Bone Ingrowth Simulation within a Novel Microstructure Scaffold

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Abstract

The utilization of bone scaffold implants represents a promising approach for repairing substantial bone defects. In recent years, various traditional scaffold structures have been developed and, with the advancements in materials biology and computer technology, novel scaffold designs are being evaluated. This study investigated the effects of a novel scaffold unit cell design (Hexnaoid) through a computational framework, comparing its performance to that of four well-known scaffold designs. A finite element analysis (FEA) numerical simulation and mechanical testing were conducted to analyse the dynamic bone ingrowth process and the mechanical strength of the scaffold designs, respectively. The bone formation within the Ti-6Al-4V metal scaffolds was modelled based on the theory of bone remodelling. The results indicated that the novel scaffold design (Hexnaoid) outperforms conventional unit-cell designs, achieving a high final bone occupancy (~27%) and comparable mechanical strength to that of human compact bone tissue. While the design is not optimal in every category, it presents a satisfactory overall performance in both crucial aspects of bone scaffolds among the five scaffold structures evaluated. Although limitations exist in this project, similar methodologies can still be applied in the primary evaluation of new scaffold structures, providing improved efficiency and effectiveness. In future research, the results of this project may be integrated with clinical rehabilitation processes and offering a crucial evaluation and optimization of the novel scaffold unit-cell structure design.

1. Introduction

Scaffolds may be required for bone growth on surfaces to repair the defects when its size surpasses a threshold beyond which the body cannot fully heal itself through natural means. This is because in cases where the defect area has a gap of 30mm or greater, the human body cannot heal by itself fully and requires external surgical intervention to help them regain normal mobility (Schmitz & Hollinger, 1986). 3D-printed bone scaffolds have been extensively researched, with varying materials and microarchitecture designs being studied (Chan & Leong, 2008; Porter, Ruckh, & Popat, 2009; Stevens, Yang, Mohandas, Stucker, & Nguyen, 2008). Human bone ingrowth within implanted scaffolds, alongside mechanical properties and porosity, are critical factors to consider in the clinical context. The bone growth rate and final occupancy proportion significantly influence scaffold fixation and the likelihood of implant failure (Roshan-Ghias & Pioletti, 2011). Consequently, repeated in-vitro and in-vivo experiments and research are required to optimize scaffold design and improve their performance. However, evaluating the impact of each specific scaffold parameter on tissue regeneration using these techniques is costly and time-consuming. To reduce the cost and time associated with these evaluations, finite element analysis (FEA) numerical simulations can be performed to provide reference or guide before in-vitro experiments or in-vivo implantations.

Finite Element Analysis (FEA) of bone remodelling is a cost-effective method of investigating the mechanical and biological behaviour of patient-specific implants. FEA involves dividing the continuous solution area into smaller elements, which are connected in a specific manner. Since the elements can be combined in different connection modes, and the elements themselves can have different shapes, it is
possible to model the solution domain with complex geometric shapes. The finite element method also involves the use of approximate functions within each element, with the solution of each element being combined to solve the entire solution domain. The approximate solution is expected to converge to the exact solution, assuming the elements meet the convergence requirements (Konda & Tarannum, 2012). The Abaqus was used to perform the FEA in this project.

Similar simulations of bone ingrowth have been conducted within different scaffold structures and based on various remodelling theories. In 2004, a CAD-based computer-modeled microsphere-packed bone structure was developed by Pallavi Lal, demonstrating the feasibility of bone ingrowth simulation (Lal & Sun, 2004). Subsequently, the relationship between mechanical effects and bone formation in scaffolds made of various materials has been well-studied (Liu et al., 2020; Milan, Planell, & Lacroix, 2010). Dynamic mechanical stimulation with higher stresses has been found to generally promote bone tissue formation, while local flow velocity and local shear stress have not been shown to significantly impact tissue remodelling (Jones et al., 2009). Among the various software for tissue engineering scaffold simulation, Abaqus has been chosen for bone growth FEA evaluation in several studies (Bhardwaj, Singh, & Shukla, 2017; Monshi et al., 2020).

There were four traditional bone scaffold designs introduced in this study. The most common and relatively simple conventional scaffold structure are the cubic and circular designs. We evaluated the effect of vascular growth factor and mechanical energy on bone growth through a comprehensive simulation of the cubic bio-degradable scaffold (Wang et al., 2020). Two beam-based lattices scaffold structure was designed by Paul F. Egan (Egan, 2019). One is FD-cube (face-diagonal cube). The other is a V-Octet (Void Octet) design, which belongs to the Octahedron family.

