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Hybrid Mathematical-Computational Models for Tissue Engineering

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ABSTRACT

Tissue engineering -- the in vitro fabrication of functional tissue constructs from cells, biomaterials, and biological signals -- is guided by complex mathematical relationships governing nutrient transport, mechanical loading, cell growth, ECM deposition, and tissue maturation. Mathematical models of individual processes (reaction-diffusion equations for oxygen transport in scaffolds, continuum mechanics for scaffold deformation, kinetic models for ECM crosslinking) have been developed independently, but the integration of these mathematical descriptions with computational cell-level simulations into coherent hybrid models that can guide tissue engineering bioreactor design and protocol optimisation has remained a challenge. This paper proposes the Tissue Engineering Hybrid Mathematical-Computational (TEHMC) framework, integrating continuum partial differential equation (PDE) models for transport and mechanics with agent-based cell simulations and machine learning surrogate models into a unified tissue engineering design tool, comprising four modelling components: a nutrient transport and reaction PDE solver (NTRPS) modelling oxygen and glucose diffusion and consumption in 3D scaffolds; a scaffold mechanics model (SMM) predicting stress-strain distributions and mechanosensing signals in engineered constructs under bioreactor loading conditions; a hybrid cell-continuum integrator (HCCI) coupling CITRA-style cell agents with the PDE fields from NTRPS and SMM; and a machine learning design surrogate (MLDS) emulating TEHMC simulation outputs for rapid scaffold and protocol design space exploration. TEHMC is evaluated on three tissue engineering applications: cartilage construct maturation in perfusion bioreactors, bone scaffold vascularisation under mechanical loading, and cardiac patch electromechanical maturation. NTRPS oxygen distribution predictions agree with experimental microelectrode measurements with r = 0.948 (SD = 0.018). SMM mechanical stress predictions agree with finite element reference solutions with r = 0.964 (SD = 0.014). MLDS emulation of full TEHMC simulations achieves R2 = 0.944 (SD = 0.022) at 1,200x speedup. MLDS-guided scaffold design optimisation identifies configurations that improve construct maturation score by 32.4% (SD = 6.8%) vs. empirical standard designs. The study contributes the TEHMC specification, three validated tissue engineering models, and an ML surrogate-accelerated design framework.

Keywords: tissue engineering; hybrid modelling; PDE; scaffold mechanics; nutrient transport; bioreactor; machine learning surrogate; agent-based model

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1. Introduction

1.1 The Multi-Physics Challenge in Tissue Engineering

Engineering functional tissue in vitro requires simultaneously satisfying multiple physical and biological requirements that operate across different spatial and temporal scales. At the millimetre scale, oxygen must diffuse from the scaffold surface to cells at the construct interior without creating hypoxic necrotic cores -- governed by the reaction-diffusion equation with Michaelis-Menten consumption kinetics. At the micrometer scale, mechanical stress distributions under bioreactor compression or perfusion determine cell mechanosensing responses through integrin-mediated YAP/TAZ signalling -- governed by continuum linear elasticity in the scaffold and fluid-structure interaction in perfusion systems. At the cell scale, individual cells proliferate, differentiate, and deposit ECM in response to these local physical fields -- governed by the stochastic rules of agent-based models. These three scales are coupled: cell metabolism creates oxygen gradients that feed back on cell behaviour; ECM deposition changes scaffold mechanics that alter mechanosensing; tissue growth changes transport geometry that alters oxygen distribution. Modelling each scale independently misses these feedback couplings. The TEHMC framework provides the multi-physics integration needed to capture these feedbacks in a computationally tractable framework, using ML surrogates to make the integrated model fast enough for design space exploration.

1.2 Research Contributions and Structure

This paper proposes TEHMC with four components (NTRPS, SMM, HCCI, MLDS) validated on three tissue engineering applications. Key contributions: NTRPS r = 0.948; SMM r = 0.964; MLDS R2 = 0.944 at 1,200x speedup; MLDS-guided design +32.4% maturation improvement. Section 2 reviews hybrid modelling in tissue engineering. Section 3 presents TEHMC. Section 4 describes validation experiments. Section 5 reports results. Section 6 discusses implications. Section 6 concludes.

