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REVIEW

# Machine learning approaches for biomechanical and bioelectrical regulation in developmental tissue engineering

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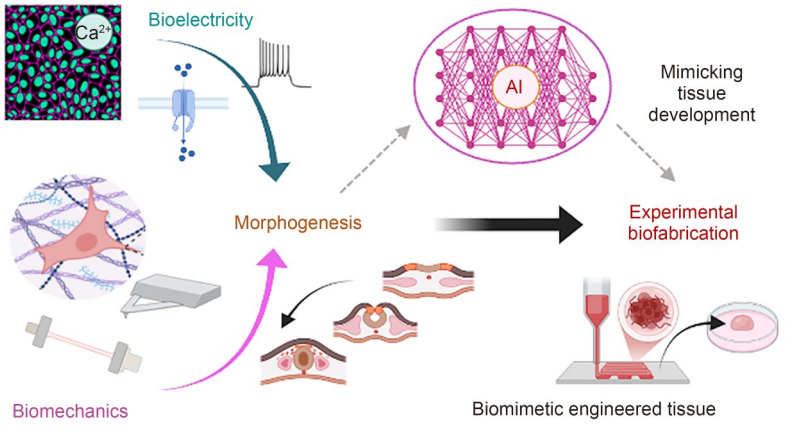
## Abstract

Developmental tissue engineering is increasingly guided by the principles of morphogenesis, cellular self-organization, and dynamic microenvironmental regulation, moving beyond static scaffold design and towards adaptive, development-inspired strategies. Integrating insights from developmental biology has revealed new structural–functional relationships and more robust tissue maturation pathways, thereby unlocking biofabrication strategies that harness intrinsic biological regulatory mechanisms rather than imposing static architectures on engineered tissue. This review examines machine learning (ML) applications to tissue engineering within a developmental context, emphasizing how bioelectric, biomechanical, and morphogenic cues influence cell fate, tissue organization, and adaptive growth. We highlight how data-driven and physics-based models, surrogate modeling, and generative design can integrate complex biological data, simulate evolving microenvironments, and guide experimental biofabrication. Despite these advances, significant challenges remain, such as the integration of heterogeneous and multiscale biological data, limitations in model interpretability and generalizability, and ethical and regulatory considerations regarding data use and artificial intelligence (AI)-guided decision-making in biofabrication applications. Through the coupling of developmental principles with computational tools, ML-driven tissue engineering is nevertheless well positioned to enable more predictive, adaptive, and reproducible paradigms for creating functional living systems.

## Graphical abstract




**Keywords** Machine learning · Tissue engineering · Artificial intelligence · Biomechanics · Bioelectronics · Morphomechanics · Closed-loop control

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## 1 Introduction

The integration of artificial intelligence (AI) techniques into biofabrication is rapidly transforming how engineered tissues, scaffolds, and living systems are conceptualized and realized [1, 2]. Traditional approaches to biofabrication (for printing scaffolds, seeding cells, guiding tissue maturation, etc.) largely rely on trial-and-error, heuristic decisions, and iterative experimental feedback; these efforts can be time-consuming and limited in scope. Machine learning (ML) provides a complementary toolkit capable of navigating vast design spaces, integrating complex multidimensional data, and accelerating predictive modeling, thereby enabling biofabrication at a scale and precision previously unattainable [2]. Such advances have already led to applications such as organoids for drug testing, personalized tissue models, and predictive platforms for regenerative medicine, demonstrating the potential of ML-driven biofabrication methods for improving health [3].

Some emerging areas that leverage ML for transformative impact in biofabrication include biomaterials for tissue engineering (TE), bioelectric cell–cell communication, and developmental TE processes. For example, scaffold geometry, porosity, material composition, and mechanical properties are central for directing cell growth, signaling, and tissue function [4–8]. Generative AI approaches enable rapid exploration of scaffold designs that optimize multiple criteria simultaneously, such as mechanical integrity, nutrient transport, biocompatibility, and manufacturability [9–11]. This may lead to accelerated design cycles, more personalized scaffolds, and higher functional fidelity.

Similarly, bioelectric phenomena (such as ionic currents, membrane potentials, and endogenous electric fields) play critical roles in tissue development, regeneration, and functional behavior [12–14]. Traditional computational models—while powerful—can be computationally intensive and face limitations at scale [15, 16]. ML methods, like surrogate models and physics-informed neural networks, can approximate and accelerate these simulations, allowing prediction and control of electrical signaling in tissues such as cardiac and neural constructs [15, 17–19]. In the future, ML may facilitate the understanding and harnessing of developmental bioelectricity, become essential for replicating developmental tissue formation processes, and achieve greater structural accuracy and functional competence in engineered tissue constructs.

By shaping the physical environment, modeling signaling dynamics, and guiding tissue maturation, generative scaffold design, cell communication modeling, and ML for developmental TE can address complementary aspects of biofabrication; this may become increasingly relevant as biofabrication grows in spatial scale and functional complexity [20]. In fact, engineered tissues are becoming larger, more structurally heterogeneous, and functionally multifaceted, thus demanding computational frameworks capable of capturing multiscale interactions across cellular, tissue, and construct levels [1]. Meanwhile, the availability of high-dimensional, multimodal datasets (including mechanical, electrophysiological, molecular, and imaging data) offers rich input spaces that can be integrated and interpreted more effectively by ML than by conventional models. In addition, research in TE is generally shifting from structural replication to functional fidelity, thereby requiring engineered constructs to reproduce native physiological behaviors and spatiotemporal developmental patterns [21–26].

Within this context, ML provides powerful frameworks for developmental TE; such approaches in a way emulate natural morphogenesis by orchestrating cell differentiation, organization, and matrix remodeling [2, 21, 27]. By analyzing diverse datasets, ML can uncover latent developmental patterns, optimize culture conditions, and predict tissue trajectories, thus bridging the gap between in vitro constructs and their in vivo counterparts. In this manner, biofabrication techniques can be advanced towards more predictive, adaptive, and functionally competent tissue systems [1, 28]. In addition, ML applications can extend beyond merely optimizing initial biofabrication conditions and also control tissue dynamics: understanding how cells and biomaterials evolve into functional tissue over time will require ML for the investigation of other influential factors, such as cell–cell communication and biomechanics.

As shown in Fig. 1, different classes of ML algorithms can cover specific tasks, for example, predicting scaffold properties and cell fate (supervised learning), identifying cell states (unsupervised learning), designing scaffolds (generative models), and controlling biomanufacturing equipment like bioprinters or bioreactors (reinforcement learning). Whereas most reviews considering ML applied to TE have focused on the selection and variation of primary biofabrication components (e.g., scaffolds, cells, and biofactors) [2, 29], here we emphasize the relevance of ML for addressing the temporal and dynamic aspects of tissue development. Highlighting algorithm–task mapping and the transition from static design to dynamic closed-loop TE, Fig. 1 illustrates how ML could support TE applications from initial biofabrication inputs to modeling and steering of tissue evolution. To frame ML applications through the lens of developmental TE, we focus on how computational tools can integrate and predict bioelectric, biochemical, and biomechanical cues that drive morphogenesis, cellular self-organization, and emergent tissue functionality.

Therefore, we discuss how ML can integrate multiple dimensions of tissue formation, including mechanical coordination in emergent tissue architectures, cell–cell communication via bioelectric networks, and cell fate specification processes (such as stem cell differentiation). Beyond simply

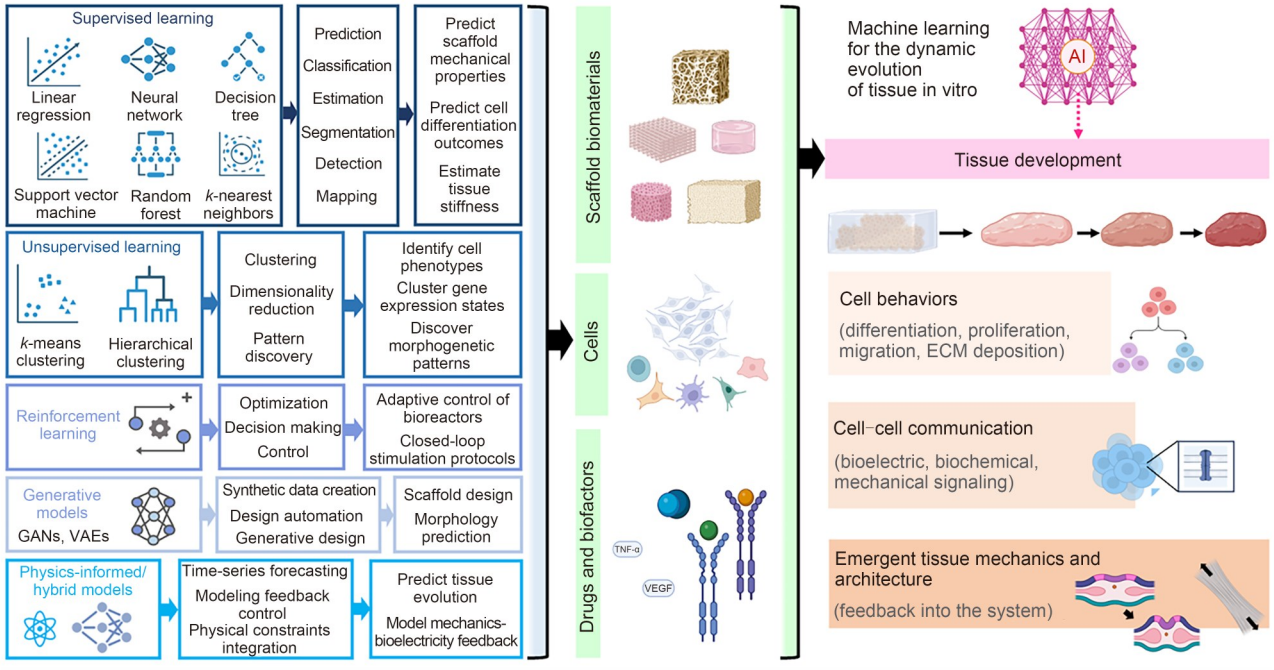


**Fig. 1** Machine learning (ML) in tissue engineering (TE): from static design to dynamic tissue evolution. Different classes of ML algorithms support distinct tasks in TE: supervised learning methods enable the prediction of scaffold properties, cell fate, and tissue mechanics from experimental data; unsupervised learning approaches can identify cell states and spatial organization patterns, while generative models might assist in designing scaffolds and microenvironments; reinforcement learning and control-oriented ML enable adaptive regulation of bioreactors and stimulation protocols. These algorithmic tools can be applied to optimize initial biofabrication inputs (scaffolds, cells, and biofactors) and, critically, to model and steer tissue dynamics over time. Tissue development depends on cell–cell communication and biomechanical feedback, and thereby integrates various biochemical, bioelectrical, and mechanical cues. The pictured framework highlights how specific ML strategies map to different stages and challenges of tissue evolution, emphasizing the transition from static design to future ML-TE approaches that unlock predictive, closed-loop developmental biofabrication. GANs: generative adversarial networks; VAEs: variational autoencoders; TNF-α: tumor necrosis factor-α; VEGF: vascular endothelial growth factor; AI: artificial intelligence; ECM: extracellular matrix

cataloging existing methods, we present a mechanistic, multiscale framework that links general ML strategies to developmental processes, highlight adaptive feedback approaches for guiding tissue maturation, and discuss challenges in data integration, interpretability, and ethical implementation.

After reviewing the main methods for simulating tissue formation, we further examine ML-driven scaffold generation, biofabrication feedback control, and bioelectronic regulation as pathways toward intelligent, adaptive, and reproducible TE. Together, these perspectives identify ML not just as a predictive tool, but as an active driver of developmental and biofabrication processes.

