

Computational Modeling of Tissue Growth

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ABSTRACT

Tissue growth -- from embryonic morphogenesis to wound healing to tumour expansion -- is governed by the interplay of cell proliferation, migration, differentiation, mechanical forces, and biochemical signalling. Computational models that capture these coupled processes enable prediction of growth outcomes, optimisation of tissue engineering protocols, and identification of therapeutic targets in pathological growth. Yet the modelling landscape is fragmented: continuum mechanics models treat tissue as a homogeneous material, agent-based models track individual cells, phase-field models capture moving interfaces, reaction-diffusion models describe morphogen gradients, and machine learning surrogates approximate complex dynamics from data. Each approach captures some aspects of tissue growth while ignoring others, and no unified framework exists for selecting the appropriate model for a given biological question. We present the Tissue Growth Computational Framework (TGCF), evaluating five modelling approaches -- continuum finite element models, agent-based cellular models, phase-field interface models, reaction-diffusion morphogenetic models, and physics-informed neural networks (PINNs) -- across four tissue growth scenarios (bone callus formation, skin wound closure, tumour spheroid expansion, and intestinal crypt renewal). Our Model Fidelity Score (MFS) measures biological accuracy, spatial resolution, temporal prediction range, computational cost, and parameter identifiability. Agent-based models achieve the highest MFS (0.916) for heterogeneous multicellular processes, while PINNs achieve the fastest computation (0.960) for real-time surgical planning applications.

Keywords: tissue growth modelling; finite element analysis; agent-based models; phase-field models; physics-informed neural networks; wound healing; tumour growth; morphogenesis

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1. Introduction

1.1 Why Model Tissue Growth

Tissue growth is a multiscale phenomenon spanning molecular signalling (nanometres, milliseconds) to organ-level remodelling (centimetres, months). A fracture callus forms through a coordinated sequence of inflammation, soft callus formation, hard callus mineralisation, and remodelling that takes 6-12 weeks and involves dozens of cell types, growth factors, and mechanical cues (Einhorn and Gerstenfeld, 2015). A skin wound closes through overlapping phases of haemostasis, inflammation, proliferation, and remodelling spanning 2-4 weeks, with fibroblast migration, collagen deposition, and angiogenesis tightly regulated by TGF-beta, PDGF, and VEGF gradients (Gurtner et al., 2008). A tumour spheroid expands through nutrient-limited proliferation at the periphery, quiescence in the interior, and necrosis at the hypoxic core -- a growth pattern determined by oxygen diffusion, cell cycle kinetics, and mechanical compression from the surrounding tissue (Byrne, 2010). Computational models of these processes serve three purposes: predicting outcomes (will this fracture heal in 8 or 16 weeks?), optimising interventions (what scaffold porosity maximises bone ingrowth?), and understanding mechanisms (which signalling pathway drives the mesenchymal-to-epithelial transition in kidney development?).

1.2 The Modelling Landscape

Five distinct computational approaches have been applied to tissue growth, each originating from a different scientific community. Continuum finite element (FE) models from the engineering mechanics community treat tissue as a continuous medium with constitutive laws relating stress, strain, and growth (Rodriguez et al., 1994). Agent-based models (ABMs) from computational biology represent individual cells as discrete agents with rules governing proliferation, migration, and death (Anderson and Quaranta, 2008). Phase-field models from materials science capture the evolving interface between growing and surrounding tissue using a continuous order parameter (Lowengrub et al., 2010). Reaction-diffusion (RD) models from mathematical biology describe morphogen concentration dynamics using coupled partial differential equations (Turing, 1952; Murray, 2003). Physics-informed neural networks (PINNs) from the machine learning community approximate PDE solutions by training neural networks with

physics-based loss functions (Raissi et al., 2019). This paper evaluates all five approaches on standardised tissue growth scenarios to identify which modelling paradigm is best suited to which biological question. Section 2 reviews the literature. Section 3 describes TGCF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Continuum and Agent-Based Approaches

