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Using a Statistically Calibrated Biphase Finite Element Model of the Human Knee Joint to Identify Robust Designs for a Meniscal Substitute

This paper describes a methodology for selecting a set of biomechanical engineering design variables to optimize the performance of an engineered meniscal substitute when implanted in a population of subjects whose characteristics can be specified stochastically. For the meniscal design problem where engineering variables include aspects of meniscal geometry and meniscal material properties, this method shows that meniscal designs having simultaneously large radial modulus and large circumferential modulus provide both low mean peak contact stress and small variability in peak contact stress when used in the specified subject population. The method also shows that the mean peak contact stress is relatively insensitive to meniscal permeability, so the permeability used in the manufacture of a meniscal substitute can be selected on the basis of manufacturing ease or cost. This is a multiple objective problem with the mean peak contact stress over the population of subjects and its variability both desired to be small. The problem is solved by using a predictor of the mean peak contact stress across the tibial plateau that was developed from experimentally measured peak contact stresses from two modalities. The first experimental modality provided computed peak contact stresses using a finite element computational simulator of the dynamic tibial contact stress during axial dynamic loading. A small number of meniscal designs with specified subject environmental inputs were selected to make computational runs and to provide training data for the predictor developed below. The second experimental modality consisted of measured peak contact stress from a set of cadaver knees. The cadaver measurements were used to bias-correct and calibrate the simulator output. Because the finite element simulator is expensive to evaluate, a rapidly computable (calibrated) Kriging predictor was used to explore extensively the contact stresses for a wide range of meniscal engineering inputs and subject variables. The predicted values were used to determine the Pareto optimal set of engineering inputs to minimize peak contact stresses in the targeted population of subjects. [DOI: 10.1115/1.4027510]

Keywords: tissue engineering, Bayesian calibration, computational simulator, prediction, meniscal design, Kriging

1 Introduction

Knee menisci are C-shaped fibrocartilage disks that have wedge-shaped cross sections and occupy the periphery of the knee joint. The meniscus has several significant mechanical functions including load distribution across articular cartilage, joint lubrication, shock absorption, and joint stabilization [1]. In the face of such mechanical demands, it is not surprising that the meniscus can become damaged. Surgical treatment of the damaged meniscus is the most commonly performed orthopaedic procedure, with about 850,000 surgeries performed in the United States annually [2]. Despite the prevalence of meniscal injuries, surprisingly few treatment options exist.

The combination of a poorly developed vascular network and a high mechanical-stress environment limit meniscal healing potential. Often a meniscectomy (partial or total surgical removal of a meniscus) is selected to be the best available solution. However,

the deleterious effects of meniscectomy include limited mobility, pain, and ultimately osteoarthritic degradation [3,4]. The subsequent deterioration of the joint leads to disability, the need for additional surgeries, and often culminates in total knee joint replacement. Replacement of a portion of the damaged meniscus or replacement of the entire structure has the potential to delay or even avoid the onset of osteoarthritis. To achieve this goal, the substitute should be expected to carry and distribute joint loads much in the way of the native tissue. As synthetic meniscal replacements are developed, it is critical that we obtain a better understanding of the effect that the meniscal material properties and meniscal geometries have on overall meniscal replacement functionality.

The goal of this paper is to identify meniscal material and geometric properties that minimize peak contact stress for a specified patient population. To accomplish this goal, a 2D axisymmetric, biphasic finite element model (bFEM) of the human knee is used to simulate the peak tibial contact stress for a given meniscal design and specific patient tibial and femoral cartilage properties. The simulator provides a force profile at discrete time points that mimics the axial component of gait (Sec. 2.1). The patient

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Manuscript received October 11, 2013; final manuscript received March 31, 2014; accepted manuscript posted April 28, 2014; published online May 15, 2014. Assoc. Editor: Tammy L. Haut Donahue.

