Multiscale Biomechanical Computation & Imaging (T1)

Steven Abramowitch, University of Pittsburgh

Enabling Technology Testbeds Leadership

T1
Multiscale Biomechanical Computation & Imaging

T2
Mechano-organs

T3
Clinically Deployable Devices

T4
Big Data and Bio-informatics

Spandan Maiti, Pitt

Biomedical Engineering, Mechanical Engineering & Materials Science, Computational Mechanics

Steven Abramowitch, Pitt

Bioengineering, Computational Modeling of Pelvic Floor, Soft Tissue Characterization, Vaginal Mesh Design

Helen Lu, CU

Biomedical Engineering, Biomaterials and Tissue Engineering, Biofabrication

Christine Hendon, CU

Electrical Engineering, Imaging, Cardiac Electrophysiology

Itsik Pe'er, CU

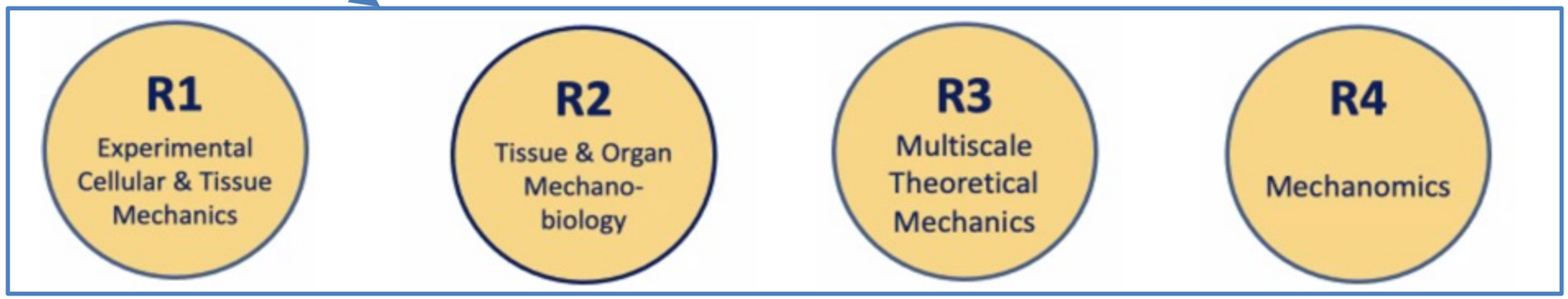
Computer Science, Computational Methods in Germline Human Genetics

Center Integration & Convergence

Systems Research Testbeds

Enabling Technology Testbeds

Fundamental Research



Our Team Spans Disciplines & Schools

Spandan Maiti, Pitt

Biomedical Engineering, Mechanical Engineering & Materials Science, Computational Mechanics

Steven Abramowitch, Pitt

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Biomedical Engineering, Mechanics of Soft Tissues, Preterm Birth, Hydrated Biomaterials

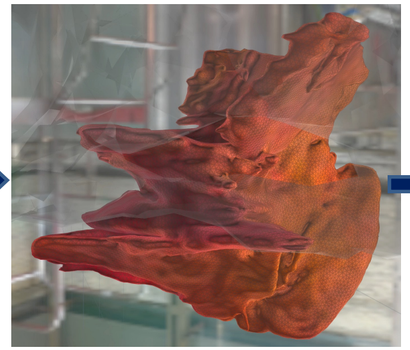
Kristin Myers, CU

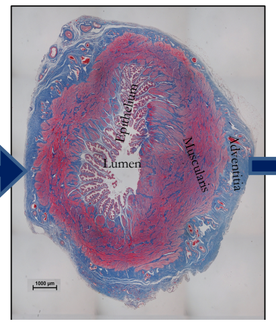
Mechanical Engineering, Mechanics of Soft Tissues, Preterm Birth, Hydrated Biomaterials

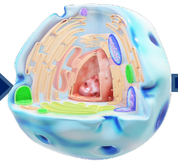
Michelle Oyen, WUSTL

Biomedical Engineering, Material Science, Mechanobiology of Implantation, Fetal Membrane Mechanics

Multiscale Modeling Challenges in Women's Health







Population and Length Scales

It's not just mommy's mechanics

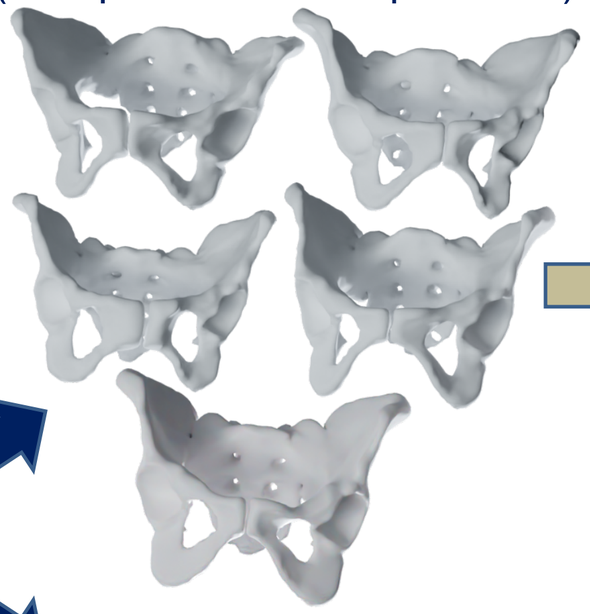
Time Scales

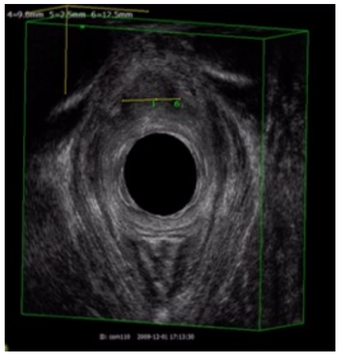
Gestational Time

AGING

Imaging, Stats, and Simulation to Tackle Scales

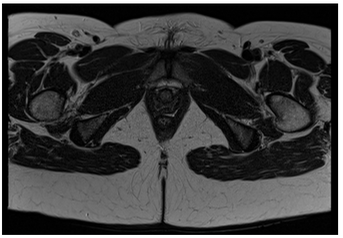
Subject Geometries
(multiple ind. or multiple times)





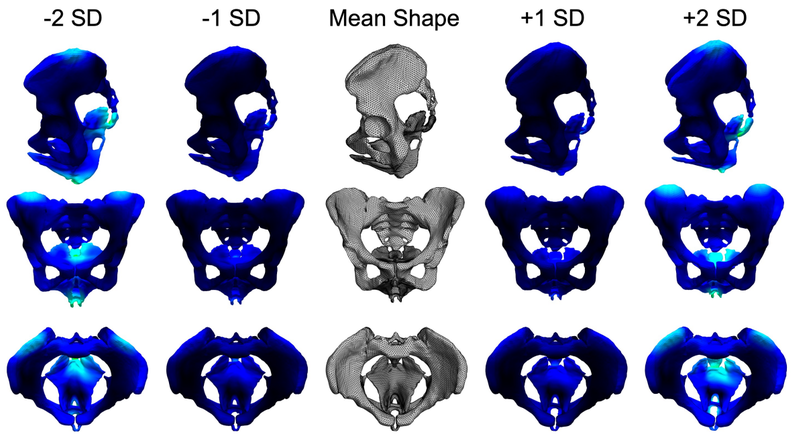
3D Ultrasound

First 7T Scanner

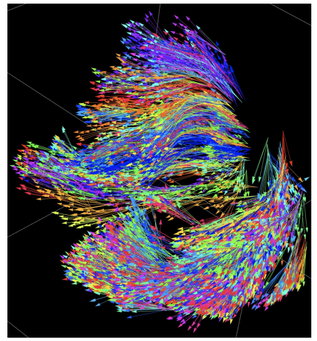


Segmentation
Deep Neural
Networks

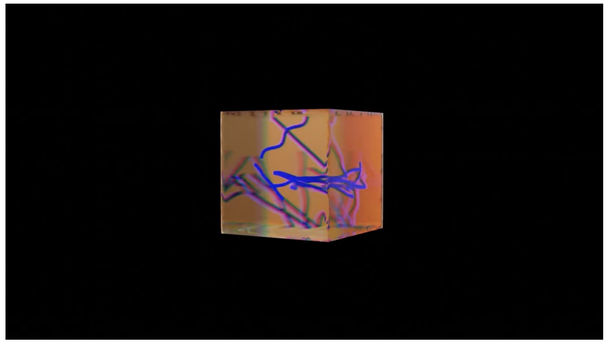
Statistical Shape Models



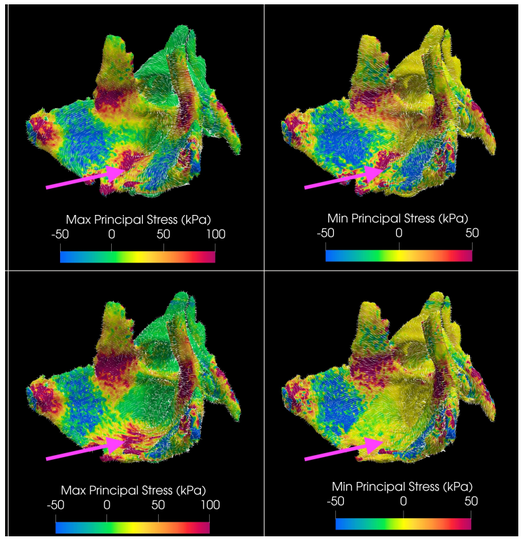
Microstructural Data



Representative Volume Elements



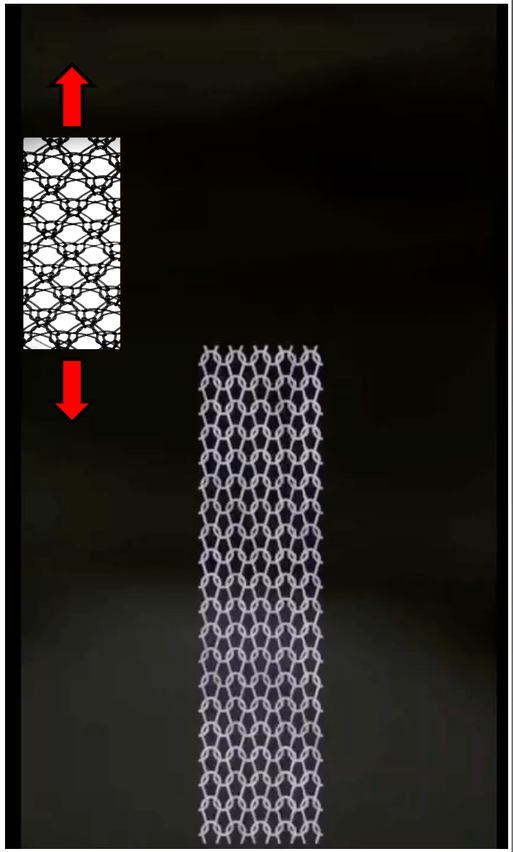
Computational
Simulations
(High/Low Fidelity)



