MULTISCALE CARTILAGE BIOMECHANICS

from a research niche to routine practice

Ahmet Erdemir
Computational Biomodeling (CoBi) Core
Department of Biomedical Engineering
Lerner Research Institute
Cleveland Clinic

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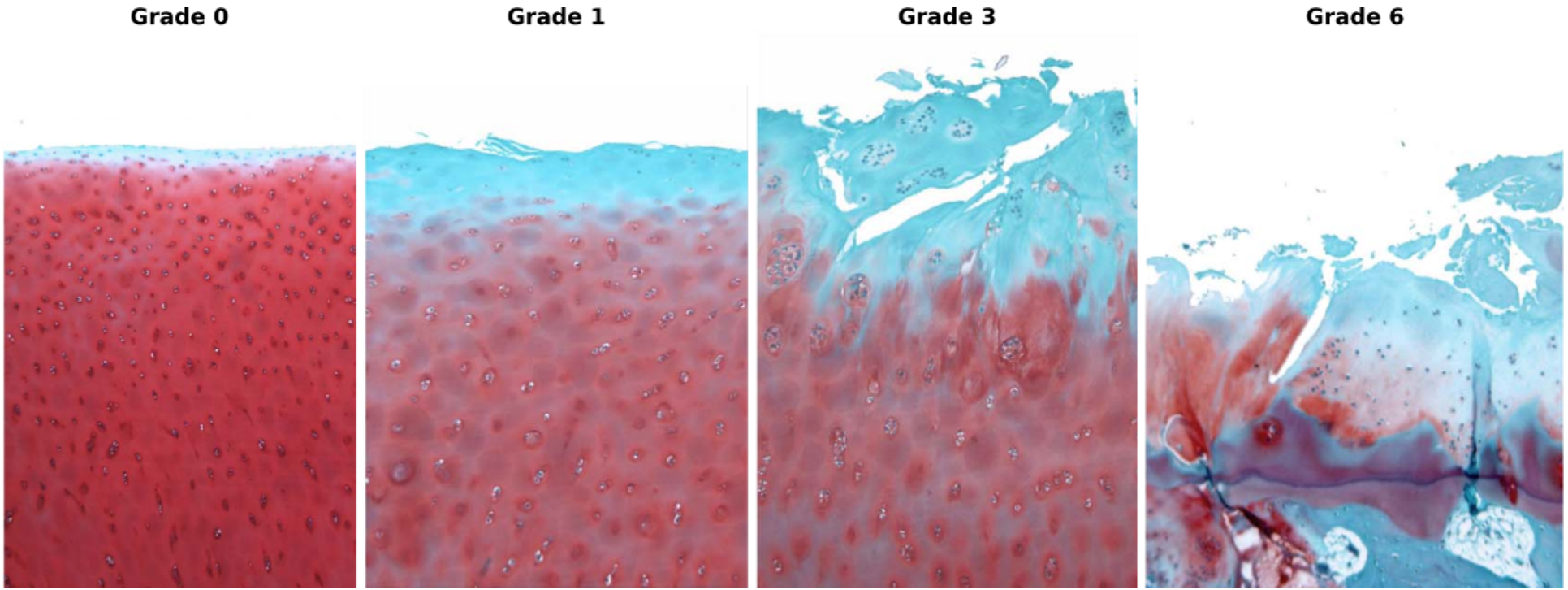
Multiscale Modeling Consortium Meeting
National Institutes of Health

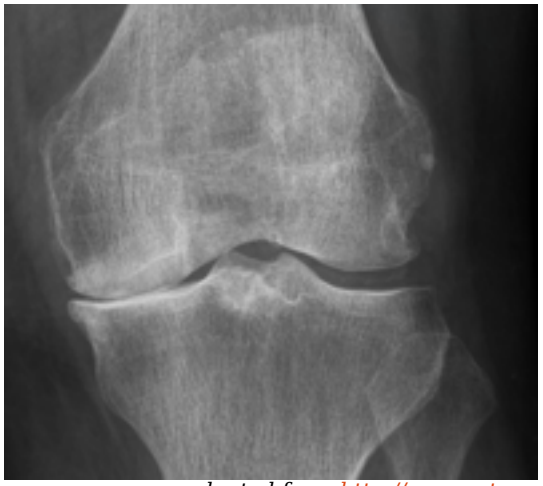
CLINICAL PROBLEM

Osteoarthritis influences **~26.5 million** people only in the United States. Rate of osteoarthritis dramatically **increases with age**.

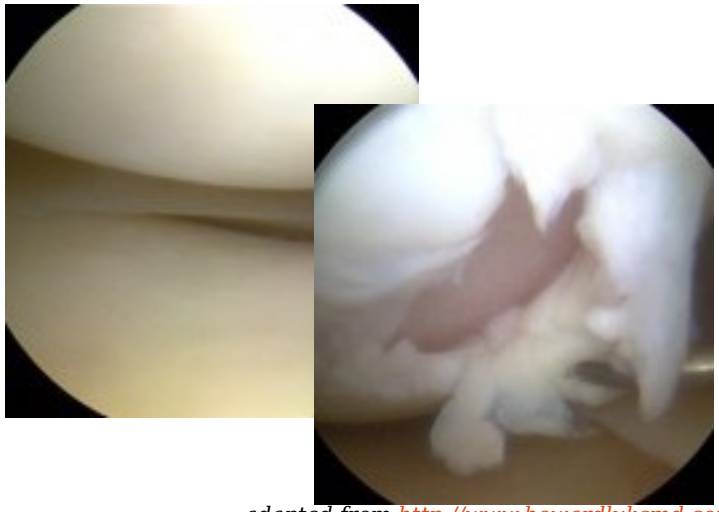


adapted from Pritzker et al. (2006)

CLINICAL PROBLEM



adapted from http://www.artros.si



adapted from http://www.howardluksmd.com

Osteoarthritis

Most common form of arthritis
- **33.6% of adults +65 yrs**
- 55% of arthritis related hospitalization
- 35% of knee and hip replacements

Common sites
- Hand
- Feet
- Knee (16% of adults +45 yrs)
- Hip

80% of patients have movement limitations

$7.9 billion in 1997 – knee and hip replacements
$3.4 – 13.2 billion – job-related costs per year

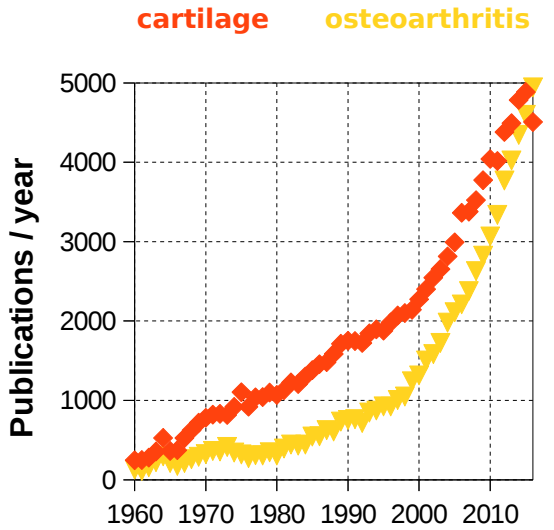
adapted from http://www.cdc.gov/arthritis/basics/osteoarthritis.htm

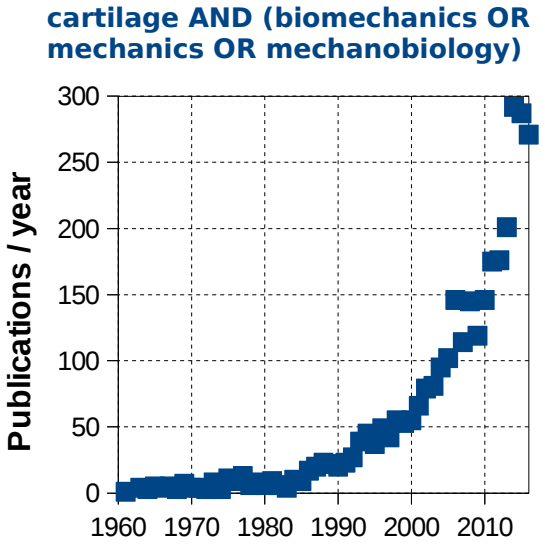
Other cartilage disorders

Tears
Trauma
Chondral injuries
Osteochondral defects

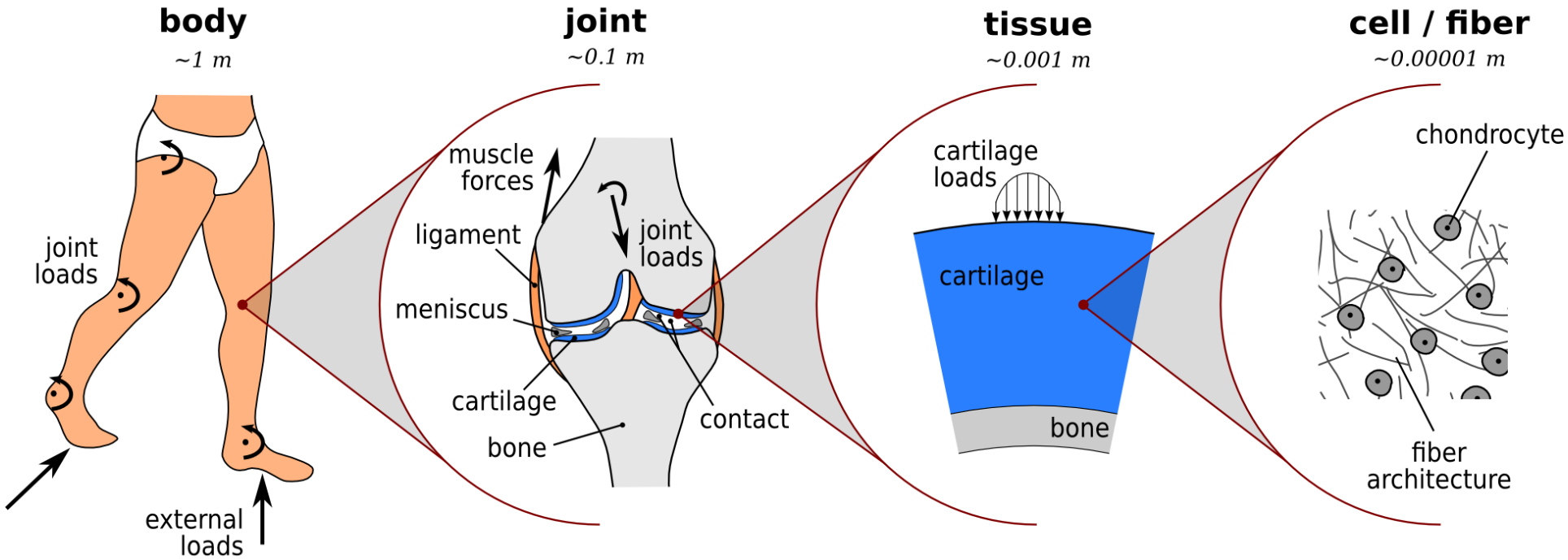
ROLE OF MECHANICS

- Cartilage is a **prominent load-bearing tissue** in musculoskeletal joints.
- Load-bearing capacity depends on **maintenance** of its architecture, which can be **modulated by mechanical signals**.
- **Mechanically induced damage** to extracellular matrix and chondrocytes may be irrecoverable, requiring intervention.
- Aging, joint disorders, interventions directly or implicitly **alter mechanical capacity and environment** of the body, joints, tissues, cells and microstructure; and therefore cartilage function.





