene oxide	Exfoliation rate, layer number, and thickness of the sheet; oxidation rate; locations and types of different lattice defects for labeling; type of silicon (Si)	Micromechanical exfoliation of graphite Liquid-phase exfoliation of graphite	Identification of epitaxial grown and exfoliated graphene film layer via spectral clustering Defect analysis in the	Classification of different spectra can be enabled by providing advanced algorithms	Performing an exact fit with multiple components might be complex because of phonon scattering	[120–123]

		<p>dopant; rough estimation of graphene-layer twisting angle</p>	<p>Graphite oxidation Chemical vapor deposition (CVD) Electric arc Thermal decomposition of silicon carbide Epitaxial growth of graphene on a surface</p>	<p>graphene vacancies via fully convolutional networks (FCNs) Raman spectroscopy for the characterization of CVD graphene films through the k-means algorithm</p>		
<p>Nickel-titanium (NiTi)</p>	<p>Chemical structure investigation: Ni, Ti, and trace elements content ratio; surface area; pH; solution volume; immersion time Manufacturing: laser scanning speed; laser power; hatch spacing; servo voltage; pulse on/off time; wire and current speed Physical property analysis: sintering temperature and time; compaction pressure</p>	<p>Powder metallurgy, conventional method; conventional sintering; self-propagating high-temperature synthesis; hot isostatic pressing; metal injection molding; spark plasma sintering Advance manufacturing: selective laser melting; selective laser sintering; laser engineered net shaping; electron beam melting Casting: vacuum induction melting; vacuum arc remelting</p>	<p>Multilayer feed-forward neural network (MLFFNN) for optimum chemical structure analysis of NiTi alloy 3D-printed and laser manufacturing analysis of the effects of input parameters on NiTi alloy physical properties through ANN methods Effect of input parameters on the hardness and porosity of NiTi through ANFIS</p>	<p>Saturation and modifying gradient tools allows outliers to be predicted with fewer errors</p>	<p>The convergence of the AI-assisted method might not be accomplished owing to inconvenient exponential methods</p>	<p>[53–56,124,125]</p>
<p>Nanofibers</p>	<p>Polyvinylidene fluoride (PVDF)</p>	<p>Physical methods: electrospinning; physical vapor deposition; laser ablation; plasma sputtering; pulsed laser deposition; thermal evaporation Chemical methods: electrochemical deposition; chemical vapor deposition; polyol synthesis; microemulsion; phase-separation; sol-gel method; hydrothermal synthesis Biological methods</p>	<p>Long short-term memory (LSTM) algorithm for observing real-time electrical signals in response to five different gestures</p>	<p>Smooth and porous surface morphology of the nanofibers can be induced to obtain efficient electrical outputs</p>	<p>Owing to the patterned morphologies, the cost and scalability of the AI-based process may be challenging</p>	<p>[4,1,126]</p>

