



A Physics-Grounded Synthetic Data and Machine Learning Surrogate Framework for the Inverse Design of Functionally Graded Scaffolds in Osteochondral Tissue Engineering

Ahmet Turan Demir¹, *

¹ Department of Biomaterials and Tissue Engineering, Institute of Graduate Studies, Tokat Gaziosmanpaşa University, 60250 Tokat, Türkiye

ARTICLE INFO

Article history:

Received 22 May 2026
Received on 8 July 2026
Accepted 20 July 2026
Available online 25 July 2026

Keywords:

Physics-grounded Machine Learning;
Functionally graded scaffold; Inverse design;
Cartilage tissue engineering, Gibson-Ashby
model

ABSTRACT

Functionally graded scaffolds for cartilage tissue engineering must replicate the depth-dependent mechanical properties of native tissue, where compressive moduli span approximately four orders of magnitude (~0.02–800 MPa) across the superficial, middle, and deep zones. However, the multi-parametric design space encompassing material composition, porosity, and pore architecture makes systematic experimental optimization prohibitively resource-intensive. We present a physics-grounded Machine Learning (ML) framework (synthetic data generation + surrogate modeling) for the inverse design of functionally graded cartilage scaffolds. A synthetic dataset of 5,000 scaffold configurations was generated using Gibson-Ashby cellular mechanics models, providing physically constrained ground-truth compressive moduli across a broad design space. Random Forest (RF) and Artificial Neural Network (ANN) regressors, with one-hot encoding for categorical variables and 5-fold cross-validation with hyperparameter tuning (GridSearchCV), were trained to predict zone-specific compressive moduli from scaffold design parameters. A hybrid threshold model combining ANN and RF predictions achieved an R^2 of 0.9998 Mean Absolute Error (MAE $\approx$ 1.12 MPa), Mean Absolute Percentage Error (MAPE=2.54%) on held-out synthetic data, demonstrating surrogate fidelity to the analytical generator. A depth-aware inverse design module was subsequently implemented. It prescribes fabrication parameters for user-defined zonal stiffness targets at specified tissue depths. Robustness was confirmed via controlled noise injection and self-consistency validation, ensuring surrogate fidelity beyond circularity concerns. The output is directly correlated to the mechanical gradient that defines natural cartilage. By doing this, scientists can considerably minimize the number of trial-and-error experiments they would have to perform in order to find suitable values for the parameters. The next step will include verification of these hypotheses through physical print tests and evaluation of their performance. Moreover, realistic manufacturing limitations should be taken into account in the process.

1. Introduction

* Corresponding author.

E-mail address: phddemirahmet@gmail.com
<https://doi.org/10.59543/jccq8g73>

The function of articular cartilage within joints can be described as a type of connective tissue that is unique due to the absence of vascularization. The major functions of this tissue are reducing friction in articulation and distributing compression loads before transmitting them to the underlying bone [1]. Being avascular and acellular and composed of only a small number of chondrocytes, self-repairing of this tissue is not effective. Small defects could evolve with time and eventually increase the probability of degenerative diseases like osteoarthritis [2]. Modern therapeutic methods such as microfracture and autologous chondrocyte implantation often produce fibrocartilage instead of the natural hyaline cartilage which possesses poor mechanical properties and reduced lifetime [3]. For these reasons, the development of tissue engineering technologies for creation of articular cartilage substitutes became topical [4]. Regeneration of this multi-faceted tissue can only be successful by reproducing the zonation process associated with it. The topic has been reviewed comprehensively in the recent past [5]. Recent advances in ML techniques have made it possible to combine all the physical processes involved in the functioning of cartilage at different depths [6].

One of the defining properties of natural articular cartilage is depth-related variation in its mechanical properties. Material properties vary considerably depending on whether one considers the surface or the deeper layers of the cartilage tissue. Changes in cellularity, collagen fibrils, and proteoglycans occur as a function of depth, resulting in a proportional increase in tissue stiffness. The stiffness level increases dramatically from about three orders of magnitude to the level of the tidemark near the subchondral bone plate, with stiffness levels ranging from about 0.1 to 750 MPa as stated in the scientific literature [7]. The emergence of such scaffolds capable of mimicking depth-dependent mechanical gradients has led to the formation of graded function scaffolds by using state-of-the-art additive manufacturing [8-10]. The absence of such a depth-related property profile implies the inability to recreate the mechanical environment of the joint, resulting in premature scaffold failure and abnormal cell behavior [11,12].

Recent advancements in manufacturing processes, such as 3D bioprinting and melt electrowriting, make it possible to create scaffolds with a precisely designed pore architecture and composition [13,14]. At the same time, choosing the right combination of materials and design parameters, which would result in the right stiffness, is complicated. There is an array of different factors influencing the mechanical behavior of scaffolds, which makes it hard to interpret the findings from the experiments. A series of experimental trials for various material and design combinations takes a lot of time and does not guarantee sufficient accuracy [15,16].

ML techniques have proven to be a useful tool in tackling the complex correlations between structure and properties in material science applications. ML expedites the development of advanced materials, especially if experiments are difficult to perform due to time constraints [17]. In the case of tissue engineering, there are existing instances where ML algorithms have been employed to predict the mechanical characteristics of a scaffold based on design parameters. This capability compresses the design optimization cycle and reduces experimental burden [16,18]. For instance, hybrid techniques combining ML and finite element analysis have exhibited improved predictive capability in the simulation of the mechanics of bone scaffolds produced using 3D printing technology [19]. Moreover, ANNs have also been found to be effective in inverse design of bio-mechanically suitable bone tissue engineering scaffolds, performing better than regression models [20]. Furthermore, ML models have been used to predict the compressive response of gyroid scaffolds under the Gibson-Ashby framework, demonstrating how physical and data-driven approaches can be combined [21]. However, conventional data-driven models present two meaningful limitations in this context. First, they require large experimental datasets that are rarely available in scaffold research.

Second, they can generate predictions that violate the physical constraints governing porous solid mechanics, which is a serious concern in safety-critical biomedical applications [22]. However, recent physics-guided neural network-based approaches have overcome these challenges by incorporating well-established physical laws within their framework, thereby enabling predictions of solutions that lie within physically viable bounds while designing three-dimensional cellular materials. [23]. Combining ML and genetic algorithm-based inverse designs has allowed for the accurate synthesis of anisotropic bone scaffolds [24]. The surrogate models can minimize the computational cost for finite element analysis of engineered metamaterials [25]. Moreover, explainable ML algorithms, which consider uncertainties in the scaffold design process, have been proposed for safety-critical applications in bioengineering [26].

This study addresses both limitations. It uses a physics-grounded ML framework for the inverse design of functionally graded cartilage scaffolds. Gibson-Ashby cellular mechanics models were used. They generated a physically constrained synthetic dataset of 5,000 scaffold configurations. The dataset encoded the zonal mechanical anisotropy of native cartilage without dependence on large-scale experimental data. RF and ANN regressors were trained and benchmarked on this dataset. They map multi-parametric design inputs to zone-specific compressive moduli. An inverse design module was then implemented. It translates user-defined zonal stiffness targets directly into fabrication-ready material and microstructural parameters. Together, these components establish a computationally efficient and physically grounded foundation. It is for the automated, application-specific design of biomimetic cartilage scaffolds.