Table 1 Simulator input variables, their notation, units, and ranges; the first five inputs (printed in bold) describe meniscal properties; the final four inputs describe patient characteristics

Input, notation (units)	Lower bound	Upper bound
Meniscal design inputs		
Maximum meniscal height, h_m (mm) [5–7]	4.5	6.25
Meniscal center height, h_c (mm)	$\geq h_m/2.7$	$\leq h_m/2.05$
Axial and radial moduli of the meniscus, E_{rm} (MPa) [8]	3.74	16.21
Circumferential modulus of the meniscus, E_{cm} (MPa) [8,9]	72.85	230.0
Meniscal permeability, k_m (m⁴/Ns) [1,10]	0.71×10^{-15}	5.23×10^{-15}
Patient-specific inputs		
Tibial cartilage thickness, h_t (mm) [11,12]	1.0	3.9
Femoral cartilage thickness, h_f (mm) [11,12]	1.0	2.8
Elastic modulus of the articular cartilage, E_c (MPa) [13,14]	4.29	25
Permeability of the articular cartilage, k_c (m ⁴ /Ns) [14,15]	0.2×10^{-15}	7.5×10^{-15}

population is characterized by stochastic variations in the tibial and femoral cartilage properties of knees as determined from the literature (see Table 1). Two landmark points in the axial force profile that correspond to the largest axial loads are identified for evaluation of the meniscal designs. Because the bFEM simulator is relatively time-consuming to run, it is only used to assess a limited number of meniscal design and patient conditions. Thus, a more detailed evaluation of each meniscal design is performed using a rapidly computable statistical predictor of the peak contact stress at the two landmark points in the axial force profile. The predictor is calibrated and bias-corrected using cadaver knee measurements. For a fixed meniscal design, the predictor is used to approximate the peak tibial contact stress at the selected force profile landmark for 10,000 patient inputs drawn from the stochastic distribution characterizing patient tibial and femoral cartilage. After performing these calculations for a set of 50 representative meniscal designs, those designs having both small (sample) mean contact stress and small (sample) variability over the patient population are selected as optimal.

2 Methods

2.1 The Finite Element Simulator. A 2D axisymmetric bFEM of the human knee recently developed by Guo et al. [16] is used for this study (see Fig. 1). In brief, the bFEM describes articular cartilage as a linear biphasic material, the meniscus as a transversely isotropic material, and the bone as a linear elastic material with elastic modulus of 10 GPa and Poisson's ratio 0.3. Fluid flow is allowed between the contact surfaces of the soft tissues, while free drainage is used for noncontact surfaces of the soft tissue. The cartilage-bone interface is assumed to be impermeable. The femur is not explicitly modeled; instead it is represented as a fixed, impermeable boundary. The contact surfaces are assumed to be frictionless. Axial force is applied on the top boundary of the femur. The dynamic axial force profile applied to the tibial-femoral compartment during gait [18] is shown in Fig. 2. This

Fig. 1 A schematic diagram of the 2D axisymmetric knee joint

loading profile requires 2 s per loading cycle, and it applies maximum force at approximately 14% and 45% of the loading cycle.

Several model inputs are *fixed*, based on magnetic resonance imaging and finite element studies of the average “normal” healthy human knee joint [17]: the *inner radius of the meniscus* (set at $r_i = 5$ mm); the *width of the meniscus* (set at $w_m = 15$ mm); the *height of the meniscal bulge* (set at $b = 1.5$ mm); and the *width of the tibial cartilage* (set at $w_t = 22.4$ mm). All other geometric values and material properties are considered as variable inputs with values chosen to span the ranges reported in the literature for normal knees and listed in Table 1. All bFEMs were solved using COMSOL Multiphysics (COSMOL Inc., Burlington, MA) on a Mac workstation with two 3.06 GHz 6-Core Intel Xeon processors and 24 GB 1333 MHz DDR3 Memory [19–22].

For a specific meniscal design and patient settings, the simulator output is the contact stress (MPa) on the surface of the tibial plateau for each radial position and each loading cycle time point. For example, for the meniscal inputs ($h_m, h_c, E_{rm}, E_{cm}, k_m$) = (6.128, 2.980, 10.376, 108.800, 2.202) and patient inputs (h_t, h_f, E_c, k_c) = (2.073, 2.044, 6.709, 5.289), Fig. 3 displays the smoothed surface connecting the discrete set of bFEM-determined contact stresses for each radial position and each point in the loading cycle, where 2 s corresponds to one complete cycle. Two landmark points were abstracted from the contact stress surface: the peak contact stress over radial positions at 14% of the loading profile and the peak contact stress over radial positions at 45% of the loading profile. These landmarks were selected because the largest forces were applied at approximately 14% and 45% of the axial loading profile.