ROLE OF MECHANICS



load sharing pathway – mechanical environment

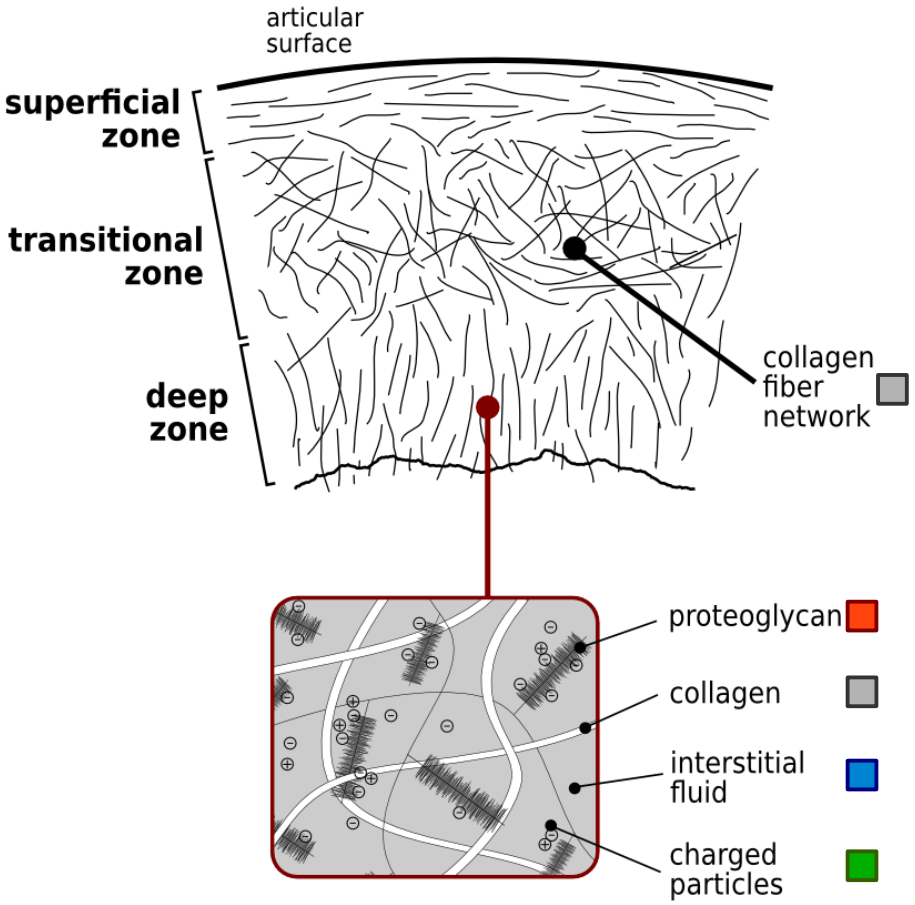
role of structure on function – mechanical capacity

CHARGE FOR PRESENTATION

To set the stage from a **historical perspective** on the evolution of multi-scale modeling and the **impact of IMAG** on that evolution, coupled with a forward looking perspective

- to discuss current work in multi-scale modeling in ***cartilage biomechanics*** as an example of progress, success, and remaining challenges
- to address how progress in computational modeling, especially through IMAG and MSM, has contributed to advancing ***cartilage biomechanics***
- to address future directions for ***cartilage biomechanics*** and how IMAG might meet the needs of emerging multi-scale modeling challenges

MSM: STRUCTURE-FUNCTION



Multiphase Material Response

Solid Phase - (flow independent)

Nonlinear elasticity
- hyperelastic behavior
- tension-compression nonlinearity

Depth-dependent properties
- inhomogeneity
- anisotropy

Viscoelasticity

Fluid Phase - (flow dependent)

Fluid flow
Depth-dependent permeability
Creep behavior
Stress relaxation

Ion/Solute Phase - (flow dependent)

Ion/Solute transport
- diffusion
- convection

Electrokinetic effects
Osmolarity
Swelling

MSM: STRUCTURE-FUNCTION

Motivations for micro- to macro- M&S are that:

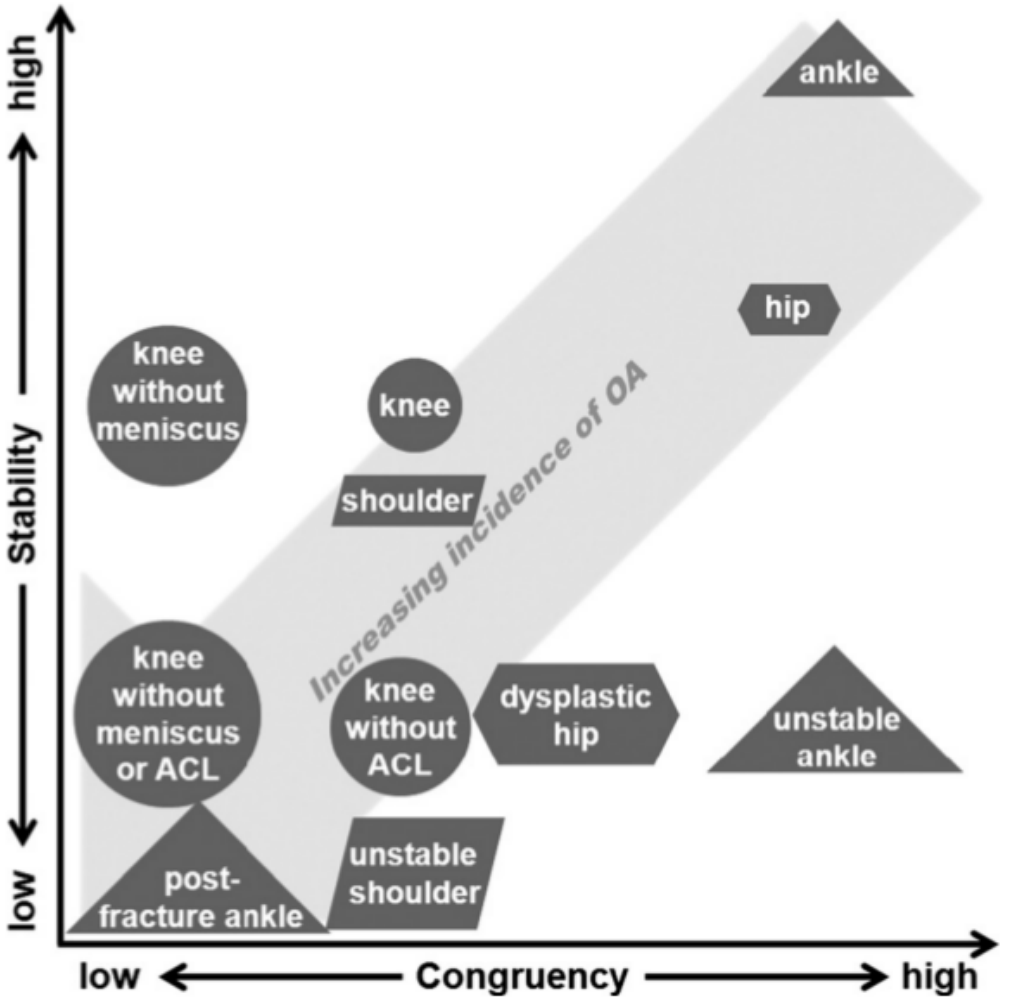
- Constituents and their organization indicates **macroscopic mechanical properties** of cartilage.
- Influence of microstructure on apparent material property provides a **blueprint for tissue engineering** of cartilage.
- Development, growth, and maintenance of extracellular matrix are partly driven by mechanics.
- **Imaging markers** may be associated with micro-scale constituents, providing the opportunity for individualized modeling and **mechanical assessment**.

biomechanical properties

markers for
risk assessment, diagnostics, intervention performance

for a review, see Halloran et al. (2012)

MSM: LOAD SHARING



adapted from Henak et al. (2013)

Joint **stability** (active or passive) and **congruency** of articulating surfaces are indicators of healthy **cartilage mechanics**, and risk of **cartilage degeneration**.

