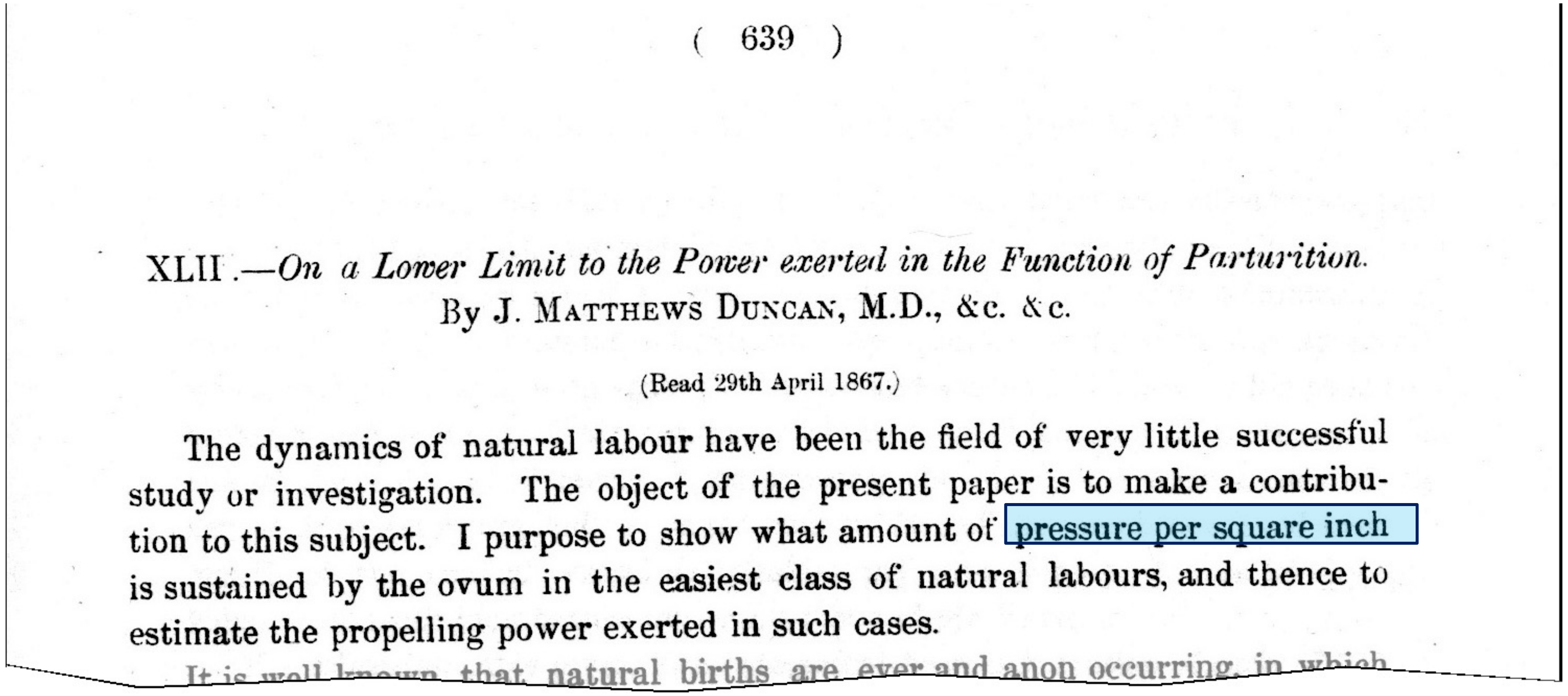
IMWEL Research Thrusts

Michelle L. Oyen, Washington University in St. Louis

IMWEL Research Focus: Physical Forces in Women's Health

Duncan JM, Trans. Roy. Soc. Edinburgh 24 (1867) 639.

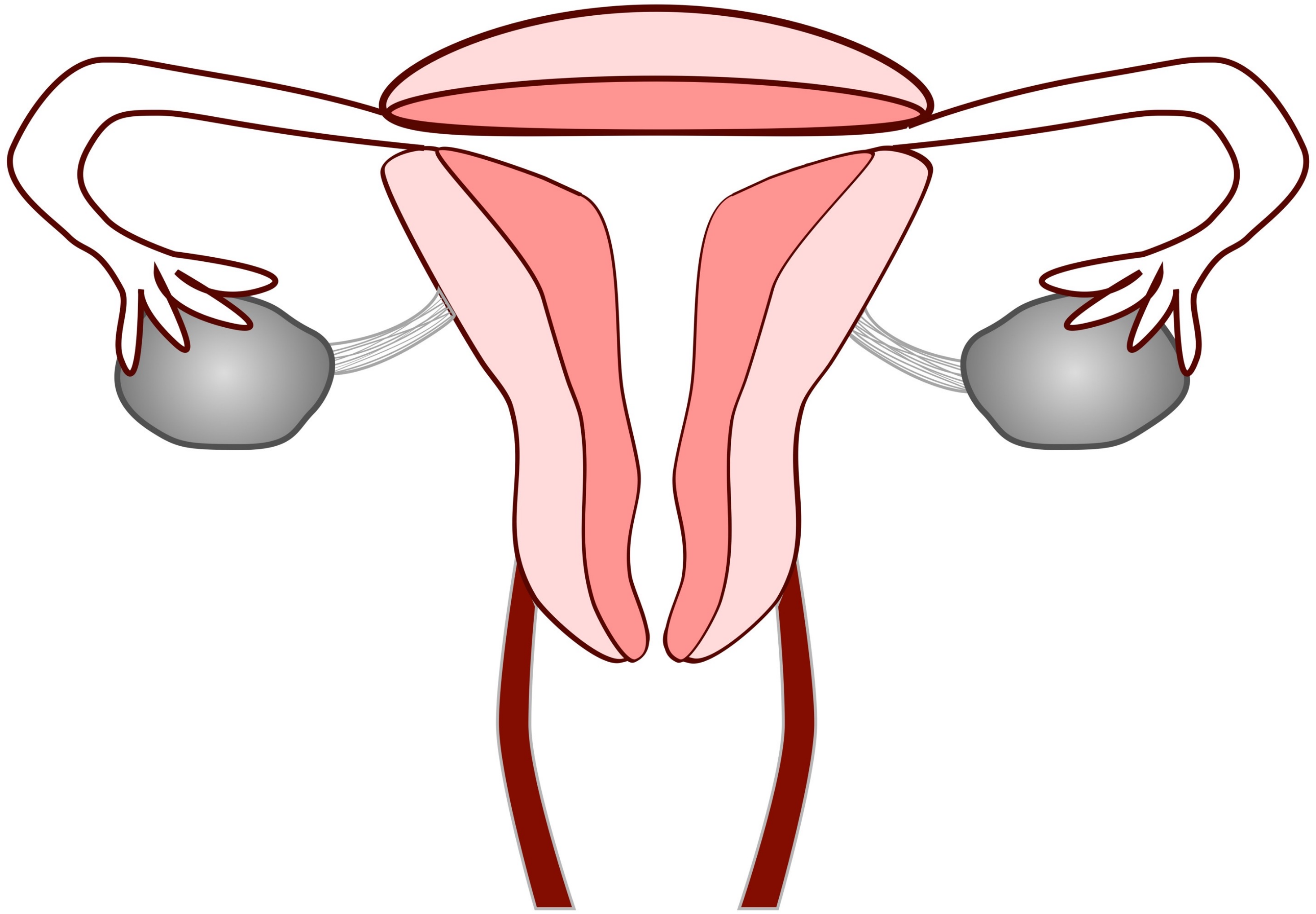

(639)

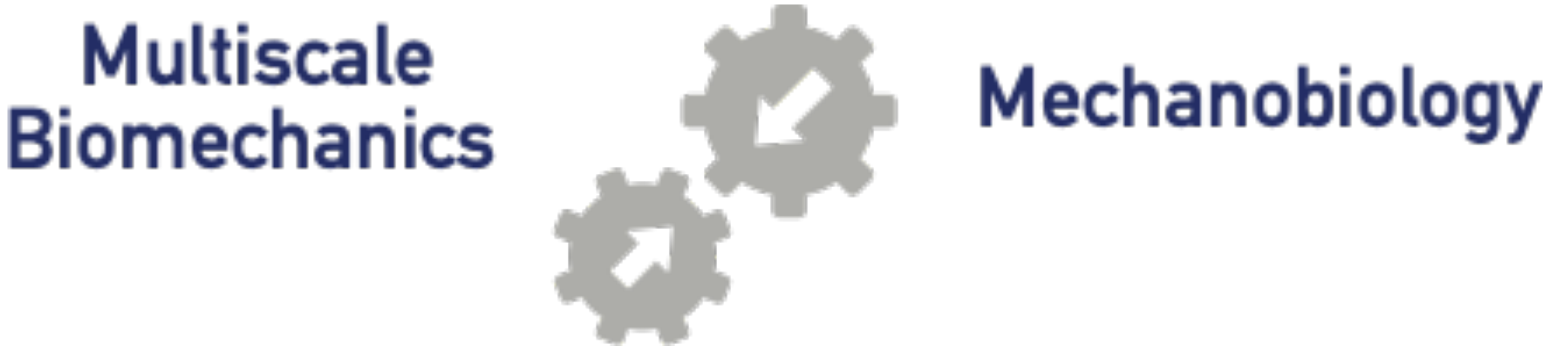
XLII.—*On a Lower Limit to the Power exerted in the Function of Parturition.* By J. MATTHEWS DUNCAN, M.D., &c. &c.

(Read 29th April 1867.)

The dynamics of natural labour have been the field of very little successful study or investigation. The object of the present paper is to make a contribution to this subject. I purpose to show what amount of pressure per square inch is sustained by the ovum in the easiest class of natural labours, and thence to estimate the propelling power exerted in such cases.

It is well known that natural births are ever and anon occurring, in which



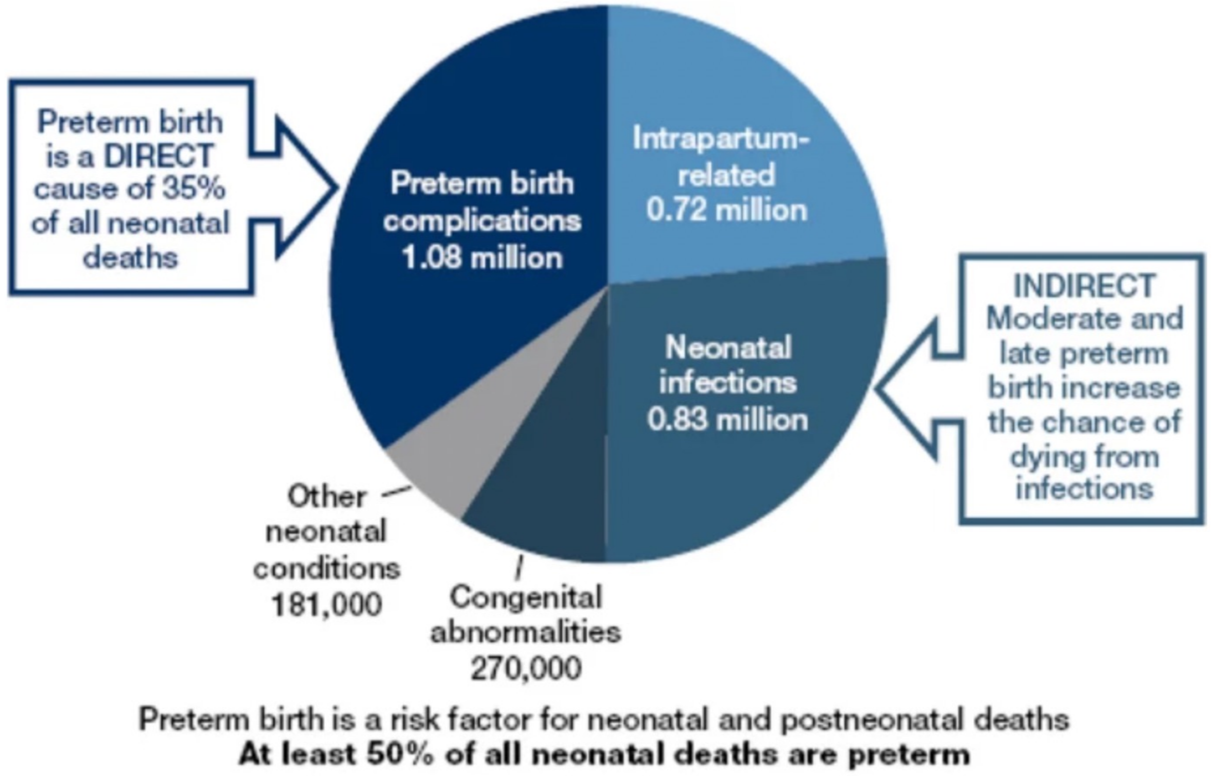


Preterm Birth affects 10% of Pregnancies and is associated with both Fetal and Maternal Mortality