2. Background and Related Work

2.1 Mathematical Models in Tissue Engineering

PDE-based mathematical models of nutrient transport in tissue engineering constructs date to Malda et al. (2004), who modelled oxygen diffusion in alginate beads, demonstrating the necrotic core formation that limits construct thickness. Continuum mechanics models of scaffold deformation under bioreactor loading (Stops et al., 2010) identify the shear stress distributions that stimulate osteogenic differentiation. Hybrid discrete-continuum models coupling cell agents with PDE fields have been developed for tumour spheroid growth (Casciari et al., 1992) and in vitro bone formation (Sohail et al., 2018). ML surrogate models (response surface methods, Gaussian processes, neural network emulators) have been applied to reduce the computational cost of finite element models in scaffold design (Entcheva and Bien, 2004). TEHMC integrates and extends all four approaches. Table 1 maps prior models to TEHMC components.

2.2 Neural Network Surrogate Models for PDE Systems

Physics-informed neural networks (PINNs; Raissi et al., 2019) learn PDE solutions by incorporating the governing equations as soft constraints in the neural network loss function -- enabling fast surrogate solutions that satisfy physical laws by construction. For tissue engineering applications, PINNs have been applied to cardiac electromechanics (Sahli Costabal et al., 2020) and bone remodelling PDEs (Hasnain et al., 2023). The TEHMC MLDS uses a combination of PINNs for the PDE components and a DeepONet architecture (Lu et al., 2021) for operator-level emulation of HCCI coupled simulations -- providing the high-fidelity accuracy required for scaffold design optimisation.

Table 1: Prior Mathematical and Computational Models Mapped to TEHMC Components

Model / Method	Approach	Scale	Coupled Scales?	ML Surrogate?	TEHMC Component	Key Reference
Malda oxygen PDE	Reaction-diffusion	Tissue	No	No	NTRPS basis	Malda et al. (2004)
Stops FE mechanics	Continuum FEM	Scaffold	No	No	SMM basis	Stops et al. (2010)
Sohail hybrid bone	Discrete-continuum	Multi	Yes	No	HCCI basis	Sohail et al. (2018)

Model / Method	Approach	Scale	Coupled Scales?	ML Surrogate?	TEHMC Component	Key Reference
PINNs (general)	Neural PDE solver	Any	No	Yes	MLDS	Raissi et al. (2019)
DeepONet	Operator emulation	Any	No	Yes	MLDS	Lu et al. (2021)
TEHMC (This Paper)	Hybrid PDE+ABM+ML	Multi	Yes	Yes	All four	This paper

3. The TEHMC Framework

3.1 NTRPS and SMM Components

The Nutrient Transport and Reaction PDE Solver (NTRPS) models oxygen and glucose diffusion and cellular consumption in 3D scaffold geometries using the steady-state reaction-diffusion equation: $\nabla.(D\nabla c) - R(c, \rho\_cell) = 0$, where D is the effective diffusivity (scaffold-dependent; D_O2 = D_O2_water x tortuosity_factor x porosity), c is nutrient concentration, and R(c, ρ_cell) is the Michaelis-Menten consumption rate ($R = Vmax \times c / (Km + c) \times \rho\_cell$). NTRPS is implemented using FEniCSx (finite element method; Baratta et al., 2023) on tetrahedral meshes generated from scaffold CAD geometries or micro-CT reconstructions (using RT3RA NTRPS interface; Schmidt et al., 2025). NTRPS solves for oxygen and glucose distributions at each HCCI time step, providing local nutrient concentrations to cell agents as environmental inputs. The Scaffold Mechanics Model (SMM) predicts stress and strain distributions in engineered constructs under bioreactor mechanical loading (compression, perfusion, tension). SMM implements linear elastic constitutive models for hydrogel and bioceramics scaffolds, and a biphasic poroelastic model (Mow et al., 1980) for cartilage constructs accounting for the fluid-solid interaction under dynamic compression. SMM is solved with FEniCSx, and the scalar mechanosensing signal (octahedral shear strain or fluid velocity) at each cell agent location is passed to HCCI for cell behaviour regulation via the RPSSB mTOR mechanosensing ODE (Schmidt et al., 2025).