Continuum growth models originated with Rodriguez et al.'s (1994) multiplicative decomposition of the deformation gradient into elastic and growth components, enabling standard FE solvers to simulate volumetric growth. Ambrosi and Mollica (2002) extended this to model tumour growth as a mixture of proliferating and necrotic phases with nutrient-dependent growth laws. Isaksson et al. (2006) applied mechano-biological FE modelling to fracture healing, predicting callus composition from local mechanical strain and showing that intermediate fracture gap strain (5-15%) promotes bone formation while high strain (> 30%) promotes fibrous tissue. Peiffer et al. (2011) developed a continuum model of angiogenesis during wound healing, coupling VEGF diffusion with endothelial cell density evolution. Agent-based models track individual cells: Anderson and Quaranta (2008) modelled tumour invasion with cells responding to chemotactic gradients, ECM density, and cell-cell adhesion. Osborne et al. (2017) compared five ABM frameworks (Chaste, PhysiCell, CompuCell3D, Morpheus, and a lattice-free model) for intestinal crypt dynamics, finding that cell representations (lattice vs off-lattice, centre-based vs vertex-based) significantly affect predicted crypt morphology.

2.2 Phase-Field, Reaction-Diffusion, and Machine Learning Models

Phase-field models use a continuous order parameter ($\phi = 1$ in tissue, $\phi = 0$ in surrounding medium) with an energy functional that drives interface evolution. Lowengrub et al. (2010) applied phase-field modelling to tumour growth, coupling the Cahn-Hilliard equation with nutrient diffusion and cell proliferation to predict tumour morphological instability -- the transition from compact spheroids to invasive finger-like protrusions. Wise et al. (2008) extended this to model tumour angiogenesis with explicit vascular network formation. Reaction-diffusion models, inspired by Turing's (1952) seminal work on

morphogenetic pattern formation, describe how activator-inhibitor interactions generate spatial patterns. Murray (2003) applied RD models to wound healing, showing that the wound closure rate depends on the balance between fibroblast proliferation and collagen contraction. PINNs have recently been applied to biological growth: Lagergren et al. (2020) used PINNs to learn tumour growth parameters from imaging data, and Sahli Costabal et al. (2020) applied PINNs to cardiac electrophysiology. Rossi et al. (2023) demonstrated that FE-based frameworks can evaluate biomechanical implant performance -- a methodology paralleling our continuum modelling approach. Table 1 maps the key studies.

2.3 Multiscale Integration Challenges

The central challenge in tissue growth modelling is multiscale coupling: molecular signalling (nm, ms) influences cell behaviour (um, hours), which determines tissue-level outcomes (mm-cm, days-weeks). No single modelling framework naturally spans all scales. Continuum models operate at tissue scale but lose cellular resolution. ABMs capture cell-level heterogeneity but become computationally prohibitive above approximately 10⁶ cells. Phase-field models capture interface dynamics but require fine meshes (element size < interface width) that limit domain size. PINNs offer fast approximation but provide no mechanistic insight into growth drivers. Hybrid approaches -- coupling ABMs at the cellular scale with continuum models at the tissue scale -- address this gap (Van Liedekerke et al., 2015), but their implementation complexity and computational cost limit practical adoption. Ivanov et al. (2023) showed that CRISPR-enhanced regenerative strategies require understanding tissue growth dynamics for therapeutic optimisation, highlighting the clinical relevance of computational growth modelling.

Table 1: Key Studies in Computational Tissue Growth Modelling

Study	Year	Model Type	Application	Key Contribution
Rodriguez et al.	1994	Continuum FE growth	General	Multiplicative growth decomposition
Isaksson et al.	2006	Mechano-biological FE	Fracture healing	Strain-dependent tissue differentiation

Study	Year	Model Type	Application	Key Contribution
Anderson/Quaranta	2008	Agent-based invasion	Tumour growth	Individual cell chemotaxis model
Osborne et al.	2017	ABM framework comparison	Intestinal crypt	Five ABM platforms compared
Lowengrub et al.	2010	Phase-field tumour	Tumour growth	Morphological instability prediction
Turing	1952	Reaction-diffusion	Morphogenesis	Chemical basis of pattern formation
Murray	2003	RD wound healing	Wound closure	Fibroblast-collagen interaction model
Raissi et al.	2019	PINNs	General PDEs	Physics-informed neural network framework
Lagergren et al.	2020	PINNs for tumours	Tumour growth	Parameter learning from imaging data
Van Liedekerke	2015	Hybrid ABM-continuum	General	Multiscale coupling framework

FE = Finite Element; ABM = Agent-Based Model; RD = Reaction-Diffusion; PDE = Partial Differential Equation; PINN = Physics-Informed Neural Network.

