

Mechanobiology-Guided Digital Twin Simulation of Tibial Fracture Healing: Patient-Specific Prediction of Non-Union and Union After Revision Fixation

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Abstract

Fracture healing is governed by the local mechanical environment, but its patient-specific effects remain difficult to quantify clinically. Most computational approaches represent either static measurements based on treatment and weight-bearing, or dynamic simulations based on generic cellular assumptions. Longitudinal assessment combining patient-specific mechanics with biological input is not yet clinically established. We present a patient-specific digital twin framework for fracture-healing simulation combining computed tomography-based geometry reconstruction, individualized gait-derived loading, and a biomechanoregulatory model of tissue regeneration for longitudinal healing simulation. The model describes oxygen transport, cell activity, extracellular matrix formation, and mechanically regulated tissue progression within the fracture region. The framework was applied to a tibial shaft non-union case where initial fixation failed and revision surgery resulted in union. Simulations predicted persistent non-union under the initial fixation and progression toward union after revision, consistent with the clinical course. The predicted pattern of mineralized tissue formation qualitatively agreed with follow-up radiographs. Controlled in-silico variations in fixation and loading highlighted the dominant influence of mechanics on healing progression, while sensitivity analyses indicated a secondary effect of oxygen transport on consolidation timing. These findings demonstrate the potential of patient-specific mechanobiological digital twins for mechanistic analysis and in-silico comparison of fixation and loading scenarios.

Introduction

Fracture healing is a spatially and temporally evolving mechanobiological process in which tissue regeneration is strongly influenced by the local mechanical environment^{1–5}. Although most long-bone fractures heal uneventfully, a relevant proportion progresses to delayed union or non-union, leading to repeated interventions, prolonged rehabilitation, and substantial socio-economic burden^{1,6,7}. Assuming freedom from infection, the causes of impaired healing are multifactorial and include fracture morphology, fixation stability, vascular supply, and patient-specific biological conditions^{1,8,9}. From a biomechanical perspective, however, the local mechanical conditions within the fracture region remain a central determinant of tissue progression because they directly influence the formation, persistence, or breakdown of repair tissue^{3–5,10–14}.

Despite advances in fracture fixation and postoperative care, the patient-specific mechanical environment during healing remains difficult to quantify in clinical routine^{1,8,9}. Radiographs and clinical follow-up provide indirect evidence of progression, but they do not resolve the underlying local stimulus conditions that govern tissue differentiation and consolidation^{1,15–17}. As a result, clinically similar fractures may follow markedly different healing trajectories because construct mechanics, loading during rehabilitation, and biological support interact in ways that are difficult to infer from imaging alone^{5,12–15,17–21}. This limitation motivates computational approaches that can link patient-specific anatomy, fixation, and loading to spatially resolved predictions of healing progression^{15,17–23}.

In this context, patient-specific digital twins have emerged as a promising framework for integrating clinical imaging, biomechanical simulation, and subject-specific data into individualized computational models^{24–30}. In orthopaedic trauma applications, such models offer the possibility to evaluate fixation strategies, explore rehabilitation-related loading scenarios, and analyse their implications for fracture healing in-silico^{27,29,30}. For these applications to be meaningful, however, the digital representation must be coupled to a healing model that reflects the interplay between mechanics and biology rather than construct stability alone^{8,9,16,17}.

The mechanobiological basis of fracture healing has been shaped by several seminal concepts. Wolff's law² established bone adaptation to mechanical loading as a fundamental determinant of skeletal structure. Pauwels' concept of causal histogenesis³ proposed that local mechanical stimuli, particularly compression and shear, influence tissue differentiation during repair. Perren's strain theory³¹ further emphasized interfragmentary movement and local deformation as key mechanical determinants of healing progression. Building on these concepts, mechanoregulation models introduced explicit stimulus formulations to predict tissue differentiation, including combinations of octahedral shear stress or strain with hydrostatic stress or strain^{4,10,11}, as well as poroelastic approaches based on pore-fluid pressure and interstitial fluid velocity⁵. Together, these frameworks established the principle that healing outcome is strongly linked to the local mechanical state within the fracture region^{2–5}.

On this foundation, biomechanoregulatory healing models aim to represent tissue formation and resorption as stimulus-driven, spatially resolved processes. Claes-inspired approaches frequently employ fuzzy-logic formulations with perfusion and cell concentrations as state variables^{11,12}, thereby translating local mechanobiological cues into continuous rule-based tissue updates. In parallel, mechanoregulation-driven differentiation models¹³ have incorporated progenitor cell migration and stimulus-dependent transitions into distinct tissue phenotypes. Biological extensions, including angiogenesis models¹⁴, have further improved mechanistic realism by accounting for vascular ingrowth and its interaction with tissue differentiation. Complementary continuum and population-based approaches describe tissue and cell dynamics through growth factor-dependent regulation and cell-phenotype-specific activity, thereby providing a broader representation of the biological processes underlying repair^{15,32–34}. Comprehensive reviews of these model classes are provided by Wang et al.¹⁶ and Ghiasi et al.¹⁷.

More recent advances in computational fracture-healing simulation have progressed from simplified two-dimensional concepts toward fully three-dimensional, spatially resolved finite-element frameworks that more realistically capture the mechanical and biological complexity of bone repair. Morgan et al.¹⁸ introduced a strain-based three-dimensional algorithm capable of predicting a range of healing outcomes, including non-union. Degenhart et al.¹⁹ translated a mechanobiological healing model to patient-specific three-dimensional geometries reconstructed from clinical imaging and demonstrated prediction of non-union in surgically treated diaphyseal femur fractures. Razavi et al.²¹ further extended

three-dimensional modelling by integrating mechanoregulation, angiogenesis, stem cell migration, and physiologic callus growth, while Schwarzenberg et al.²³ enabled domain-independent and spatially adaptive callus formation in mechanoregulated simulations. In addition, sensor-supported validation approaches²² have begun to link experimentally measured loading or construct behaviour with mechanobiological simulation outcomes, thereby strengthening the translational relevance of such models.

Alongside mechanistic models, data-driven approaches and machine-learning-based predictors^{35,36} have recently shown promise for fracture-healing outcome prediction. However, these methods often face challenges related to interpretability, extrapolation beyond the training domain, and consistency with established mechanobiological principles^{35,36}. In contrast, mechanistic patient-specific models offer the possibility to relate anatomy, fixation, and loading directly to the spatial and temporal evolution of the healing environment. Nevertheless, there remains a limited number of clinically feasible, patient-specific workflows^{24,27,29,30} that combine three-dimensional imaging, individualized loading, and a biologically informed healing model within a digital twin framework suitable for case-specific in-silico analysis.

In the present study, we address this gap by embedding a partial-differential-equation-based biomechanoregulatory healing model within a patient-specific digital twin pipeline for fracture-healing simulation. The framework combines computed tomography-based reconstruction of fracture geometry and fixation with individualized loading derived from gait measurements, thereby enabling case-specific representation of the mechanical environment during healing. The healing model describes the coupled spatiotemporal evolution of oxygen transport, cell activity, extracellular matrix formation, and mechanically regulated tissue progression within the fracture region, linking local mechanics with biological supply in a spatially resolved manner. We apply the framework to a tibial shaft non-union case in which initial fixation failed, and revision fixation subsequently resulted in union. By comparing the two fixation states and their associated loading conditions, we evaluate whether the model can reproduce the observed transition from persistent non-union to progression toward healing and thereby provide a mechanistic basis for in-silico analysis of fixation- and loading-dependent fracture-healing trajectories.

