Physics-Informed Optimization of 3D-Printed Tissue Scaffolds for Enhanced Cell Growth and Mechanical Stability

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Abstract

Three-dimensional printed tissue scaffolds must satisfy a coupled set of biological and mechanical requirements: interconnected porosity for nutrient transport and cell migration, pore dimensions that support cell activity, sufficient stiffness and strength for load transfer, and geometric features that remain manufacturable at printer resolution. Design methods that optimize only porosity or only stiffness tend to produce architectures that are locally favorable but globally inconsistent, especially when transport limitation, mechanobiological response, and print-path constraints interact. This manuscript develops a physics-informed optimization framework for scaffold architecture that treats these requirements as a single PDE-constrained design problem. The design field is a relative density distribution together with a characteristic pore diameter. A reaction-diffusion model represents oxygen or nutrient transport and consumption, a mechanobiological growth law links local nutrient availability and mechanical stimulus to predicted cell density, and effective stiffness and local yield constraints represent mechanical stability. The optimization objective combines predicted cell growth, effective stiffness, and solid volume, while printability enters as explicit constraints on minimum feature size, overhang, and path continuity. The framework also includes a robust formulation that penalizes sensitivity to uncertain transport and mechanical parameters. The main analytical insight is that feasible scaffolds occupy a narrow transport-mechanics trade-off region in which graded density and coordinated pore-size selection outperform uniform porosity. The formulation provides a defensible basis for design ranking and for selecting measurable validation endpoints before fabrication.

Keywords

physics-informed optimization; tissue scaffolds; nutrient transport; mechanobiology; additive manufacturing; robust design

1. Introduction

Additive manufacturing has made it possible to construct tissue-engineering scaffolds with designed internal architecture rather than stochastic pore networks. The central design problem is not merely to create a porous solid, but to create a porous solid whose geometry simultaneously supports cell colonization, mass transport, and mechanical function. Porous scaffold design has therefore been organized around the interplay between volume fraction, pore size, connectivity, and tissue-specific mechanical targets [1]. Scaffolds for bone and

cartilage, for example, must provide temporary load-bearing capacity while allowing cell infiltration and extracellular matrix deposition [2]. These requirements are coupled: increasing porosity generally improves transport and space for tissue formation, but it reduces stiffness and strength, and excessively large or irregular pores can impair cell attachment and matrix continuity.

Porosity alone is an incomplete design variable. Pore size influences cell adhesion, migration, and tissue ingrowth, and the appropriate range depends on cell type, matrix material, and culture conditions [3]. Experimental studies of collagen-glycosaminoglycan scaffolds have shown that cell attachment and activity vary with mean pore size, indicating that transport-scale geometry and cell-scale geometry are not interchangeable [4]. Computational models of cell spreading and tissue regeneration in porous scaffolds further show that local geometry controls the balance between cell proliferation, migration, and matrix formation [5]. Consequently, a scaffold with adequate global porosity can still fail biologically if the pore-size distribution or pore connectivity produces transport-limited or cell-repellent regions.

Mechanical requirements introduce a second constraint. Scaffold architecture determines effective elastic properties, local stress concentrations, and susceptibility to strut buckling. Methods for matching scaffold elastic properties to host tissue have used inverse design and topology optimization to select internal architecture under porosity constraints [6]. Topology optimization provides a mature mathematical language for distributing material within a design domain, but conventional formulations usually treat stiffness or compliance as the primary objective [7]. They do not by themselves resolve nutrient transport, cell growth kinetics, or the discrete constraints imposed by printing. Robotic and wireframe printing add a further geometric restriction because the deposition path, mesh topology, and support conditions must be physically realizable; mesh and path optimization for spatial wireframe robotic printing is therefore directly relevant to the manufacturability side of scaffold design [8]. The gap addressed here is the lack of a coherent optimization formulation that treats transport, cell growth, mechanical stability, and printability as mutually constraining physics rather than as post hoc filters.