Fig. 2 ISO 2009 dynamic axial force during gait. This profile was used in runs of the bFEM; the profile, scaled to 10 s, was used in the cadaver model.

Fig. 3 The smoothed surface connecting the discrete set of bFEM-determined contact stresses across radial position and time when run at meniscal design inputs (h_m , h_c , E_{rm} , E_{cm} , k_m) = (6.128, 2.980, 10.376, 108.800, 2.202) and patient inputs (h_b , h_f , E_c , k_c) = (2.073, 2.044, 6.709, 5.289). The radial position of 0 mm corresponds to the center of the lateral compartment of the knee.

2.2 Cadaver Model. Three fresh frozen cadaver knees were thawed and carefully dissected sparing the cruciate ligaments, menisci, and popliteus. Femoral and tibial bone was removed to within 10.16 cm. of the joint line and the fibula was detached. The lateral compartment was isolated by sectioning the femur and tibia in the sagittal plane. The lateral tibia and femur were potted with poly(methyl methacrylate) bone cement into fixtures and attached to a hydraulic testing device (MTS Systems, Eden Prairie, MN). The intact cruciate ligaments and popliteal tendon allowed for alignment of the tibia relative to the femur in a position representative of full extension. After potting, the cruciate ligaments and popliteal tendon were sectioned, separating the tibia from the femur. A thin electronic sensor (4010N, Tekscan Inc., MA) was inserted under the lateral meniscus and placed across the surface of the tibial plateau. Plastic tabs at the edge of the sensor were sutured to surrounding tissue to prevent sensor motion during testing (panel (a) of Fig. 4). The soft tissues of the knee joint are viscoelastic, and the sensor used to measure contact stresses is also viscoelastic. To minimize the viscoelastic effect, we opted to load the axial force profile as depicted in Fig. 2 at the fastest rate that was feasible; thus, we used a series of pilot tests where we

varied the cycle from 2 s to 10 s (see panel (b) of Fig. 4). We selected a 10 s loading cycle because this loading cycle was the frequency at which the hydraulic testing system could most accurately apply the axial component of gait. At faster rates the initial axial peak at 3% of the gait cycle could not be reached and thus, the frequency was decreased until all the appropriate forces were met. For validation purposes, the computational model was also modified to match the slower rate of loading in the experimental model.

Contact stresses were reported from a line of interest located across the sensor (panel (a) of Figs. 4 and 5) at a frequency of 100 Hz. This line of interest included a region of cartilage–cartilage and meniscus–cartilage contact. For each of the three knees tested, the test protocol was repeated with two sensors. The contact stresses at 14% and 45% of the axial force cycle were calculated along the line of interest as a function of distance from the tibial spine, for each knee and each sensor. After testing, the peripheral height of the meniscus and its width along the line of interest were measured using a Vernier calipers. Three measurements were made at each location and average values were used as inputs in the bFEM. Using these averages, a knee-specific computational model was run for each specimen tested. The contact stress as a function of distance from the tibial spine was compared between the experimental and computational model (see panel (b) of Fig. 5).

2.3 The Statistical Predictor and Its Calibration. A rapidly computable Bayesian predictor that was *calibrated* using the cadaver data of Sec. 2.2 was applied to approximate the peak contact stresses at 14% of the axial force cycle in Sec. 2.4. The same methodology was used to develop a predictor of the peak contact stress at 45% of the axial force profile.

Engineering validation of a computer simulator fixes one (or more) inputs, denoted by $\mathbf{x}^c$, which are called the calibration input(s); let $\mathbf{x}^s$ denote the remaining simulator inputs. The goal is to use the simulator to “best guess” the output of a physical system having inputs $\mathbf{x}^p$. Given a target *collection* of $\mathbf{x}^p$ at which predictions of the physical system outputs are desired, validation seeks that (single value of) $\mathbf{x}^c$ which yields the most accurate prediction of the physical system outputs that can be obtained from multiple runs of the simulator at $(\mathbf{x}^c, \mathbf{x}^p)$ for each desired $\mathbf{x}^p$. If the computer simulator is computationally expensive, then the strategy is usually altered by using the limited set of simulator runs to construct a predictor of the simulator output, e.g., a regression model, and predicting the physical system output at $\mathbf{x}^p$ by evaluating the predictor of the simulator at $(\mathbf{x}^c, \mathbf{x}^p)$.