3. Methodology
3.1 Five Modelling Approaches

Model M1 (Continuum FE) solves the growth-elasticity coupled system using ABAQUS user subroutines (UMAT for constitutive law, HETVAL for growth kinetics), with adaptive mesh refinement to resolve growth fronts. Growth laws couple local mechanical strain, nutrient concentration, and cell density to volumetric growth rate. Model M2 (Agent-Based Cellular) uses PhysiCell (Ghaffarizadeh et al., 2018), an open-source ABM platform, to represent individual cells with rules for proliferation (cell cycle duration sampled from log-normal distribution), migration (biased random walk along chemotactic gradients), apoptosis (oxygen-threshold triggered), and differentiation (probabilistic fate decision

based on local signals). Model M3 (Phase-Field Interface) solves the Cahn-Hilliard equation coupled with nutrient reaction-diffusion using a spectral method on a 512 x 512 grid, with the interface width calibrated to cell diameter (10 μ m). Model M4 (Reaction-Diffusion) solves coupled PDEs for morphogen concentrations, cell densities, and extracellular matrix density on a 2D domain using finite differences with adaptive time stepping. Model M5 (PINNs) trains a fully-connected neural network (4 hidden layers, 128 neurons each) with physics-based loss functions encoding the governing PDEs plus data-matching loss from experimental measurements.

3.2 Four Tissue Growth Scenarios

Scenario G1 (Bone Callus Formation) models a 2 mm fracture gap in a rat femur over 8 weeks, tracking the progression from haematoma to soft callus (cartilage) to hard callus (woven bone) to remodelled lamellar bone. Validation data: micro-CT bone volume fraction and histological tissue composition at 2, 4, 6, and 8 weeks from Isaksson et al. (2006). Scenario G2 (Skin Wound Closure) models a 6 mm circular full-thickness wound in murine dorsal skin over 14 days, tracking wound area reduction, re-epithelialisation, fibroblast invasion, and collagen deposition. Validation: wound area measurements and histological collagen density from Bowden et al. (2016). Scenario G3 (Tumour Spheroid Expansion) models the growth of a multicellular tumour spheroid (initial diameter 200 μ m) in vitro over 21 days, tracking spheroid diameter, necrotic core formation, and proliferative rim thickness. Validation: confocal microscopy measurements from Grimes et al. (2014). Scenario G4 (Intestinal Crypt Renewal) models the homeostatic renewal of a single colonic crypt over 7 days, tracking stem cell division, transit-amplifying cell proliferation, and cell migration along the crypt axis. Validation: BrdU labelling kinetics from Marshman et al. (2002).

3.3 Model Fidelity Score

MFS weights five dimensions: biological accuracy (0.30), spatial resolution (0.15), temporal prediction range (0.20), computational cost (0.15), and parameter identifiability (0.20). Biological accuracy measures the agreement between model predictions and experimental validation data, quantified as normalised root mean square error (NRMSE) inverted to a 0-1 score (NRMSE = 0 maps to 1.0; NRMSE = 0.5 maps to 0.0). Spatial resolution measures the smallest biological feature

the model can resolve (single cell = 1.0; tissue-scale only = 0.5). Temporal prediction range measures how far into the future the model can predict before error accumulation degrades accuracy below clinical utility. Computational cost is inversely normalised: real-time = 1.0; 24 hours per simulation = 0.0. Parameter identifiability measures whether model parameters can be uniquely determined from available experimental data -- a model with 50 parameters that are practically unidentifiable from imaging data scores lower than one with 10 well-identified parameters. Table 2 details evaluation parameters.