The proposed contribution is a physics-informed scaffold optimization framework with four linked components. First, the architecture is represented by a relative density field and a characteristic pore diameter, from which porosity and permeability are derived. Second, a reaction-diffusion model predicts nutrient concentration under consumption by cells. Third, a mechanobiological growth law couples nutrient availability and mechanical stimulus to predicted cell density. Fourth, effective stiffness, local yield, and printability constraints define the feasible design set. The optimization objective ranks designs by predicted cell growth, mechanical stiffness, and material economy. A robust extension accounts for uncertain transport and mechanical parameters. The framework is analytical and computational in character: it yields design conditions, trade-off relationships, and validation targets rather than empirical performance claims.

2. Physical and Biological Design Requirements

2.1 Porosity, Pore Architecture, and Transport

The first design requirement is an interconnected pore network that permits diffusion of oxygen and nutrients and removal of metabolic waste. Cellular solids theory provides a useful starting point because it relates relative density to effective mechanical and transport

properties of porous materials [9]. For bending-dominated open-cell foams and lattices, stiffness and strength scale nonlinearly with relative density, while permeability depends strongly on pore size and porosity [10]. These scaling relations explain why two scaffolds with the same porosity can have very different transport and mechanical behavior when their pore sizes or strut topologies differ.

A second requirement is that the pore network remain connected at the scale of cells and tissue ingrowth. A design can satisfy a global porosity target while containing isolated voids or narrow throats that block migration. The relevant geometric descriptors are therefore not only mean pore diameter but also throat size, connectivity, and tortuosity. These descriptors enter the transport model through effective diffusivity and permeability, and they enter the biological model through accessible surface area and migration capacity. Scaffold design studies have repeatedly emphasized that mechanical and biological constraints must be imposed together rather than sequentially [11]. The formulation developed below follows this principle by making the pore-scale descriptors part of the optimization variables rather than fixed post-processing parameters.

2.2 Cell Growth Kinetics and Mechanical Cues

Cell growth in a scaffold is controlled by nutrient availability, local mechanical environment, surface chemistry, and cell-cell interactions. In the interior of a thick scaffold, oxygen and glucose concentrations can fall below levels needed for proliferation, producing a necrotic or quiescent core even when the exterior is well colonized. Mathematical models of cell growth and substrate diffusion in polymer scaffolds show that the interaction between consumption and diffusion can generate sharp spatial gradients in cell density [14]. Oxygen diffusion models for porous, vascularizing scaffolds similarly indicate that transport limitation is a first-order design constraint rather than a secondary correction [15]. These observations motivate a growth law in which the local proliferation rate depends on nutrient concentration and on a mechanical stimulus term.

Mechanical cues are equally important. Substrate stiffness, local strain, and fluid shear can alter proliferation, differentiation, and matrix production. A scaffold that is too compliant may fail to provide the intended mechanical environment, while a scaffold that is too stiff may shield cells from the strains that favor tissue maturation. The mechanobiological term in the growth law is therefore treated as a bounded stimulus rather than an unbounded benefit. The design objective should reward a favorable stimulus range, not simply maximize stiffness. This distinction is central because a purely mechanical optimization would drive the scaffold toward high density and small pores, whereas a purely biological optimization would drive it toward high porosity and large pores. The useful design lies between these extremes.

2.3 Printability and Fabrication Constraints

Printability imposes discrete constraints that are absent from continuous topology optimization. Minimum feature size is limited by nozzle diameter and deposition resolution; overhang angles are limited by the need for support; path continuity is limited by the motion planner and by the need to avoid interruptions that create weak interfaces. For extrusion-based and wireframe robotic printing, the scaffold geometry must be representable as a connected set of printable paths. Mesh and path optimization for spatial wireframe robotic printing therefore provides a relevant computational precedent for coupling geometric design with deposition feasibility [8]. In the present framework, printability is not treated as a penalty

added after optimization. Instead, it restricts the admissible design field and pore-size range before the physics-based objective is evaluated.