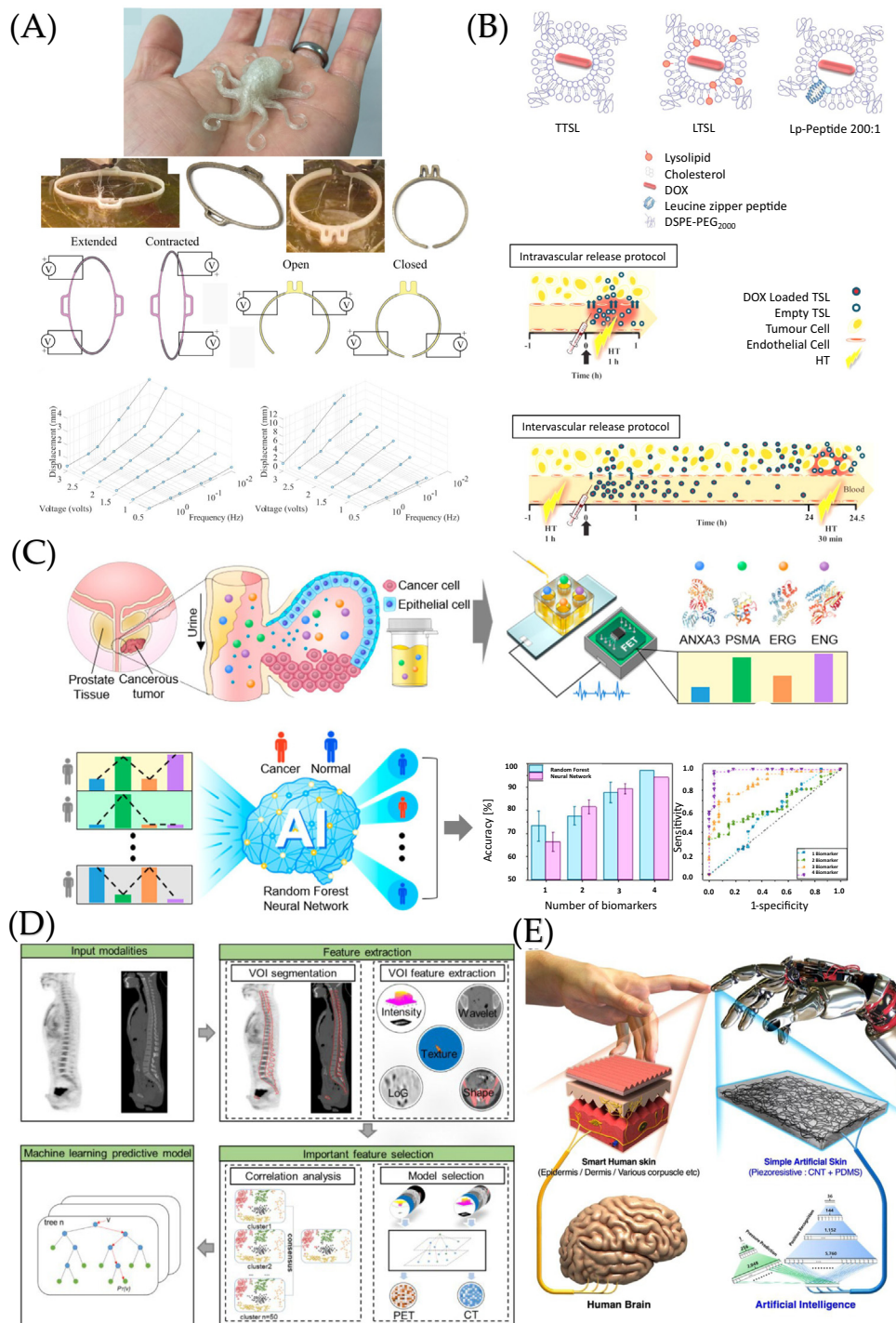
forest, gradient boosting tree, and logistic regression) were found to be highly effective. In addition, **support vector regression (SVR)** and **least-squares support vector machine (LS-SVM)**-based techniques are powerful tools to model non-linear relationships and can tackle the challenges associated with real-world applications more efficiently than ANNs [71]. Using such techniques, there was excellent consistency between the predicted and experimentally observed mechanical properties of poly(NIPAAm-co-AAc) IPN hydrogels as a function of pH, temperature, and time, thus facilitating the practical design of hydrogels for various applications [31].

AI-assisted drug design and modeling of drug release

SMs typically have complex thermomechanical and shape-memory behavior, as well as poor fatigue properties, which may affect their drug-release kinetics and compromise model predictions [67]. However, the drug-release behaviors of SMs can be accurately predicted via AI-based methods using training data based on the type, size, and structure of material and drug, material–drug interactions, the type of external stimulant, and other factors [72] (Figure 2). The input–output relationships in the experimental data can be trained in AI-based systems to predict drug-release kinetics. AI-assisted studies reliant on drug-release modeling have garnered significant attention in many fields. For example, riboflavin release from pH- and temperature-sensitive hydrogels was modeled using an ANN in conjunction with a three-layered feed-forward backpropagation network, and this predicted that increasing temperature (up to 52°C) at a more basic pH (pH 7) resulted in more drug release. The AI-based model was more accurate than the conventional **response surface methodology (RSM)** model. The same AI model developed on an ANN was also used to estimate the release of doxorubicin from hydrogels under different pH and temperature conditions [69]. After data-training with the **Levenberg–Marquardt (LM) algorithm** optimization method supported by LS-SVM and SVR, the predicted data exhibited excellent consistency with the experimental data. ML and perturbation theory have been recently combined to train a large dataset (chemical and physicochemical structures of NPs, coating agent, and drug) obtained from over 30 000 preclinical assays [73]. A final dataset of over half a million drug-delivery systems was successfully designed to predict the activity/toxicity profiles of the drugs released. A similar AI-based technique was also used to design a release system for drug–vitamin mixtures for cancer cotherapy [74]. Recently, 3D printing technology has been widely used to produce drug delivery and drug release systems [75]. Specific parameters such as shape, dimensions, weight, and layer thickness were trained in ML models. As an example, the trained data from different formulations allowed the accurate prediction of drug release times. Similarly, ANNs, SVMs, and **ensembles of regression trees** were shown to be highly effective in predicting *in vitro* dissolution profiles and drug release [76]. So far, the data acquired from thousands of studies can be effectively trained in AI systems to predict the outcome of drug design and release systems for future medical applications such as cancer therapy, immunotherapy, and bacteriophage therapy [77,78].