Results

The patient-specific digital twin was used to compare the initial fixation state associated with clinical non-union and the revised fixation state associated with subsequent union. Results are presented in four steps. First, the simulated spatial progression of bone matrix formation is described. Second, the temporal evolution of the mechanical stimulus environment is analysed to identify the mechanistic effect of fixation and loading. Third, the sensitivity of healing progression to oxygen transport is evaluated. Finally, simulated radiographs are compared qualitatively with clinical follow-up images.

Healing simulation results

Figure 1 and Fig. 2 show the spatial-temporal development of the normalized bone matrix within the callus on representative coronal and sagittal sections at intervals of 100 days. The sections cover the fracture region consisting of the bone ends, the individual bone fragments, the intramedullary nail and the fracture gap. They enable a spatial assessment of the healing process within the fracture gap at different points in time.

At the inception of the healing process, the entire callus area is characterized by the presence of soft tissue. By day 100, new bone tissue has formed in the sagittal plane, but only at the superior and anterior inferior bone ends, and the fracture gap remains unfilled. However, in the coronal plane, the areas where new bone tissue has grown from the bone ends are significantly larger. Furthermore, the fracture gap at the medial inferior bone end has been filled by a large bone splinter with bone tissue, thereby stabilizing this area.

In the subsequent 100 days, the areas will continue to extend from the bone ends in both views. In the sagittal view, the region occupied by soft tissue is notably diminished, despite the absence of bone matrix formation in the posterior region between the bone fragments. Furthermore, the medial aspect of the callus in the coronal view demonstrates a significant residual fracture gap.

These trends persist as healing progresses, resulting in the formation of a bridging of the lateral and anterior callus areas with bone matrix shortly after the 300th day of healing. The posterior side follows shortly thereafter, while the medial areas take the longest for the bone matrix to form and the fracture gap to be completely bridged. As of day 400, complete restoration of mechanical stability is observed for both views.

Mechanical stimulus during healing

As illustrated in Fig. 3, the mechanical-stimulus environment within the fracture callus undergoes a temporal progression, which is expressed as the percentage of callus points allocated to each stimulus category. The distribution undergoes a transformation from a heterogeneous initial state to a bone-dominated stimulus state, with the most pronounced shift occurring at the transition from initial to revision fixation.

During the initial fixation phase, the bone stimulus category increases steadily, indicating a gradual expansion of callus regions experiencing conditions conducive to bone formation. In the initial phase of healing, a significant portion of the callus is classified under the destructive stimulus category, thus making it one of the predominant early states. The higher degree of weight bearing around the six week timepoint is a significant event in this context. At this time, the destructive stimulus increases sharply, rising from approximately one quarter of callus points to about one half. This increase corresponds with a significant decrease in fibrous tissue and cartilage stimuli, suggesting that the rise in destructive stimulus primarily occurs at the expense of stimulus conditions associated with soft-tissue formation. During this interval, resorption remains comparatively small, while the bone stimulus fraction continues

to increase more gradually across the initial fixation phase. However, it does not become dominant before revision.

The observations indicate that the application of full weight bearing resulted in a mechanical stimulus shift, thereby introducing a more damaging environment to a significant portion of the callus. It is noteworthy that the redistribution process appears to reduce the prevalence of soft-tissue-associated stimulus states rather than directly converting regions into conditions that favour bone formation. This pattern is consistent with a mechanical environment that is less conducive to organized tissue progression within the callus, thereby plausibly contributing to delayed healing. In this context, the sustained elevation of destructive stimulus following full weight bearing provides a mechanistic explanation for impaired consolidation during initial fixation and supports the clinical need for subsequent revision fixation. This is followed by a rapid transition to a predominantly bone-associated stimulus regime and suppression of destructive and soft-tissue-associated stimuli for the remainder of healing.

At the transition to revision fixation, the stimulus distribution undergoes another abrupt change. The proportion of callus points in the bone category exhibited a precipitous rise, rapidly approaching a state of near saturation. Thereafter, it remained essentially stable for the remainder of the observation period. Concurrently, destructive stimuli undergo a rapid decline, reaching near-zero levels almost immediately after the revision process is initiated. Cartilage stimuli, conversely, decreases to negligible values shortly after the fixation change, while fibrous tissue stimuli decline more gradually, tapering toward zero over the subsequent healing period. Resorption demonstrates a transient increase during the period of revision, subsequently transitioning to a prolonged, stable phase of healing.

Taken together, these results indicate that revision fixation coincides with a rapid homogenization of the callus mechanical environment toward a predominantly bone-associated stimulus regime, accompanied by suppression of destructive and soft-tissue-associated stimulus states. The trends further suggest that the most significant qualitative transition in stimulus exposure occurs at the fixation change. The initial fixation phase is characterized by a gradual, progressive redistribution from destructive and soft-tissue stimuli toward conditions that favour bone.

Effect of oxygen transport

The temporal development of the mean, normalized tissue matrix concentrations for bone, cartilage and soft tissue is shown in Fig. 4 for two oxygen diffusion coefficients ($D_{O_2} = 0.65$ and $0.975 \frac{mm^2}{day}$). In both cases, the three tissue matrices show the same growth up to day 42 (switch to full load).

The first effects of the different diffusion coefficients become apparent in the further course up to the revision surgery. It was found that the bone matrix shows a stronger increase at a higher diffusion value than at a low one. Analysis of the data revealed that at the time of revision surgery, the mean value of bone matrix concentration was 0.6 for the higher diffusion coefficient, whereas it was 0.52 for the lower diffusion coefficient. The opposite trend was observed for cartilage tissue. The present study concludes

that, after initial formation, the cartilage matrix is degraded more rapidly in the case of a high diffusion value than in the case of a low value. Initial differentiation is not possible in the case of fibrous tissue. In both cases, there is an almost identical decline in the mean value of the soft tissue matrix until the revision surgery. It was found that the aforementioned influences intensify after revision surgery. As a result, the mean bone matrix value of 0.9 is reached earlier (after approximately 275 days) than in the case with lower diffusion capacity (after approximately 396 days). The simulations show that in both cases, almost complete ossification is achieved at the end of the simulation period. In the case of lower diffusivity, the cartilage tissue remained elevated and showed a secondary maximum around day 245, while in the case of higher diffusivity, it was almost completely degraded earlier and without a pronounced secondary peak. A comparable course manifests itself, which also affects the soft tissue and is comparable to that of the cartilage tissue. In the case of low diffusion capacity, the mean value of the fibrous tissue remains at a constant value of approximately 0.02 over a longer period, while in the case of high diffusion capacity, it approaches negligible values more quickly.

In summary, these results indicate that increased oxygen transport accelerates the transition from fibrous/cartilaginous tissue to bone and shortens the duration of the intermediate soft tissue phases.

Radiographic comparison of simulation and clinical follow-up

To verify the predicted healing outcome on a qualitative basis, a comparison is made of X-ray images generated virtually with the patient's follow-up X-ray images at two time points in the healing process (see Fig. 5).

The initial measurement was taken at the revision surgery, conducted approximately six months after the primary surgical procedure. In both X-ray images, the lateral side of the fracture remains clearly unbridged, indicating a persistent gap despite mineralization having begun at the proximal and distal bone ends. Furthermore, on the medial side, both demonstrate an absence of continuous mineralized connection at the proximal and distal ends between the large bone fragments and the main tibial segments. Between these two points, a distinct mineralization is observable in both the virtual and the patient's X-ray images

Following revision fixation, both the clinical and virtual radiographs indicate progression towards consolidation. The fracture region appears more continuous, and there is bridging mineralized tissue present across the defect. The wedge fragment also appears more integrated with the main bone. Compared with the revision time point, the virtual radiograph also shows an increased extent of mineralized continuity, which is consistent with advancing healing.

