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Experimental and Numerical Models of Complex Clinical Scenarios; Strategies to Improve Relevance and Reproducibility of Joint Replacement Research

This research review aims to focus attention on the effect of specific surgical and host factors on implant fixation, and the importance of accounting for them in experimental and numerical models. These factors affect (a) eventual clinical applicability and (b) reproducibility of findings across research groups. Proper function and longevity for orthopedic joint replacement implants relies on secure fixation to the surrounding bone. Technology and surgical technique has improved over the last 50 years, and robust ingrowth and decades of implant survival is now routinely achieved for healthy patients and first-time (primary) implantation. Second-time (revision) implantation presents with bone loss with interfacial bone gaps in areas vital for secure mechanical fixation. Patients with medical comorbidities such as infection, smoking, congestive heart failure, kidney disease, and diabetes have a diminished healing response, poorer implant fixation, and greater revision risk. It is these more difficult clinical scenarios that require research to evaluate more advanced treatment approaches. Such treatments can include osteogenic or antimicrobial implant coatings, allo- or autogenous cellular or tissue-based approaches, local and systemic drug delivery, surgical approaches. Regarding implant-related approaches, most experimental and numerical models do not generally impose conditions that represent mechanical instability at the implant interface, or recalcitrant healing. Many treatments will work well in forgiving settings, but fail in complex human settings with disease, bone loss, or previous surgery. Ethical considerations mandate that we justify and limit the number of animals tested, which restricts experimental permutations of treatments. Numerical models provide flexibility to evaluate multiple parameters and combinations, but generally need to employ simplifying assumptions. The objectives of this paper are to (a) to highlight the importance of mechanical, material, and surgical features to influence implant–bone healing, using a selection of results from two decades of coordinated experimental and numerical work and (b) discuss limitations of such models and the implications for research reproducibility. Focusing model conditions toward the clinical scenario to be studied, and limiting conclusions to the conditions of a particular model can increase clinical relevance and research reproducibility.
[DOI: 10.1115/1.4032368]

1 Introduction

Through clinically focused biomechanical, biomaterial, and biologically based research, artificial joint replacement has evolved from its early days with cemented implants, nondurable articulations, and limited sizes [1,2], to a predictable and highly successful operation [3]. Orthopedic surgeons now have a variety of means available to successfully treat arthritic joints. However, an increasingly large pool of patients with joint replacement implants are living longer and are more active [4]. This has already caused an increase in revision surgeries to replace failed primary implants [5]. Revision operations have lower survival rates [6], are more complex surgically, have higher infection rates [7], the implants do not yet have the durability of primary implants,

and they do not integrate into the host bone as well as primaries [7–9].

Solutions to improve fixation of revision implants are expected to increase their clinical longevity. Solutions can be implant-based, surgery-based, and patient based. Implant coatings such as hydroxyapatite have been shown clinically to provide durable fixation in primary and revision settings [10,11], and other coatings are being evaluated for prevention of implant-based infection [12]. Clinically, promising revision results have been shown with features to provide secure initial fixation, such as with long tapered stems that bypass areas of bone loss and provide initial stability through intramedullary fit [13]. Further highlighting the importance of initial bone–implant interface stability, recent studies report a relationship between early acetabular component instability and later component loosening [14,15].

Research to improve the outcome and function of revision joint replacements (and in general, the more recalcitrant bone healing with comorbidities) requires more complex preclinical experimental and numerical models, to better understand and tackle these
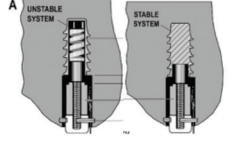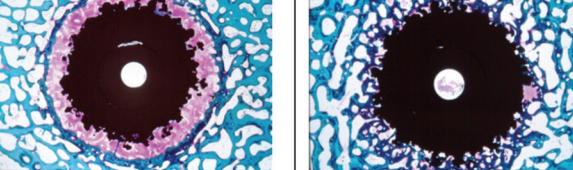
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Model: Intra-articular implant either (a) pistons axially 500 microns in 0.75 mm gap per flexion loading or (b) is stable, with no loading.	Results: Implant subjected to relative motion (unstable implant) grows fibrous membrane in initial gap, while implant that is loaded but not subjected to relative motion (stable implant) grows bone in initial gap and adjacent to implant surface; Titanium plasma spray implant (Ti), [7]. Ground sections, Green = bone; pink = fibrous tissue.	Implication for numerical model: - mechanical conditions change tissue response, despite same implant configuration and gap size.
		Challenge: - how to represent (and validate) the tissue response due to motion.

Fig. 1   Differential effect of implant motion with the same implant coating (titanium)

problems. The models need to adequately represent the specific but important details of the clinical presentations, and need to control for exacerbating medical or mechanical conditions [8]. Numerical models have the advantage of being able to parametrically evaluate a large number of interrelated variables, but necessarily need to simplify (and omit) many factors defining the clinical and biological environment. Experimental models incorporate biology and introduce a physiologic response, but are limited in the number of permutations of interface conditions and mechanical and biologic factors that can be evaluated.

Joint replacement models have a subset of fundamental features that drive bone–healing response. One of these is relative motion. Motion or instability is well known to prevent healing of a fractured bone, and to reduce bone–implant fixation by predictably producing a fibrous interfacial membrane around a joint replacement implant [16]. Another fundamental condition is the surgical preparation of the implant site, and whether line-to-line press-fit fixation is achieved, or whether there are localized gaps between the implant and bone [17,18]. These different features can be a main driver of differential results, yet may not be readily possible to include in numerical models [17–20].