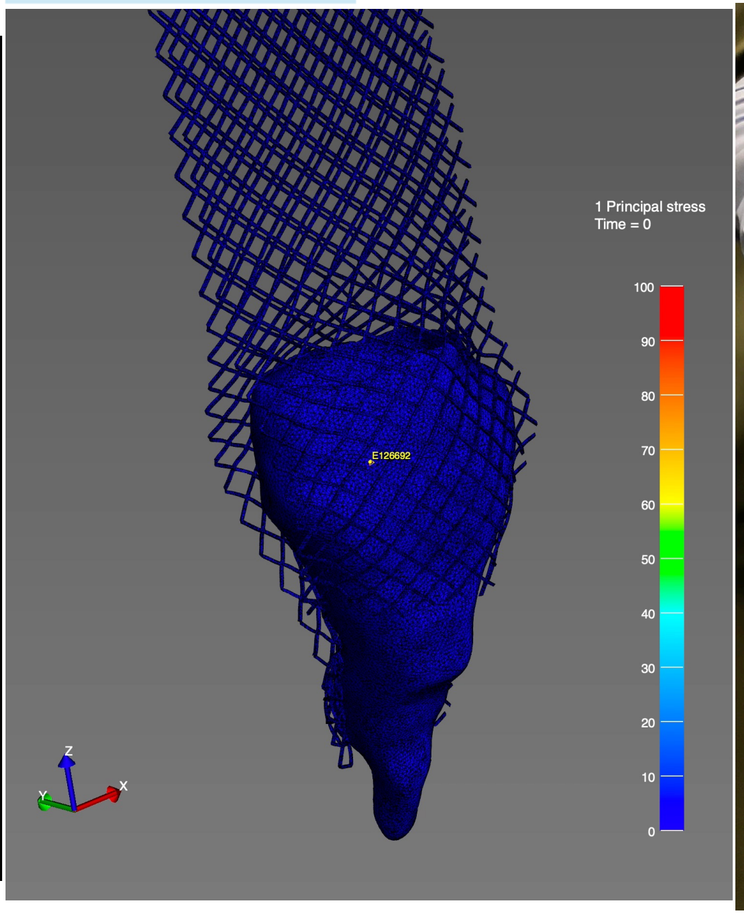
Computational Studies Inform Device Analysis