## 2 Simulating morphogenesis, mechanobiology, and stem cell fate

Morphogenesis is the biological process through which cells, tissues, and organs achieve their target shape, structure, and functional organization during development [30]. This process is driven by coordinated cellular behaviors such as proliferation, differentiation, migration, apoptosis, and extracellular matrix (ECM) remodeling; these are all tightly regulated by genetic, biochemical, and mechanical cues. Cellular-level determinants include intracellular signaling pathways, cytoskeletal dynamics, cell polarity, cell–cell and cell–matrix adhesion, and mechanotransduction [31]. Positional information is often delivered through biochemical gradients of morphogens and signaling molecules, ultimately guiding the spatial organization of differentiation, growth–resorption balance, and tissue patterning [32]. Notably, mechanical inputs such as actomyosin contractility, ECM stiffness, intercellular tension, and fluid shear further shape collective cell behaviors [18, 33].

Predicting morphogenesis is challenging due to its multiscale and nonlinear nature, which encompasses molecular networks within cells, tissue-scale dynamics, organ-level biomechanics, and interactions across multiple organs. Sophisticated computational frameworks are therefore necessary to integrate heterogeneous datasets and model the spatiotemporal evolution of these multiscale structures [34]. Specifically, this requires numerically-stable, computationally-efficient algorithms capable of real-time analysis of high-dimensional experimental or simulated data, so as to achieve predictive fidelity. While ML excels at capturing complex tissue dynamics and discovering hidden patterns in data,

and is thus an excellent choice for this task, traditional approaches also exist. Thus, we first review the key computational models that have historically guided morphogenesis simulations before turning to ML applications.

From the perspective of soft matter mechanics, tissue morphogenesis is often modeled through governing equations that couple growth, remodeling, and mechanical deformation via constitutive laws describing nonlinear material responses [34]. Following discretization, these equations are solved using numerical methods such as finite element or phase-field approaches to capture large deformations, active stresses, and evolving morphologies. This computational morphogenic framework—enriched by advances in high-performance computing—has provided insights into how complex tissue architectures emerge from coupled biochemical and mechanical processes. For instance, asymptotic numerical methods and risk-based path-following techniques allow for nonlinear processing of interactions, curvatures, and boundary conditions, enabling the exploration of multiple bifurcations while minimizing perturbations caused by material heterogeneity [35].

Beyond the pure mechanics of soft matter, several theoretical and computational models have attempted to replicate the physical mechanisms of morphogenesis. For instance, mean-field approaches capture population-averaged behaviors, while discrete, agent-based, or cellular automata models treat individual cells as agents with defined behaviors [36–38]. These frameworks have been used to simulate cell–cell interactions, tissue organization, and morphogenesis, highlighting the importance of properties like adhesion, motility, and proliferation. For example, in aiming to generate a broadly applicable framework that describes both in vitro and in vivo cell motion, Szabó et al. [39] expanded the cellular Potts model to include active cell motility with polarity feedback; they were then able to reproduce experimentally observed collective behaviors in endothelial monolayers. Moreover, by combining experimental and in silico analyses of glioblastoma multiforme cultures, Melo et al. [40] applied a simple particle-based model to infer the rates of key cellular mechanisms, and demonstrated that reproducing the observed spatial correlations requires a density-dependent decrease in cell−cell adhesion; this is consistent with experimental observations of epithelial-to-mesenchymal transitions.

While discrete models capture individual cell behaviors, continuum models based on biophysical principles can simulate the mechanics of tissue growth and deformation, typically considering factors such as stress, deformation, and growth over time. For example, they have been applied to simulate bile duct formation, where mechanical forces drive the organization of cellular assemblies [41, 42]. Operating at similar scales, reaction-diffusion frameworks such as the Fisher–Kolmogorov equation have been applied to model cell motility and proliferation, predicting traveling-wave invasion in a manner consistent with experimental observations, and estimating diffusion coefficients under varying conditions [43]. In particular, this study provided a framework for analyzing cancer cell invasiveness and optimizing TE applications such as skin and corneal repair.

To capture both single-cell behavior and tissue-level mechanics, hybrid approaches integrating agent-based modeling with continuum mechanics have been developed and used, for example, in cancer tissue growth modeling [44]. Hybrid approaches often form the core of multiscale coarse-grained frameworks, bridging single-cell dynamics and tissue-level phenomena. This is important since extending data and principles across multiple biological scales is key for comprehensive simulations of developmental processes [45].

Finite element models (FEMs) are widely used to optimize the mechanical properties and designs of TE scaffolds [46, 47]. However, when simulating multiscale biological systems with complex tissue structures, FEM approaches can be computationally expensive, resulting in scalability and feasibility limitations for TE applications [47, 48]. Phase-field models for vessel formations have shown that hypoxia-induced angiogenic factor gradients drive vessel anastomosis and shape resilient vascular networks, with tissue cell distribution and growth factor concentration largely determining the final network morphology [49]. In addition to their use in FEM-based tissue mechanics, phase-field and diffuse-interface models are widely applied to simulate evolving tissue boundaries, interface tracking, and collective cell migration; thus, they can be used to generate highly versatile systems that replicate dynamic morphological changes, including tissue boundary evolution and collective cell motion [50, 51].

Vertex and Voronoi models have emerged as key tools for geometrically explicit representations of morphogenesis, predicting emergent collective dynamics in epithelial and soft tissues while maintaining physical density, close cell packing, and mechanical coupling [52–54]. Both approaches can couple cell-level biophysics and tissue-scale morphology, thereby enabling quantitative assessment of how local mechanical rules lead to global shape and function. For example, vertex models have been used to simulate cell rearrangement, tissue folding, and morphogenesis in epithelial tissues, while also considering rigidity transitions and the effects of cell-shape anisotropy on tissue dynamics [55]. Furthermore, they can depict the interplay between tissue properties and purse-string processes that occur during the healing of wounded epithelia [56]. Voronoi models have been employed to study the spatial organization and mechanical properties of tissues, accounting for cell sorting phenomena between different tissue types, tissue stiffness, and the effects of cell shape on tissue dynamics [55, 57]. Moreover,

network-based or graph-theoretic models can effectively analyze dynamic processes related to connecting networks [58, 59], such as vascular networks, signaling pathways, and tissue connectivity, complementing geometric approaches (e.g., vertex and Voronoi models) by emphasizing topological and connectivity properties. For example, Alves et al. [60] demonstrated through graph analysis that one can quantify the organization and dynamics of endothelial cell clusters during vasculogenesis in chicken embryos. Also, Okoro et al. [59] introduced a graph-theoretic approach to quantitatively analyze endothelial tube formation, capturing morphological differences and temporal maturation in vascular networks.

Despite these advances, models still tend to neglect non-equilibrium dynamics and heterogeneity from cell proliferation, which are critical in proliferative cell microenvironments; this is especially relevant for growing, regenerating, or abnormal tissues like cancer [40, 61, 62]. In contrast, stochastic and probabilistic models can incorporate the inherent variability in cellular processes, ranging from genetic expression to cellular-level events (such as proliferation and differentiation), as these are in fact influenced by random fluctuations and multifactor microenvironmental interactions [63–65]. Thus, such tools are useful for studying tumor heterogeneity, as they enable the simulation of diverse cell fates and responses to therapies, and hold promise for improved modeling of cancer progression.

Ranging from discrete and agent-based methods to continuum, hybrid, and geometric approaches, this classification of models offers complementary perspectives that bridge scales from individual cells to tissues and organs; accordingly, this enables researchers to integrate mechanistic insights with predictive simulations of morphogenesis and TE [66]. But despite their conceptual power, traditional computational models are inherently constrained by the need to predefine governing equations and make assumptions about cellular behavior, material properties, and boundary conditions. As a result, they can struggle to capture the full complexity of living systems, particularly when confronted with nonlinear, context-dependent, and/or poorly parameterized biological processes.

ML-based methods offer a novel and increasingly influential paradigm: rather than prescribing rules in advance, they learn relationships directly from experimental data, uncovering patterns and interactions that may be difficult (or impossible) to encode explicitly. In this way, ML complements classical modeling by enabling data-driven discovery while retaining the possibility of integration with physics-based reasoning. Such hybrid strategies are especially attractive for problems characterized by heterogeneity, high dimensionality, and incomplete mechanistic understanding.

Increasingly, computational frameworks are being coupled with ML and experimental imaging data to achieve data-driven morphomechanical modeling. By analyzing complex datasets encompassing cellular behavior, tissue dynamics, and environmental factors, ML facilitates predictive insights into tissue growth, regeneration, and potential design of engineered tissues and organoids [28, 67]. With a foundation on traditional methods in place, the next section now focuses on the growing repertoire of ML techniques that are redefining how tissue systems are analyzed and engineered.

## 3 Machine learning approaches for tissue development

Building on deterministic and stochastic frameworks, ML offers data-driven methods to model morphogenesis and enhance predictions [1, 2]. By training on digital libraries of tissue morphologies (typically derived from simulations such as finite element analysis, or from experimental imaging and biophysical measurements), ML models can efficiently predict morphological evolution and uncover complex hidden relationships between parameters, as well as their constitutive laws. Since various approaches that are commonly used in TE have been described in recent reviews [1, 2, 68, 69], here, we briefly summarize the major algorithm categories before discussing the prediction of focused phenomena related to mechanics, cell communication, and cellular fate decisions during in vitro tissue development.

Briefly, regression models—such as linear and logistic regression—can predict cell behavior and classification tasks, although they perform best on linearly separable data [70–72]. Support vector machines (SVMs) generate robust generalizations in high-dimensional feature spaces, and have found wide application in classifying cell types or differentiation stages [73]. Unsupervised identification of cellular or morphological subpopulations can be performed effectively with *k*-means clustering [74], while *k*-nearest neighbor (KNN) offers simple yet accurate classification based on feature similarity [75]. Decision trees (DTs) and random forests (RFs) enhance interpretability and robustness in predicting biomaterial properties or gene expression profiles [76, 77]. Artificial neural networks (ANNs) and deep learning architectures, particularly convolutional neural networks (CNNs) [78] and recurrent neural networks (RNNs) [79–81], have tremendously improved image-based analysis, scaffold design, and dynamic modeling of tissue growth [2, 68].

Deep learning architectures particularly excel at extracting patterns from large-scale imaging, multi-omics, and biomechanical datasets [82–84], and enable predictive modeling of tissue formation and remodeling. CNNs and graph neural networks (GNNs) capture spatial correlations among

cells and ECM components [85–87], while RNNs and temporal convolutional models handle dynamic processes such as tissue growth and morphogenetic signaling over time [88–91]. Generative models—including variational autoencoders (VAEs) and diffusion models—can simulate plausible morphogenetic trajectories, predicting the spatiotemporal evolution of cellular arrangements under varying biochemical or mechanical conditions [92]. Furthermore, reinforcement learning has introduced adaptive, feedback-based control, enabling real-time optimization of bioprocesses and self-organizing tissue systems [93]. These frameworks also enable exploration of optimal interventions—such as mechanical perturbations, substrate stiffness tuning, or modulation of morphogen gradients—so as to guide tissue self-organization toward desired outcomes [94]. By integrating mechanobiological data, ML models can reveal how mechanical forces interact with biochemical signals to orchestrate collective cellular behavior and shape tissue formation.

Finally, integrating ML with physical principles (commonly referred to as physics-informed ML) can augment predictive accuracy by bridging data-driven inference with mechanistic fidelity [95, 96]. Physics-informed ML frameworks offer the potential to solve high-dimensional partial differential equations governing morphogenetic processes while accounting for experimental noise and complex geometries. For example, this technique can incorporate equations describing thermo-elastic material deformation or diffusion-driven swelling, enabling a more faithful representation of tissue dynamics. Moreover, ML can identify latent physical mechanisms and state variables, and quickly generate predictive morphological models. Together, these approaches form an integrated ML toolkit for understanding, predicting, and engineering complex biological phenomena.