AI-assisted biosensors to accelerate clinical decisions

Biosensors are platforms that contain biological recognition elements to capture specific analytes [79]. Despite their widespread use in clinics, they may suffer from insufficient accuracy [80,81]. In addition, SM-integrated biosensors are highly susceptible to environmental factors, and regeneration between each measurement may be highly variable [82]. However, the accuracy and response time of electrochemical biosensors can be improved by using AI-based techniques (Table 2). Conventional methods usually involve quantitative modeling of the kinetic behavior of the biosensor. ANN and SVM techniques were recently applied to glucose oxidase biosensors to analyze overlapping signals, which is not possible using linear models [79]. Excellent consistency between the predictors and the response time of the sensor was presented in this study. Non-invasive biosensors typically facilitate signal acquisition such that health-related data can



Trends in Biotechnology

Figure 2. Artificial intelligence (AI)-assisted materials and their applications in different fields of biotechnology. (A) Design of machine learning (ML) methods to synthesize soft polymer-based robotics. Reproduced, with permission, from [64]. (B) Perturbation-theory ML data preprocessing and processing workflow for drug design and drug release kinetic analysis. Reproduced, with permission, from [72]. (C) Workflow of preprocessing classical calculation of an ML-assisted (Figure legend continued at the bottom of the next page.)

Table 2. Accuracy of AI-assisted diagnostics, therapeutics, and clinical decision techniques

AI-ML method	Mechanism	Targeted analyte and discipline	Accuracy	Refs
Artificial neural network and support vector machine	Electrochemical sensor	Glucose oxidase biosensors	95%	[79]
Biovitals™ analytics engine	Electrochemical sensor	Early detection of COVID-19	95%	[90]
Chan–Vese-based level set segmentation method	Image processing	Brain tumor detection	≥90%	[92]
Deep neural network	Image processing	Lesion detections	≥80%	[93]
Deep neural network	Image processing	Adenocarcinoma enumeration via miRNA biomarkers	95%	[95]
Artificial neural network	Surface-chemistry dependent characterization	Breast cancer diagnosis	90%	[96]
Random forest algorithm	Image processing	Bone marrow involvement in subjects with suspected relapsed acute leukemia	≥62.5%	[97]
Random forest, support vector machines, and neural network	Strain sensor	Human gait analysis	93%	[100]
Deep neural network	Optic tactile sensor	Electronic tactile sensor for	28–61%	[101]

be rapidly processed [83]. Plasmonic biosensors, for instance, measure resonance shifts caused by the excitation of surface plasmons once biomolecular interaction occurs [84,85]. Despite their label-free nature that allows real-time and continuous measurements with high sensitivity, they still face limitations such as immobilization effects, steric hindrance with binding, and mass transport limitations [86]. There have been attempts to use AI-assisted systems to overcome these challenges. A label-free meta-plasmonic biosensor was recently designed through ML-based algorithms (i.e., multilayer perceptron and autoencoder) and provided 13-fold higher detection sensitivity than the conventional system, and also resulted in fewer errors and higher accuracy than interpolation methods in predicting reflectance curves and resonance angles [87]. Moreover, in non-invasive biosensor systems, AI methods can eliminate the high rate of false-positives in prostate cancer screening [88]. In this study, using training data from 76 urine specimens, random forest and ANN algorithms screened prostate cancer patients with over 99% accuracy and minimized false-positive outcomes [88]. From a mobile health (mHealth) perspective, the precision of smartphone-assisted wearable biosensors is also improved through the use of AI strategies [89]. Recently, continuously collected data from different physiological conditions of 34 patients with COVID-19 symptoms were used to train a **Biovitals™ analytics engine** – an ML system [90] – and multivariate analysis was highly accurate in detecting COVID-19 patients. Overall, AI-enabled biosensors have significantly improved the diagnostic accuracy of patients with different conditions.

