Using Combined Physical and Computer Experiments to Engineer Prosthetic Tissues

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Joint work with Research Groups from
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The Ohio State University (Columbus, OH)

Outline

Overview

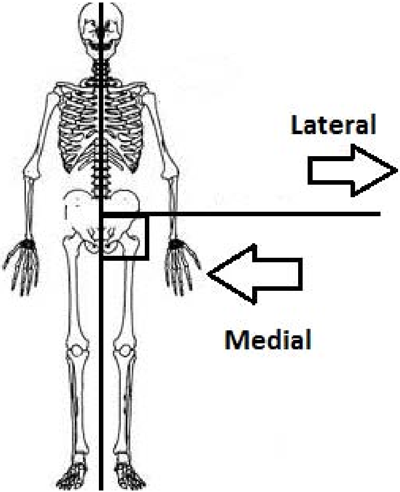
- Bioengineering seeks to solve problems at the confluence of Engineering and Biology.
- Classical Bioengineering (== "Biomechanics") applies mechanical engineering principles to study the movements ("kinematics') and forces on bones, joints, ligaments, and tendons. Biomechanics develops replacement joints ("prosthetic joint") to treat joint anomalies.
- Need for joint replacements
  - the hip ($\approx$ 300,000/year);
  - the knee ($\approx$ 600,000/year);
  - the shoulder;
  - the elbow; the foot; and the ankle, ...

"You break it, we fix it" –– "frangis, figimus"

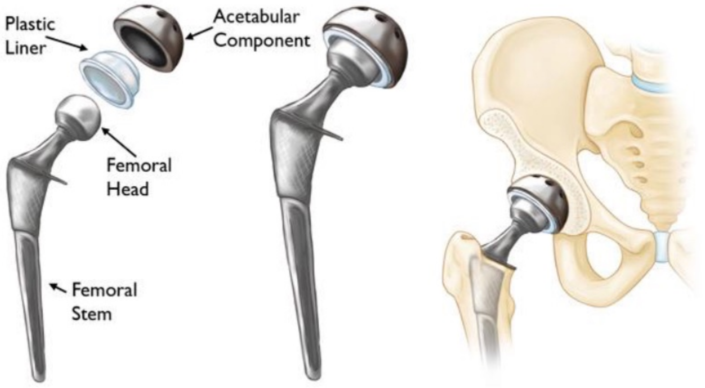
- More modern Bioengineering applications are concerned with designing replacement tissues, and analyzing the behavior of alternative treatments for joint tissue injuries.

Outline

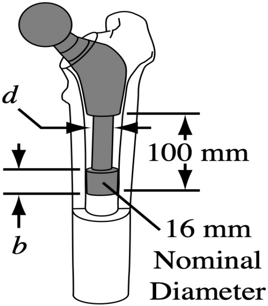
A little Body Nomenclature



A litte Hip Nomenclature



A Biomechanics Example: Designing a Hip Implant



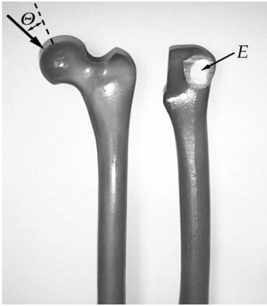
- Two Prosthesis Design ("control"; "engineering design") Variables:
  1. b = bullet-tip length
  2. d = midstem diameter

Practical Issues in choice of the stem design (b, d): minimize bone stress shielding (stem can't be too stiff) while providing (adequate) resistance to implant toggling (stem can't be too flexible)

Goldilocks Solution for (b, d)

Example: Designing a Hip Implant

- Environmental Variables (only other inputs)



1. E = elastic modulus of the trabecular bone (subject-specific bone material property)
2. μ = interface friction
3. Θ = joint force angle (subject use input)

- Regard (E, Θ, μ) as having a distribution that describes a specific patient population with particular bone properties/gait patterns

Example: Designing a Hip Implant

- Distribution of $\boldsymbol{X}_e = (E, \Theta, \mu)$?
  1. 1. (E, Θ) ind of μ
  2. 2. Choose values from previous (gait) laboratory studies: joint distribution of (E, Θ) used here

		Θ			
		-10	-5	5	10
	60	0.0375	0.0875	0.0875	0.0375
E	200	0.0750	0.1750	0.1750	0.0750
	400	0.0375	0.0875	0.0875	0.0375

  1. μ: 10 point uniform distribution on $[0, 0.42]$

- Goal: Determine the hip implant design (b, d) that minimizes stress shielding (in femur) while providing (“adequate”) resistance to implant toggling

Numerically Achieving Prosthesis Design Goal??

