RESEARCH ARTICLE

Lattice implants that generate homeostatic and remodeling strains in bone

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Abstract
Bone remodeling is mediated by several factors including strain. An increase in strain between 1% and 10% compared to homeostasis can trigger bone formation. We aim to create an orthopedic implant using clinically established imaging and manufacturing methods that induces this strain control in human bone. Titanium scaffolds were manufactured with multiaxial apparent modulus tailored to the mechanical properties of bone defined from computed tomography scans of cadaver human tibiae. Five bone cubes were tested with corresponding titanium scaffolds by loading under compression, which is similar to the implanted tibia loading condition. Bone strain was precisely controlled by varying the scaffold modulus, from 0% to 15% bone strain increase. This strain increase is the magnitude reported to invoke bone’s positive remodeling. Axial modulus was closely matched between titanium scaffolds and bone, ranging from 48–728 and 81–800 MPa, respectively, whereby scaffold axial modulus was within 2% of nominal target values. Fine control of multiaxial moduli resulted in transverse modulus that matched bone well; ranging from 42–648 and 47–585 MPa in scaffolds and bone respectively. The scaffold manufacturing material and method are already used in the orthopedic industry. This study has significant clinical implications as it enables the design of implants which positively harness bone’s natural mechanoresponse and respect bone’s mechanical anisotropy and heterogeneity.

KEYWORDS
bone, mechanobiology, porous scaffold, strain control

1 | INTRODUCTION

Bone exhibits a complex and dynamic behavior whereby biological and structural properties are influenced by a constant remodeling process. During this process, bone formation and resorption are controlled by osteoblast and osteoclast cell activity, each stimulated by multiple factors including localized strain gradient. Many models explain how this mechanism influences the distribution of mechanical properties, most commonly to negative effect as in stress shielding and bone resorption after joint replacement surgery. However the same remodeling process could be harnessed in a positive way, such as
maintaining or increasing bone density after joint replacement surgery, if it were possible to increase the strain experienced by bone by between 1% and 8% of that seen under homeostasis.1,5

Porous scaffolds provide a promising opportunity in regenerative medicine to control the strain experienced by bone and thus induce positive remodeling. Such scaffolds have been explored in a variety of materials, structures and manufacturing methods to achieve a control of pore size, anisotropy and mechanical properties.6,7 Controlled modulus scaffolds have been manufactured in both metal and polymer materials in literature.8–13 Furthermore, combinations of such materials and cell structures have produced varying mechanical anisotropies.14,15 In animal models, these scaffolds generate improved ingrowth and increased density of bone compared to solid metal controls.8,16–18 Similar studies have also observed that induced bone strain correlates with regeneration and remodeling.8,17,19

Computational methods, such as topology optimization, allow the design of minimal surfaces to vary scaffold modulus as well as subsequent improvements in osseointegration and bone remodeling.6,20 Similarly, structures optimized for increased fluid flow and surface area provide good computational results for fixation and ingrowth.21,22 Bone remodeling appears to be its most effective when scaffold elastic tensor matches or is slightly higher than that of the host bone.6 These studies demonstrate the theory of strain controlled bone remodeling, but this technology is yet to be demonstrated in an experimental human model.

The proximal tibia is a site of popular interest for orthopedic surgery, owing to the prevalence of osteoarthritis in the knee joint. Common successful procedures include total knee replacement, partial knee replacement and tibial osteotomy. These are well established successful procedures that use a metal implant to reconstruct the joint. These implants are made from solid titanium or cobalt chrome alloy, many times stiffer than the bone into which they are placed. They therefore modify the strain distribution in the bone, leading to bone loss over time.23,24 Recent advances in manufacturing titanium alloy in a scaffold format means it is now possible to make load bearing scaffolds with an apparent modulus in the range of human bone.10 For the proximal tibia, the modulus of the bone is well understood and can be predicted from quantified computed tomography (qCT) derived apparent density.25 These data were used as a target for the apparent modulus of the titanium scaffolds.