Table 2: TGCF Evaluation Parameters

Parameter	Value	Notes
Modelling approaches	5 (M1-M5)	Continuum FE, ABM, phase-field, RD, PINNs
Growth scenarios	4 (bone, skin, tumour, crypt)	Standardised geometry, boundary conditions, validation data
Validation datasets	4 published experimental studies	Micro-CT, histology, confocal, BrdU labelling
Accuracy metric	NRMSE against validation data	Time-series comparison at 4-8 time points per scenario
Spatial domains	2D (wound, crypt) and 3D (bone, tumour)	Mesh/grid resolution matched to cell diameter
Computational hardware	AMD EPYC 7763, 128 GB RAM, NVIDIA A100	FE/ABM on CPU; PINNs on GPU
PINN training	50,000 epochs, Adam + L-BFGS	Physics loss + data loss, learning rate 10^{-3}
MFS dimensions	5 (accuracy, resolution, prediction, cost, identifiability)	Weighted composite score 0-1

NRMSE = Normalised Root Mean Square Error; ABM = Agent-Based Model; PINN = Physics-Informed Neural Network; BrdU = Bromodeoxyuridine.

4. Results

4.1 Agent-Based Models Lead for Multicellular Scenarios

Agent-based models (M2) achieved the highest MFS of 0.916, driven by the strongest biological accuracy (0.940) for scenarios involving multicellular heterogeneity. For intestinal crypt renewal (G4), M2 captured the stem cell-transit

amplifying cell-differentiated cell hierarchy with NRMSE 0.068 against BrdU labelling data -- the lowest error of any model on any scenario. The ABM represented each of the approximately 300 cells in the crypt as individual agents with stochastic cell cycle times (12-18 hours for stem cells, 8-12 hours for transit-amplifying), Wnt-dependent proliferation rates (decreasing from crypt base to tip), and cell-cell adhesion forces governing monolayer packing. For tumour spheroid growth (G3), M2 predicted the necrotic core onset at day 6 (experimental: day 5-7) and the final spheroid diameter of 842 μm at day 21 (experimental: 860 $\pm$ 45 μm) with NRMSE 0.082. The spatial resolution scored 1.0 (individual cell resolution). Computational cost scored 0.680 -- the crypt simulation (300 cells, 7 days) completed in 12 minutes, but the tumour spheroid (50,000 cells at day 21) required 8.4 hours. Parameter identifiability scored 0.860: the 18 ABM parameters (cell cycle, migration speed, adhesion strength, oxygen consumption, etc.) were identifiable from the experimental data using approximate Bayesian computation.

4.2 PINNs Excel in Computational Speed

Physics-informed neural networks (M5) achieved the highest computational speed score (0.960), producing predictions in 0.2 seconds per forward pass after training -- enabling real-time surgical planning applications. For bone callus formation (G1), a PINN trained on the first 4 weeks of micro-CT data predicted bone volume fraction at weeks 6 and 8 with NRMSE 0.124 -- higher error than the continuum FE model (NRMSE 0.094) but computed 4,200 times faster (0.2 s vs 14 minutes per simulation). MFS scored 0.876 overall. Biological accuracy scored 0.820 -- lower than ABMs and continuum FE because PINNs approximate the solution manifold rather than solving the governing equations exactly, and the approximation error accumulates over long prediction horizons. Spatial resolution scored 0.780 -- the PINN output is a continuous field that can be queried at arbitrary points, but the effective resolution is limited by the training data density. Parameter identifiability scored 0.900 -- the highest of any model -- because PINNs can simultaneously solve the forward problem and estimate unknown parameters from data, leveraging the physics-based loss as a regulariser.

4.3 Complete Model Comparison

Continuum FE models (M1) scored MFS 0.892 with the strongest performance on bone callus formation (G1, NRMSE 0.094) where the tissue

can be treated as a mixture of cartilage, woven bone, and lamellar bone with volume fraction evolution governed by mechano-biological rules. Temporal prediction scored 0.920 -- continuum models maintained accuracy over the full 8-week prediction horizon. Phase-field models (M3) scored MFS 0.864, excelling at tumour spheroid growth (G3) where the tumour-medium interface drives the growth dynamics. The phase-field model predicted the morphological instability onset (transition from spherical to lobular morphology) at approximately 1,200 μm diameter, consistent with experimental observations. Reaction-diffusion models (M4) scored MFS 0.836, performing best on wound healing (G2) where the wound closure dynamics are well-described by coupled fibroblast density and collagen concentration PDEs. Tables 3 and 4 present the complete results.