Prolapse Mesh

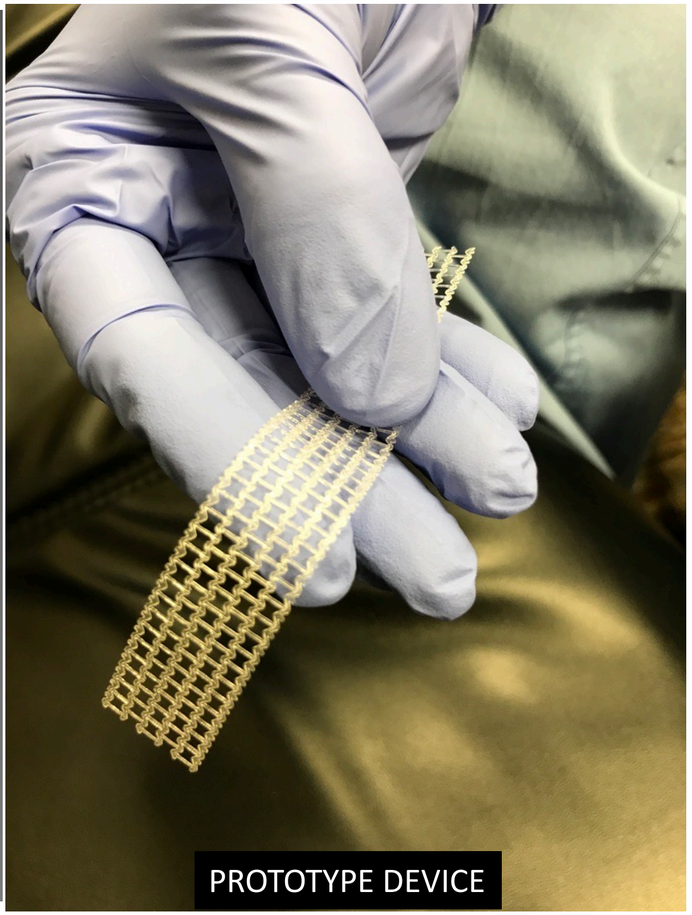
Measure



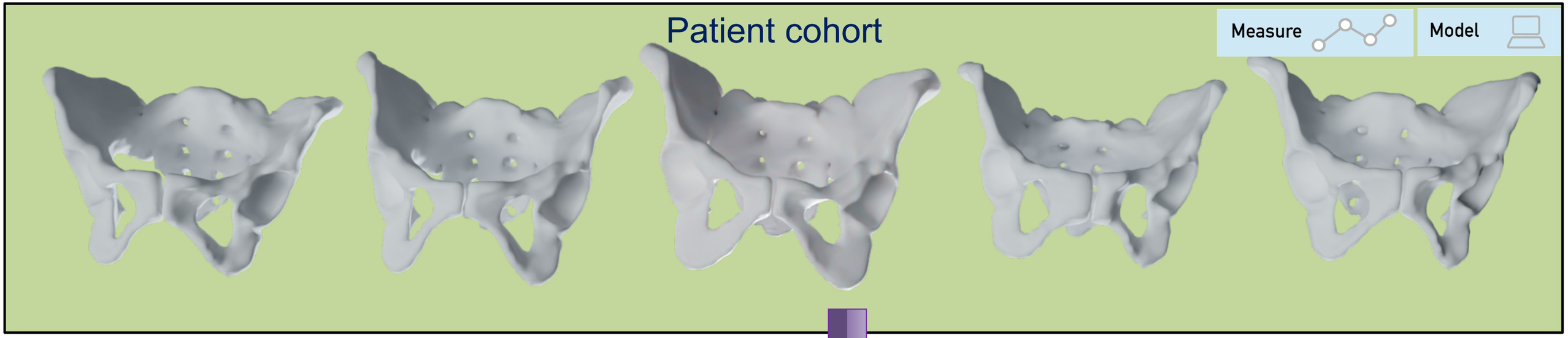
Model



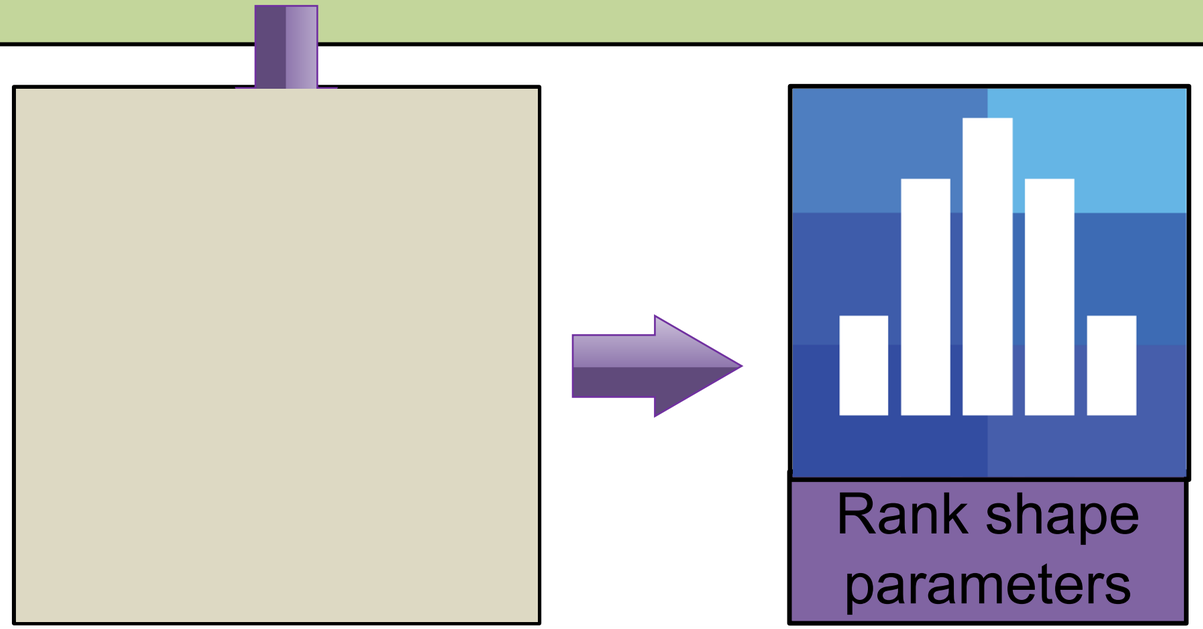
Make



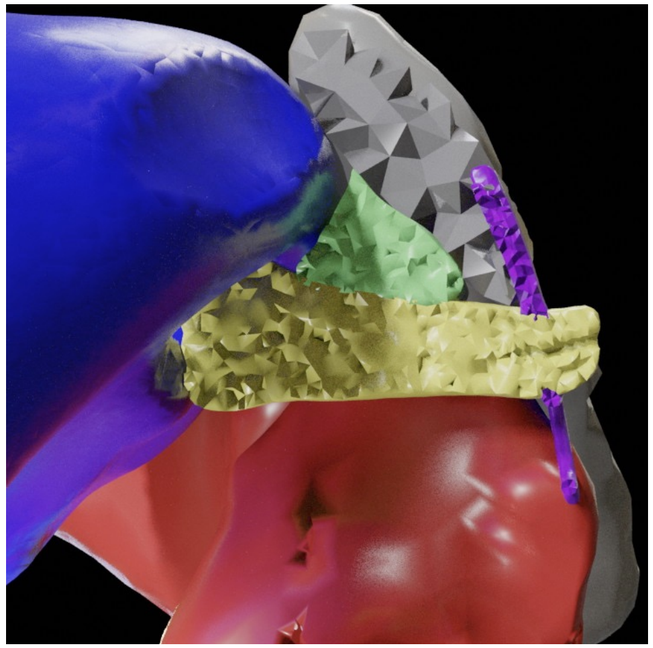
Technological Innovation 1: Quantify Geometry



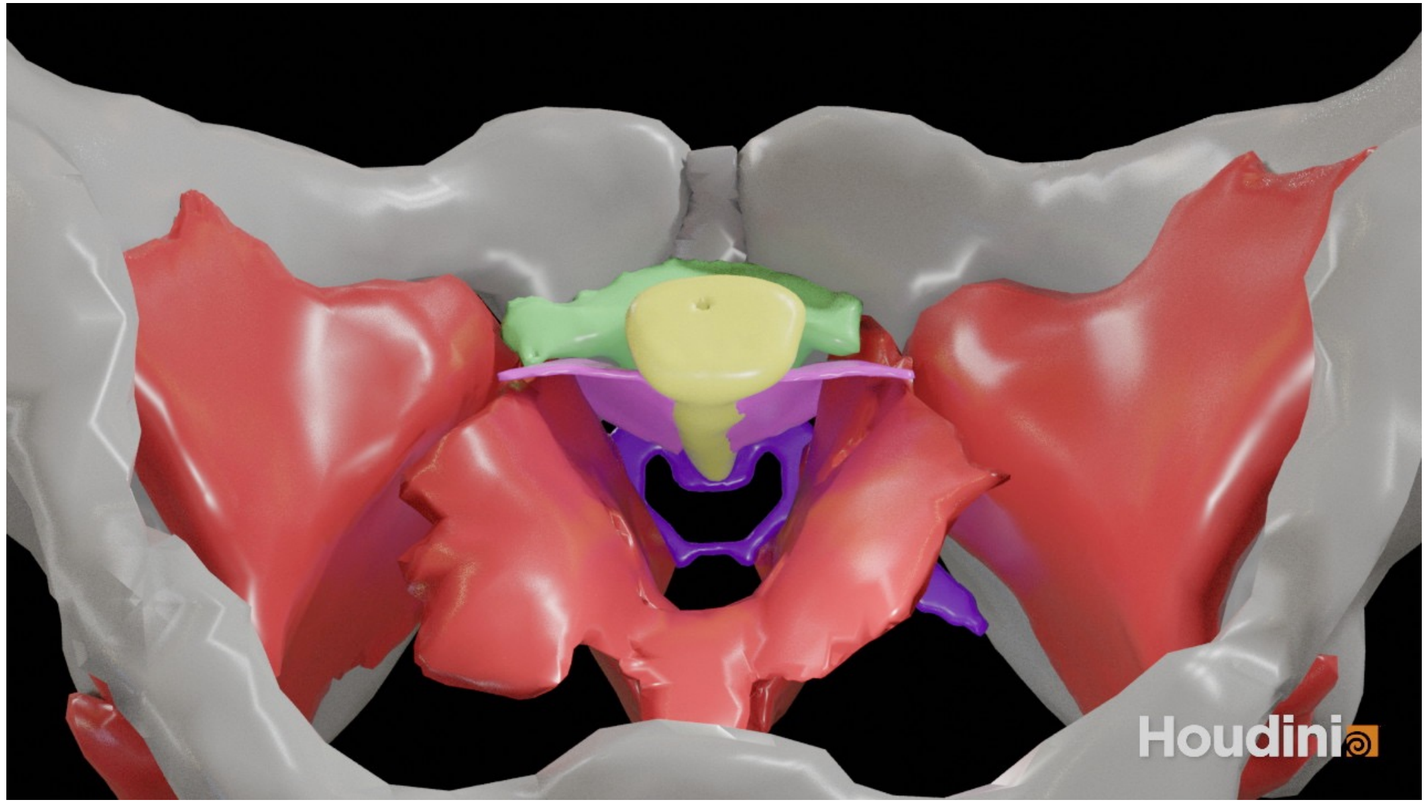
- Statistical shape analysis to quantify changes and variations
- Population aware modeling paradigm
- Clinically usable risk score that can be used for diagnostics
- Translating high fidelity modeling into lower fidelity clinical tools and measurements



Technological Innovation 2: Improved Simulations



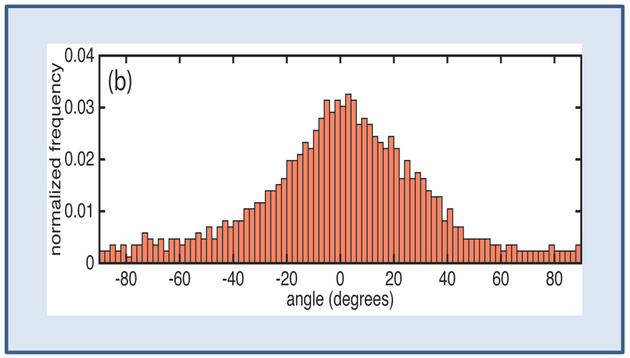
- Time Efficient Computational Simulations
- Very Large Deformations
- Multi-deformable body contact
- Necessary for simulations of delivery and device interactions with tissues



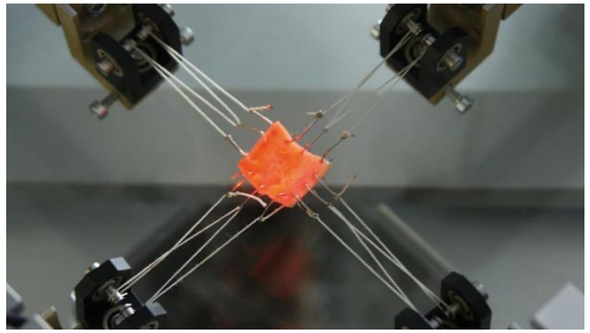
Technological Innovation 3: Multiscale w/ G&R

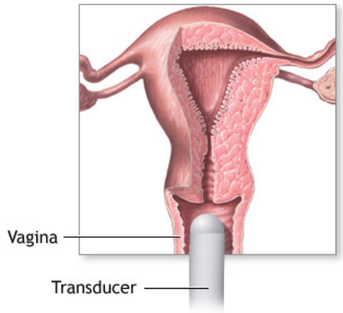
Measure | Model

Image quantification

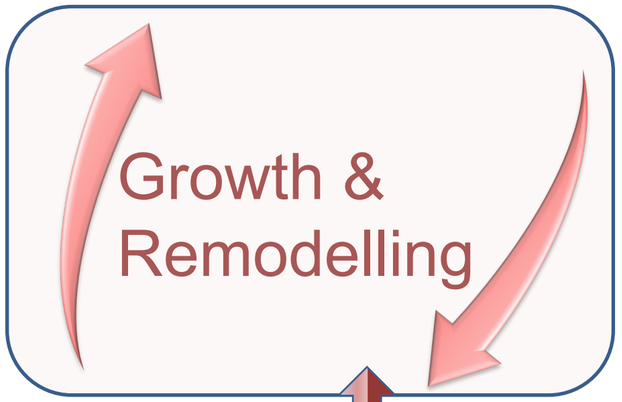


Ex-vivo/In-vivo Biomechanical Measurements





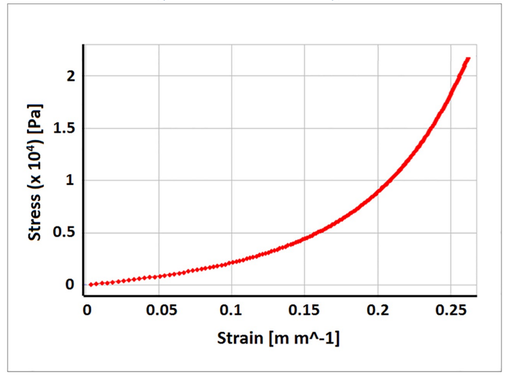
ADAM.