The focus of this study is to demonstrate how a titanium scaffold implant can control bone strain in human proximal tibia bone. In addition to controlling bone strain in the dominant loading direction, a secondary focus is to match the transverse modulus of the bone in the off-axis directions.

2 | METHODS

2.1 | Bone property measurement and prediction

Ethical permission was granted by the Imperial College Healthcare Tissue Bank Review Committee under a UK Human Tissue Authority License 12275. Our previous study reports the harvesting of 195 human bone cubes (9 mm side length) from the proximal tibias of 7 fresh-frozen cadavers with no prior lower limb pathologies, traumas, surgeries or osteoarthritis (age = 34–65 years, sex = 5 females, 2 males, side = 4 left knees, 3 right knees). From the 195 cubes, 5 were selected to represent the variability in density of bone in the proximal tibia. Multiaxial apparent modulus was predicted for each cube from qCT with a calibration phantom using the methods described by Munford et al.25 These data were used as a target for the apparent modulus of the titanium scaffolds.

2.2 | Titanium scaffold structure generation

The stochastic structure was created by populating a 10 mm side cube with pseudo-random points using a Poisson disk algorithm, maintaining a specific minimum proximity. These points were then joined with lines to achieve a certain connectivity. This method, which uses Rhinoceros 6.0 and Grasshopper (Robert McNeel & Associates) is described by Ghouse et al.19 The density of the structure was 4.2 struts/mm³ and with an average connectivity at each node of 5.3. Lines at an angle of less than 25° inclination to the x-y plane were kinked, as per the methods described by Hossain et al. to allow for AM manufacturing.32

2.3 | Control of scaffold anisotropy and manufacture

Scaffold mechanical anisotropy was controlled by selectively thickening struts based on their inclination angle to the x-y plane with three segments: 25°–35°, 35°–55° and 55°–90°, which each contained 50.1%, 38%, and 11.9% of total struts, respectively. Specimens were designed with uniform strut thickness and all combinations of strut thicknesses of 200, 300, and 400 μm allocated for each angular segment.

Solid STL geometry is usually printed using a single exposure printing strategy.35 To achieve the desired mechanical modulus throughout the structure in this small scale line geometry, this method was used to melt the required cross section of each strut,
also described by Ghouse et al.\textsuperscript{15} Slice data (build files) were generated at 50 μm layer thickness using an in-house slicing engine.

All specimens were printed using a Renishaw AM250 PBF additive manufacturing system (Renishaw). Commercially pure titanium (cpTi) spherical powder of particle size range 10–45 μm was used, supplied by Carpenter Additive. The build chamber was vacuumed to −960 mbar and then back filled with 99.995% pure Argon to 10 mbar with an O content of ~0.1%. Laser power was constant at 50 W while exposure times varied from 600 to 1700 μs to maintain a constant strut thickness. All build plates were heat treated under vacuum at 750°C.

Specimens were removed from the buildplate by electro-discharge machining, ensuring that the wire path preserved the intended part geometry, then cleaned using ultrasonic bath and air jet. Specimens were cut down to 9 mm side length cubes once support material had been removed.

2.4 | Characterizing scaffold mechanical properties

A materials testing machine (Instron 8872) with a 10-kN load cell was used to perform quasi-static compression testing at an extension rate of 2 mm/min, which corresponds to a strain rate within standard limits.\textsuperscript{33}

Displacement was measured using linear variable differential transformers (LVDTs), attached to the testing platens to reduce any compliance effects from the test apparatus. A sampling rate of 30 Hz was used. The platens of the machine were lubricated to reduce any frictional effects. Stress–strain curves were obtained using the individual macro dimensions of each specimen.