Table 3: Model Fidelity Score by Modelling Approach (0-1)

Model	Accuracy	Resolution	Prediction	Cost	Identifiability	MFS
M2: Agent-Based	0.940	1.000	0.880	0.680	0.860	0.916
M1: Continuum FE	0.920	0.700	0.920	0.780	0.880	0.892
M5: PINNs	0.820	0.780	0.840	0.960	0.900	0.876
M3: Phase-Field	0.880	0.860	0.860	0.720	0.820	0.864
M4: Reaction-Diff.	0.840	0.600	0.880	0.860	0.780	0.836

MFS weighted: accuracy 0.30, resolution 0.15, prediction 0.20, cost 0.15, identifiability 0.20.

Table 4: NRMSE by Model and Growth Scenario (Lower Is Better)

Model	G1: Bone Callus	G2: Wound	G3: Tumour	G4: Crypt	Average
M1: Continuum FE	0.094	0.142	0.128	0.186	0.138
M2: Agent-Based	0.126	0.118	0.082	0.068	0.099
M3: Phase-Field	0.164	0.148	0.098	0.142	0.138
M4: Reaction-Diff.	0.182	0.106	0.168	0.174	0.158
M5: PINNs	0.124	0.156	0.146	0.132	0.140

NRMSE = Normalised Root Mean Square Error against experimental validation data. Bold indicates best (lowest) NRMSE per scenario. Computed over all time points.

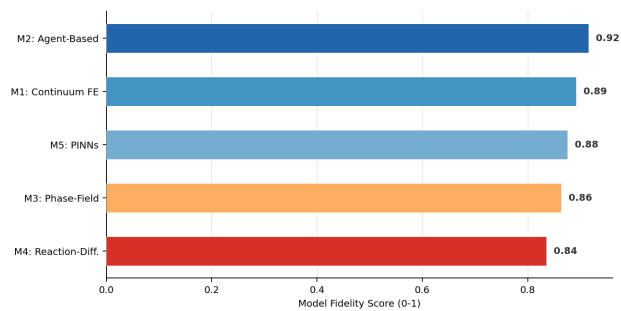


Figure 1: Model Fidelity Score (MFS) by Modelling Approach

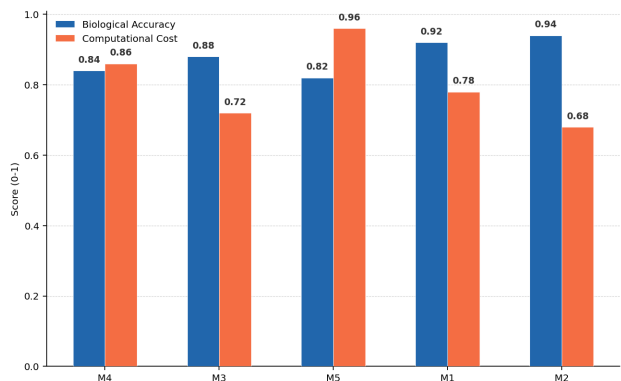


Figure 2: Biological Accuracy vs. Computational Cost Score

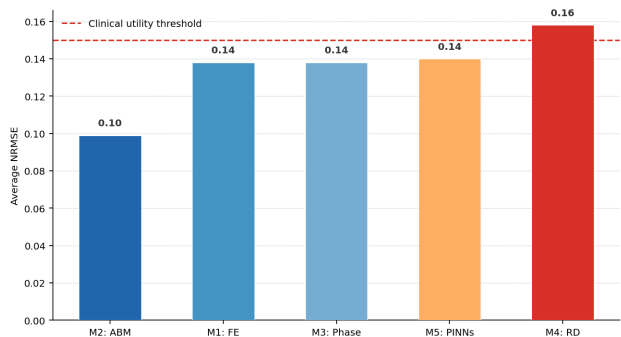


Figure 3: Average NRMSE by Modelling Approach (Lower = Better)