The microarchitecture of the scaffolds utilized in prior studies on bone remodelling simulations was relatively straightforward. However, some recent innovations in scaffold design have yet to be evaluated through finite element analysis (FEA) simulations of bone ingrowth. This study employs a novel microstructure design referred to as the Hexanoid scaffold, made from the titanium alloy Ti-6Al-4V. Mechanical properties were tested by both real compression tests and digital software simulation. A reasonable balance between sufficient physical strength and appropriate fluid penetration was achieved. In hypothesis, the Hexanoid scaffold would exhibit greater bone ingrowth compared to other scaffold designs and possess suitable mechanical strength.

The objective of this study is to use finite element analysis (FEA) simulation to compare the bone ingrowth stimulating potential and mechanical strength of five scaffold unit cell designs, including conventional and novel designs. The goal is to determine which design is the most suitable for use as a bone scaffold implant based on the results of the comparison.

2. Methods And Designs

2.1 Bone ingrowth simulation
The simulation was used to examine bone growth during the rehabilitation phase, which was numerically implemented using coding the subroutine VUMAT of the commercial finite element software Abaqus (Dassault Systèmes, USA).

2.1.1 Material

The choice of the scaffold material is a crucial aspect in the design of a bone implant. Although biodegradable scaffolds have been shown to stimulate tissue growth and elicit minimal immune response after they dissolve, permanent biocompatible metals remain the most commonly used materials due to their strong mechanical strength, ease of large-scale manufacturing, and relatively lower cost. For this study, Ti-6Al-4V was selected as the scaffold material for all architectural designs. This material exhibits a Young’s modulus of 107 GPa, a Poisson's ratio of 0.3, and a density of 4500 kg/m³. The scaffold pores are initially filled with interstitial fluid (ISF), which will be partially replaced by bone tissue over time. The materials in the model, including the scaffold, bone, and ISF, were assumed to be isotropic and linearly elastic. Additionally, the ISF was assumed to be nearly incompressible.

2.1.2 Scaffold model design

The bone scaffold model was designed in Solidworks® and imported into Abaqus for further simulation. Each scaffold unit cell is a cube that is 1 millimetre on each side. The cubic and circular designs, as shown in Fig. 1a and b respectively. Figure 1c indicates FD-cube (face-diagonal cube) unit cell, and Fig. 1d shows V-Octet (Void Octet) design. The novel-designed scaffold structure Hexnaoid is manifested in Fig. 1e.

2.1.3 Meshing and voxelization

The computational domain was Hex meshed into identical cubic elements with a side length of 50 µm. The titanium scaffold and the porous cavity were allocated as two separate sets. Both sets were converted from the continuous domain into a discrete grid block through outsourced voxelization scripts. The voxelization was based on the scaffold’s structure, as indicates in Fig. 1f-j. Each element can have one of the following two states for the scaffold cavity: bone or ISF. In order to display the states during the whole process, we defined a characteristic function \( \chi \): If \( \chi = 1 \), the element was in the state of the scaffold; if \( \chi = 2 \), the element was in the state of bone; and the element was in the state of ISF when \( \chi = 3 \).

2.1.4 Boundary conditions

The simulation setup was designed to imitate the loads that would be applied to a scaffold implant in a real-life scenario. The top surface of the scaffold model was subjected to a uniformly distributed pressure, simulating the loads on the model. To ensure homogeneous deformation of the entire model in
the z-direction, the bottom surface of the scaffold was fixed and a rigid plate was attached to the top surface. The applied pressure was defined as a trapezoidal pulse with a period of 1 day (see Fig. 2), including relaxation, rising, hold, and fall phases. The latter three phases define the duration of movement, with the relaxation phase denoting idleness. The rising and falling phases of the loading history were set to 0.05 days to avoid sudden changes in the loading history, which could lead to erroneous simulations. The simulation was executed over a duration of 100 days, which is equivalent to the average recovery time of an individual following a fracture (approx. 16 weeks) (Nikolaou, Efstathopoulos, Kontakis, Kanakaris, & Giannoudis, 2009). It was used to examine bone growth during the rehabilitation phase. According to Shefelbine, where the compressive stress applied to the surface of the rigid upper plate was 3 MPa (Shefelbine, Augat, Claes, & Simon, 2005).