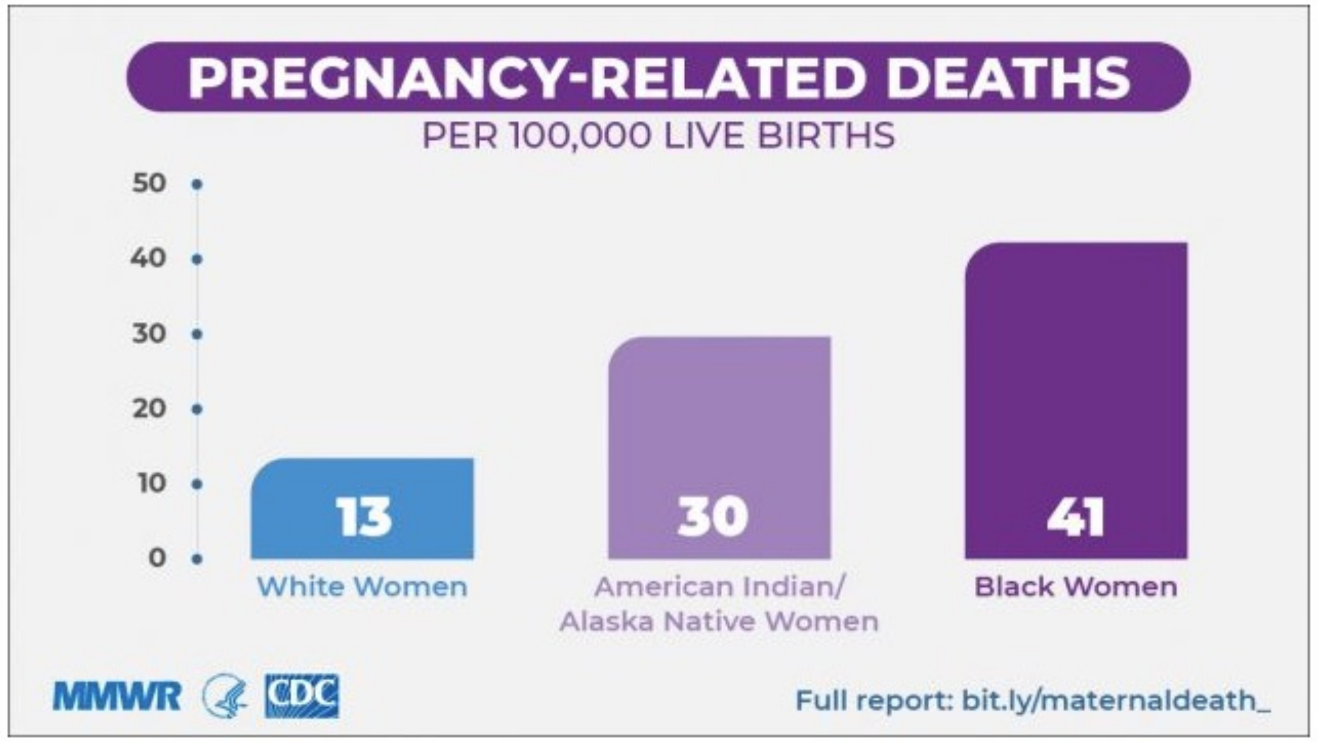
march of dimes

Fetal Mortality: 35% of neonatal deaths due to preterm birth

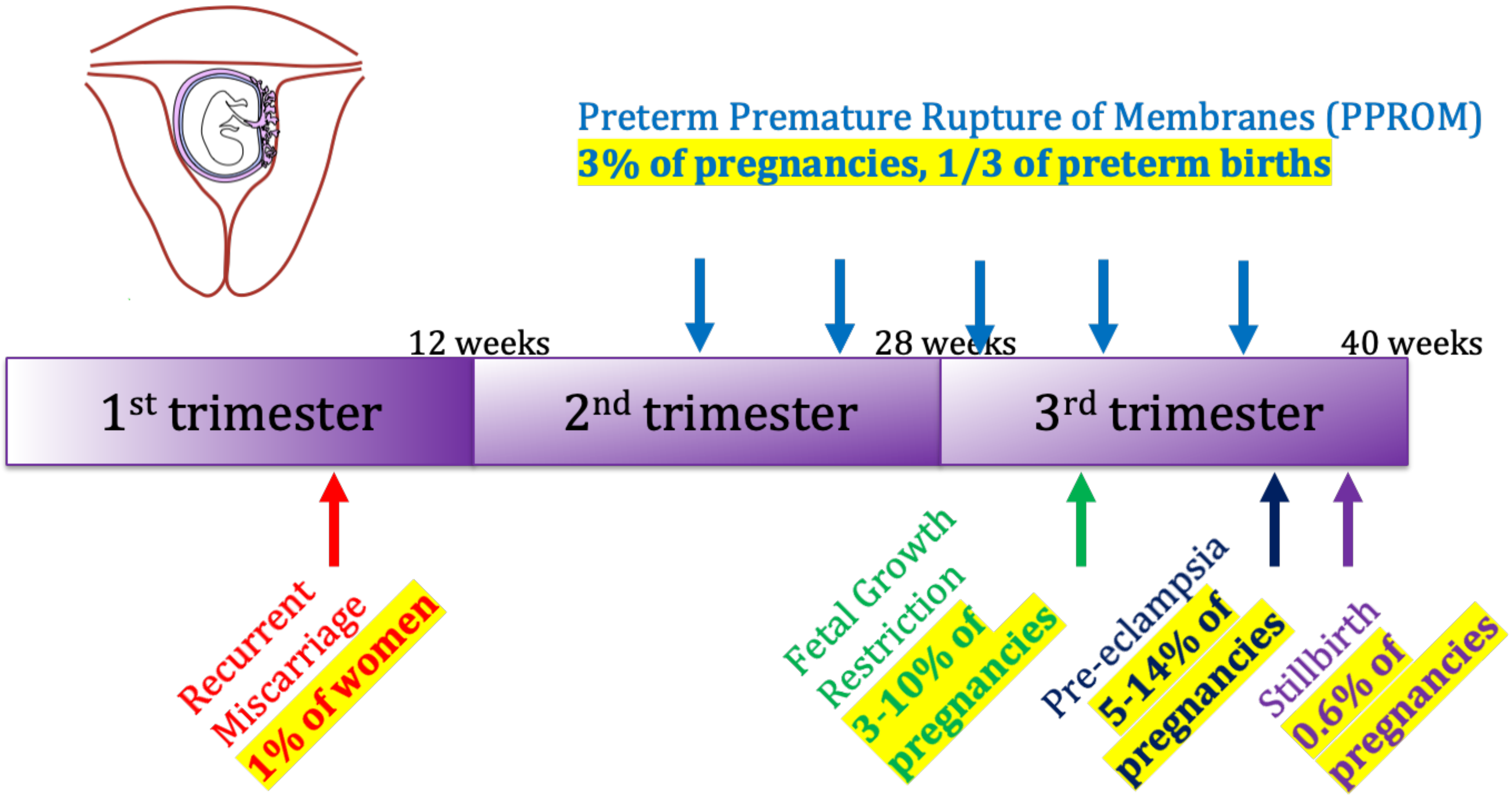
Maternal Mortality: 3x higher in black women



Estimated distribution of causes of 3.1 million neonatal deaths in 193 countries in 2010.
Source: Updated from Lawn et al., 2005, using data from 2010 published in Liu L, et al., 2012.



Pregnancy Complications Can Occur Throughout Gestation and for Different Reasons



A ☰ Popular Latest *The Atlantic* My Account

HEALTH

When a Placenta Tries to Kill a Mother

How C-sections increase the risk of a rare and devastating disorder

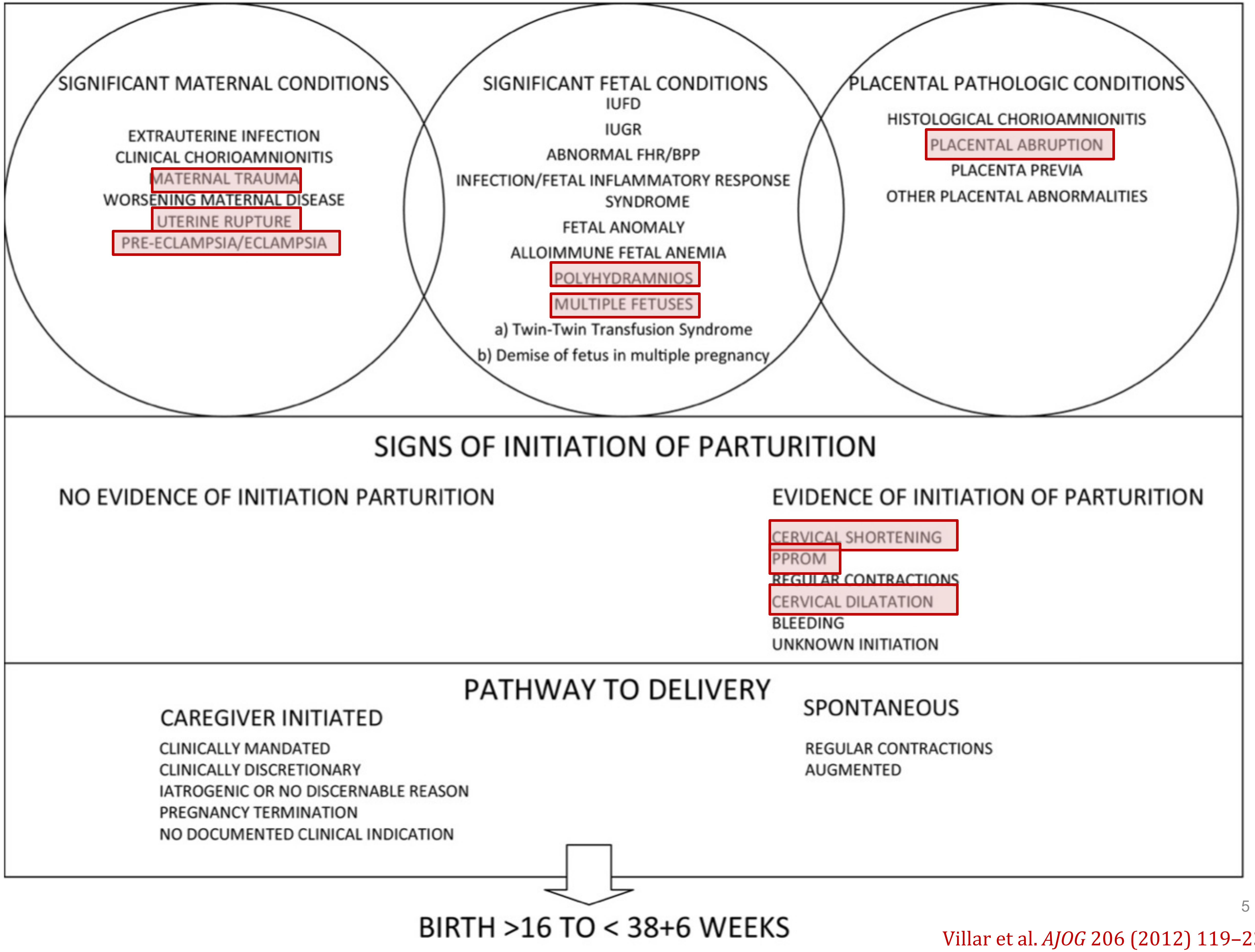
By Chavi Eve Karkowsky

Preterm birth is due to:
- Maternal factors
- Fetal factors
- Placental factors
- Birth factors

Preterm Birth with an apparent mechanical factor:

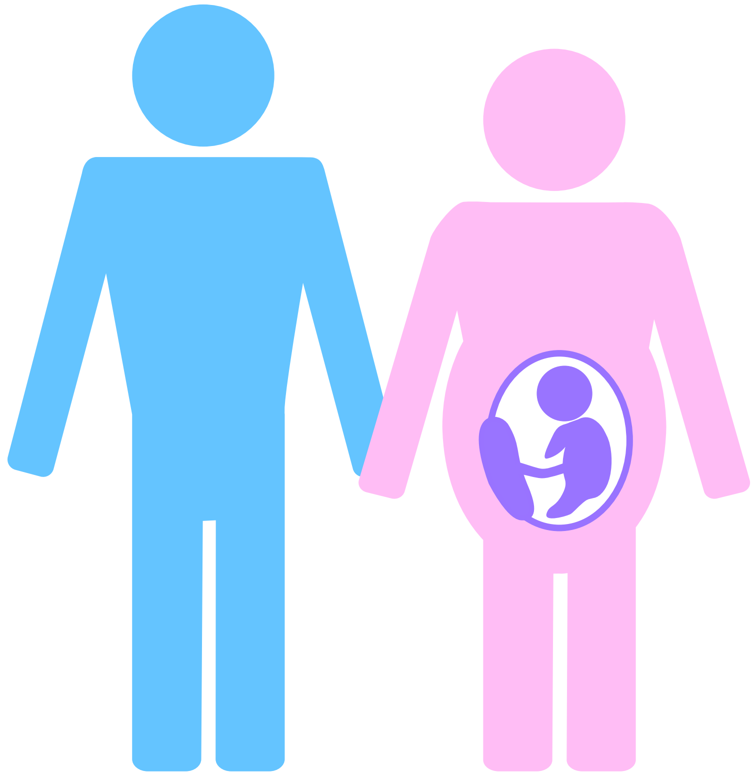
- Maternal trauma
- Uterine Rupture
- Pre-eclampsia
- Polyhydramnios
- Multiple fetuses
- Placental abruption
- Cervical shortening
- PPROM
- Cervical dilatation

FIGURE
Phenotypic components of the preterm birth syndrome



Villar et al. *AJOG* 206 (2012) 119–23.