AI improves image-guided theranostic drug delivery: a combination of diagnostics and therapeutics

The concept of theranostics combines both therapeutics and diagnostics. Theranostic materials coupled with advanced imaging techniques (i.e., optical, nuclear, ultrasound, etc.) have the potential to revolutionize precision medicine [91]. However, a major drawback in the design of theranostic systems is that multiple components are required, leading to structural heterogeneity

multimarker biosensing device for prostate cancer screening using a drop of urine and its sensing performance. Reproduced, with permission, from [88]. (D) An ML-based prediction model for ¹⁸F-fluoro-deoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) radiomic analysis for identifying bone marrow involvement in patients with suspected relapsed acute leukemia. Reproduced, with permission, from [97]. (E) The basic concept of e-skin and deep neural network architecture for reliable sensing. Reproduced, with permission, from [103].

and low reproducibility. AI techniques would significantly improve treatment schedules. For instance, tumor segmentation involves the separation of the tumor from normal tissues during radiopharmaceutical therapy [92], and AI-assisted models were recently generated to automate the segmentation process and allow accurate prediction of the absorbed dose and the outcome of therapy [93]. Deep learning also has the potential to estimate tumor profiles non-invasively. An ML approach, for instance, was previously used to analyze microRNAs (miRNAs) as non-invasive biomarkers for theranostic applications in prostate cancer [94]. Another deep-learning model was used to predict tumor immune profiles using the CytAct biomarker with fluorodeoxyglucose positron emission tomography (FDG-PET) in lung adenocarcinoma [95]. The model successfully predicted CytAct, which is related to cytotoxic CD8⁺ T cell activity against the tumor, thus providing a potentially feasible theranostic method to define immunotherapy response. ML was also able to identify the presence and type of cancer using luminescent carbon NPs, and could accurately determine cancer stages [96]. Neural network interneuron connections were used to map the relationships between the input and output data, and they showed superior results compared to conventional methods. The diagnosis of ¹⁸F-FDG PET/CT-based leukemic bone marrow involvement (BMI) is a crucial issue in patients with acute leukemia. Data obtained from 41 patients were recently used to train an ML model, and **radiomic analysis** showed high precision in identifying BMI in patients [97]. Further delivery of ¹⁸F-FDG in combination with nanotherapeutics to the target site would be a promising technique as a theranostic system. Ongoing expansion of theranostic systems is expected to accelerate the transition from experimental design to clinical decision making in the near future.

Integration of ML into electronic skins (e-skins) and soft robots

e-Skins can continuously receive and process tactile signals from human skin and allow real-time health monitoring in patients with different conditions. e-Skins should possess specific properties such as minimal latency, high sensitivity, and rapid response. They are usually made of soft and conformable materials with mechanical durability [98,99]. Recent advances in materials science, data processing, and ML have led to the design of novel e-skins. As an example, ML was recently applied to diagnose human gait disorders using e-skins made of four stretchable textile-based strain sensors patched on an ankle brace [100]. Three supervised ML algorithms processed the data obtained from different human gait phases and showed >90% diagnostic accuracy. Recently, a tactile glove composed of 548 active sensors in a matrix form was manufactured [101], and convolutional neural networks were trained a large-scale dataset of tactile maps acquired from the sensor array. Artificial analogs of the natural mechanoreceptor network would be a potential tool for the future design of prosthetics. Such prosthetic design can be improved using ML algorithms. For example, AI-assisted design was used to design a graphene-based piezoresistive sensor with enhanced performance, high durability, and improved sensitivity to vibrations in epidermal signal monitoring at different arteries [102]. Similarly, a biomimetic and porous nanofiber-based sensor assisted with an ML algorithm of 'long short-term memory' successfully distinguished between different human actions and pressure stimuli [41]. The network architecture, composed of 200 hidden input layers and five output layers, exhibited well-distributed pressure-level results for designing an accurate strain sensor. Another macroscale e-skin was constructed using a single-layered piezoresistive multi-walled carbon nanotube (MWCNT)-polydimethylsiloxane (PDMS) composite film which was computed through a **deep neural network (DNN)** consisting of two channels for position and pressure recognition. This platform processed the alterations in electrical resistance induced by a mechanical stimulus [103]. Moreover, by using a set of half a million datapoints, the DNN-assisted e-skin sensor outperformed most of the previously reported sensors in terms of pressure sensitivity. Various ML algorithms were also tested to predict the deformation magnitude of soft optoelectronic sensory foams made of silicone rubber [104]. The defined model outperformed standard algorithms such as