In the following subsections, we discuss key ML contributions to understanding tissue development both in vivo and in vitro. The discussion is organized to follow the progression from fundamental biological processes to applied engineering strategies (Table 1). First, we examine how ML helps decipher morphogenetic dynamics, mechanobiological inputs, and cell–cell bioelectrical communication, highlighting specific insights into tissue maturation. Building on this biological understanding, we then consider how these insights have informed scaffold design for TE. Finally, closed-loop ML systems that regulate tissue formation are explored, illustrating how knowledge from fundamental processes can guide predictive and adaptive interventions in both natural and engineered tissues. Together, these subsections trace a trajectory from underlying biology to TE application, and reflect the overarching theme of using ML to connect biological insights with practical design.

### 3.1 Mechanobiology–machine learning frameworks

Mechanobiology explores the multiscale interactions through which mechanical forces govern cellular behavior, collective tissue organization, and ultimately the functional architecture of entire organs [110, 111]. Studying how physical forces and mechanical properties regulate cellular behavior is crucial for both theoretical and applicative understanding of histomorphogenesis. By sensing and measuring mechanical cues through focal adhesions, integrins, and cytoskeletal tension, cells can translate these signals into biochemical responses that govern a variety of cellular behaviors—such as differentiation, proliferation, and migration [32, 112]. For most cells in physiological conditions, the typical physical cues that modulate their mechanobiological machinery are caused by both endogenous and exogenous forces, such as intracellular cytoskeletal contractility, gravity, shear stress, and tensile and compressive forces that govern the surrounding microenvironment [110].

Furthermore, ML approaches enable quantitative modeling of mechanotransduction pathways and their impact on tissue-level outcomes. Their relevance lies in the capability of coupling the dynamics of cellular mechanics, force propagation, and tissue remodeling, thereby facilitating the rational design of scaffolds, mechanical conditioning protocols, and culture environments that can achieve the desired morphologies [113]. However, the predictive power of such ML models is often constrained by limited and heterogeneous experimental datasets. Many studies rely on small-scale or highly curated data, which can reduce model robustness and limit generalization to new cell types, tissue constructs, or experimental conditions [1]. Scarcity of data remains a key barrier to clinical translation and wider adoption of ML-guided mechanobiology frameworks [1, 114].

In terms of applications for different domains of ML, supervised learning is able to correlate ECM stiffness, applied shear stress, or cyclic strain with stem cell lineage commitment or migration patterns [115, 116], while unsupervised approaches can identify emergent mechanical phenotypes across developing tissue constructs [117]. Generative adversarial networks (GANs) can be used to predict cellular traction forces directly from phase-contrast images [118], or fluorescence images of diverse cellular markers such as the adhesion protein zyxin [119].

To reconstruct mechanotransduction networks, data from imaging, transcriptomics, and traction force microscopy can be combined via GNN and other integrative ML methods. For example, Oria et al. [113] described how activated RhoA/ROCK and Piezo1 signaling modulate nuclear mechano-sensing as well as the formation of focal adhesion and cytoskeletal tension. By analyzing high-resolution live-cell imaging of actin and myosin dynamics, CNNs predicted

**Table 1** A comparative overview of machine learning (ML) algorithms that have been employed in tissue engineering (TE), including representative applications and reported performance metrics

| ML algorithm | Application | Task | Dataset/Input feature | Performance metric | Advantage | Disadvantage | Ref. |
|---|---|---|---|---|---|---|---|
| Ensemble learning: RF, LASSO, XGBoost, SVR | Predicting droplet velocity and volume in inkjet bioprinting | Regression models trained via an ensemble approach to predict droplet formation characteristics (velocity and volume) based on process parameters for inkjet bioprinting; improves predictive robustness by combining multiple base learners | Polymer concentration; excitation voltage; dwell time; rise time (full factorial design of experiments) | RMSE, relative error (RE), and $R^2$ reported for velocity and volume prediction; ensemble models capable of accurate prediction (better than individual base learners) | Accurate prediction of droplet formation; supports optimization of printing parameters; reduces the number of trial-and-error experiments; robust to nonlinear process dependencies | Dataset-specific; limited generalizability to other printer setups; model performance sensitive to input parameter range; moderate interpretability | [97] |
| Ensemble learning: NN, RR, KNN, RF | Predictive modeling of cell viability in dynamic optical projection stereolithography-based bioprinting | An ensemble model trained to predict cell viability outcomes under varying SLA bioprinting conditions by combining predictions from four base learners, which can also assess the importance of different process parameters | UV intensity, UV exposure time, GelMA concentration, and layer thickness; target: measured cell viability (experimental data) | High prediction accuracy reported (evaluated using multiple error metrics such as mean error, MAE, RMSE; ensemble outperformed individual base learners); RF analysis quantified parameter importance | Accurate prediction of post-printing cell viability; non-invasive assessment; supports process optimization; enables rapid evaluation of printing parameters | Limited to the tested bioink and printer setup; moderate model interpretability; dataset-specific; may require retraining for new materials or conditions | [98] |
| Supervised regression surrogate models: RF, gradient boosting, feed-forward neural networks | Predictive modeling of bone ingrowth in tissue scaffolds | Multiscale surrogate regression models trained on scaffold architectural descriptors and in vivo longitudinal imaging data to predict time-dependent bone formation, replacing computationally expensive finite element simulations while capturing nonlinear relationships between the scaffold structure, mechanical environment, and biological response | Scaffold geometric descriptors, material properties, and longitudinal bone formation markers from imaging data | Accurate approximation of $FE^2$ simulations; validated against an in vivo tibia model; substantial reduction in computational time | Accurate surrogate for multiscale $FE^2$ simulations; reduces computational cost; captures nonlinear scaffold–bone interactions; supports design optimization | Requires high-quality longitudinal data; limited generalizability to new scaffold types; model complexity may reduce interpretability | [99] |
| XGBoost | Predicting cellular behavior on CTE scaffolds | Classification of cell adhesion and proliferation patterns on different scaffold compositions; ensemble method combining the top five classifiers to improve prediction robustness | Scaffold material, porosity, surface properties | XGBoost accuracy: 87%; AdaBoost-Voting ensemble accuracy: 93% | Predicts cell behavior accurately; supports cardiac scaffold design; integrates multiple scaffold/cell features; facilitates early assessment of cell response | Limited to cardiac scaffolds; dataset-specific; model interpretability is moderate; may require retraining for new scaffold types | [100] |
| Supervised regression models: XGBoost, AdaBoost | Predicting mechanical properties of composite bone scaffolds | Regression models trained to map scaffold composition (PLA/cHAP ratios), porosity, and density to mechanical outcomes (compressive and tensile strength), enabling predictive optimization of scaffold design for load-bearing bone TE | Composition ratios, scaffold porosity, scaffold density; measured tensile and compressive strength | XGBoost $R^2 \approx 0.9173$ (compressive); AdaBoost $R^2 \approx 0.8772$ (tensile) | High predictive accuracy for mechanical properties; supports scaffold design optimization; handles multiple outputs; data-driven material tuning | Limited to trained material composites; dataset-specific; moderate interpretability; may require retraining for new compositions | [101] |

To be continued

Table 1 (continued)

| ML algorithm | Application | Task | Dataset/Input feature | Performance metric | Advantage | Disadvantage | Ref. |
|---|---|---|---|---|---|---|---|
| Linear regression, SVR, DT regressor, RF regression, extra trees regression | Predicting the presence/absence of cells in droplets and the number of printed cells in inkjet-based bioprinting | A proof-of-concept study using high-throughput optical monitoring and ML models to predict whether a droplet contains cells (classification proxy), and to estimate the total number of printed cells within multiple droplets by tracking droplet velocity profiles along the nozzle-substrate distance; models were compared to identify the best algorithm for each task | Droplet velocity at two measurement points (captured optically); datasets include single-droplet and batch droplet profiles | RF: highest single-droplet accuracy (≈80%); ETR: lowest mean error for multiple droplets (≈12%); comparative performance across LR, SVR, DT, RF, and ETR | Accurate prediction of cell number; real-time droplet monitoring; supports process control; uses high-throughput imaging data | Dependent on a precise imaging setup; system-specific; limited generalizability; sensitive to droplet variability | [102] |
| Regression tree, RF, AdaBoost, gradient boosting | Predicting scaffold performance (nanofibrous scaffold outcomes) | Regression models applied to correlate scaffold physico-chemical features with functional performance metrics for nanofibrous scaffolds used in skin TE; evaluation of multiple ML regressors and clustering to identify the best predictive model | Dataset with scaffold features and scaffold performance outcomes (physico-chemical descriptors and performance measures) | AdaBoost: accuracy up to 99.6%, MAPE ~1.41%, $R^2$≈ 0.999 for overall predictions; tree-based models were compared and AdaBoost demonstrated optimal performance across groups | High predictive accuracy; handles multiple scaffold performance metrics; supports scaffold design optimization; robust regression models | Limited to specific scaffold types; dataset size constraints; requires careful selection of features; moderate interpretability | [71] |
| Polynomial fit, DT, RF | Predictive modeling of bioink viscosity for extrusion-based 3D bioprinting | Predicts the rheological property (viscosity) of a novel hybrid hydrogel bioink as a function of bioink composition and shear rate, so as to guide formulation and improve printability; multiple ML models were compared to identify the best predictive tool | 169 rheological measurements; input features: alginate (%), gelatin (%), TEMPO-Nano fibrillated cellulose (%), shear rate (0.1–100 $s^{-1}$) | RF highest: $R^2$=0.99, MAE= 0.09; DT: $R^2$=0.988, MAE= 0.13; PF: $R^2$=0.95, MAE= 0.28 (comparison of coefficient of determination and MAE) | Accurate property prediction; reduces experimental effort; supports bioink formulation optimization; practical for extrusion workflows | Small dataset; limited generalizability; black-box interpretability; material-specific scope | [103] |
| Classification models (RF, SVC, KNN, DT); regression models (RF, DT, SVR, KNN, linear, LASSO, ridge) | Classification and regression predictive modeling of inkjet droplet characteristics | Automated image analysis captures droplet videos/images during 3D inkjet printing to classify droplet type (no drop, satellite, normal) and to predict droplet velocity and volume using ML models; classification uses RF, SVC, KNN, DT; regression uses both linear (linear/LASSO/ridge) and nonlinear regressors (RF, DT, SVR, KNN) | Input process parameters: frequency, voltage, temperature, meniscus vacuum; output targets: droplet type (qualitative), droplet velocity (continuous), droplet volume (continuous); automated image-derived features serve as labels | Classification: RF, KNN, DT ~98%–99% mean accuracy ($k$-fold cross-validation); SVM 92% at $k$=5. Regression: nonlinear models (RF, DT, KNN) $R^2$≈ 0.98 and very low MSE at $k$=5; SVR moderate ($R^2$≈0.88). Linear models underfit (low $R^2$) | High predictive accuracy; automated image-based features; real-time process monitoring; robust classification and regression; supports quality control | Requires extensive image acquisition; setup-specific models; sensitive to imaging conditions; difficult to transfer to new printers | [104] |
| Supervised regression and flexible statistical models: GLM, GAM, GAMLSS, DT, RF, SVM, ANN | Predicting scaffold morphology, topography, and mechanical properties | Trained multiple supervised models to map electrospinning process parameters (solvent compositions and concentrations) to scaffold outputs, including fiber diameter, inter-fiber separation, roughness, Young's modulus, ultimate tensile strength, and strain at break; enables predictive control of scaffold microstructure and mechanics for TE | 2214 observations with input: $dH_2O$ (%), HAc (%), DMSO (%); outputs: diameter, separation, roughness, Young's modulus, tensile strength, and strain at break | GAMLSS models improved $R^2$ vs. baseline by ~6.9% and reduced MAPE by ~21%, highlighting improved performance over traditional regressors | Multi-output prediction of morphology and mechanics; supports scaffold design optimization; flexible ML models; improved efficiency of experimental design | Requires large datasets; limited generalizability to other scaffold materials; model interpretability is moderate; system-specific | [105] |