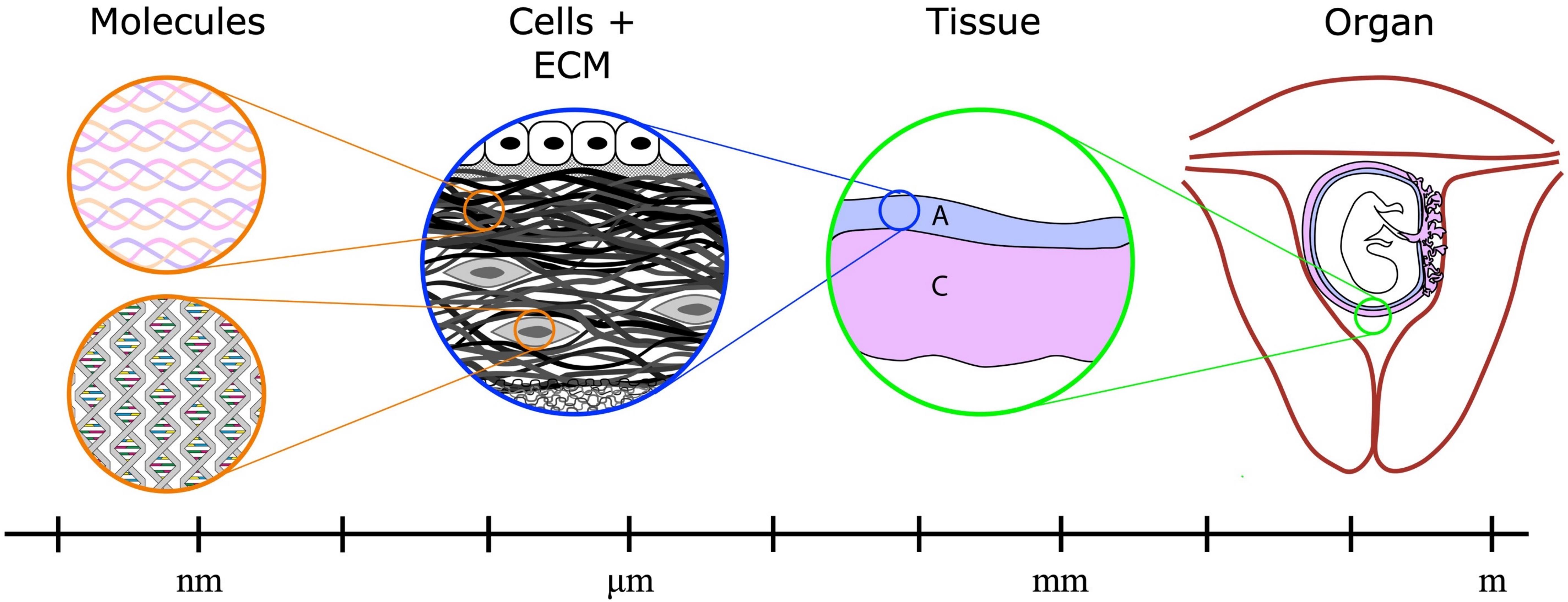
IMWEL's Challenging Research Questions Require New Engineering Approaches



- Three distinct genetic entities in one pregnancy
- Ethically challenged or impossible to perform research studies on pregnant women
- Deep integration needed across engineering, basic biological sciences, physiology, social science, and clinical medicine
- Diagnosis ←→ Prevention ←→ Intervention

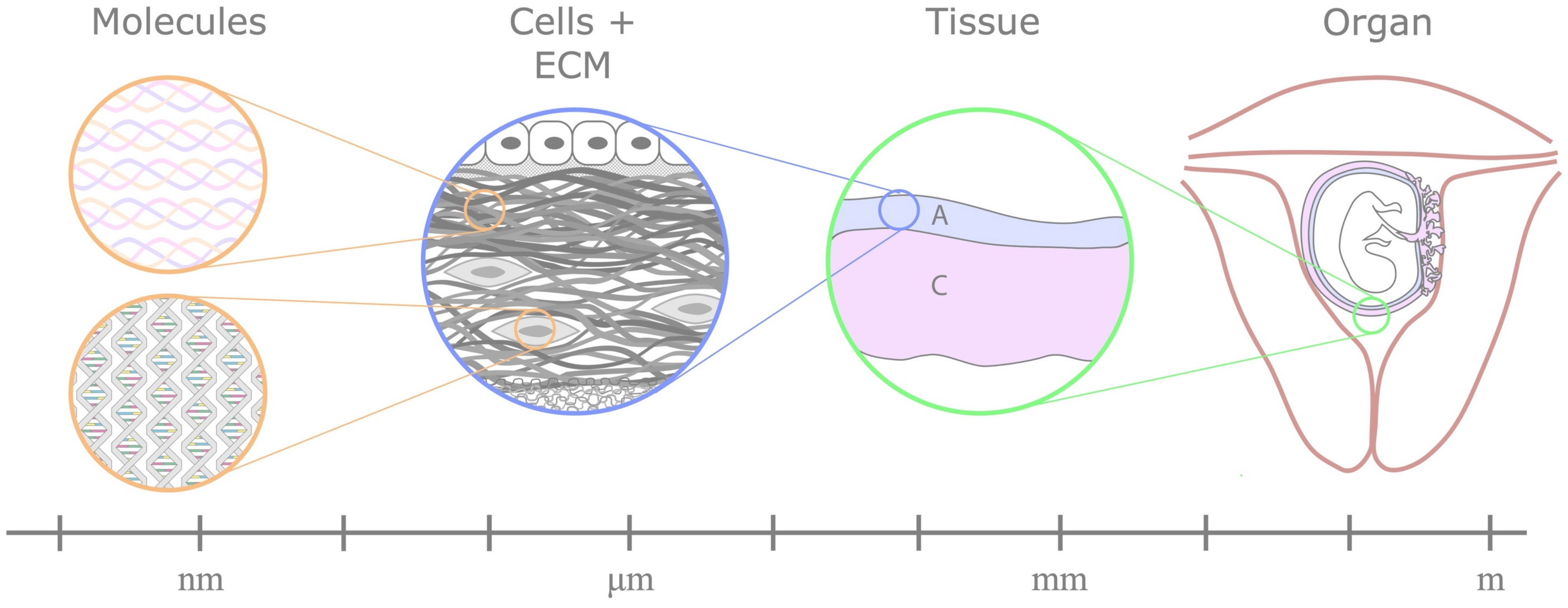
IMWEL Research Paradigm

- Women's health research has significant challenges spanning an extremely large range of length-scales



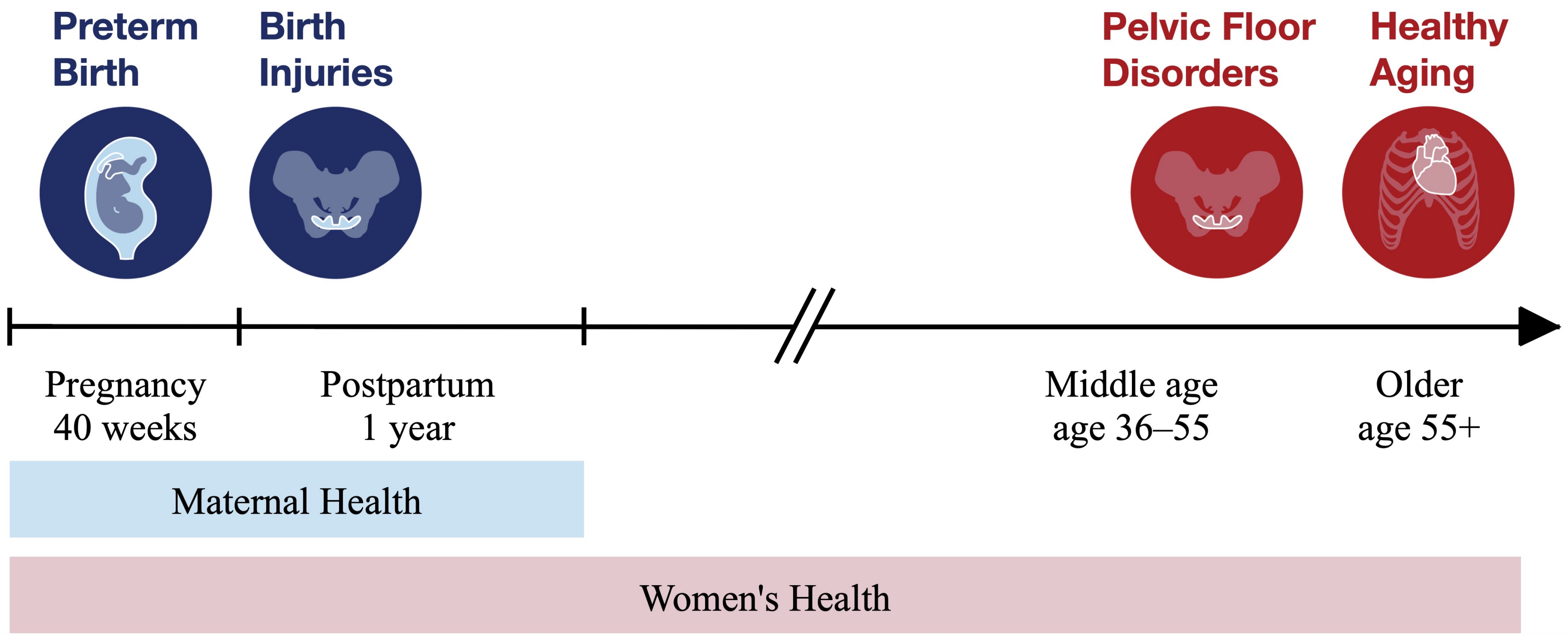
IMWEL Research Paradigm

- Women’s health research has significant challenges spanning an extremely large range of length-scales and time-scales