Lack of fidelity of a model to the critical features of the clinical condition it represents, lessens our ability to provide an adequate host challenge to new therapeutic approaches, and to predict clinical responses in humans. Importantly, lack of consideration of the critical features of a clinical condition, or over-interpreting simple or focused models, can introduce irreproducibility to the larger field, and can confound efforts to create a consistent body of knowledge [21,22].

The overall objective of this research review is to call attention to the need to carefully consider confounding variables in study design for orthopedic research in joint replacement. We do this by presenting modeling approaches from a series of coordinated experimental and numerical implant studies of factors influencing revision joint replacement. Considering these studies as a group provides an opportunity to highlight several mechanical, material, and surgical features of joint replacement models that influence healing outcomes. These features include implant stability, surgical technique, revision setting, implant coating, interfacial bone gaps, and bone graft in the gaps. We also present a parametric numerical model based on one of the experimental revision implants, as an example of the opportunities a coordinated
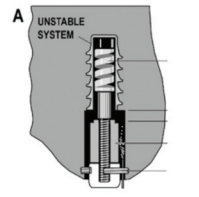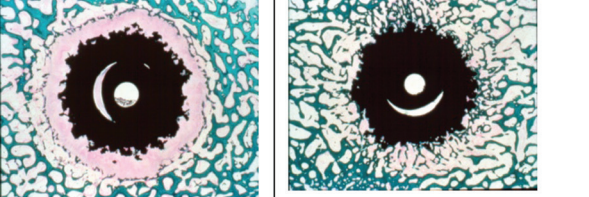
Model: Unstable, intraarticular implant pistons 500 microns axially in 0.75 mm gap, per flexion loading	Results: Instability induced fibrous membrane produced under identical mechanical conditions is replaced by bone with hydroxyapatite (HA) osteoinductive surface (right, below), but persists as fibrous tissue with titanium (Ti) implant surface (left, below), 16 weeks, [7]. Ground sections, Green = bone; pink = fibrous tissue.	Implication for numerical model: - the osteopromotive nature of the coating changes experimental outcome, despite identical mechanical conditions.
	Unstable, titanium *Unstable, hydroxyapatite*	Challenge: - how to represent (and validate) the coating's osteopromotive effect that induced bone growth to stabilize an unstable implant.

Fig. 2   Differential effect of implant coating (titanium and hydroxyapatite) when an implant undergoes relative motion (unstable implant)

Model: Unloaded, stable, extra-articular implant with 1.0 mm concentric gap. Plasma spray Ti, HA, electrodeposited HA and electodeposited HA with collagen [8].	Results:	Implication for numerical model: - tissue constituents of fibrous membrane are different for different types of HA coating - mechanical interface properties vary per coating.

Results (chart):

	Ultimate Shear Strength (MPa)	Apparent Shear Stiffness (MPa/mm)	Total Energy Absorption (J/m²)
P-Ti	0.0 (0.0–0.3)	0.0 (0.0–1.3)	0 (0–45)
P-HA	2.1 (1.5–3.2)[a,b]	7.8 (4.2–17.9)[a,b]	535 (213–574)[a,b]
E-HA	2.0 (0.7–3.4)[a]	9.0 (2.7–16.6)[a]	339 (92–618)[a]
E-HA-Col	0.5 (0.1–2.1)	2.5 (0.6–8.9)	73 (7–456)

Data presented as median and interquartile ranges. n = 7.

Challenge: - how to predict (and validate) growth of different constituents of tissue, and mechanical consequences, for the same class of treatment.
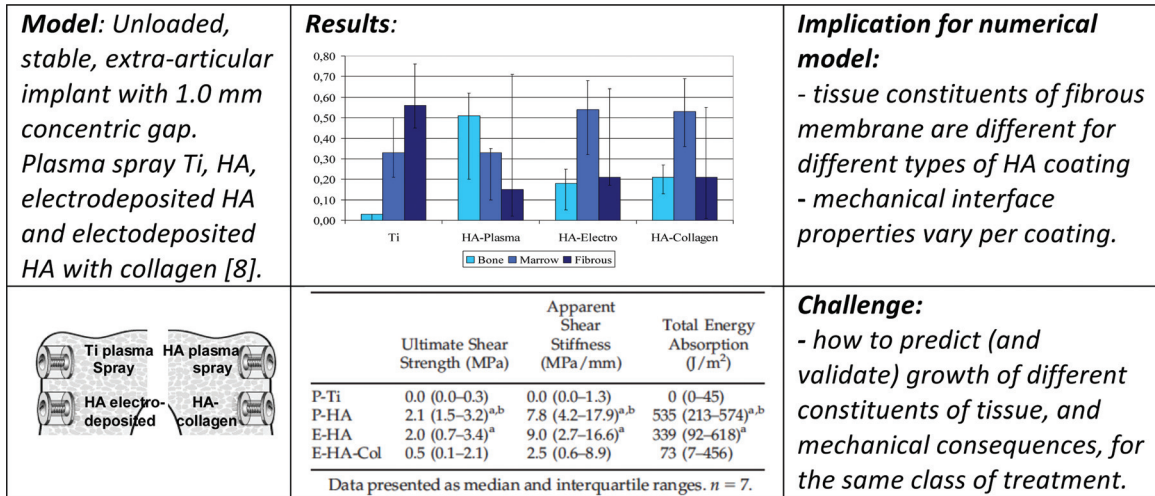
Fig. 3 Differential effect of various compositions of the same osteopromotive coating (titanium control and three compositions of Hydroxyapatite), under unloaded gap conditions

computational approach provides, as well as its limitations. The relationship of all models to the clinical implant setting, and to data reproducibility will be discussed.