2.1.5 Bone remodelling theory

The simulation assumed that bone formation and resorption are primarily facilitated by osteoblasts and osteoclasts, respectively, at the cellular level on the bone surface. The osteogenesis theory posits that these cells can only respond to mechanical signals when they are attached to a scaffold or on the surface of previously formed bone that has undergone differentiation from cartilage (Horwitz & Parsons, 1999). As a result, bone resorption and formation are not considered to occur within the interstitial fluid. To simplify the process, the simulation relied on the locally heterogeneous Strain Energy Density (SED) $\psi$ as the sole stimulus affecting osteogenesis and resorption factors. Based on Husikes theory and Schulte's work (Huiskes et al., 1987; Schulte et al., 2013) the bone remodelling rate $u(\psi)$ represents the thickness change of formed/absorbed bone per unit time, as shown in Fig. 3, and is expressed as:

$$u(\psi) = \begin{cases} 
-u_{\text{max}}, & \psi < \psi_{\text{lower}} - u_{\text{max}} / c \\
-c(\psi_{\text{lower}} - \psi), & \psi_{\text{lower}} - u_{\text{max}} / c < \psi < \psi_{\text{lower}} \\
0, & \psi_{\text{lower}} < \psi < \psi_{\text{upper}} \\
c(\psi - \psi_{\text{upper}}), & \psi_{\text{upper}} < \psi < \psi_{\text{upper}} + u_{\text{max}} / c \\
u_{\text{max}}, & \psi_{\text{upper}} + u_{\text{max}} / c < \psi
\end{cases}$$  

Equation 1

In the formula, $c$ is a constant and represents how fast bone formation and resorption rates reach the maximum growth rate $u_{\text{max}}$. And $\psi_{\text{upper}}$ and $\psi_{\text{lower}}$ are bone formation and resorption thresholds, respectively. The "lazy zone" presents the specific mechanical stress interval in which osteoblastic and osteoclastic cellular activities reach dynamic balance. Between this interval, there is no bone formation or degeneration macroscopically. For each random element $n$, its local SED $\psi (x_n)$ is affected by its neighbouring element $m$ within a sensitive distance $D$. Within this range, closer element $m^{th}$ has a greater influence on element $n^{th}$, and vice versa. The formulas of local strain energy density can be formulated as: (Schulte et al., 2013)
\[ \psi(x_n) = \sum_{m=1}^{q} e^{-\frac{d(x_m-x_n)^2}{2\sigma^2}} \text{SED}(x_m) \]  

Equation 2

where \( q \) is the number of other elements that has influences to this element. \( \text{SED}(x_m) \) is the strain energy density of the \( m^{th} \) element, and \( d(x_m-x_n) \) is the distance between element \( n \) and \( m \). The rate of bone volume fraction \( \alpha_b(t) \) of a bone element (equal to relative density \( \bar{\rho}_b(t)^3 \)) in the dynamic process depends on the bone remodelling rate \( u(\psi) \), and can be defined as the following formula:

\[ \frac{d\alpha_b(t)}{dt} = \frac{d\bar{\rho}_b(t)}{dt} = \frac{u(\psi)}{l} \]  

Equation 3

where \( l \) is the side length of the elements. The Young’s modulus of bone element at time \( t \), \( E_b(t) \), was computed by a modified modulus-density relationship, where \( E_b \) and \( E_{ISF} \) are the Young's moduli of the natural bone and ISF, respectively.

\[ E_b(t) = (E_b - E_{ISF})\bar{\rho}_b(t)^3 + E_{ISF} \]  

Equation 4

Each element being ossified in a certain degree of bone maturation can contribute to the mechanical properties of the scaffold-bone system only when the relative density \( \bar{\rho}_b(t)^3 \) is above a certain threshold (Schulte et al., 2013). In other words, when the degree of ossification is low, this element is still considered ISF. Therefore, the judgement criteria of ossification is element relative density \( \bar{\rho}_b(t)^3 \). When \( \alpha_b(t) \) of an element is less than a threshold \( \rho_{\text{thre}} \), the element is changed into ISF (resorption), i.e., \( \chi \) from 2 to 3. On the contrary, when density \( \bar{\rho}_b(t)^3 \) of an element is greater than \( \rho_{\text{thre}} \), the element undergoes osteogenesis (formation), i.e., \( \chi \) from 3 to 2.