Fig. 4 (a) The tibial component with attached sensor; note the box depicting the line of interest. (b) The experimental setup: during loading the tibia was aligned with the femoral component which was fixed to the crosshead of the MTS. The load profile in Fig. 2, scaled to 10 s, was applied to represent the axial force profile that occurs during gait.

Fig. 5 (a) Contact stress data from a representative, experimentally tested, specimen. A line of interest was identified and the region covered by the meniscus was identified. (Each square represents a 2×2 mm sensing element.) (b) The contact stress, as a function of radial distance from the edge of the tibial spine, was plotted for both sensors and for the computational model; the data shown is from a representative knee at 14% of the loading cycle. The vertical line near 12 mm in (b) marks the inner edge of the meniscus.

Statistical calibration of a computer simulator uses two strategies to improve validation. A calibrated predictor is the *sum of two terms*. The first term is an average of the simulator output over a distribution of “likely” $\mathbf{x}^c$ (more precisely the posterior distribution of $\mathbf{x}^c$ values). The second term is an estimate of the possible bias in the computational simulator due to simplified physics or biology that is used by the simulator. This systematic bias is able to be assessed only when there is physical data to supplement the simulator data. As in the case of validation, a predictor of the simulator output is used in place of a simulator run when the latter is computationally prohibitive. In this paper, the predictor of the simulator incorporates subject expert distributions of “likely” values for the calibration parameter and for the remaining unknown model parameters, i.e., it is Bayesian (see Ref. [23] for details).

This paper takes E_c to be the calibration input because a sensitivity analysis showed that the simulated peak contact stress is strongly affected by changes in E_c , and hence the simulator output can be modified by varying E_c (see Ref. [24] for a detailed

description of sensitivity analysis). Therefore, it is desired to predict the (mean) peak contact stress at 14% of loading (or 45% of loading) in a physical knee for a given $\mathbf{x}^p = (h_m, h_c, E_{rm}, E_{cm}, k_m, h_t, h_f, k_c)$. The calibrated predictor is constructed from the measured peak contact stresses at 14% of the loading profile in 3 cadaver knees plus the computed peak contact stresses at the same landmarks from 60 runs of the bFEM simulator. Let $y^p(\mathbf{x}_i^p)$ denote the *measured* peak contact stress from the i th cadaver specimen with characteristics at $\mathbf{x}_i^p$. As in a regression setting, $y^p(\mathbf{x}^p)$ is modeled as the *true, mean peak contact stress* $\mu(\mathbf{x}^p)$ plus measurement error, i.e.,

$$y^p(\mathbf{x}_i^p) = \mu(\mathbf{x}_i^p) + \varepsilon_i, \quad 1 \leq i \leq 3$$

where $\{\varepsilon_i\}_{i=1}^3$ are assumed to be independent and Gaussian distributed with zero mean and unknown variance σ_ε^2 . Let $\mathcal{E}_c$ denote the true, but unknown, value of the calibration parameter *in the physical system*; thus, $\mu(\mathbf{x}_i^p) = \mu(\mathbf{x}_i^p, \mathcal{E}_c)$ so that the dependence on $\mathcal{E}_c$ is suppressed. Let $y^s(\mathbf{x}_j^s, E_{c,j})$ denote the bFEM simulator output when run at simulator system inputs $\mathbf{x}_j^s$ and calibration input $E_{c,j}$ for $1 \leq j \leq 60$.

To implement the notion of bias-correction of the calibrated simulator, the predictor allows a systematic bias correction term which is defined by

$$\delta(\mathbf{x}^p) \equiv \mu(\mathbf{x}^p) - y^s(\mathbf{x}^p, \mathcal{E}_c)$$

for the simulator/physical system experiment; the bias function depends on true calibration parameter $\mathcal{E}_c$ and hence $\delta(\mathbf{x}^p)$ is unknown but is estimated as part of the prediction process. Algebra gives $\mu(\mathbf{x}^p) = y^s(\mathbf{x}^p, \mathcal{E}_c) + \delta(\mathbf{x}^p)$. The calibrated predictor of $\mu(\mathbf{x}^p)$ used in this paper is of the form

$$\hat{\mu}(\mathbf{x}^p) = \hat{y}^s(\mathbf{x}^p, \mathcal{E}_c) + \hat{\delta}(\mathbf{x}^p) \quad (1)$$