2 Modeling Approaches to Study Bone–Implant Interface

In this section, methods and selected results for a set of coordinated experimental and numerical modeling studies of the bone–implant interface will be presented [16–18,23–28].

2.1 Experimental Models—Background. In Vivo animal models studying host response to mechanical, material, and surgical conditions are presented in Sec. 2.2. Challenges and cautions to constructing the corresponding numerical models are outlined. This is not meant to be an exhaustive review of

all experimental models for joint replacement; summaries of models pertinent to the field can be found in review articles such as Ref. [29] and examples of other species and types of bone and approach can be found in articles such as Refs. [30–32].

2.2 Experimental Models—Examples. Experimental details for these studies are found in the original publications [16–18,23–28]. In brief, retrieved bone–implant specimens are cut into two pieces. This separates the 6.0 mm diameter, 10.0 mm long implant into a histomorphometric specimen that is fixed, dehydrated, and stained (inner 6.5 mm), and a pushout specimen that is tested fresh (outer 3.0 mm). MicroCT images are obtained on the 3.0 mm pushout specimens prior to their mechanical testing. Outcomes are presented (a) qualitatively with images of ground sections of bone and tissue surrounding the implant and

Model: Loosening protocol (8 weeks) consists of Intra-articular implant pistoning axially 500 microns in 0.75 mm gap per flexion loading, with PE particles.	Results:	Implications for numerical model: - primary and revision implants produce different healing [9] - bone graft influences healing [9-10]

Results:

Pushout parameters	Stable Primary	Stable Revision	Stable + graft Primary	Stable + graft Revision	Unstable Primary	Unstable Revision
Strength (MPa)	0.26 (0.08)	0.16 (0.03)	4.2 (0.93)	1.0 (0.36)	0	0
Stiffness (MPa/mm)	0.91 (0.33)	0.43 (0.12)	19 (3.8)	4.1 (1.3)	0	0
Energy (J/m)	0.81 (0.26)	0.53 (0.10)	13 (2.8)	3.1 (1.0)	0	0

Primary: 4 weeks without preceding loosening protocol. Revision: 4 wks with preceding loosening protocol. Graft: Morselized allograft packed in gap. Ground sections of retrieved specimens.

Grafted Primary (stable)   Grafted revision (stable)
Black = implant, Green = bone and bone graft, Red = fibrous membrane

