Challenges in Designing and Using Simulator Experiments in Biomechanics and Biomaterials Research

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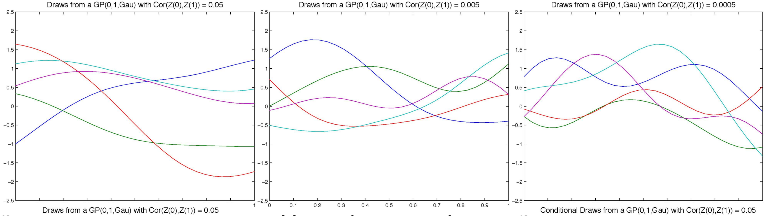
Outline

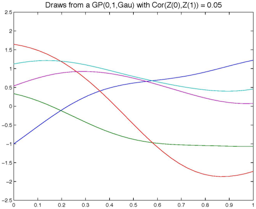
Introduction

Introduction-Some Important Methodologies

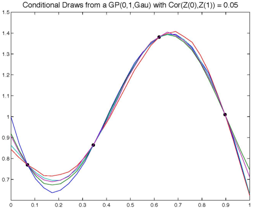
- **Problem 1: Prediction** Given simulator output ("training data") $\left(\boldsymbol{x}_i^{tr}, y^s(\boldsymbol{x}_i^{tr})\right)$, $1 \leq i \leq n_t$ predict $y^s(\cdot)$ at test input sites $\boldsymbol{x}_j^{te}$, $j = 1, \ldots, n_e$
- Methodologies: Regression; GP regression; Bayesian GP regression; blind krigling; Composite GPs; BART, ...

GP regression





Uses data to select a GP (parameter estimation); limits draws to those consistent with training data



- **Problem 2: Sensitivity Analysis** Identify the active inputs to $y^s(x_1, \ldots, x_d)$

- Methodologies: Calculate Elementary Effects (EEs); estimate Sobol´ Indices; examine estimated Correlation Parameters in a fitted GP with Gaussian correlation function

- The EE of the j^{th} input at $\boldsymbol{x}$ having span δ is

$$d_j(\boldsymbol{x}) = \frac{y(x_1, \ldots, x_{j-1}, x_j + \delta, \ldots, x_d) - y(\boldsymbol{x})}{\delta} = \frac{y(\mathbf{x} + \delta\ \boldsymbol{e}_j) - y(\mathbf{x})}{\delta}$$

where $\boldsymbol{e}_j = (0, 0, \ldots, 1, 0, \ldots, 0)$ is the j^{th} unit vector, i.e., EEs are the slopes of secant lines parallel to each of the input axes.

Introduction-Some Important Methodologies

Problem 3: Calibration Given

- n_p observations $\left(\boldsymbol{x}_i^p, y^p(\boldsymbol{x}_i^p)\right)$, $1 \leq i \leq n_p$ from a physical experiment ("physical system data"; "observational data") where $\boldsymbol{x}_i^p$ has d inputs all controllable by the experimenter.
- $y^p(\boldsymbol{x}^p)$ reasonably viewed as a draw from

$$Y^p(\boldsymbol{x}^p) = \mu(\boldsymbol{x}^p) + \text{measurement error}$$

- n_s runs $((\boldsymbol{x}_i^s, \boldsymbol{t}_i^s), y^s(\boldsymbol{x}_i^s, \boldsymbol{t}_i^s))$, $1 \leq i \leq n_s$ from a (possibly imperfect) simulator of the physical system where $\boldsymbol{x}^s$ is the same controllable inputs as for the physical experiment and $\boldsymbol{t}^s$ is a q vector of unknown model/physics inputs that can be used to "adjust" the simulator output (a total of $d + q$ inputs, all controllable in the simulator runs)
- a prior $\pi(\cdot)$ on the true values of $\boldsymbol{t}^s$

Goals:

- Learn about the true values (distn of) $\boldsymbol{t}^s$ by refining the prior to a posterior
- Use simulator and physical experimental output to predict $\mu(\boldsymbol{x}^p)$

Introduction-Biomechanics

- Biomechanics: In humans, biomechanics studies how combined prosthesis-skeletal-connective tissue systems perform in a given environment, e.g.,

  1. what are the stresses and strains in the bone that occur during loading (normal gait on a level surface; running; climbing stairs; descending stairs; getting up/down from a chair),
  2. S/S in cartilage? in connective tissues? in the prosthesis? (during loading)
  3. How do the S/S depend on bone quality, patient weight,. . . ?

  following repair to a knee, hip, or elbow.