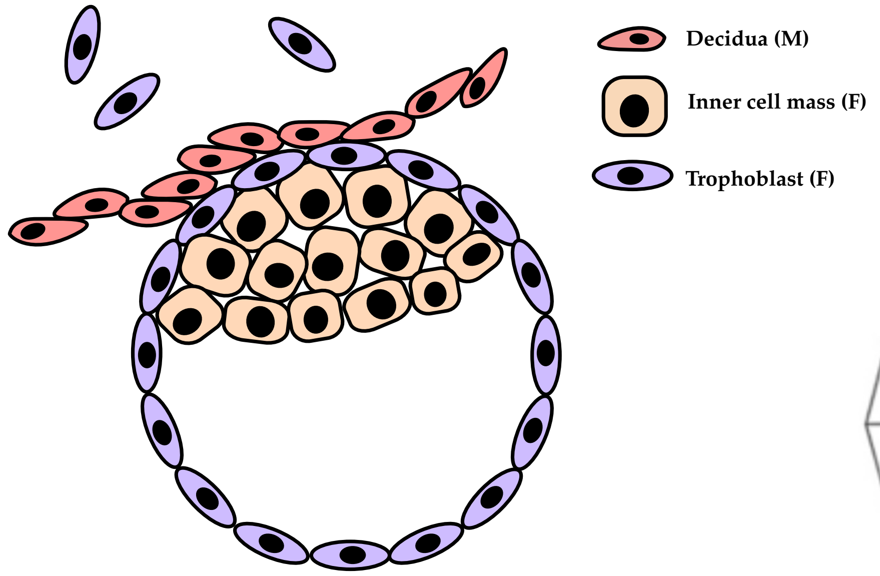
Maternal Health:
During pregnancy and up to one year postpartum

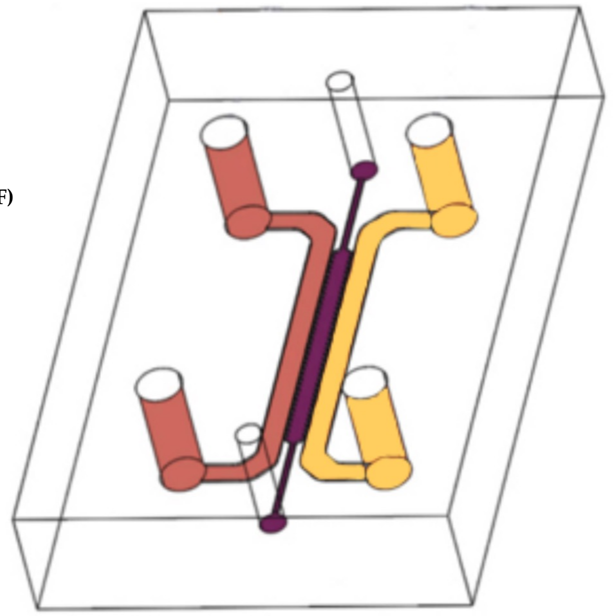
Women’s Health:
Includes long-term sequelae of pregnancy and birth



IMWEL Research Paradigm

- Women's health research presents unique opportunities to engineer new *in vitro* and *in silico* approaches

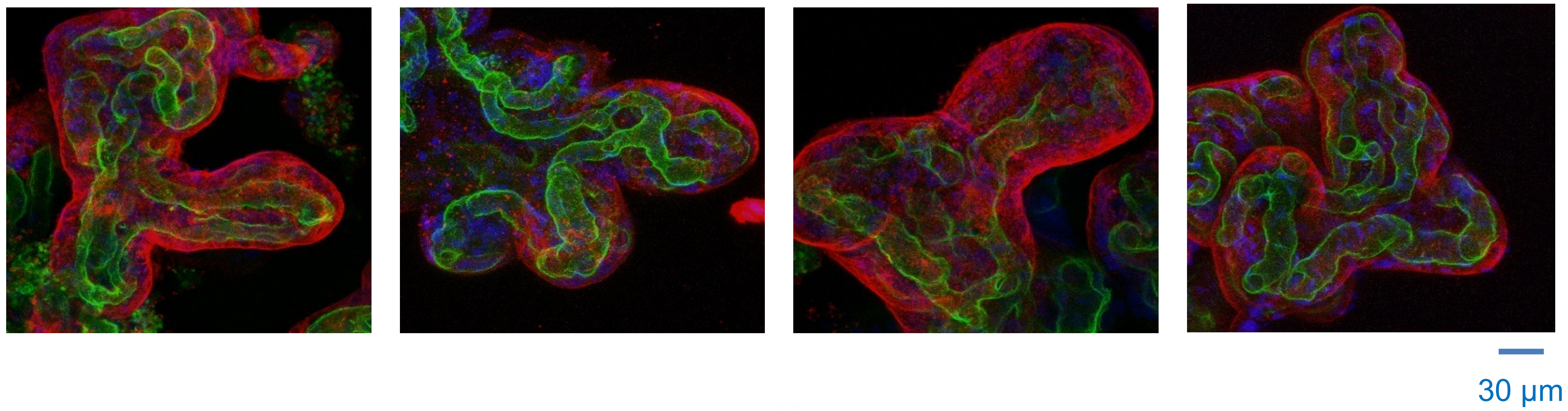


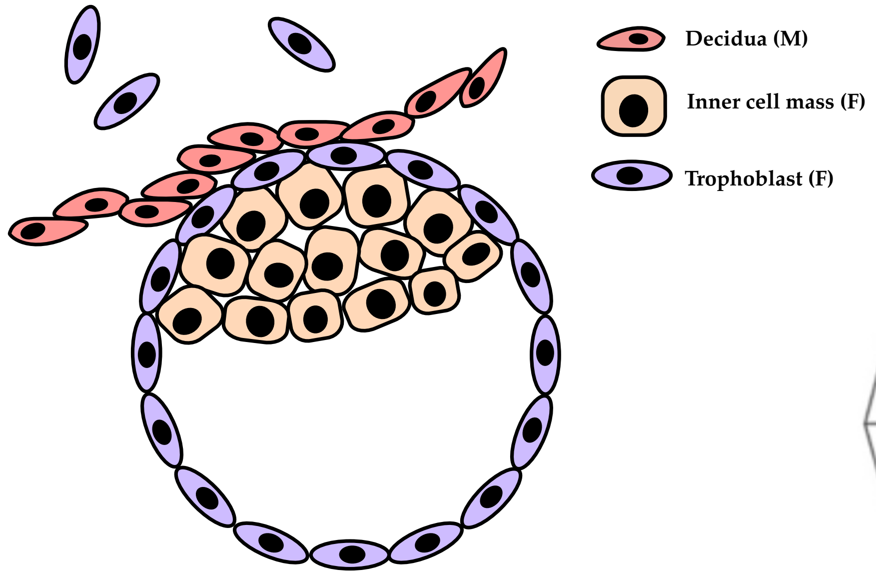


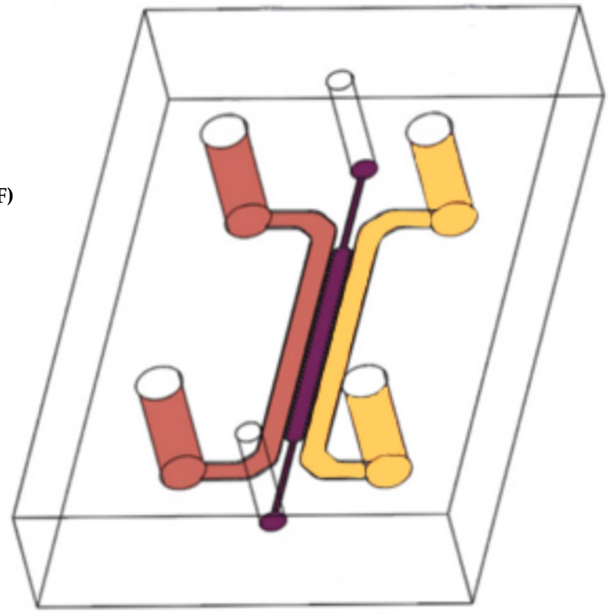
IMWEL Research Paradigm

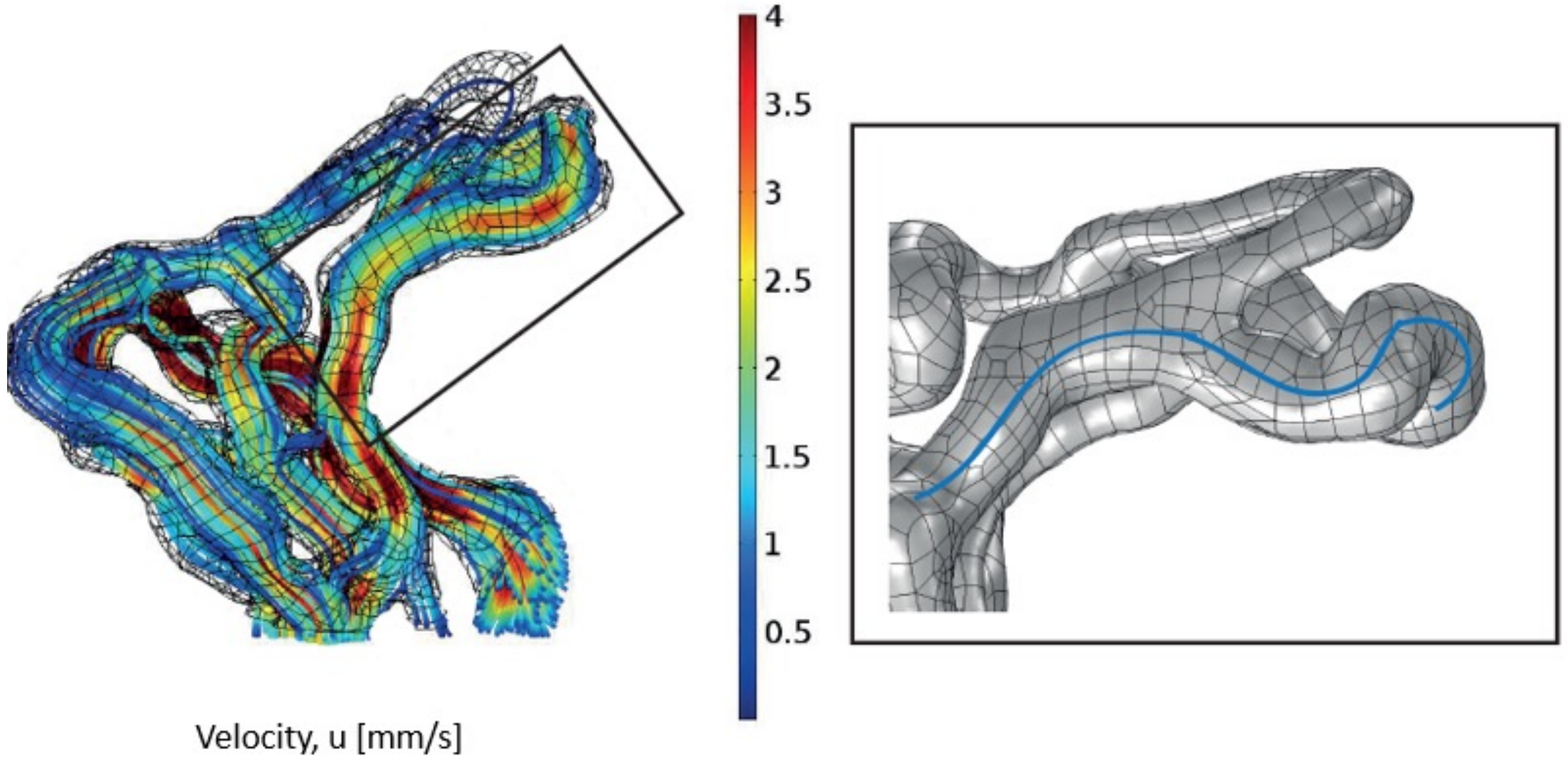
- Women's health research presents unique opportunities to engineer new *in vitro* and *in silico* approaches

Placenta:

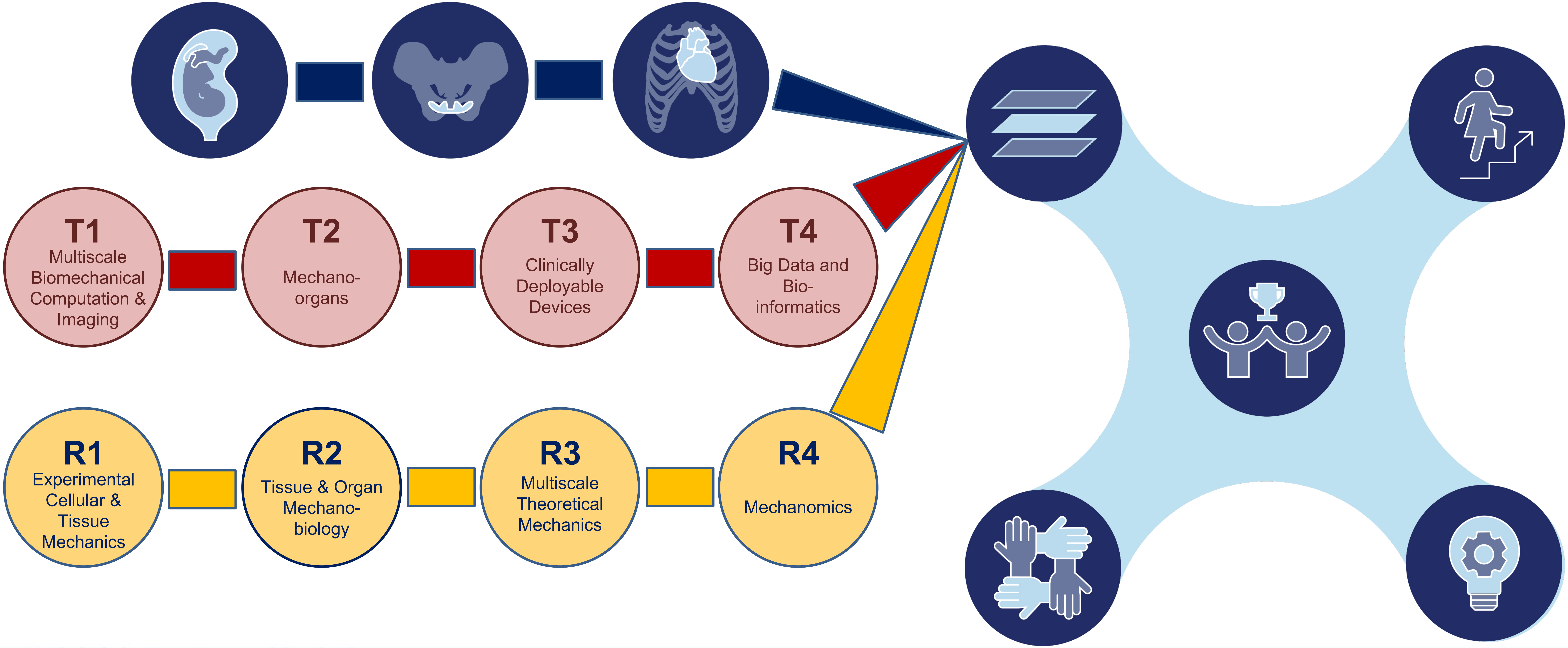




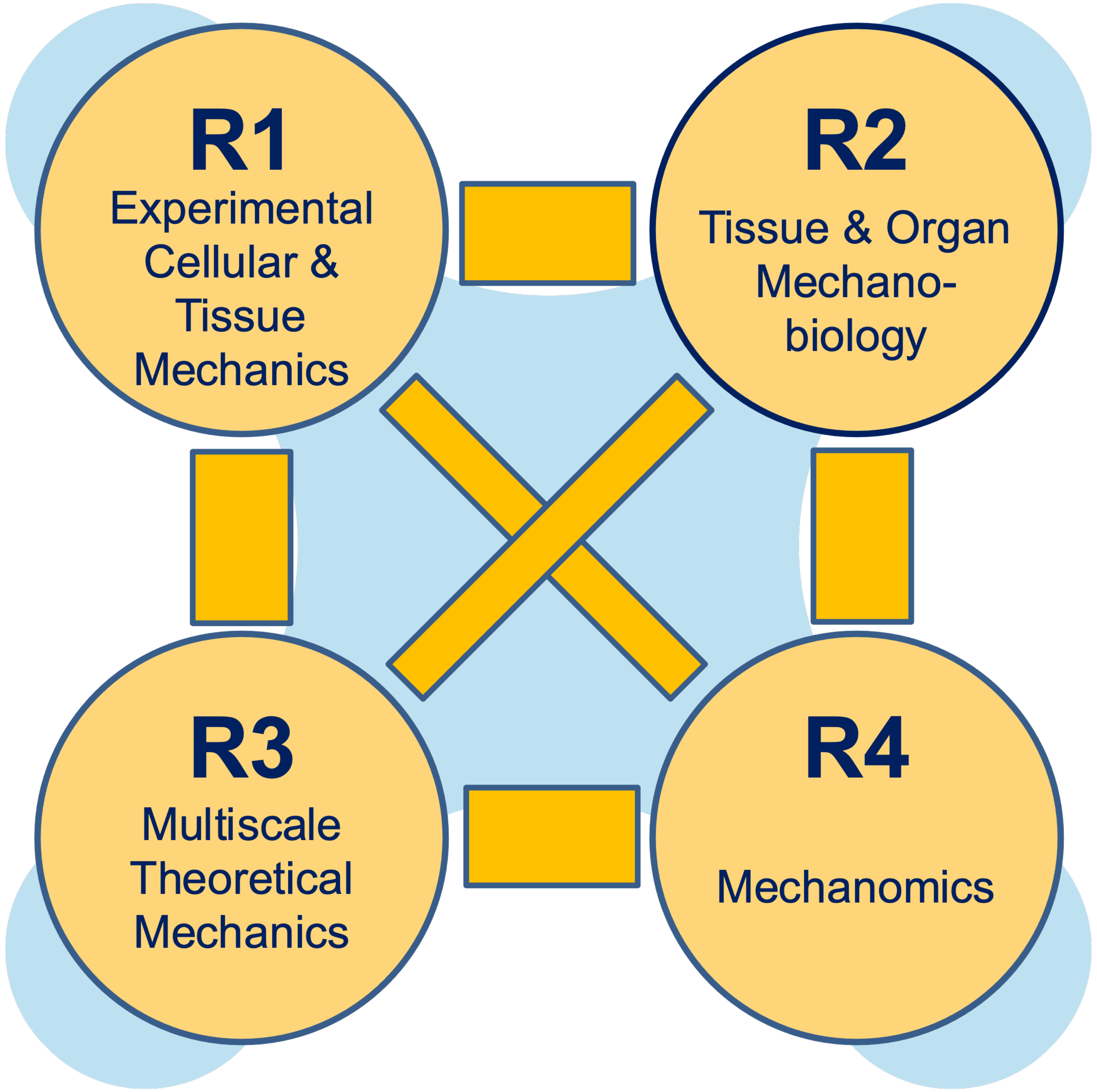




IMWEL Research Integration



IMWEL Research Approach: Measure–Model–Make



Measure

- Researchers will ***measure*** multiscale aspects of genetics and cell biology and tissue biomechanics;

Model

- They will construct *in silico* ***models*** of both normal and pathological conditions in all three Testbeds;

Make

- Researchers and companies will ***make*** new devices to deploy for use in both research and clinical treatment, improving the lives of half the world's population and future children

Experimental Cellular and Tissue Mechanics (R1) Multiscale Theoretical Modeling (R3)

Our Team Spans Disciplines & Schools

Michelle Oyen, WUSTL

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

Steven Abramowitch, Pitt

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

Philip Bayly, WUSTL

Mechanical Engineering, Biomedical Engineering, Cell and Tissue Biomechanics, Computational Modeling of Pelvic Floor

Timothy Downing, UCI

Biomedical Engineering, Tissue Engineering, Regenerative Biology, Mechanobiology

X. Edward Guo, CU

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

Christine Hendon, CU

Electrical Engineering, Imaging, Cardiac Electrophysiology

Elisa Konofagou, CU

Biomedical Engineering, Radiology, Ultrasound Imaging, Elasticity Imaging, Soft Tissue Biomechanics

Katrina Knight, Pitt

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

Spandan Maiti, Pitt

Biomedical Engineering, Mechanical Engineering & Materials Science, Computational Mechanics

Gerard Ateshian, CU

Mechanical Engineering, Biomedical Engineering, Soft Tissue Mechanics

Spencer Lake, WUSTL

Mechanical Engineering, Materials Science, Soft Tissue Mechanics

Wendy Liu, UCI

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

Jerry Lowder, WUSTL

OB/GYN, Pelvic Floor Clinical Intervention

Pamela Moalli, Pitt

OB/GYN, Bioengineering, Uryo/Gyn, Vaginal Mesh Expert, Female Pelvic Floor Health

Kristin Myers, CU

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

Yong Wang, WUSTL

OB/GYN, Radiology, Biomedical Engineering, Uterine Functional Imaging, Electrophysiology

Grand challenges

Measure

R1
Experimental Cellular & Tissue Mechanics

Model

R3
Multiscale Theoretical Mechanics

Properties of pregnancy related cells and tissues

Uterus and cervix
Fetal membrane and placenta
Trophoblast cell migration and invasion

Growth and remodeling

Properties of pelvic floor cells and tissues

Pelvic floor fascia, ligaments, muscles
Perineum

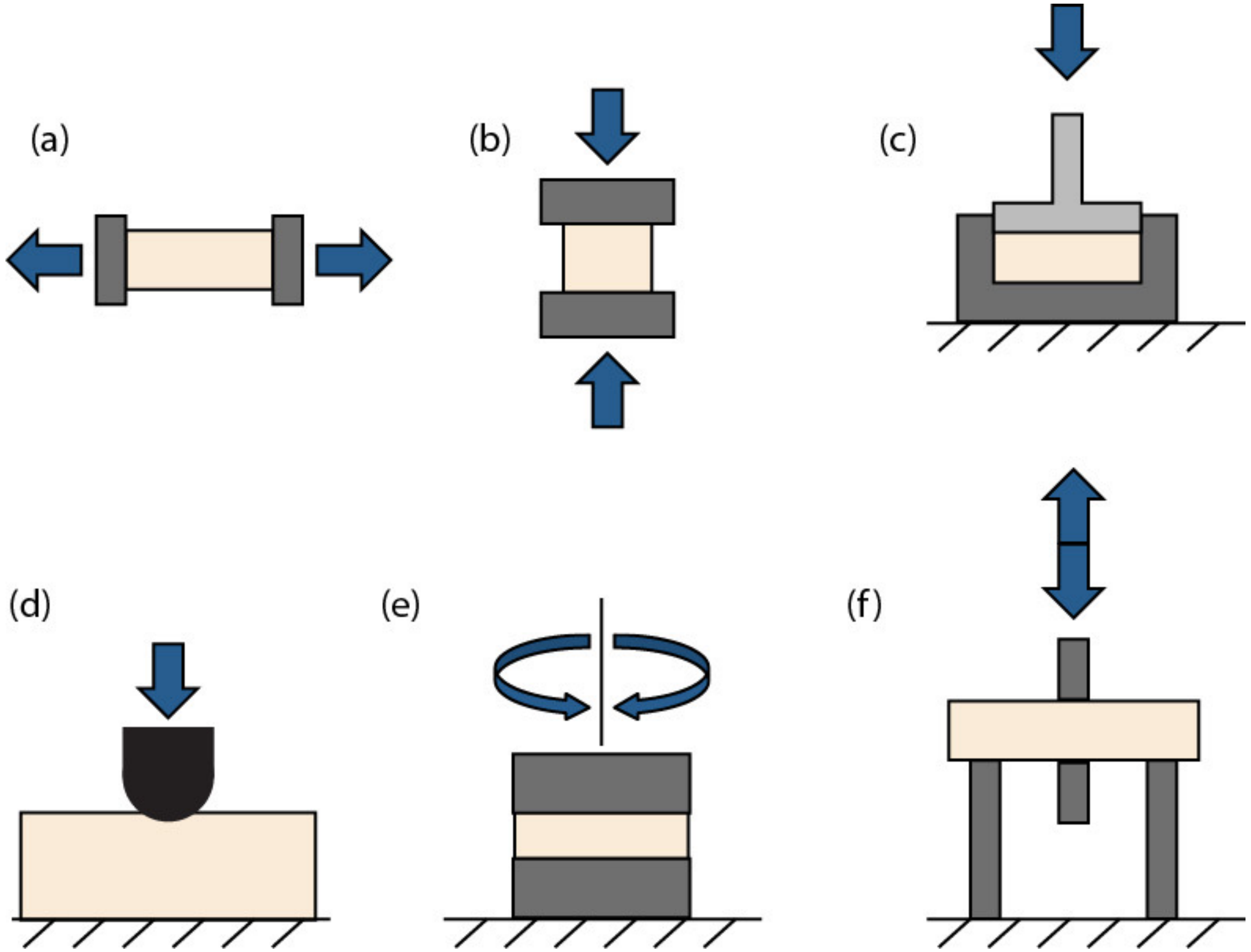
Tissue fracture behavior

Properties of tissues as a function of hormones

Cardiovascular and musculoskeletal tissues

Mechanomics

Experimental Tissue Testing Modalities



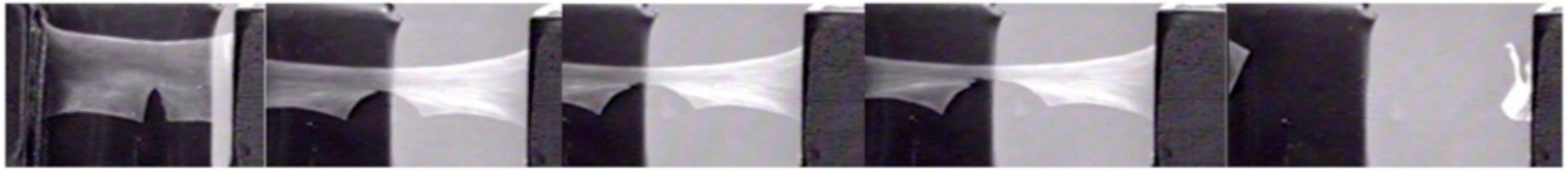
- Reproductive system tissues have been little-studied biomechanically