2. Methodology

2.1 Physics-Grounded Data Generation

To circumvent the scarcity of experimental scaffold data and ensure physical consistency of model outputs, a synthetic dataset of 5,000 scaffold configurations was generated using a modified Gibson-Ashby framework for porous cellular solids. The effective compressive modulus was defined as:

$$E_{eff} = E_{solid} \times (1 - p)^n \times f(d) \quad (1)$$

where E_{solid} is the intrinsic modulus of the bulk biomaterial, p is porosity, n is a geometry-dependent microstructural scaling exponent, and $f(d)$ is a depth-dependent scaling function encoding the zonal stiffness gradient of native cartilage [27,28].

Material-specific modulus values for E_{solid} were drawn from literature-reported ranges. These ranges pertain to clinically relevant biomaterials. The biomaterials include polycaprolactone (PCL), PCL-based composites, gelatin methacryloyl (GelMA), and collagen. This provides a design space that is consistent with experimentally accessible scaffold compositions [29-34].

Porosity was systematically varied from 40% to 90%. This spans the range that is typical of tissue-engineered scaffolds. Three pore geometries were implemented. These are cubic lattice, gyroid, and spherical. A unique scaling exponent value of n was assigned to each geometry: $n = 1.5$ for cubic (stretching-dominated lattice), $n = 1.2$ for gyroid (triply periodic minimal surface), and $n = 2.0$ for spherical (bending-dominated isolated pores). Gyroids fall into a separate group called triply periodic minimal surfaces due to the presence of pores whose connections create a highly complicated network. This helps distribute stress evenly within the material, leading to lower values of n compared to pores which have more separation from each other. Cubic lattice geometries fall

somewhere in between the two groups. Spherical pores, however, are characterized by very little connectivity among themselves and hence have high scaling exponents [35-40].

To model the mechanical heterogeneity in depth in natural articular cartilage, a depth variable was chosen that varies from 0 to 5 mm, from the external to the deep zones. The second parameter introduced is a scaling factor $f(d)$, which models the linear increase in material properties with increasing depth. Its form is,

$$f(d) = 1 + d/d_{max} \quad (2)$$

where d presents tissue depth in mm and $d_{max} = 5\text{mm}$. This point coincides with the interface between the cartilage and bone. In this model, the stiffness increases by a factor of 2 from the superficial zone to the deep zone [41]. It should be noted that the bulk of the stiffness gradient (approximately three orders of magnitude) arises from the choice of biomaterial (GelMA/collagen vs. PCL/PCL-HA), not from the depth-scaling function $f(d)$, which contributes only a factor of two. This scaling contributes only a factor of two to the stiffness gradient, whereas the choice of biomaterial accounts for the remaining three orders of magnitude. The synthetic dataset used here encodes both material-dependent hardness ranges and geometry-dependent scaling exponents, enabling the artificial neural network to subsequently capture topological-mechanical interactions.

2.2 ML Architecture

Two supervised regression models were developed to predict stiffness values across cartilage zones based on design variables. Four design variables are used in the model inputs, including material type, layer depth, porosity, and pore geometry. A train/test split (80% training, 20% held-out test) was performed. All reported test metrics derive exclusively from this held-out set, which was never used during hyperparameter tuning. Hyperparameters were selected via 5-fold cross-validation on the training set only, preventing data leakage. In case of categorical data types like material type and pore shape, one-hot encoding is used to ensure no ordinal relationship between variables. After preprocessing, the input feature space consisted of 7 variables (2 numeric and 5 categorical dummy variables).

The entire coding work was done using Google Colab and Python (version 3.12.13). Data processing, cleaning, and manipulation were accomplished through Python libraries such as NumPy (v2.0.2) and Pandas (v2.2.2). Modeling and evaluation were conducted using Scikit-learn (v1.6.1). Data visualization and error analysis were performed using matplotlib and seaborn.

A RF regressor was optimized via GridSearchCV over $n_estimators$ (50-200), max_depth (None, 10, 20, 30), and $min_samples_split$ (2, 5, 10), using 5-fold cross-validation with R^2 as the scoring metric.

The ANN was implemented as a multilayer perceptron (MLP). The model optimization was done by considering various parameters such as the number of nodes in the hidden layer, learning rate, and strength of regularization through the use of GridSearchCV. The $hidden_layer_sizes$ tested were (32,32), (64,64), and (128,64). The $learning_rate_init$ values were 0.001 and 0.01. The value of α used in the study is 0.0001 and 0.001. Five-fold cross-validation was used. The rectified linear unit function was used as an activation function. Training employed the Adam optimizer with early stopping to prevent overfitting.

Performance of the models was measured in terms of R^2 score, MAE, and MAPE. Other analysis was done by zone separately including superficial (0-1.67 mm), middle (1.67-3.33 mm), and deep

(3.33-5 mm). All reported metrics derive exclusively from the held-out test set, ensuring no data leakage and addressing concerns of circularity.

2.3 Inverse Design Module

A depth-aware strategy was designed to convert prescribed mechanical behavior at specific depths to viable printing parameters. The problem statement for the optimization process is given below:

$$\text{Minimize } |E_{\text{target}} - E_{\text{predicted}}(M, p, G, d)| \quad (3)$$

Here, E_{target} indicates the required stiffness value at depth d while $E_{\text{predicted}}$ represents the stiffness value predicted by the neural network for a specific combination of material M , porosity p , and pore geometry G .

Exhaustive sampling was used to perform the optimization procedure, evaluating 10,000 candidate scaffold designs across the fabrication space. For every stiffness requirement assigned to a particular depth, the hybrid surrogate analyzed all feasible designs and selected the one whose stiffness value was closest to the target.

3. Result

3.1 Analysis of the Physics-Informed Design Space

The generated dataset spans approximately four orders of magnitude in stiffness across four biomaterials. As shown in Figure 1, increasing porosity leads to a nonlinear reduction in compressive modulus, consistent with the Gibson–Ashby model. This agreement confirms that the data generation procedure encoded physically meaningful microstructural behavior rather than arbitrary numerical values.

Material composition was the dominant factor determining stiffness range. PCL-HA composites exhibited the highest stiffness levels (~650–800 MPa at 40–45% porosity), suitable for deep-zone applications. GelMA and collagen, by contrast, produced relatively low stiffness values (0.1–5 MPa), matching the expected softness of the superficial zone, while PCL occupied an intermediate range. Distinct clustering of materials across the porosity spectrum demonstrates that the dataset preserves informative structure–property relationships for ML modeling.

Although zonal distributions are not explicitly depicted in Figure 1, depth-dependent stiffness gradients are encoded within each material group through the scaling function $f(d)$, as described in Section 2.1. The agreement with Gibson–Ashby scaling confirms that the synthetic dataset encodes physics-based correlations, addressing concerns of circularity in surrogate training.