MSM: LOAD SHARING

Body-joint scale distribution

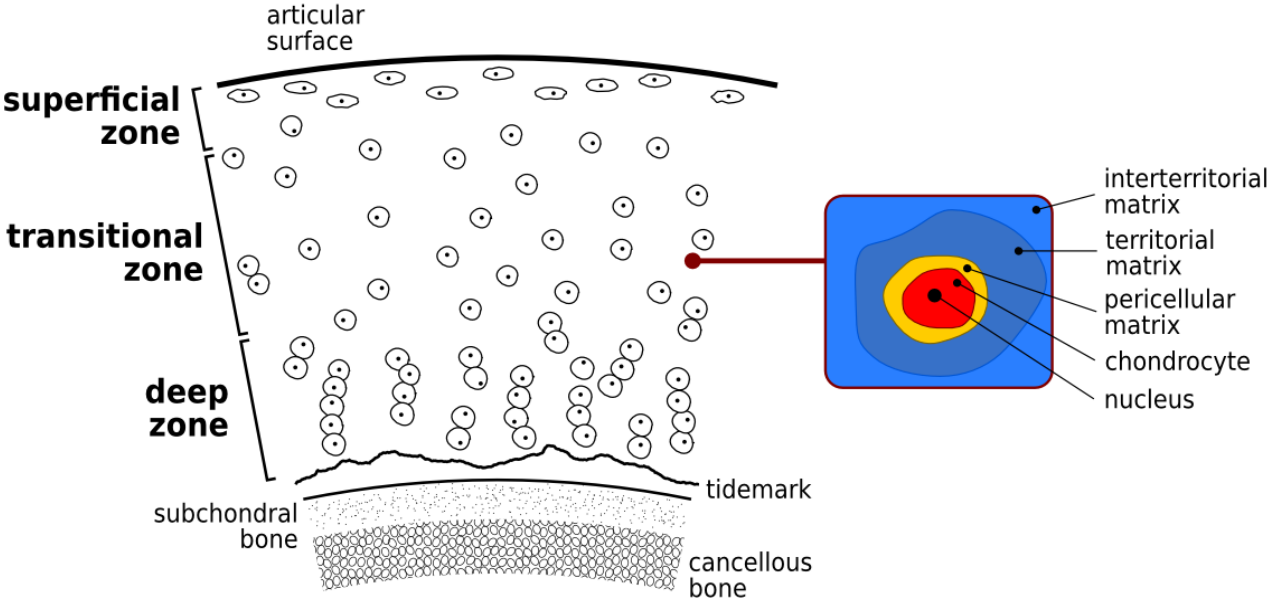
Activities of daily living
Muscle load sharing
 hip - knee - ankle

Joint-tissue scale distribution

Tissue load sharing
 ligaments – menisci
Compartment loads
 medial - lateral

Cell scale distribution

Zonal architecture
Cellular anatomy
 size - shape
Cellular organization



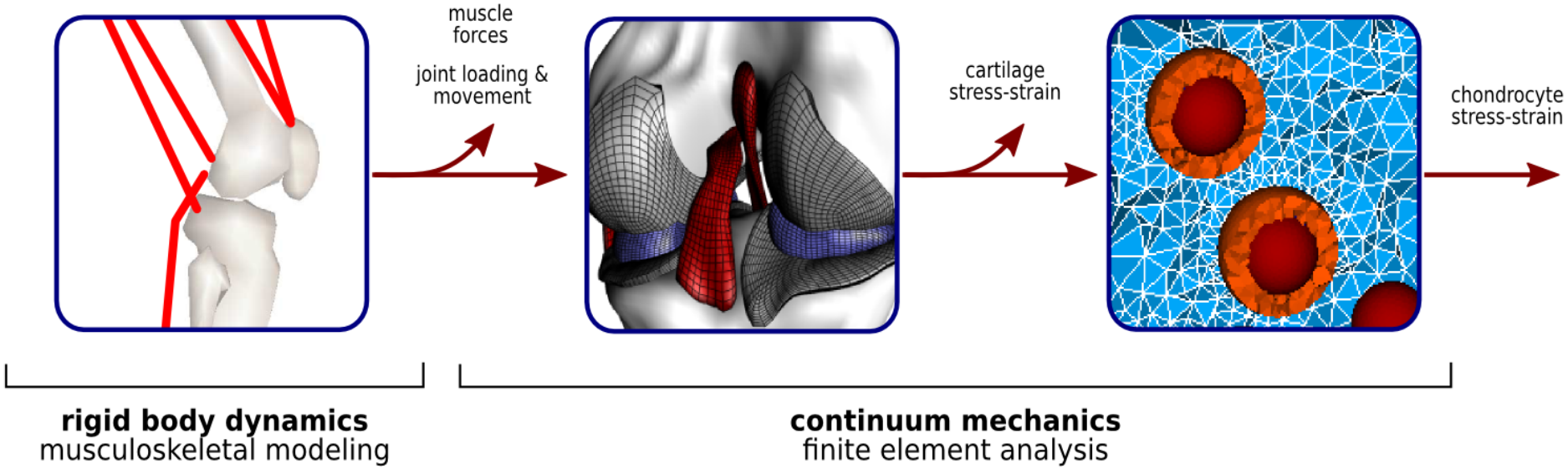
Chondrons

Zonal organization & properties
Chondrocyte(s)
Pericellular matrix
 primarily type VI collagen

MSM: LOAD SHARING

Motivations for macro- to micro- M&S are that:

- Joint loading and properties dictate cartilage and chondrocyte mechanics through multiscale load sharing.
- Mechanics plays a role in chondrocyte activity, differentiation, and vitality and extracellular matrix damage.
- Pathologies, injuries, and interventions may have different impacts at joint, tissue, and cell scales.



for a review, see Halloran et al. (2012)

MSM: LOAD SHARING

Motivations for macro- to micro- M&S are that:

- Joint loading and properties dictate cartilage and chondrocyte mechanics through multiscale load sharing.
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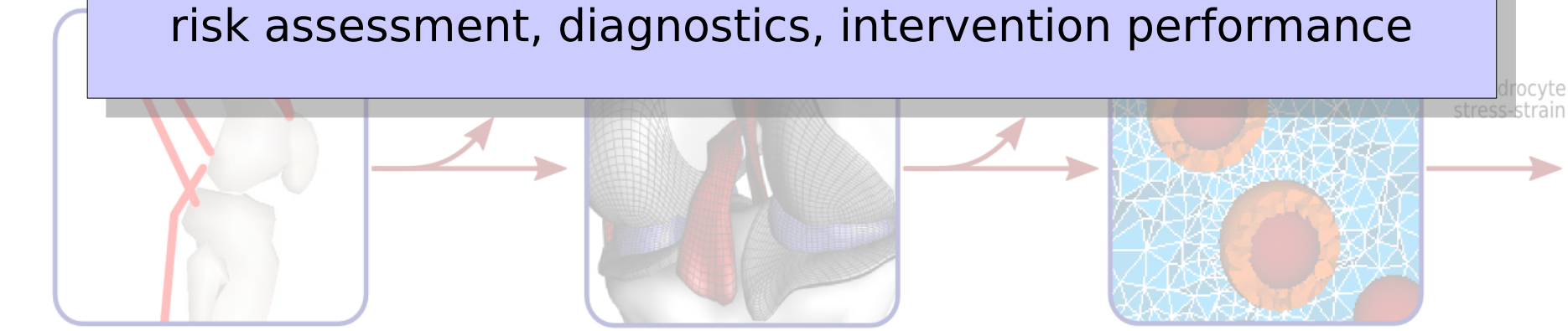
- Pat… nt, tiss…

biomechanical response

markers for
risk assessment, diagnostics, intervention performance



rigid body dynamics
musculoskeletal modeling

continuum mechanics
finite element analysis

for a review, see Halloran et al. (2012)

IMAG/MSM FOR CARTILAGE

2006

Dynamic Simulation of Joints Using Multi-Scale Modeling
PI: Guess

Predicting Cell Deformation from Body Level Mechanical Loads
PI: Erdemir

2010

A Multi-Scale Finite Element Musculoskeletal Modeling Framework Applied to Current Issues in Joint Replacement
PI: Shelburne

A Multi-Scale Modeling Construct of Knee Mechanics following ACL Reconstruction

2014

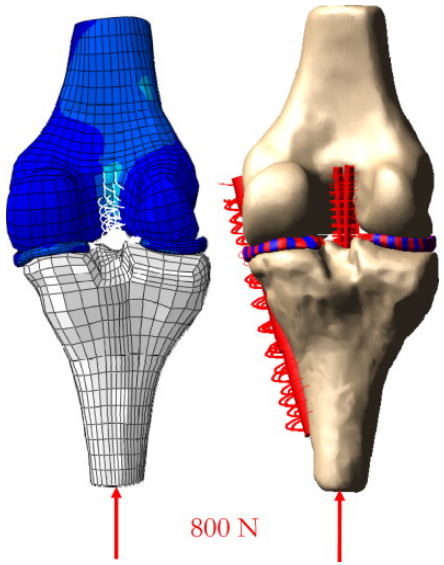
Co-PIs: Dhaher, Thelen

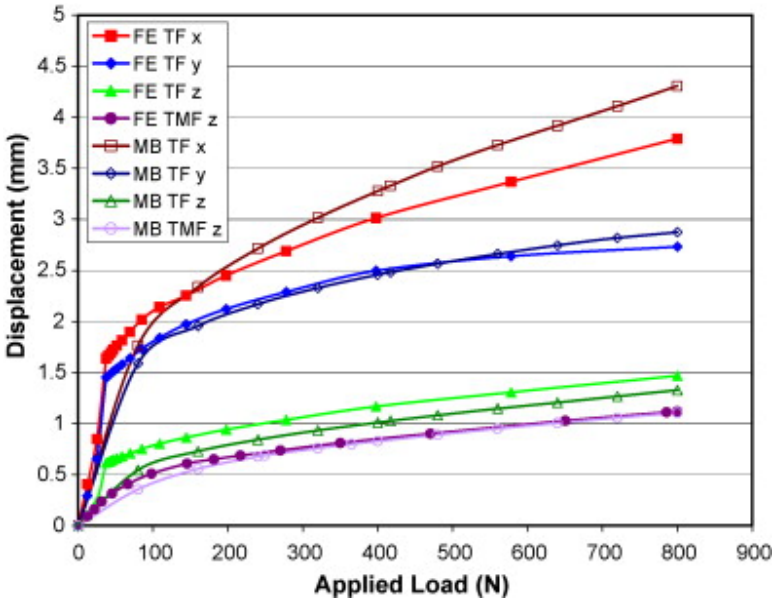
IMAG/MSM FOR CARTILAGE

Dynamic Simulation of Joints Using Multi-Scale Modeling - PI: Guess

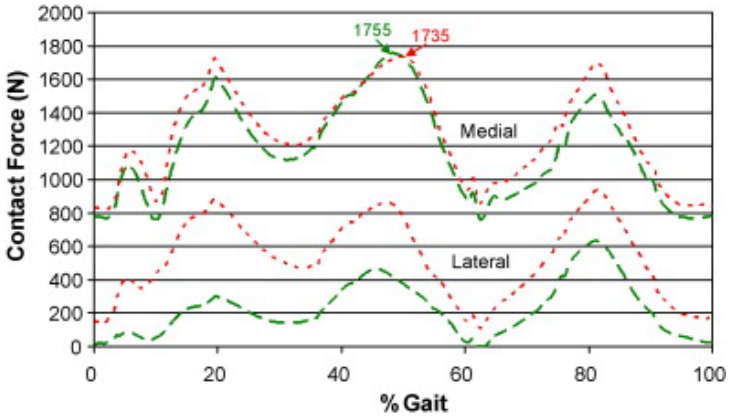
Integrating meniscus in multibody models