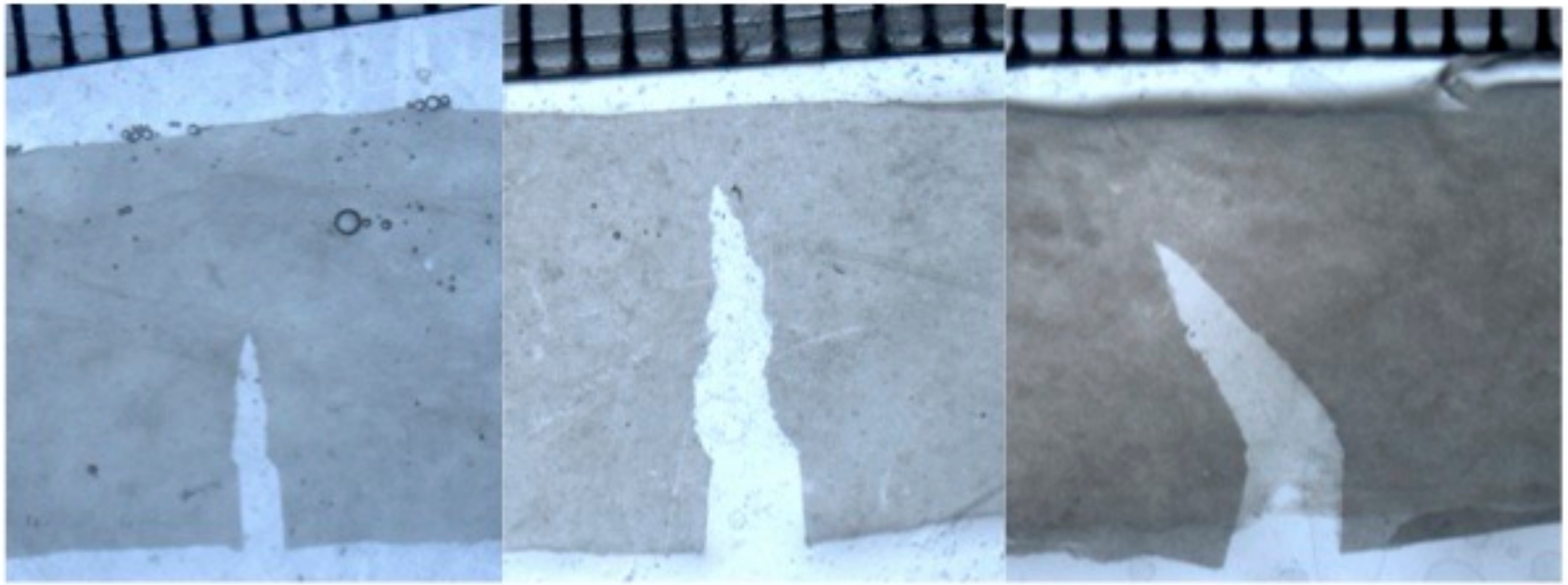
- Pelvic floor tissues have been little-studied biomechanically

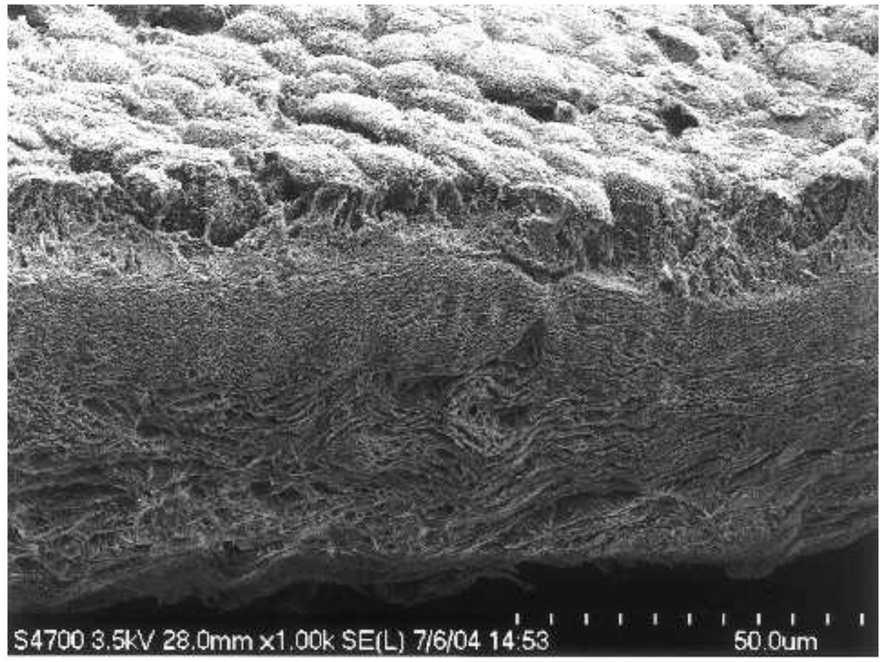
- Musculoskeletal and cardiovascular tissues that *have* been studied previously have not had sufficient attention paid to hormonal effects

Inter. Mater. Rev. 59 (2014) 44–59.

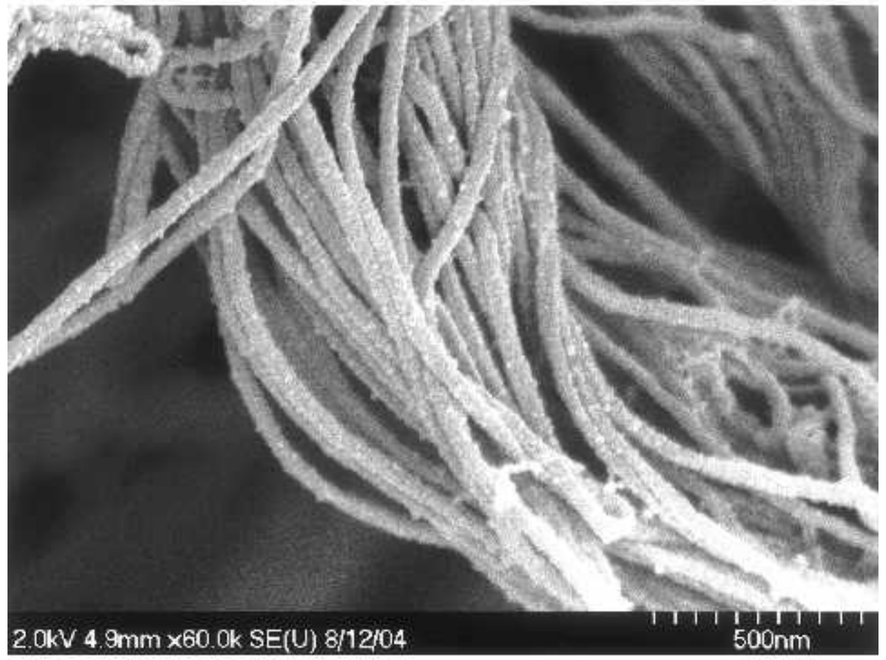
Advancing Engineering: Multiscale Fracture







(a)

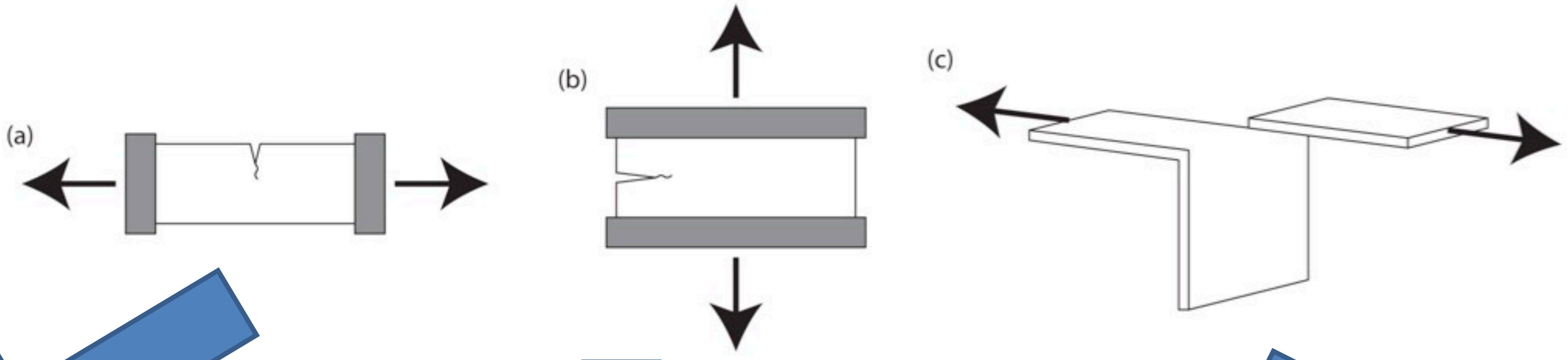


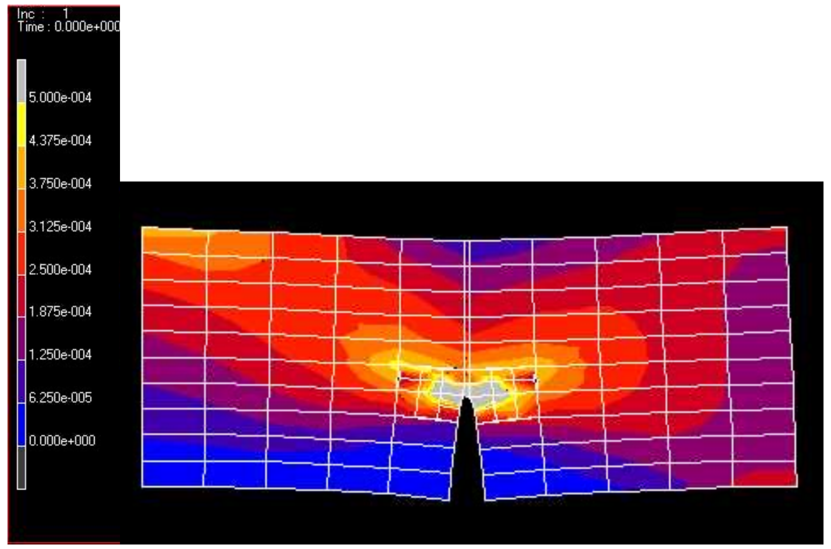
Fetal membrane rupture

Perineal tears

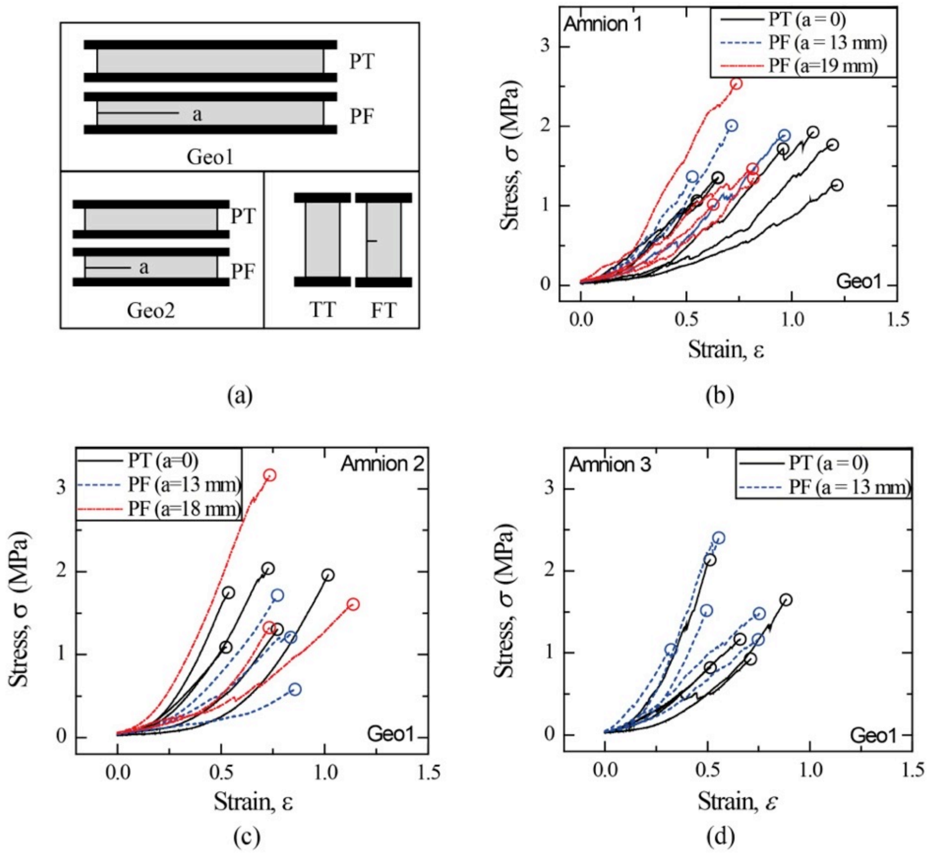
Advancing Engineering: Multiscale Fracture Tests