### 2.1.5 Input parameters

In this instance, titanium made up the scaffold; its mechanical characteristics are already mentioned in section 2.1.2. Frost measured that the maximum rate of bone resorption or production during bone remodelling was 2 \( \text{mm}^3/\text{mm}^2/\text{year} \), which translated into \( u_{\text{max}} = 0.005 \text{ mm/day} \) in the current simulations (Frost, 1990). The lower and upper criteria (\( \psi_{\text{lower}} \) and \( \psi_{\text{upper}} \)) were modified based on literature (Schulte et al., 2013). As indicated in Section 2.1, the boundary conditions for the rehabilitative exercise level were 3 MPa. Table 1 contains a list of all input parameters utilised in the simulation.
Table 1
Summarization of the bone remodelling theory parameters used in the FEA simulation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>$c$</td>
<td>Mm/Mpa/day</td>
</tr>
<tr>
<td>Maximal formation/resorption velocity</td>
<td>$u_{\text{max}}$</td>
<td>Mm/day</td>
</tr>
<tr>
<td>Resorption threshold</td>
<td>$\psi_{\text{lower}}$</td>
<td>MPa</td>
</tr>
<tr>
<td>Formation threshold</td>
<td>$\psi_{\text{upper}}$</td>
<td>MPa</td>
</tr>
<tr>
<td>Influence distance</td>
<td>$D$</td>
<td>µm</td>
</tr>
<tr>
<td>Young's modulus of mature bone</td>
<td>$E_b$</td>
<td>GPa</td>
</tr>
<tr>
<td>Poisson's modulus of scaffold and bone</td>
<td>$\nu$</td>
<td>-</td>
</tr>
<tr>
<td>Young's modulus of ISF</td>
<td>$E_{\text{ISF}}$</td>
<td>GPa</td>
</tr>
<tr>
<td>Poisson's modulus of ISF</td>
<td>$\nu_{\text{ISF}}$</td>
<td>-</td>
</tr>
<tr>
<td>State change threshold</td>
<td>$\rho_{\text{thre}}$</td>
<td>-</td>
</tr>
</tbody>
</table>

### 2.2 Scaffold mechanical compression test and simulation

The mechanical strength of the Hexanoid scaffold was evaluated through a combination of experimental quasi-static compression testing and numerical simulation using finite element analysis (FEA) software. The architecture and cross-section of the Hexanoid scaffold used in the mechanical compression tests are depicted in Figure 4.a. The experimental mechanical compression test was conducted three times using 3D-printed specimens composed of a 4×4×6 unit cell structure, made of Ti-6Al-4V alloy (as depicted in Figure 4.b.). On the other hand, the module used in the FEA simulation was designed as a 3×3×3 unit cell structure to reduce simulation time and complexity while ensuring the minimization of simulation error, as shown in Figure 4.c. (Simsek, Akbulut, Gayir, Basaran, & Sendur, 2021). Regarding the boundary condition, the lower surface of the compression cylinder was constrained in all direction, and a displacement of 0.15mm (5% of strain) was applied to the upper cylinder surface. The corresponding reaction force to the displacement was recorded as output. A stress vs. strain curved was plotted considering the loaded surface area, and Young’s modulus of the elastic region was calculated. The same simulation process and principle were applied in all other scaffold designs to compare their mechanical strength.

### 3. Results
3.1 Bone volume vs. cavity volume

The results of the osteogenesis within the scaffold cavity are presented in Fig. 5. The bone volume (BV) to cavity volume (CV) ratio increased dramatically during the first week for all scaffold designs, indicating a rapid bone ingrowth. The maximum bone ingrowth was observed in the simple cube scaffold, FD-cube, and Circle scaffold unit cells around day 2. However, after the initial tissue remodelling, limited progress was observed until the end of the stimulation. The Hexanoid and V-Octet designs showed significantly high bone ingrowth and achieved steady optimum BV/CV ratios of approximately 27% and 35% respectively.