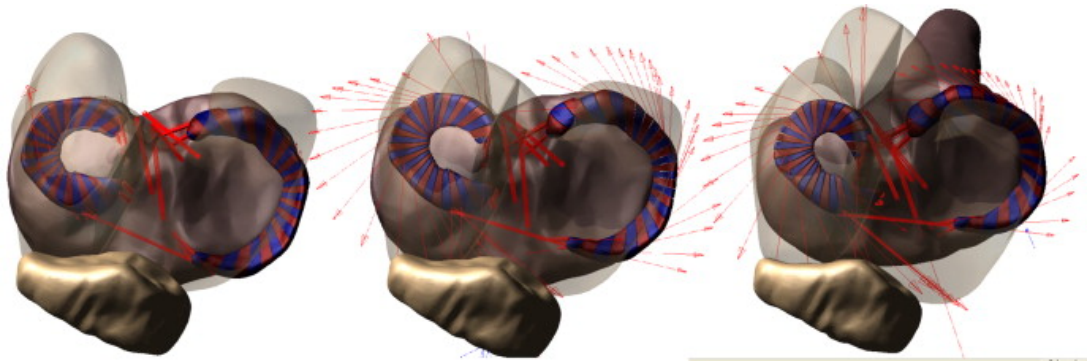
Calibration of multibody model with FE model





Role of meniscus on contact load distribution



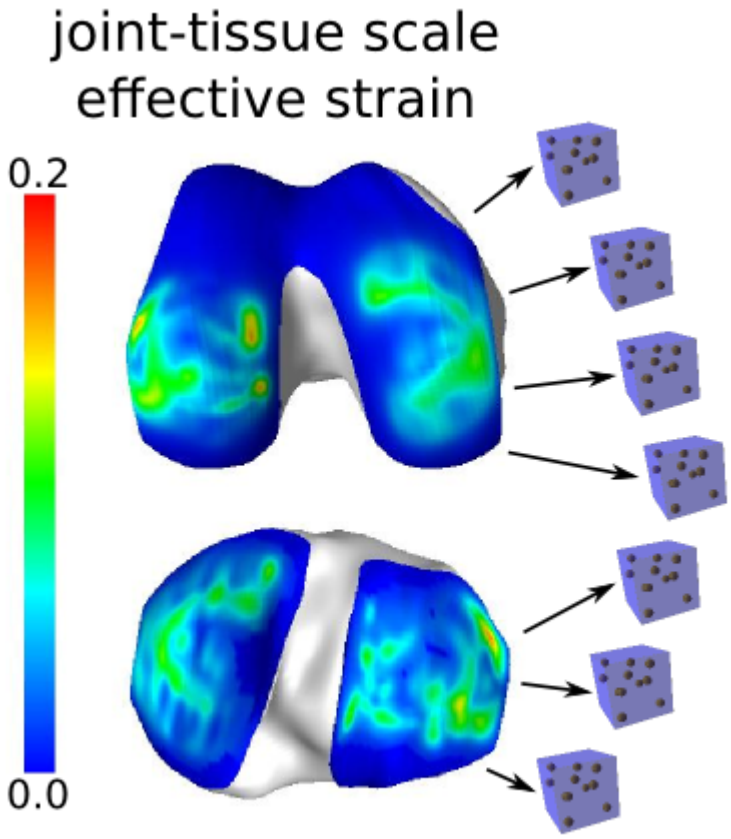


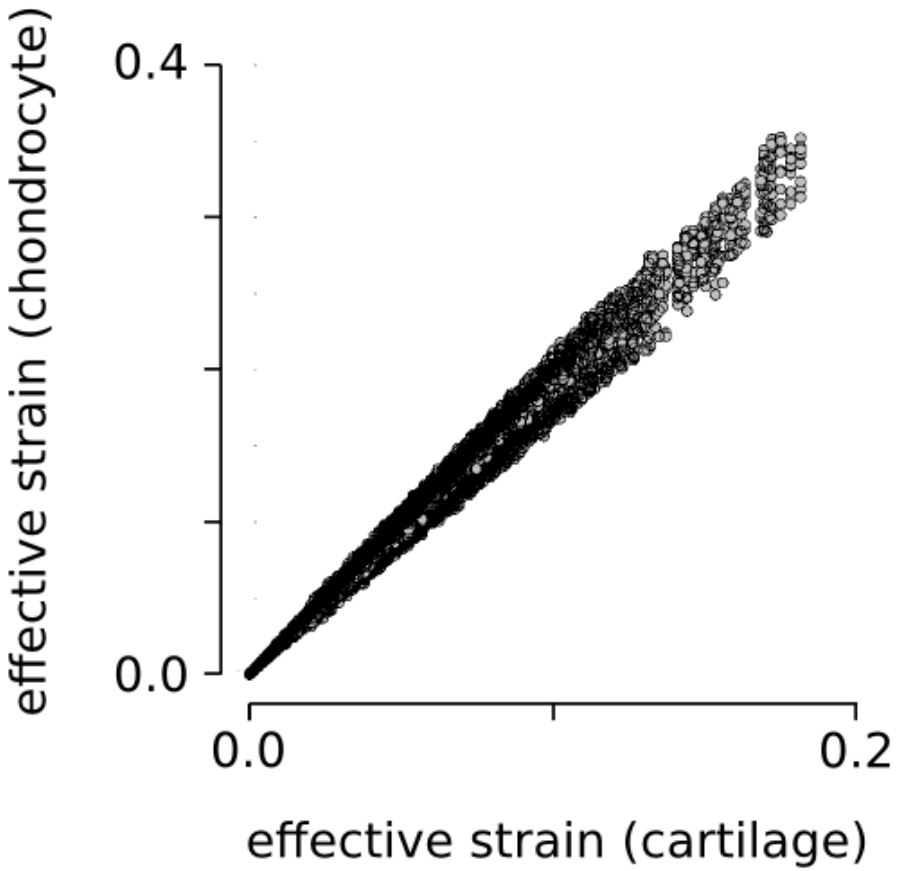
adapted from Guess et al. (2010)

IMAG/MSM FOR CARTILAGE

Predicting Cell Deformation from Body Level Mechanical Loads - PI: Erdemir

Feasibility of simulations from joint scale to cell scale

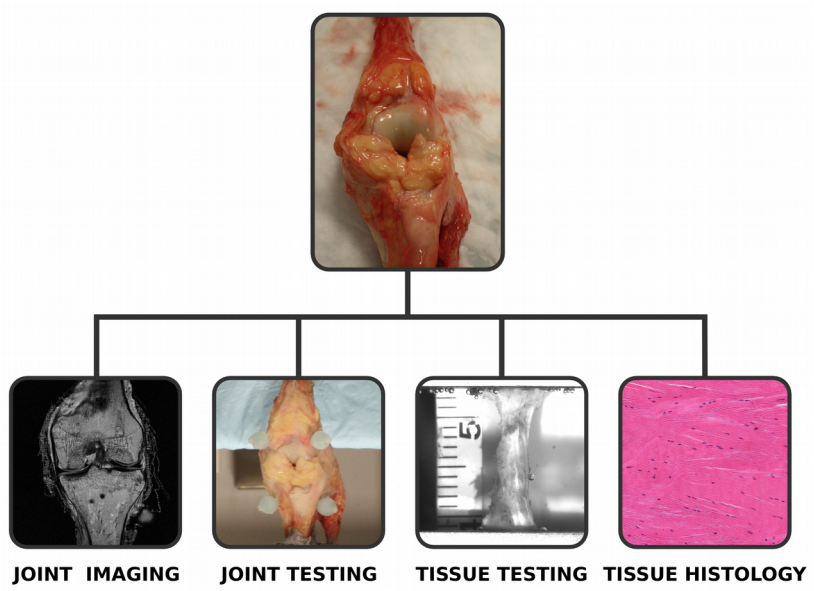




adapted from Sibole and Erdemir (2012)