There are notable differences between the clinical and virtual radiographs, which can be attributed to two main factors. Firstly, the healing model does not fully reproduce bone remodelling features that are visible in clinical X-rays. In the simulation, the elastic modulus assigned to the newly formed bone is effectively limited to values representative of trabecular bone, rather than allowing progression towards cortical bone stiffness. Consequently, the model only partially captures the maturation processes

associated with corticalization and structural reorganization, meaning that the virtual radiographs underrepresent remodelling-related densification and the development of sharper cortical contours apparent in the clinical images.

Secondly, additional discrepancies arise from the virtual X-ray generation procedure itself. Virtual radiographs are derived from the simulated distribution of mineralized tissue and do not incorporate surrounding soft tissue or realistic radiographic image formation effects, such as anatomical superposition, scatter, projection-dependent contrast changes, or implant-related artefacts. This simplification yields cleaner images with sharper boundaries and more uniform intensity patterns, whereas clinical radiographs exhibit heterogeneous radiodensity and a more complex texture. These differences in imaging can affect the perceived callus contour and local density variations, even when the overall fracture morphology and healing trends are in good qualitative agreement.

Discussion

This study shows that a patient-specific mechanobiology-guided digital twin can reproduce the clinically observed contrast between persistent non-union under the initial fixation and progression toward union after revision fixation. In this case, the model not only predicted the overall healing outcome, but also captured the spatial progression of mineralized tissue formation in qualitative agreement with follow-up radiographs. These findings support the potential of combining patient-specific geometry, fixation, loading, and mechanobiological regulation within a digital twin framework for fracture-healing analysis.

A key result is that the transition from non-union to healing was primarily associated with a marked change in the local mechanical environment. Under the initial fixation, destructive stimulus states remained prominent and increased after full weight bearing, indicating an unfavourable mechanical construct for organized bridging, with low stability further worsened by increased patient weight bearing. After revision fixation, the simulated stimulus distribution shifted rapidly toward a predominantly bone-associated regime, while destructive and soft-tissue-associated states were strongly reduced. This suggests that, in the present case, the revision procedure restored a mechanical environment permissive for consolidation and that construct mechanics were the dominant driver of the different healing trajectories.

An important strength of the present work is the patient-specific workflow. The digital twin was based on CT-derived reconstruction of fracture geometry and fixation and incorporated individualized loading derived from gait-related measurements, enabling a realistic comparison of the pre- and post-revision states within the same patient. This is particularly valuable because it reduces confounding by inter-individual variability and allows the effect of altered fixation and loading conditions to be assessed more directly than in cross-patient comparisons.

The comparison between simulated and clinical radiographs in a challenging fracture geometry further supports the spatial plausibility of the model. In both, the fracture remained incompletely bridged at revision and showed progression toward consolidation thereafter. However, this agreement should be

interpreted as qualitative rather than quantitative validation. The model predicts three-dimensional tissue evolution, whereas the clinical reference is based on two-dimensional projection imaging. In addition, the virtual radiographs do not fully capture cortical remodeling or realistic radiographic image-formation effects, which explains part of the discrepancy in density distribution and contour sharpness between simulated and clinical images.

The oxygen sensitivity analysis indicates that biological transport conditions mainly influenced the timing of healing rather than the overall qualitative outcome in this case. Increased oxygen transport accelerated the transition from fibrous and cartilaginous tissue to bone, whereas lower diffusion delayed consolidation. This suggests that the distinction between failure and healing was mainly mechanically driven, while biological parameters modulated the speed of progression once a mechanically favorable environment had been established. At the same time, this also highlights a current limitation of patient-specific healing simulations: key biological inputs remain difficult to measure directly in clinical routine, which constrains temporal prediction accuracy.

Several limitations should be acknowledged. First, this is a technique description with a single-case based qualitative assessment and therefore does not allow conclusions about general predictive performance across broader patient cohorts or treatment strategies. Second, the loading conditions necessarily simplify real postoperative behavior and cannot fully represent variability in daily activity, rehabilitation compliance, or compensatory gait adaptations. Third, uncertainties in segmentation, material assignment, and fixation representation may affect the predicted local mechanical environment. Finally, key patient-specific biological inputs remain difficult to quantify in clinical routine. Overall, the present work demonstrates that a biomechanoregulatory fracture-healing model embedded in a patient-specific digital twin can reproduce a mechanically induced non-union state after initial fixation and the subsequent healing response after revision fixation. The qualitative agreement between virtual and clinical radiographs further supports the spatial plausibility of the approach. Future work should validate the workflow in larger cohorts, compare its predictions with existing fracture-healing models, quantify uncertainties in mechanical and biological inputs, and incorporate patient-specific biological and lifestyle parameters where ethically and clinically available. More quantitative imaging endpoints, such as CT-derived callus metrics, should also be integrated where feasible. These developments may enable mechanobiology-guided digital twins to support both retrospective explanation of healing failure and prospective assessment of fixation and rehabilitation scenarios.

Methods

Biomechanoregulatory healing model

The healing model presented here describes the temporal and spatial development of oxygen supply (c_{O_2}), cell concentrations, and the growth and degradation of the extracellular matrix (ECM), accounting for both biological and mechanical stimuli. In this study, the focus is on four cell types: mesenchymal

stem cells (c_{msc}), fibroblasts (c_f), chondrocytes (c_c) and osteoblasts (c_b). In addition to these cells, the extracellular matrices (m_f , m_c and m_b) are also considered.

$$\frac{\partial c_{O_2}}{\partial t} = \nabla D_{O_2} \nabla c_{O_2}$$

1

$$\frac{\partial c_{msc}}{\partial t} = \nabla D_{msc}(m) \nabla c_{msc} + f_{msc}^{PR}(\psi, c_{space}) c_{msc} - F_i^D(\psi, c) - f_{msc}^{AP}(\psi) c_{msc}$$

2

$$\frac{\partial c_f}{\partial t} = \nabla D_f(m) \nabla c_f + f_f^{PR}(\psi, c_{space}) c_f - F_i^D(\psi, c) - f_f^{AP}(\psi) c_f$$

3

$$\frac{\partial c_c}{\partial t} = \nabla D_c(m) \nabla c_c + f_c^{PR}(\psi, c_{space}) c_c - F_i^D(\psi, c) - f_c^{AP}(\psi) c_c$$

4

$$\frac{\partial c_b}{\partial t} = \nabla D_b(m) \nabla c_b + f_b^{PR}(\psi, c_{space}) c_b - F_i^D(\psi, c) - f_b^{AP}(\psi) c_b$$

5

$$\frac{\partial m_f}{\partial t} = f_f^{PM}(\psi, m_{space}) c_f - f_f^{EO}(\psi) c_b m_f - f_f^{DEG}(\psi) m_f$$

6

$$\frac{\partial m_c}{\partial t} = f_c^{PM}(\psi, m_{space}) c_c - f_c^{EO}(\psi) c_b m_c - f_c^{DEG}(\psi) m_c$$

7

$$\frac{\partial m_b}{\partial t} = f_b^{PM}(\psi, m_{space}, |\nabla m_b|) c_b - f_b^{DEG}(\psi) m_b$$

8

The initial equation (see Eq. 1) describes the change in oxygen concentration resulting from angiogenesis. This refers to the growth of new capillaries and blood vessels that provide messenger substances, growth factors and nutrients for the biological supply of the callus. It is therefore regarded as a biological stimulus ψ_{bio} that is effective during the healing process. The influence of this stimulus

on cell proliferation and differentiation, as well as on extracellular matrix formation and degradation, is well documented^{37–39}.

