

Design and Prediction of Soft-to-Hard Transitions Using Bioinspired Hierarchical-Gradient Designs and Hybrid Stacking Machine Learning

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Abstract

The fabrication of soft-to-hard transition phases poses significant challenges due to the disparity in mechanical properties across the interface. Among all soft-to-hard natural tissues, the tendon-to-bone interface is particularly complex, exhibiting both hierarchical and gradient structural characteristics. This study aims to design, fabricate, and optimize bioinspired structures that replicate tendon-to-bone interfaces by investigating their fundamental relationships with their natural counterparts. To achieve this, various designs featuring simple and hierarchical architectures with negative Poisson's ratio (NPR) were integrated with simple and gradient positive Poisson's ratio (PPR) structures to mimic the physical properties of enthesis. The results demonstrated that the novel hierarchical-gradient designs enhanced Young's modulus and failure force by up to 58.1%. The finite element method (FEM) was employed to accelerate the prediction

of mechanical properties, and a hybrid stacking machine learning (HSML) model trained on FEM results further improved the prediction accuracy, achieving an error of 2%. The HSML method outperformed traditional approaches like decision trees and convolutional neural networks (CNNs) on small datasets, highlighting its suitability for such applications. Additionally, this study demonstrates that mimicking the energy-absorbing interface between natural soft and hard tissues significantly improves both Young's modulus and failure force in these complex structures.

Keywords: Bioinspiration, Soft-to-hard metamaterials, Machine learning, Hierarchical-gradient structures

1. Introduction

The rapid changes in modern lifestyles, coupled with the challenges of an aging global population, have led to a significant increase in degenerative diseases and a growing demand for organ replacement therapies [1, 2]. However, the repair and substitution of damaged organs remain considerably challenging [3]. This challenge is even more complex at soft-hard tissue interfaces due to the wide range of load-bearing capacities across different tissues. Evolutionary adaptations have improved the load-bearing behavior of these interfaces in natural systems [4, 5].

The enthesis, the transitional zone between soft tendon and stiff bone, plays a crucial role in effectively dissipating stress. To achieve this, nature has evolved a hierarchical structure in this area, characterized by gradients in both physical and mechanical properties [6, 7]. Beyond mechanical differences, physical properties, such as Poisson's ratio, also vary significantly between tendon and bone. For instance, the Poisson's ratio in the tendon region can exhibit negative values, sometimes reaching as low as -3, while in the bone region, it transitions to positive values [8-11]. Replicating this complex transition zone, with its varying physical and mechanical properties, presents a significant engineering challenge. Traditional gradient designs and conventional fabrication methods are often inadequate for accurately mimicking such intricate structures.

Metamaterials, particularly auxetic metamaterials, have gained increasing attention in biomedical applications due to their unique ability to mimic the physical and mechanical properties of natural tissues [12-14]. These negative Poisson's ratio (NPR) structures contract under compressive loads and expand under tensile loads, contributing to their high fracture toughness and energy absorption

capacity [15-17]. However, fabricating such complex structures requires advanced manufacturing techniques. Three-dimensional (3D) printing has emerged as a promising approach, allowing for the precise and intricate construction of these metastructures. This technology also enables the integration of gradient patterning to replicate the hierarchical structures found at tendon-to-bone interfaces. Additionally, 3D printing offers the flexibility to combine NPR and positive Poisson's ratio (PPR) structures within a single design [18-20].

Nonetheless, the adequate fabrication of such structures remains time-consuming and costly, primarily due to the need for iterative refinement informed by comprehensive experimental tests to evaluate their physical and mechanical properties. The finite element method (FEM) is a powerful numerical approach that enables a cost-effective prediction of mechanical properties in scaffolds. Moreover, FEM provides valuable insights into the behavior of entire components within a fabricated scaffold under external loads [21-23]. Despite these advantages, FEM simulations can still be computationally intensive, especially when evaluating multiple design configurations. To address this, machine learning (ML) approaches are emerging as a potent tool for predicting the mechanical properties of 3D-printed structures [24]. Unlike traditional approaches such as standalone artificial neural networks, hybrid machine learning models can offer improved interpretability and competitive accuracy [25]. By integrating hybrid ML with FEM, the design evaluation process can be significantly accelerated, reducing the time required for simulations [26, 27]. In addition to these advantages, machine learning has demonstrated significant potential across a wide range of disciplines. For example, it has been applied in epidemiology for predicting the progression of severe illnesses [28, 29], in civil engineering for estimating mechanical properties of materials [30, 31], and in geotechnical engineering for forecasting friction angles in soils [32].

Previous studies have developed structures with tunable Poisson's ratios, ranging from negative to positive. However, these efforts have faced significant limitations across various applications related to tissue scaffolds, soft actuators, and shape-matching systems [33-35]. A key constraint was the dependence on a single unit cell design, typically the re-entrant geometry, modulated by angle variations to achieve different Poisson's ratios. This approach limits generalizability across broader structural configurations. Furthermore, most existing designs lack bioinspired principles and do not provide a clear rationale for optimizing the interface to enhance mechanical properties

[34, 35]. Moreover, although many researchers have highlighted the exceptional strain behavior observed in soft-to-hard tissue transitions within the human body, such as at the tendon-to-bone interface, previous studies have primarily focused on natural tissue observations without quantitatively analyzing this gradient or designing structures to replicate it [36, 37]. As a result, its critical role in enhancing mechanical performance has been largely overlooked in engineered systems.

The present study aims to address these challenges by designing and evaluating three distinct structures capable of replicating the varying negative and positive Poisson's ratios observed in the natural enthesis. Specifically, three different auxetic structures were developed to cover a wide range of NPRs, mimicking the auxetic behavior of tendon tissue. For the bony part of the enthesis, both gradient and non-gradient honeycomb structures with PPRs were employed, and the Young's moduli of the soft-to-hard structures were predicted using a hybrid ML method. A key innovation of this study is the controlled transition of auxeticity within the tendon region, enabling a smooth shift from the soft NPR to the stiff PPR behaviors. Furthermore, this study aims to pave the way for the fundamental designing of soft-to-hard structures that accurately reproduce the complex behavior of natural tissue interfaces. An overview of the design and evaluation methods of this study is presented in Figure 1 and 2.

The remainder of this manuscript is organized as follows. Section 2 (Research Significance) outlines the current limitations in the field, highlights how the proposed bioinspired design approach advances the state of the art, and discusses the contribution of our findings to improving the understanding of structure–function relationships in engineered systems. In Section 3 (Materials and Methods), we describe the design and fabrication of the structures, along with the procedures for evaluating and predicting their mechanical properties. Section 4 (Results) presents the physical and mechanical characteristics of the unit cells and the full tendon-to-bone-inspired structures, including the predicted mechanical properties and the analysis of local strain behavior. Section 5 (Discussion) provides an in-depth interpretation of the results, emphasizing the biomechanical relevance and broader implications of the findings. Finally, Section 6 concludes the study with a summary of key contributions and future perspectives.