Crack opening "Pure shear" Trouser tear



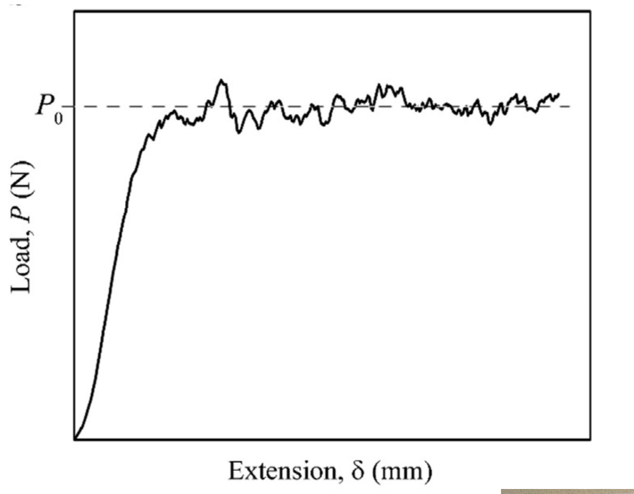


Strain at notch

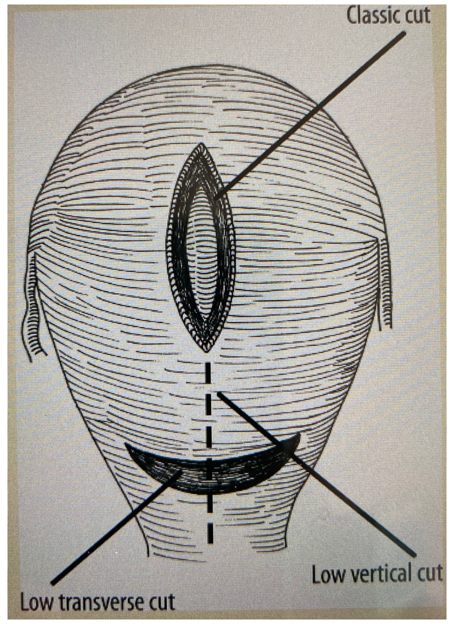


Amnion tissue
notch insensitivity

Rivlin and Thomas (1953):