Moreover, the mechanical stimulus ψ_{mech} is known to influence cellular healing and transformation as well as the extracellular matrix. Consequently, the combined effect of these factors results in an overall stimulus ψ (ψ_{bio}, ψ_{mech}), that favors the development and growth of a specific cell type and the associated extracellular matrix. The proliferation of stem cells is only impeded by a deleterious stimulus^{8–10,13}.

The phenomenon of cell migration is described by a diffusion term in the equations given in equations 2–5. The potential for migration is subject to the influence of the extracellular matrix, with an increase in matrix concentration resulting in a corresponding inhibition of migration. Therefore, the available free space for tissue growth is hereby defined as

$$m_{space} = m_{max} - (m_f + m_c + m_b)$$

The diffusion coefficient D_i , where i denotes the depending cell type (m_{sc}, f, c, b) results in

$$D_i(m) = D_i \cdot m_{space}$$

The process of cell proliferation is modelled using the term $f_i^{PR}(\psi, c_{space}) c_i$. The proliferation rate of $f_i^{PR}(\psi, c_{space})$ is contingent upon both biological and mechanical stimuli. Furthermore, the proliferation of cells is constrained by the maximum spatial capacity that is available. To consider this, the free space of the concentrations is introduced. It is derived from the total available concentration space and the current concentrations, as follows

$$c_{space} = c_{max} - (c_{m_{sc}} + c_f + c_c + c_b)$$

This approach is predicated on the recognition of the physical limitations inherent in the tissue, thereby ensuring the prevention of concentrations that would otherwise be considered unrealistic.

The process of differentiation of mesenchymal stem cells (MSC's) into fibroblasts, chondrocytes or osteoblasts is described by $F_i^D(\psi, c)$. The outcome of this process is contingent on the prevailing stimuli and cell concentrations, which in turn determine the cell line into which the stem cells differentiate. Low oxygen levels are conducive to the process of chondrogenesis, while high oxygen levels and mechanical stress are known to promote the process of osteogenesis.

Excessive mechanical stress or insufficient biological supply has been shown to increase apoptosis, consequently leading to cell loss. To account for this effect, the apoptosis-related term $f_i^{AP}(\psi) c_i$ is introduced. This term represents the influence of mechanical and biological stimuli on cell concentration. Following the approach described by Isaksson et al.³⁴, f_i^{AP} is considered a constant apoptosis rate that becomes active when the prevailing stimulus fails to support the survival of the given cell type.

As demonstrated in equations 6–8, the processes of formation and degradation of the extracellular matrix are governed by specific mathematical models. The term f_j^{PM} represents matrix production by the corresponding cell types, while f_j^{DEG} characterises matrix degradation. j denotes here the depending matrix type (f, c, b) . The modulation of both production and degradation rates is influenced by biological and mechanical stimuli.

In particular, endochondral ossification has been identified as playing a pivotal role in the healing process. The transition from cartilage to bone tissue is a complex process that occurs in several phases. Initially, mesenchymal stem cells undergo differentiation into chondrocytes, which in turn contribute to the formation of the cartilage matrix⁴⁰. Angiogenic signals have been demonstrated to enhance oxygen supply, thereby inducing the differentiation of osteoblasts. These processes involve the degradation of the cartilage matrix, which is characterized by $f_c^{EO}(\psi) c_b m_c$. The result of this process is the replacement of the cartilage matrix with bone matrix. The process is found to be highly dependent on the local oxygen concentration and mechanical conditions⁴¹. It has been shown that low oxygen levels are conducive to the process of chondrogenesis, while higher levels are more conducive to the process of osteogenesis⁴².

Mechanical and biological stimulus

The mechanical stimulus is determined based on the magnitude of dilatational and distortional strain¹², cf. Figure 6. The boundaries separating these regions are characterized as ranges rather than thresholds. Therefore, the mechanical Stimulus ψ_{mech} is a nonbinary value between 0 and 1 for each of the stimulated cells and tissues, evaluated according to the membership function of a fuzzy logic by Simon et al.¹².

Mesenchymal stem cells always count as being stimulated, except at destructive strains. For very high strains (Destructive window), no cell types are stimulated, and only apoptosis takes place. All tissue and cell types are degraded if the stimulus is destructive. A minimal stimulus can result in the resorption of bone tissue through the actions of osteoclasts.

As mentioned before, the biological stimulus ψ_{bio} is determined by using oxygen supply. High oxygen concentrations promote bone formation by enhancing the differentiation and activity of osteoblasts. Elevated oxygen levels support mineralization processes and favor the development of ossified tissue. In contrast, low oxygen availability encourages cartilage formation, as reduced oxygen tension creates an environment that maintains cells in a chondrogenic state^{37,42–44}. This mimics the early stages of endochondral ossification, where cartilage serves as a template before being replaced by bone. Oxygen levels, therefore, split the biological stimulus into an ossification and chondrogenesis-promoting part, as shown in Fig. 7.

Implementation for patient-specific healing simulations

A 3D computational model was constructed from patient-specific CT data, which were segmented and meshed using ScanIP™ (Synopsys, Mountain View, CA, USA). The bone was modelled as an isotropic, linearly elastic material, with Young's modulus derived from the corresponding Hounsfield units and the corresponding Poisson ratio taken from literature. Since mechanical stimulation is caused by walking during healing, patient-specific walking data were collected, and the resulting knee joint forces and moments were integrated into the loading conditions. In order to conduct the simulation, a constant load was calculated. This was determined as the component-wise mean of the individual step vectors' peak force.

Within this framework (see Fig. 8), COMSOL® Multiphysics v6.3 (COMSOL AB, Stockholm, Sweden) was utilized to perform the mechanical "step" and healing model simulations. In the interval between simulations, the LiveLink™ (COMSOL AB, Stockholm, Sweden) for MATLAB® R2024b (The MathWorks Inc., Natick, Massachusetts, USA) was utilized to ascertain the mechanical stimulus and to calculate the updated material properties following each healing iteration. The initial procedure in this sequence of events is the execution of a "step" simulation, the purpose of which is to compute the local mechanical strains within the callus. The resulting mechanical stimuli were then evaluated and imported as input for the healing simulation, which simulates a one-day healing process. Subsequently, alterations in tissue matrix concentrations result in novel mechanical properties, which are recalculated following each healing iteration. These were subsequently re-imported into COMSOL®, where they modified the material properties for the following mechanical simulation. Through this iterative exchange, the healing model was advanced in daily increments, enabling a dynamic and consistent representation of the progression of tissue regeneration.

Patient-specific adaptations

The patient exhibited a tibial shaft non-union following initial fixation with an 8 mm intramedullary nail, signifying inadequate mechanical stability to facilitate normal fracture healing. In response to this complication, the treatment strategy that was selected involved the replacement of the original implant with a larger 11 mm intramedullary nail following the process of reaming of the medullary canal. The surgical intervention involved the removal of additional endosteal bone and the introduction of a thicker nail. This was done with the aim of increasing construct stiffness, reducing interfragmentary movement, and thereby creating a biomechanical environment more conducive to union ²⁹.