To be continued

Table 1 (continued)

| ML algorithm | Application | Task | Dataset/Input feature | Performance metric | Advantage | Disadvantage | Ref. |
|---|---|---|---|---|---|---|---|
| MLP, DT, RF, PR, LSTM | Predictive modeling and optimization of cellular droplet volume | Supervised regression models trained to predict droplet size based on bioprinting parameters in high-throughput cellular droplet bioprinting; used for optimization of printing parameters to achieve desired organoid droplet sizes | Bioink viscosity, nozzle size, printing time, printing pressure, cell concentration; droplet volume measurements made from image processing | MLP had the highest prediction accuracy; DT displayed the shortest computation time; $R^2$, MAE, and RMSE were compared across algorithms; MLP and LSTM outperformed traditional ML on accuracy metrics | Accurate droplet placement; supports high-throughput optimization; reduces trial-and-error; enables closed-loop process control | Setup-specific; dependent on initial sampling; limited generalizability; moderate interpretability | [106] |
| SVR | Parameter optimization model for extrusion-based 3D bioprinting | Linking bioprinting process parameters to a composite grey relational grade that quantifies printing quality (extrusion swelling ratio + fiber formability) for sodium alginate–gelatin hydrogels; guiding the optimization of printing precision | Process parameters: nozzle diameter, layer height, printing speed, extrusion speed; output: grey relational grade | Mean error ~5.15% in predicting printing precision; $R^2$ (training) 0.922; $R^2$ (test) 0.805; RMSE ~0.061 (train)/0.065 (test) | Predictive optimization of printing quality; supports multi-parameter tuning; robust for small datasets; reduces experimental effort | Limited to sodium alginate-gel hydrogels; kernel/model dependent; black-box interpretability; may not generalize to other bioinks | [107] |
| RF regression | Quantitative prediction of protein adsorption on polymer brush surfaces | Supervised regression model predicting the amount of protein adsorbed (BSA, lysozyme) on well-defined polymer brush surfaces with diverse chemical properties. The model also analyzes contributions of electrostatic and hydrophobic interactions to adsorption, and predicts related surface properties (contact angle, $\zeta$ potential) | Polymer brush descriptors: grafted structure (thickness), contact angle, $\zeta$ potential; protein type (BSA or lysozyme) | RF showed the best predictive performance for adsorption amount across different conditions; model enables quantitative and explainable predictions incorporating physicochemical descriptors (exact numeric performance metrics not detailed in abstract, but described as accurate) | Accurate adsorption prediction; facilitates biomaterial screening; handles multiple polymer chemistries; accelerates design cycles | Dataset-specific; limited extrapolation to unseen polymer types; requires curated descriptors; model interpretability is moderate | [108] |
| Deep learning (ResNet-50), LASSO, RF | Predictive modeling of osteogenic differentiation of mesenchymal stem cells | Supervised models trained on high-throughput morphological and omics (gene/protein expression) data to predict whether MSCs will successfully differentiate toward osteogenic lineage, enabling early, non-destructive assessment of regenerative potential, and feature discovery for MSC implants | Cellular morphology metrics, and omics features (gene sets, biomarkers) related to osteogenic status | Reported comparisons across multiple models; performance varied by model and data type, with deep learning and ensemble models achieving high predictive accuracy for differentiation states | Early prediction of cell fate; non-invasive assessment; supports biomarker discovery; high predictive accuracy on omics/morphology data | Data-intensive; sensitive to feature selection; model complexity reduces interpretability; limited to MSCs and the tested conditions | [109] |

The table summarizes representative ML algorithms, their applications, and specific tasks across various subdomains of TE—including bioprinting process optimization, scaffold design, cell fate prediction, and protein–material interactions. The versatility and cross-cutting applicability of ML approaches are highlighted across multiple subdomains of TE and development. RF: random forest; SVR: support vector regression; RMSE: root mean squared error; NN: neural network; RR: ridge regression; KNN: *k*-nearest neighbors; SLA: stereolithography; UV: ultraviolet; GelMA: gelatin methacrylate; MAE: mean absolute error; $FE^2$: multilevel finite element; CTE: cardiac tissue engineering; PLA: polylactic acid; cHAP: calcium hydroxyapatite; DT: decision tree; ETR: extra tree regression; LR: linear regression; MAPE: mean absolute percentage error; PF: polynomial fit; SVC: support vector classifier; SVM: support vector machine; MSE: mean squared error; GLM: generalized linear model; GAM: generalized additive model; GAMLSS: generalized additive models for location, scale, and shape; ANN: artificial neural network; $dH_2O$: distillate water; HAc: acetic acid; DMSO: dimethyl sulfoxide; MLP: multilayer perceptron; PR: polynomial regression; LSTM: long short-term memory; BSA: bovine serum albumin; MSC: mesenchymal stem cell

RhoA/ROCK pathway activation, yielding quantitative spatial–temporal patterns of cytoskeletal remodeling in response to mechanical stimuli [120]. As a result, one can rapidly infer cell contractility changes under different substrate stiffnesses or pharmacological perturbations. Another example of ML applied to mechanosensitive cellular responses was provided by Bonnevie et al. [121], who treated calcium imaging data with supervised learning algorithms (RFs and SVMs) to identify and classify Piezo1 channel activation events. Mechanical stress and shear forces were correlated with downstream gene expression changes as a result of the model's learning from patterns of calcium influx.

However, we must mention that while these predictive frameworks are promising, they often function as "black boxes," making it difficult to interpret why certain cellular responses are predicted. Limited interpretability poses challenges to validating mechanistic hypotheses and to ensuring that model outputs align with established biological knowledge, particularly in translational or clinical contexts.

The predictive utility of mechanobiology–ML hybrid models extends beyond cellular mechanics to encompass the large-scale mechanics of tissues and organs, broadening the impact of ML so that it considers the dynamic functionality of the human body as an interconnected system of hard and soft tissues [69, 122, 123]. Building on the algorithm-centric framework presented in Fig. 1, which mapped different ML strategies to TE tasks, Fig. 2 shifts the focus to a biology-centric perspective, highlighting how ML integrates mechanotransduction and biomechanical processes across cellular, tissue, and organ scales. Here, we illustrate how ML can model the effects of physical forces across scales: predicting mechanosensitive signaling and force generation at the cellular level, capturing ECM remodeling and tissue-level force propagation, and modeling organ-scale biomechanics.

Considering the musculoskeletal system, understanding the biomechanics of hard tissues—particularly bone—is crucial for understanding injury mechanisms and improving medical implant design; however, conventional imaging-based diagnosis of such issues is often limited by noise and operator dependence. To address this, ML models (like CNNs, ANNs, and SVMs trained on imaging and finite element data) have been successfully applied to classify bone fractures and predict patient-specific fracture risk [124–128]. For instance, ANNs were used to model the relationship between bone density and elastic modulus for the two main types of bone tissue—cortical and trabecular—using simulated mechanical behavior and stiffness measurements as input data [129]. Bone stiffness in stress conditions (e.g., repeated compressive loading) could be accurately predicted by leveraging an ANN as a regression model, feeding it with various input parameters such as the amount and duration of applied force, age of individuals, and anatomic bone features [130]. Despite these encouraging results, the predictive accuracy of ANNs and other ML models can be limited when they are applied to patient populations or experimental conditions that differ from the training dataset [131]. Moreover, the opaque nature of these models complicates clinical interpretation, reducing trust in model outputs for decision-making and highlighting the need for interpretable or hybrid mechanistic-ML approaches.

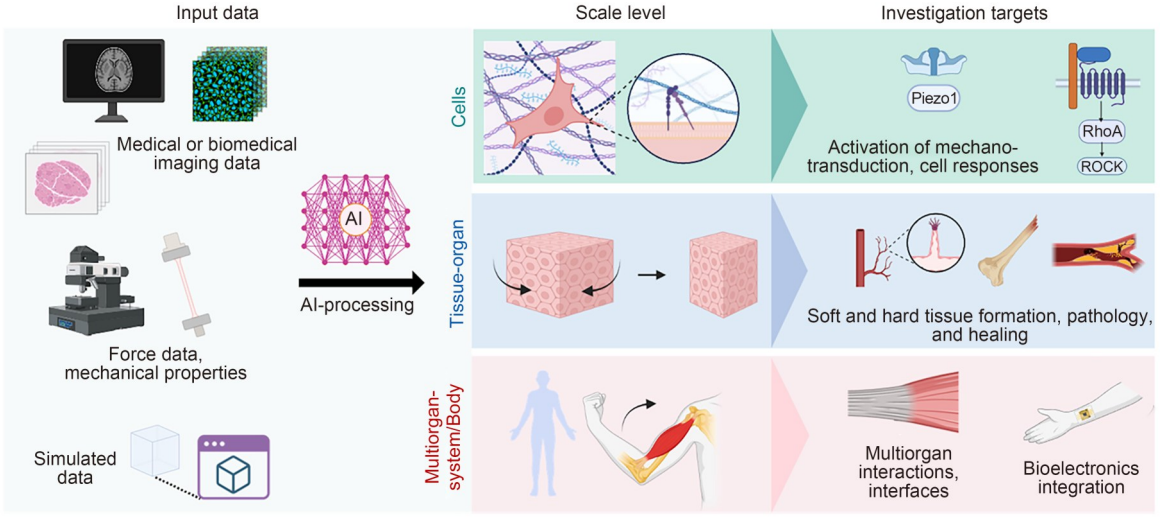


**Fig. 2** Machine learning (ML)-enabled multiscale mechanobiology and biomechanics. ML links cellular mechanotransduction with tissue and organ biomechanics by modeling how physical forces regulate biological function across different scales. At the cellular level, ML can predict force generation and mechanosensitive signaling from imaging and molecular data. At the tissue level, it can capture force propagation, extracellular matrix (ECM) remodeling, and morphological adaptation. At the organ level, ML can model the mechanical behavior of hard and soft tissues, improving predictions of tissue formation, injury, and adaptation. Together, these approaches provide a unified, multiscale view of mechanobiology guided by ML. AI: artificial intelligence

Interestingly, Zhong et al. [132] developed a framework that effectively simulated the mechanobiological role of periodontal ligaments and holds promise for application in a broad range of soft-/hard-tissue interfaces. Aiming to understand the adaptive functionality of such ligaments in order to regulate the mechanical stimuli to the surrounding alveolar bone, they combined deep learning leveraging a U-net CNN with the Gaussian mixture method to compare over 5000 microstructural variations to natural non-uniformities of ligaments; as such, they discovered a narrow physiological regulation window that preserved equilibrium between the ligament hydrostatic pressure and the strain energy of the alveolar bone [132].