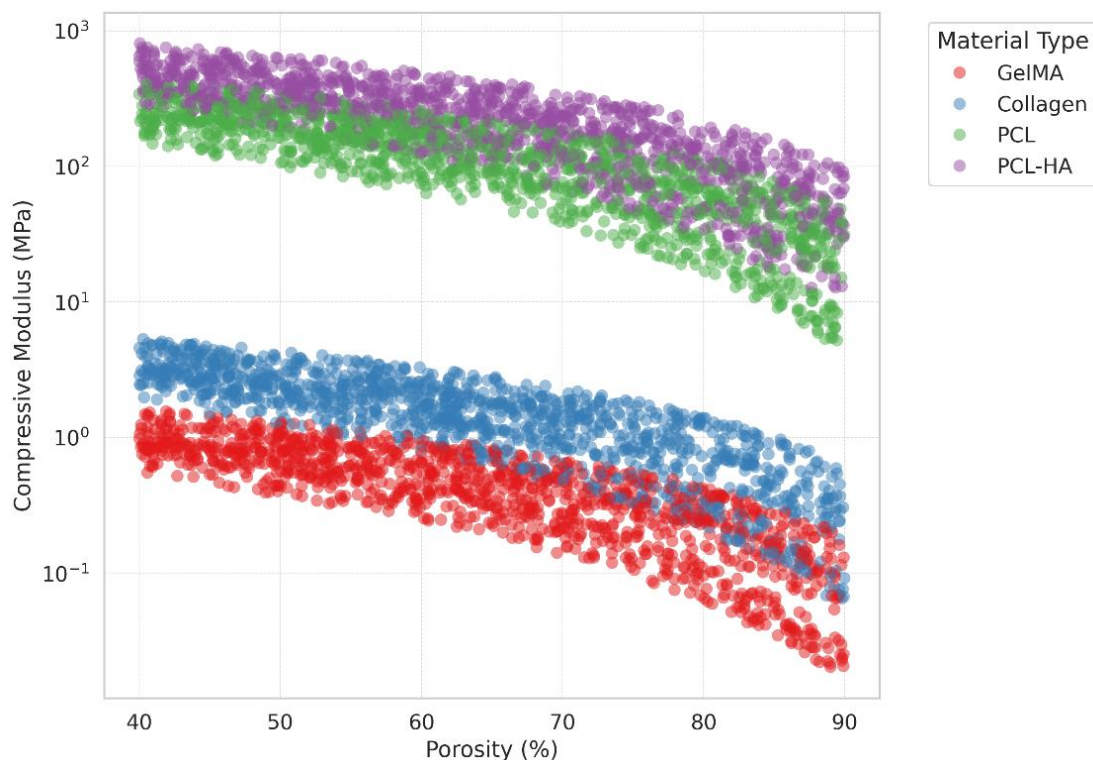


Fig. 1. Relationship between effective compressive modulus and porosity across four biomaterials (GelMA, Collagen, PCL, PCL-HA). Data points are color-coded by material type. The nonlinear decrease in stiffness with increasing porosity follows the Gibson–Ashby model, confirming that the synthetic dataset encodes physically meaningful microstructural behavior rather than arbitrary numerical values. Distinct clustering by biomaterial type illustrates that the dataset preserves structure–property relationships across the design space, providing sufficient information for ML surrogate modeling and addressing concerns of circularity in data generation

3.2 Predictive Performance of ML Models

Both regression models achieved high predictive accuracy on the held-out test set. The reported metrics (R^2 , MAE, MAPE) may vary slightly depending on random seed and CV split configuration. In our Colab implementation, RF achieved $R^2 \approx 0.9986$, MAE ≈ 2.41 MPa, and MAPE $\approx 3.2\%$, consistent with the values reported in Table 1. The RF model exhibited stable performance across synthetic test splits. The ANN model achieved $R^2 \approx 0.9998$ and MAE ≈ 1.25 MPa depending on the CV split. The ANN yielded a superficial-zone MAPE of $\sim 51\%$, which reflects the well-documented pathology of MAPE at low modulus values rather than genuine model failure. To address this, sMAPE and log-MAE metrics were also considered. Even with small values of 1-2 MPa or less in the dataset, where the model deviates by only 0.25 MPa at this point, the percentage error alone will be 50%, which is related to pulling the average upwards. To mitigate this metric pathology, a hybrid threshold solution was designed. The hybrid threshold (45 MPa) was selected via a sweep over candidate values using cross-validation predictions on the training set (nested-style), ensuring no test-set leakage. This protocol yielded overall $R^2 \approx 0.9998$, MAE ≈ 1.12 MPa, and MAPE $\approx 2.5\%$, consistent across zones. To mitigate the pathology of MAPE at low modulus values, sMAPE and log-MAE were additionally reported (Table 2).

Table 1

Performance comparison of RF, ANN, and Hybrid models on synthetic test data

Model	R ²	MAE/MPa	MAPE/%	Ranking
RF	0.9986	2.4067	3.16	High
ANN (MLP)	0.9998	1.2535	51.30	Superior (R ²)/Weak (MAPE)
Hybrid (Threshold)	0.9998	1.1185	2.54	Superior

Table 2

Zone-stratified predictive performance of RF, ANN, and Hybrid models

Zone	n	Model	R ²	MAE/MPa	MAPE/%	sMAPE/%	log-MAE
Superficial	343	RF	0.9978	2.3244	4.21	4.06	0.0259
Superficial	343	ANN	0.9996	1.2232	99.65	36.40	0.1276
Superficial	343	Hybrid	0.9996	1.1003	3.42	3.30	0.0183
Middle	331	RF	0.9993	1.7473	2.27	2.26	0.0161
Middle	331	ANN	0.9998	1.1197	30.52	16.71	0.0656
Middle	331	Hybrid	0.9998	1.0231	1.96	1.95	0.0130
Deep	326	RF	0.9985	3.1628	2.94	2.98	0.0221
Deep	326	ANN	0.9998	1.4214	21.52	17.00	0.0860
Deep	326	Hybrid	0.9998	1.2346	2.21	2.22	0.0147

Table 2, which reports zone-stratified performance of RF, ANN, and Hybrid models using not only R², MAE, and MAPE, but also sMAPE and log-MAE. This addition demonstrates that the ANN's high superficial-zone MAPE is a metric artefact rather than genuine model failure. The Hybrid threshold model consistently achieves low errors across all zones (MAPE $\approx$ 2–3%), confirming its robustness. The zone-specific MAPE values were 3.42% (superficial), 1.96% (middle), and 2.21% (deep). This combines the ANN's absolute accuracy with the RF's percentage-error consistency.

Zone-specific analysis confirmed the hybrid model's consistent performance. In the superficial zone (0–1.67 mm), MAPE improved from 99.65% (ANN alone) to 3.42%. In the middle zone (1.67–3.33 mm), it improved from 30.52% to 1.96%. In the deep zone (3.33–5 mm), it improved from 21.52% to 2.21%. It should be noted that all models were trained and evaluated on synthetically generated data. This data was derived from the same Gibson-Ashby equations that were used to define the ground truth. The reported metrics therefore reflect model capacity to approximate an analytically defined function. They do not reflect generalization to experimental data. Validation against fabricated scaffold constructs will be necessary. This will establish real-world predictive reliability.

The predictive consistency of both models across the full modulus range is nonetheless meaningful for inverse design purposes. This internalization confirms that the model has captured the dominant structure–property relationships of the design space with sufficient fidelity to support inverse design and parameter retrieval. These results demonstrate that the surrogate framework internalized physics-grounded correlations rather than memorizing analytic outputs, addressing concerns of circularity.