- One important goal of Tissue Engineering is to regenerate damaged tissues by combining the desired cell replacements from the body with highly porous scaffold biomaterials. The scaffold guides the growth of new tissue. goal of Tissue engineering
- Another goal of Tissue Engineering is to develop synthetic replacement tissues, such as meniscus substitutes.

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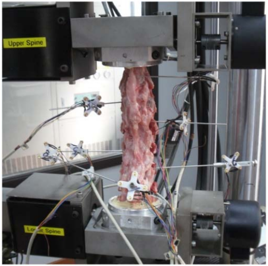
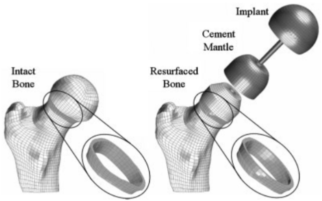
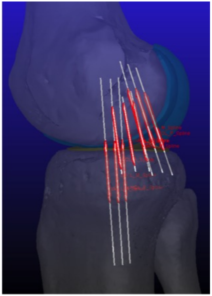
1. Cadaver components or prosthetic devices
2. MTS systems (Rawlinson et al. (2006))



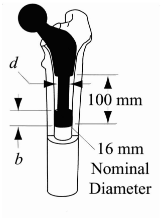
- Deterministic simulators ("in silico" experimental platforms/models): based on physics or other mathematically-based models or macro level model
  - Finite element models (FE models) with varying numbers of nodes;
  - Multibody models, e.g., Kia et al. (2016)
  - Hardly ever see CFD models used



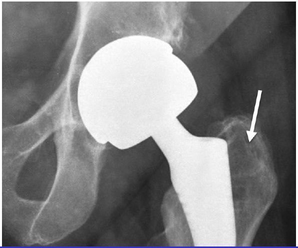


- Many (most) biomechanics studies involve multiple outputs and multiple objectives

1. Bone resorption vs loosening in the neck of prosthetic hip (Chang et al. (1999)) (Too much toggling causes implant loosening and too little causes “shielding” of the femoral neck with subsequent bone resorption)



2. There are multiple measures of periprosthetic joint space in the fit of an acetabular cup (Ong et al. (2006))



Some Aspects of Empirical Biomechanics Research

	Simulator Calculated Output Measures
1	Total potential ingrowth area
2	Change in gap volume (during loading)
3	Gap volume
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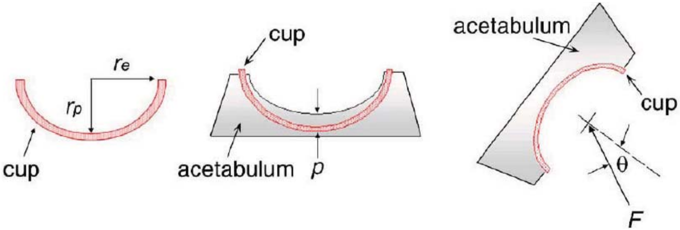
- Non-rectangular Input Regions
- Simulator model Inputs: In addition to engineering design variables, many simulator models include patient or other environmental variables, e.g.,

    1. Chang et al. (1999): bone elastic modulus and the magnitude of the loading were varied

2. Ong et al. (2006): Loading {Peak gait load magnitude; Gait load polar direction}; Surgical Skill {Cup penetration on insertion; Deviations from nominal reaming dimension at cup equator; Deviations from Nominal reaming dimension at pole; Reamed cup roughness (4 inputs) }



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  - **UQ** of given prosthesis system

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  - **Univariate or Multivariate Optimization** of a calibrated simulator wrt engineering design variables
  - **UQ** of given prosthesis system
  - **Validation** of a calibrated simulator model when additional data from a physical system is available

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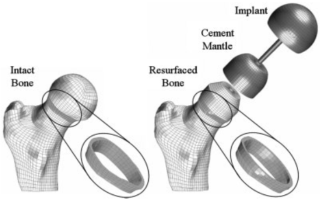
- What was observed? Excessive short-term femoral neck fracture for a hip resurfacing treatment that consists of placing a stiff cobalt-alloy implant around the femoral head



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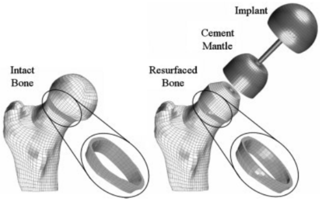