Challenge: - how to represent (and validate) the tissue response due to second surgery and revision protocol and due to bone graft.
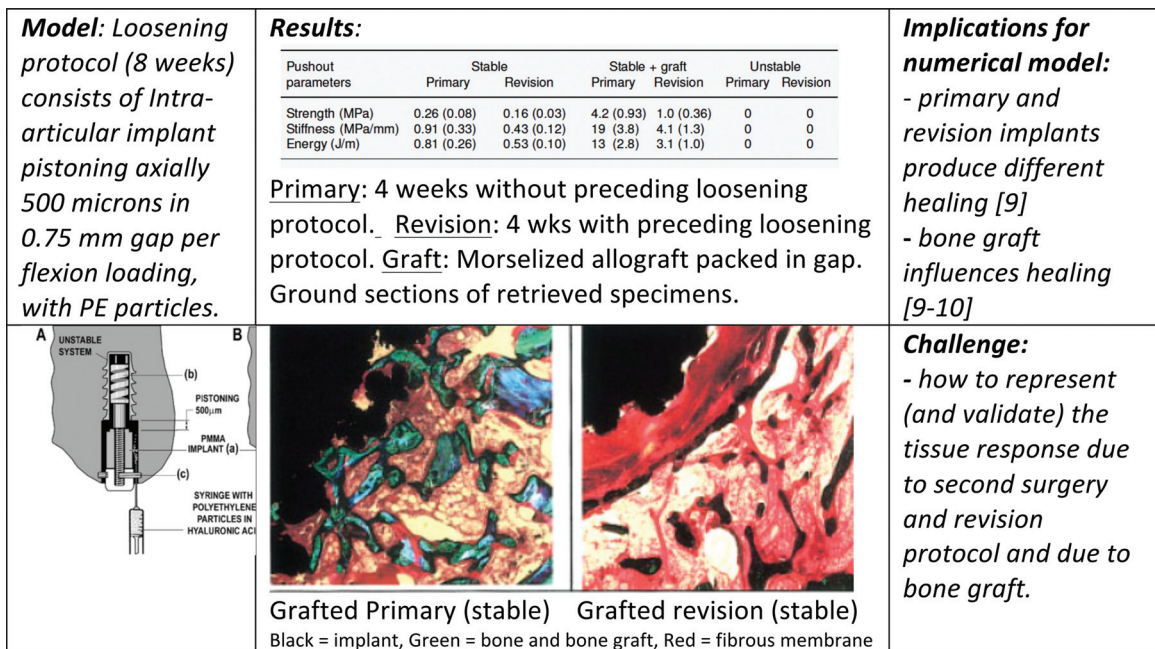
Fig. 4 Differential effect of surgical technique of implant revision (second surgery) and of bone graft, with the same implant coating (titanium)
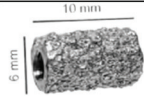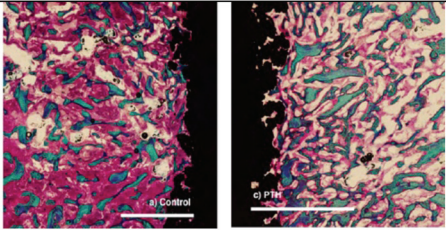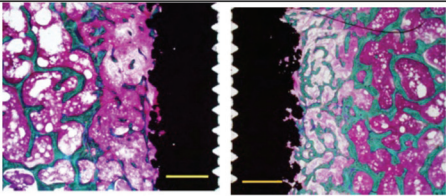
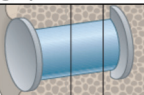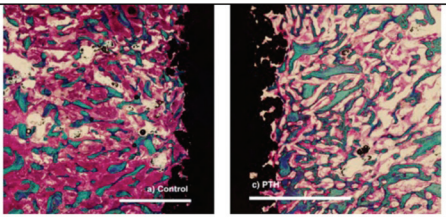| Model:	Results:	Implications for numerical model:
Systemic Parathyroid (PTH) given for 4 weeks (PTH (1-34) 5.0 microgram/kg); fixation evaluated for 3 settings (Studies I-III)	 <table><tr><td></td><td></td><td>Study I:</td><td>Study II:</td><td>Study III:</td></tr><tr><td>Histomorphometry</td><td>Interface: Bone in contact fraction</td><td>↑</td><td>—1)</td><td>—</td></tr><tr><td></td><td>Gap region: Bone fraction</td><td>n/a</td><td>↑</td><td>↑</td></tr><tr><td></td><td>Intact bone region: Bone fraction</td><td>—</td><td>—</td><td>—</td></tr><tr><td>Mechanical testing</td><td>Max Shear Stiffness</td><td>—</td><td>↑</td><td>—</td></tr><tr><td></td><td>Total Energy Absorption</td><td>—</td><td>↑</td><td>—</td></tr><tr><td></td><td>Max Shear Strength</td><td>—</td><td>—2)</td><td>—</td></tr></table> Detailed results in references [11-14]. Ground sections of bone-implant interface, green=bone, pink=fibrous tissue	- the same systemic treatment (PTH) resulted in different peri-implant fixation at each site.
Study I: Extra-articular implant, press-fit (no surgical gap); (Studies I-III) in proximal tibia.	Control (press-fit) systemic PTH	Results summary: - *Press fit fixation w/ PTH increased bone in contact but not mechanical fixation;* - *empty gap with PTH increased new bone in gap region, and also increased mechanical stiffness & energy* - *grafted gap with PTH increased total bone in gap region (new bone and retained graft), but not mechanical fixation.* **Challenge:** - how to model (and validate) different correspondence between histomorphometry and mechanical results, that are dependent on surgical implant interface characteristics.
Study II: Extra-articular implant, 1.0 mm empty surgical gap.	Control (gap) systemic PTH	
Study III: Extra-articular implant, 2.5 mm surgical gap packed w/ morselized allograft	Control (gap+graft) systemic PTH	

Fig. 5 Differential effect of a systemic treatment (PTH) for three implant settings (press-fit, empty surgical gap, grafted surgical gap) with the same implant coating (titanium)

(b) quantitatively in terms of histomorphometric parameters (bone and tissue at implant surface and in surrounding gap), pushout shear strength. MicroCT images are used as input for numerical analysis.

For each section, the following presents the main details of the experimental model, with figures demonstrating the different qualitative and quantitative responses to the conditions being evaluated. Caveats for numerically modeling each scenario are discussed.

2.2.1 Effect of Relative Motion With a Single Implant Coating. Adding relative motion at the bone–implant interface will cause primarily fibrous tissue to form, whereas a stable bone–implant interface (without relative motion) will cause primarily bone to form. Figure 1 shows the differential effect of implant motion for identical titanium (Ti) implants [16]. Implants were inserted with a 0.75 mm concentric gap at the time of surgery; histomorphometric images clearly show the fibrous membrane that forms with implant motion and the bone that forms in
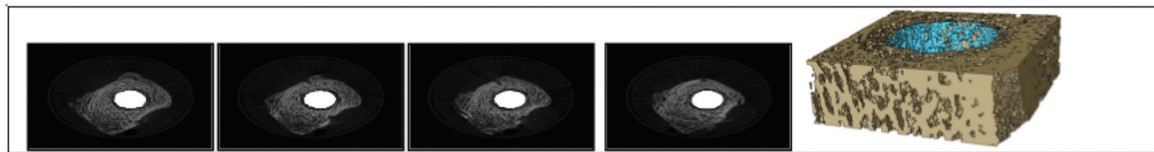