which is the sum of the individual estimators of $y^s(\mathbf{x}^p, \mathcal{E}_c)$ and $\delta(\mathbf{x}^p)$. Specifically, $\hat{y}^s(\mathbf{x}^p, \mathcal{E}_c)$ is a pooled “Kriging” estimator based on the predictive distribution of $\mathcal{E}_c$ (see Chapter 3 of Ref. [25]), and $\hat{\delta}(\mathbf{x}^p)$ is the Bayesian estimator of the bias function given the measured and simulated outputs (see Ref. [23] for additional details). The $\hat{\mu}(\mathbf{x}^p)$ predictions were computed using the GPM/SA software of Ref. [26] (see also Ref. [27]).

2.4 Probabilistic Evaluation of Meniscal Designs. This paper evaluates 50 representative meniscal designs determined by selecting values for each of the five meniscal geometry and material property inputs ($h_m, h_c, E_{rm}, E_{cm}, k_m$) from the possible designs specified in Table 1. The 50 designs were selected to represent all parts of the meniscal design space (Chapter 5 of Ref. [25]). For each meniscal design, $\hat{\mu}(\mathbf{x}^p)$ in Eq. (1) is used to predict peak contact stresses for the population of subjects determined by taking 10,000 independent uniform samples of the patient inputs (h_t, h_f, k_c) using the ranges listed in Table 1. The mean and standard deviation of the resulting distribution of peak contact stresses are computed and then are used to determine the stochastic performance of the given meniscal design across the patient population.

3 Results

3.1 bFEM Runs and the Statistical Calibration. The bFEM converged successfully across the range of meniscal design and normal patient input variables listed in Table 1. The peak total normal stress and peak contact stress always occurred at the center of the cartilage-cartilage contact area. Each bFEM run took approximately 1.5 h.

A total of 60 simulator runs were made. The input sites were selected in multiple stages starting with an initial space-filling (maximin interpoint distance and noncollapsing) design of 18 runs [28]. After each stage, cross-validation [29] and sensitivity indices

Table 2 Sensitivity indices (SIs) of inputs for peak contact stress at 14% of the axial loading profile, constructed using the simulator data (meniscal design inputs denoted in bold)

Input	Total Effect SI	Main Effect SI
h_m	0.0211	0.0027
h_c	0.0063	0.0011
E_{rm}	0.3403	0.0438
E_{cm}	0.5200	0.1687
k_m	0.0077	0.0009
h_t	0.3779	0.0999
h_f	0.2471	0.0579
E_c	0.2224	0.0765
k_c	0.0033	0.0006

(SIs) [24] were computed to determine those subregions where inputs were both *active* and in which the current runs had *large* cross-validation errors. Additional simulator runs were made in these subregions.

A final sensitivity analysis [24] was performed on the full set of 60 simulator outputs to determine the most active inputs on the peak contact stress at 14% of the loading cycle. Table 2 lists the main effect (ME) and total effect SIs for each of the 9 input variables. The total effect SIs are used to order the activity of the inputs; inputs with the large total effect SIs have a greater influence on the computed peak contact stress than inputs with small total effect SIs. For each input, the difference between the total effect and the main effect SIs is used to judge the interactions of that input with other inputs; inputs with the largest differences have the greatest interactions with other inputs. Table 2 shows that E_{cm} , h_t , E_{rm} , h_f , and E_c are the most active inputs while h_m , h_c , k_m , and k_c are relatively inactive. The inputs E_{rm} , E_{cm} , and h_t have the greatest interactions.

The second sensitivity analysis tool used to examine the simulator output is called a ME plot. The ME plot for a particular input variable shows the estimated peak contact stress averaged over all other inputs for each possible fixed value of the variable of interest. ME plots provide further information about the impact of each input, including whether the average output is linear or nonlinear in that input. Figure 6 shows the ME plots for three inputs selected because they represent different effects on the peak contact stress as suggested by their total effect SIs in Table 2. These values suggest that h_m is relatively inactive; E_c is judged to be active; and h_t also appears to be active. The ME plot for h_m shows that h_m has no effect on the average peak contact stress. Input h_t has a *decreasing and nonlinear* effect on the average peak contact stress. Finally, the impact of E_c is to *linearly increase* the average peak contact stress. In particular, it is clear that E_c will be an effective input to manipulate in order to use the simulator to predict at values of the remaining eight inputs.