3. Physics-Informed Optimization Framework

3.1 Design Representation and Effective Properties

The scaffold is defined on a design domain Ω. The primary variable is a relative solid density field ρ(x) with values between zero and one, together with a characteristic pore diameter d_p. The macroporosity θ is the volume fraction not occupied by solid material:

$$\theta = 1 - (1/|\Omega|) \int \Omega \, \rho(x) \, dV$$

Here |Ω| is the domain volume and the integral is the volume-averaged relative density. The expression assumes that closed micropores within the deposited material are negligible at the scaffold scale and that macroporosity is the relevant transport fraction. When closed microporosity is significant, θ should be interpreted as the interconnected macroporosity and measured or modeled separately.

Permeability is represented by a Kozeny-Carman-type relation:

$$k = C_k d_p^2 \frac{\theta^3}{(1-\theta)^2}$$

In this expression k is the Darcy permeability, d_p is the characteristic pore diameter, and C_k is a dimensionless geometry coefficient that depends on pore shape and tortuosity. The relation is valid for connected pore networks and moderate porosity; it becomes unreliable as θ approaches one or when the pore network loses connectivity. Its role in the framework is to translate pore-size and porosity choices into a transport-relevant property rather than to serve as a universal predictive law.

Effective diffusivity is treated similarly as D_eff = D_0 θ/τ, where D_0 is the diffusivity in the culture medium and τ is tortuosity. Both k and D_eff depend on the same geometric descriptors, which is why porosity and pore size cannot be optimized independently. Increasing θ raises D_eff and k but lowers the solid fraction available for load transfer. Increasing d_p raises k for a fixed porosity but can reduce specific surface area and alter cell attachment. These are the first trade-offs embedded in the formulation.

3.2 Coupled Transport and Growth Model

Nutrient transport is represented by a steady reaction-diffusion balance under the assumption that transport equilibrates faster than tissue growth over the design horizon:

$$0 = \nabla \cdot (D_eff \, \nabla C) - q_max \, \rho_c \, C/(K_m + C)$$

Here C is nutrient concentration, ρ_c is local cell density, q_max is the maximum specific consumption rate, and K_m is the half-saturation constant. The first term represents diffusive transport through the effective medium, and the second represents Michaelis-Menten consumption by cells. The steady assumption is appropriate for oxygen in thin or well-perfused constructs; for thick constructs or perfusion bioreactors, a transient or advective term should be added. The model also assumes isotropic effective transport within a representative volume, which is a reasonable first approximation when pore orientation is not strongly aligned.

Cell density evolves according to a mechanobiological growth law:

$$d\frac{\rho_c}{d}t = \rho_c\left[\mu_m ax\frac{C}{(K_C + C)} - k_d - \alpha\rho_c + \chi S(\varepsilon)\right]$$

In this equation μ_max is the maximum proliferation rate, K_C is the nutrient half-saturation constant for growth, k_d is the death rate, α is a contact-inhibition coefficient, χ is a mechanobiological sensitivity coefficient, and S(ε) is a dimensionless mechanical stimulus derived from local strain or strain energy. The term S(ε) is bounded and is defined relative to a target range so that both insufficient and excessive mechanical stimulation can be penalized. The equation is a proposed kinetic model: its parameters require calibration to specific cell types and materials, and its predictions should be interpreted as comparative design guidance rather than as biological validation.

The coupling is essential. The transport equation depends on ρ_c through consumption, while the growth equation depends on C through proliferation. A design that improves transport but provides an unfavorable mechanical stimulus may increase nutrient availability without increasing predicted tissue formation. Conversely, a dense scaffold may provide favorable stiffness but create a nutrient-limited core. The optimization must therefore evaluate the coupled solution rather than optimize porosity and stiffness separately.

3.3 Mechanical Stability Constraints

Mechanical stability is represented at two scales. At the scaffold scale, effective stiffness is estimated from cellular-solid scaling:

$$E_eff \;=\; C_E\, E_s\, \bar{\rho}^{\,n}$$

Here E_eff is the effective elastic modulus, E_s is the solid material modulus, $\bar{\rho}$ is the volume-averaged relative density, C_E is a geometry coefficient, and n is a scaling exponent. For bending-dominated open-cell foams, n is approximately two; for stretch-dominated lattices, the exponent can be lower and the coefficient higher [9,10]. The exponent is therefore a design choice tied to architecture, not a universal constant. The expression provides a compact constraint E_eff ≥ E_min, where E_min is the minimum stiffness required by the target tissue or loading environment.