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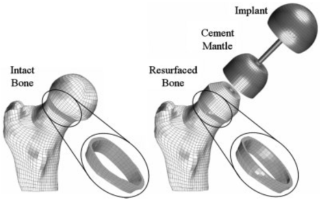

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- An alternative explanation of these unexplained fractures: they are caused by large magnitude strains near the implant rim (which cause an accumulation of bone damage at the femoral neck and eventual neck fracture)

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• The Data Based on 80 FEM simulator runs for intact and resurfaced hip. The simulator runs varied 3 engineering design variables and 6 environmental variables

- Bone elastic modulus
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The simulator output was a volume-weighted mean (VWM) strain in the neck region.

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• A kriging emulator was developed for the output from an FEM of strain-based output .

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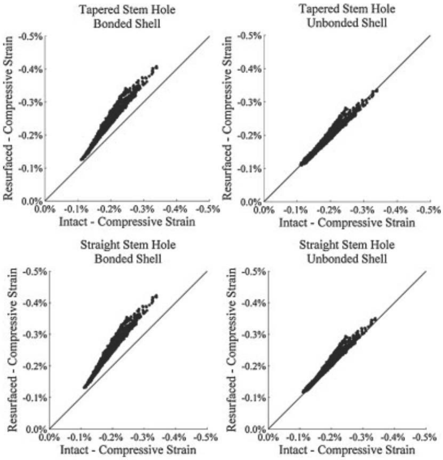
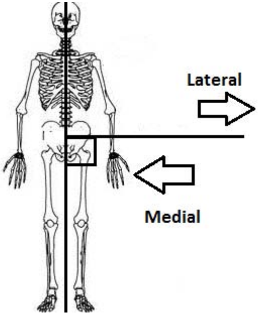
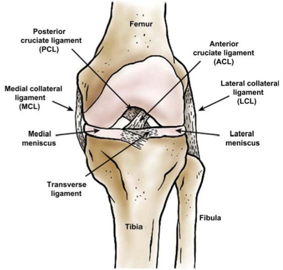


Outline

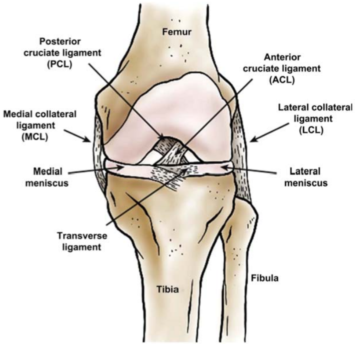
Meniscal Functioning

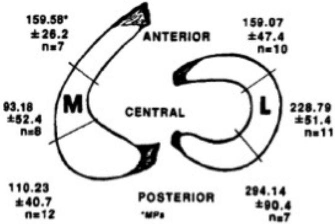
- Use the combined data from a simulator model and cadaver studies to help design replacement meniscal tissue
- **The meniscus** is a C-shaped fibrocartilage body that is located on the top of the tibial knee cartilage. The meniscus serves a number of significant mechanical functions: load distribution across articular cartilage, and joint stabilization

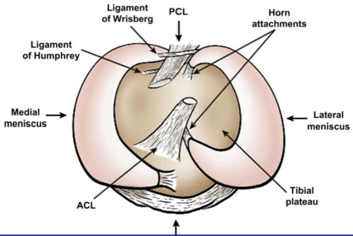




Knee Meniscus







Goal of a Meniscal Substitute

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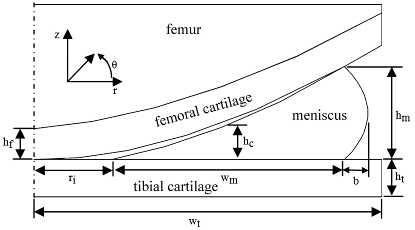
- Bad News current meniscal treatments do not prevent cartilage degeneration.
- Goal Identify the material properties and geometry for a meniscal replacement to insure that the biomechanical design produces low peak cartilage contact stresses on the tibial plateau when used in the knees of a patient population. Tissues with desirable geometries and material properties can be manufactured.