Fig. 6   Selected bone–implant images of retrieved specimens from microCT slices [28], with reconstructed computer model (right)
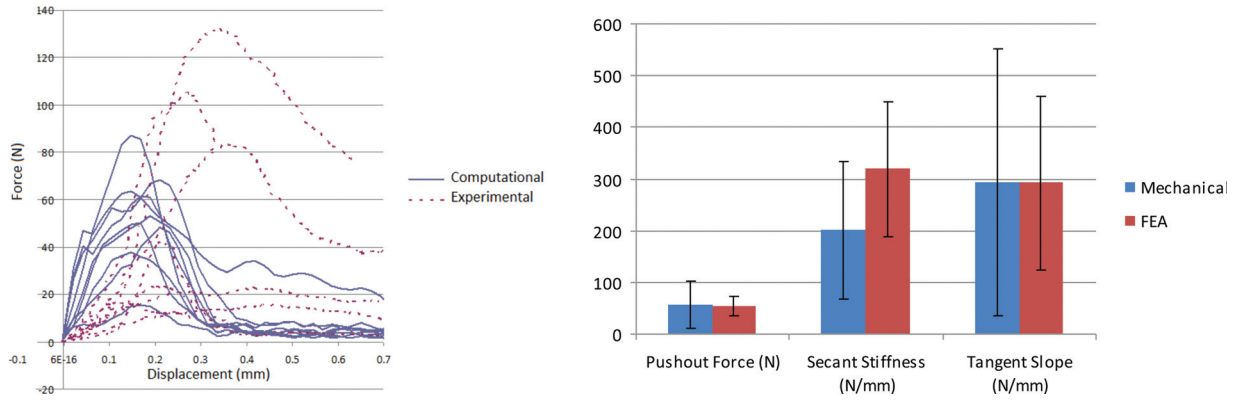
Fig. 7 Comparison of experimental pushout results with subject-specific finite element output
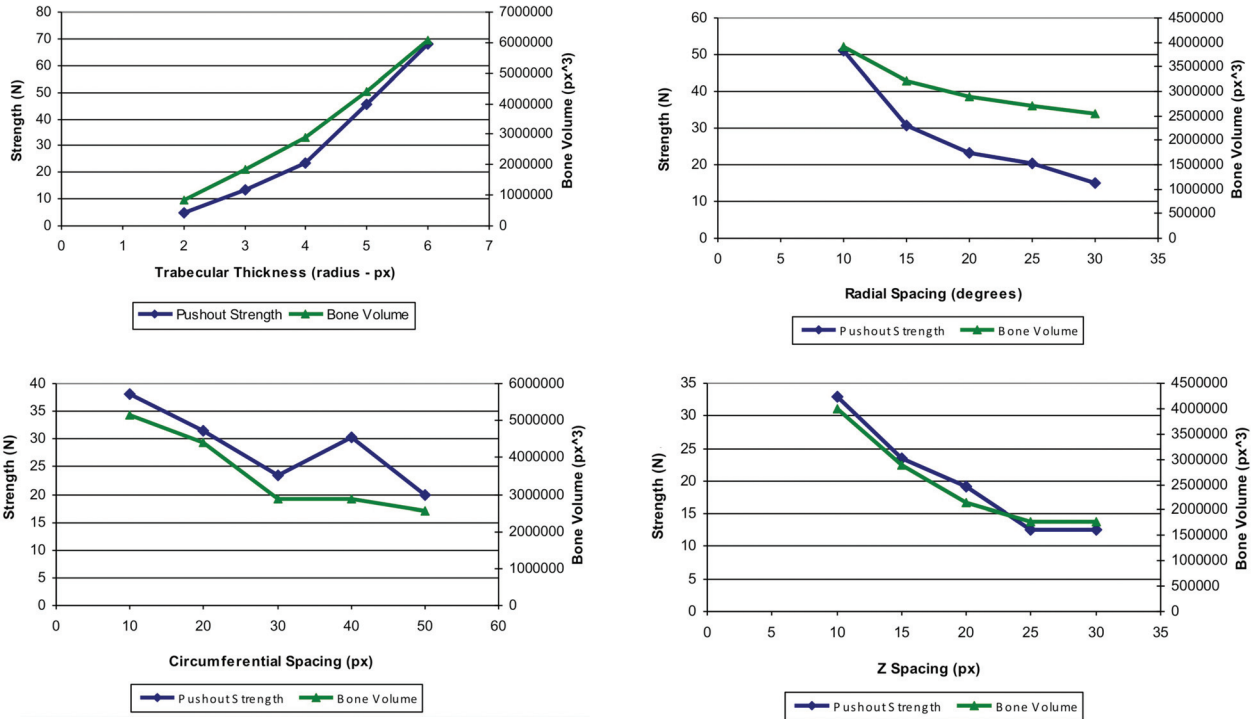

Fig. 8 Implant pushout strength as a function of trabecular thickness, radial spacing, circumferential spacing and depth
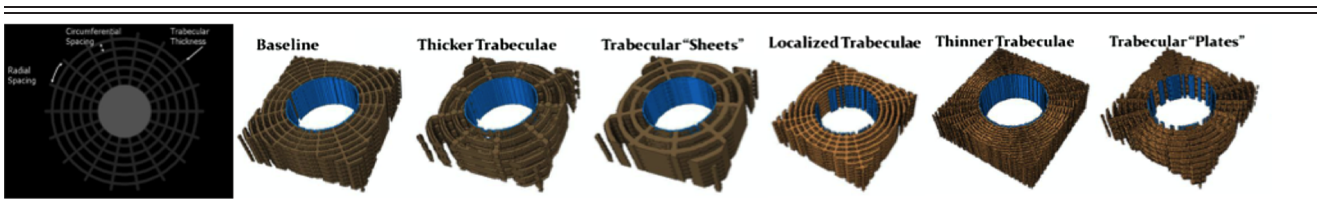
the absence of implant motion. Note, a numerical model would need to include the ability to represent relative motion between implant and bone.