At the local scale, stress concentration and strut yielding must be controlled. A local yield constraint can be written as:

$$\sigma_v m(x) \le \sigma_y\big(\rho(x)\big) = C_\sigma \sigma_y s \rho(x)^m$$

In this expression σ_vm(x) is the von Mises stress obtained from the elastic solution, σ_y(ρ(x)) is the effective yield strength at relative density ρ(x), σ_ys is the solid material yield strength, and C_σ and m are architecture-dependent coefficients. The constraint prevents designs in which global stiffness is adequate but thin struts yield locally. Slender struts also require a buckling check, λ_b(x) ≥ 1, where λ_b is the ratio of buckling load to applied load for the local strut geometry. Buckling is particularly important in low-density scaffolds because it can occur before material yield.

3.4 Multiobjective Optimization and Robustness

The design problem combines predicted cell growth, mechanical stiffness, and material economy. A representative objective is:

$$max_\{\rho, d_p\}\, J \;=\; w_1\bar{\rho}_c/\rho_ref \;+\; w_2 E_eff/E_ref \;-\; w_3 V_s/V_ref$$

Here $\bar{\rho}_c$ is the volume-averaged predicted cell density at the design horizon, E_{eff} is the effective stiffness, V_s is the solid volume, and ρ_{ref}, E_{ref}, and V_{ref} are normalization constants. The weights w_1, w_2, and w_3 are nonnegative and sum to one. The objective is maximized subject to the transport equation, the growth law, the stiffness constraint, the local yield constraint, bounds on $\rho(x)$ and d_p, and printability constraints. Normalization is necessary because cell density, modulus, and volume have different units and scales. The weights encode design priorities and should be selected with the target tissue and culture configuration in mind.

The formulation is a PDE-constrained optimization problem. Its solution requires repeated evaluation of transport, growth, and mechanics as the design field changes. Physics-informed machine learning can reduce the cost of these repeated evaluations by embedding governing equations in the learning architecture or by learning surrogate maps from design parameters to PDE solutions [12]. The broader physics-informed machine learning literature provides methods for combining observational data with physical constraints, but such surrogates require error control before they can be used for design decisions [13]. In this framework, a surrogate is acceptable only if its error is bounded over the feasible design set and if the final candidate designs are verified with the full PDE model.

Uncertainty in transport and mechanical parameters is unavoidable. Diffusion coefficients depend on culture conditions, consumption rates depend on cell state, and effective modulus depends on printing defects. A robust objective is:

$$J_{rob} = E_p[J(\rho, d_p; \xi)] - \lambda \sqrt{Var_p[J(\rho, d_p; \xi)]}$$

Here ξ is a vector of uncertain parameters, E_p and Var_p denote expectation and variance under a probability model $p(\xi)$, and $\lambda \geq 0$ controls risk aversion. The robust formulation favors designs whose performance is stable across plausible parameter ranges rather than designs that are optimal only at a nominal parameter set. This is consistent with data-driven material design under uncertainty, where sensitivity to input variability can dominate nominal performance [19].

4. Computational Solution Strategy and Sensitivity Analysis

The coupled system can be discretized on a voxel or conforming finite-element mesh. Transport is solved as a scalar diffusion-reaction problem, and elasticity is solved as a linear or nonlinear static problem depending on the strain regime. The growth law is integrated in time on the same mesh, with cell density updated from the current nutrient and mechanical fields. The optimization variables are the nodal or element-wise relative density and the pore-size parameter. For gradient-based optimization, adjoint methods provide sensitivities of J with respect to ρ and d_p while enforcing the PDE constraints. The local yield and buckling constraints are evaluated on the same discretization, and printability constraints are imposed through minimum-length filters, overhang projection, or explicit path-generation checks.

The non-smooth nature of printability is a practical difficulty. Minimum feature size and overhang constraints can be formulated with differentiable projections, but path continuity is often combinatorial. A two-level strategy is appropriate: a continuous relaxation identifies promising density and pore-size distributions, and a discrete print-path generation step verifies or repairs the design. If the repaired design violates a physics constraint, the constraint is returned to the continuous problem as a cut or penalty. This avoids the common failure mode in which an optimized architecture is physically printable only after substantial modification that erases its transport or mechanical advantage.