2. Research significance

Despite substantial progress in the design of mechanical metamaterials and biomimetic scaffolds, current approaches still face limitations in replicating the hierarchical-gradient mechanical behavior observed in soft-to-hard tissue transitions, such as the tendon-to-bone interface. Most existing models rely on simplified or repetitive unit cell geometries that fail to capture local strain gradients and interface optimization, limiting their applicability in biomedical contexts [33-35].

The present study addresses these limitations by introducing a bioinspired structural design that integrates tunable mechanical properties across hierarchical levels. Unlike conventional designs, our approach quantitatively considers strain gradient behavior observed in natural tissue transitions and uses machine learning models to predict mechanical responses efficiently. The findings contribute to the field by demonstrating a structure-function relationship that mimics biological systems more closely, offering a foundation for the development of next-generation tissue scaffolds. This advancement enhances the current understanding of how engineered materials can be tailored to achieve biomechanical compatibility and functional integration.

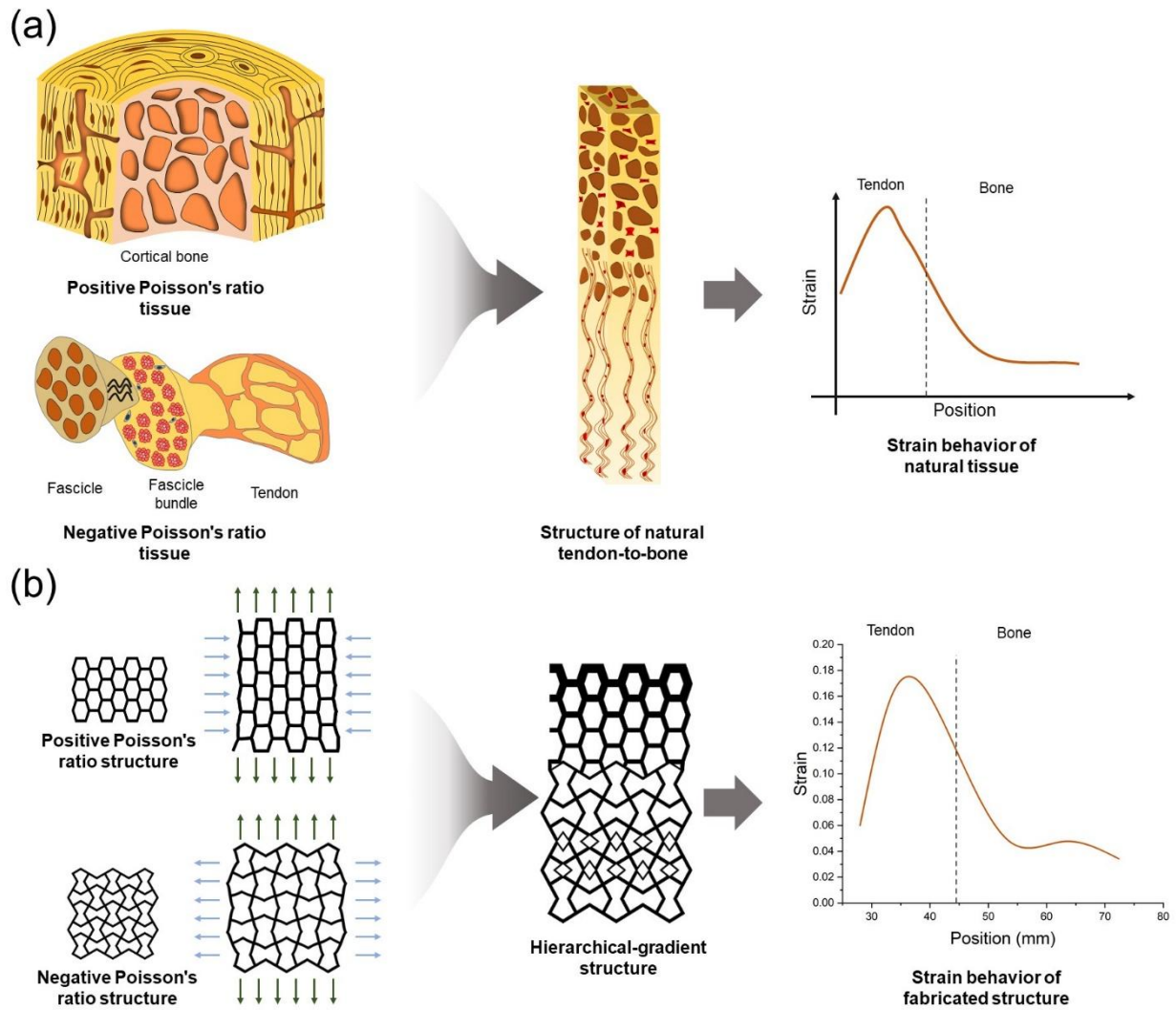


Figure 1. Overview of the (a) bioinspiration and (b) design of tendon-to-bone structures.