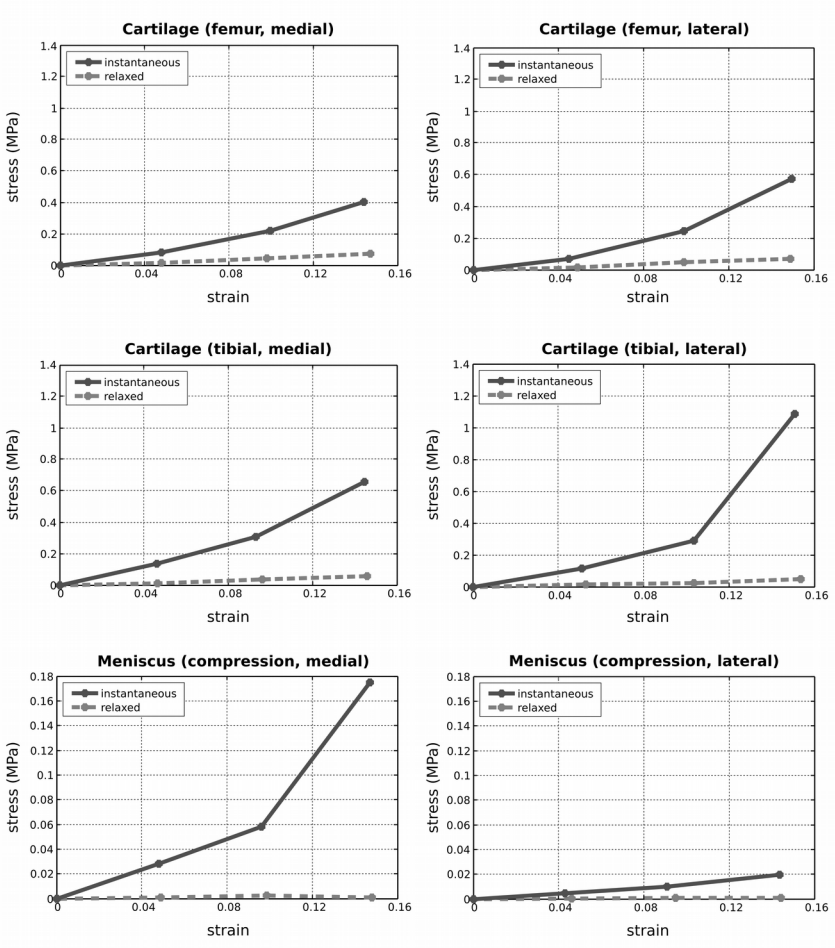
IMAG/MSM FOR CARTILAGE

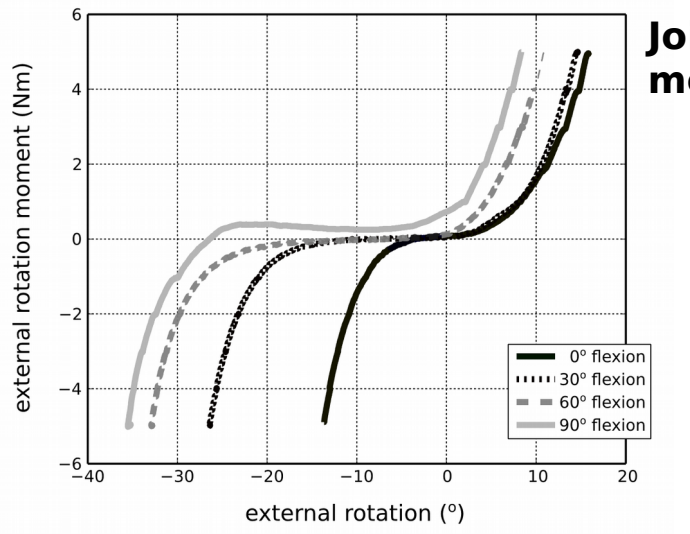
Predicting Cell Deformation from Body Level Mechanical Loads - PI: Erdemir



Specimen-specificity at multiple scales

Tissue scale mechanical properties





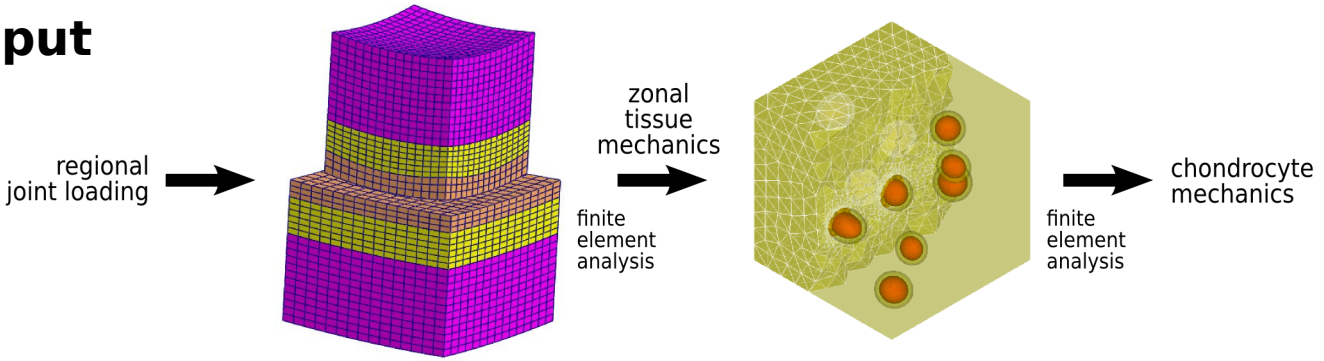
Joint scale mechanics

adapted from Chokhandre et al. (2015)

IMAG/MSM FOR CARTILAGE

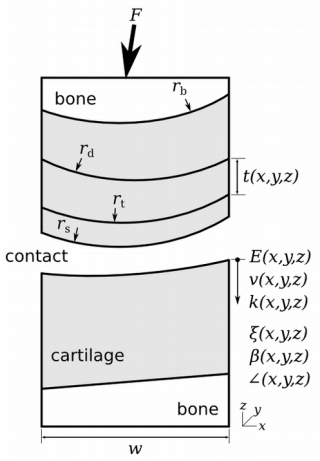
Predicting Cell Deformation from Body Level Mechanical Loads - PI: Erdemir

High-throughput M&S



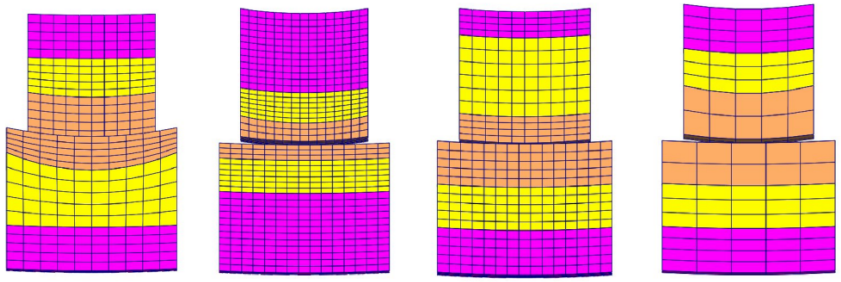
regional joint-tissue scale model

zonal tissue-cell scale model



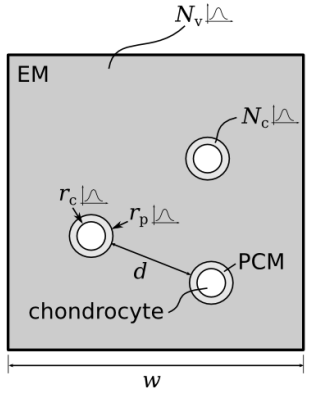
Parametric modeling

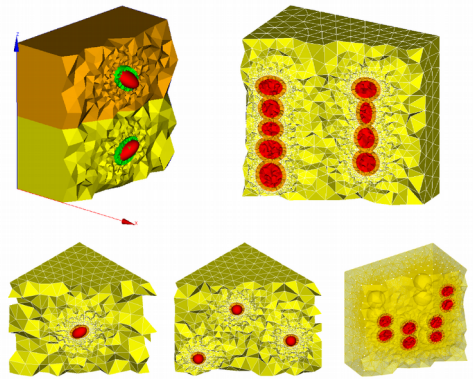
Zone anatomy
Zonal material properties



Parametric modeling

Cell anatomy
Cellular organization
Cell/PCM/EM material properties



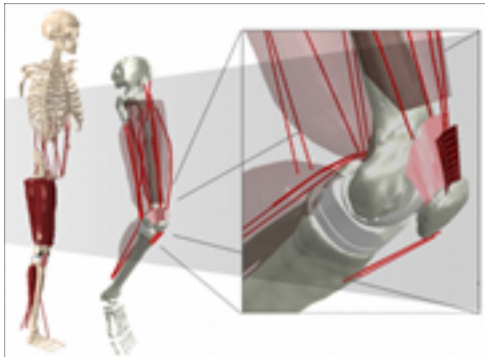


adapted from Erdemir et al. (2015)

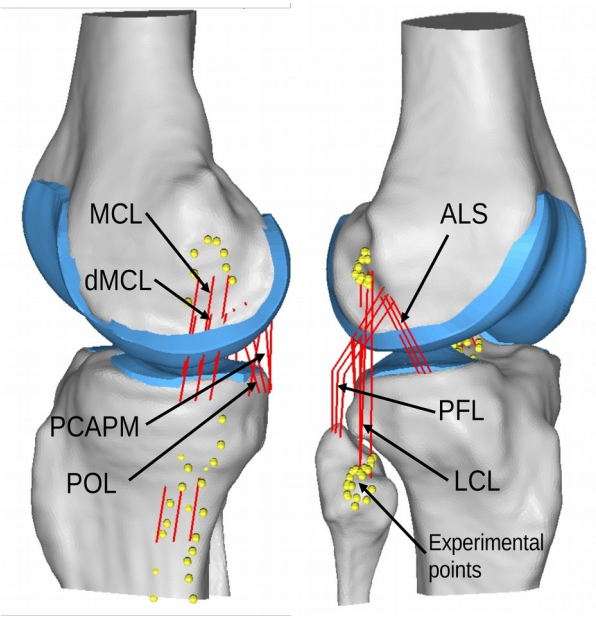
IMAG/MSM FOR CARTILAGE

A Multi-Scale Finite Element Musculoskeletal Modeling Framework Applied to Current Issues in Joint Replacement - PI: Shelburne