Variables that May Affect Contact Stresses on Tibial Plateau

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

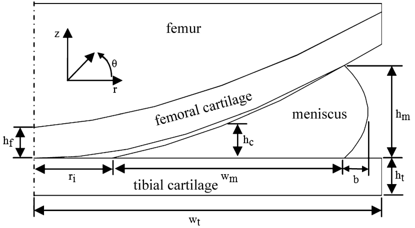
Simulator Models of Contact Stress

- There are a number of increasingly complex simulator models for contact stress.
- Simplest simulator model is a 2-d biphasic FE model (Guo and Spilker (2011); Guo et al. (2013))



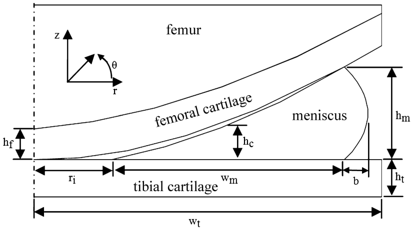
- The 2-d Model rotates the above figure around its center line.

Geometric Inputs to the Meniscal Simulator



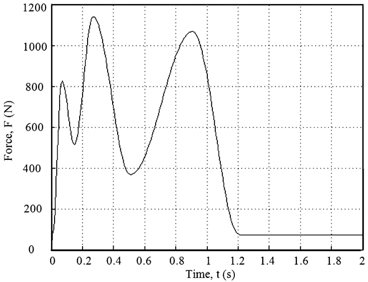
- Maximum meniscal height, h_m (mm)
- Meniscal center height, h_c (mm)
- Thickness of tibial cartilage, h_t (mm)
- Thickness of femoral cartilage, h_f (mm)

Material Property Inputs to the Meniscal Simulator



- Axial/radial modulus of the meniscus, E_{rm} (MPa)
- Circumferential modulus of the meniscus, E_{cm} (MPa)
- Meniscal permeability, k_m (m^4/Ns)
- Elastic modulus of the articular cartilage (tibial and femoral), E_c (MPa)
- Permeability of the articular cartilage (tibial and femoral) , k_c (m^4/Ns)

Output of the Simulator Model under Axial Loading



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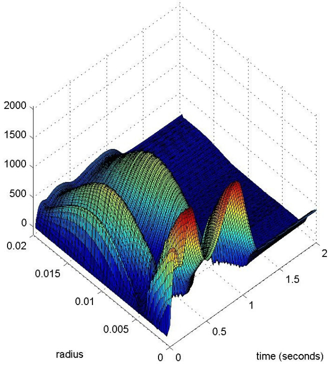
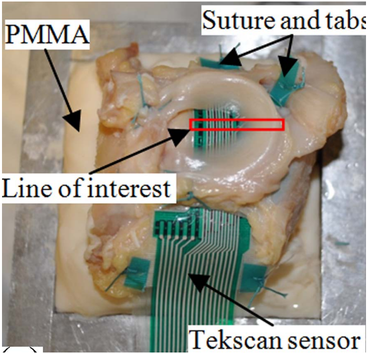


- Some Inputs and the model outputs are functional. Here the primary outputs are the peak contact stress over the radial positions measured at 14% and 45% of gait. (In other cases, can summarize output as the coefficients of a basis function expansion of the functional output)

- Using the same axial loading and measured geometries and material properties, several cadaver knees were examined in a mechanical testing frame



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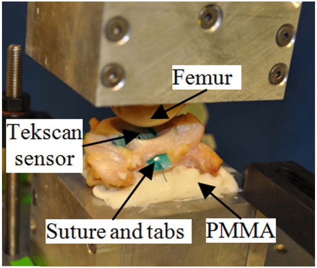
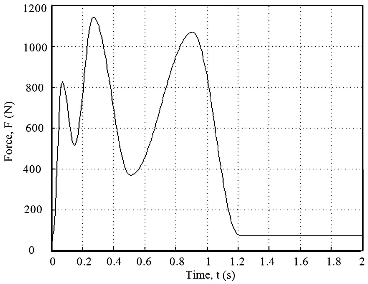


Cadaver-Knee Contact Stress Under Axial Loading



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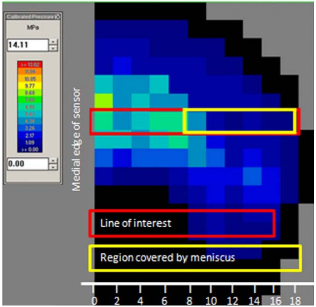

Simulator Model Characteristics

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- After each stage: (1) cross-validated prediction error was calculated, (2) SA performed: main effect (ME) plots; joint effect plots; total effect and ME sensitivity indices were computed (Saltelli et al. (2000)).