• P. Chang developed deterministic computer simulator (Finite Element (FE) code(s)) that calculate

1. $S = S(b, d, E, \Theta, \mu)$ = a measure of bone stress shielding (smaller is better)
2. $T = T(b, d, E, \Theta, \mu)$ = a measure of implant toggling (also, smaller is better)

for a given environment (E, Θ, μ).

• $S(\cdot)$ and $T(\cdot)$ are competing objectives

• Some mathematical methods of finding an "optimal" (b, d)

Example: Mathematical Design of a Hip Implant

Formulation 1: Minimize

$$y(b, d, E, \Theta, \mu) = \omega \times S + (1 - \omega) \times T$$

where $\omega \in [0, 1]$ is a researcher-specified value that measures the relative importance of the two objectives.

Formulation 2: Minimize

$$y(b, d, E, \Theta, \mu) = S(b, d, E, \Theta, \mu)$$

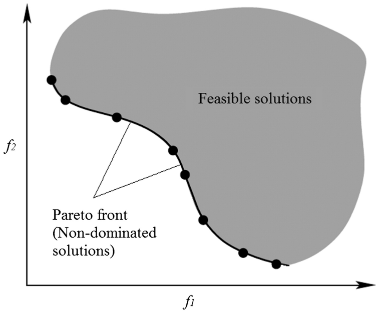
subject to a given upper bound on $T(b, d, E, \Theta, \mu)$.

Criticisms: Choice of ω? How to choose the $\boldsymbol{x}_e \equiv (E, \Theta, \mu)$ at which to minimize $y(\cdot)$? (Neither Formulation 1 nor 2 differentiates $\boldsymbol{x}_c \equiv (b, d)$ and $\boldsymbol{x}_e$). Replace $S(b, d, E, \Theta, \mu)$ & $T(b, d, E, \Theta, \mu)$ by $S(b, d, E\{E\}, E\{\Theta\}, E\{\mu\})$ & $T(b, d, E\{E\}, E\{\Theta\}, E\{\mu\})$.

Formulation 3: Find the set of Pareto minimizers of
$s(b, d) = E_{\boldsymbol{X}_e}\{S(b, d, E, \Theta, \mu)\}$ & $t(b, d) = E_{\boldsymbol{X}_e}\{T(b, d, E, \Theta, \mu)\}$

Pareto Optimum

$(f_1(\boldsymbol{x}), f_2(\boldsymbol{x})) \in \mathcal{X} \quad \Rightarrow$

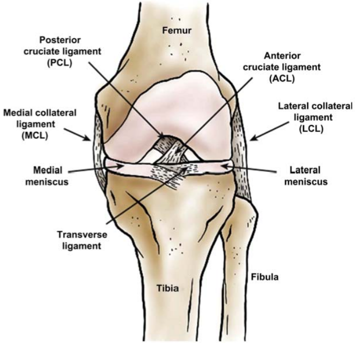


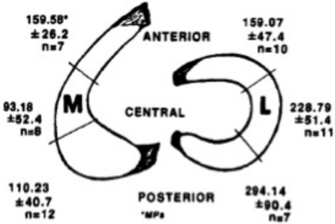
Suppose $\boldsymbol{f}(\boldsymbol{x})) \equiv (f_1(\boldsymbol{x}), \ldots, f_p(\boldsymbol{x}))$ is defined on domain $\mathcal{X}$ and each $f_j(\boldsymbol{x})$ is real-valued. The input $\boldsymbol{x}^o \in \mathcal{X}$ is a Pareto optimal for $\boldsymbol{f}(\boldsymbol{x})$ means there is no $\boldsymbol{x}^\star \in \mathcal{X}$ that simultaneously decreases $f_1(\boldsymbol{x}), \ldots, f_p(\boldsymbol{x})$. Such $\boldsymbol{x}^o$ are called non-dominated inputs and $\{\boldsymbol{f}(\boldsymbol{x})) : \boldsymbol{x} \text{ non-dominated}\}$ is Pareto Front(ier).