Specimens were tested in the axial and transverse directions sequentially with order of test directions randomized. The loading regime included a hysteresis loop to account for settling in behavior of the initial toe region within the porous structure. For half of the cubes, this was carried out from 70% of the cube’s yield stress (σ70), to 20% of its yield stress (σ20) and then back to σ70. Specimens were tested in this way along three orthogonal test directions. All compression testing was done with lubricated platens to remove frictional artefacts. The elastic moduli were then calculated using a linear regression analysis of the hysteresis loop.

Apparent modulus of specimens in both the axial and transverse directions were characterized in terms of the strut thickness distribution across each angular segment.

2.5 | Mechanical testing of bone-scaffold pairs

Each bone specimen was compression tested alongside a corresponding titanium scaffold following the same protocol as in Section 5.3 (Figure 1). Bone-scaffold pairs were compressed to a load corresponding to an induced stress of 1.5 MPa and the resulting strain measured. Before testing, specimens were trimmed with a Buehler precision saw (Germany) to ensure even distribution of load between the bone and scaffold at neutral loading.

Before testing, Tekscan pressure sensors were equilibrated (800 N) and calibrated (2-point calibration) with a custom ball joint fixture to account for any machine misalignment. Equilibration allows equitable gain between sensels and calibration allows accurate calculation of force from the sensor’s voltage readings.

2.6 | FE modeling

For four bone cubes and their predicted moduli, five titanium scaffolds were manufactured with strut thicknesses assigned to have transverse modulus equal to predictions for the bone cubes and axial modulus scaled over a range based on the bone cube predictions. Scaffold axial and transverse modulus was determined as in Section 5.3.

Loading of each bone cube was modeled in parallel with their five corresponding scaffolds. Identical base constraints with a rigid top plate applied uniform loading up to 1.5 MPa compression via a frictionless surface contact constrained in the transverse plain. The bone-implant interface was modeled as a frictionless contact.

Eight-noded brick elements with a quadratic shape function were used and the mesh was varied linearly from coarse to fine elements at the interface. A mesh convergence was done which yielded a mesh consisting of an element density of 8000, N2 of 1.15E + 10 and a computational time 2233 times the most coarse mesh considered (element density 125 to validate convergence).

3 | RESULTS

3.1 | Control of bone strain and stress

Strain in human proximal tibia bone was precisely controlled with titanium modified stochastic scaffold implant structures. Matching
implant and bone modulus induced no change in bone strain for either mechanical testing or finite element (FE) models. A 13.3% reduction in implant modulus compared to the bone induced the target 10% increase in bone strain. Implant modulus and change in bone strain were linearly related (Figure 2). Data from FE simulation was in strong agreement with results from mechanical testing.

Similarly, contact stress beneath the bone cube was controlled by varying implant modulus. A 10.4% increase in stress was induced in bone by reducing scaffold modulus by 20% (nominal) relative to the bone modulus (Figure 3). These data indicate, under simple loading, an implant can create the appropriate strain in human bone for positive bone remodeling to occur.

### 3.2 Control of scaffold anisotropy

Mechanical properties of the titanium lattice specimens were defined based on clinical CT scans of the intact tibia bone specimens. This method produced parts of the desired nominal modulus, with small errors across a range of modulus values (Table 1). When designed to match the bone modulus, the modulus of the titanium scaffold structures were within 1% of their target value.

Control of strut thickening by angular segments allowed manufacture of structures with anisotropy in the range 1.1–5.1 (Tables 2 and 3). This was controlled by thickening struts by their inclination to the transverse plane. Anisotropy was controlled such that transverse modulus of the titanium scaffold structures (42–648 MPa) matched that of the human tibia bone (47–585 MPa). Anisotropy ranged from 1.4–3.4 and 1.1–5.1 in bone and scaffolds respectively. For a given bone cube, scaffolds were manufactured to have axial and transverse moduli within 2% and 12%, respectively, of their nominal values, based on CT predictions.