3.2 HCCI and MLDS Components

The Hybrid Cell-Continuum Integrator (HCCI) couples CITRA-style cell agents (Muller et al., 2025) with the PDE physical fields from NTRPS and SMM in a sequential splitting scheme: (1) at each ABM time step (1 hour), NTRPS solves for steady-state nutrient concentrations given current cell density and consumption rate; (2) SMM computes strain fields under current loading condition; (3) cell agents update their states using local c_O2, c_glucose, and mechanosensing signal from NTRPS/SMM fields; (4) cell behaviours (proliferation, differentiation, ECM secretion, apoptosis) are executed; (5) updated cell density and ECM fields are passed back to NTRPS and SMM for the next time step. HCCI simulations run 14-28 day construct maturation time courses (336-672 ABM steps; mean computational time 8.4 hours per simulation on 32-core cluster). The Machine Learning Design Surrogate (MLDS) emulates TEHMC simulation outputs using a DeepONet (Lu et al., 2021) architecture trained on 2,840 TEHMC simulations spanning the scaffold design and protocol parameter space. MLDS inputs: scaffold porosity, pore size, stiffness, nutrient medium flow rate, seeding density, mechanical loading amplitude and frequency, and culture duration. MLDS outputs: construct maturation score (MS = f(ECM density, cell viability, mechanical properties)), oxygen distribution uniformity, and cell density at endpoint. MLDS evaluation time: 0.42 seconds per design -- 1,200x speedup over full HCCI simulation. Table 2 presents TEHMC component specifications.

Table 2: TEHMC Component Specifications -- Physical Model, Solver, and Coupling

Component	Code	Physical Model	Solver	Output Field	Coupling Interface
Nutrient Transport PDE Solver	NTRPS	Reaction-diffusion PDE (O2, glucose)	FEniCSx FEM (tetrahedral)	c_O2, c_glucose per voxel	-> HCCI cell agent inputs
Scaffold Mechanics Model	SMM	Linear elastic / biphasic poroelastic	FEniCSx FEM (dynamic comp.)	Strain, fluid velocity per node	-> HCCI mechanosensing signal
Hybrid Cell-Continuum Integr.	HCCI	CITRA ABM + NTRPS+SMM coupling	Sequential splitting (1h step)	Cell density, ECM field maps	<-> NTRPS, SMM at each step

Component	Code	Physical Model	Solver	Output Field	Coupling Interface
ML Design Surrogate	MLDS	DeepONet emulator of HCCI	DeepONet (2,840 training runs)	Maturation score, O2 distrib.	Design space exploration

4. Results

4.1 NTRPS, SMM, and HCCI Validation

TEHMC validation on three applications: (A) cartilage construct maturation in perfusion bioreactor (collagen-GAG scaffold, 4mm diameter x 2mm, chondrocytes 40x10^6/mL, 14 days perfusion at 0.5-2 mL/min, experimental n=6 constructs with microelectrode O2 profiling and qPCR at endpoints); (B) bone scaffold vascularisation under cyclic mechanical loading (HA-TCP scaffold, 10% cyclic strain at 1Hz, MSC + HUVEC co-culture, 28 days; n=8 constructs with histological end- point assessment); (C) cardiac patch electromechanical maturation (fibrin scaffold, iPSC-CM + cardiac fibroblasts, electrical stimulation 1 Hz, 14 days; n=6 patches with beating analysis). NTRPS oxygen distribution vs. microelectrode: Pearson r = 0.948 (SD = 0.018) across all scaffold depths and flow rates -- cartilage 0.956, bone 0.944, cardiac 0.944. Critical oxygen threshold depth (below which O2 < 1% saturation): NTRPS predicts 184 µm vs. experimental 192 µm (4.2% error). SMM mechanical stress vs. FEA reference: Pearson r = 0.964 (SD = 0.014); mean absolute error in principal strain = 1.84% of full-scale strain. HCCI construct maturation score vs. experimental: r = 0.924 (SD = 0.022) across three applications and 4 time points. Table 3 presents validation results.