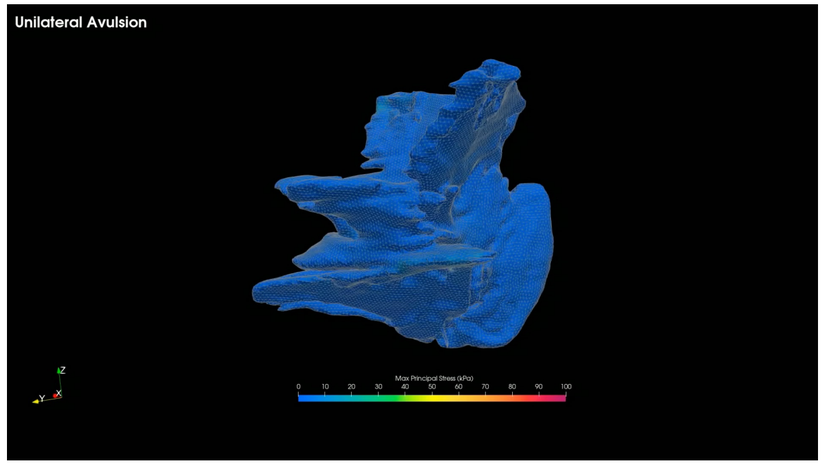
Temporal evolution of tissue properties

Validation

Numerical homogenization



Computed tissue behavior



Finite element simulation

Enabling Tech Will Feed Into Systems Level Goals

Image & Image Analysis Tools

Patient Specific

Pop

Pati

Our tools indicate that you will deliver a healthy baby at term without significant injury

win

dict

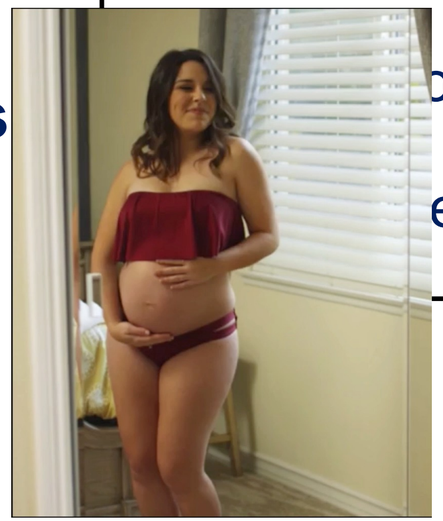
omes

Computational Tools

Risk Assessment

ormance Analysis

escriptions



Mechano-Organs (T2)

Steven Abramowitch, University of Pittsburgh

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Biomedical Engineering, Biomaterials and Tissue Engineering

X. Edward Guo, CU

Biomedical Engineering, Mechanics of Soft Tissues, Preterm Birth, Hydrated Biomaterials

Kam Leong, CU

Biomedical Engineering, Advanced Tissue Biofabrication

Wendy Liu, UCI

Biomedical Engineering, Chemical & Biomolecular Engineering, Materials & Microfabrication, Regulating Cell Behavior, Multicellular Behavior, Cardiovasculature

Michelle Oyen, WUSTL

Biomedical Engineering, Material Science, Mechanobiology of Implantation, Fetal Membrane Mechanics

Gordana Vunjak-Novakovic, CU

Biomedical Engineering, Medicine, Dental Medicine, Regenerative Medicine, Tissue Engineering, Organs on a chip

Steven Abramowitch, Pitt

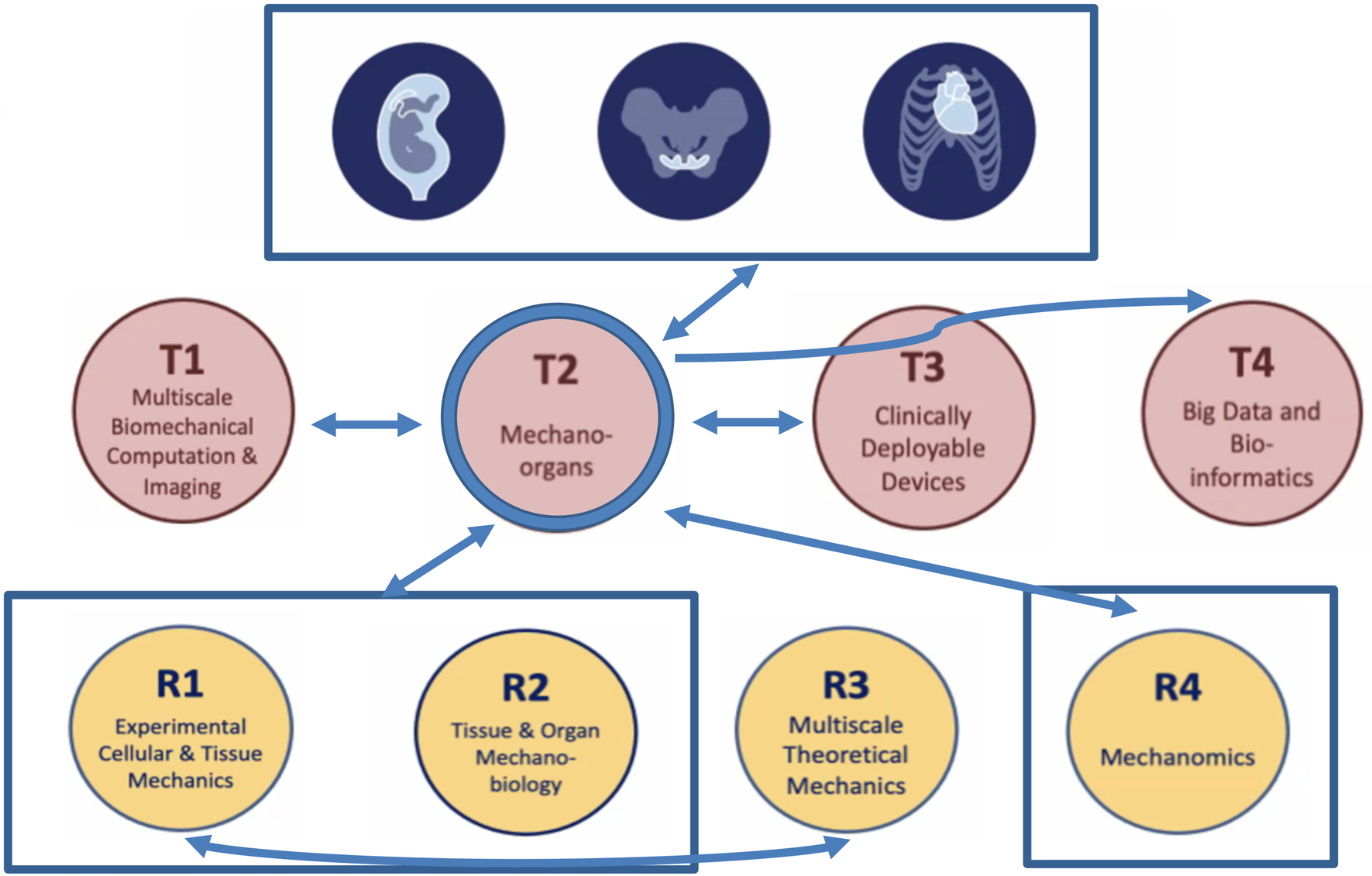
Bioengineering, Computational Modeling of Pelvic Floor, Soft Tissue Characterization