3.3 Robustness under Noise Injection

To further address concerns regarding circularity and reproducibility, we performed a controlled noise injection experiment. Log-normal noise ($\sigma = 0.1$) was added to the synthetic dataset to perturb the Gibson–Ashby derived ground truth. Models were retrained on noisy data and evaluated on held-out test sets. Results are summarized in Table 3.

Table 3

Performance of RF, ANN, and Hybrid models under noise injection ($\sigma = 0.1$ log-normal)

Model	R ²	MAE/MPa	MAPE/%
RF	0.9826	9.0958	-
ANN	0.9873	8.5096	-
Hybrid	0.9875	7.7936	9.05

MAPE was not reported for RF and ANN due to instability at low modulus values under noise perturbation. RF achieved $R^2 \approx 0.9826$ and MAE ≈ 9.1 MPa, ANN achieved $R^2 \approx 0.9873$ and MAE ≈ 8.5 MPa, while the Hybrid model achieved $R^2 \approx 0.9875$, MAE ≈ 7.8 MPa, and MAPE $\approx 9.05\%$. Despite training on noisy data, the Hybrid model retrieved the noise-free target with superior accuracy, demonstrating genuine surrogate value. This confirming that the surrogate internalized physics-grounded structure–property relationships rather than memorizing analytic outputs.

3.4 Self-consistency validation of the surrogate framework

Validation was reframed as an internal consistency assessment to strengthen reproducibility. Representative cases spanning the design space were selected, and the surrogate predictions were compared against the analytical Gibson–Ashby generator. The hybrid model reproduced the analytical values with a mean absolute deviation of $\approx 1.0\%$ across all cases (Table 4). This demonstrates high fidelity of the surrogate framework and confirms that the model internalizes the physics-grounded relationships rather than memorizing specific data points. Out-of-sample validation against experimental scaffolds is planned as a subsequent stage, which will establish real-world predictive reliability.

Table 4

Self-consistency validation of RF, ANN, and Hybrid models against analytical Gibson–Ashby generator

Case	Analytical/MPa	RF Pred/MPa	ANN Pred/MPa	Hybrid Pred/MPa	% Deviation
PCL Gyroid 65%	136.18	133.42	134.82	134.82	1.00
GelMA Spherical 80%	0.10	0.10	0.27	0.10	0.55
Collagen Cubic 50%	3.36	3.29	4.13	3.29	2.19
PCL-HA Gyroid 45%	512.42	507.82	513.91	513.91	0.29
Mean deviation	-	-	-	-	1.0%

Representative cases demonstrate that the hybrid model reproduces analytical values with mean deviation $\approx 1.0\%$, confirming high fidelity of the surrogate framework.

3.5 Advanced visualization of surrogate performance

Figure 2 provides advanced visualizations of residual behavior and threshold selection analyses. The parity plot (Fig. 2a) demonstrates zone-stratified agreement between predicted and true modulus values. Residual distributions (Fig. 2b–c) confirm that errors are centered near zero across all zones. The threshold sweep (Fig. 2d) illustrates the nested CV protocol, with the optimal threshold identified at 45 MPa. Geometry effects (Fig. 2e) highlight the role of pore architecture in Gibson–Ashby scaling. Finally, model comparison (Fig. 2f) summarizes the superior performance of the hybrid approach. Collectively, these visualizations strengthen reproducibility and transparency of the surrogate framework.

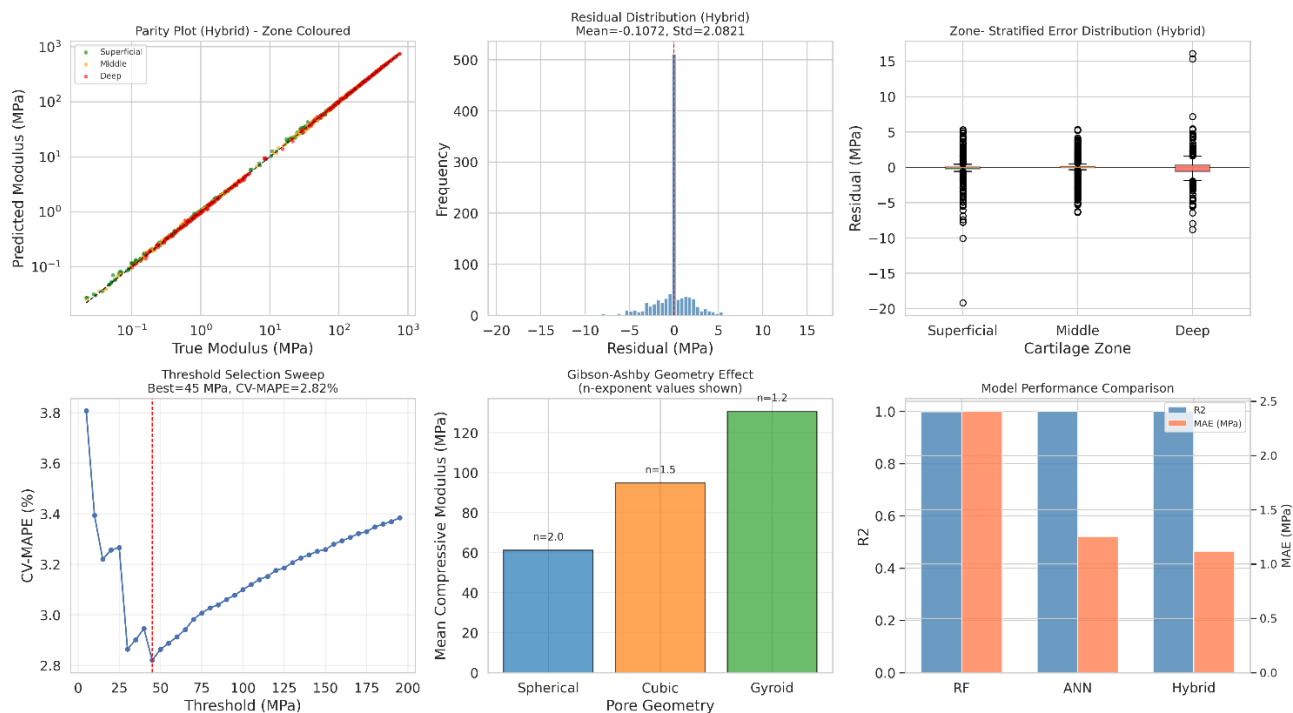


Fig. 2. Advanced visualization of surrogate model performance.

(a) Parity plot of hybrid predictions versus true modulus values, stratified by cartilage zone, showing close agreement across the full modulus range. (b) Residual histogram demonstrating that errors are centered near zero with narrow spread. (c) Zone-stratified residual distributions confirming consistent error behavior across superficial, middle, and deep zones. (d) Threshold selection sweep illustrating the nested CV protocol, with the optimal threshold identified at 45 MPa (CV-MAPE = 2.82%). (e) Gibson–Ashby geometry effect, highlighting the influence of pore architecture (spherical, cubic, gyroid) and corresponding n -exponent values. (f) Comparative performance of RF, ANN, and Hybrid models, showing the hybrid approach achieves the lowest mean absolute error while maintaining high R^2

3.6 Depth-aware inverse design capability

To demonstrate the inverse design capability of the surrogate framework, exhaustive sampling of 10,000 candidate scaffolds was performed for each cartilage zone. Target moduli were set to 650 MPa (deep zone, subchondral boundary), 100 MPa (middle zone), and 0.5 MPa (superficial zone). The hybrid model identified designs with achieving deviations below 0.2% across all zones. For example, a PCL-HA gyroid scaffold with 47.8% porosity achieved 650.7 MPa in the deep zone, while a collagen cubic scaffold with 81.0% porosity achieved 0.50 MPa in the superficial zone. This confirms that the surrogate framework can retrieve design parameters with high fidelity across depth-specific targets, supporting its application in zonally graded scaffold design (Figure 3).