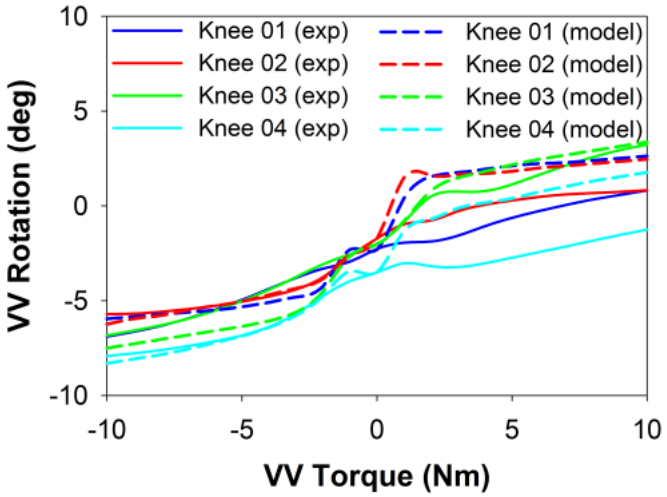
Model calibration for individualization

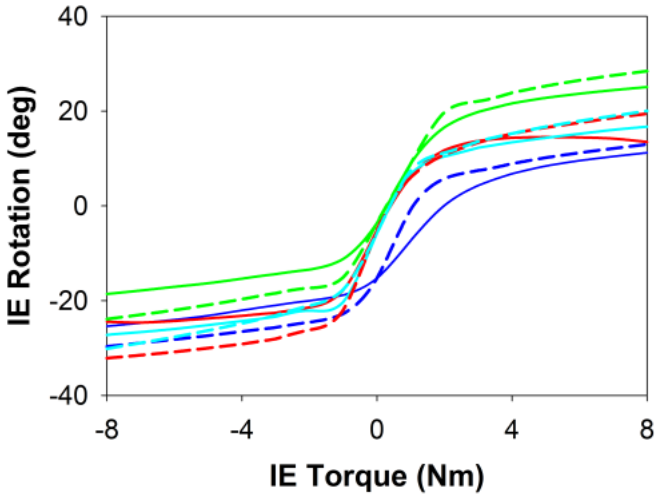


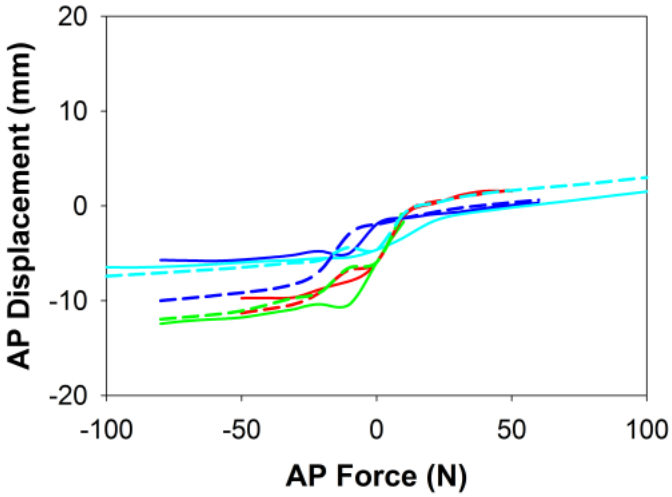
Multibody / FE modeling
Optimization



Identification of ligament properties to match kinematics-kinetics







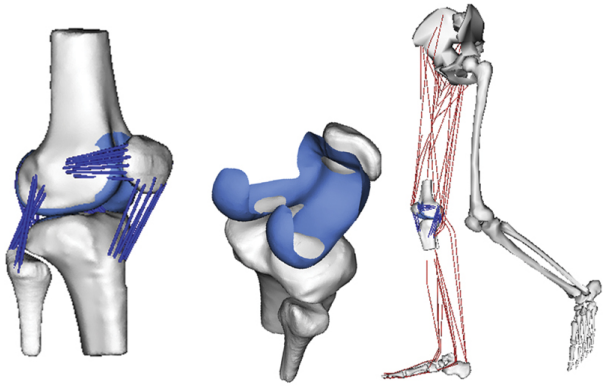
adapted from Harris et al. (2016)

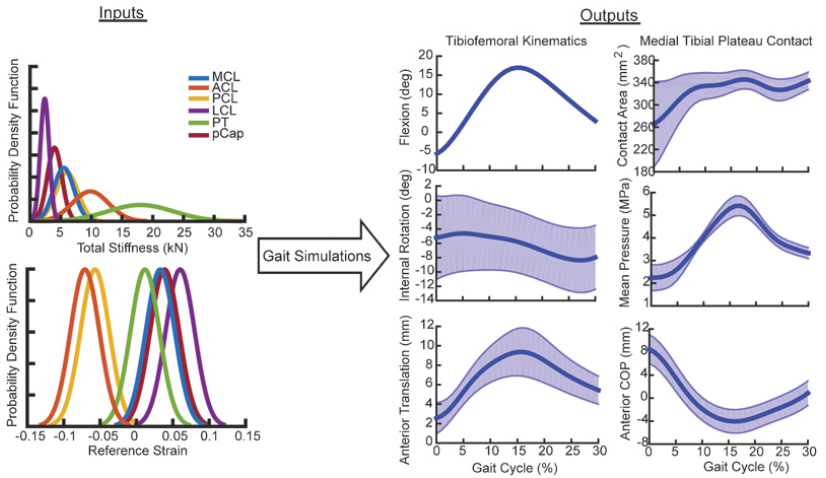
IMAG/MSM FOR CARTILAGE

A Multi-Scale Modeling Construct of Knee Mechanics following ACL Reconstruction - Co-PIs: Dhaher, Thelen

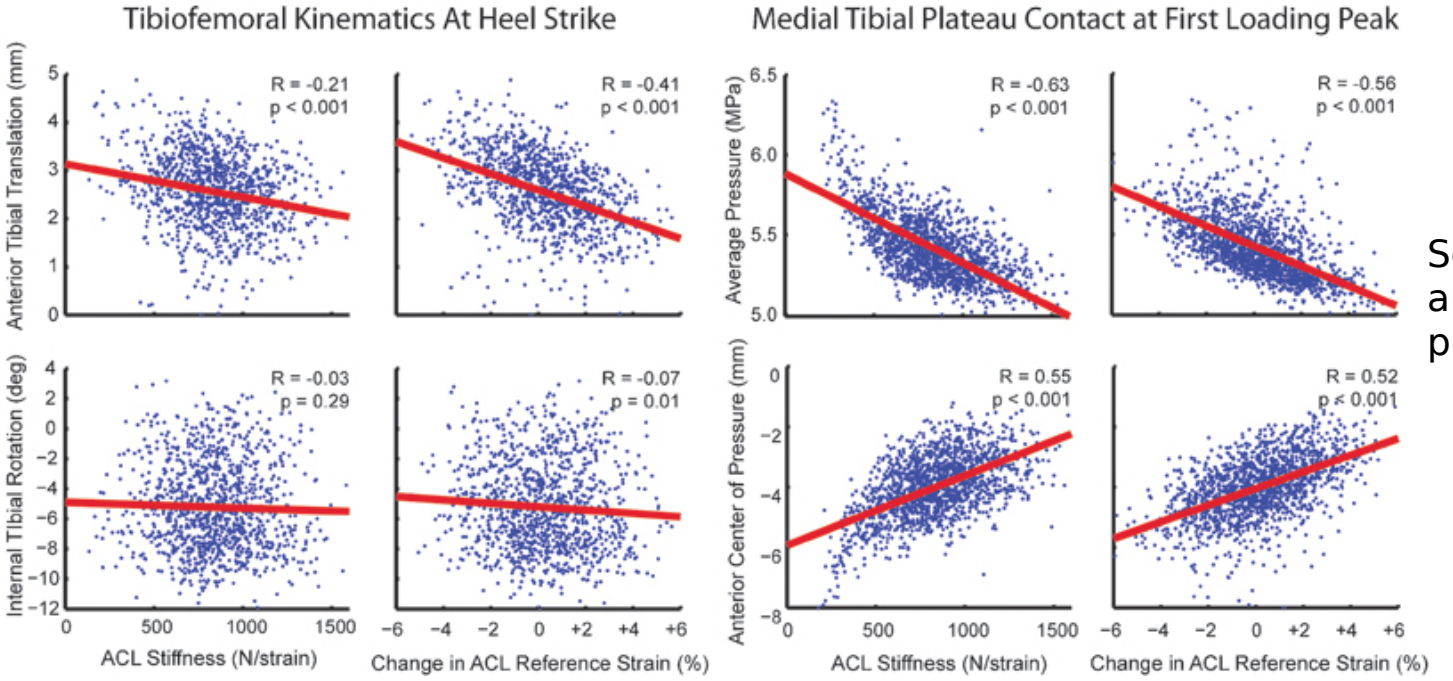
High-throughput M&S for sensitivity analysis

Multibody knee model





Monte Carlo analysis



Sensitivity of kinematics and contact on ligament properties

adapted from Smith et al. (2016)

IMAG/MSM FOR CARTILAGE

In summary, MSM projects' deliverables included:

- New **knowledge** on cartilage biomechanics as a function of musculoskeletal activity and joint, tissue, cell properties.
- **High-throughput tools** to connect domains of musculoskeletal movements with tissue and cell mechanics.