2.2.2 Effect of Relative Motion Differs Between Two Different Implant Coatings. Different implant coatings can cause a different response even under identical mechanical conditions of relative motion at the bone–implant interface. Figure 2 shows the different effects of two implant coatings (titanium and hydroxyapatite) for identical amounts of relative motion in the same 0.75 mm surgical

gap [16]. An unstable implant with hydroxyapatite coating is able to convert a motion-induced fibrous membrane into bone, while the fibrous membrane persists for an unstable implant with titanium coating. Note, a numerical model would need to include the ability to represent an osteopromotive coating.

2.2.3 Effect of Formulation and Application of an Osteopromotive Coating. Three different formulations of hydroxyapatite cause different amounts of fibrous tissue, and different mechanical fixation, when all are inserted in the same surgical gap. Figure 3

Table 1 Bone morphology for varying trabecular thickness, radial location and shape
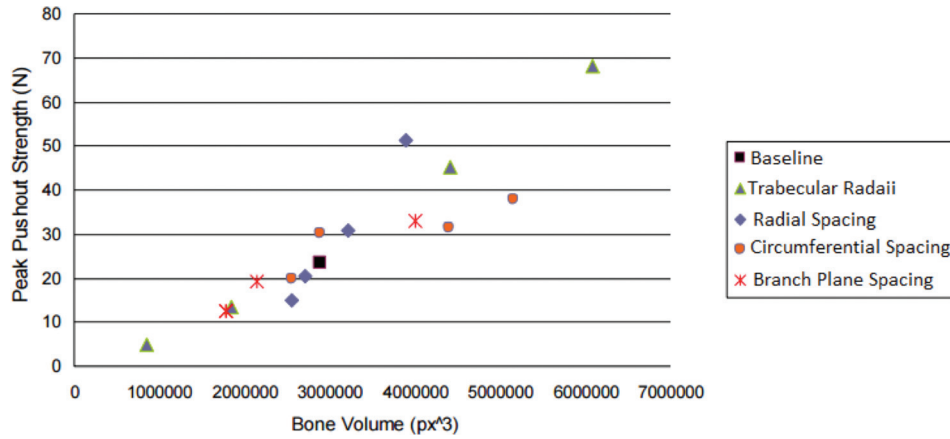
Fig. 9 Relationship of implant pushout strength with bone volume and geometric arrangement
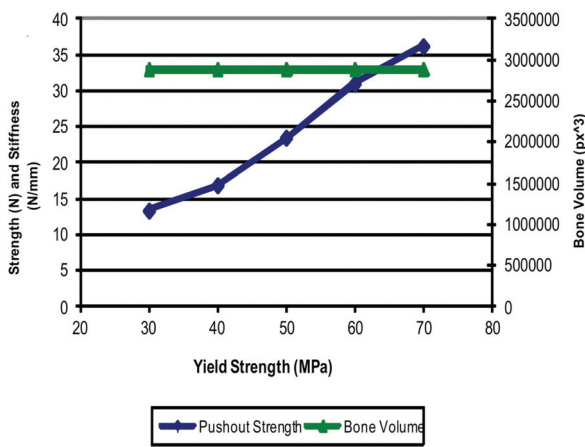

Fig. 10 Effect of the strength of the bone material on implant pushout strength, with bone volume held constant

shows the differential effect among (a) titanium alone and hydroxyapatite coating applied as (b) plasma spray, (c) electrode-posited, and (d) mixed with collagen, under surgical conditions of a 1.0 mm circumferential gap [23]. While the three compositions and coating methods all stem from the same hydroxyapatite mineral, their fabrication engenders different amounts of bone, fibrous membrane and marrow at the implant interface. Note, a numerical model would need to include the ability to represent different levels of osteopromotive response due to the coating.

2.2.4 Separate and Combined Effect of Implant Revision, Surgical Technique, and Bone Graft. A revision implant that is placed into a site following removal of a loose implant demonstrates a fibrous membrane at the implant interface, whereas a primary implant without previous surgery demonstrates bone at that interface. Bone graft enhances fixation for both settings, but the effect is greater in the primary than the revision setting. Figure 4 demonstrates the differential effect of surgical technique of implant revision (second surgery) and of bone graft, with the same implant coating (titanium) [24,25]. Note, a numerical model would need to include the ability to represent the formation of a sclerotic shell, and altered healing response in primary and revision conditions.

2.2.5 Different Effects of Systemic Treatment, Depending on the Surgical Peri-Implant Bone Gap. Systemic parathyroid hormone (PTH) engenders a different bone and tissue response depending on amount of gap between the implant and surrounding bone. Figure 5 demonstrates the differential effect of systemic PTH for three implant settings (press-fit, empty surgical gap, grafted surgical gap) with the same implant coating (titanium) [17,18,26,27]. Note, a numerical model would need to include the ability to represent healing across different gap sizes, and the effect of bone graft.

Summary of Experimental Models. These five examples show the important role that factors such as relative implant motion,

| Human: *Left* – loosened uncemented implant. *Right* – revised implant with bone loss, allograft strut and reattached trochanter. | Human: 3 transverse sections retrieved post-mortem uncemented femoral component (proximal to distal) [18]. Sclerotic shell and gap in bone at implant interface is evident. | Experimental model: Ground section showing sclerotic bone and fibrous tissue (pink) after 8 week revision protocol. |

Fig. 11 Relevance of experimental model to represent local features of revision implant fixation

surgical gap, implant coating, bone graft, and systemic administration of an anabolic factor can have on the integrity of the bone–implant interface. Studies need to account for such factors, either in the model itself or in the discussion of applicability of data.