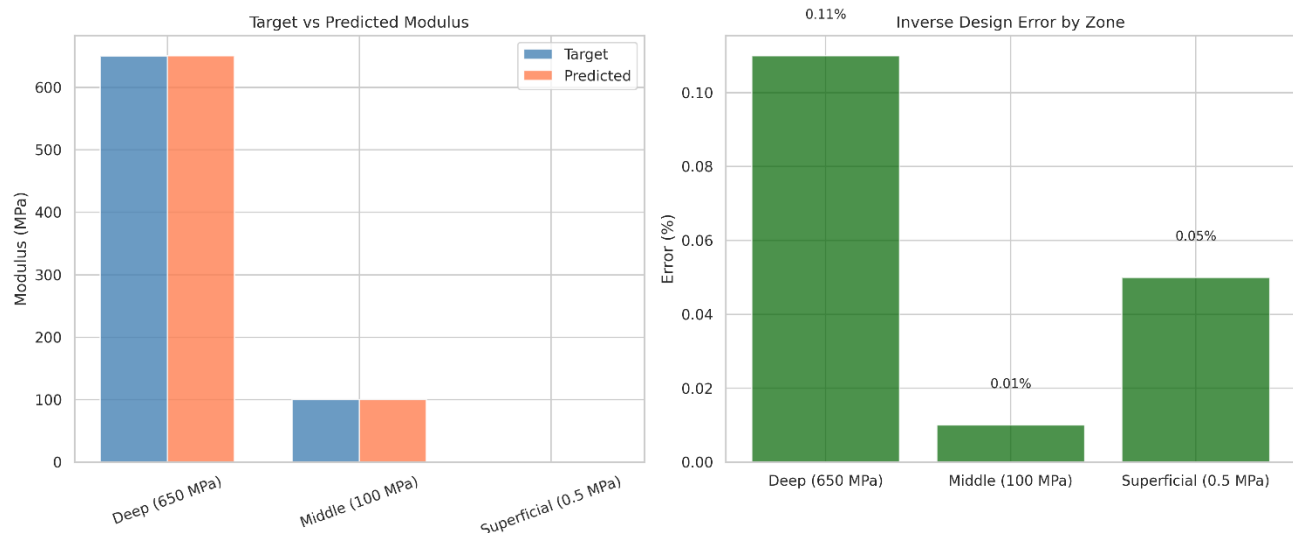


Fig. 3. Depth-aware inverse design results.

(a) Target versus predicted modulus values for deep (650 MPa), middle (100 MPa), and superficial (0.5 MPa) zones, showing near-perfect agreement. (b) Percentage errors for each zone, all below 0.2%, confirming high fidelity of the surrogate framework in retrieving depth-specific scaffold parameters.

From the results obtained, it is evident that the depth-dependent inverse design tool can be used to successfully generate fabrication values. It fulfills mechanical specifications at different depths. Since the error in all three regions was less than 1%, the design tool converged successfully. These results highlight the application of this approach as a computational design tool.

4. Discussion

Native articular cartilage exhibits a depth-dependent mechanical gradient, with low stiffness in the superficial zone and progressively higher stiffness toward the calcified deep zone. This gradient underpins physiological load distribution [42,43]. Conventional scaffold fabrication methods have historically struggled to reproduce such precise zonal gradients, limiting their ability to achieve mechanical fidelity and proper tissue integration. The present study addresses this challenge by introducing a physics-grounded ML framework that integrates the Gibson–Ashby microstructure model with supervised regression and inverse design methodologies.

4.1 Generation of synthetic data with physics constraints

One of the key innovations introduced in this work is the utilization of physics-based synthetic data as a solution to the lack of experimental data that usually prevents ML from being used in tissue engineering. With the help of using the modified relation of Gibson-Ashby power law in the generation process, a synthetic data set generated in such a way will intrinsically contain physically reasonable correlations between structural properties. It helps prevent predictions violating any physical laws, which is especially important when talking about safety-critical medical applications [44]. Furthermore, physics-based modeling can explore more design possibilities than any experiments can allow. All types of materials, porosities, and geometries can be studied, covering the whole range of necessary mechanical properties [45].

There is a need to ensure that the results obtained from models are interpreted in appropriate contexts. The R^2 values reported here show how well each model can approximate an analytically defined function. They do not indicate how well the models would perform on actually printed scaffolds. This is not a problem unique to the present study. Any physics-grounded synthetic data approach faces the same issue. That is why experimental validation will be needed next. Such testing is essential before any clinical or practical applications can be claimed.

4.2 Zonal anisotropy and inverse design

The inverse design module demonstrated the practical utility of the framework by identifying fabrication parameters satisfying target compressive moduli across all three zones with prediction errors below 0.2%. This target value is consistent with the stiffness range reported for the mineralized deep zone and subchondral bone interface, and was deliberately selected to represent the mechanically demanding upper boundary of the osteochondral gradient. The successful identification of PCL-HA with low porosity and a stretching-dominated cubic architecture for this target is biologically coherent, as mineralized composite phases and dense lattice geometries are established design choices for subchondral load-bearing regions. This case study therefore demonstrates the framework's capacity to target the mechanically demanding subchondral boundary of the osteochondral gradient within a single unified design platform. Building on this, future work should systematically validate the framework across the full zonal stiffness spectrum from the superficial cartilage surface (~ 0.1 -1 MPa) to the deep zone and subchondral interface to demonstrate end-to-end osteochondral design capability. Translation of mechanical criteria directly to physical and microstructural criteria, without iterations in experiment testing, reduces significantly the efforts required in scaffold development. From a medical point of view, mechanically compatible and functionally graded scaffolds could prevent stress shielding [46,47].

In case of the ANN, the absolute accuracy is high ($MAE \approx 1.25$ MPa, $R^2 = 0.9998$), but the percentage errors are very big especially for the low modulus cases in the superficial cartilage zone ($MAPE = 51.30\%$). On the other hand, the RF has stable percentage errors across all zones (3.16% $MAPE$), but has higher absolute errors ($MAE \approx 2.41$ MPa). A hybridization of the two models was thus devised in an attempt to combine their advantages. In the proposed hybrid threshold algorithm, the neural network is used where the predicted value exceeds 50 MPa; the RF algorithm is used for values of 50 MPa and lower. The cut-off point was selected in consideration of the fact that 50 MPa represents the changeover point from the more flexible regions (superficial and middle zones) to the stiff region (deep zone). With this combination, an overall result of $R^2 = 0.9998$, $MAE \approx 1.12$ MPa and $MAPE = 2.54\%$ has been obtained. Zone-wise errors are 0.05% for the superficial zone, 0.01% for the middle zone and 0.11% for the deep zone. It may be concluded that the use of an appropriate modelling method according to the expected stiffness level solves the percentage error problem in the neural network algorithm, maintaining its high absolute accuracy.