  Joint loads → contact mechanics → zonal mechanics → chondrocyte mechanics
- Documentation of **uncertainties** in prediction of cartilage biomechanics due to assigned joint, tissue and cell properties and coupling assumptions.
- **Individualization** of models
- New **data** and **models**

  https://simtk.org/projects/mb_knee/ **-** *PI: Guess*

  https://simtk.org/projects/j2c **-** *PI: Erdemir*

  http://digitalcommons.du.edu/natural_knee_data/ **-** *PI: Shelburne*

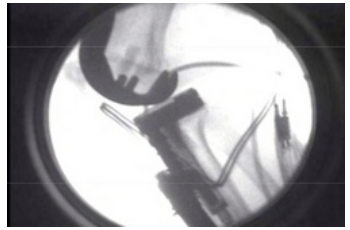
MEANWHILE, IN CARTILAGE WORLD

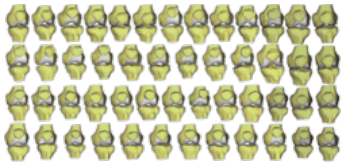
Intensive research activities for

- Joint biomechanics
- Cartilage biomechanics
- Extracellular and chondrocyte biology & mechanotransduction
- New strategies for modeling mechanics & mechanobiology at single scales
- Simulations of multiscale interactions
- Osteoarthritis
- Comprehensive data acquisition

Open Knee(s)
website

Grand Challenge Competition to Predict In Vivo Knee Loads
website



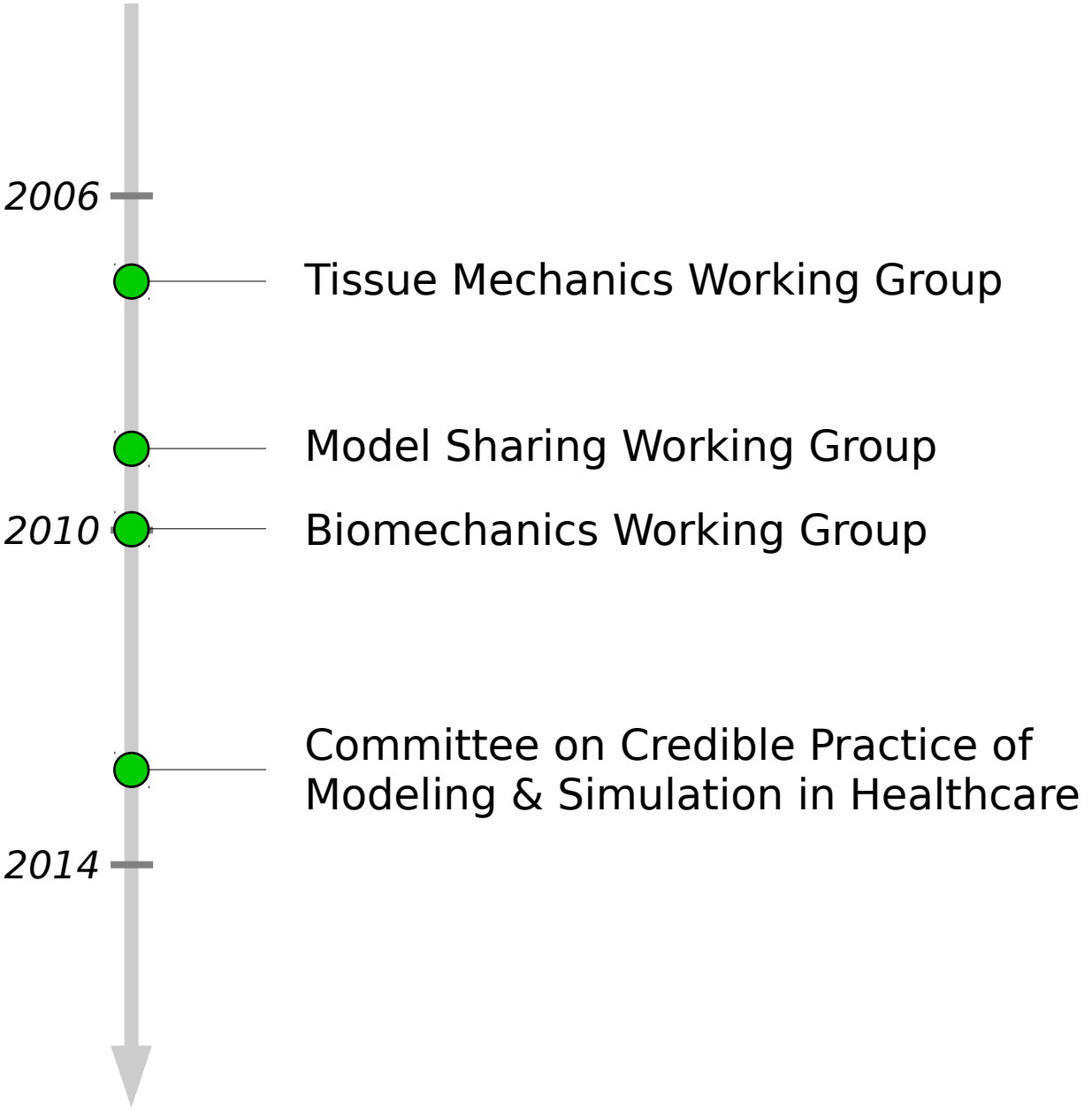


Statistical Shape Model of the Knee
website

MAP
Musculoskeletal Atlas Project
website

Osteoarthritis Initiative
website

IMAG/MSM FOR M&S



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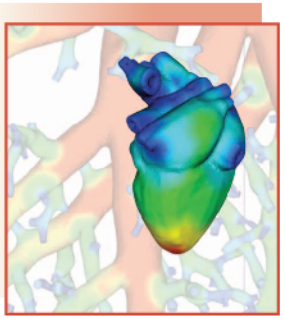

© Images courtesy of Daniel Einstein

Multiscale Modeling in Computational Biomechanics

Determining Computational Priorities and Addressing Current Challenges

MULTISCALE MODELING PART 2

BY MERRYN TAWHAI, JEFF BISCHOFF, DANIEL EINSTEIN, AHMET ERDEMIR, TRENT GUESS, AND JEFF REINBOLT

Biomechanics is broadly defined as the scientific discipline that investigates the effects of forces acting on ... model development and validation, the large variability in anatomical and functional properties, and the readily nonlinear

adapted from Tawhai et al. (2009)

© Images courtesy of Dani

BY MERRYN TAV
DANIEL EINSTEIN
TRENT GUESS, A

Multiscale Modeling in Computational

MULTISCALE

Journal of Biomechanics 45 (2012) 625–633

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Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Perspective article

Considerations for reporting finite element analysis studies in biomechanics

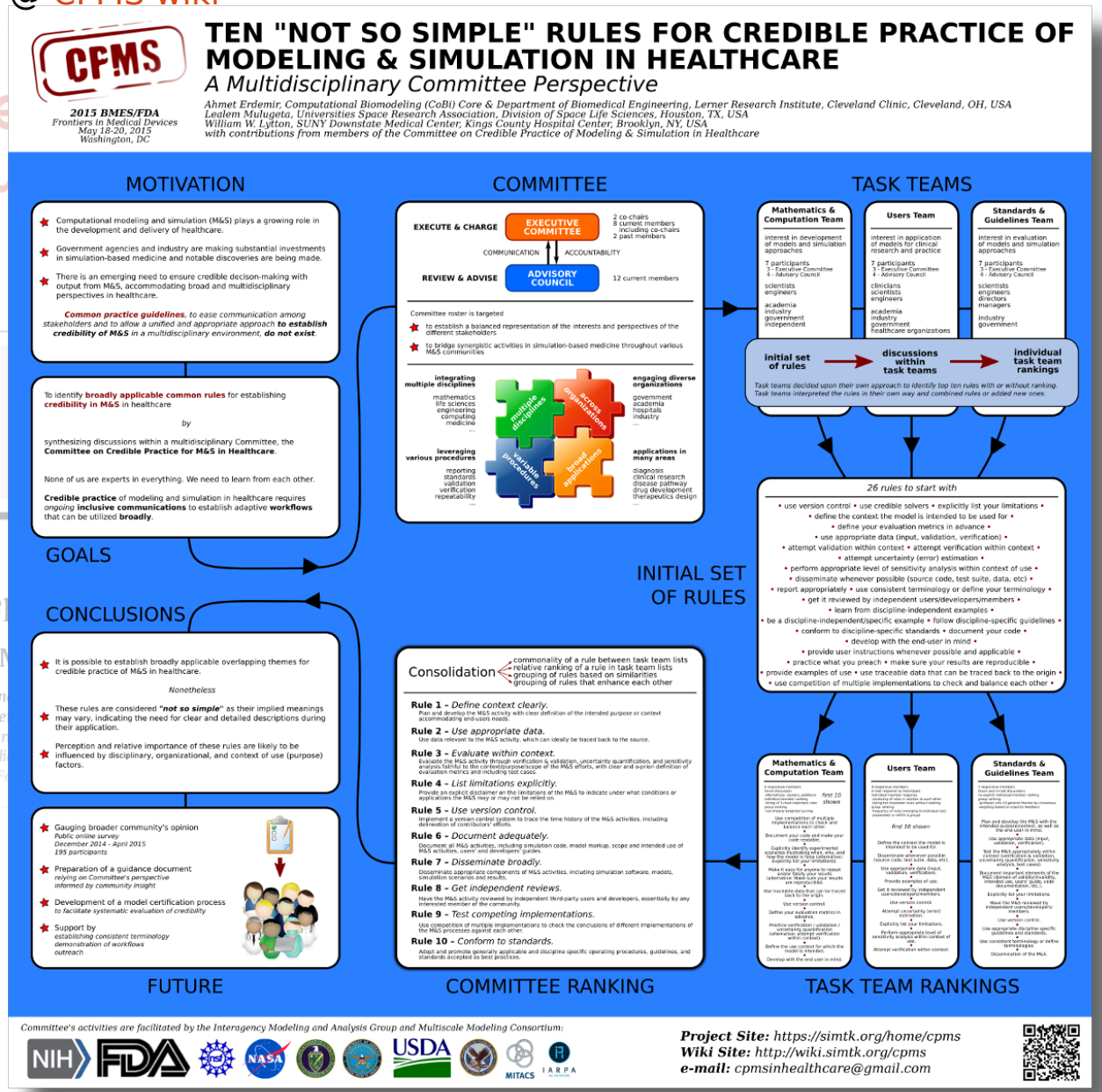
Ahmet Erdemir [a,b,*], Trent M. Guess [c], Jason Halloran [a,b], Srinivas C. Tadepalli [d], Tina M. Morrison [e]

[a] Computational Biomodeling (CoBi) Core, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA
[b] Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA
[c] Department of Civil and Mechanical Engineering, University of Missouri – Kansas City, Kansas City, MO 64110, USA
[d] Department of Orthopaedics and Sports Medicine, University of Washington, Seattle, WA 98195, USA
[e] Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD 20933, USA

adapted from Erdemir et al. (2012)

IMAG/MSM FOR M&S

@ CPMS wiki



IMAG/MSM FOR M&S

Commentary on the Integration of Model Sharing and Reproducibility Analysis to Scholarly Publishing Workflow in Computational Biomechanics

Ahmet Erdemir*, *Member, IEEE*, Trent M. Guess, Jason P. Halloran, Luca Modenese, Jeffrey A. Reinbolt, Darryl G. Thelen and Brian R. Umberger