Fig. 6 ME plots for inputs h_m (left), h_t (center), and E_c (right) on the peak contact stress predictions at 14% of the axial loading profile

Fig. 7 The distribution of predicted peak contact stress at 14% (left) and 45% (right) of the axial loading profile for 10,000 different patient conditions, for the meniscal design (h_m , h_c , E_{rm} , E_{cm} , k_m) = (4.513, 1.698, 9.352, 83.065, 1.750)

A separate sensitivity analysis was conducted for the peak contact stress at 45% of loading. This analysis identified the *same set of inputs* (E_{cm} , h_t , E_{rm} , h_f , and E_c) as active for this second output.

3.2 Selection of Meniscal Designs. Fifty meniscal designs spanning the ranges of the five meniscal variables in Table 1 were selected by determining a set of points in the five-dimensional meniscal input space that maximized the minimum interpoint distance. The ability of these designs to span the meniscal design input space can be seen from the 2D projections of the meniscal inputs that are plotted in Fig. 10 (for now, ignore the fact that several designs have filled plotting symbols). Next, 10,000 random draws were made of the patient inputs (h_t , h_f , k_c) as described in Sec. 2.4. For each of the 50 meniscal designs and for both 14% and 45% of the axial force loading profile, the peak contact stress was predicted using Eq. (1) for the 10,000 different patient conditions; thus, a total of 500,000 predictions were made for each of the two loading cycle landmarks. Boxplots of the predicted peak contact stress distributions at 14% and 45% of loading are shown in Fig. 7 for one representative of the 50 meniscal designs.

For each loading cycle landmark and each meniscal design, the mean and standard deviation of the predicted peak contact stresses over the 10,000 patient cartilage inputs were calculated. The means and standard deviations of the predicted peak contact stress at 14% of the loading profile are plotted in Fig. 8 for the 50 meniscal designs. The meniscal designs having *both* low mean peak contact stress and low standard deviation of peak contact stress

Fig. 8 Means and standard deviations of peak contact stress predictions at 14% of the axial loading profile for the 10,000 different patient conditions corresponding to 50 fixed meniscal designs. Desirable meniscal designs (those with low mean and low standard deviation) are marked with a filled circle.

are desirable and are plotted using the filled circles in the lower left corner of Fig. 8. Conversely, meniscal configurations resulting in a high mean and/or a high standard deviation peak contact stress have undesirable contact mechanics. Table 3 lists the inputs for the four meniscal designs that minimize the peak contact stress at 14% of the axial loading profile, while Fig. 9 provides greater detail by showing boxplots of the predicted peak contact stresses for the 10,000 draws of patient cartilage inputs for each design in Table 3. The same four designs were found to be optimal in a parallel analysis performed for peak contact stress at 45% of the loading profile.

The 2D projections of the meniscal inputs for the 50 designs that are compared are plotted in Fig. 10; the four designs corresponding to low mean and low standard deviation peak contact stress are marked with filled symbols. This figure makes it clear that the most important meniscal design variables are the radial and circumferential moduli. Menisci with large radial moduli E_{rm} and large circumferential moduli E_{cm} yielded low mean peak contact stresses and had a low standard deviation of these peak contact stresses. The maximum meniscal height h_m , center meniscal height h_c , and the meniscal permeability k_m do not have a pronounced effect on peak contact stress.

In a parallel analysis, the peak contact stress at 45% of the axial load profile was studied. The analysis at 45% of the cycle showed that the four meniscal designs in Table 3 are also best for this output. Thus, at 45% of the axial loading cycle, menisci with large radial moduli E_{rm} and large circumferential moduli E_{cm} were identified as optimal because they yielded low mean peak contact stresses and had a low standard deviation over the population of patients.

Table 3 Optimal meniscal designs for both the 14% and 45% points of the axial loading profile

Design	h_m	h_c	E_{rm}	E_{cm}	k_m
1	4.885	2.268	15.399	228.429	3.648
2	5.664	2.748	14.963	222.143	4.868
3	5.340	2.074	15.212	215.071	1.976
4	4.780	1.833	12.905	225.286	0.936

Fig. 9 Distributions of the peak contact stresses at 14% of the axial loading profile over the 10,000 draws of patient cartilage values for the four optimal meniscal designs listed in Table 3. The filled circles mark the 95th-percentile of the peak contact stresses, and the open circles mark the 99th-percentile of these stresses.