Center Integration & Convergence

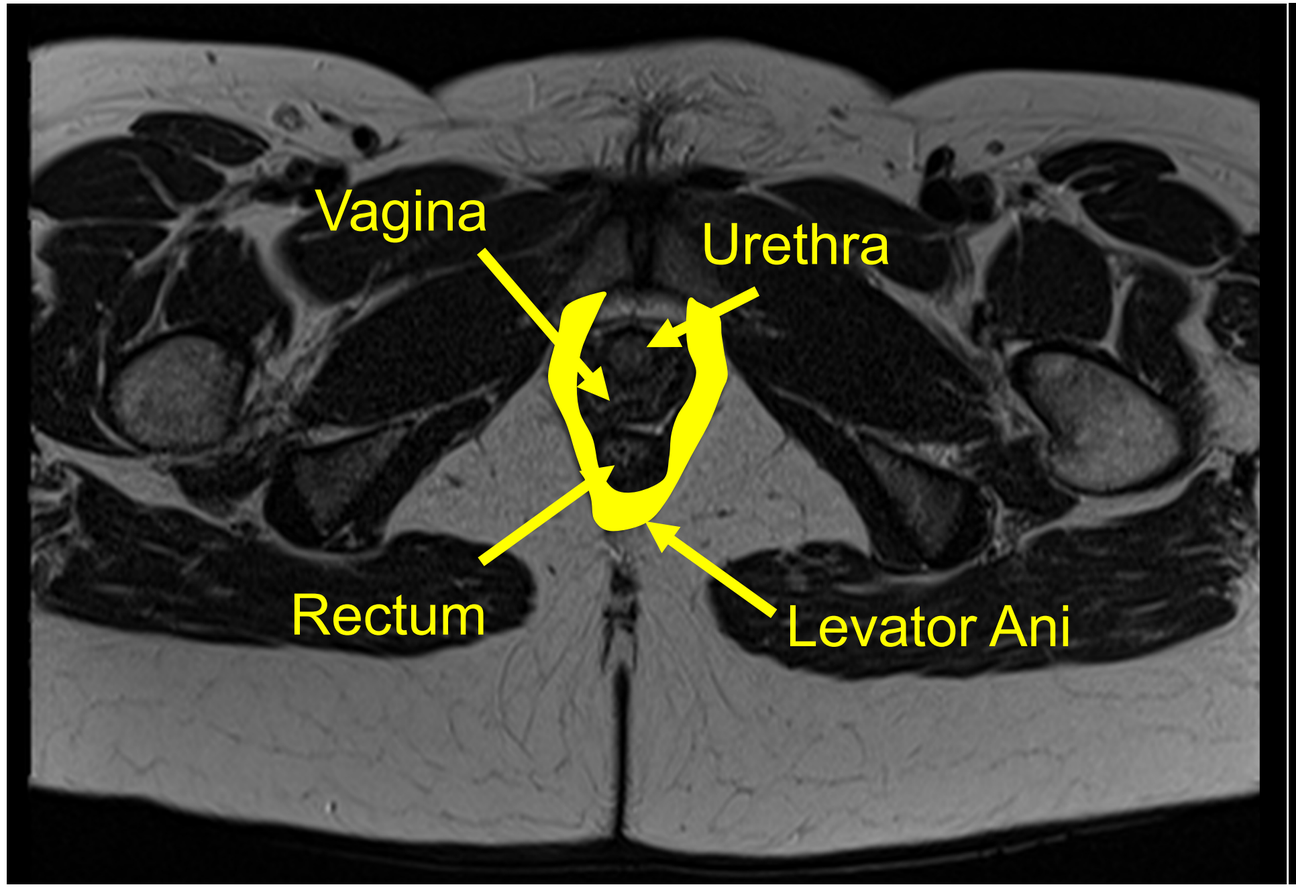
Systems Research Testbeds

Enabling Technology Testbeds

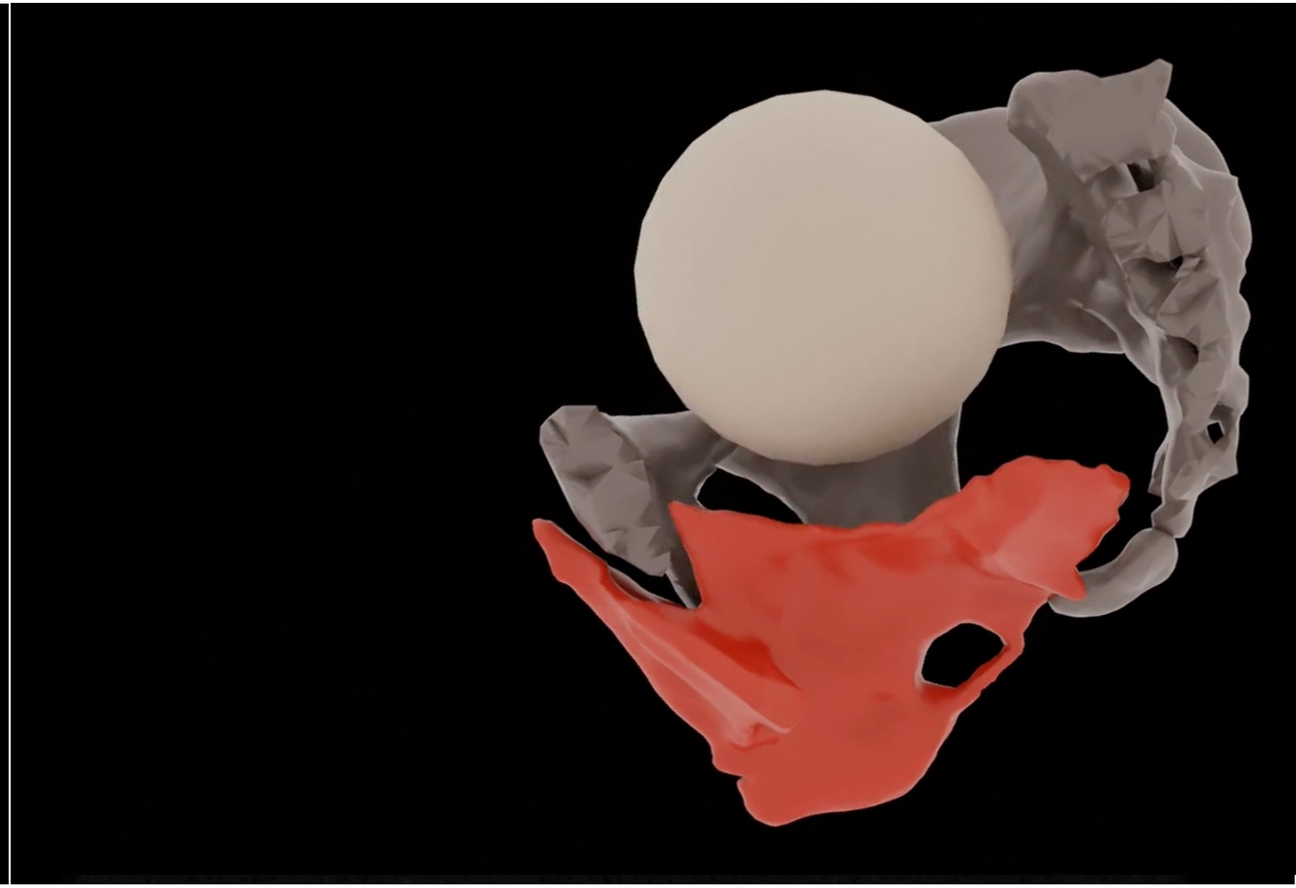
Fundamental Research/ Research Thrusts



No Treatment for Levator Ani Injury



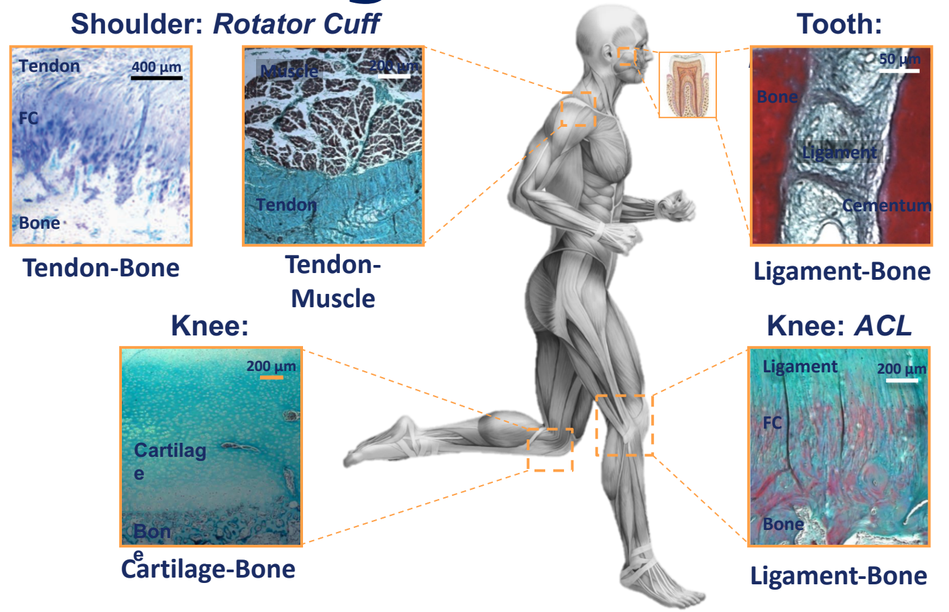
Normal

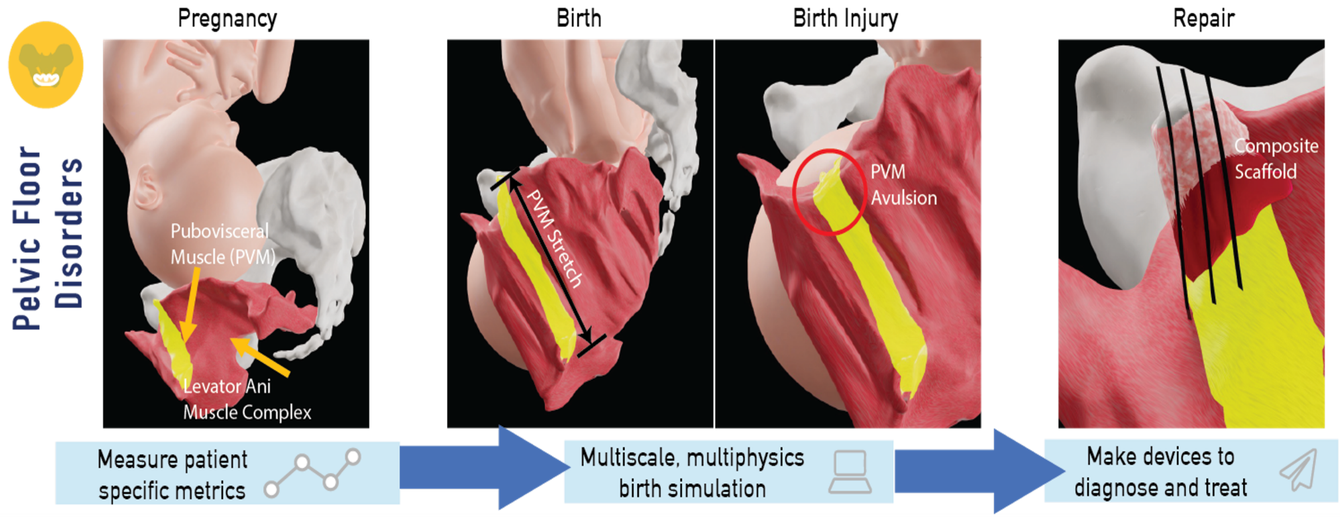


Unilateral Avulsion

Pelvic Floor Disorders- Tissue integration

- **Heterotypic Tissue Interfaces**
  - ubiquitous in the body
- Critical in reproductive health and treatment of pelvic floor disorders
- Repair solutions require fundamental knowledge of pelvic tendon-bone interface
- Goal: Functional enthesis recapitulation
- Mechanobiology of healing in the context of estrogen dynamics