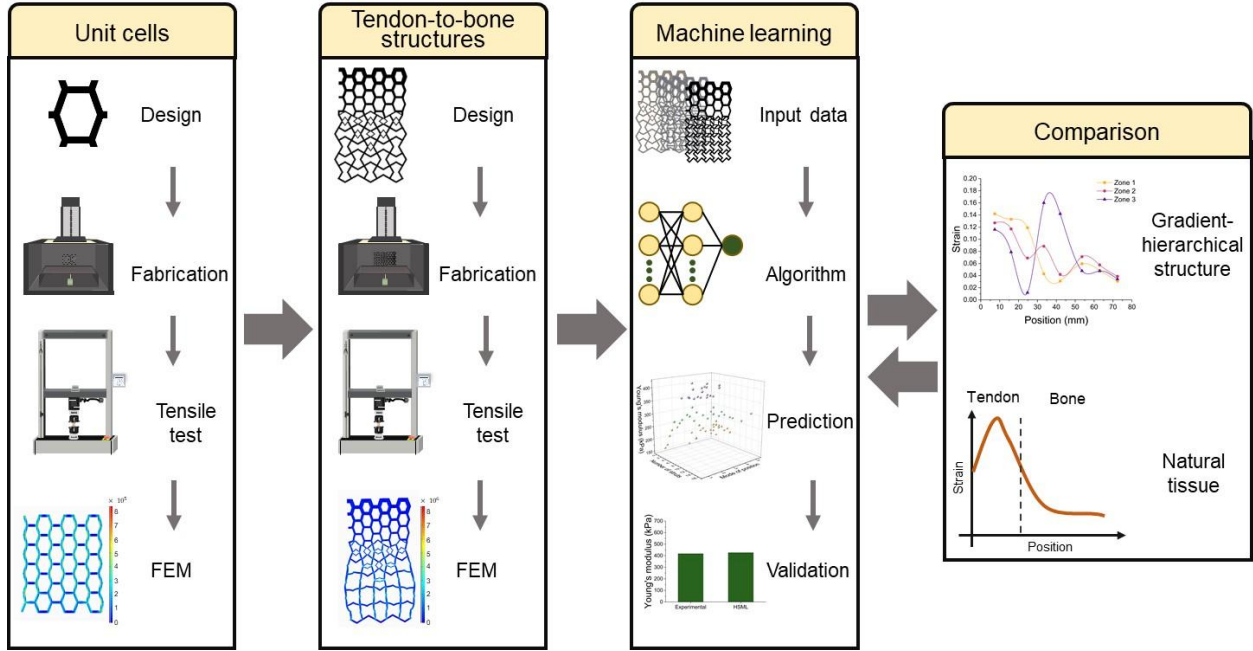


Figure 2. Sequential process of design, fabrication, evaluation, and comparative analysis of unit cells, hierarchical structures, gradient structures, and hierarchical-gradient structures.

3. Materials and methods

Figure 1 illustrates the inspiration behind this study, which aims to replicate the physical and mechanical behavior of natural tendon-to-bone tissues. These tissues exhibit varying physical properties and levels of auxeticity, making it challenging to achieve a smooth transition in mechanical properties that reduces the risk of tearing at the interface. The complexity is further increased by the need to balance different physical characteristics and auxeticity levels. For example, the auxeticity in tendons, such as the Achilles tendon, can reach values as low as -3.81, while the Poisson's ratio in bone ranges from 0.12 to 0.63 [8, 11, 38]. Managing this transition from a highly auxetic tendon to a bone with a positive Poisson's ratio under mechanical loads presents significant challenges. To address these obstacles, this study introduces a novel strategy for controlling auxeticity and mechanical properties, ultimately enhancing the tendon-to-bone interface.

3.1. Design and fabrication of bioinspired scaffolds

The tendon-to-bone structures were fabricated using stereolithography (Form 3L, Formlabs) and elastic resin (Figure 4a). The designs included three base auxetic (NPR) structures: SS, Re, and

M-Rib, which were integrated with both gradient and non-gradient honeycomb (Hc) architectures representing positive Poisson's ratio (PPR) designs (Figure 4a). Details of the unit cell sizes for each design are shown in Figure 3a. The NPR architectures were incorporated into the PPR designs using three distinct approaches. The first design featured gradient PPR architectures, the second employed a hierarchical NPR morphology, and the third combined both techniques to create a comprehensive tendon-to-bone interface design with hierarchical-gradient structures (Figure 4a).

3.2. Assessment of mechanical properties

Tensile properties of both the porous bioinspired structures and bulk dumbbell-shaped samples were investigated using a universal testing machine (UTM; LR5K Plus, LLOYD Instruments) equipped with a 5 kN load cell. The dumbbell-shaped samples were designed in accordance with ASTM D638 standards to facilitate comparison with FEM results. The strain rate was set at 1 mm/min to ensure semi-static loading conditions during the assessments. The tensile tests were conducted until failure to generate complete stress-strain curves for the samples. A mounted camera was used to record video and capture images of the specimens to determine the Poisson's ratio. The calculations for Poisson's ratio followed the procedures outlined in our previous studies [9, 10].

3.3. Finite element simulations

The mechanical properties of the tendon-to-bone scaffolds were studied by FEM software (COMSOL Multiphysics, COMSOL Inc.), specifically utilizing the Solid Mechanics Module. This software required computer-aided design (CAD) models to apply boundary conditions analogous to experimental tests. In the next step, an appropriate meshing strategy with the 3D structural element (tetrahedral) was used to precisely calculate the mechanical properties of scaffolds. This process was repeated for all samples with a mesh sensitivity analysis to calculate the optimum number of elements.

3.4. Machine learning predictions

Predicting mechanical properties using FEM can be time-consuming. To enhance speed and accuracy, machine learning (ML) methods were employed to train and refine FEM predictions. In this study, three different ML models were implemented and evaluated with small datasets (Figure

6b). Details of the datasets used are provided in Tables S1 to S3. First, the decision tree (DT) method was applied. This method involves constructing a model that starts with a parent node and recursively splits into child nodes until further subdivision is impractical [39]. Hyperparameters for the DT model were fine-tuned using GridSearchCV from the Scikit-Learn toolkit in Python. Next, CAD files were converted into images for training using the CNN method. CNNs are highly effective for image recognition tasks due to their ability to reduce the number of parameters and accelerate processing time [40, 41]. However, CNNs are data-intensive and typically require large datasets. In this regard, hybrid machine learning algorithms have been utilized to employ the advantages of both methods [26].

To leverage the strengths of both DT and CNN methods, a hybrid machine learning approach was used. In this ensemble model, the outputs of the DT and CNN base models served as inputs to the HSML model, which optimally combined these results for improved prediction accuracy [42]. All input data—images and physical properties—were appropriately normalized prior to training to ensure consistency and enhance model performance [43]. Overfitting is a common problem in machine learning, where models perform well on training data but fail to generalize to unseen data [44, 45]. To address this issue, several regularization techniques were employed. In the CNN model, dropout layers with a probability of 0.5 [26], and L2 weight regularization were applied. Data augmentation strategies (e.g., rotation, shift, zoom, flip) were also used to increase training variability. Early stopping was implemented to automatically halt training once the validation loss stopped improving, thereby preventing overtraining. For the decision tree model, hyperparameter tuning was performed via 5-fold cross-validation using grid search. All machine learning models were implemented in Python 3.10, incorporating various libraries such as *TensorFlow/Keras*, *Scikit-learn*, *NumPy*, and *Pandas*. Accuracy was evaluated using mean squared errors (MSEs), a20 indexes [46, 47], and R-squared (R^2) metrics, calculated as follows:

$$MSE = \frac{1}{n} \sum_{i=1}^n (y_i - \hat{y}_i)^2 \quad (1)$$

$$\text{a20-index} = \frac{m20}{n} \quad (2)$$

$$R^2 = 1 - \frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{\sum_{i=1}^n (y_i - \bar{y})^2} \quad (3)$$

where n stands for the number of samples in the dataset, y_i and $\hat{y}_i$ are the i th FEM value and the predicted value, respectively. Furthermore, $\bar{y}$ is the mean value of y , which can be calculated by the following formula:

$$\bar{y} = \frac{1}{n} \sum_{i=1}^n y_i \quad (4)$$

Additionally, m_{20} represents the total count of samples where the ratio of the experimental value to the predicted value falls between 0.80 and 1.20, inclusive.