[1]*Abstract— Objective:* The overall goal of this document is to demonstrate that dissemination of models and analyses for assessing the reproducibility of simulation results can be process. *Significance:* Model sharing and reproducibility analysis in scholarly publishing will result in a more rigorous review

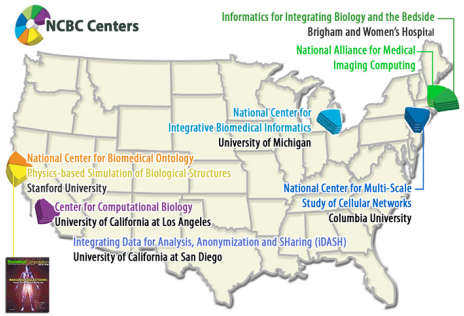
adapted from Erdemir et al. (2016), part of IEEE Transactions in BME Special Section on Model Sharing & Reproducibility

MEANWHILE, IN M&S WORLD

Intensive activities for

- New methods and algorithms for modeling & simulation
- Strategies for uncertainty estimation, sensitivity analysis, verification & validation
- Approaches to reproducibility and credibility
- Sustained development of simulation software
- Increased computing capacity
- Development of repositories
- Collaboration infrastructure

Government Initiatives



National Centers for Biomedical Computing
website

MEDICAL DEVICE INNOVATION CONSORTIUM
website

Public-Private Partnerships

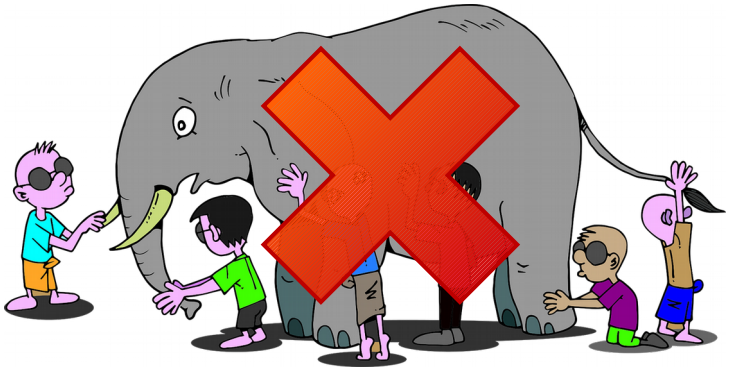
European Activities

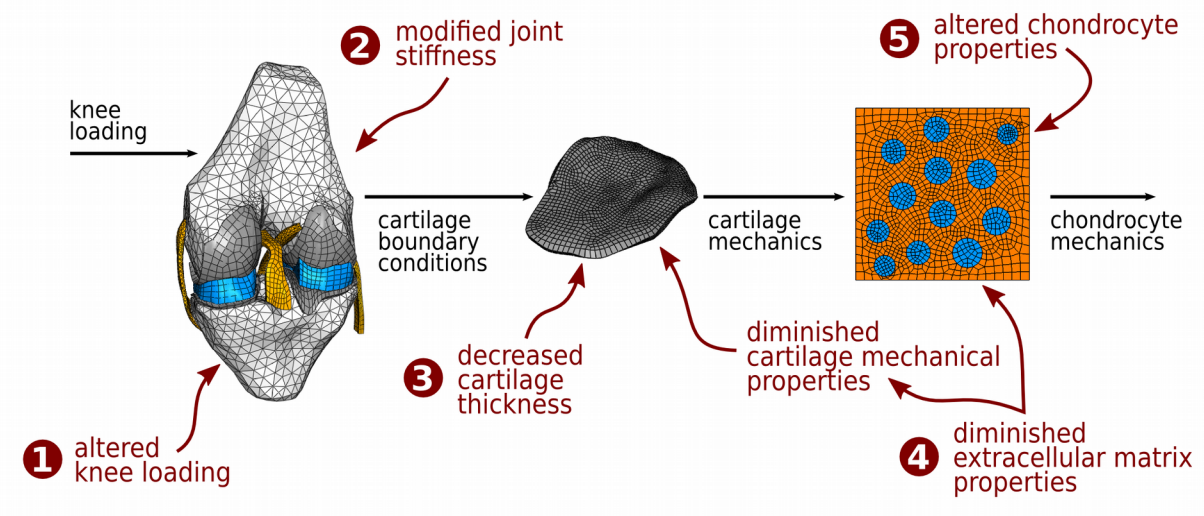
AVICENNA *website*
A Strategy for *in silico* Clinical Trials

WHERE ARE WE NOW?

A **M&S framework** to explore **cartilage biomechanics** in its entirety, across scales, in health, disease, aging, and following interventions is possible.

- Comprehensive understanding of cartilage biomechanics at single spatial scales
- Computational tools for high-throughput M&S across scales
- Know-how for treatment of multi-scale coupling
- Appreciation of sources of uncertainty
- Powerful simulation software
- Access to high-performance computing
- Accessible datasets and models





WHERE TO GO?

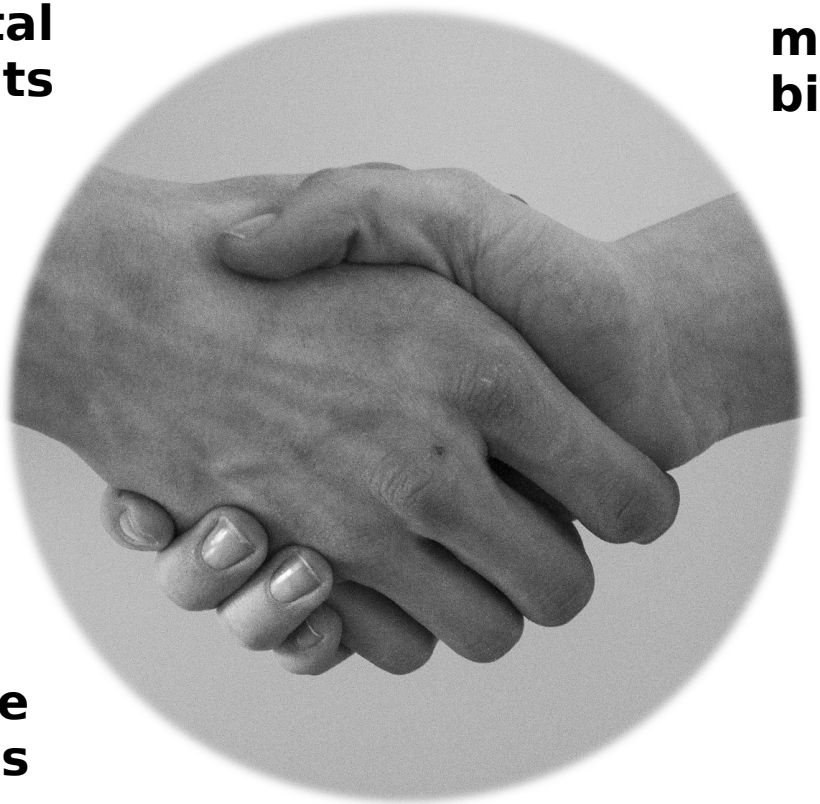
neuromuscular control

musculoskeletal movements

matrix biology

joint biomechanics

chondrocyte mechanobiology



cartilage mechanics

biochemical markers

chondrocyte mechanics

imaging markers

biomechanical markers

clinical outcomes

HOW?

multiscale modeling strategies

Multibody/FEA/ABMs

ODEs/PDEs

scale/domain coupling

deterministic/stochastic

big data approaches

machine learning

natural language processing

voluminous literature
electronic health records
activity monitors

consolidate data
in vivo/in vitro/clinical
human/animal

reuse data/models/software

WHY?

Individualized and actionable
knowledge

to guide

scientific discovery,
innovation, and clinical care

in a

credible and accessible
manner

PERCEIVED ROLE OF IMAG/MSM

What is the MSM Mission?

- To **grow** the field of **multiscale modeling** in biomedical, biological & behavioral systems
- To **promote** multidisciplinary scientific **collaboration** among multiscale modelers
- To **encourage future generations** of multiscale modelers
- To **move** the field of biological **computational modeling forward**
- To **develop accurate methods** and **algorithms** to cross multiple spatiotemporal scales
- To **promote model sharing** and the development of reusable multiscale models
- To **disseminate** the models and insights **to the larger research community**

The Consortium provides various opportunities to:

- present and share your project and **network**
- easily **converse with** program officers from **government agencies**
- **participate** in focused Working Group discussions, virtual scientific presentations, annual meetings of the MSM Consortium
- **learn** about the latest modeling and MSM related activities from around the world
- **access** various **resources** for modeling

adapted from IMAG/MSM FAQ

PERCEIVED ROLE OF IMAG/MSM

What is the MSM Mission?

- To **grow** the field
- To **promote** mult
- To **encourage fu**
- To **mov**
- To **develop accu**
- To **promote mod**
- To **disseminate**

- Sustain the mission
- Establish synergy with nationwide and international efforts
- Diversify funding opportunities
- Expand community to industry and clinicians

The Consortium provides various opportunities to:

- present and share your project and **network**
- easily **converse with** program officers from **government agencies**
- **partici** meetin
- **learn** about the la
- **access** various **resources** for modeling

- Exploit the opportunities

adapted from IMAG/MSM FAQ

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Multiscale Cartilage Mechanics

NIH/NIBIB
R01EB009643
8/1/2009 - 7/31/2013

Open Knee(s)

NIH/NIGMS
R01GM104139
9/16/2013 - 5/31/2017

Contributors

Eindhoven University of Technology
Cees Oomens, Rene van Donkelaar, Mark van Turnhout, Stefan de Vries, Carlos E. C. Leal

University of Utah
Jeff Weiss, Ben Ellis, Steve Maas, David Rawlins

Duke University
Farshid Guilak

Community
Sean Davis, Akhil Reddy

CONTACT

Ahmet Erdemir
erdemira@ccf.org
+1 (216) 445 9523

Laboratory: http://www.lerner.ccf.org/bme/erdemir/lab
J2C: https://simtk.org/projects/j2c
Open Knee(s) Wiki: https://simtk.org/plugins/moinmoin/openknee/

LICENSING

TRADEMARKS & OWNERSHIPS