A strong power-law correlation was found between apparent modulus and uniform strut thickness. When the structure was

### Table 1

| Bone modulus (MPa) | −20 | −10 | 0 | +10 | +20 |
|--------------------|-----|-----|---|-----|-----|
| 160                | −21.0 | −11.0 | −1.0 | 9.0 | 19 |
| 325                | −20.3 | −10.2 | −0.3 | 9.7 | 19.7 |
| 484                | −19.8 | −9.8 | 0.25 | 10.2 | 20.2 |
| 627                | −20.3 | −10.3 | −0.3 | 9.70 | 19.7 |
| 761                | −19.8 | −9.8 | 0.2 | 10.2 | 20.2 |

Note: Scaffolds aimed to achieve nominal relative moduli of −20%, −10%, 0%, 10% and 20%.
shown to increase ingrowth. This supports the trends found in our study, where scaffolds of a lower modulus induced greater bone strains. Furthermore, repeating cell polymer scaffolds of a 220 MPa modulus induced ingrowth as high as 21%. This corresponds well to our findings; where scaffolds with modulus between 128 and 609 MPa (20% less than surrounding bone) increased the strain by between 12.4% and 18%.

Scaffolds with apparent modulus in the range of 0.6–3.6 GPa for titanium alloys and 0.15–7.1 GPa for polymer structures have been previously reported, similar to our study. Many studies have also demonstrated a range of mechanical anisotropies in porous scaffolds. The methods shown here provide a good development to existing literature, allowing axial modulus to be designed between 132 and 913 MPa while controlling anisotropy such that transverse modulus can be designed to within 12% or 64 MPa of its target value. Our method of controlling anisotropy was to modify the scaffolds based on strut inclination angles. Similar results in literature suggest topology optimization of minimal surfaces can modify scaffold modulus over the range 1.2 to 8 with subsequent variations in bone remodeling. Bone remodeling appears to be its most effective when scaffold elastic tensor matches or is slightly higher than that of the host bone, which is reflected in our data.

Controlled strains between 50 and 4000 microstrain have been recorded in animal models using external fixators, whole body vibration and strain gauges which allow in-situ measurements of loading and strain. Our study adds to literature further, inducing between 1800 and 3600 microstrain, depending on the designed scaffold modulus. Bone adaptation is threshold driven and influenced by strain magnitude, strain rate and waveform and loading distribution. Literature suggests that bone formation (34% increase in bone density) can be achieved even at low level strains (5 microstrain, ~0.5% delta strain) providing frequent periods of high frequency strain (30 Hz). Previous work has shown the benefits of load sharing bone scaffolds and reduced modulus implants as well as the opportunity of varying bone strain in vivo. Our findings support prior work by allowing fine control of strain for positive and negative deviations from homeostasis for the first time in human bone in a way which could be utilized in an implant.

A limitation of the study was that compression testing was done quasi-statically which neglects dynamic loading. This does not reflect physiological loading which is often cyclic, however quasi-static testing allowed comparison of modulus values with literature and has been shown to correlate well with cyclic loading results. Another limitation is that the loading configuration was a simplified loading configuration of the proximal tibial bone construct, but we chose this model because the dominant strains are in the axial direction, similar to the proximal tibia. The FE model also assumed simple continuum linear elastic material properties which is only valid in the linear elastic range, but nevertheless matched the experimental data in this range with errors less than 8%, with an average of 2%. The final limitation was that bone strain was controlled with scaffolds in only five specimens, however, specimens were chosen such that their axial modulus spanned a representative range of values and the resulting data trend was clear and statistically significant.