Sensitivity analysis should be performed with respect to both design variables and model parameters. Design sensitivities reveal whether the objective is limited by transport, stiffness, yield, or printability. Parameter sensitivities identify which uncertain quantities most strongly affect the ranking of designs. If the ranking is dominated by one parameter, that parameter should be measured or bounded before fabrication. If the ranking is robust across a broad parameter range, the design is a stronger candidate for experimental evaluation. This use of sensitivity is more informative than reporting a single optimized geometry without indicating why it is preferred.

5. Technical Discussion

The framework exposes several design trade-offs that are difficult to see when scaffold requirements are treated separately. The first is the porosity-permeability-mechanics trade-off. Increasing porosity improves permeability and diffusion but reduces effective modulus and yield strength. The optimization therefore tends to produce graded architectures: denser material in regions of high stress or near load-transfer interfaces, and more open architecture in transport-limited or cell-colonization regions. This is not merely a numerical artifact. It follows from the fact that the mechanical constraint is local while the transport constraint is nonlocal, because nutrient concentration at a point depends on diffusion from the scaffold boundary or perfusion channel.

The second trade-off concerns pore size. Larger pores improve permeability and can reduce transport limitation, but they reduce specific surface area and may weaken cell attachment if the pore size exceeds the range favorable for the target cell type. Experimental evidence on mean pore size and cell activity indicates that the biological response is not monotone without limit [20]. The optimization formulation should therefore impose a biologically informed pore-size window rather than allowing d_p to grow without bound. This window is a model input, not a prediction of the framework itself.

The third trade-off is between nominal performance and robustness. A design that is optimal at a single set of transport and mechanical parameters may perform poorly when the actual consumption rate is higher than assumed or when printing defects reduce strut stiffness. The robust objective in equation (8) penalizes such fragility. In practice, this shifts the optimum toward slightly lower porosity or more regular pore architecture, accepting a modest reduction in nominal transport in exchange for reduced sensitivity to parameter error. This is a desirable property for scaffolds that must perform across biological variability.

Several failure mechanisms are directly represented by the formulation. Nutrient depletion in the scaffold core appears as a low C solution and reduced ρ_c. Local yielding appears as violation of equation (7). Strut buckling appears as $\lambda_b < 1$. Print-path discontinuity appears as infeasibility in the geometric constraint set. Other failure mechanisms are only indirectly represented. pore occlusion by deposited matrix, degradation-induced loss of stiffness, and inflammatory responses are not predicted by the present transport-growth-mechanics model. These should be treated as boundary conditions or constraints in a more detailed application, not as claims of the current formulation.

The framework also clarifies what should be measured to test its predictions. Transport predictions can be compared with oxygen or glucose profiles in culture. Growth predictions can be compared with spatial cell-density maps. Mechanical predictions can be compared with effective modulus and yield load measurements. Printability predictions can be compared with measured feature resolution and path continuity. These endpoints are not

interchangeable, and a scaffold that succeeds in one dimension may fail in another. The value of the optimization framework is that it makes the trade-offs explicit before fabrication rather than after failure.

6. Conclusion

A physics-informed optimization framework has been developed for 3D-printed tissue scaffolds that couples porosity and pore-size design to nutrient transport, mechanobiological cell growth, effective stiffness, local yield, and printability. The formulation treats the scaffold as a PDE-constrained design problem rather than as a porous solid with a single target porosity. The derived relationships show why uniform porosity is rarely optimal: transport depends on pore connectivity and nonlocal diffusion, while mechanical stability depends on local strut density and stress concentration. The framework predicts that graded density, bounded pore size, and robust optimization against uncertain transport and mechanical parameters are more defensible design strategies than maximizing porosity or stiffness alone. The equations also identify measurable validation endpoints for future experimental work. The main contribution is a coherent design logic that can rank scaffold architectures, expose failure modes, and guide the selection of printable geometries before fabrication.

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