4. Results

Replicating the complex architecture of natural tissues, particularly their gradients in mechanical and structural properties, remains one of the most formidable challenges in tissue engineering. This difficulty is especially pronounced at soft-to-hard interfaces, where abrupt transitions in material behavior demand precise control over both geometry and functionality. To address this, the present study introduces novel bioinspired hierarchical structures that closely mimic the physical and mechanical features of tendon-to-bone interfaces.

4.1. Physical and Mechanical Properties of the Unit Cells

All tendon-to-bone structures were fabricated using stereolithography-based 3D printing. The physical and mechanical properties of each unit cell were evaluated and compared as shown in Figure 3b-c, with their geometric specifications detailed in Figure 3a. As a first step, the honeycomb (Hc) structure was designed, printed, and analyzed through both experimental testing and finite element modeling (FEM). Once validated, additional designs, including sharp sinus (SS), sharp sinus-hierarchical (SSH), re-entrant (Re), re-entrant-hierarchical (ReH), missing-rib (M-Rib), missing-rib-hierarchical (M-RibH), and honeycomb-gradient (HcG), were assessed using FEM simulations. Stress-strain curves, porosity, and Poisson's ratio values were calculated for all structures. The Hc and HcG structures exhibited the highest mechanical stiffness with positive Poisson's ratios, indicating their suitability for mimicking bone tissue. In contrast, the auxetic designs exhibited lower moduli but demonstrated a wide range of auxetic behavior, making them appropriate for tendon analogs.

4.2. Mechanical properties of tendon-to-bone structures

The unit cells shown in Figure 3a were connected in various architectures to represent different structural designs for the tendon-to-bone interface, as described in Figure 4a. Three primary design strategies were explored: (1) a simple auxetic structure combined with a gradient PPR structure, (2) a hierarchical auxetic structure incorporated with a simple PPR structure, and (3) a hierarchical auxetic structure paired with a gradient PPR structure. Among these, controlling auxeticity through hierarchical auxetic designs significantly improved the mechanical performance across all configurations (Figure 4b-d). The combined use of hierarchical auxetic and gradient PPR architectures resulted in notably high mechanical properties. This improvement was most evident in the ReH-HcG structure. The ReH-HcG structure showed the best mechanical performance compared to all the other structures that were tested. Specifically, it had the highest value of Young's modulus (meaning it was the stiffest) and the highest failure force (meaning it could withstand the greatest load before breaking). Based on these results, SSH-HcG, ReH-HcG, and M-RibH-HcG structures, integrating the hierarchical auxetic and gradient PPR structures, were selected for further investigation and numerical optimization.

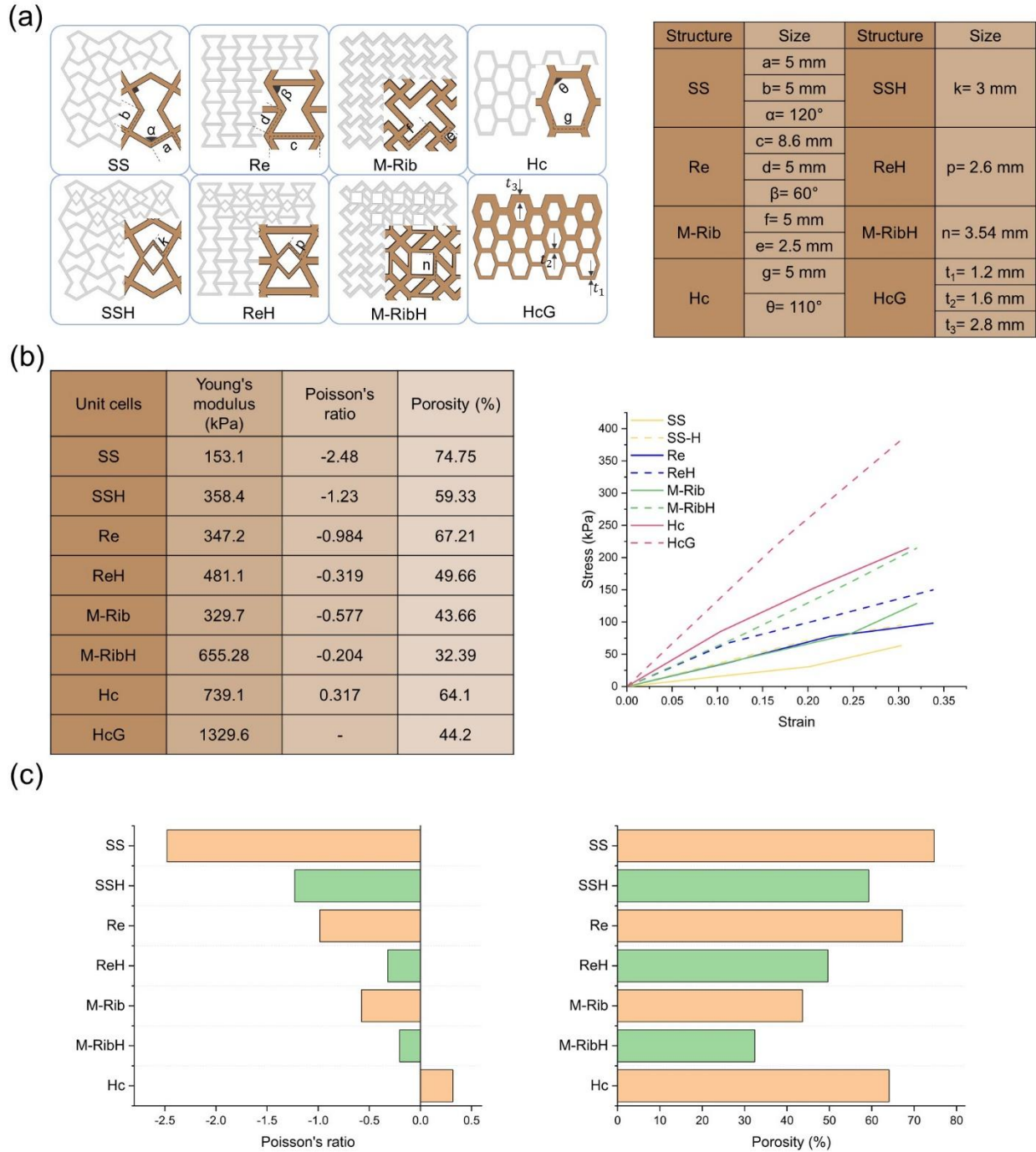


Figure 3. (a) Designs and variables of the NPR and PPR unit cells. (b) Mechanical and physical properties of all structures. (c) Comparison between Poisson's ratio and porosity of various structures. (Abbreviation: SS: sharp sinus, SSH: sharp sinus-hierarchical, Re: re-entrant, ReH: re-entrant-hierarchical, M-Rib: missing-rib, M-RibH: missing-rib-hierarchical, Hc: honeycomb, HcG: honeycomb-gradient)