- Computer Simulators can have several types of inputs $\boldsymbol{x} = (\boldsymbol{x}_d, \boldsymbol{x}_e, \boldsymbol{x}_c, \boldsymbol{x}_t)$
  - $\boldsymbol{x}_d \equiv$engineering design (control, manufacturing, prosthesis design) inputs
  - $\boldsymbol{x}_e \equiv$ noise (field, environmental) input variables
  - $\boldsymbol{x}_c \equiv$ calibration (model) variables – adjusted to bring the simulator output closer to the modeled physical system
  - $\boldsymbol{x}_t \equiv$ numerical tuning parameters, e.g., mesh densities, solution tolerances, discretizations of continuous inputs.
  - Usually only some of the $\boldsymbol{x}_d$,$\boldsymbol{x}_e$,$\boldsymbol{x}_c$,$\boldsymbol{x}_t$ types are present in any application.
- Most practical problems have multiple (competing) outputs or even functional output
- Target Environmental Conditions $\boldsymbol{X}_e \sim \pi_e(\cdot)$ often are solicited from experts/literature or specified as operating conditions
- Most numerical simulators $y(\boldsymbol{x})$ are biased for the physical system that they are meant to describe b/c of simplified physics or biology or numerical methods used in the code

Outline

Some Knee Meniscus Nomenclature





The menisci are a pair of C-shaped fibrocartilage bodies that sit on top of the tibial knee cartilage. The meniscus helps distribute load across the cartilage, and provide joint stabilization

Preliminary–Meniscal Substitutes

- Currently available meniscal implants
  1. Collagen meniscus implant
  2. Built on Actifit “scaffold”
- Unfortunately, no current meniscal substitute prevents cartilage degeneration (b/c the meniscal substitute changes the loading of the tibial cartilage)
- Current Meniscal Design Principle Identify the geometry and material properties for a meniscal replacement to insure that the replacement tissue produces small peak cartilage contact stresses on the tibial plateau when used in the knees of a patient population.

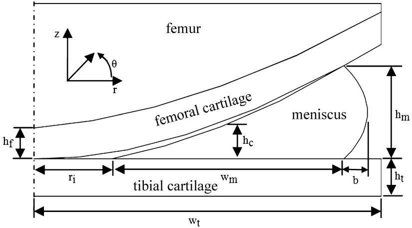
Preliminary–Meniscal Substitutes

In addition to meniscus geometry and material properties, there are other variables that can affect contact stresses on the Tibial Plateau

- Knee size
- Thickness of articular (femoral/tibial) cartilage
- Material properties of articular cartilage (elasticity & permeability)

A Simple Simulator Model of Contact Stress

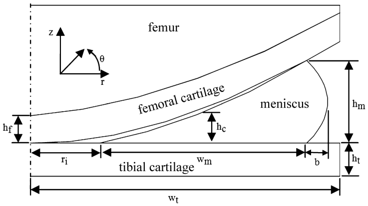
- There are a number of increasingly complex simulator models for tibial cartilage contact stress.
- Arguably, the simplest simulator model is a 2-d biphasic (fluid/solid) FE model. The 2-d model below rotates the figure below around its center line. and is loaded axially.

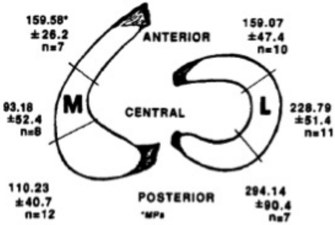


Guo and Spilker, 2012, *Jour. Biomechanical Engineering*;

Guo, Maher, and Spilker, 2013, *Medical Engineering & Physics*

Meniscal Geometry Inputs

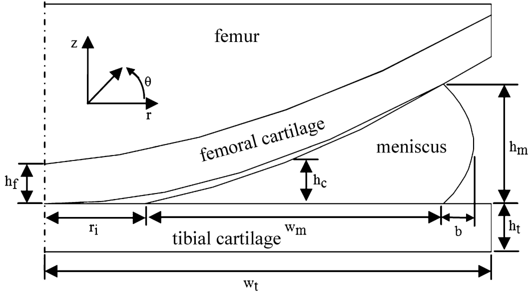




Meniscus Inputs

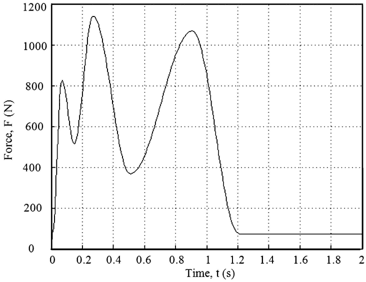
- Maximum meniscal height, h_m (mm)
- Meniscal center height, h_c (mm)
- Axial/radial modulus of the meniscus, E_{rm} (MPa)
- Circumferential modulus of the meniscus, E_{cm} (MPa)
- Meniscal permeability, k_m (m^4/Ns)