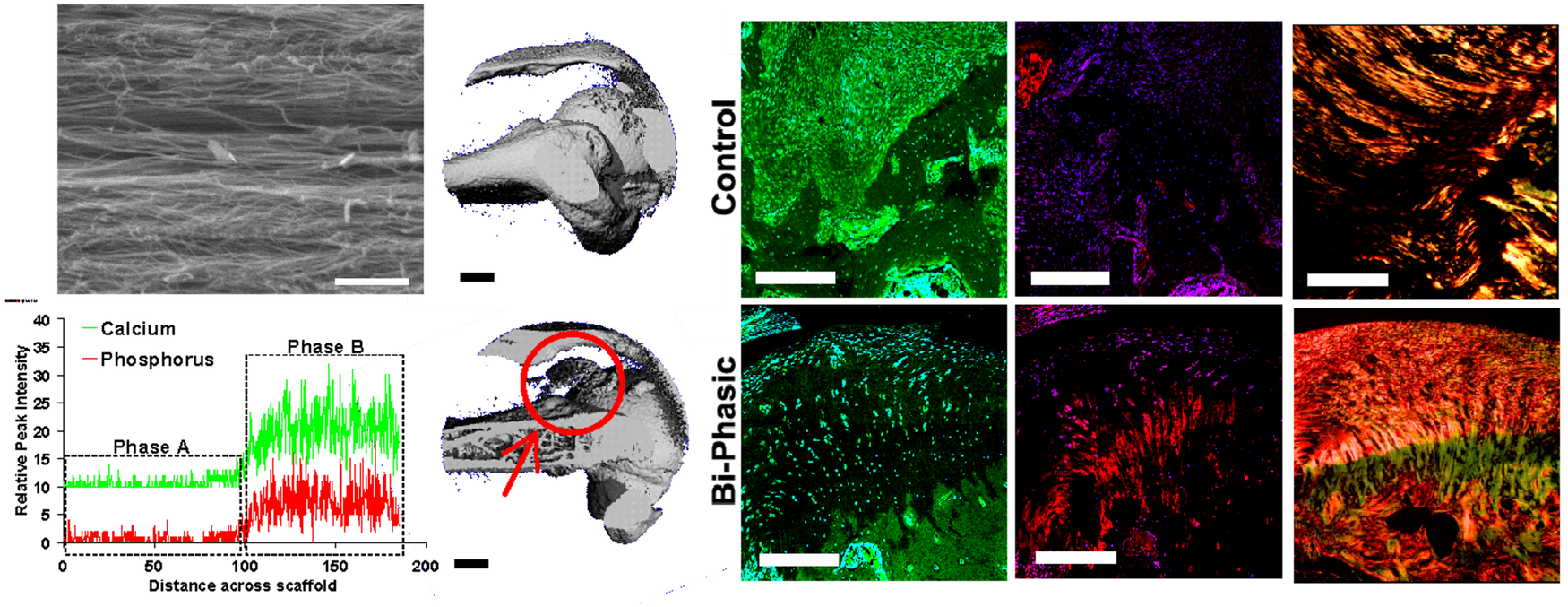
Novel Device for Pelvic Floor Disorders

Biolayer scaffold for Enthesis Regeneration

Measure patient specific metrics

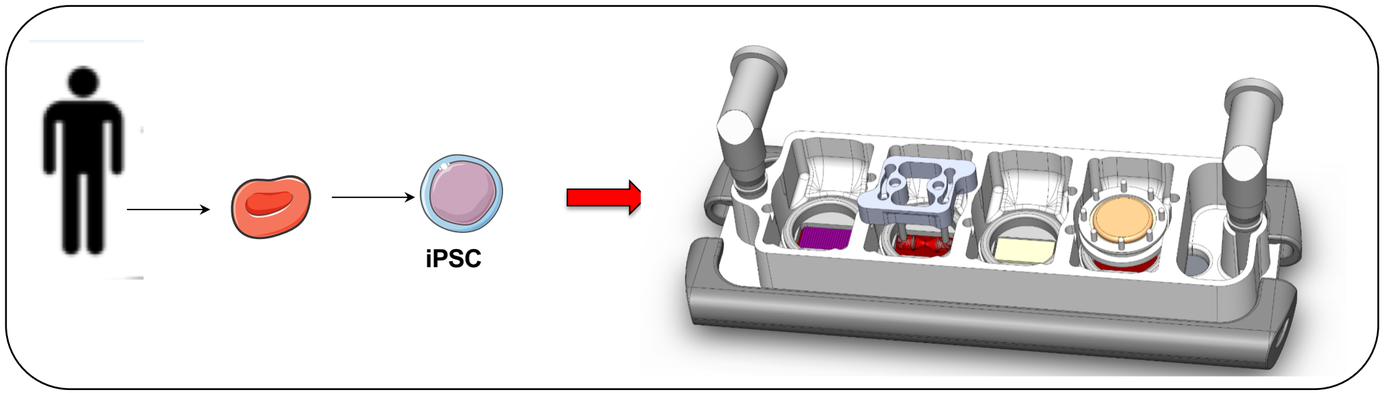
Multiscale, multiphysics pregnancy simulation

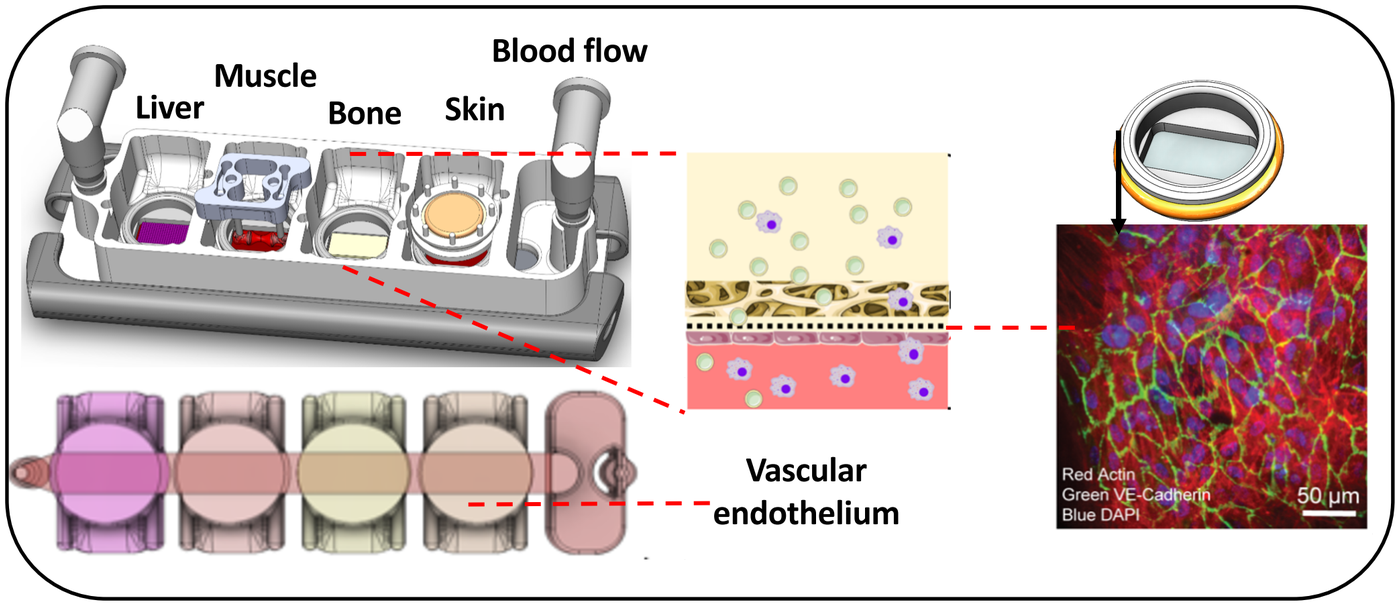
Make devices to diagnose and treat



- Biolayer scaffold customized for PVM enthesis and grown in bioreactor
- Tissue model formed with patient-derived cells
- Investigate the effect of reproductive hormones on interface regeneration
- *Biological Fixation of Tendon to Bone for the PVM*

Organs-on-a-chip:





Modular, configurable

- To model patho/physiology of uterus
- Whole body context

Tissue connectivity

- Links by vascular flow, as in the body
- Organ-organ interactions

Biological specificity

- Individualized settings, “she on a chip”
- To develop therapies for healthy aging

Stable & mature tissue phenotypes

- Weeks to months of culture

Functional readouts in real time

- On-line data, longitudinal studies

Enables studies

- Age, gender, ancestry, reproductive hormonal cycles

*Ronaldson-Bouchard and Vunjak-Novakovic **Cell Stem Cell** (2018); Vunjak-Novakovic et al **Cell** (2021); Tavakol et al. **Cell Stem Cell** (2021); Lock et al **Nature Reviews Materials** (2021)*