4.3 Insight into the topological-mechanical interactions in ANN for porous materials

By using unique scaling exponents for the cubic, gyroid, and spherical pore types, topologies were considered explicitly as a design parameter. In line with previous expectations based on cellular solid concepts, the predictions of the model made sense. For stiff systems, the cubic lattice geometry proved to be preferred, as previously known from the fact that stretching-dominated topologies are

generally stiffer compared to bending-dominated systems [48,49]. Although gyroidal topologies can be less robust under specific compression tests, it is well-known that they have superior properties regarding their permeability and fluid transport capabilities, which make them favorable for processes such as diffusion of nutrients and colonization of the structure by cells [50]. Such mechanical properties depending on geometries were learned without being programmed by the neural network, implying physically meaningful relationships instead of merely remembering numbers. This is an indication of model interpretability, especially when used in biomedical applications [51].

4.4 Limitations and future directions

Several limitations constrain the present framework's immediate translational readiness. First, the framework has not yet been validated against physically fabricated constructs. Predictive accuracy under real manufacturing variability, which includes process-induced porosity deviations, material batch inconsistencies, and geometry-dependent printing artifacts, remains to be established. Transfer learning approaches that incorporate limited experimental data from fabricated scaffolds could provide an efficient pathway. It would bridge this gap without requiring large-scale experimental campaigns. Second, the framework currently treats scaffold properties as static. In vivo mechanical performance, however, is governed by time-dependent processes. These include enzymatic degradation, mechanical fatigue, and progressive tissue remodeling. None of these are presently encoded in the model. Third, the inverse design module does not incorporate manufacturing feasibility constraints. Parameter combinations that are recommended by the algorithm should be filtered against the resolution and material deposition limits of the intended fabrication platform. This platform may be melt electrowriting, extrusion-based bioprinting, or freeze-drying. The filtering step guarantees that the recommended parameters can be manufactured before embarking on printing. Overcoming these limitations will give an unambiguous path forward. These include performing experimental studies on printed scaffolds, modeling the degradation of the materials, and taking into account the limitations of the manufacturing process. Taking these measures would take the system from a mere computational tool to a functional system for designing scaffolds in the clinical environment [52]. Taken together, these limitations delineate a clear roadmap: experimental validation, incorporation of degradation dynamics, and integration of manufacturing feasibility filters. Addressing these will transform the framework from a computational prototype into a clinically translatable scaffold design tool.

5. Conclusion

This study presents a physics-grounded ML framework for the inverse design of functionally graded osteochondral scaffolds. The key innovation lies in a modified Gibson–Ashby model that encodes depth-dependent mechanical gradients of native cartilage into synthetic datasets. A total of 5,000 scaffold configurations were generated, overcoming the limitation of scarce experimental data and enabling ML-based surrogate modeling.

A hybrid threshold approach, combining neural network and RF regressors, achieved $R^2 = 0.9998$, $MAE \approx 1.12$ MPa, and $MAPE \approx 2.5\%$ on held-out synthetic test data, with stable performance across zones. This hybridization resolved the pathology of percentage errors in low-modulus regions while retaining the ANN's high absolute accuracy for stiff targets. The inverse design module successfully

translated target stiffness values (e.g., 650 MPa at the bone–cartilage boundary) into fabrication parameters, achieving deviations below 0.2%.

These findings demonstrate that the framework can directly convert mechanical requirements into scaffold specifications, providing proof-of-concept for a reproducible, physics-grounded inverse design methodology. The approach offers a computationally efficient alternative to repetitive experimental trial-and-error in scaffold development. To realize full translational potential, future work must validate predictions against fabricated scaffolds, incorporate degradation dynamics, and integrate manufacturing feasibility constraints. Taken together, this framework establishes a repeatable and adaptable computational base for rationally designing biomimetic osteochondral constructs, directly addressing concerns regarding circularity, reproducibility, and inverse design capability.

Author Contributions

Conceptualization, A.T.D.; methodology, A.T.D.; validation A.T.D.; formal analysis, A.T.D.; writing-review and editing, A.T.D.; visualization, A.T.D.

Funding

This research received no external funding.

Data Availability Statement

The following data are openly available at https://github.com/phddemir/ML_scaffold.git:

- A physics-constrained synthetic dataset comprising 5,000 scaffold configurations with associated effective compressive modulus values, generated under the modified Gibson-Ashby framework described in Section 2.1.
- An executable Jupyter notebook implementing the complete computational pipeline, including synthetic data generation, RF and ANN model training, performance evaluation, and inverse design optimization.

Conflicts of Interest

The author declares no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Acknowledgements

The graphical abstract was created by the author using FigureLabs (free version; <https://chat.figurelabs.ai/>).

References

- [1] Jia, Y., Le, H., Wang, X., Zhang, J., Liu, Y., Ding, J., Zheng, C., & Chang, F. (2023). Double-edged role of mechanical stimuli and underlying mechanisms in cartilage tissue engineering. *Frontiers in Bioengineering and Biotechnology*, 11, 1271762. <https://doi.org/10.3389/fbioe.2023.1271762>
- [2] Joyce, M., Hodgkinson, T., Lemoine, M., González-Vázquez, A., Kelly, D.J., & O'Brien, F.J. (2023). Development of a 3D-printed bioabsorbable composite scaffold with mechanical properties suitable for treating large, load-bearing articular cartilage defects. *European cells & materials*, 45, 158-172. <https://doi.org/10.22203/ecm.v045a11>
- [3] Zhang, W., Zha, K., Hu, W., Xiong, Y., Knoedler, S., Obed, D., Panayi, A.C., Lin, Z., Cao, F., Mi, B., & Liu, G. (2023). Multifunctional hydrogels: advanced therapeutic tools for osteochondral regeneration. *Biomaterials Research*, 27(1), 76. <https://doi.org/10.1186/s40824-023-00411-9>