To quantitatively assess the mechanical effect of this intervention, two 3D digital models were generated in which only the nail diameter differed, while all other anatomical and implant parameters remained unchanged. The healing results from the first simulation -representing the patient's non-union under the initial 8 mm nail - were used as the initial conditions for the second model incorporating the 11 mm nail.

Additionally, the patient's fractured fibula was not treated during the initial surgery. As demonstrated by Orth et al. ⁴⁵, an untreated fibular fracture results in the tibia carrying nearly the entire load transmitted through the knee joint. By the time of the revision surgery, however, the fibula had fully healed, thereby

restoring its physiological load-sharing capacity. Under these conditions, the tibia is expected to bear approximately 80% of the knee joint forces. These distinct loading scenarios were accordingly implemented in both simulations to accurately reflect the biomechanical environment in both cases.

Declarations

Ethics approval and consent to participate

The study involving a human participant was approved by the Institutional Ethics Committee of the University of Tuebingen (Project Number 318/2022BO2). The study was conducted in accordance with local legislation and institutional requirements. Written informed consent to participate was obtained from the participant.

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Conflict of interest

The authors declare no competing interests.

Supplementary material

No supplementary material

Author Contribution

FS conceptualized the model and its numerical implementation, prepared and wrote the manuscript. M.R., S.D. and B.B. reviewed and wrote the manuscript. A.A. performed the movement analysis and the digital twin generation. T.H. and M.M. contributed to the research design and provided scientific guidance for the various aspects of the research. All authors have read and approved the submitted and final version of the manuscript.

Data Availability

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author. Researchers who wish to request access to data should send an

email indicating the purpose of the research. Each request will be reviewed by the responsible institutional review boards, considering the risk of patient re-identification and compliance with applicable data-protection rules.

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Figures

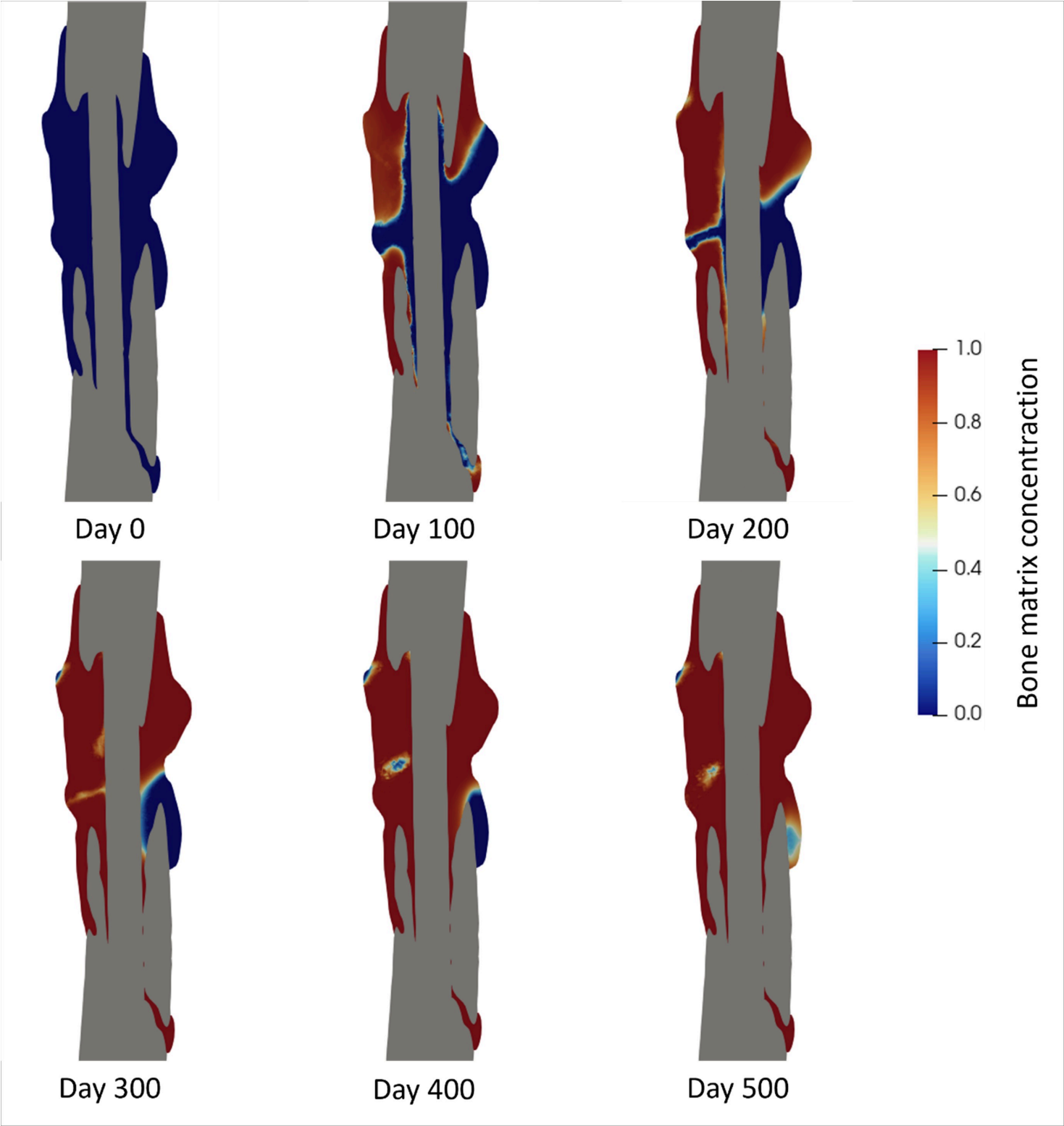


Figure 1

Spatial bone matrix distribution at 100 day steps inside the callus on a representative coronal slice