Input	Tot Eff SI	Main Eff SI	Input	Tot Eff SI	Main Eff 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			

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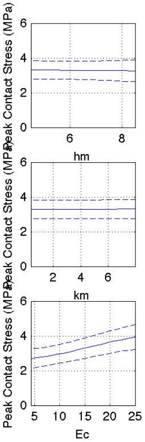
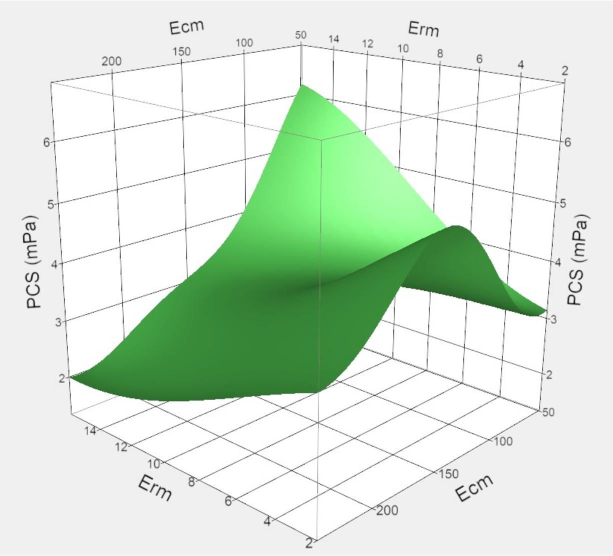
E_{cm}	0.5200	0.1687	k_c	0.0033	0.0006
k_m	0.0077	0.0009			

- Subregions where the current inputs had large cross-validation errors and the inputs were active where examined further.

Simulator Model Characteristics: ME Plots



Simulator Model Characteristics: $E_{cm} \times E_{rm}$ JE Plots



Bayesian Calibration of the Simulator Output

- Apply Kennedy and O'Hagan (2000) model assuming that it desired to optimize the meniscal design by allowing h_m, h_t, E_{rm}, E_{cm}, and k_m to be control variables.
- Also take the subject-specific inputs h_t, h_f are physical dimensions and "easy" to measure so that this design can be thought of as personalized medicine. Take E_c to be a calibration factor, t (k_c could also be a calibration parameter, although it is inactive)
- Assume the simulator output $y_s(\boldsymbol{x}, t)$ can be modeled as a draw from a $SGP\left(\beta_0, \lambda_s, R(\cdot|\ \boldsymbol{\rho}_s)\right)$.
- Assume that $\delta(\boldsymbol{x}) \equiv E\left\{Y_p(\boldsymbol{x})\right\} - y_s(\boldsymbol{x}, \boldsymbol{\theta})$ where $\boldsymbol{\theta}$ is the mean of the distribution of the calibration input can be modeled as a draw from a $SGP\left(0, \lambda_\delta, R(\cdot|\ \boldsymbol{\rho}_\delta)\right)$

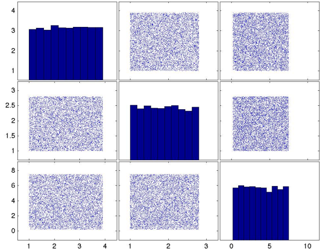
Bayesian Calibration of the Simulator Output

- Assume that a prior can be provided for the *GP* parameters $\boldsymbol{\psi} = [\beta_0, \lambda_s, \lambda_\delta, \lambda_\epsilon, \boldsymbol{\rho}_s, \boldsymbol{\rho}_\delta, \boldsymbol{\theta}]$ (based on subject matter expertise and standardizations of the date)
- Then predict $E\left\{Y_p(\boldsymbol{x})\right\}$ by

$$E\left\{Y_s(\boldsymbol{z}_0, \boldsymbol{\theta}) + \delta(\boldsymbol{z}_0) \middle|\ \text{data}\right\} = E_{[\boldsymbol{\psi}|\text{data}]}\left\{E\left\{Y_s(\boldsymbol{z}_0, \boldsymbol{\theta}) + \delta(\boldsymbol{z}_0) \middle|\ \boldsymbol{\psi}, \text{data}\right\}\right\}$$

Application

- Meniscal Designs Compared Select a fixed number of meniscal designs $(h_m, h_c, E_{rm}, E_{cm}, k_m)$ using a Mm LHD.
- Assess the quality of each meniscal design, by its 95% percentile in draws from (h_t, h_f, k_c) patient "population" (at 14% and 45% of gait low PCS values are better)



- Alternative to Using Percentiles as Output For a fixed point in the gait cycle and symmetric PCS output distributions, selecting the design with smallest value of mean PCS $+ 2\times$PCS-standard-deviation