Patient-specific Inputs



- Thickness of tibial cartilage, h_t (mm)
- Thickness of femoral cartilage, h_f (mm)
- Elastic modulus of the articular (tibial and femoral) cartilage, E_c (MPa)
- Permeability of the articular (tibial and femoral) cartilage, k_c (m^4/Ns)

Simulator Output Under Axial Loading



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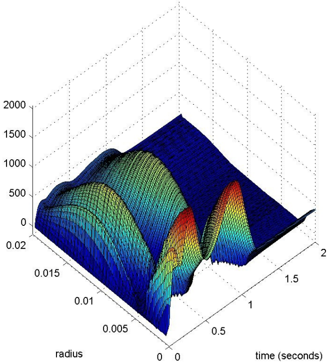
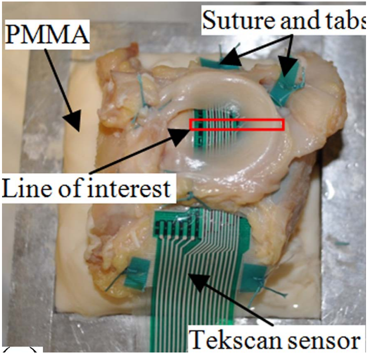


- Output is functional (depends on the radial position and the point in the gait cycle). Here the peak contact stress over the radial positions measured at 14% and 45% of gait (two peak loading points during gait) were taken to be the primary outputs.

Cadaver Studies of Contact Stress

- The stresses on the tibial plateau were measured in several cadaver knees in a mechanical testing frame using a Tekscan sensor for the same axial loading



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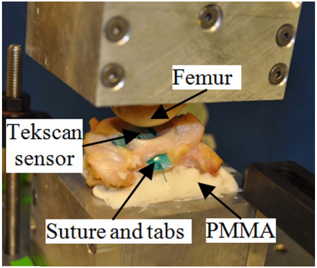
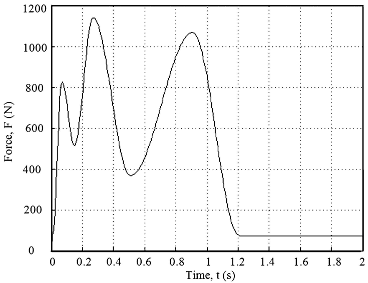


Cadaver Studies of Peak Contact Stress



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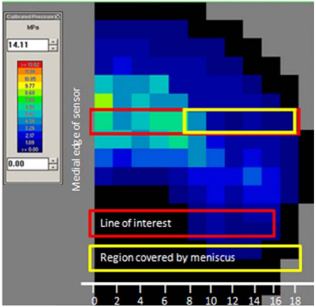
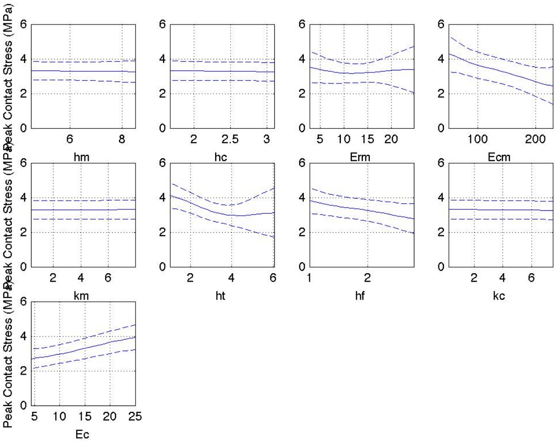