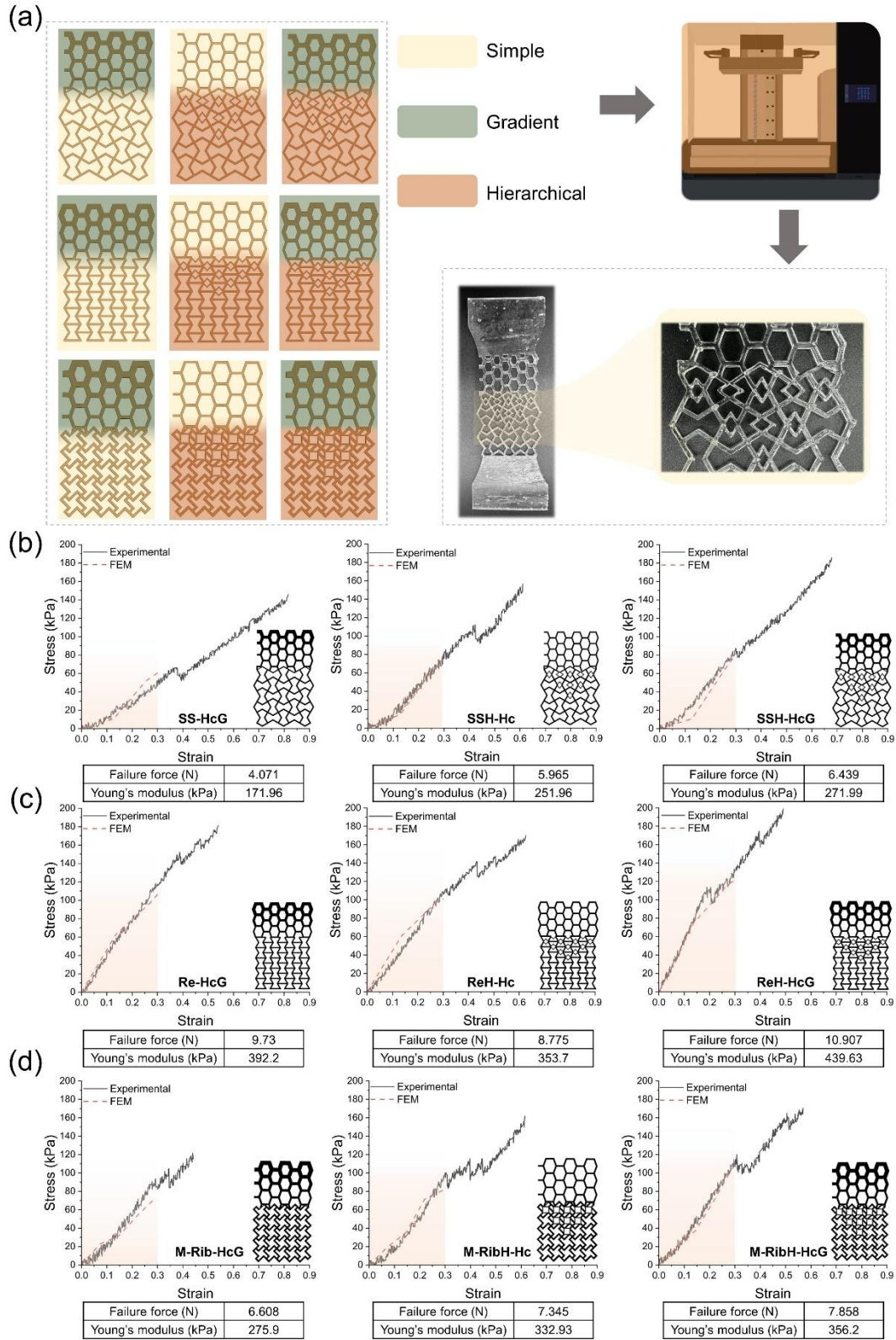


Figure 4. (a) Design and fabrication and (b-d) mechanical properties of different bioinspired tendon-to-bone structures: SS-HcG, SSH-Hc, SSH-HcG, Re-HcG, ReH-Hc, ReH-HcG, M-Rib-HcG, M-RibH-Hc, and M-RibH-HcG.

4.3. FEM predictions

As noted above, hierarchical-gradient structures were chosen for further investigation. To reduce the time and cost associated with extensive experimental trials, FEM simulations were conducted on 48 structural variations generated using CAD software and analyzed in COMSOL Multiphysics. The subunit configurations were systematically adjusted to enhance the Young's modulus of the tendon-to-bone structures, as shown in Figure 5.

Figures 5a-c and Figure S1 illustrate how the mechanical performance of the hierarchical-gradient architectures depends on the position and number of subunits. Among the tested designs, the SSH-HcG, ReH-HcG, and M-RibH-HcG designs showed improvements in Young's modulus of 56.5%, 11.2%, and 54.7%, respectively, compared to the combination of simple auxetic and gradient PPR designs. While porosity, primarily determined by the number of subunits, is generally considered a key factor in influencing the mechanical properties, the results shown in Figure 5a indicated that the position of subunits also plays a critical role. Therefore, porosity alone does not fully account for the observed mechanical behaviors, suggesting that both the number and position of subunits must be considered simultaneously in the design process. These findings indicate that the mechanical properties of the transition area are less dependent on scaffold porosity than initially expected.

4.4. Machine learning investigation

Although FEM aids in design validation, it is not well-suited for the vast number of simulations required to evaluate various design combinations, and it suffers from computational burdens when accurately replicating the boundary conditions of experimental tests. Additionally, meshing procedures and simulation runtimes are resource-intensive, especially when dealing with large datasets. To address these challenges, an appropriate ML strategy can expedite the entire prediction process for new designs.

However, the conventional decision tree (DT) method struggled to accurately predict the mechanical properties of the hierarchical-gradient structures. Meanwhile, despite the data-intensive nature of the convolutional neural network (CNN) method, it exhibited lower predictive accuracy compared to the DT method (Figures 5d and 6b). To enhance predictive performance, a hybrid stacking machine learning (HSML) model was implemented, combining the outputs of both

DT and CNN models. The results shown in Figure 5d demonstrate the HSML model significantly improved the precision of predictions, yielding a lower mean squared error (MSE) and an excellent R^2 value, which reached 0.98. Beyond statistical metrics, the reliability of the HSML model was validated through experimental comparison. A new design was fabricated using the same materials and procedures, and its experimentally measured Young's modulus was compared to HSML predictions. As shown in Figures 6a-c, the prediction errors for the SSH-HcG, ReH-HcG, and M-RibH-HcG structures were 2.19%, 1.91%, and 4.84%, respectively, confirming the high accuracy and reliability of the HSML method across all evaluated structures.