SVM and predicted the deformation level with high accuracy. Such approaches hold great promise for the design of soft e-skins and robotics with the desired responsiveness to external stimuli, thereby enabling soft robots to intelligently interact with their surroundings. Despite the accuracy of the AI models, fault detection in e-skins remains challenging. Notably, the training data may not be entirely representative and may be noisy, and incorrect model assumptions are often encountered, leading to modeling failures. Hence, obtaining relatively low variance is crucial for the success of a model [104]. Defining which architectures are the most simple and fastest to use for data training will pave the way to the design of e-skins and soft robots that are more conscious of themselves and their environment [105].

Concluding remarks and future perspectives

Industry 4.0 is a new stage of industry in which manufacturing and **information and communication technologies (ICTs)** merge to form a cyber-physical system which is simultaneously monitored and controlled by complex computer-based algorithms in a robust manner. Such a dynamic system requires a specific group of materials to meet the growing requirements of the Information Age. SMs possess unique characteristics that are sensitive to changes in an external stimulus, and have far-reaching potential in diverse fields. Despite their immense potential, SM fabrication and integration into biosystems remain in their infancy. The worldwide biotechnology market for SMs is continuously growing. Aerogel-based [106], metal foams [107], biocomposites, and bioconjugates (i.e. artificial spider silk) [108] for diagnostic devices, bone regeneration, wound healing, and drug delivery are rapidly advancing [109]. The use of graphene, carbon nanotubes, and amorphous metals is becoming an essential part of biodesigns [110]. We foresee that meeting the requirements of SM market will only be possible with the assistance of AI. AI-based self-replicating technologies would greatly accelerate the implementation of SMs in biomedical and biorobotic platforms, particularly in the design of novel drugs (e.g., identification of new DDR1 kinase inhibitor), biosensors (e.g., contact lenses and mouth guards), theranostics (tumor monitoring), e-skins, and soft/wet/hard robotics. AI-assisted systems will be the mainstay not only of biosystem models but also for resolving administrative issues, data design and management, and the production of advanced software and hardware. Biomonitoring using AI-assisted products is set to revolutionize healthcare across human society. However, several major challenges remain to be overcome in integrating SMs into real-world applications, as well as in evaluating economic outcomes and AI ethics. Process automation combined with new insights provided by combining AI with advances in biology, engineering, mathematics, and computation offers a real prospect of surmounting these obstacles (see [Outstanding questions](#)).

Acknowledgments

F.I. gratefully acknowledges support from the Scientific and Technological Research Council of Turkey (TÜBİTAK) 2232 International Fellowship for Outstanding Researchers (Project No: 118C254) and the Turkish Academy of Sciences Outstanding Young Scientists Award Program (TÜBA-GEBİP). I.E. also thanks the support from TÜBİTAK 2232 Project (Project No: 118C254). However, the entire responsibility of the publication/article belongs to the owner of the publication/article. The financial support received from TÜBİTAK does not mean that the content of the publication is approved in a scientific sense by TÜBİTAK. K.S. and F.I. also thank the TÜBİTAK 1001 Scientific and Technological Research Projects Funding Program (Project No: 120Z445) for support. This work was also supported by the Young Scientist Awards Program (BAGEP) award from the Science Academy.

Declaration of interests

The authors declare no conflicts of interest.

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Outstanding questions

Can we predict how novel SMs will respond to external stimuli?

Can SMs be organized and designed for specific goals in biosystems?

What are the most promising AI tools for the production, characterization, and benchmarking of SMs?

What are the main contributions of AI methods and/or ML-based algorithms to recent innovations in advanced materials used in biotechnology?

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