Design of the Simulator Experiment

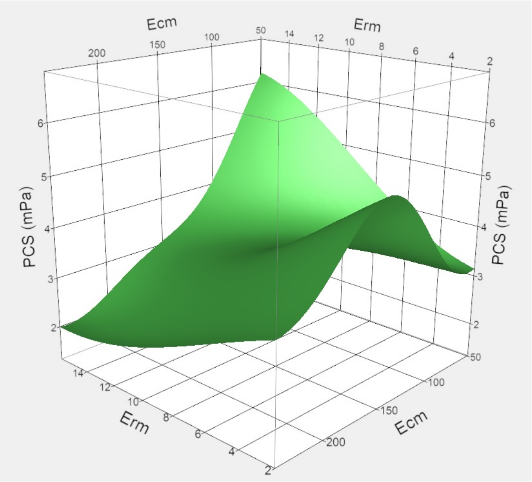
- Each simulator run required roughly 1.5 hours
- Simulator Output ==PeakConStr at 14% & at 45% (will only describe 14% case here.)
- The input sites were selected in multiple stages starting with an initial 18 run space-filling maximin inter-point distance LHD
- After each stage: (1) cross-validation was performed, (2) main effect (ME) and joint effect plots estimated, and (3) total effect and ME sensitivity indices were computed. Subregions where inputs were both active and in which the current runs had large cross-validation errors where examined further using additional simulator runs.
- A total of 60 simulator runs were made.
- ME and TE SIs of each input on PeakConStr

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

Main Effect Plots for the 9 Simulator Inputs



E_{rm} vs E_{cm} Joint Effect Plots

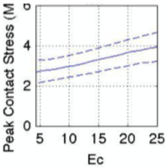


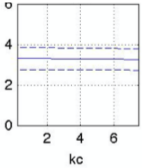
1mPa (==1 mega pascal) = prev. 1MPa $=$ 1N/(mm^2) $=$ 145 psi $=$ 10.2 kg/cm^2

Classical Bayesian Calibration of Simulator Output

- Denote simulator calculations of peak contact stress by $y_s(\boldsymbol{x}_i)$, $i = 1, \ldots, 60$.
- Suppose $\boldsymbol{x} = (\boldsymbol{z}, \boldsymbol{t})$ where $\boldsymbol{t}$ denotes inputs
  1. that can be controlled in the simulator model;
  2. difficult/impossible to measure in a physical experiment
  3. have a substantial influence on the simulator output.

  Here $\boldsymbol{t}$ are called calibration inputs; $\boldsymbol{z}$ denotes all other inputs.
- In this meniscus design application, we took $\boldsymbol{t} = E_c$ denote the modulus of cartilage the (sole) calibration parameter. The subject-specific inputs h_t, h_f are physical dimensions and easy to measure. The permeability k_c could also be taken to be a calibration input but $y_s(\boldsymbol{x})$ is relatively insensitive to k_c. Thus $\boldsymbol{z}$ is 8×1.





- Let θ denote the true value of $\boldsymbol{t}$

- Model the Simulator Output $y_s(\boldsymbol{x})$, $\boldsymbol{x} = (\boldsymbol{z}, \boldsymbol{t})$, as draws from a stationary Gaussian stochastic process $Y_s(\boldsymbol{x})$, $GP\,(\beta_0, \lambda_s, R(\boldsymbol{h}|\, \boldsymbol{\rho}^s))$ so that

$$E\{Y_s(\boldsymbol{x})\} = \beta_0,\, Var(Y_s(\boldsymbol{x})) = 1/\lambda_s$$

and

$$Cor\left(Y_s(\boldsymbol{x}^1), Y_s(\boldsymbol{x}^2)\right) = R(\boldsymbol{x}^1 - \boldsymbol{x}^2|\, \boldsymbol{\rho}^s) = \prod_{j=1}^{9} (\rho_j^s)^{4(x_j^1 - x_j^2)^2}$$

so that ρ_j^s is the correlation between two inputs $\boldsymbol{x}^1$ and $\boldsymbol{x}^2$ that differ only in their j^{th} input with $|x_j^1 - x_j^2| = \frac{1}{2}$

- Model Physical System $y_p(\boldsymbol{z})$ output as a realization of

$$Y_p(\boldsymbol{z}) = \mu^p(\boldsymbol{z}) + \epsilon(\boldsymbol{z}),$$

where $\epsilon(\boldsymbol{z})$ is measurement error, assumed be $N(0, 1/\lambda_\epsilon)$ and $\mu^p(\boldsymbol{z}) = \mu^p(\boldsymbol{z}, \boldsymbol{\theta})$ is the true mean of the physical system response at $\boldsymbol{z} = (h_m, h_c, E_{rm}, E_{cm}, k_m, h_t, h_f, k_c)$.