Transitioning from hard to soft tissues, biomechanical investigations have focused on defining the mechanical rules that govern the functions of such tissues in their roles as connectors, supporters, and stabilizers of organs and bones [28, 133]. Softness—as well as multiphasic and structural heterogeneity—comes with intricate nonlinear properties, whose elucidation requires sophisticated, adaptive, and comprehensive analytical tools [1]. Thus, ML techniques have flourished in soft tissue biomechanics. A study from Cilla et al. [133] introduced an ML-based framework to determine material parameters in constitutive models of soft biological tissues. By training support vector regressors, bagged DTs, and ANNs on analytical uniaxial test data to define the parameters of the Gasser–Ogden–Holzapfel strain energy function, they generated predictions nearly identical to analytical results. In addition to high training effectiveness, they achieved excellent predictive performance when applying the model to unseen data. The accuracy in replicating the material behavior was then demonstrated on experimental uniaxial tests of cardiovascular tissue, showing potential for application in soft tissue characterization and model fitting.

Physics-informed training of a GNN using the principle of minimum potential energy was able to efficiently and accurately simulate soft tissue mechanics while considering unique, patient-specific anatomical features [96]. Avoiding low-order approximations, this approach captured more realistic deformation than data-driven approaches. Moreover, Huff et al. [134] introduced StrainNet, a deep learning framework that accurately predicts tissue deformation from in vivo image data. When applied to simulated tendon deformation experiments after training on datasets accounting for realistic imaging artifacts, this framework outperformed conventional strain measurement methods (by up to 90%). When applied to ultrasound imaging of contracted human flexor tendons, it efficiently tracks in vivo deformations. Furthermore, CNNs and SVMs have been applied to determine atherosclerotic plaque rupture risk by describing the stress distribution on vessel walls; this was achieved by using finite element analysis-derived stress data as ground truth labels for training, and providing arterial geometrical and pressure data as inputs [135, 136].

Incorporating mechanobiological insights with ML-based modeling enables a multiscale understanding of how cellular forces propagate across tissues, linking microscopic mechanotransduction to macroscopic biomechanical functions. However, realizing this multiscale predictive capability in practice remains challenging. Sparse and heterogeneous datasets—as well as the often limited interpretability of complex ML models—can reduce confidence in predictions, particularly when extrapolating from experimental constructs to patient-specific tissues [137–139]. Addressing these limitations is critical for translating mechanobiology-ML frameworks into reliable clinical and biofabrication tools.

## 3.2 Generative machine learning in scaffold design

The field of biofabrication is witnessing a paradigm shift from traditional trial-and-error methodologies to data-driven approaches that leverage advanced computational techniques [2, 140]. Generative ML has emerged as a transformative tool in scaffold design, as it enables the creation of complex, functional, and biologically relevant structures. By harnessing the power of ML, researchers will likely design scaffolds that not only mimic the mechanical properties of natural tissues, but also support cellular behaviors that are essential for tissue regeneration [29]. The core generative AI techniques in this field are GANs, VAEs, and deep reinforcement learning (DRL) (Fig. 3).

Despite these promising factors, the application of generative ML in scaffold design remains constrained by the limited availability of high-quality training data and incomplete biological validation [137]. Most current studies rely on relatively small datasets derived from specific materials or fabrication platforms, which restricts model generalizability when applied to new tissue types, scaffold architectures, or clinical contexts. These data bottlenecks—together with the scarcity of standardized and well-annotated data sources—continue to limit the robustness and transferability of ML-driven design strategies. Moreover, many generative models primarily focus on optimizing geometric or mechanical properties without direct incorporation of downstream biological outcomes, creating a gap between computationally optimized designs and functionally validated scaffolds [2]. As a result, models that are trained within narrow experimental domains may struggle when applied to new materials or fabrication protocols; this reflects broader challenges in biomedical generative AI applications, where performance often degrades on unseen data. Against this backdrop, the following subsections examine how GANs, VAEs, and DRL are being applied in scaffold engineering, along with their practical constraints.

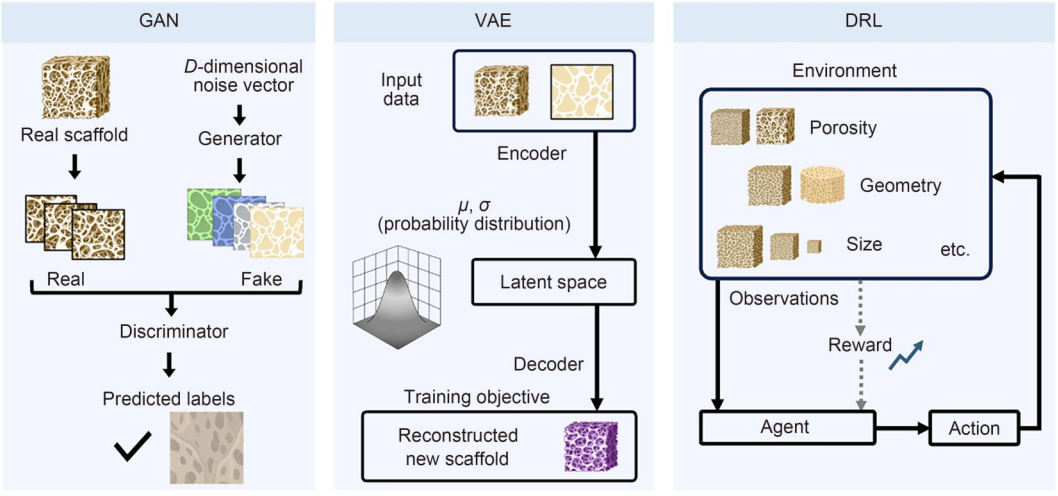


**Fig. 3** Generative artificial intelligence (AI) for scaffold optimization. In generative adversarial networks (GANs), the generator creates scaffold designs from random noise, while the discriminator tries to distinguish these designs from real scaffolds. Through training, the generator learns to fool the discriminator and the discriminator improves at detecting fakes, which continues until the generated scaffolds closely resemble real ones. A variational autoencoder (VAE) consists of three main components: (i) an encoder, which compresses input data, like the scaffold structures, into a lower-dimensional representation; (ii) a latent space ($z$-space); (iii) a decoder, which reconstructs the data from $z$, learning to generate scaffold designs that resemble (or improve upon) the training examples. In deep reinforcement learning (DRL), the model (i.e., agent) learns to make a sequence of decisions that maximizes some cumulative reward. Each decision changes the environment, and the agent uses feedback to improve its behavior over many iterations. Generative models can predict scaffold properties (particularly mechanical and architectural features), thereby guiding designs that influence tissue mechanics and morphogenesis in developmental tissue engineering (TE)

#### 3.2.1 Generative adversarial networks

A GAN consists of two neural networks: a generator that creates new data and a discriminator that evaluates its authenticity [141–144]. This adversarial process drives the generator to produce highly realistic outputs. In scaffold design, GANs have been utilized to generate intricate three-dimensional (3D) structures that replicate the complexity of natural ECM [145–147]. These structures can be tailored to create specific mechanical properties and porosities, enhancing cell infiltration and tissue integration [148]. GANs are able to learn the intricate structural features of native ECMs, and can thus be used to design and create synthetic scaffolds with controlled pore sizes and hierarchical structures that replicate the complexity of original tissue [149, 150]. This offers a way to produce biomimetic materials for various biomedical applications.

However, GAN-based approaches often require large, well-curated datasets of validated scaffold designs, which are rarely available in TE [1]. As a result, such models are frequently trained on narrow design spaces, which increases the risk that generated scaffolds fail when transferred to different fabrication methods or biological systems. Also, the internal decision logic of GANs is typically opaque, making it difficult to determine which learned features drive a particular design outcome. Moreover, GAN training can suffer from mode collapse and instability, resulting in limited diversity and reduced practicality of generated scaffold structures [151].

#### 3.2.2 Variational autoencoders

VAEs are probabilistic models that learn to encode input data into a latent space and then decode it in order to reconstruct the original data [152]. VAEs can create new designs by learning a compressed representation (the latent space) of existing data, and then sampling points from this space to generate novel, often more optimized, structures [153]. This process is used in fields like drug discovery and materials science to propose new molecules or structures based on properties learned from the initial dataset [154, 155]. In TE, VAEs can be used to generate novel scaffold designs by sampling from the learned latent space [156]. VAEs are particularly useful for exploring design spaces and generating variations of scaffold architectures that meet predefined criteria, such as mechanical strengths or degradation rates [157–159]. By rapidly generating thousands of novel two-dimensional (2D) lattice structures, GANs and VAEs can achieve computational efficiency that is several orders of magnitude higher than traditional topology optimization methods [157, 158, 160]. These models provide a scalable and efficient approach for exploring vast and complex design spaces, opening new possibilities in scaffold design.

Although VAEs offer a powerful means of exploring design spaces, their practical utility is often limited by the quality and diversity of the input data used to construct the latent space. Latent representations derived from small or biased datasets may inadvertently constrain generated designs

to a narrow subset of possibilities, thereby limiting innovation and robustness. Furthermore, the biological significance of latent variables is rarely interpretable, which complicates efforts to relate generated scaffold features to underlying mechanobiological mechanisms. Among generative models, GANs and VAEs particularly lack transparency in terms of how latent representations map to biologically relevant design features, thus complicating interpretation and clinical trust; this is a limitation that is common for generative models in healthcare [1, 161].

#### 3.2.3 Deep reinforcement learning

DRL involves training agents to make sequences of decisions by rewarding them for achieving specific goals [162]. In scaffold design, DRL can be applied to optimize the layout of structural elements within a scaffold to maximize functionality [163], such as for optimal nutrient diffusion [148] or mechanical strength [11, 148, 164]. By defining appropriate reward functions, DRL algorithms can iteratively improve scaffold designs to meet complex, multi-objective criteria.

Nevertheless, DRL-based optimization frameworks are highly sensitive to the choice of reward functions and simulation environments [165]. Poorly defined or oversimplified objectives can lead to designs that may perform well in silico, but fail to capture practical constraints such as manufacturability, biocompatibility, or patient-specific variability. Additionally, the sequential decision-making process learned by DRL agents is typically difficult to interpret, which poses challenges for validation and regulatory acceptance in clinical practice [166].

In summary, generative AI has been leveraged in scaffold engineering to enhance structure, functionality, and personalization [77]. These models can optimize scaffold architecture to achieve ideal porosity and mechanical performance for tissue development, embed bioactive compounds or growth factors to direct cell behavior, and create patient-tailored scaffolds from individual anatomical information. At the same time, ML enables a holistic design methodology, simultaneously addressing mechanical durability, degradation profiles, and biocompatibility, and thereby advancing precision in regenerative medicine.

Despite its potential, the adoption of generative AI in scaffold design faces several obstacles. While generative ML can accelerate design exploration, current approaches often prioritize computational efficiency over biological validity and clinical robustness. High-quality, annotated datasets are often scarce or proprietary, which limits model training [167]. This scarcity of standardized, multi-institutional datasets also hampers objective benchmarking of different generative models, making it difficult to assess reproducibility or compare methods from various studies.

The complexity of AI models can also hinder interpretability, thus complicating clinical validation and regulatory approval [168]. Meanwhile, translating ML-generated designs into physical scaffolds requires advanced fabrication methods such as 3D bioprinting, which may not always match the design specifications [169]. Additionally, regulatory and ethical considerations around safety, efficacy, and accountability must be addressed to responsibly deploy such technologies in medical applications [170].

Moreover, for all generative approaches, computational cost and scalability remain significant constraints. The substantial training and inference requirements of advanced models limit their practical feasibility; this is particularly relevant for high-resolution 3D scaffold representations and large design spaces, thus restricting deployment in clinical environments or research laboratories with limited resources [80, 114]. These technical barriers echo broader challenges for ML in TE, where model interpretability and reliable translation to clinical practice remain significant hurdles due to data heterogeneity, limited generalizability, and the lack of standardized validation frameworks.