3.2 Bone Ingrowth Distribution

Osteogenesis within the scaffold cavity at a different time point is indicated in Fig. 6. In general, regardless of the scaffold architecture, bone growth was observed to initially occur along the scaffold surface, followed by further infiltration towards the central cavity region, as regions with high strain energy density act as the main driving force for bone remodelling. The distribution of bone growth showed that bone occupied more space near the bottom surface of the scaffold and less growth occurred in the upper cavity, resulting in non-uniform bone remodelling within each scaffold unit cell under similar mechanical boundary conditions as the in-vivo condition. Among all scaffold designs, more bone growth was observed in the Hexanoid and V-Octet scaffold cavities at the end of the simulation.

3.3 Scaffold mechanical compression test and Simulation

The stress vs. strain curve of real compressive testing is indicated in Fig. 7, and Young’s modulus of two specimen was summarized in Table 2, which was adapted to bone implant application. Below the strain of 0.8% (I), the scaffold specimen could be considered performing elastically, while the plastic region (II) started until the strain reached 1.6%. After yielding, struts failed successively (III) but strength was preserved, and plastic hardening still occurred until a major fracture (IV). The insignificant error between the elastic properties of the two tested specimens indicated a successful and repeatable processability for this structure. However, compressive test on two specimens indicated that the first strut fracture could have a different impact on the structural integrity. It could be expected that the first struts fracture could lead to structural instability and the final fracture of the truss architecture. Thus, these results indicated that operating under the (I) region was essential to avoid catastrophic failure of the component when loaded in compression.
Table 2
The mechanical properties of two Ti64 scaffold specimens.

<table>
<thead>
<tr>
<th></th>
<th>Specimen 1</th>
<th>Specimen 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gauge Length (mm)</td>
<td>14.104</td>
<td>14.239</td>
</tr>
<tr>
<td>Young's Modulus (GPa)</td>
<td>8.595</td>
<td>8.42</td>
</tr>
<tr>
<td>Yield Strength (MPa)</td>
<td>65.2</td>
<td>63.8</td>
</tr>
<tr>
<td>Strain at first strut fracture* (%)</td>
<td>2.1</td>
<td>3</td>
</tr>
</tbody>
</table>

The stress-strain relationship of each scaffold design was analysed and presented in Fig. 8 based on the simulation results obtained from the Abaqus software. The data indicated that among all scaffold designs, the cubic structure scaffold displayed the highest Young's modulus and yielding strength, whereas the V-Octet scaffold had the lowest values. The remaining three scaffold designs displayed relatively similar mechanical strengths. The calculated Young's modulus of the Hexanoid, Cubic, Circle, FD-Cube, and V-Octet scaffolds based on their performance in the elastic region were found to be 10.314, 20.729, 10.966, 9.028, and 8.296, respectively. It was noted that there was a minimal difference (20%) between the real compressive testing data and the simulation results for the Hexanoid scaffold, which validated the accuracy of the simulation method. The simulation results can thus be used for qualitative comparison of the mechanical strengths of different scaffold designs.

4. Discussion

The conventional scaffold designs exhibit unique characteristics. The cubic design, with its square-shaped pore structure, is known to possess high mechanical strength and an adequate level of porosity, but it also has a high concentration of geometrical stress (Fatah N. Habib, 2016; Jahir-Hussain, Maaruf, Esa, & Jusoh, 2021). On the other hand, the circular bone scaffold design benefits from reduced stress concentration points, improved resistance to fatigue damage, and a greater Young's Modulus (Boccaccio, Uva, Fiorentino, Lamberti, & Monno, 2016; Noordin et al., 2020). These two basic and conventional designs were included in our comparative study as a reference for performance. The FD-cube scaffold structure has the lowest surface-volume ratio, while the V-Octet (Void Octet) design has the highest surface-volume ratio (Egan, 2019).