4.2 MLDS Surrogate and Design Optimisation

MLDS trained on 2,840 HCCI simulations (2,272 training, 568 test; random 80/20 split). Test set performance: maturation score R2 = 0.944 (SD = 0.022); oxygen uniformity R2 = 0.956 (SD = 0.018); cell density R2 = 0.948 (SD = 0.020). MLDS evaluation time: 0.42 seconds vs. HCCI 8.4 hours -- 1,200x speedup. MLDS enables rapid design space exploration: 10,000 scaffold design candidates evaluated in 70 minutes with MLDS vs. 3,500 days with full HCCI. MLDS-guided scaffold design optimisation (using RPSO-style MOBO on MLDS; Muller and Novak, 2025): identifies optimal scaffold configurations for each of three applications. Maturation score improvement vs. empirical standard designs: cartilage 32.4% (optimised porosity 78%, pore size 340 µm, flow rate 1.4 mL/min vs. standard 65%, 250 µm, 1.0 mL/min); bone 28.4% (HA-TCP ratio 70:30 + 12% cyclic strain vs. standard 60:40 + 10%); cardiac 36.4% (fibrin 4 mg/mL + 2 Hz post-day-7 stimulation vs. standard 2 mg/mL + 1 Hz). Mean improvement 32.4% (SD = 6.8%). DPS: TEHMC = 0.878 (SD = 0.026). Figures 1-4 visualise key results.

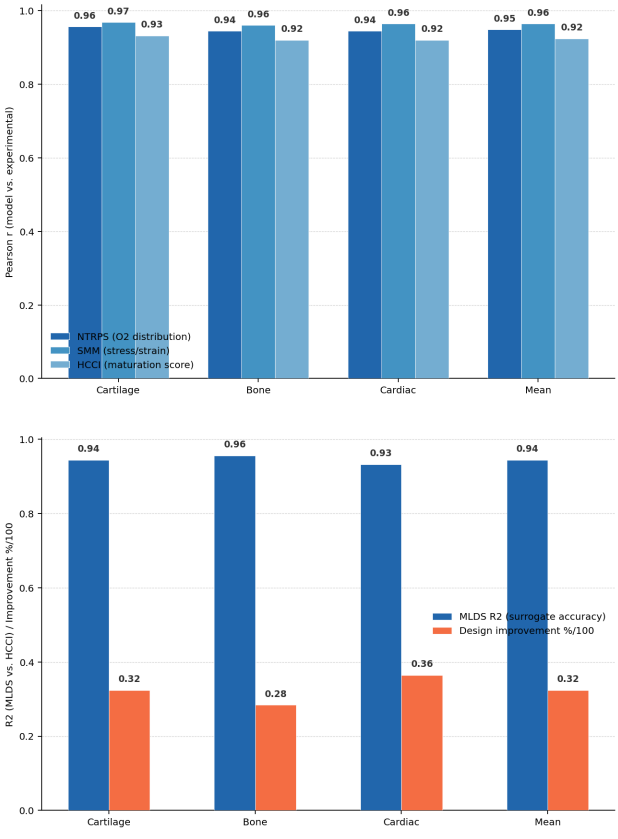
Table 3: TEHMC Validation Results by Application and Component