To address such challenges, future research should prioritize developing comprehensive high-fidelity datasets encompassing diverse scaffold architectures and their associated biological responses [171, 172]. Enhancing the interpretability of ML models will be critical for fostering transparency, clinical confidence, and regulatory acceptance. In addition, aligning ML-generated designs with advanced fabrication technologies will enable more effective translation into clinical practice, while developing clear regulatory and ethical frameworks in collaboration with relevant authorities will promote responsible integration of ML into scaffold design and biofabrication. Overcoming these hurdles will enable generative scaffold design to transition from an experimental curiosity to a dependable, interpretable, and clinically relevant TE practice.

### 3.3 Artificial intelligence as a modeling surrogate for bioelectricity

A fundamental challenge in TE is to decode and replicate the dynamic interplay of mechanical, biochemical, and bioelectrical cues that govern morphogenesis [30, 32, 173, 174]. While traditional models have elucidated key roles of mechanical forces and molecular signaling [110], the emergent influence of bioelectricity (encompassing transmembrane potentials ($V_{mem}$), ion fluxes, and intercellular electrical communication) has gained recognition as a central regulator of cellular behavior and tissue organization [12, 13, 15, 31]. A living cell exhibits an intrinsic electrical potential across its membrane, which is maintained through selective ion permeability and channel activity [12, 14]. These voltage gradients extend beyond individual cells, forming networks of

coupled bioelectrical domains that are interconnected via gap junctions [18, 175–177]. Bioelectric phenomena orchestrate developmental processes such as proliferation, migration, differentiation, and pattern formation; they therefore represent a promising yet underexplored domain for computational modeling and predictive control [18, 177–179]. Moreover, spatiotemporal variations in membrane potential have been shown to guide morphogenetic events ranging from embryonic axis establishment and limb regeneration, to stem cell differentiation and wound healing [175, 176, 180–184]. Importantly, changes in $V_{mem}$ not only reflect cellular physiological states, but also actively encode instructive information that shapes pattern formation [14, 18].

The "bioelectric code" dictates tissue geometry and determines functions, thereby underpinning morphomechanics—the study of how coordinated mechanical interactions drive tissue self-organization [185]. A key principle of morphomechanics is that changes in $V_{mem}$ reflect mechanical stress rather than randomness, with mechanically activated ion channels converting forces into electrical signals that inform cells of their membrane's mechanical state [32]. Piezo1 channels, which are broadly expressed, play key roles in embryonic development and the maintenance of physiological processes in adult tissues [181, 186, 187]. Cellular behavior is shaped not only by a cell's own $V_{mem}$ but also by the bioelectric states of neighboring cells, with gap junctions forming electrically coupled networks that coordinate collective tissue responses.

Being both evolutionarily ancient and developmentally foundational, and emerging with the establishment of membrane potentials [188], bioelectricity likely influences both individual and collective cell behaviors in processes such as embryonic development, tissue repair, and disease [12]. Although most related research has focused on neural tissues [189, 190], emerging evidence indicates that bioelectric signaling also plays key roles in diverse underexplored non-neural morphogenetic contexts. In concert with biomechanical feedback, bioelectric signals establish a dynamic interplay that governs the self-organization of tissues. This offers a powerful framework for understanding the morphomechanical logic of development, and opens new territory for predictive ML in biofabrication. Indeed, while the complexity of these multilevel, multiphysical networks often exceeds that of traditional mechanistic models, ML-driven methods can integrate bioelectric data to generate predictive models for simulating and guiding multiscale tissue morphogenesis.

Traditional computational models, such as reaction-diffusion systems [191, 192], finite element analyses [192, 193], and multi-agent frameworks [194], have been used to approximate ion flux and potential propagation in tissues. However, these methods often involve prohibitive computational costs and rely on numerous assumptions about underlying biophysical mechanisms. In contrast, ML and deep learning approaches can act as surrogate models, learning complex nonlinear relationships directly from experimental data and reproducing bioelectric dynamics at unprecedented speed and scale [195–197]. Meanwhile, top-down theoretical frameworks offer complementary insights by focusing on system-level control rather than molecular details. As described by Pezzulo and Levin [198], emphasizing system-wide goals allows the modeling of higher-level organization (via bioelectric signaling and pattern memory) so as to direct cellular behavior. Evidence from planarian regeneration supports this approach, suggesting that targeting large-scale anatomical outcomes is a powerful control strategy for regeneration and synthetic bioengineering.

Hansali et al. [199] further explored how bioelectrical patterns shaped morphogenesis using neural cellular automata (NCA) simulations and planarian regeneration experiments (Fig. 4). By modeling artificial organisms with different bioelectric encoding strategies (direct, indirect, and binary), they demonstrated distinct developmental robustness and sensitivity to disruptions. Notably, direct encoding ensured stable patterning, indirect encoding promoted resilience to partial perturbations, and binary encoding required precise timing. Experimental treatments with selective serotonin reuptake inhibitors validated that disruption of bioelectric signaling led to variable or bistable morphologies, identifying bioelectric cues as key regulators of developmental stability.

GNNs and physics-informed neural networks (PINNs) have been used to model spatiotemporal voltage dynamics, capturing emergent synchronization patterns and ion flux propagation [200−203]. Similarly, RNN and CNN architectures have demonstrated the ability to predict the evolution of bioelectric fields from initial conditions, effectively learning the "rules" of tissue-level electrical communication from empirical voltage imaging data [204]. Such models have also shown promise in parameter inference, enabling reconstruction of ion channel kinetics and intercellular coupling strengths from partial experimental observations; these are tasks that are typically intractable for traditional solvers.

At finer scales, hybrid architectures combining CNNs and RNNs have been used to analyze electrophysiological recordings, capturing temporal patterns of ion channel activity and membrane potential fluctuations with high fidelity [205]. Recurrent mechanistic models that couple neural networks with state-space dynamics have also provided interpretable simulations of membrane currents and neural circuit behavior [206]. Beyond the single-cell or microcircuit level, CNN- and RNN-based frameworks have been applied to optical and electrophysiological data to predict phase maps, localize rotors, and decode spatiotemporal electrical activity patterns [207−209]. Deep networks trained on optical-mapping

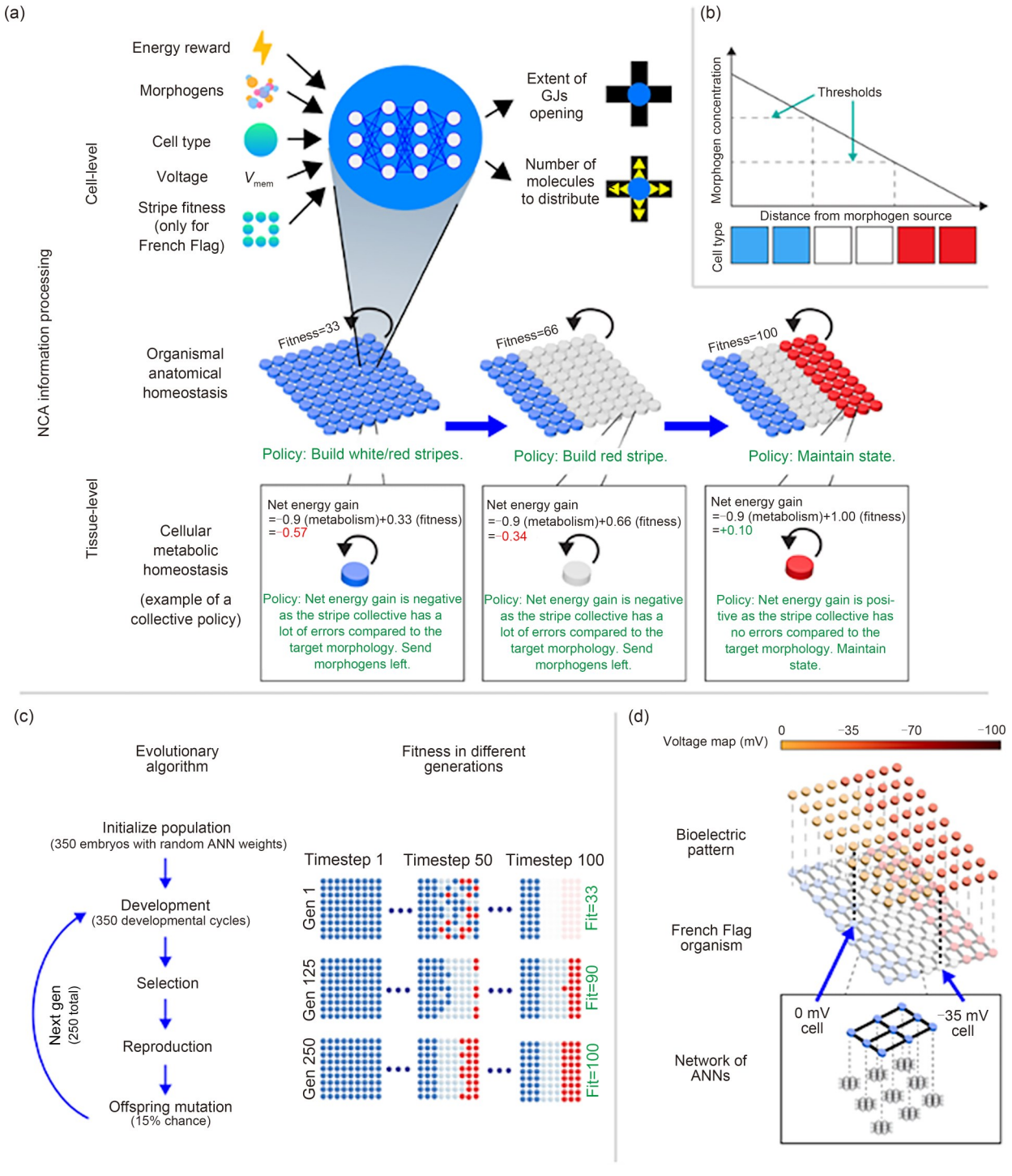


**Fig. 4** Neural cellular automata (NCA) for bioelectric signaling models. The NCA system models tissue and cellular information processing, where cells use artificial neural networks (ANNs) to regulate gap junctions and molecular distributions, and to maintain metabolic homeostasis (a). The French Flag problem illustrates how morphogen gradients guide cell fate (b), while evolutionary cycles optimize organisms' anatomical fitness over generations (c). Cells' bioelectric states map to voltages that interface with their ANNs to coordinate development (d). These models illustrate how machine learning (ML) can predict and regulate cell- and tissue-level behaviors, supporting strategies for biomimetic morphogenesis in developmental tissue engineering (TE). Reproduced from [199], licensed under CC BY-NC-ND

videos (like voltage-sensitive dye data) can directly compute phase maps and detect phase singularities (rotors); i.e., they can learn tissue-scale spatiotemporal electrical dynamics from cardiac imaging data [207]. CNN and RNN architectures applied to electrogram/optical mapping data can identify rotational drivers and mechanistic features, which is

relevant for learning and localizing tissue-scale electrical patterns [210]. Recently, ML-powered signal processing and classification have demonstrated enhanced diagnostic accuracy, therapeutic monitoring, and personalized medicine. We refer the readers to the review from Alfonso et al. [211], which explores how AI has improved the interpretation and application of medical bioelectrical signals such as electroencephalography, electroretinography, electromyography, electrooculography, and electrocardiography.