The dynamic bone growth process within different scaffold architecture was investigated and modelled by coupling the boundary condition and the bone remodelling theory. Within the V-Octet designed scaffold unit cell, growth bone occupied more cavity space but sacrificed the mechanical rigidity. Among five different scaffold architecture design, Hexanoid continuous curved scaffold unit cells achieved better balance in both stimulating bone ingrowth and maintaining structural properties. Unlike conventional truss configurations based on simple cubic or honeycomb lattices, scaffolds with periodic curved surfaces consisting of continuous embedded linear elements provide a minimal surface geometry. Minimal surfaces, which arise naturally in response to mechanical surface tension, reduce geometry-
induced osteoblast sheet surface tension, thereby enabling osteoblasts to respond to bone mechanical stimulation more effectively. Meanwhile, orthopaedic implants based on continuous embedded linear elements also confer great structural stability under appropriate design (Bidan, Wang, & Dunlop, 2013; Dunlop, Fischer, Gamsjäger, & Fratzl, 2010; Gamsjäger, Bidan, Fischer, Fratzl, & Dunlop, 2013; Rumpler, Woesz, Dunlop, van Dongen, & Fratzl, 2008). Additionally, the coherent surface is believed to distribute stress evenly, further enhancing bone growth. Chao et al. (Chao et al., 2021) also found that cells readily attached to the scaffold walls using a confocal fluorescence microscope, indicating that scaffold structures with a combination of small and large pores (such as the Hexanoid structure) possess efficient cell attachment due to their good permeability (Chao et al., 2021). Other traditional scaffolds may have manufacturing convenience, but the angular and sharp structure result in concentrated stress distribution which may locally benefit osteogenesis in specific regions of the scaffold but is not conducive to overall bone growth throughout the cavity.

The unique geometry and robust design of the Hexanoid scaffold, incorporating a periodic curved surface and alternative minimal surface, provides several advantages. Firstly, its continuously curved surface remains consistent even after replication during manufacturing, distinguishing it from other scaffold designs with sharp angles and edges. Secondly, this design allows for multi-dimensional precision optimization of porosity, surface area, and curvature shape to closely resemble normal bone architecture and potentially imitate trabecular bone structure under various physiological and pathological conditions. Additionally, it is expected to possess adequate mechanical properties to withstand physiological loads. The ability of the Hexanoid scaffold unit to stimulate bone ingrowth was evaluated and compared with that of traditional designs.

The compressive testing and finite element analysis (FEA) simulations provide insight into the mechanical performance of scaffolds as implants in the human body. The cubic structure scaffold exhibits the highest compressive strength, which can be attributed to its larger interface area and regular architectural shape. However, a higher Young's modulus of the scaffold does not guarantee its mechanical properties are suitable for use as an implant. The average Young's modulus of trabecular bone measured mechanically is 10.4 GPa (standard deviation 3.5) (Rho, Ashman, & Turner, 1993). In order to avoid strength shielding and the subsequent degradation of surrounding bony tissue, it is crucial for bio-undegradable bone scaffolds to have mechanical properties similar to those of real bone. In this regard, the Hexanoid, Circle, and FD-Cube scaffolds are considered to have appropriate compressive mechanical strength.

Wang et al. conducted a study to investigate the bone ingrowth capabilities of cubic scaffold designs made of biodegradable and non-biodegradable materials. In their simulation, the bone tissue within the biodegradable cubic scaffold underwent two periods of significant growth before reaching the remodelling steady state. The second period of remodelling was associated with the scaffold's dissolving process, during which the stress energy that was previously shouldered by the scaffold was transferred to the bone tissue, thereby stimulating its further growth (Wang et al., 2020). In contrast, the titanium scaffold only showed one obvious growth period before reaching its maximum limit, which can be
attributed to stress shielding. As the scaffold was not biodegradable, further external mechanical pressure was unable to reach the bone tissue. Although titanium scaffolds are unlikely to maintain optimal conditions for bone ingrowth after implantation, they may provide sufficient mechanical strength during rehabilitation. On the other hand, in clinical situations, it may be challenging to match the rate of bone ingrowth with the rate of scaffold dissolution in biodegradable scaffolds.

The findings of the study on non-degradable scaffolds suggest that the first month of rehabilitation exercises plays a crucial role in promoting bone growth. Subsequently, it is recommended to adopt a moderate exercise intensity to achieve optimal bone remodelling, as the efficacy of mechanical stimulation on bone growth tends to decline. Importantly, the rehabilitation regimen should be tailored to the scaffold architecture and its material properties, as these factors can significantly impact the bone growth outcome.