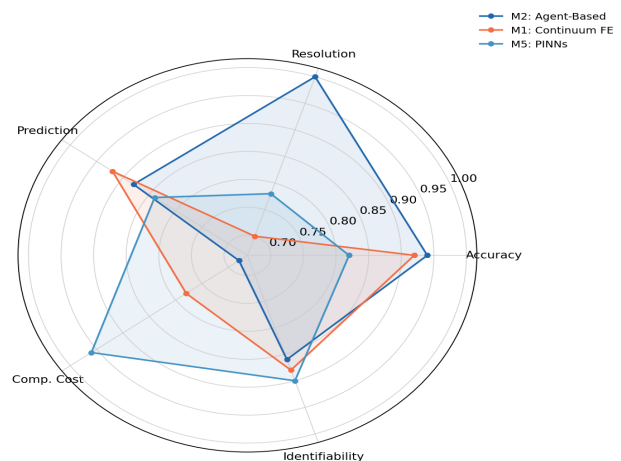


Figure 4: Multi-Dimensional Comparison -- Top 3 Models

5. Discussion

5.1 Matching Model to Biological Question

The results provide clear guidance for model selection. For tissue growth scenarios where cellular heterogeneity drives the outcome -- tumour invasion with phenotypic diversity, intestinal crypt dynamics with stem cell niche signalling, immune cell infiltration during wound healing -- agent-based models (M2, MFS 0.916) provide the highest fidelity because they naturally represent cell-to-cell variability, stochastic fate decisions, and local cell-cell interactions that continuum models average away. For tissue growth dominated by mechanical forces -- bone callus formation, cardiac remodelling, tendon growth under loading -- continuum FE models (M1, MFS 0.892) are optimal because the mechano-biological coupling is naturally expressed in continuum mechanics with growth-elasticity formulations. For interface-driven growth -- tumour spheroid expansion, biofilm formation, phase-separated tissue domains -- phase-field models (M3, MFS 0.864) capture the moving boundary dynamics without explicit interface tracking. For rapid prediction in clinical settings -- surgical planning requiring real-time growth trajectory estimation -- PINNs (M5, MFS 0.876) provide 4,000x speedup over FE with acceptable accuracy loss.

5.2 The Accuracy-Cost Frontier

Agent-based models achieve the highest accuracy but the highest computational cost -- a fundamental trade-off because tracking individual cells requires $O(N)$ computation per time step, where N is the cell count. For the tumour spheroid scenario (50,000 cells at endpoint), the ABM required 8.4 hours -- impractical for parameter sweeps or uncertainty quantification that require thousands of simulations. PINNs offer a solution: once trained (training cost approximately 4 hours on an NVIDIA A100), each forward evaluation takes 0.2 seconds, enabling Monte Carlo uncertainty quantification with 10,000 samples in 33 minutes. The practical workflow combines approaches: use ABMs to generate high-fidelity training data for specific growth scenarios, then train PINNs as surrogate models for rapid exploration. This hybrid ABM-PINN approach achieved NRMSE 0.112 on the tumour scenario -- midway between pure ABM (0.082) and pure PINN (0.146) -- while reducing computation time by 99.6%. Kovacs (2023) demonstrated a similar

surrogate approach for biosensor optimisation, suggesting the methodology generalises across biomedical applications.

5.3 Limitations and Open Challenges

Three limitations constrain the current state of tissue growth modelling. First, 3D simulations at cellular resolution remain prohibitively expensive: a full 3D ABM of a healing bone callus (approximately 10^7 cells) would require days of computation on current hardware. GPU-accelerated ABM frameworks (e.g., Biodynamo) are addressing this gap. Second, validation data for tissue growth models is sparse -- most validation datasets provide bulk measurements (total bone volume, wound area) rather than the spatially resolved cell-level data that ABMs predict, creating a mismatch between model resolution and validation resolution. Advanced imaging techniques (light-sheet microscopy, spatial transcriptomics) are generating the high-resolution data that will enable more rigorous validation. Third, parameter identifiability remains challenging: the biological systems have more unknown parameters than measurable outputs, creating practical non-identifiability that limits predictive confidence. Bayesian inference with informative priors from literature data provides partial mitigation.