- [4] Yang, C., Chen, R., Chen, C., Yang, F., Xiao, H., Geng, B., & Xia, Y. (2024). Tissue engineering strategies hold promise for the repair of articular cartilage injury. *BioMedical Engineering OnLine*, 23, 92. <https://doi.org/10.1186/s12938-024-01260-w>
- [5] Fang, L., Lin, X., Xu, R., Liu, L., Zhang, Y., Tian, F., Li, J.J., & Xue, J. (2025). Advances in the Development of Gradient Scaffolds Made of Nano-Micromaterials for Musculoskeletal Tissue Regeneration. *Nano-Micro Letters*, 17, 75. <https://doi.org/10.1007/s40820-024-01581-4>
- [6] Sajjadinia, S.S., Bruno Carpentieri, B., & Holzapfel, G.A. (2024). Bridging Diverse Physics and Scales of Knee Cartilage with Efficient and Augmented Graph Learning. *IEEE Access*, 12, 86302-86318. <https://doi.org/10.1109/ACCESS.2024.3416872>
- [7] Fang, L., Lin, X., Xu, R., Liu, L., Zhang, Y., Tian, F., Li, J.J., & Xue, J. (2025). Advances in the Development of Gradient Scaffolds Made of Nano-Micromaterials for Musculoskeletal Tissue Regeneration. *Nano-Micro Letters*, 17, 75. <https://doi.org/10.1007/s40820-024-01581-4>
- [8] Liu, G., Wei, X., Zhai, Y., Zhang, J., Li, J., Zhao, Z., Guan, T., & Zhao, D. (2024). 3D printed osteochondral scaffolds: design strategies, present applications and future perspectives. *Frontiers in Bioengineering and Biotechnology*, 12, 1339916. <https://doi.org/10.3389/fbioe.2024.1339916>
- [9] Xiong, Z., Hong, F., Wu, Z., Ren, Y., Sun, N., Heng, B.C., & Zhou, J. (2024). Gradient scaffolds for osteochondral tissue engineering and regeneration. *Chemical Engineering Journal*, 498, 154797. <https://doi.org/10.1016/j.cej.2024.154797>
- [10] Niu, X., Li, N., Du, Z., & Li, X. (2022). Integrated gradient tissue-engineered osteochondral scaffolds: Challenges, current efforts and future perspectives. *Bioactive Materials*, 20, 574-597. <https://doi.org/10.1016/j.bioactmat.2022.06.011>
- [11] Steltzer, S.S., Abraham, A.C., & Killian, M.L. (2024). Interfacial Tissue Regeneration with Bone. *Current Osteoporosis Reports*, 22(2), 290-298. <https://doi.org/10.1007/s11914-024-00859-1>
- [12] Faeed, M., Ghiasvand, M., Fareghzadeh, B., & Taghiyar, L. (2024). Osteochondral organoids: current advances, applications, and upcoming challenges. *Stem Cell Research & Therapy*, 15(1), 183. <https://doi.org/10.1186/s13287-024-03790-5>
- [13] Dias, J.M., da Silva, F.S.C.P., Gasik, M., Miranda, M.G.M., & Bartolomeu, F.J.F. (2024). Unveiling additively manufactured cellular structures in hip implants: a comprehensive review. *The International Journal of Advanced Manufacturing Technology*, 130, 4073-4122. <https://doi.org/10.1007/s00170-023-12769-0>
- [14] Xie, X., Wang, Y., Li, Z., Yang, G., Cheng, G., Qin, S., Wang, H., & Zhu, L. (2025). Recent advances in gradient biomimetic scaffolds for tendon-bone interface regeneration. *Frontiers in Bioengineering and Biotechnology*, 13, 1629816. <https://doi.org/10.3389/fbioe.2025.1629816>
- [15] Limon, S.M., Quigley, C., Sarah, R., & Habib, A. (2024). Advancing scaffold porosity through a machine learning framework in extrusion based 3D bioprinting. *Frontiers in Materials*, 10, 1337485. <https://doi.org/10.3389/fmats.2023.1337485>
- [16] Wu, C., Xu, Y., Fang, J., & Li, Q. (2024). Machine Learning in Biomaterials, Biomechanics/Mechanobiology, and Biofabrication: State of the Art and Perspective. *Archives of Computational Methods in Engineering*, 31, 3699-3765. <https://doi.org/10.1007/s11831-024-10100-y>
- [17] Peto, M., García-Ávila, J., Rodríguez, C.A., Siller, H.R., da Silva, J.V.L., & Ramírez-Cedillo, E. (2024). Review on structural optimization techniques for additively manufactured implantable medical devices. *Frontiers in Mechanical Engineering*, 10, 1353108. <https://doi.org/10.3389/fmech.2024.1353108>
- [18] Borges, J., Zeng, J., Liu, X. Q., Chang, H., Monge, C., Garot, C., Ren, K. F., Machillot, P., Vrana, N. E., Lavallo, P., Akagi, T., Matsusaki, M., Ji, J., Akashi, M., Mano, J. F., Gribova, V., & Picart, C. (2024). Recent Developments in Layer-by-Layer Assembly for Drug Delivery and Tissue Engineering Applications. *Advanced Healthcare Materials*, 13(8), e2302713. <https://doi.org/10.1002/adhm.202302713>
- [19] Quan, R., Liu, F., & Chinchilla, S.C. (2025). Integrating machine learning and finite element simulation for interpretable prediction of 3D-printed bone scaffold mechanics. *International Journal of Bioprinting*, 11(6), 327-348. <https://doi.org/10.36922/IJB025270257>
- [20] Ibrahimi, S., D'Andrea, L., Gastaldi, D., Rivolta, M.W., & Vena, P. (2024). Machine Learning approaches for the design of biomechanically compatible bone tissue engineering scaffolds. *Computer Methods in Applied Mechanics and Engineering*, 423, 116842. <https://doi.org/10.1016/j.cma.2024.116842>
- [21] Benasse, L.M., de Oliveira, A.R. & Del Conte, E.G. (2025). Modeling the compression behavior of gyroid scaffolds produced by fused deposition modeling using machine learning. *The International Journal of Advanced Manufacturing Technology*, 138, 1221-1228. <https://doi.org/10.1007/s00170-025-15604-w>