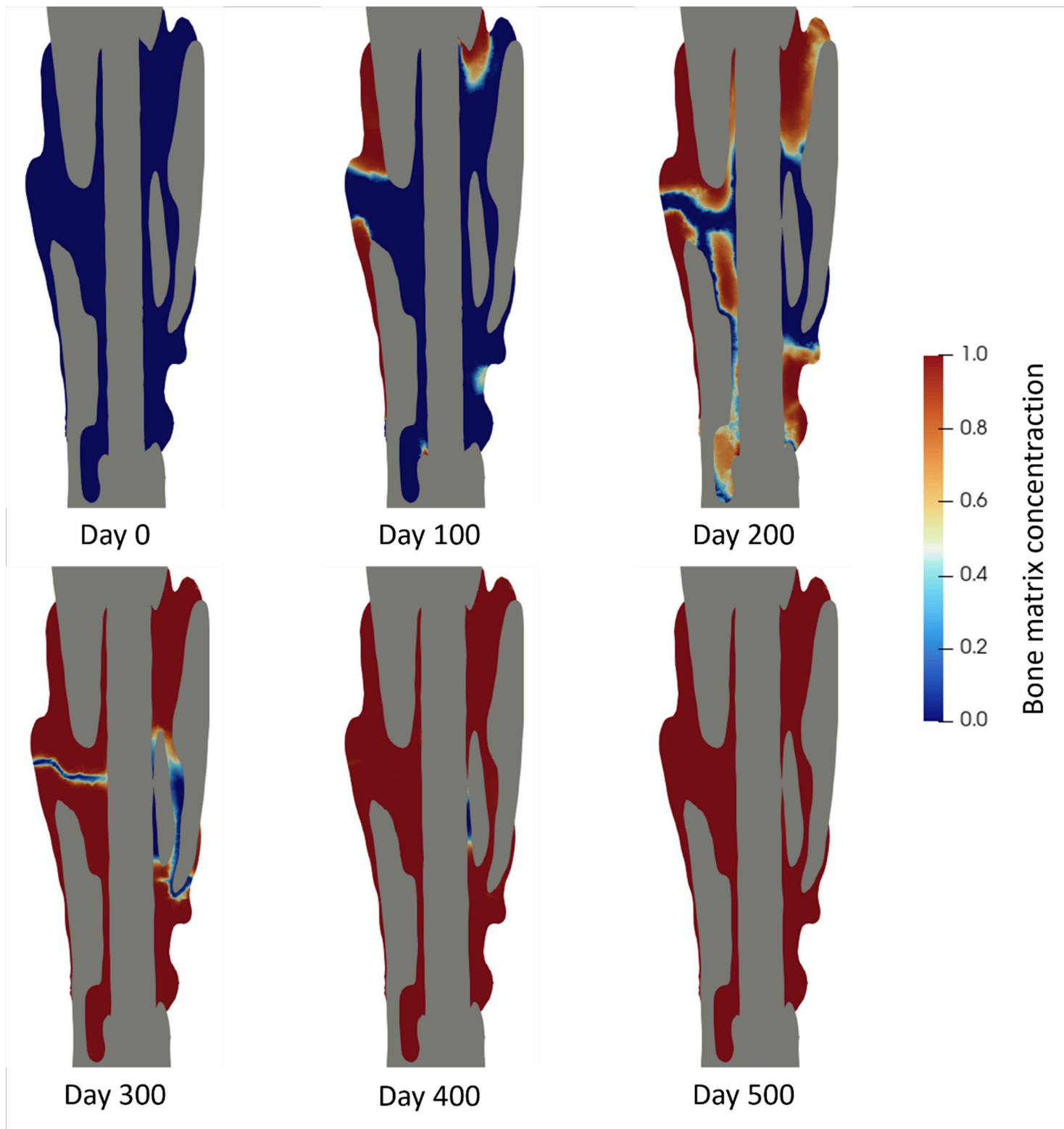


Figure 2

Spatial bone matrix distribution at 100 day steps inside the callus on a representative sagittal slice

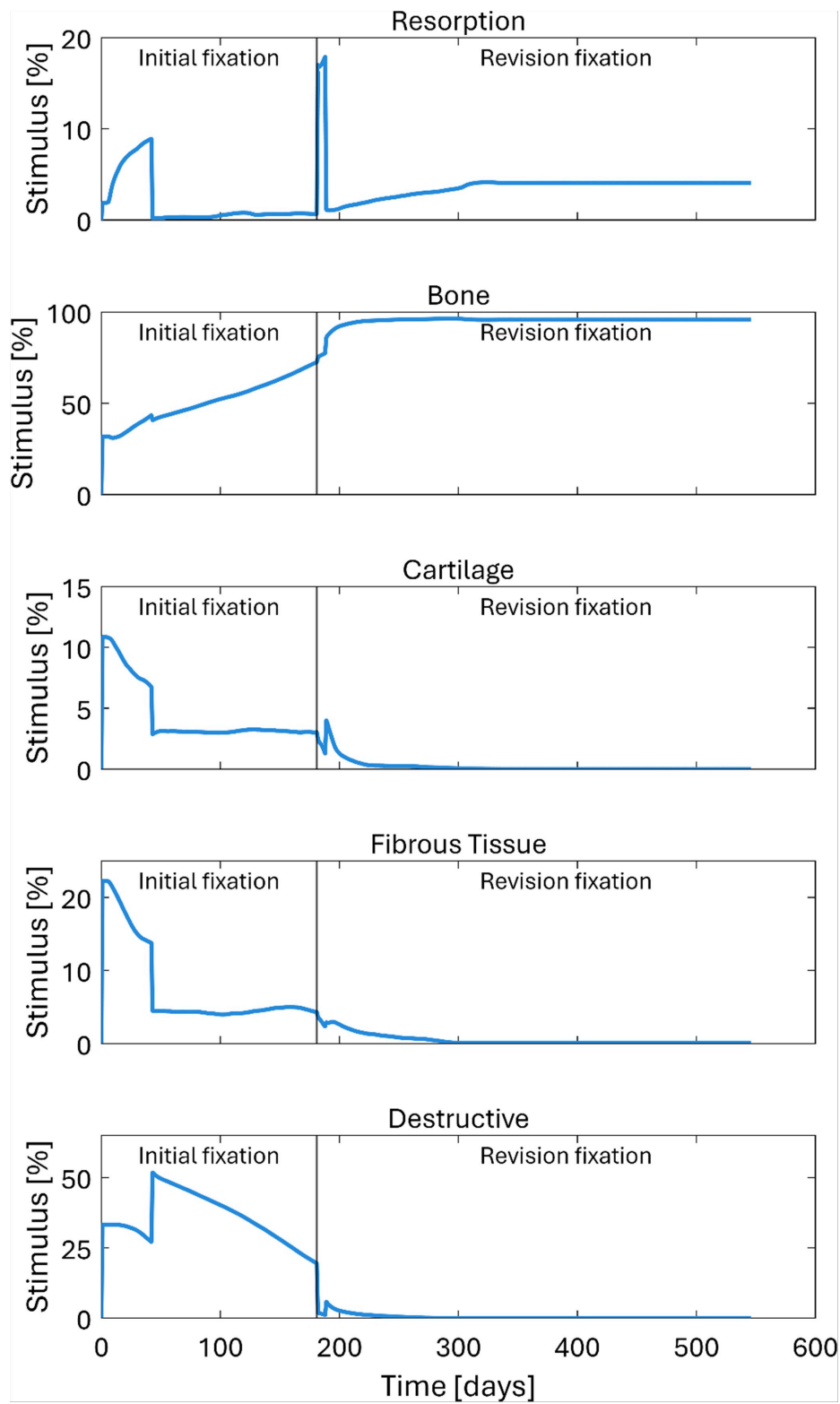


Figure 3

Temporal evolution of mechanical-stimulus exposure within the fracture callus.