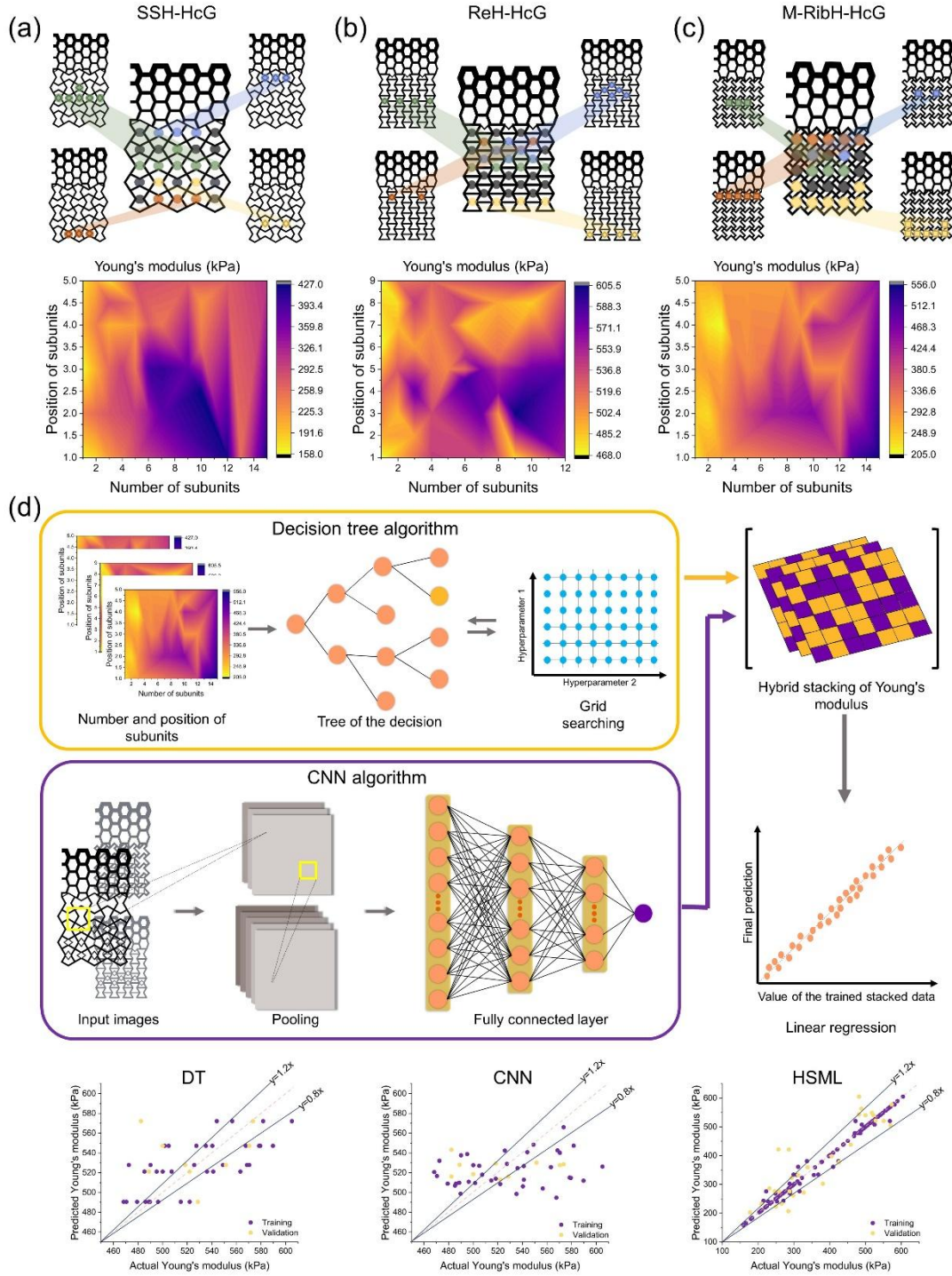


Figure 5. Mechanical properties of hierarchical-gradient datasets based on the (a) SSH-HcG, (b) ReH-HcG, and (c) M-RibH-HcG structures. (d) Machine learning strategy and the prediction accuracy of the CNN, DT, and HSML methods in the prediction of Young's modulus. (Abbreviation: Abbreviation: SSH-HcG: sharp sinus-hierarchical-honeycomb-gradient, ReH-HcG: re-entrant-hierarchical-honeycomb-gradient, M-RibH-HcG: missing-rib-hierarchical-honeycomb-gradient, DT: decision tree, CNN: convolutional neural network, HSML: hybrid stacking machine learning)

4.5. Effects of strain dependency on the mechanical properties and failure

Establishing a clear correlation between mechanical properties and design parameters can be complex. The distribution of Young's modulus (Figure 5a-c) and failure force (Figure S1) reveals a dependency on physical design parameters, but identifying a robust and consistent correlation among these design variables, mechanical properties, and failure behavior remains challenging. In this regard, various combinations of the number and location of added subunits were explored. In the SSH and M-Rib structures, the position of subunits could range from 1 to 5, moving from the tendon area to the bony zone (Figure S2). In the ReH structures, this range extended from 1 to 9 due to the zigzag arrangement across layers. The final location value was selected based on the mode of the set of subunit positions. For instance, if a structure contained two subunits in layer 1 and two in layer 3, the average of the two modes (1 and 3), yielding 2, was used (Figure S2). In this study, strain path analysis was employed to examine why different architectures exhibit varying mechanical properties. Figures 6d-f divide the hierarchical-gradient structures into three groups: low-, medium-, and high-modulus regions. From each group, one representative structure was randomly selected to evaluate the relationship between strain and position. The bony region was highlighted in green to ease the detection of the hard zone in the interface area. The results showed that, in all three structures, the high modulus designs exhibited high strain in the transition area before reaching the bony region. This behavior closely resembles what is observed in natural tendon-to-bone interfaces (Figure 7a) [48]. To confirm these observations, five different structures from each modulus group were examined (Figure S4). The findings consistently supported the conclusion that strain distribution plays a critical role in determining both the mechanical and failure properties of the hierarchical-gradient structures. Due to the significantly similar distribution of failure force (Figure S3) and Young's modulus values, further analysis of failure force was considered redundant in this study.