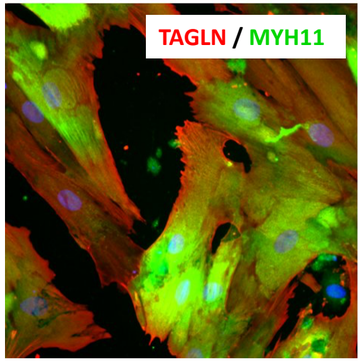
Enabling Technology for Preterm Birth

Smooth Muscle tissue-on-a-chip

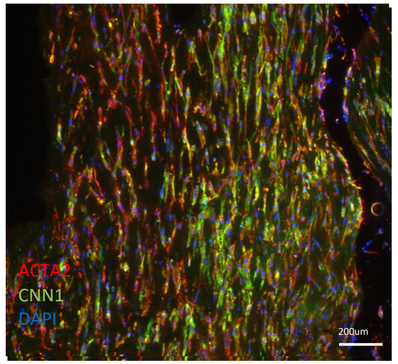
Measure patient specific metrics

Multiscale, multiphysics pregnancy simulation

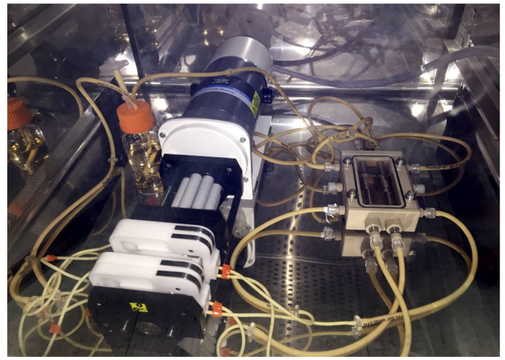
Make devices to diagnose and treat



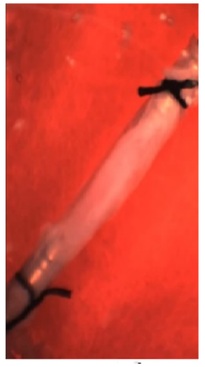
iPSC-derived SMC (iSMC)



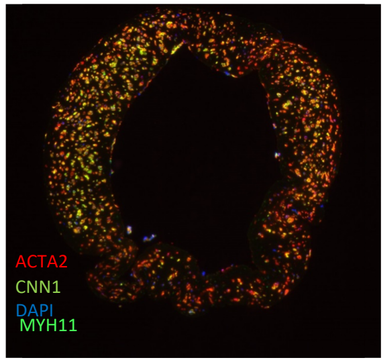
iSMC layers formed in dense collagen gel

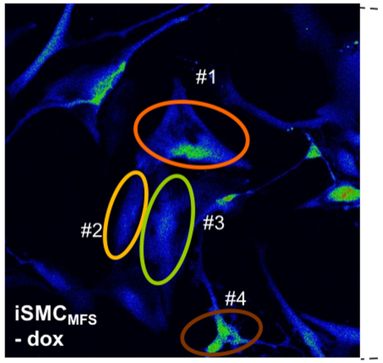


Maturation of iSMC layers in perfusion bioreactor



Formulation of tubular SMC tissue





Calcium transient activity

Drug Treatment

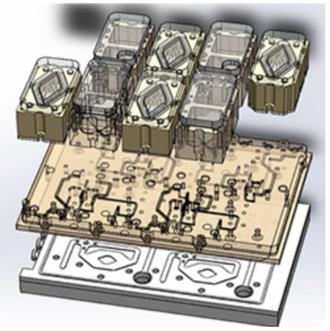
Contractility analysis (strips and rings): frequency, amplitude, dose-response
Tissue analysis: proteomics, protein phosphorylation, cytokine profile, RNAseq

Near-Term

Understand the molecular mechanisms that trigger the onset of labor
Develop effective drug treatment strategies to prevent preterm birth

Long-Term

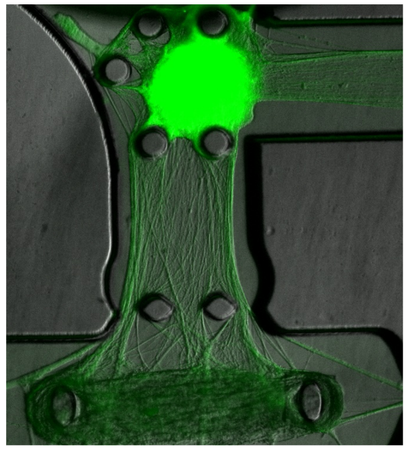
Biomimetic female reproductive system:
Study linkage between genetic factors and preterm birth (e.g. *EBF1, EEFSEC and AGTR2)*

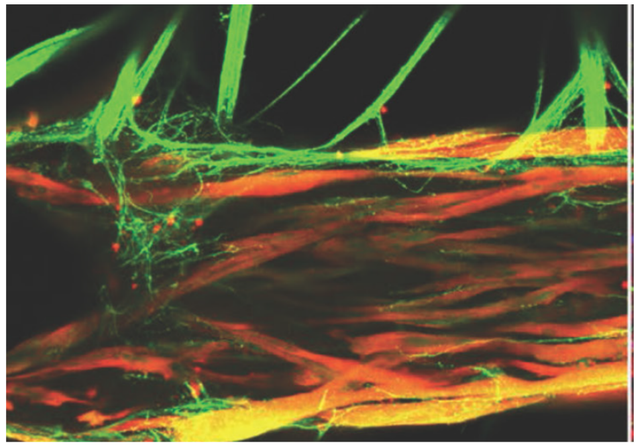


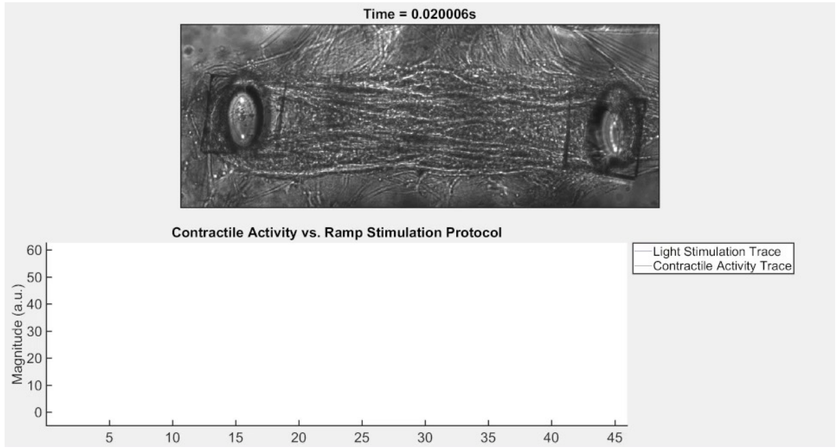
Female reproductive system on-a-chip (NCATS)

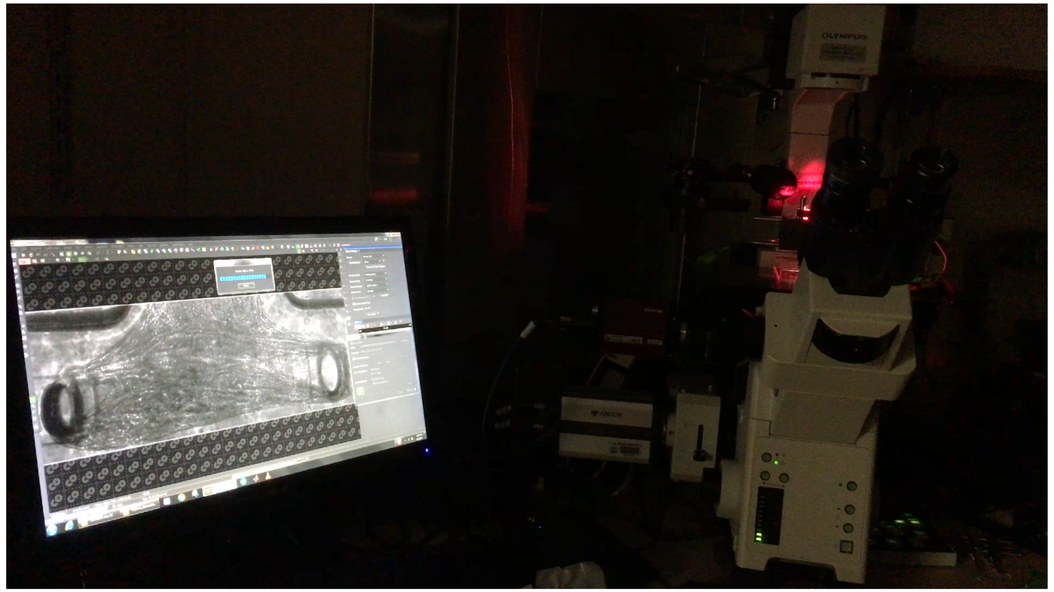
Stem Cell Rep (2016); *Sci Rep* (2016); *Biomaterials* (2018); *Adv Biol* (2020)

Innervated Uterus Tissue-on-a-chip









Neurons and Smooth Muscle from same starting cells

Optogenetically edited to become light sensitive to control contractions via laser light

Contractile behavior as a function of innervation, hormones, age, drugs

Near-Term

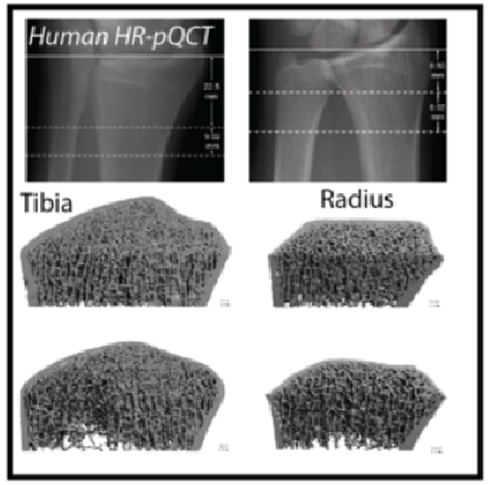
- Decouple effects of hormonal and mechanical factors driving onset of labor
- Demonstrate ability for drug testing