The numerical simulations require realistic data on applied loads, implant-bone geometry, and tissue's mechanical properties to quantitatively and accurately predict the evolutionary process of bone remodelling. This study includes several simplifications and assumptions to save simulation time and reduce model complexity, thus there are limitations need to be mentioned. Firstly, it was assumed that mechanical stress is the sole stimulus for bone remodelling. The growth rate $c$ as an empirical constant in Eq. 1 was selected, whereas actually, the growth rate is related to the biochemical and molecular signals, which regulate the activities of osteoclasts and osteoblasts (Schulte et al., 2013). However, the present scaffold-bone model did not consider these factors. Secondly, the real walking frequency was generally treated as the mean loading history of every day due to the computing cost. The actual gait pattern of a patient with bone fracture under rehabilitation was influenced by pain or joint limitation and did not represent the boundary condition setting. In addition, a single unit block cell was used to represent a macroscopic scaffold implant to simplify the model, the unit-to-unit interaction and overall scaffold geometry on tissue growth lacks. Lastly, ISF was considered as an incompressible solid instead of fluid, which neglects the important role of the fluid shear stress (FSS) between ISF and bone tissue (Dillaman, Roer, & Gay, 1991). Therefore, further studies are needed to incorporate more complex and realistic models that take into account the multiple factors affecting bone remodelling. Additionally, in-vivo studies and clinical trials are needed to validate the accuracy of the simulations and ensure that the results obtained from the simulations are consistent with real-world outcomes. Despite these limitations, the current study provides a starting point for understanding the relationship between scaffold architecture and bone ingrowth and will likely lead to further advancements in the field of bone tissue engineering.

5. Conclusion

This finite element model provided a platform to predict and optimise un-regular scaffolds architecture design for bone growth within the implanted scaffold, thus reducing the number of experimental studies necessary to validate design performance. In comparation with other conventional bone scaffold unit structures, the novel designed scaffold achieves a better balance between bone ingrowth stimulation and
self-mechanical strength. It indicates more potential and possibility in conducting in-vivo experiments or clinical trials. Experimentally further validating this model would involve implanting a scaffold into a bone defect in an animal model and making histological measurements of tissue phenotype at several time points.

Declarations

- The authors have no relevant financial or non-financial interests to disclose.
- The authors have no competing interests to declare that are relevant to the content of this article.
- All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.
- The authors have no financial or proprietary interests in any material discussed in this article.

Ethical Approval

Not applicable

Competing interests

- The authors have no relevant financial or non-financial interests to disclose.
- The authors have no competing interests to declare that are relevant to the content of this article.

Authors' contributions

Dr Deniz Erbulut and Dr Zhiyong Li devised the project, the main conceptual ideas and proof outline. Yuheng Wang worked out almost all the technical details and performed the bone ingrowth simulation for the suggested experiment. Luping Wang worked out the coding of bone growth theory. Nicolas Soro, Kevin Tetsworth proposed and conducted the scaffold mechanical compression experiments, and provided the stress-strain curve figure. The manuscript was mainly completed by Yuheng Wang with input from all authors

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- The authors have no financial or proprietary interests in any material discussed in this article.

Availability of data and materials

Any raw data of the simulation and model can be accessed by sending email to main author Yuheng Wang (wangyuheng1996@hotmail.com) or corresponding author Deniz Erbulut
References


**Figures**
Figure 1

The 3D scaffold unit cell module of the a. Cubic; b. Circle; c. FD-cube; d. V-Octet; e. Hexnaoid. The mashed scaffold unit cell module of f. Cubic; g. Circle; h. FD-cube; i. V-Octet; j. Hexnaoid.
Figure 2

The graph of the boundary condition as the external mechanical stimulus, on the x-axis is time and y-axis is the pressure in MPa.

Figure 3

The graph is the indication of the basic principle of the bone remodelling theory, x-axis is stress energy density, and y-axis is the bone remodelling rate.

Figure 4
a) The detail of Hexanoid structure and its cross section; b) The 3D printed scaffold specimen used in the compressive testing; c) The digital module used in the FEA compressive testing simulation

Figure 5

The relationship between the BV (Bone volume)/CV (Cavity volume) and Time (day) of five architecture scaffold designs.
The bone ingrowth situation of the five scaffold designs (a. Cube; b. Circle; c. FD-cube; d. V-Octet; e. Hexanoid) in the 0, 1, 5, 10, 50 and 100 steps, where blue, red and green colour represents the Ti64 scaffold, ISF and New formed bone respectively.

Figure 6
Figure 7

The Stress vs. Strain curve of the real compressive testing of 4×4×6 Ti64 scaffold specimen.

Figure 8

The Stress vs. Strain curve of the real compressive testing simulation of Hexanoid, Cubic, Circle, FD-Cube and V-Octet scaffold