5. Discussion

This study focuses on a comprehensive design and optimization strategy for three types of tendon-to-bone interface architectures, including hierarchical, gradient, and hierarchical-gradient structures, with potential applications in biomedical engineering. Three distinct auxetic structures, each with unique physical and mechanical properties, were designed, analyzed, and optimized using a combination of experimental testing and numerical simulations. The tendon regions were

inspired by the negative Poisson's ratio and lower mechanical properties of natural tendons, while the bone regions were based on the positive Poisson's ratio and the higher mechanical properties of cortical bone [8, 11, 38]. Moreover, varying porosities and different Young's moduli in the tendon-to-bone area were mimicked using auxetic structures, as well as Hc and HcG structures with higher mechanical properties. FEM was used to predict the Young's modulus of the designed structures, providing essential training data for ML models. Three ML approaches, including DT, CNN, and HSML, were developed to accelerate the prediction process. In addition, a strain-based analysis was conducted to examine the relationship between the bioinspired HSML-predicted mechanical performance and the soft-to-hard structural transitions that mimicked the microarchitectures of human tissues. It is worth noting that the present approach can help overcome the disadvantages of multi-material printing, such as poor interfacial bonding, and reduce fabrication complexity [49, 50].

Three different auxetic structures, each with varying levels of hierarchy, were integrated with either simple or gradient structures. In the bony gradient structure, porosity ranged from 64.0% to 44.2%, which is higher than that of natural cortical bone (less than 30%) to ensure adequate nutrient diffusion within the scaffolds [51, 52]. Additionally, natural tendons exhibit dense structures with low porosity [36, 53], highlighting the importance of auxeticity control through the addition of struts. Therefore, design selection prioritized optimizing structures that achieved the highest Young's modulus and failure force.

Each auxetic structure (Figure 4a) was fabricated in both simple and hierarchical forms, while the bone region was implemented with both simple and gradient structures. In all designs and their combinations, controlling auxeticity and incorporating gradient architecture significantly improved both Young's modulus and failure force. For example, in the SSH-HcG design, controlling auxeticity with subunits increased the Young's modulus and failure force by 58.1% in both properties. This improvement can be attributed to the control of bending and shear deformation in areas with low levels of auxeticity [54]. Moreover, controlling auxeticity and implementing gradient architecture positively affected stress distribution within the porous scaffolds [10].

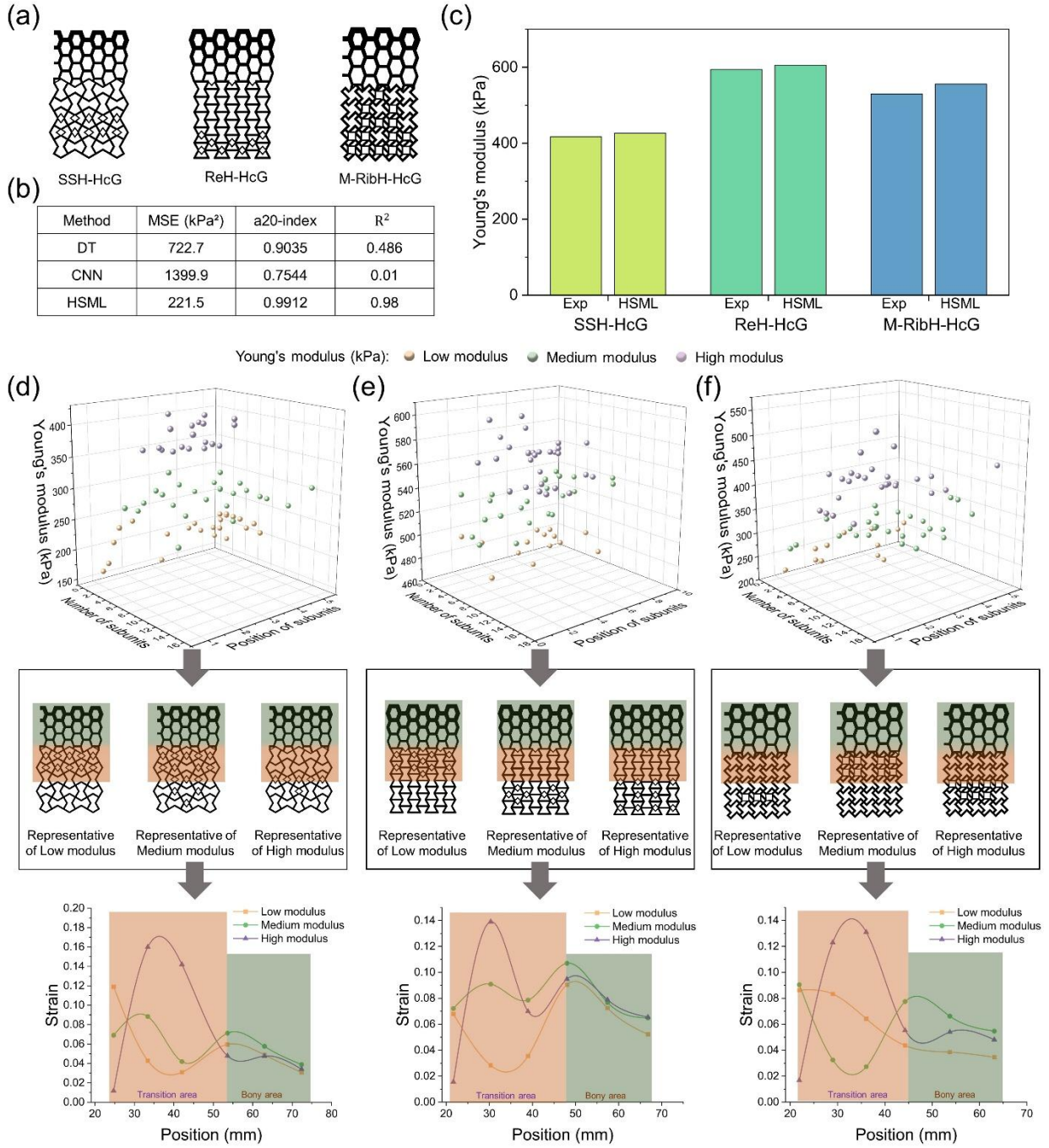


Figure 6. (a) Design and fabrication of the highest mechanical properties of hierarchical-gradient designs. (b) Comparison between DT, CNN, and HSML methods. (c) Calculated mechanical properties with experimental and HSML methods. Prediction of mechanical properties of various hierarchical-gradient structures and their strain behavior under tensile load: (d) SSH-HcG, (e) ReH-HcG, and (f) M-RibH-HcG. (Abbreviation: Exp: experimental and HSML: hybrid stacking machine learning)