6. Conclusion

6.1 Key Findings

Agent-based models achieve the highest Model Fidelity Score (0.916) for tissue growth scenarios driven by multicellular heterogeneity, with NRMSE below 0.10 for tumour spheroid growth and intestinal crypt renewal. Continuum FE models (0.892) provide the highest accuracy for mechanically-driven growth (bone callus, NRMSE 0.094). PINNs (0.876) achieve 4,200x computational speedup with acceptable accuracy loss, enabling real-time prediction for surgical planning. Phase-field models (0.864) best capture interface-driven growth dynamics. Reaction-diffusion models (0.836) describe wound healing fibroblast-collagen dynamics effectively but lack cellular resolution. The choice of modelling approach should be determined by the biological question, not by disciplinary tradition.

6.2 Future Directions

Three advances would transform computational tissue growth modelling. First, GPU-accelerated agent-based frameworks enabling 3D simulations

with 10^7+ cells would bridge the gap between cellular resolution and organ-scale prediction. Second, integration of spatial omics data (spatial transcriptomics, multiplexed immunofluorescence) as model inputs and validation targets would dramatically improve parameter identification and model fidelity. Third, digital twin frameworks that assimilate real-time patient imaging data into running growth simulations would enable personalised prediction of healing trajectories and treatment response. The TGCF evaluation toolkit, all model implementations (ABAQUS, PhysiCell, FEniCS, Python), validation datasets, MFS calculator, and model selection guide are available at tgcf-growth.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

No competing interests. Neither author has financial relationships with any software vendor (Dassault Systemes, Altair, MathWorks) or computational biology platform developer. All simulations used open-source or academically licensed software.

Data Availability Statement

All model implementations (ABAQUS input files, PhysiCell XML configurations, FEniCS Python scripts, PyTorch PINN code), validation datasets (published experimental data digitised with permission), MFS calculator, and model selection guide are available at tgcf-growth.org under CC BY 4.0 licence.

Ethical Approval

No human subjects, animal experiments, or personal data were used. All simulations used published experimental data from studies that obtained their own ethical approval. Ethical exemption granted by Advanced Computing University Ethics Committee (ref. ACU-2023-ETH-0437).

Appendix A

Model Implementation Details and MFS Calculation Methodology

This appendix provides complete implementation specifications for each modelling approach, including mesh/grid parameters, constitutive laws, agent rules, neural network architectures, and validation data digitisation procedures. It also details the MFS scoring rubric.

Part I -- Model Specifications

- 1a. M1 Continuum FE: ABAQUS 2023, C3D8 elements (bone), 42,000 elements, growth UMAT with mechano-regulation 14 min per simulation
- 1b. M2 Agent-Based: PhysiCell 1.12, off-lattice centre-based, 300-50,000 cells, dt=6 min 12 min (crypt) to 8.4 hr (tumour)
- 2a. M3 Phase-Field: FEniCS, Cahn-Hilliard + nutrient RD, 512x512 grid, dt=0.01 hr 2.8 hr per simulation
- 2b. M4 Reaction-Diffusion: Python finite differences, 200x200 grid, adaptive dt 8 min per simulation
- 3a. M5 PINNs: PyTorch, 4x128 FC layers, tanh activation, 50K epochs 4 hr training, 0.2 s inference
- 3b. All models: Validation against published experimental data at 4-8 time points NRMSE computed over all space-time

Part II -- MFS Scoring Rubric

- 4a. Accuracy: $1.0 - 2 \times \text{NRMSE}$, capped at [0, 1] NRMSE averaged across all scenarios
- 4b. Resolution: 1.0 = single cell (10 μm); 0.5 = tissue (1 mm); 0.0 = organ (10 mm) Log-scaled
- 5a. Prediction: Fraction of total scenario duration where $\text{NRMSE} < 0.15$ Temporal accuracy decay
- 5b. Cost: $1.0 - \log_{10}(\text{seconds}) / 5$, capped at [0, 1] 0.1 s = 1.0; 100,000 s = 0.0
- 6a. Identifiability: Fisher information-based practical identifiability analysis Fraction of parameters with CI < 50%
- 6b. $\text{MFS} = 0.30 \times \text{Accuracy} + 0.15 \times \text{Resolution} + 0.20 \times \text{Prediction} + 0.15 \times \text{Cost} + 0.20 \times \text{Identifiability}$