Long-Term

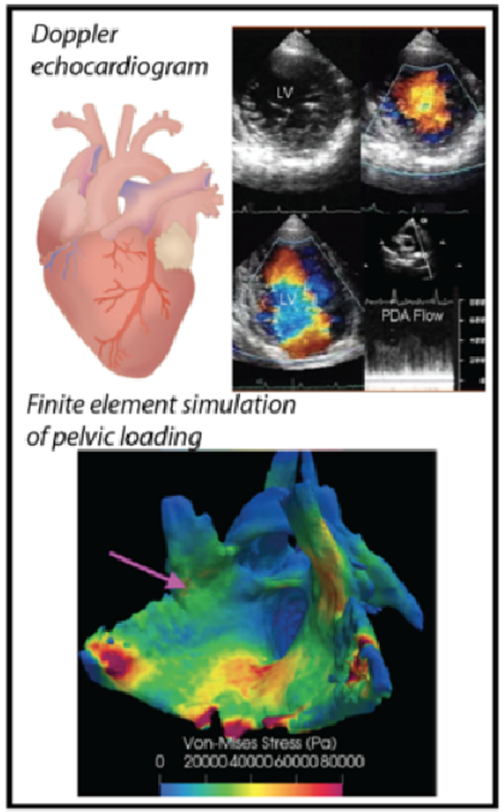
- Investigate the role of genetics & ancestry
- Therapies for controlling contractility
- Strategies for healthy aging (fibroids)

Vila et al, ***Theranostics*** *(2019);* ***Biomaterials*** *(2021); Liberman et al* ***JOVE*** *(2022)*

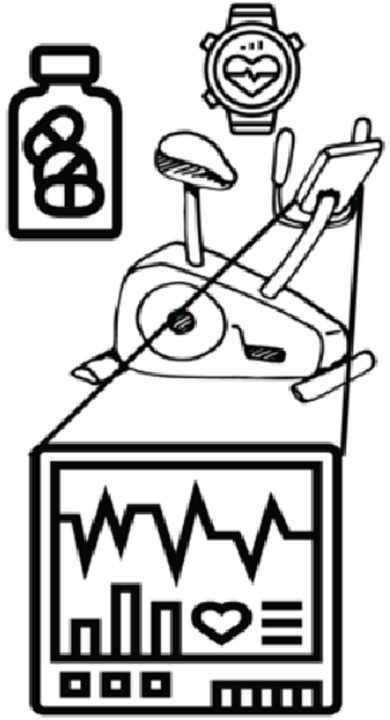
Healthy Aging



Measure pro-health mechanomics signature



Multiscale, multiphysics exercise and aging simulation



Example: Custom exercise regimen and supplements

Make devices to support healthy aging

Reproductive Tissues

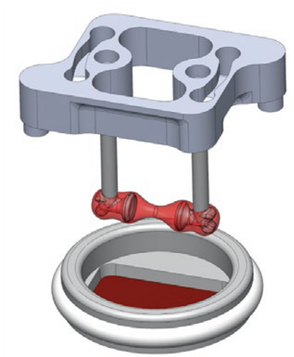
- Age-related changes – puberty, pregnancy, menopause
- Pelvic floor disorders manifest decades after injury
- Increase in the age of mother at 1st pregnancy

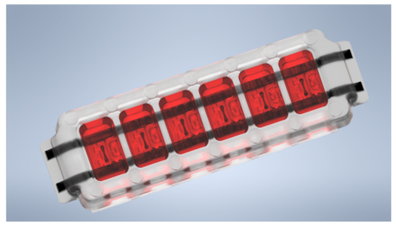
Key Challenge – how to support and ensure healthy aging

Enabling technology platforms

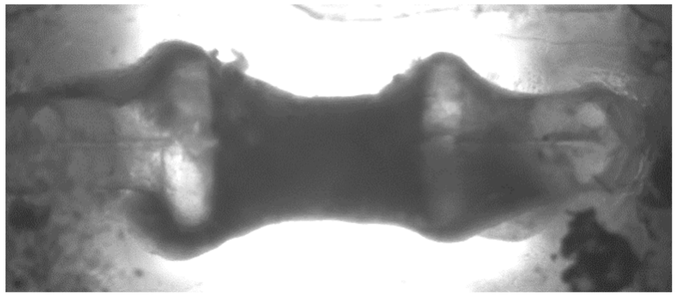
- Smooth muscle-on-a-chip
- Neuro-Muscular junction (NMJ)-on-a-chip
- Enthesis-on-a-chip
- **Cardiovascular organs-on-a-chip**

Heart Muscle Tissue-on-a-chip

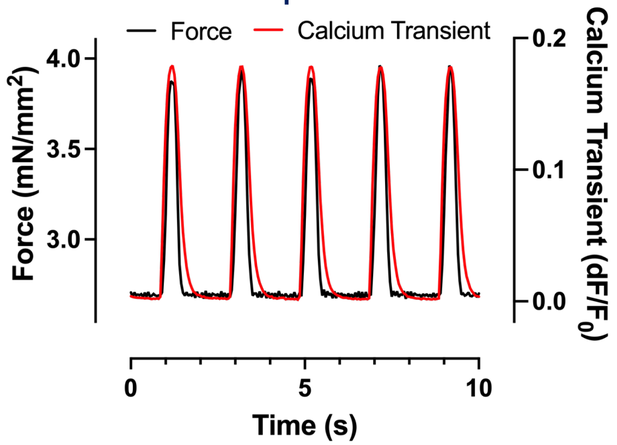


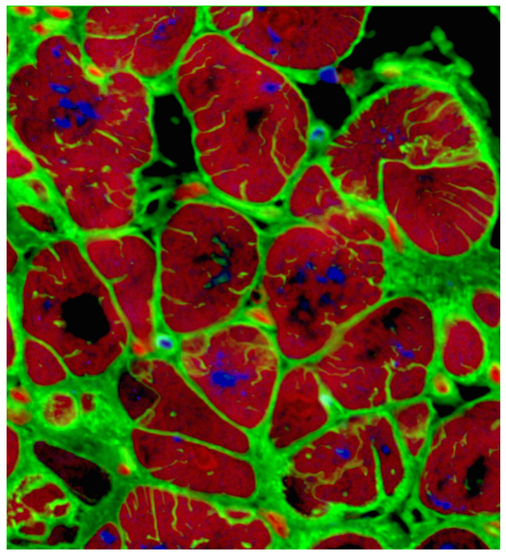


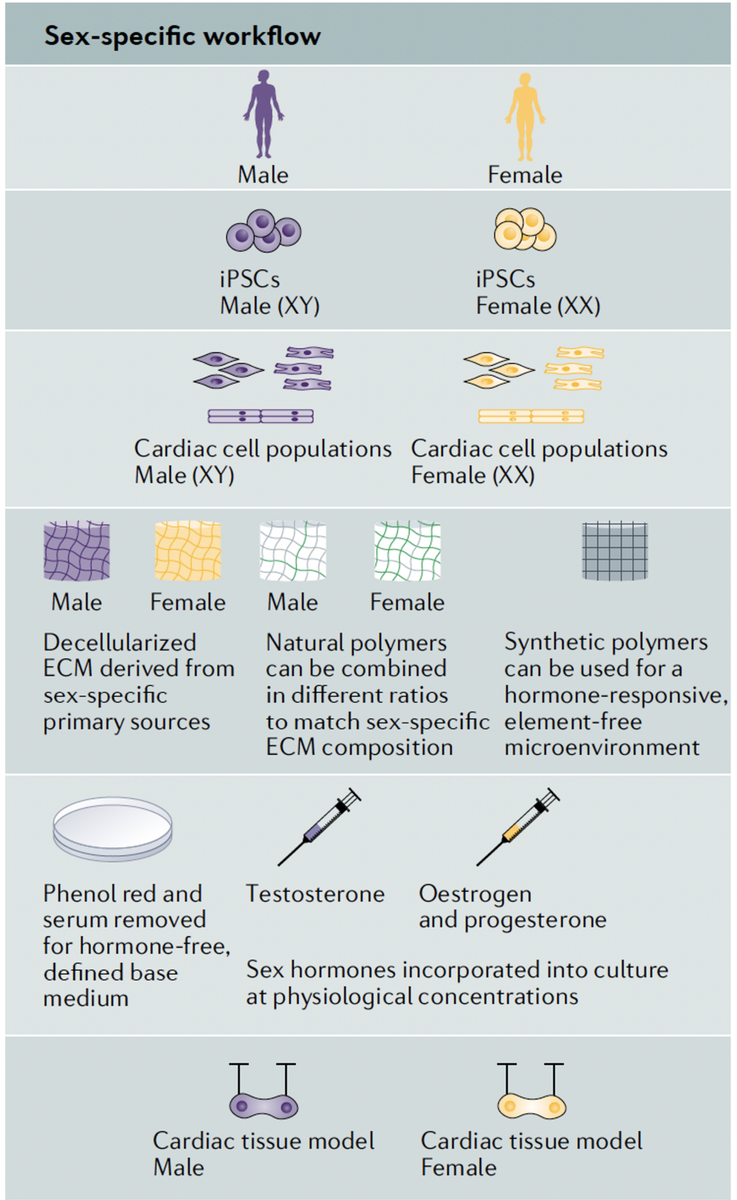
Vascularized heart muscle



Real-time force measurement via GCaMP reporter







Ronaldson-Bouchard et al, ***Nature*** *(2018), Lock et al* ***Nature Reviews Materials*** *(2021)*

Mechano-organ Testbed Goals

YEARS 1–2

Incorporate identified human organ-tissue-cell benchmarks, structural and ultrastructural properties

Build out *ex vivo* tissue model systems uterus, cervix, placenta, and supportive tissues of the pelvic floor to design and

Develop bioreactors, high-throughput ex vivo culturing systems.

SUMMARY

- Biomimetic Mechano-tissue Platforms
- High Investigative and Therapeutic potential
- Discover and Translate Mechanobiology Insights
- Bridge for Women Centered Device Design
- Treat Preterm Birth and Pelvic Floor Disorders
- Improve Women’s Health & Enable Healthy Aging