Building on these multiscale predictive models, ML-driven surrogate frameworks can also be applied in developmental and regenerative contexts, enabling forecasting of how bioengineered constructs evolve in an incubator, including spatial reorganization of membrane potentials, stabilization of collective cell states, and emergence of bioelectric domains that interact with mechanical and biochemical cues. de Carvalho [212] proposed a framework combining DRL and lab automation to manipulate bioelectric signals in real time, using feedback from optogenetics, voltage-sensitive dyes, and advanced imaging to guide tissue regeneration and morphogenesis; accordingly this enables precise bioelectric control, mechanistic insights, and novel applications in regenerative medicine and bioengineering. Such predictive capabilities are crucial for TE, where early knowledge of developmental trajectories enables optimized culture conditions and interventions. Collectively, these approaches demonstrate the capacity of deep learning to extract, interpret, and forecast bioelectrical dynamics across various scales, laying the groundwork for predictive modeling of tissue morphogenesis and bioelectric field evolution.

We must emphasize that bioelectric cues do more than guide cell fate: they shape the mechanical landscape of tissues across numerous mammalian systems. Ionic currents and membrane potentials can modulate cytoskeletal tension, cell−cell adhesion, and ECM remodeling, effectively tuning tissue stiffness and force transmission during morphogenesis [13, 188]. When coupled with biomechanical feedback, these electrical signals create a dynamic interplay that orchestrates tissue self-organization and functional maturation. This universality suggests that insights from one tissue type may be applicable to a diversity of engineered tissues.

Emerging computational and ML models should aim to simulate bioelectric−mechanical crosstalk, in particular predicting how electrical patterns drive morphomechanical behaviors and scaffold remodeling. Integrating electrical signaling with mechanical stress−strain relationships through ML and physics-based simulations allows exploration of how bioelectrical patterns influence tissue morphogenesis [211]. For instance, models can predict the spatial coordination of contractile forces in response to bioelectric gradients, revealing mechanical behaviors that are difficult to capture experimentally.

Such integrated approaches could guide the design of adaptive scaffolds and biofabrication protocols that harness bioelectric–mechanical interplay to optimize structural organization and functional maturation. By embracing these insights, TE constructs can be designed to adapt, self-organize, and evolve towards more predictive and functional tissue architectures.

### 3.4 Predictive models for stem cell fate and tissue self-organization

A critical application of ML in developmental TE is the prediction of stem cell fate and tissue self-organization. Single-cell transcriptomics, proteomics, and imaging can provide high-dimensional datasets describing cellular states, signaling dynamics, and spatial organization. ML models—such as RFs, gradient boosting, and deep neural networks—can map these features to differentiation outcomes, enabling predictions of lineage commitment in heterogeneous cell populations. However, it is important to recognize that these datasets are often noisy, sparse, and subject to platform-specific biases. Variability across sample preparations and experimental conditions can limit model robustness, and models trained on such data may perform well in controlled experiments but fail to generalize to broader biological or clinical contexts [213]. This underscores the urgent need for larger, standardized, and representative training cohorts in order to realize the full potential of ML applications in stem cell biology.

One major route to achieve effective predictions of cell fate is integrating ML with morphological data. Recent progress in ML and image processing has unlocked high-throughput, automated extraction of cellular morphological features. Deep learning models, particularly CNNs, have been applied to rapidly analyze large-scale images of cells undergoing differentiation [109]. For example, by training a CNN on transmitted light microscopy images, Waisman et al. [214] differentiated between pluripotent stem cells and early-stage differentiated cells. Deep learning models that can detect neural stem cell differentiation from brightfield images without the need for labeling have also been developed [215]. Moreover, the automated deep learning system established by Kusumoto et al. [216] identified endothelial cells generated from induced pluripotent stem cells.

The osteogenic CNN is a deep learning model using single-cell laser scanning confocal microscopy images to predict osteogenic differentiation of rat bone marrow mesenchymal stem cells (MSCs) [217]. Importantly, ResNet-18 and ResNet-50 have emerged as popular networks for the classification of stem cell differentiation [214, 218−220]. When compared to three other CNNs (VGG19, InceptionV3, and ResNet-18) in terms of the ability to determine adipogenic and osteogenic differentiation in human MSCs,

the ResNet-50 was found to provide the best performance (area under the curve >0.96). This was because of its design with residual blocks, which helps maintain gradient flow and limits information loss during training, thus keeping it more stable and effective [221]. When CNNs were applied to quantify cell area and edge roughness, the ResNet-50 predicted osteogenic differentiation from early time point data (day-1 images) with high accuracy (96.3%), outperforming conventional experimental biochemical tests. However, to achieve robust model performance, large high-quality imaging datasets are required. Additionally, striking performance metrics may obscure underlying vulnerabilities, such as overfitting or dataset bias, thus highlighting a critical hurdle: without diverse and representative data, ML models risk limited applicability in real-world biological or clinical contexts [213].

By capturing global cellular features, vision transformers represent an alternative ML approach. For example, working on small datasets and correlating morphological and biochemical markers is possible with feature-selection methods like LASSO and ridge regression. Forming links between cellular shape and genetic hallmarks is possible with multimodal GNN-based frameworks, which allow for morphological integration with transcriptomics [222]. Moreover, overfitting on small datasets can be mitigated with GANs [223]. Yet, integrating multimodal multiscale datasets comes with its own challenges: uneven noise, mismatched data scales, and limited standardization in harmonization can all compromise model reliability and obscure biologically meaningful signals [213].

To dissect and model MSC differentiation, researchers have combined ML with non-imaging experimental datasets. For example, integrating ML with single-cell RNA sequencing data enables characterization of MSC heterogeneity, identification of subpopulations, and prediction of osteogenic differentiation through analysis of transcriptomic, epigenetic, and key gene features (e.g., vitamin D receptor (VDR) and ZNF521) [224–227]. Applying ML to proteomics, metabolomics, and spatial-omics further improves prediction accuracy by capturing time-delayed gene–protein interactions, metabolic changes, and microenvironmental cues [228, 229]. Algorithms such as RFs, LightGBM, and GNNs can effectively link such features to differentiation outcomes [109].

Although challenges remain in multi-omics data integration and model interpretability, ML facilitates rapid, high-throughput, and precise modeling of stem and progenitor cell differentiation; as such, it can provide insights into complex tissue-level phenomena such as regeneration and morphogenesis. Overall, combining spatially resolved differentiation data with tissue biomechanics and cell–cell communication information could enhance understanding of collective tissue behaviors, including branching morphogenesis, lumen formation, and organoid self-patterning.

In recent studies, ML algorithms have been applied to analyze and predict the intricate dynamics of such processes [230–232]. For instance, a hybrid physics-based data-driven framework was developed to simulate the morphogenesis of organoids, incorporating cell behaviors and mechanical interactions to predict branching patterns and lumen formation [230]. Additionally, ML models have been used to analyze time-lapse imaging data, enabling the identification of key factors that influence branching and lumen development in organoid cultures [233]. For instance, de Medeiros et al. [234] developed a pipeline that processed long-term live imaging data of organoid development and converted these movies into "digital organoids," which can be used to train ML models to predict lumen emergence and dynamics. While branching morphogenesis has been predominantly modeled using reaction-diffusion or geometry-based frameworks (e.g., Turing models) [235], ML approaches are beginning to reverse-engineer morphogenetic parameter spaces. For example, Halupka et al. [236] presented a deep neural network that detected tree-like branching structures (such as vasculature) and performed instance segmentation of branching topology.

These advancements highlight the potential of ML to elucidate the self-organizing principles underlying tissue morphogenesis, and to inform the design of more effective organoid models for biomedical research. Importantly, while high predictive scores can be appealing, in stem cell differentiation studies, they rarely tell the full story: this is because the paths by which morphological cues or gene expression patterns drive lineage commitment often remain hidden, causing models to struggle to guide hypothesis generation or inform experimental design [237].

Looking towards the future, cell differentiation models could be integrated with graph-based ML approaches to map cell–cell networks and positional cues, while generative models might forecast emergent tissue structures over time [92]. The path forward lies in confronting data inconsistencies, interpretability hurdles, and translational bottlenecks; provided these issues are addressed, ML models may evolve from simple exploratory tools into predictive engines capable of informing TE strategies and clinical interventions.

### 3.5 Machine learning and closed-loop mechanisms for autonomous tissue engineering processes

By combining predictive modeling with closed-loop experimental feedback, ML can inform interventions (chemical, mechanical, or electrical) that steer stem cell populations toward desired tissue architectures; this may enhance the reproducibility of engineered constructs and ensure their functional fidelity. Exemplifying a predictive approach to stem

cell engineering, Klontzas et al. [238] applied ML algorithms to metabolomics data to predict osteogenic differentiation of MSCs in both 2D and 3D cultures. Through this study, they identified key metabolites associated with differentiation and informed culture conditions that promoted desired outcomes. Moreover, an AI-driven quality monitoring system was developed for stem cell cultures, incorporating real-time feedback to optimize differentiation protocols; this enabled adaptive interventions to maintain stem cell populations in their intended differentiation trajectories [239]. Similarly, Hojo et al. [240] merged ML and phase contrast imaging to determine the differentiation efficiency of muscle stem cells derived from induced pluripotent stem cells. By predicting differentiation outcomes up to approximately 50 d in advance, this tool enables early interventions that can optimize differentiation protocols, thereby enhancing reproducibility in human stem cell therapies—even in those using complex and expensive technologies, such as induced pluripotent stem cells.

Cardiomyocytes developed from these cells tend to exhibit immature, fetal-like characteristics, which might be recovered using a specific maturation medium supplemented with lipids. Scheurer et al. [241] addressed this problem by developing an approach for non-invasive assessment of cardiac maturation: they performed dynamic analysis of the contractile cell behavior with an SVM to classify early- and late-stage cardiomyocytes with high accuracy. By identifying various dynamic features (like displacement, relaxation-rise time, and beat duration), AI-driven optical analysis has emerged as a reproducible and pragmatic tool for functional evaluation and drug testing of cells and tissues endowed with specialized contractility, such as muscle cells [242−244]. In addition, real-time data from integrated sensor technologies—such as embedded mechanical sensors—will likely be essential for linking feedback control systems to the biomechanics of in vitro tissue models [245, 246]. Future ML developments in this area are expected to enhance the consistency, reproducibility, and quality of engineered tissues.

A study by Jafari et al. [247] highlighted the potential of merging ML with bioelectronics to achieve closed-loop control of biological systems. By integrating computational models with bioelectronic platforms, ML can serve as a core hub that processes real-time sensor and actuator data to regulate cell behavior, tissue formation, and functional outcomes. Specifically, they proposed an ML-based feedback controller to spatiotemporally regulate biological systems in a precise manner via bioelectronics under the guidance of an adaptive "sense-and-respond" learning algorithm. Because of the controller's learning capabilities and the low computational complexity of radial basis function neural networks, high stability and effectiveness were demonstrated experimentally on a pH-maintenance task performed with bioelectronic proton pumps [248]. ML-controlled bioelectronics enable adaptive interventions to maintain cellular homeostasis through appropriately regulated electronic feedback, influencing tissue development in vitro or enhancing the performance of implantable electronic interfaces in vivo, such as biosensors and biointelligent prosthetics. More broadly, ML can enhance sensor data analysis, biological modeling, and strategies to reconfigure control algorithms "on the fly," which has important implications in precision medicine [249].

Furthermore, ML can significantly contribute to automated, self-regulated biofabrication processes. Zanderigo et al. [250] presented a modular, low-cost platform for real-time monitoring and AI-based analysis in embedded 3D-bioprinting. The system integrates compact sensors with image analysis to detect defects, assess printing quality, and optimize parameters during fabrication. Using 2D in situ imaging, it can reliably estimate 3D filament geometry, capture pressure-dependent variations, and identify velocity limits for stable printing across various bioinks. This accessible and scalable approach enhances the reproducibility and automation of bioprinting workflows.