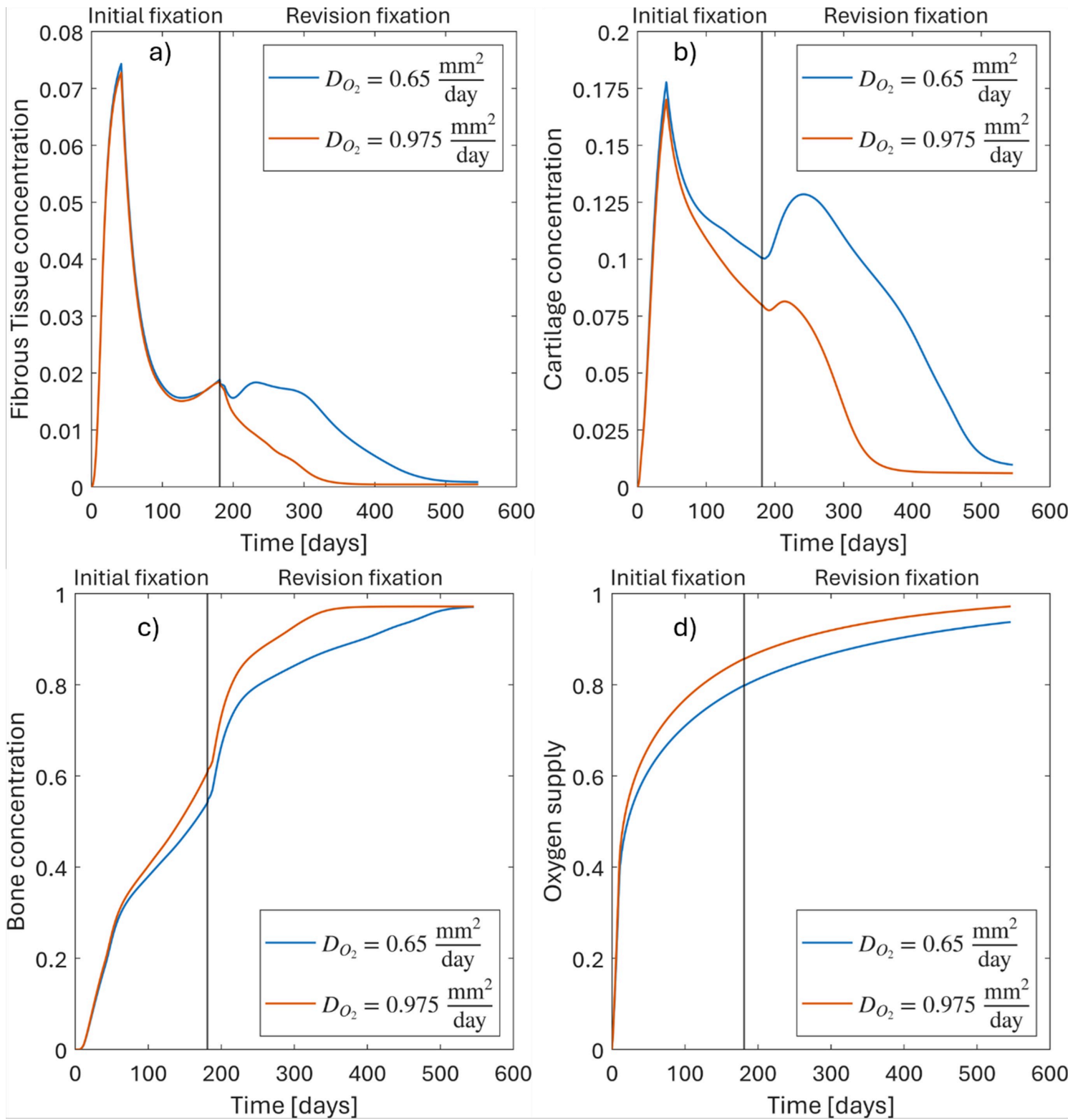


Figure 4

Temporal development of a) mean bone matrix b) mean cartilage matrix c) mean fibrous tissue matrix and d) mean oxygen supply inside the callus



Figure 5

Comparison between clinical X-ray radiographs and synthetic X-ray radiographs. A) Clinical anterior–posterior tibia X-ray image at the revision OP b) Virtual anterior–posterior tibia X-ray image at the revision OP c) Clinical anterior–posterior tibia X-ray image after 18 months d) Virtual anterior–posterior tibia X-ray image after 18 months

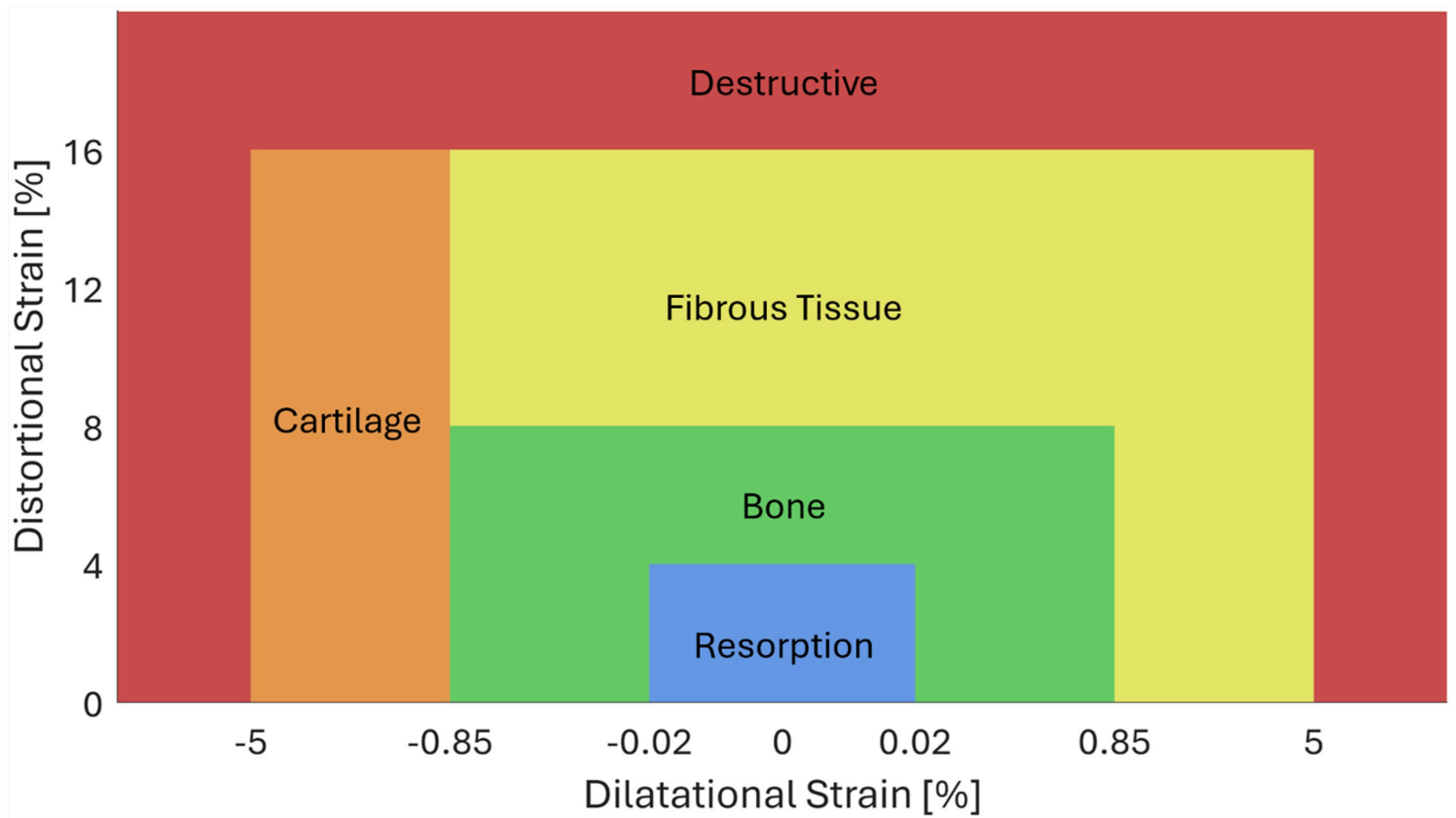


Figure 6

Determination of mechanical stimulus based on dilatational and distortional strain.