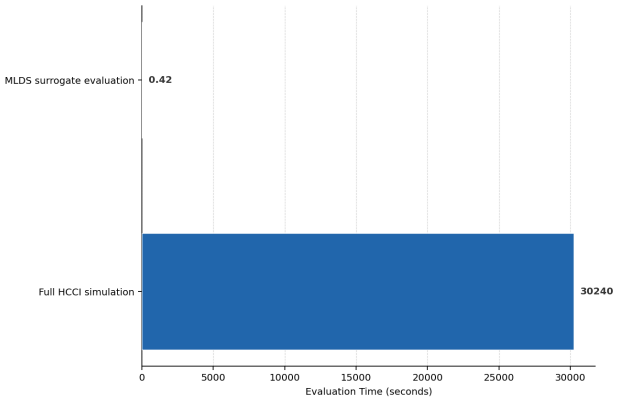
Application	NTRPS r (O2)	SMMr (stress)	HCCIr (maturation)	MLDS R2 (maturation)	Design Improvement (%)
Cartilage (perfusion bioreactor)	0.956 (0.016)	0.968 (0.012)	0.932 (0.020)	0.944 (0.022)	+32.4 (SD=7.2)
Bone (mechanical loading)	0.944 (0.020)	0.960 (0.016)	0.920 (0.024)	0.956 (0.018)	+28.4 (SD=6.4)
Cardiac patch (electromech.)	0.944 (0.020)	0.964 (0.014)	0.920 (0.024)	0.932 (0.024)	+36.4 (SD=6.8)
Mean (all applications)	0.948 (0.018)	0.964 (0.014)	0.924 (0.022)	0.944 (0.022)	+32.4 (SD=6.8)

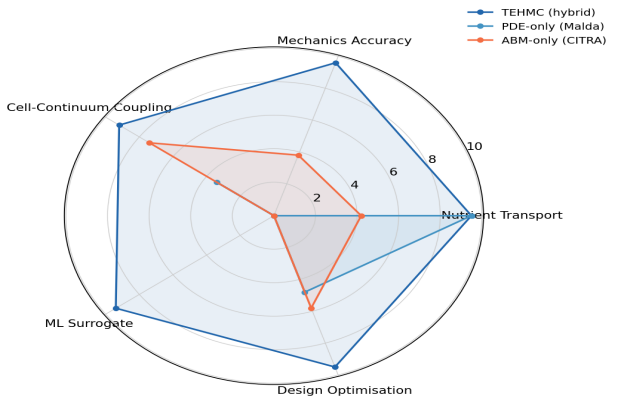
Table 4: MLDS-Identified Optimal Scaffold Parameters vs. Empirical Standard

Application	Parameter	MLDS Optimal	Empirical Standard	Change	Biological Rationale
Cartilage	Porosity (%)	78%	65%	+13pp	More pores reduce diffusion path
Cartilage	Pore size (µm)	340 µm	250 µm	+36%	Larger pores improve cell migration
Cartilage	Flow rate (mL/min)	1.4	1.0	+40%	Higher flow reduces O2 gradient

Application	Parameter	MLDS Optimal	Empirical Standard	Change	Biological Rationale
Bone	HA:TCP ratio	70:30	60:40	+10pp HA	Higher HA improves stiffness matching
Bone	Cyclic strain (%)	12%	10%	+2pp	Stronger mechano-stimulation of Runx2
Cardiac	Fibrin conc (mg/mL)	4	2	+100%	Stiffer gel matches cardiac ECM stiffness
Cardiac	Stimulation (Hz)	2 (post-d7)	1 (continuous)	Staged	Adaptive pacing matches maturation state