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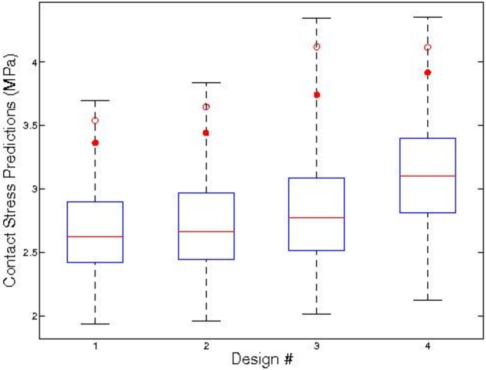
4. Optimal designs tend to depend more on h_m (h_m should not be "too thick") and less on h_c
5. Distribution of PCS for four best designs at 14% of gait

Distribution of Peak Contact Stress in Best Meniscal Designs

Open red circle is 99% percentile of the sampled PCS and
Closed red circle is 95% percentile of the sampled PCS



Outline

Summary and Discussion

- Both tissue engineering and biomechanical design and analysis are multiple objective optimization problems: Set implant toggling to minimize both loosening and bone resorption; Optimize size of contact area and location of peak contact stress; Minimize Peak contact stress at multiple points in the gait cycle; . . . .

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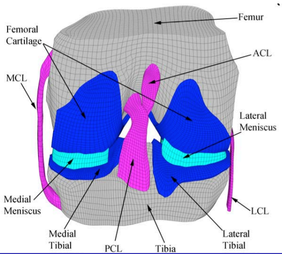
- A range of simulator models of widely varying complexity are used to study kinematics and contact mechanics, e.g.,

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



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- Calibrating/Validating simulator models with biological system data is critical
- When calibrating using Kennedy & O'Hagan
  - Having good information about the magnitude of the bias in a simulator code is essential for successful Bayesian calibration analysis
  - In biomedical applications, the calibration parameters are best thought of as having a distribution of values characteristic of some population which are to be refined by Bayesian analysis.
  - There are more efficient methods of designing a sequential experiment to identify Pareto Sets and Pareto Fronts than using a one-stage space-filling design (Chen et al. (2017))

Discussion? Questions?

Some References

Chang, P. B., B. J. Williams, W. I. Notz, T. J. Santner, and D. L. Bartel (1999). Robust optimization of total joint replacements incorporating environmental variables. *Journal of Biomechanical Engineering 121*, 304–310.

Chen, P.-H. A., T. J. Santner, and A. M. Dean (2017). Sequential pareto minimization of physical systems using calibrated computer simulators. *Statistica Sinica*, (to appear).

Guo, H., S. A. Maher, and R. L. Spilker (2013). Biphasic finite element contact analysis of the knee joint using an augmented lagrangian method. *Med. Eng. Phys. 35*(9), 1313–1320.

Guo, H. and R. L. Spilker (2011). Biphasic finite element modeling of hydrated soft tissue contact using an augmented lagrangian method. *J. Biomech. Eng. 133*(11), 111001.

Kennedy, M. C. and A. O'Hagan (2000). Predicting the output from a complex computer code when fast approximations are available. *Biometrika 87*, 1–13.

Kia, M., K. Schafer, J. Lipman, M. Cross, D. Mayman, A. Pearle, T. Wickiewicz, and C. Imhauser (2016). A multibody knee model corroborates subject-specific experimental measurements of low ligament forces and kinematic coupling during passive flexion. *Journal of Biomechanical Engineering 138*.

References

Long, J., T. Santner, and D. Bartel (2008). Hip resurfacing increases bone strains associated with short-term femoral neck fracture,. *Journal of Orthopedic Research 27*(10), 1319–1325.

Ong, K., J. Lehman, W. I. Notz, T. J. Santner, and D. L. Bartel (2006). Acetabular cup geometry and bone-implant interference have more influence on initial periprosthetic joint space than joint loading and surgical cup insertion. *Journal of Biomechanical Engineering 148*, 169–175.

Rawlinson, J. J., B. D. Furman, S. Li, T. M. Wright, and D. L. Bartel (2006). Retrieval, experimental, and computational assessment of the performance of total knee replacements. *Journal of Orthopaedic Research*, 1384–94.

Saltelli, A., K. Chan, and E. Scott (2000). *Sensitivity Analysis*. John Wiley & Sons, Chichester.