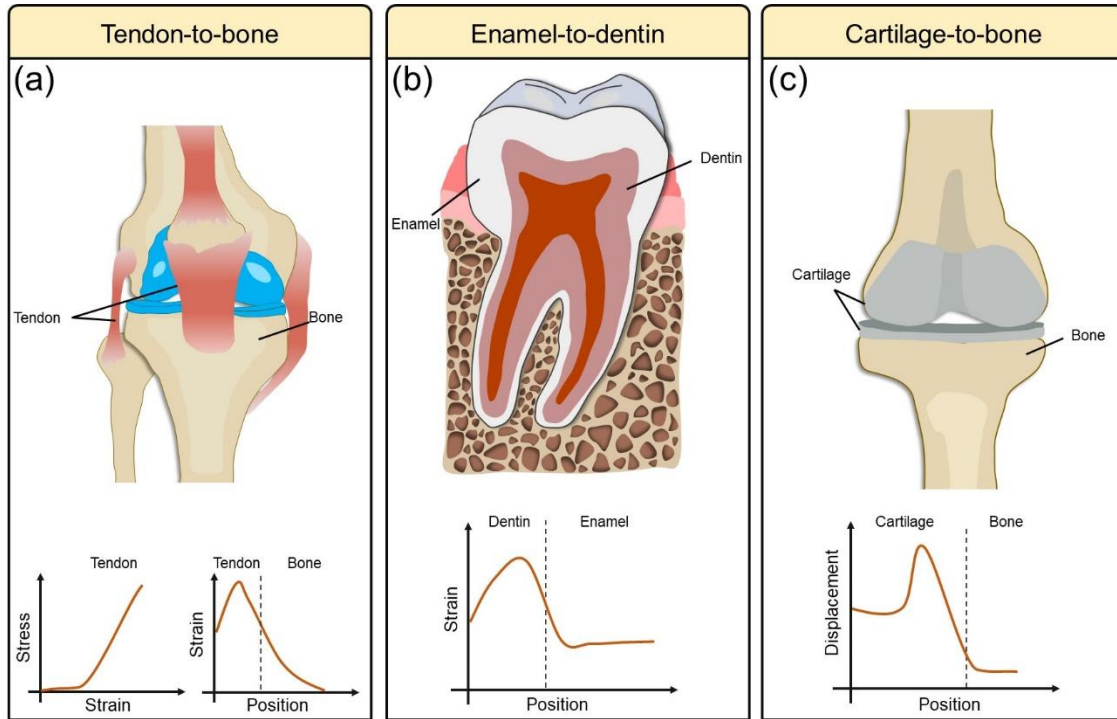


Figure 7. Mechanical properties of natural tissues: (a) tendon and tendon-to-bone, (b) enamel-to-dentin, and (c) cartilage-to-bone properties.

Among the three designs, the ReH-HcG structure demonstrated superior mechanical performance compared to the others, primarily due to its moderate auxeticity. In contrast, the SS structure, characterized by high auxeticity, experienced increased bending moments, which adversely affected its performance. On the other hand, the M-RibH-HcG structure, with its relatively low auxeticity, suffered from buckling issues in the struts, which diminished its mechanical stability and effectiveness [9, 10].

Interestingly, the stress-strain curve of SSH-HcG structures reveals a toe region with low stress up to approximately 2% strain, a behavior that closely resembles that of natural tendon tissue with high NPR characteristics (Figure 7a) [55]. To deeply investigate the mechanical behavior across the hierarchical-gradient phases, both FEM and ML approaches were employed to predict the mechanical properties with high accuracy.

The accuracy of FEM simulations was validated through comparison with experimental tests (Figures 4b-d). The FEM-predicted values were then utilized to train the DT model and, combined with CAD images, input into the CNN model. However, as shown in Figures 5d and 6b, both standalone methods exhibited relatively high error rates in terms of R^2 and MSE. These errors were

significantly reduced using the HSML method, which achieved prediction errors as low as 2% with minimized MSE. These findings demonstrate the superior predictive capability and robustness of the HSML approach in predicting the mechanical properties of complex structures, even with a small dataset [26]. Further confirmation came from comparing the HSML predictions with both experimental and FEM results, showing an error of only 8.2% in predicting Young's modulus of the intricate hierarchical-gradient structures. This validates the stacking approach as a highly effective method for mechanical prediction in small datasets and high-complexity applications [25, 26, 56]. The dataset consisted of 93 samples with two key input parameters (number and position of subunits), systematically designed to span the relevant input space. While the dataset size is modest, the low-dimensional nature of the parameter space allowed for accurate learning of Young's modulus, as confirmed by performance metrics. However, there are several potential limitations in machine learning approaches that should be carefully considered in future studies. For example, ML models can be sensitive to the underlying data distribution, which may result in reduced accuracy when applied to datasets with different characteristics [57]. Additionally, these models often struggle to generalize beyond the scope of the training data, limiting their reliability in unfamiliar or unseen scenarios [58, 59].

Fast and accurate prediction of mechanical properties is crucial for gaining deeper insights into the behavior of tendon-to-bone interfaces. Young's modulus and failure force are closely related to factors such as the number of subunits, auxeticity control, and their spatial positioning. However, these relationships are often non-linear, and in some cases, higher mechanical performance can be achieved despite increased porosity (Figure 6). Previous studies have shown that strain distribution in natural tendon-to-bone tissues offers valuable insights into this complex transition region [48]. In natural enthesis, a high-strain, energy-absorbing zone has been observed, which aligns with the strain behavior found in high-modulus designs developed in this study [48]. Similar energy-absorbing regions with compliant behavior have also been reported at other interface regions, such as enamel-to-tendon and cartilage-to-bone interfaces (Figure 7b and 7c) [36, 37]. These results suggest that the bioinspired hierarchical-gradient design strategy introduced here holds significant promise for fabricating functional soft-to-hard materials, with potential applications extending beyond orthopedic interfaces to a broad range of bioengineered tissues.

6. Conclusion

In summary, three novel tendon-to-bone structures were successfully designed, fabricated, and optimized using a combination of experimental and numerical methods. All 3D-printed structures were thoroughly examined using comprehensive mechanical testing and FEM, providing the basis for their integration into machine learning models. Both experimental and FEM results demonstrated that hierarchical-gradient designs consistently outperformed other configurations, with improvements of up to 58.1% in Young's modulus and failure force. Additionally, the hybrid stacking machine learning method significantly reduced prediction errors to approximately 2%, outperforming conventional decision tree and convolutional neural network models, which exhibited higher errors. Importantly, the modular nature of the proposed designs allows for flexibility in substituting various negative and positive Poisson's ratio structures with adjustable levels of hierarchy and gradient. Furthermore, the observed relationship between strain distribution and structural positioning revealed the presence of an energy-absorbing zone within the transition region—a biomimetic feature that mirrors natural tissue interfaces such as the enamel–dentin and cartilage–bone junctions. These findings underscore the potential of the hierarchical-gradient design strategy for broad biomedical applications involving soft-to-hard tissue integration.

Ethics statement

Ethical approval was not required for this study, as it did not involve human participants, human data, or animal subjects. The datasets used in this study were generated by the authors through in-house experiments and do not contain any personally identifiable information or elements requiring ethical clearance.

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