2.3 Combined Experimental–Numerical Models. A coordinated computational model of implant fixation illustrates opportunities and limitations of numerical models. The purpose of the model is to evaluate implant bone fixation for (a) actual bone distribution patterns following revision and (b) theoretical trabecular bone distribution patterns that were generated to parametrically evaluate features of trabecular width and spacing.

Experimental implants from a separate study investigating revision joint replacement were used as a source of bone geometry and mechanical pushout data, and serve as a validation set for the computational model [28]. MicroCT scans (Scanco, Bruettisellen, Switzerland) were obtained on pushout specimens, to provide input data defining the bone geometry for the finite element (FE) models, as described below. The pushout specimen is a transverse section of bone containing the most superficial 3 mm of the 1.0 cm implant.

2.3.1 Finite Element Model. Geometry for the finite element models of the validation set were created from the image stacks of the microCT scans of the pushout specimens [28]. The implant elements were treated as a rigid body and only the exterior of the implant was modeled. To simulate the breaking of trabeculae, a critical bone strength of 120 MPa was defined and elements exceeding this value were automatically deleted from the analysis. The analyses consisted of approximately 600,000 linear hexahedral elements and were computed in Abaqus/Explicit (Dassault Systeme, Waltham, MA) using 16 cpus (Fig. 6). The image stacks were loaded into Matlab and processed using a custom-written interactive script. Median filtering followed by Gaussian smoothing was used to despeckle and smooth the images. Thresholds were then set to segment the image into background, bone, and implant regions. The implant and bone regions were converted to voxel-based meshes of approximately 600,000 linear hexahedral elements. The bone was assigned linear elastic properties and iterations were performed to calibrate the finite element analysis results to the experimental results, resulting in a bone elastic modulus of 1 GPa.

2.3.2 Finite Element Validation. Figure 7 shows that the predicted response from the simulated computational pushout curves under shear loading conditions have tangent stiffness and interfacial shear strengths of similar pattern and magnitude to the experimental results. This suggests that the simplified numerical model was able to represent the ex vivo response that incorporates physiologic events at different scales. Despite this, one specimen of eight showed a measured force of 50 N greater than its companion FE model. We are unable to confirm, but we assume this could be due to local differences in architecture between the inner 6 mm of the implant/bone region (on which microCT and FE model were based), and the outer 3 mm of the same implant/bone region (from which experimental results were obtained). Since the specimens for the microCT scans for the validation set were not from the exact transverse bone/implant specimens used for the pushout tests, so a one-to-one agreement was not expected. The experimental results also include a "toe" region not captured by the linear-elastic bone model used in the numerical analysis.

2.3.3 Parametric Analysis of Idealized Trabecular Networks. Following the validation of the model, we utilized a parametric variation in features of trabecular bone to look for trends in bone–implant interface strength depending on the shape, size, volume, and connectivity of idealized trabeculae. Idealized trabecular networks were generated using a custom Matlab (MathWorks, Natick, MA) script (Table 1). Trabecular skeletons were composed of circumferential rings connected by radial branches and

vertical struts originating from the ring/radial intersections. Image processing techniques were then used to thicken the skeleton to specified trabecular radii. The idealized trabecular networks could then be defined by four parameters: spacing of circumferential rings (mm), spacing of radial branches (degrees), spacing of ring/radial branch planes (mm), and trabecular radaii. The morphological representation of each of the generated networks was quantified using BONEJ [33], to derive measures of connectivity, bone volume, surface area, and branching. The idealized trabecular networks were then converted to voxel meshes and analyzed using ABAQUS/EXPLICIT in the same manner as previously described for the validation set.

2.3.3.1 Morphology Perturbations. Figure 8 shows the effect of each of the four idealized geometry inputs for bone morphology on the resulting pushout strength. Pushout strength increases with trabecular thickness and decreases with increased spacing, with the increase or decrease in strength generally correlating with the increase or decrease in bone volume. The greatest strength for a given volume generally occurred with larger trabecular thickness and lower trabecular spacing. Figure 9 shows that the pushout strength is strongly and directly correlated with bone volume, nearly independently of the geometric arrangement of the trabeculae. Figure 10 shows that the pushout strength depends on the maturity of the bone material, with Elastic modulus representing the relative maturity of the healing bone. An increase in Elastic modulus of the bone results in a nearly linear increase in pushout strength, for models having the same bone volume.

2.3.3.2 Ranking of Factor Effect on Shear Strength. The results demonstrate that the most important factor in implant fixation strength is the amount of bone adjacent to the implant. As a second-order affecter, the radial spacing resulted in the steepest increase in pushout strength per increase in bone volume. As an example, implant surfaces and surgical preparations that encourage radial trabecular bridging out from the implant were shown to increase fixation. Fixation is also increased when implants are surrounded by bone of higher Elastic modulus, but not as strongly as when there is an increase in bone volume. These simulation results agree with experimental tests by others, showing pushout stiffness to be highly correlated to bone volume and minimally related to connectivity density [34].

3 Discussion

Basic and preclinical research studies seeking to better understand and predict the utility of implant designs or therapeutic regimes often employ controlled experimental and computational models. Here, we have presented examples of models where mechanical, material, and surgical technique confounding variables were found to alter experimental measures of bone–implant fixation. The numerical evaluation aimed to identify mechanically promising morphologies for healing trabeculae, to guide develop biologic or surgical methods that will preferentially direct bone to heal in these configurations. For example, since biologic agents often have the effect of either making bone stronger or making more bone volume, it is important to have insight into whether stronger bone or more bone has a higher order effect, or whether another factor or combination of factors may predominate.