- The bias in the simulator code at $\boldsymbol{z}$ is defined to be

$$\delta(\boldsymbol{z}) \equiv \mu^p(\boldsymbol{z}) - y_s(\boldsymbol{z}, \boldsymbol{\theta})$$

- Model the bias $\delta(\boldsymbol{z})$ as a draw from $\Delta(\boldsymbol{z}) = GP(0, \lambda_\delta, R(\cdot|\,\boldsymbol{\rho}^\delta))$
- In sum, the physical system output is a realization of

$$Y_p(\boldsymbol{z}) = Y_s(\boldsymbol{z}, \boldsymbol{\theta}) + \Delta(\boldsymbol{z}) + \epsilon(\boldsymbol{z}),$$

Calibrated Prediction of $\mu^p(\boldsymbol{z})$

1. Place priors on all *GP* parameters $\boldsymbol{\psi} = [\beta_0, \lambda_s, \boldsymbol{\rho}^s, \lambda_\epsilon, \lambda_\delta, \boldsymbol{\rho}^\delta, \boldsymbol{\theta}]$ (based on subject matter expertise and standardizations of the date)
2. Predict $\mu^p(\cdot)$ at $\boldsymbol{z}_0$ by

$$\begin{aligned}\widehat{\mu}^p(\boldsymbol{z}_0) &= E\left\{Y_s(\boldsymbol{z}_0, \boldsymbol{\theta}) + \Delta(\boldsymbol{z}_0) \mid \text{data}\right\} \\ &= E_{[\boldsymbol{\psi}|\text{data}]}\left\{E\left\{Y_s(\boldsymbol{z}_0, \boldsymbol{\theta}) + \Delta(\boldsymbol{z}_0) \mid \boldsymbol{\psi}, \text{data}\right\}\right\}\end{aligned}$$

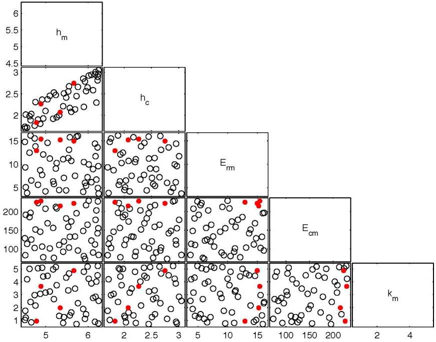
3. Can use a Gibbs/MH algorithm to sample the posterior to estimate $\boldsymbol{\psi}$ and infer $\boldsymbol{\theta}$ values (with uncertainty)
4. Optimal meniscus design minimizes

$$E_{(h_t,h_f,k_c)}\{\widehat{\mu}^p(h_m, h_c, E_{rm}, E_{cm}, k_m, h_t, h_f, k_c)\} = \tag{1}$$

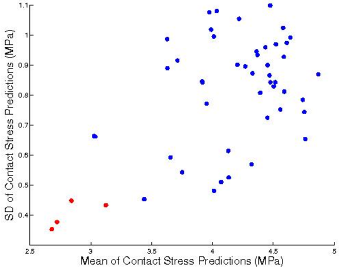
$$\text{mean of } \widehat{\mu}^p(h_m, h_c, E_{rm}, E_{cm}, k_m, h_t^o, h_f^o, k_c^o) \text{ over } (h_t^o, h_f^o, k_c^o) \tag{2}$$

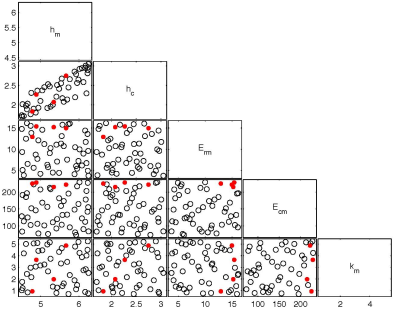
- Form a set of 50 trial meniscal designs $(h_m, h_c, E_{rm}, E_{cm}, k_m)$ from a 50 $\times$ 5 Mm LHD
- Meniscal Designs $(h_m, h_c, E_{rm}, E_{cm}, k_m)$ Cover a wide range of possible options