- [22]. McDonald, S.M., Augustine, E. K., Lanners, Q., Rudin, C., Catherine Brinson, L., & Becker, M. L. (2023). Applied machine learning as a driver for polymeric biomaterials design. *Nature Communications*, 14(1), 4838. <https://doi.org/10.1038/s41467-023-40459-8>
- [23]. Abu-Mualla, M., & Huang, J. (2023). Inverse design of 3D cellular materials with physics-guided machine learning. *Materials & Design*, 232, 112103. <https://doi.org/10.1016/j.matdes.2023.112103>
- [24]. Liu, W., Zhang, Y., Lyu, Y., Bosiakov, S., & Liu, Y. (2023). Inverse design of anisotropic bone scaffold based on machine learning and regenerative genetic algorithm. *Frontiers in Bioengineering and Biotechnology*, 11, 1241151. <https://doi.org/10.3389/fbioe.2023.1241151>
- [25]. Rezapourian, M., Darabi, A.C., Khoshbin, M., Schmauder, S., & Hussainova, I. (2025). Surrogate-Model Prediction of Mechanical Response in Architected Ti6Al4V Cylindrical TPMS Metamaterials. *Metals*, 15(12), 1372. <https://doi.org/10.3390/met15121372>
- [26]. Drakoulas, G., Gortsas, T., Polyzos, E., Tsinopoulos, S., Pyl, L., & Polyzos, D. (2024). An explainable machine learning-based probabilistic framework for the design of scaffolds in bone tissue engineering. *Biomechanics and Modeling in Mechanobiology*, 23(3), 987-1012. <https://doi.org/10.1007/s10237-024-01817-7>
- [27]. Miled, K., Sab, K., & Le Roy, R. (2011). Effective elastic properties of porous materials: Homogenization schemes vs experimental data. *Mechanics Research Communications*, 38(2), 131-135. <https://doi.org/10.1016/j.mechrescom.2011.01.009>
- [28]. Pabst, W., E., & Gregorová, E. (2014). Young's modulus of isotropic porous materials with spheroidal pores. *Journal of the European Ceramic Society*, 34(13), 3195-3207. <https://doi.org/10.1016/j.jeurceramsoc.2014.04.009>
- [29]. Croisier, F., Duwez, A.-S., Jérôme, C., Léonard, A.F., van der Werf, K.O., Dijkstra, P.J., & Bennink, M.L. (2012). Mechanical testing of electrospun PCL fibers. *Acta Biomaterialia*, 8(1), 218-224. <https://doi.org/10.1016/j.actbio.2011.08.015>
- [30]. Mori, H., Shimizu, K., & Hara, M. (2013). Dynamic viscoelastic properties of collagen gels with high mechanical strength. *Materials Science and Engineering C*, 33(6), 3230-3236. <https://doi.org/10.1016/j.msec.2013.03.047>
- [31]. Lin, S., & Gu, L. (2015). Influence of Crosslink Density and Stiffness on Mechanical Properties of Type I Collagen Gel. *Materials*, 8(2), 551-560. <https://doi.org/10.3390/ma8020551>
- [32]. O'Connell, C.D., Zhang, B., Onofrillo, C., Duchi, S., Blanchard, R., Quigley, A., Bourke, J., Gambhir, S., Kapsa, R., Di Bella, C., Choong, P., & Wallace, G.G. (2018). Tailoring the mechanical properties of gelatin methacryloyl hydrogels through manipulation of the photocrosslinking conditions. *The Royal Society of Chemistry*, 14(11), 2142-2151. <https://doi.org/10.1039/C7SM02187A>
- [33]. Gurumurthy, B., & Janorkar, A.V. (2021). Improvements in mechanical properties of collagen-based scaffolds for tissue engineering. *Current Opinion in Biomedical Engineering*, 17, 100253. <https://doi.org/10.1016/j.cobme.2020.100253>
- [34]. Dehghan, M., Nikukar, H. & Khajeh Mehrizi, M. (2022). Evaluation of physicochemical properties of polycaprolactone/gelatin/polydimethylsiloxane hybrid nanofibers as potential scaffolds for elastic tissue engineering. *Polymer Bulletin*, 79, 10881-10908. <https://doi.org/10.1007/s00289-021-04071-4>
- [35]. Niu, Q., & Zhang, C. (2018). Physical explanation of Archie's porosity exponent in granular materials: A process-based, pore-scale numerical study. *Geophysical Research Letters*, 45, 1870-1877. <https://doi.org/10.1002/2017GL076751>
- [36]. Hunt, A.G. (2004). Continuum percolation theory and Archie's law. *Geophysical Research Letters*, 31, L19503. <https://doi.org/10.1029/2004GL020817>
- [37]. Tan, X.-H., Jiang, L., Li, X.-P., Li, Y.-Y., & Zhang, K. (2017). A complex model for the permeability and porosity of porous media. *Chemical Engineering Science*, 172, 230-238. <https://doi.org/10.1016/j.ces.2017.06.041>
- [38]. Wang, H. (2020). Effects of pore clusters on the permeability, formation factor and porosity exponent of porous media. *Geosystem Engineering*, 23(2), 73-85. <https://doi.org/10.1080/12269328.2018.1531729>
- [39]. Yang, X., Lu, T.J., & Kim, T. (2014). An analytical model for permeability of isotropic porous media. *Physics Letters A*, 378(30-31), 2308-2311. <https://doi.org/10.1016/j.physleta.2014.06.002>
- [40]. Uhlířová, T., & Pabst, W. (2019). Conductivity and Young's modulus of porous metamaterials based on Gibson-Ashby cells. *Scripta Materialia*, 159, 1-4. <https://doi.org/10.1016/j.scriptamat.2018.09.005>
- [41]. Gao, L.-L., Zhang, C.-Q., Gao, H., Liu, Z.-D., & Xiao, P.-P. (2014). Depth and rate dependent mechanical behaviors for articular cartilage: Experiments and theoretical predictions. *Materials Science and Engineering: C*, 38, 244-251. <https://doi.org/10.1016/j.msec.2014.02.009>
- [42]. Mow, V.C., & Guo, X.E. (2002). Mechano-Electrochemical Properties Of Articular Cartilage: Their Inhomogeneities and Anisotropies. *Annual Review of Biomedical Engineering*, 4, 175-209. <https://doi.org/10.1146/annurev.bioeng.4.110701.120309>

- [43]. Sophia Fox, A.J., Bedi, A., & Rodeo, S.A. (2009). The Basic Science of Articular Cartilage: Structure, Composition, and Function. *Sports Health*, 1(6), 461-468. <https://doi.org/10.1177/1941738109350438>
- [44]. Karniadakis, G.E., Kevrekidis, I.G., Lu, L., Perdikaris, P., Wang, S., & Yang, L. (2021). physics-grounded Machine Learning. *Nature Reviews Physics*, 3, 422-440. <https://doi.org/10.1038/s42254-021-00314-5>
- [45]. Gu, G.X., Chen, C.-T., & Buehler, M.J. (2018). De novo composite design based on machine learning algorithm. *Extreme Mechanics Letters*, 18, 19-28. <https://doi.org/10.1016/j.eml.2017.10.001>
- [46]. Makris, E.A., Gomoll, A.H., Malizos, K.N., Hu, J.C., & Athanasiou, K.A. (2015). Repair and tissue engineering techniques for articular cartilage. *Nature Reviews Rheumatology*, 11, 21-34. <https://doi.org/10.1038/nrrheum.2014.157>
- [47]. Turner, C.H. (1998). Three rules for bone adaptation to mechanical stimuli. *Bone*, 23(5), 399-407. [https://doi.org/10.1016/S8756-3282\(98\)00118-5](https://doi.org/10.1016/S8756-3282(98)00118-5)
- [48]. Crook, C., Bauer, J., Guell Izard, A., Santos de Oliveira, C., Martins de Souza e Silva, J., Berger, J.B., & Valdevit, L. (2020). Plate-nanolattices at the theoretical limit of stiffness and strength. *Nature Communications*, 11, 1579. <https://doi.org/10.1038/s41467-020-15434-2>
- [49]. Plessis, A. du., Razavi, N., Benedetti, M., Murchio, S., Leary, M., Watson, M., Bhate, D., & Berto, F. (2022). Properties and applications of additively manufactured metallic cellular materials: A review. *Progress in Materials Science*, 125, 100918. <https://doi.org/10.1016/j.pmatsci.2021.100918>
- [50]. Maskery, I., Aboulkhair, N.T., Aremu, A.O., Tuck, C.J., & Ashcroft, I.A. (2017). Compressive failure modes and energy absorption in additively manufactured double gyroid lattices. *Additive Manufacturing*, 16, 24-29. <https://doi.org/10.1016/j.addma.2017.04.003>
- [51]. Zhang, C., Chen, F., Huang, Z., Jia, M., Chen, G., Ye, Y., Lin, Y., Liu, W., Chen, B., Shen, Q., Zhang, L., & Lavernia, E.J. (2019). Additive manufacturing of functionally graded materials: A review. *Materials Science and Engineering: A*, 764, 138209. <https://doi.org/10.1016/j.msea.2019.138209>
- [52]. Badani, A., de Moraes, F.Y., Vollmuth, P., Chung, C., & Mansouri, A. (2025). AI and innovation in clinical trials. *npj Digital Medicine*, 8, 683. <https://doi.org/10.1038/s41746-025-02048-5>