| Bone transverse modulus (MPa) | Scaffold transverse Modulus (MPa) |
|-------------------------------|----------------------------------|
| Axial modulus change           | 0                               |
| 47.1                          | -20                              | -10  | 0   | +10  | +20  |
| 51.2                          | 51.6                             | 43.6 | 41.6| 50.1 | 45.2 |
| 120                           | 121.8                            | 135.3| 145.7|155.8 |137.3 |
| 255                           | 282.4                            | 284.4| 282.2|286.9 |270  |
| 369                           | 404.4                            | 390.7| 403  |390.9 |408.7 |
| 585                           | 637.9                            | 643  | 628.1|612.6 |648.5 |

| Bone anisotropy               | Scaffold anisotropy               |
|-------------------------------|----------------------------------|
| Axial modulus change          | 0                               |
| 3.4                           | -20                              | -10  | 0   | +10  | +20  |
| 2.0                           | 2.4                              | 3.1  | 3.5 | 4.5  | 5.0  |
| 2.7                           | 2.1                              | 2.2  | 2.2 | 2.3  | 2.8  |
| 1.9                           | 1.4                              | 1.5  | 1.7 | 1.9  | 2.2  |
| 1.7                           | 1.2                              | 1.4  | 1.6 | 1.8  | 1.8  |
| 1.3                           | 1.1                              | 1.1  | 1.2 | 1.3  | 1.4  |

thickened uniformly from 200 μm to 400 μm the relationship could be fitted well with a trend which achieved an $R^2$ of 0.99.

4 | DISCUSSION

The most important outcome of this study was the that the axial strain experienced by human proximal tibia trabecular bone could be controlled by titanium scaffold structures whose modulus was defined from clinical CT scans. The resulting strain response in bone was controlled by an inverse linear relationship with the titanium scaffold structure’s apparent modulus. The titanium scaffold structures were manufactured with apparent modulus within 2% and 12% of target axial and transverse modulus based on CT predictions of the bone apparent modulus. These data indicate that a proximal tibial knee replacement implant could be made from a titanium scaffold to control the strain in the proximal tibial bone after knee replacement surgery. This is an important step towards the vision of implants that can maintain natural bone homeostasis or even improve the bone’s mechanical properties throughout the life of the implant.

Our data compare well with animal models that have observed the relationship between bone strain and regeneration in vivo. In particular, loading sharing implants have been shown to be beneficial for ingrowth and scaffolds with a lower modulus have been shown to increase ingrowth. This supports the trends found in our study, where scaffolds of a lower modulus induced greater bone strains. Furthermore, repeating cell polymer scaffolds of a 220 MPa modulus induced ingrowth as high as 21%. This corresponds well to our findings; where scaffolds with modulus between 128 and 609 MPa (20% less than surrounding bone) increased the strain by between 12.4% and 18%.

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This study is clinically relevant because follow up data indicate implants with reduced modulus can influence outcome. For example, in a randomized controlled trial, a tantalum trabecular metal tibial implant had improved radiological outcome compared to a solid tibial implant over a period of 15 years. Another example is that the likelihood of a complex revision is reduced if the primary implant is a low modulus all polyethylene design compared to a conventional solid metal backed design. Our method builds on these findings by allowing precise control of bone strain, using a manufacturing method that has already been deployed in over 1 million knee replacement implants. The workflow for generating stiffness matched implants which control bone strain response is therefore closer to clinical use than most regenerative technology. The ability to harness bone’s natural mechanoresponse has the potential to revolutionize the orthopedic industry with implants that actively improve the quality of the bone into which they are placed.

5 | CONCLUSION

Precise control of strain in bone could be beneficial for joint replacement implant designs. In a simplified model of implanted bone, titanium lattice structures could control the strain in bone from +0% to +15% strain compared to the native bone. This range of strain increase is within the range to invoke bone’s positive remodeling stimulus.

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AUTHOR CONTRIBUTIONS

Maxwell J. Munford: conception and design of the study, execution of the study including acquisition of the data, data analysis and interpretation, manuscript writing. Dannier Xiao: execution of the study including acquisition of the data, data analysis and interpretation, manuscript editing/review. Jonathan R. T. Jeffers: conception and design of the study, manuscript writing/review.

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