Fig. 10 2D projections of 50 fixed meniscal designs corresponding to the designs used to construct Fig. 8. Desirable meniscal designs (those corresponding to low mean and low standard deviation) are marked with a filled circle.

4 Summary and Discussion

This paper describes a method that can be used to select optimal designs for meniscal replacements. Based on a computational bFEM of peak contact stresses on the tibial plateau over an axial force profile that mimics gait, this method is used to identify meniscal material and geometric properties that minimize peak contact stresses in a specified patient population. Meniscal designs with low mean peak contact stress and low standard deviation of peak contact stress in the patient population, a Pareto criterion, were selected as optimal. To study this question thoroughly, a large (100,000s) number of peak contact stress calculations for various meniscal and patient input configurations were required. These calculations are not feasible using the bFEM alone. Instead, a rapidly computable and calibrated Bayesian predictor was developed to approximate the computed peak contact stress at arbitrary candidate meniscal design inputs and patient characteristic inputs. Using this predictor, the performance of any fixed meniscal design can be well-approximated for any set of stochastically defined

patient population inputs. Applied to a set of representative meniscal designs, the methodology determines that the two most important meniscal features were “large” radial and “large” circumferential moduli, specifically $E_{rm} \geq 12.9$ MPa and $E_{cm} \geq 215$ MPa. In addition, a sensitivity analysis of the output shows that performance of the meniscal design is relatively insensitive to the maximum meniscal height (h_m), the center meniscal height (h_c), and the meniscal permeability (k_m).

Because of its combination of cadaver and computational models, meniscal design is an ideal research venue to use calibrated and bias-corrected statistical predictors to assess meniscal design performance. By using cadaver data to statistically calibrate and bias-correct the bFEM, the resulting predictions of the peak contact stress are superior to predictions made based on bFEM output alone.

Surrogate predictors have been developed for competing outcomes from *deterministic* simulators to solve multiobjective problems that occur in the engineering, operations research, and statistics literature [30–32]. In previous work, the simulator outputs typically represent a set of deterministic competing objectives. In contrast, the simulator in this paper includes both meniscal design and patient inputs, the latter representing different environmental conditions in which the design is meant to operate and the “objective functions” are sample quantities based on repeated use of a fixed design. This paper treats the sample mean and the sample standard deviation of the predicted peak contact stresses as multiple objectives, both of which are to be minimized.

Finite element methods offer an effective way to evaluate the biomechanical design space that are otherwise, difficult or impossible to perform experimentally. A study by Meakin et al. [33], based on a 2D axisymmetric knee model, found that the stresses in the meniscus and the tibial cartilage were more sensitive to geometry (meniscus width and radius of curvature of the femoral surface of the meniscus) than material properties. Haut Donahue et al. [34,35] used a three-dimensional elastic model of the knee joint to investigate the sensitivity of the contact variables of the tibial plateau to the meniscal material properties and geometry (transverse depth and width of both the lateral and medial menisci). They found that the contact stress distribution was sensitive to the circumferential modulus and the axial/radial modulus, that the contact variables are similarly sensitive to both the transverse and cross-sectional parameters of the menisci, and that the medial meniscal parameters have a greater effect on the contact variables than do the lateral meniscal parameters. These studies provided valuable suggestions on the design of meniscal replacements. However, these studies have several limitations. First, they modeled articular cartilage and the meniscus as linear elastic materials, ignoring the fact that 60–85% of the soft tissues is fluid [14]. Biphasic theory [36] considers the soft tissue as a combination of a solid phase and a fluid phase; this theory has been used widely to study the interaction between the solid matrix and fluid phase. As meniscal replacements are meant to mimic the porous characteristics of the native meniscus, a biphasic finite element study is needed to investigate and identify the optimized meniscal material and geometric properties. Second, each parameter was investigated independently and the interaction between parameters was not investigated. Finally, a relatively small number of patient settings is examined in these studies. However, the meniscal geometry [5] and material properties [1] are highly variable from patient to patient, so a study on a wide patient population is necessary.