Meniscal Design Inputs		
Maximum meniscal height, h_m (mm) [12–14]	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) [15]	3.74	16.21
Circumferential modulus of the meniscus, E_{cm} (MPa) [15,16]	72.85	230.0
Meniscal Permeability, k_m (m^4/Ns) [1,17]	0.71×10^{-15}	5.23×10^{-15}



- For each $(h_m, h_c, E_{rm}, E_{cm}, k_m)$ design, estimate PkConStr for 10,000 patients with randomly drawn (h_t, h_f, k_c) values using the calibrated predictor of $\widehat{\mu}^p(\boldsymbol{z})$. Compute mean and StDev of the estimated PkConStr





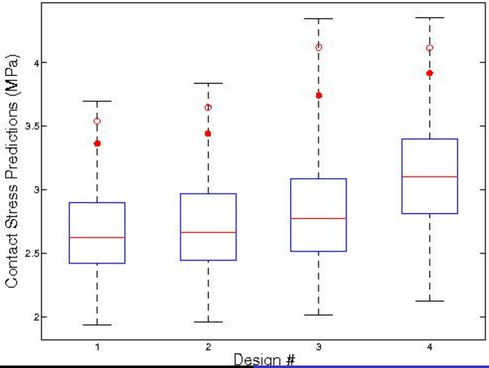
Features of the Optimal Meniscal Designs

1. Same optimal meniscal designs for 14% & 45% of Gait
2. Optimal meniscal designs among 50 runs of the Mm LHD have large E_{rm} and E_{cm}
3. Optimal designs are relatively insensitive to k_m (which is difficult to manufacture)
4. Optimal designs tend to depend more on h_m (h_m should not be "too thick"-max h_m = 6.25mm) and less on h_c

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

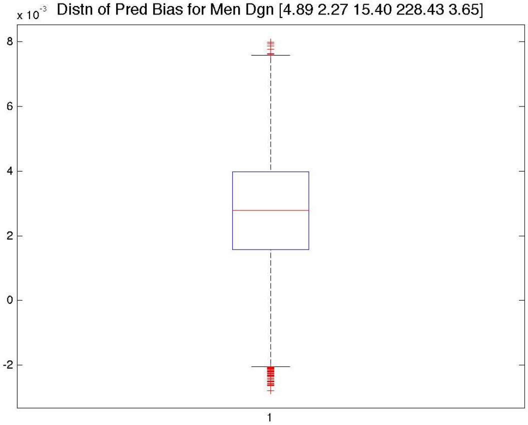
Distribution of PeakConStr in Best Meniscal Designs

- Estimate PeakConStr for 10,000 patients with randomly sampled (h_t, h_f, k_c)
- Open red circle is 99% percentile of the sampled PeakConStr and
- Closed red circle is 95% percentile of the sampled PeakConStr



Estimated Bias Function $\delta(\boldsymbol{z})$ for Meniscal Design #1

Estimated biases for the 10,000 patients with randomly sampled (h_t, h_f, E_c, k_c)



Outline

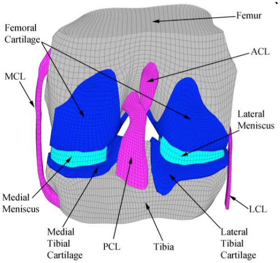
Summary and Discussion

- Using a statistically calibrated 2-d axisymmetric biphasic finite element model, we conclude that for a patient population with widely varying articular cartilage properties
  - Low peak contact stresses occurred with meniscal designs that had large meniscal radial modulus and large circumferential modulus
  - Peak contact stress was relatively insensitive to meniscal permeability and geometry
- Measure performance of a given design by the percentiles of the peak contact stress over the distribution of outcomes for the intended population.

Summary and Discussion

- Tissue engineering is a multiple objective optimization problem: Peak contact strain under axial loading over the gait cycle profile; Medial/Lateral load sharing; Size of contact area; . . .

- 3-d simulator models of knee performance under dynamic loading are much more complicated than 2-d model: many more unknown model variables, meshing issues, substantially longer run times



- Physical system output best modeled as an errors-in-variables problem
- The analysis above used FE code for a single knee. How to combine calibration over multiple knees? hierarchical approach,. . .

Discussion? Questions?

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