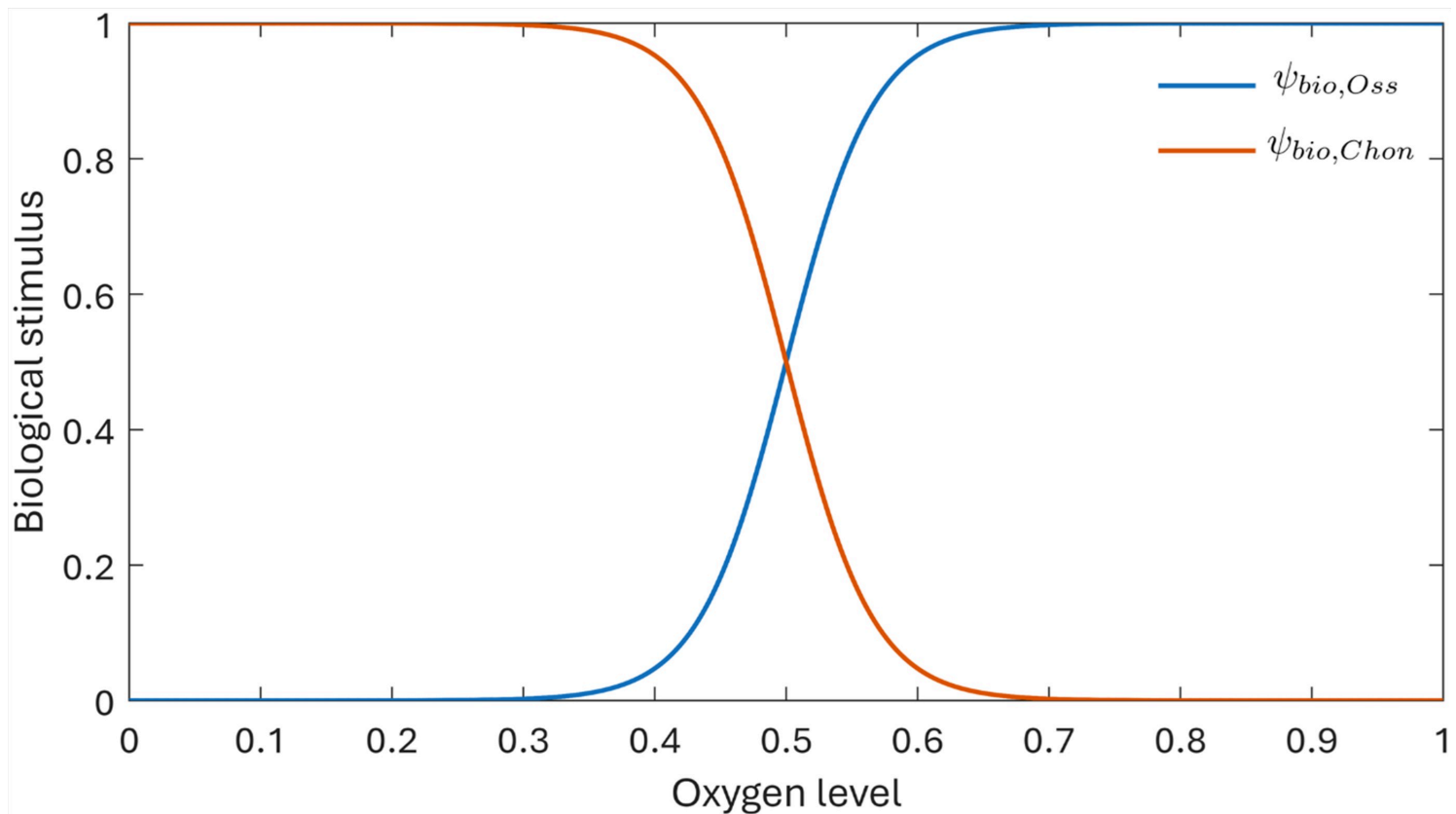


Figure 7

Determination of biological stimulus based on oxygen level

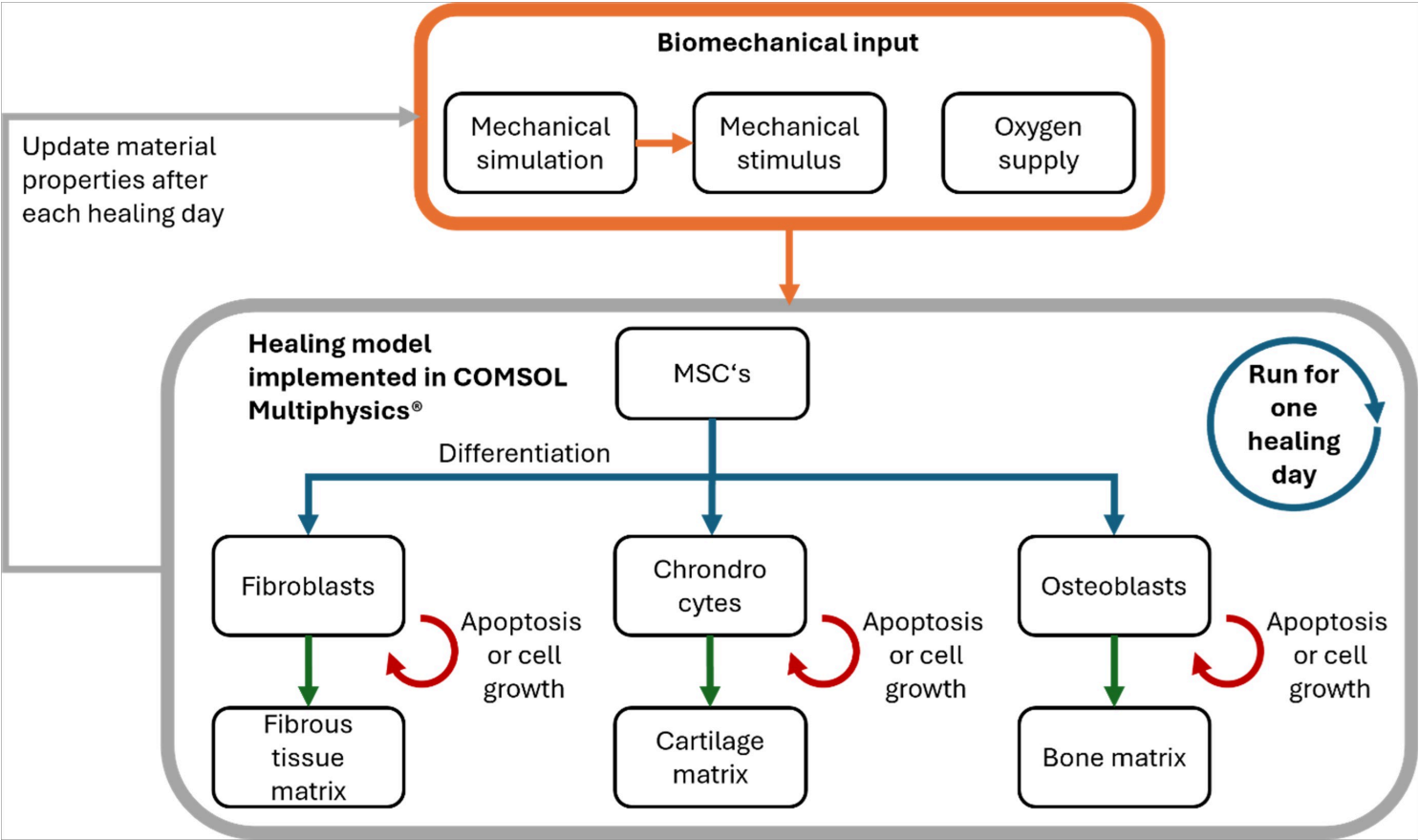


Figure 8

Healing simulation framework