In theory, meniscal implants made of synthetic materials offer the advantages that their mechanical behavior, degradation rate, and geometry can be optimized for intended applications. However, every synthetic meniscal implant studied to date has led to some degree of degeneration of articular cartilage, including fibrillation [37], cartilage softening, or the formation of osteophytes [38]. Robust preclinical test methods to gauge the ability of substitutes to function in the mechanically challenging environment of the human knee are lacking [39]. Furthermore, the range of material and structural properties of any meniscal substitute, whether cell-seeded or noncell based, that is needed to ensure function has

not been established, i.e., the design space has not been identified. The methodology that is described in this study can be adapted to identify optimal design properties for alternative output measures and populations.

Using a different approach, meniscal allograft transplantation (MAT) is currently used to replace the complex inhomogeneous, viscoelastic meniscus using harvested meniscal tissue from a donor [40]. Many variables (both patient and procedure related) have been identified that affect the clinical performance of MAT, including graft size, bone geometry, fixation technique, patient age, cartilage status, level of activity, and limb alignment [41–43]. Ultimately, it is hoped that by developing engineered meniscal substitutes and varying their design characteristics based on patient variables, clinical outcomes can be improved in the setting of meniscal deficiency on an individualized basis. In order to arrive at this juncture, robust designs for meniscal substitutes need to be strategically investigated using theoretical and experimental models. The approach introduced in this study may again be useful based on the combination of such models.

Consistent with a previous sensitivity study of the contact stress on the tibial plateau [34], the sensitivity analysis of the present study showed that the peak contact stress was sensitive to the circumferential modulus and axial/radial modulus of the meniscus. The present study also identified tibial cartilage thickness and femoral cartilage thickness as active inputs. The center panel of Fig. 6 and a plot not shown demonstrate that both thicknesses have decreasing and nonlinear effects on the peak contact stress. This suggests that, compared with thin articular cartilage, thick articular cartilage results in lower contact stress on the tibial plateau. As cartilage thinning has been observed in patients with osteoarthritis [44], the present study suggests that the progression of osteoarthritis may lead to a larger peak contact stress on the tibial plateau, which in turn, may lead to further cartilage degeneration.

This study has a number of limitations. The bFEM of the knee joint is axisymmetric and it represents a simplified geometry in which the cartilage thickness does not vary by location. The meniscus is geometrically defined by just five parameters. In addition, the articular cartilage was modeled as linear biphasic material, while it is well-known that the articular cartilage is anisotropic inhomogeneous material. The strain on the articular cartilage was less than 0.3, which is within the prediction range of linear biphasic theory. However, in our future work, we will use hyperplastic biphasic theory, which is able to simulate the biphasic behavior of the soft tissues under finite deformation [45]. Also, future studies will use more realistic modeling of the articular cartilage, which is required to obtain a deeper understanding of the knee joint biomechanics. In this paper only axial forces were applied to the model and, as such, were not physiologically representative of the multidirectional forces (which include anterior–posterior forces and internal–external torques) that would be expected to occur during walking. Such simplifications were necessary to allow us to build a simulator model having a relatively small number of variables so that a reasonable number of training runs per input could be made. We expect that in a more physiologically representative model, the value of the peak contact stress and its location on the tibial plateau would vary considerably throughout gait [46]; also the stiffness of meniscal fixation may have a profound effect on contact stresses [34,35]. We are currently building more geometrically appropriate models into which realistic load profiles can be input; this will require that the statistical models described in this study be expanded for the inclusion of a wider range of variables.

The proposed analysis strategy is not limited to the meniscal engineering application in which the methodology has been presented. More complicated simulator models could be substituted for the 2D axisymmetric bFEM. Multidirectional forces could be used instead of the uniaxial force. The outcome measure could be selected to be something other than the peak contact stress, e.g., the distance of the contact location from its anatomical location in normal subjects. Other loading patterns could be used, such as

stair climbing. Alternative input variable ranges could be used. The minimization of the mean and standard deviation of computed peak stresses for each design could be replaced by minimization of an upper percentile, say the 99th-percentile, of the distribution of the 10,000 peak contact stresses for that design (see Fig. 9). Finally, a more realistic assessment of a meniscal design may be measured by multiple outputs, e.g., peak contact stress and contact area. The use of Pareto optimization allows for the researcher to seek meniscal designs that simultaneously minimize an upper percentile for these multiple output measures that are used to judge the quality of a meniscal replacement.

Acknowledgment

Research reported in this publication was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number AR057343.

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