These examples underscore the potential of combining predictive modeling with closed-loop feedback mechanisms to guide stem cell differentiation processes, bio-integration of medical devices, and biomanufacturing processes. By leveraging real-time data and adaptive interventions, researchers can more effectively steer cell populations towards desired tissue architectures, paving the way for more reliable and functional engineered constructs in regenerative medicine. Expanding such approaches into developmental TE enables the recreation of morphogenetic programs and self-organizing behaviors, fostering the emergence of tissues that more closely mimic their native developmental trajectories and functional complexity. ML-driven adaptive paradigms resemble autonomous physiological control loops (akin to how biological systems maintain stability), and point to future TE platforms where feedback-driven interventions modulate cell fate, mechanical cues, and metabolic states without constant human supervision. Incorporating such closed-loop logic into in vitro organoid cultures, bioreactors, or even implantable interfaces could fundamentally shift how we approach reproducibility and robustness in engineered tissues; the overall goal is to transition from static protocols to continuously learning systems that are aware of their environments.

As ML-driven closed-loop interventions begin to directly influence living tissues and steer cell fate, ethical questions will become unavoidable. Autonomous or semi-autonomous systems blur traditional boundaries of control and responsibility: when an algorithm makes adjustments to cellular environments in real time, who is ultimately accountable for unexpected outcomes? Transparency, patient trust, and

meaningful oversight are at stake, especially when decisions are made by opaque models that act more quickly than human monitoring can follow [251, 252].

Beyond safety, these systems raise concerns about equity and consent: will the associated benefits be broadly accessible, and can patients truly understand interventions mediated by intelligent machines? Moving forward, the development of adaptive TE platforms must be paired with ethical guardrails: frameworks that ensure accountability, maintain transparency, respect patient autonomy, and prevent biases from amplifying existing disparities in biomedical research and clinical translation [237, 251].

## 4 Failure modes, constraints, and future opportunities

Despite substantial recent advances, the integration of ML into biofabrication and TE is constrained by multiple critical challenges; this section serves as a guide for understanding major failure modes, limitations, and areas where focused development is urgently needed to ensure safe, reliable, and biologically meaningful applications.

One primary bottleneck is the limited availability of high-quality, representative datasets. Many ML models trained on small or highly curated experimental data lack robustness and generalizability, often performing poorly when applied to new experimental platforms, fabrication techniques, or biological contexts [114, 253]. Emerging analyses warn that the growing use of synthetic data to compensate for limited biomedical and tissue-engineering datasets may introduce hidden biases and "synthetic trust," thereby undermining the robustness, reproducibility, and real-world applicability of ML models in biofabrication, regenerative medicine, and clinical usage [254].

Data scarcity not only increases the risk of overfitting (where models memorize training idiosyncrasies rather than learning underlying biological principles) but also hampers efforts to capture complex, multiscale phenomena such as scaffold–cell interactions, dynamic tissue remodeling, and morphogenetic processes [45]. These limitations exacerbate failure risks: models may confidently predict implausible outputs or misinterpret critical design parameters, particularly when they are tested beyond their training regimes [1]. Moreover, data scarcity is not a globally uniform issue: it is particularly acute in contexts where access to high-quality biomedical or clinical datasets is limited, such as healthcare AI ecosystems in developing countries [255−257]. This uneven availability of training data risks amplifying disparities in model robustness and predictive performance, potentially reinforcing inequities in healthcare delivery and access.

A second major constraint is model interpretability and mechanistic fidelity. Many ML approaches (notably deep neural networks) act as "black boxes," which means they offer limited insight into why or how predictions are made. Recent work on self-explainable AI for medical image analysis highlights that conventional post-hoc interpretability techniques may not reflect the true internal decision logic of ML models; this therefore underscores the need for mechanisms that can provide explanations aligned with underlying model mechanisms, so as to build trust and reliability in clinical contexts [258].

After applying ML methods and ensuring reproducibility, interpreting and evaluating the results is essential. Visualization techniques such as dimensionality reduction help reveal structure in the data, while benchmarking and quantitative metrics are necessary for rigorous assessment [137]. However, interpretability is not always obvious: some methods trade accuracy for transparency, whereas others argue that human oversight is sufficient and that predictive efficacy is paramount [259, 260]. Nonetheless, interpretable models are generally preferred in clinical contexts, as understanding the basis for a decision can increase adoption rates and trust among medical practitioners.

Notably, several studies have started to address these challenges in biomedical ML, demonstrating that interpretable or explainable frameworks can provide clinically meaningful insights while revealing the true features that drive predictions [261−263]. For instance, Abbas et al. [263] applied explainable ML to beta-thalassemia prediction, showing how model outputs can be linked to interpretable clinical biomarkers. Meanwhile, other studies in multi-omic or infectious disease prediction contexts have illustrated how transparent feature attribution can guide mechanistic hypotheses in biomedical settings.

In areas like mechanobiology, bioelectric signaling, and stem cell fate decisions, this opaqueness complicates scientific validation and undermines trust among domain experts, who must judge whether predictions align with established biological processes [138]. Interpretable ML methods and hybrid physics-informed models hold promise, but they remain underdeveloped in TE contexts, and often require substantial adaptation to the nuances of biological data [138, 264, 265]. Moreover, the dynamic and adaptive nature of biological systems (where temporal feedback and context-dependent behaviors are the norm) poses additional challenges for static or poorly constrained models; this increases the likelihood that ML surrogates miss critical failure modes in development or maturation pathways [266].

A few additional challenges limit the practical application of ML in TE. Generalizability remains a critical concern: models trained on specific datasets or experimental platforms may perform poorly when applied to different labs, tissue types, or patient populations, representing a domain-shift problem that undermines predictive reliability and

translational potential [267]. Highlighting these limitations can help researchers anticipate conditions under which models are more likely to fail, as well as prioritize cross-contextual validation strategies.

Integrating ML with mechanistic or physics-based models is an emerging yet underdeveloped area of ML-driven TE. Purely data-driven approaches may overlook known biophysical or biochemical constraints, limiting the mechanistic fidelity. Hybrid models that incorporate prior knowledge can make more robust predictions and generate outputs that are both accurate and biologically interpretable, but these approaches are often computationally complex and require careful design [268].

Computational cost and scalability also pose practical barriers. High-resolution TE datasets and complex ML architectures demand substantial computational resources, which can limit access to only well-funded laboratories, and hinder the development of real-time applications in adaptive biofabrication systems. Therefore, optimizing model architectures and algorithmic efficiency, or using surrogate and reduced-order models, may help address such limitations.

Significant temporal and dynamic modeling challenges also remain. TE applications often involve interactions that evolve across cells, scaffolds, and microenvironments. Capturing critical transitions, feedback loops, and rare events is difficult for models that are trained on static snapshots. Developing ML methods capable of reliably incorporating temporal and contextual information should therefore be a major emphasis of future research.

Finally, translation barriers, ethical considerations, and regulatory risks constrain the practical application of ML in biomedical and clinical settings [170]. The absence of standardized validation frameworks for ML-assisted biofabrication—along with potential algorithmic bias arising from demographic or procedural data imbalances—raises concerns about fairness, safety, and accountability as these tools move toward patient-centric applications [269]. Without clear guidelines, discrepancies in training datasets (especially those drawn from limited or region-specific sources) may lead to varying performance across populations or biological contexts, thus limiting broad adoption [270]. Furthermore, existing regulatory pathways for conventional medical devices and tissue products are not fully equipped to handle dynamically adaptive ML models, which complicates certification and clinical integration [271].

Robust interdisciplinary collaboration, transparent reporting standards, and dedicated regulatory schemes are therefore essential to mitigate these risks and ensure that ML contributes to reliable, safe, and equitable advances in TE and regenerative medicine [1].

## 5 Conclusions

Artificial intelligence is transforming the study and engineering of living systems by enabling predictive modeling of bioelectric plasticity—the ability of cells to store and reuse the electrical information that shapes tissue organization. By integrating multi-omics, imaging, and real-time biosensing data, ML can map bioelectric states to morphogenetic outcomes, forecast developmental trajectories, and suggest optimal interventions through reinforcement learning and closed-loop control. Hierarchical and physics-informed models can capture processes ranging from ion-channel kinetics to organ-level patterns, revealing how electrical, biochemical, and mechanical cues interact.

Furthermore, generative ML has demonstrated significant promise in revolutionizing scaffold design for TE and regenerative medicine. By leveraging techniques such as GANs, VAEs, and DRL, researchers can create innovative scaffold architectures that meet specific biological and mechanical requirements. However, addressing the challenges associated with such approaches is crucial for translating these computational designs into clinically viable solutions; continued interdisciplinary collaboration and technological advancements will be key to realizing the full potential of generative ML in scaffold design.

Importantly, ML may enable the prediction of biomechanical effects that intersect with scaffold properties and bioelectric signaling, thereby supporting the design of self-organizing, functional tissue constructs. Thus, a promising direction for future research is the development of ML models that simultaneously integrate bioelectric and biomechanical cues, which could enable more comprehensive predictions of tissue morphogenesis and guide the design of functional, self-organizing constructs. In the context of biofabrication, these models might inform post-assembly tissue evolution, guiding adaptive adjustments to culture conditions.

However, data scarcity remains a major challenge for ML-based tissue morphogenesis prediction, as comprehensive multiscale datasets are often difficult to collect. This issue is particularly pronounced for advanced tissue-engineered systems such as multiorgan platforms [272, 273] or biohybrid robots [244, 274], where tissue formation dynamics and functional performance rely on labor-intensive experiments. Emerging tissue-integrated sensors for real-time monitoring [245, 246] and physics-informed in silico simulations offer complementary strategies to generate and augment data for training and testing predictive models [1, 2, 140]. Moreover, future ML prediction of morphogenesis will need to systematically incorporate experimental validations to ensure model accuracy and biological relevance. For example, in bioelectrical applications, this includes comparing predicted membrane potential maps with optical voltage imaging, genetically encoded voltage indicators, or voltage-

sensitive dyes; it may also involve testing ML-predicted effects on morphogenesis through targeted perturbations such as ion channel blocking or optogenetic stimulation. Strategies to efficiently integrate these approaches will be essential for linking computational predictions to measurable tissue outcomes. Establishing closed experimental–computational validation loops should become a central benchmark for future ML-driven TE studies. Finally, looking ahead, ethical and regulatory considerations should accompany emerging approaches in developmental TE, so as to ensure that predictive and manipulative ML-driven strategies are applied responsibly and safely [1].

To translate these advances into real impact in biomedical fields, several priorities stand out. First, systematic experimental validation of ML predictions—especially through rigorous in vivo testing and functional organoid models—remains essential to confirm that computationally optimized designs faithfully emulate biological functions. Second, improving model interpretability and mechanistic transparency is critical if ML tools are to inform scientific reasoning, rather than simply serve as predictive "black boxes." Third, the field urgently needs standardized, shareable, and high-quality datasets that span different materials, cell types, and fabrication platforms; this will enable the development of models that can generalize across varying laboratories and clinical contexts. Addressing these gaps is critical for ML to evolve from a powerful analytical aid into a dependable engine for translational TE.

Overall, ML provides a promising framework for developmental TE, guiding the design of adaptive, self-regulating constructs and offering predictive insights into morphogenesis, mechanobiology, and stem cell fate. By leveraging multiscale, heterogeneous datasets, ML models can simulate and steer the self-organization of tissues. Advances in interpretable ML, multimodal integration, and physics-informed modeling are poised to enhance mechanistic understanding and predictive accuracy, accelerating the development of complex, functional, and reproducible tissue constructs.

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## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Use of generative AI tools** The language of this review was polished and checked for clarity and grammatical correctness with the assistance of AI-based tools (OpenAI ChatGPT; GPT-4, accessed 2025). All scientific content, interpretations, and conclusions are the sole responsibility of the authors.



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