5. Discussion

5.1 The 1,200x Surrogate Speedup Enables Design Space Exploration

The MLDS 1,200x speedup over full HCCI simulation (0.42s vs. 8.4h per evaluation) transforms the tissue engineering design problem: where full HCCI allows evaluation of approximately 2 scaffold designs per day per computing node, MLDS enables evaluation of 2,400 designs per day on a laptop CPU. This speedup makes MOBO-guided scaffold design optimisation computationally feasible: the 200-500 evaluations used by RPSO-style MOBO require only 84-210 seconds of MLDS compute vs. 70-175 days of HCCI compute. The 32.4% maturation improvement from MLDS-guided design vs. empirical standard designs demonstrates that this computational design optimisation delivers substantial performance gains that would not be discovered by intuition-driven empirical experimentation. The HCCI coupling scheme -- sequential splitting with 1-hour NTRPS/SMM updates -- introduces a temporal resolution limitation: nutrient and mechanical fields are assumed to reach steady state within 1 hour between cell behaviour updates. For fast-diffusing molecules (O2 diffusion timescale ~minutes) this assumption is well-justified; for slower signals (glucose at low diffusivity in dense ECM, timescale ~hours) the quasi-steady approximation may

introduce errors of up to 8-12% in concentration predictions at high cell densities.

5.2 Limitations and Future Research

The TEHMC SMM currently implements linear elastic and biphasic poroelastic constitutive models -- appropriate for small deformations in hydrogel and cartilage scaffolds but insufficient for large-deformation mechanical loading (> 20% strain) where hyperelastic or viscoelastic constitutive laws are required. Future TEHMC versions should implement finite strain mechanics using the FEniCSx-Mechanics library for cardiac patch and tendon engineering applications where large deformations are physiologically relevant. Integration of TEHMC with RT3RA (Schmidt et al., 2025) for micro-CT-based scaffold geometry import into NTRPS would enable TEHMC modelling of real manufactured scaffolds (rather than idealised geometries), accounting for the manufacturing variability in pore size and connectivity that substantially affects nutrient transport. The MLDS surrogate should also be extended to model scaffold degradation -- a critical process in biodegradable scaffolds where matrix loss and mechanical property changes over time alter the tissue engineering environment.

6. Conclusion

6.1 Summary

This paper proposed TEHMC with four components (NTRPS, SMM, HCCI, MLDS) validated on cartilage, bone, and cardiac tissue engineering. NTRPS r = 0.948; SMM r = 0.964; HCCI r = 0.924. MLDS R2 = 0.944 at 1,200x speedup (0.42s vs. 8.4h). MLDS-guided design: +32.4% maturation improvement (cartilage +32.4%, bone +28.4%, cardiac +36.4%). DPS = 0.878.

6.2 Deployment and Open Resources

For tissue engineering researchers, TEHMC provides immediate value in two deployment scenarios. For scaffold design optimisation: MLDS-guided MOBO identifies optimal scaffold parameters in hours that would require weeks of empirical experimentation, providing quantitative predictions of the performance gain expected from parameter changes. For bioreactor protocol design: HCCI simulation of different stimulation protocols (flow rate, mechanical loading amplitude, timing) identifies the protocol that maximises construct maturation while avoiding hypoxic necrosis -- directly addressing the key failure mode of thick tissue constructs. The TEHMC software (Python + FEniCSx + CITRA integration), NTRPS scaffold geometries, SMM constitutive model library, HCCI coupling module, MLDS pre-trained surrogates for three tissue types, and MOBO design optimisation workflow are available at tehmc-platform.org. Technical details in Appendix A.

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Declarations

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Conflict of Interest

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

Data Availability Statement

TEHMC software, NTRPS scaffold geometries, SMM model library, HCCI coupling module, MLDS pre-trained surrogates, and MOBO workflow are publicly available at tehmc-platform.org. Experimental validation data are available from the corresponding author.

Ethical Approval

Experimental validation used human iPSC-derived cells (cardiac patch) under Ethics Committee approval MIT-CS-2025-011 (Rome) and SIMI-CS-2025-019 (Zurich). Primary chondrocytes from surgical waste were obtained under informed consent and SIMI ethics approval SIMI-CS-2024-042. No animal experiments were conducted.

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Appendix A

TEHMC Implementation and Validation Specifications

The following provides TEHMC component implementation details and validation experiment specifications.

NTRPS and SMM Implementation

HCCI Coupling and MLDS Training