These models are designed to answer specific research questions. Simple preclinical models are appropriate for exploring initial feasibility of a treatment or concept, or to undergo parametric evaluation for optimization. More complex models can be used for more mature technologies and approaches, where increasing clinical fidelity is needed. Unwarranted assumptions or lack of clarity in experimental conditions can lead to lack of reproducibility in experimental research by separate groups.

Many features affect results (and relevance) of general experimental models. These include the choice of animal, including its sex, species, breed, age, weight, activity, type of food, and environmental conditions and observation period. Method of

processing bone graft can introduce variability (fresh, fresh frozen, irradiated, freeze dried). Surgical settings also introduce variability, including whether the operative procedure is a primary surgery, revision surgery, whether the site is cancellous or cortical, well vascularized, and in a long bone, or the flat bone of the skull, if it is extra-articular or if it communicates in the joint space with synovial fluid. A critical limitation of these models is their reductionistic formulation. This sets up a tradeoff between designing a study of manageable scope, and maintaining fidelity of the model to the important details of the clinical setting. These may vary with the research question being considered.

Importantly, ethical and logistical obstacles appropriately prevent experimental in vivo evaluation of all possible combinations and permutations of such conditions [22,29]. The 3Rs for animal experiments (Replacement, Reduction, Refinement) are important guiding principles for biomedical research. Appropriate numerical models can support the 3Rs by exploring permutations of model features in a parametric or design-of-experiments approach. The biologic and physiologic aspects can be addressed through coordinated animal models to validate key assumptions on select features.

An example of coupling of experimental and numerical modeling was presented here. Our numerical model is relatively simple in formulation and it rests on several simplifying assumptions that restrict its clinical applicability. While it employs relatively complex fracture mechanics theory to represent failure at the bone–implant interface, the linear hexahedral elements used here tend to make the structure stiffer and influence the derivation of shear energy. Comparing with quadratic elements would be beneficial, but the increased degrees of freedom come with greatly increased time for computation. Interpretation of findings needs to take these limitations into account.

While simple models may be perfectly adequate and best suited for an early stage evaluation of a concept [35], more in-depth study may require introduction of linear, nonlinear, elastic/elastic–plastic material properties and two- and three-dimensional formulations. Spatio-temporal models of the healing process can help predict time-course events, but require knowledge of governing laws for tissue adaptation, and need details of bone porosity, convective or diffusive flow. Computationally unwieldy models can occur even with simplified loading, simplified boundary conditions, simplified geometry and heterogeneity of tissue distribution and assumptions on the nature of the interface connections. While numerical models for predicting bone and tissue adaptation traditionally focus on mechanical and structural analysis, it is important to consider the contribution of other factors such as biologic and biochemical [36,37]. Incorporating complex mixed mechanics (solid + fluid, poromechanics, reactive media) carries the challenge of providing rigorous validation on clinically relevant measures [38–41]. Due to the complexity of physiologic response, use of statistical models is increasing in utility [42]. Importantly, the validation of the numerical model must be described, with more complex numerical models present challenges for experimental validation.

Determining the purview of a preclinical model depends on comparison to the clinical setting it intends to represent. The essential local features following loosening were present in the experimental revision model (dense fibrous membrane, increased joint fluid pressure, and thickened capsule with sclerotic shell in cancellous bony bed, higher inflammatory cytokines, and reduced implant fixation [25]). However, the clinical presentation remains more complex. Structural bone loss, increased infection and dislocation risk are also present in the revision setting (Fig. 11) [9,43], but are not present in the experimental model. Despite these limitations, the model's recalcitrant healing following the revision protocol does provide a more stringent environment that the more straightforward primary bone bed. This provides the opportunity to identify treatments that may be more effective in the reduced healing and altered structure (sclerotic bone shell) of a revision environment, as compared to the more forgiving primary setting

[24], or in conditions where a coating behaves differently when the implant is placed under loading as compared to being protected from load [20,44]. The same ability to represent clinical features of a revision setting, for example, is not straightforward for numerical models.

Ultimately, well-conducted clinical studies serve as the translational link between the preclinical research setting and the clinical setting. For new joint replacement technologies and approaches, radiostereometry (RSA) has been proven to provide a reliable short-term method of predicting the ultimate clinical function of an implant [14,45]. Multiple clinical studies in humans have shown that quantifying early implant motion and subsidence (with precision as obtained through RSA techniques) is associated with later implant loosening [14,45]. Longer-term outcome requires data registries and prospective studies [4,7].

4 Conclusion

Advancing knowledge requires rigor in scientific method. Here, we have shown a set of related experiments in joint replacement research that demonstrate nuances in tissue response based on mechanical, material, and surgical conditions. Simple models (both experimental and numerical) can be useful in framing response to generalized conditions and allow detailed parametric analysis (e.g., trabecular arrangement and interface shear strength). Complex clinical scenarios are the vexing situations that require new therapies. Making models to study these conditions must be done with diligence and care. Interpreting all models must be done with restraint, to maintain data relevance and reproducibility. Ultimately, clinical outcome studies and registries are needed to demonstrate the utility (or not) of new therapies, but these are best preceded by rigorous basic and preclinical research.

Nomenclature

  HA = hydroxyapatite
PTH = parathyroid hormone (PTH (1-34))
RSA = radiostereometry (Roentgren Stereophotogrammetry)
  Ti = titanium

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