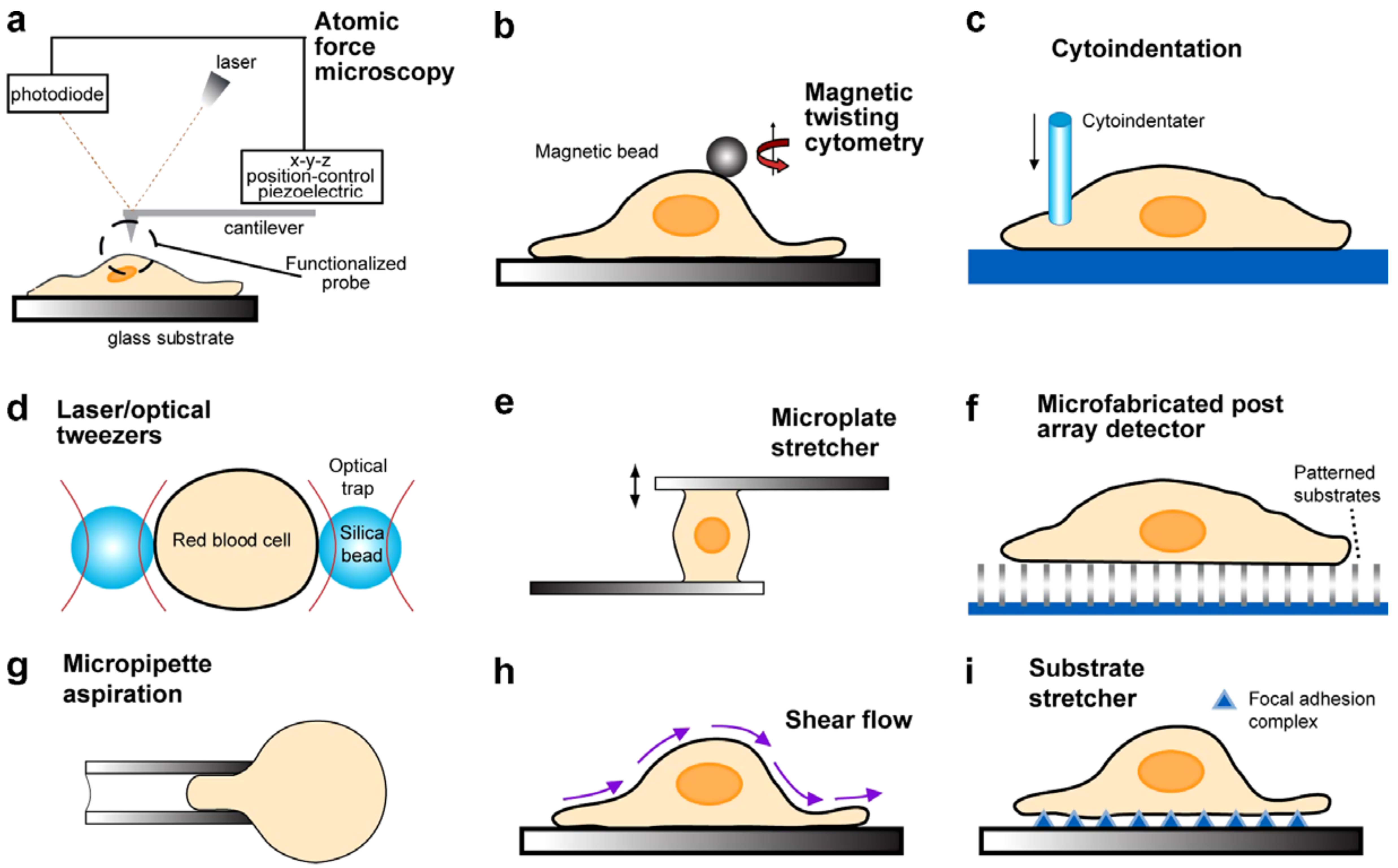


$T \sim 2P_0 / t$



Uterine rupture after C-section
depends on scar geometry

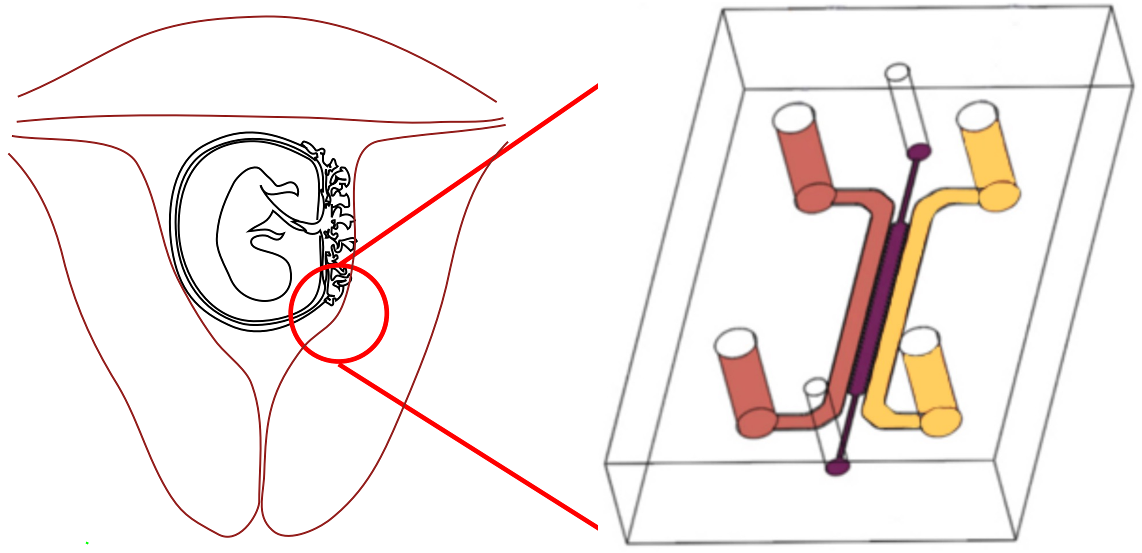
Experimental Cell Testing Modalities

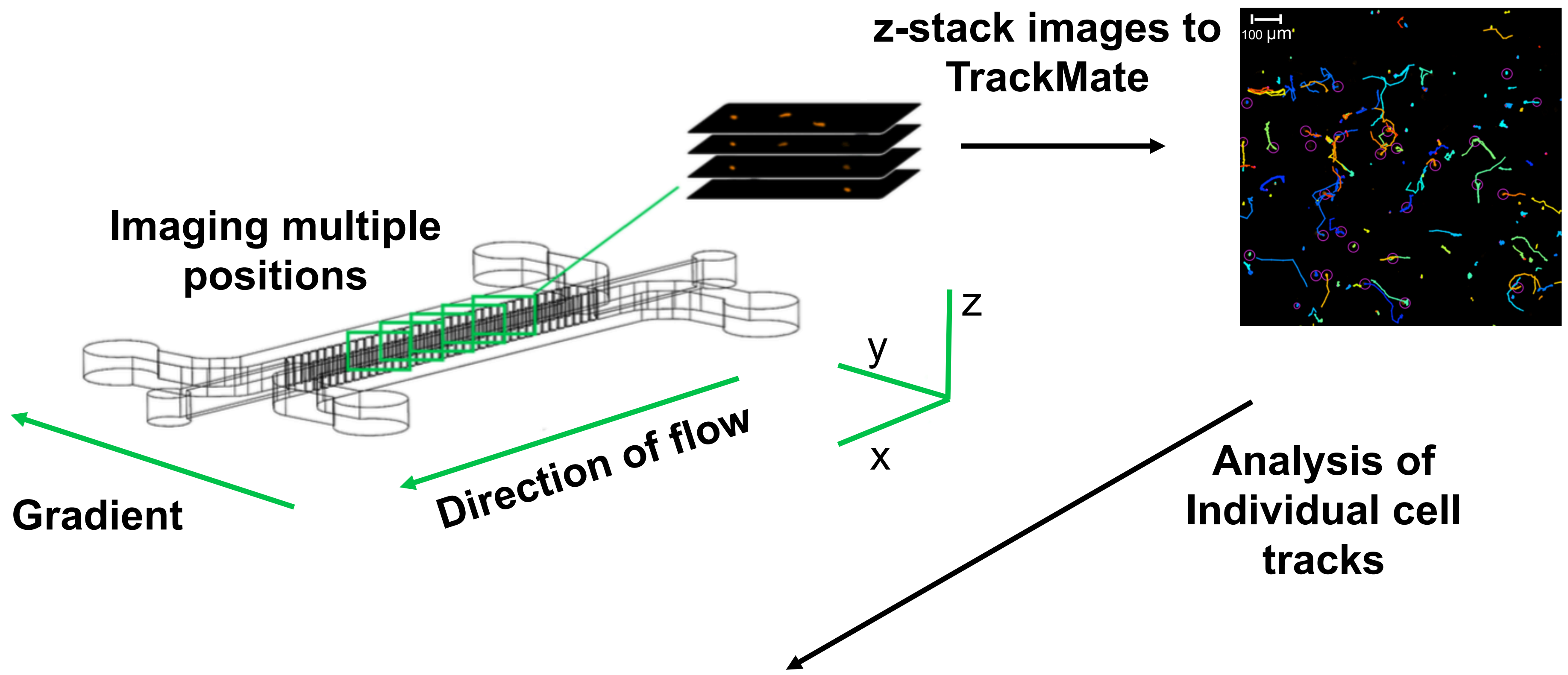


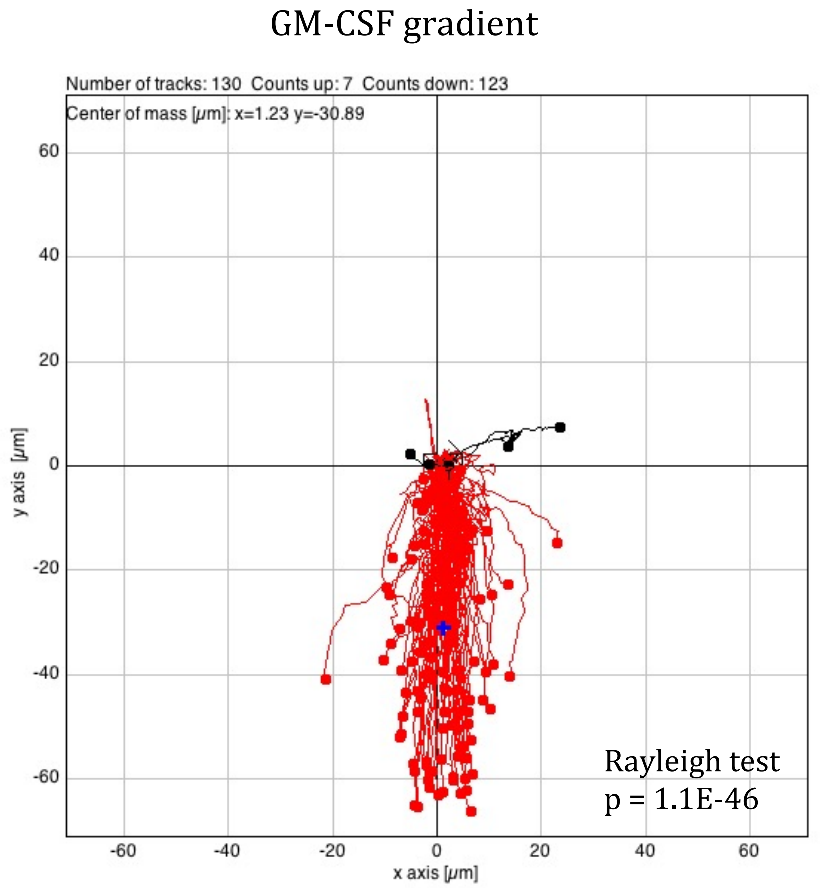
S. Suresh *Acta Biomat.* 3 (2007) 413-38.

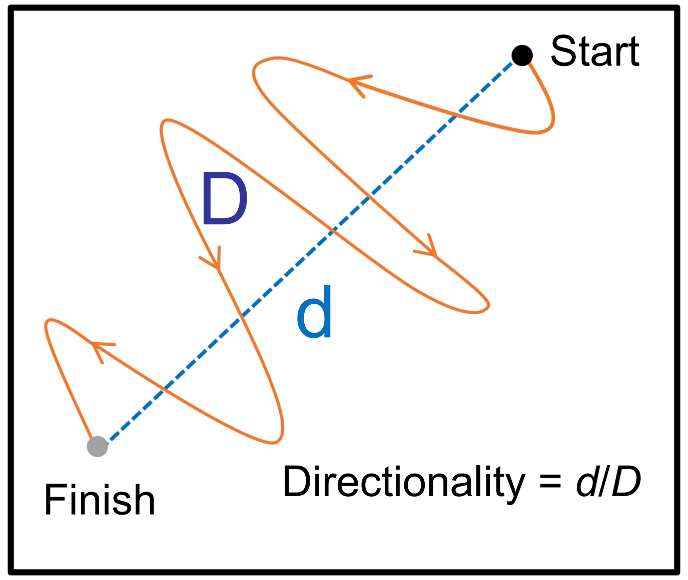
- Mechanotransduction
- Cell-matrix interactions
- Chemotaxis and durotaxis
- Cell growth and division
- Stretch-activated channels
- ’Omics

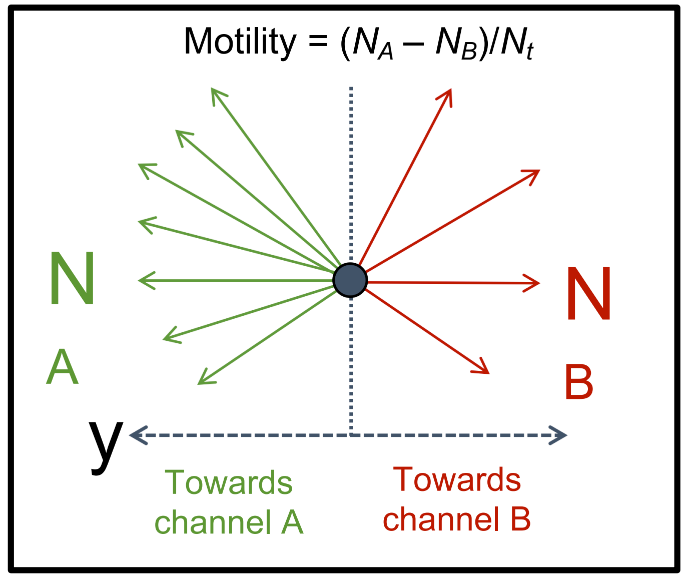
Advancing Engineering: Cell Mechanics





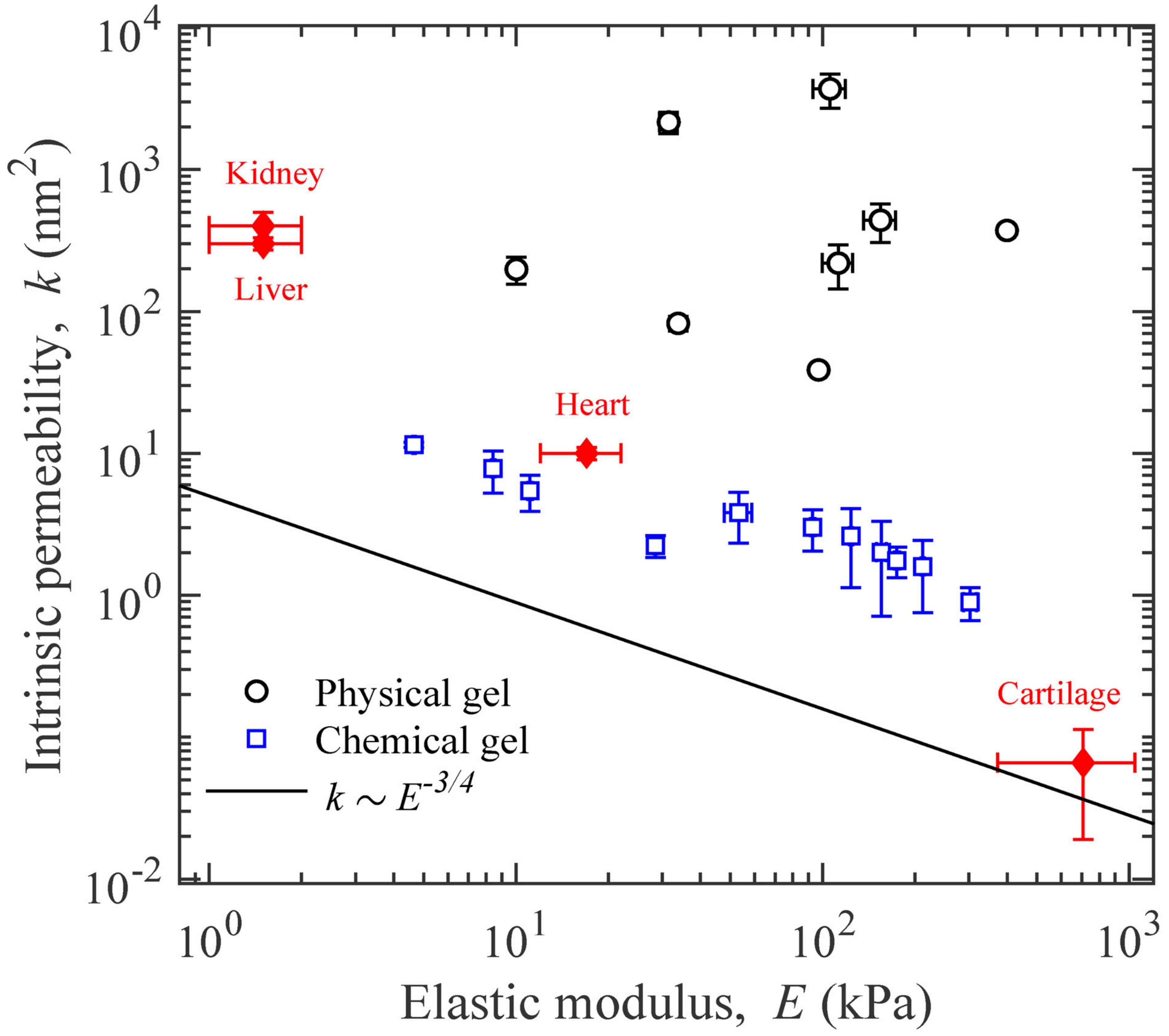


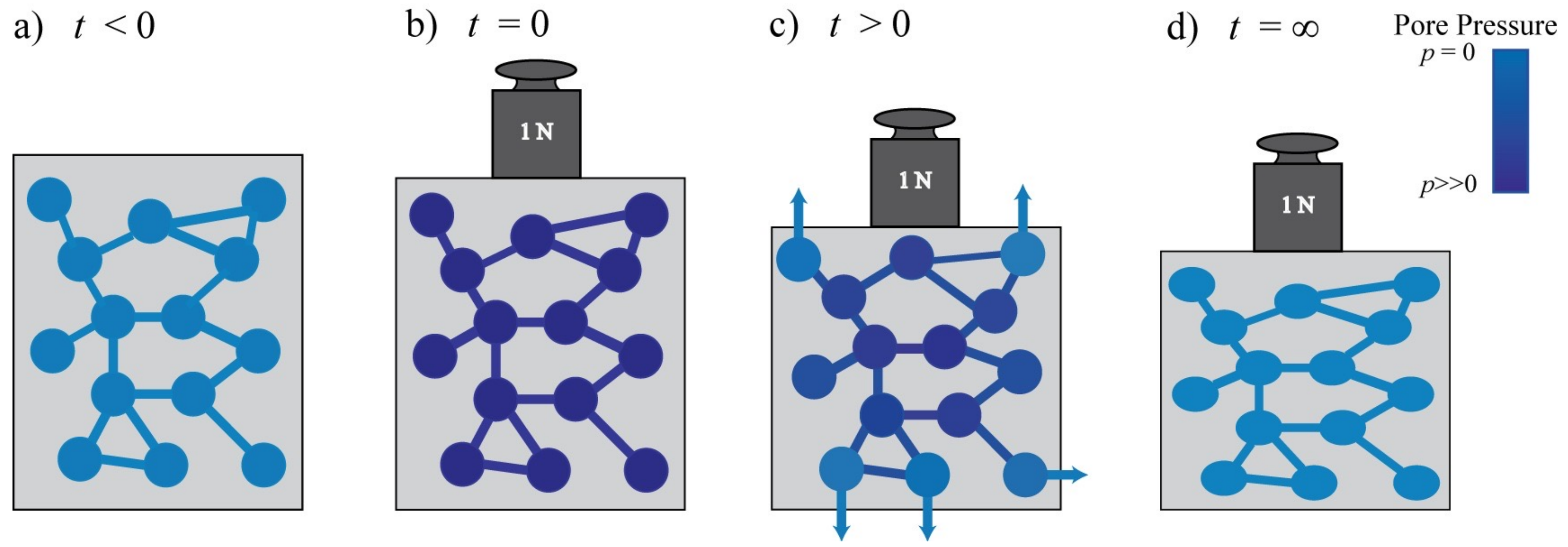


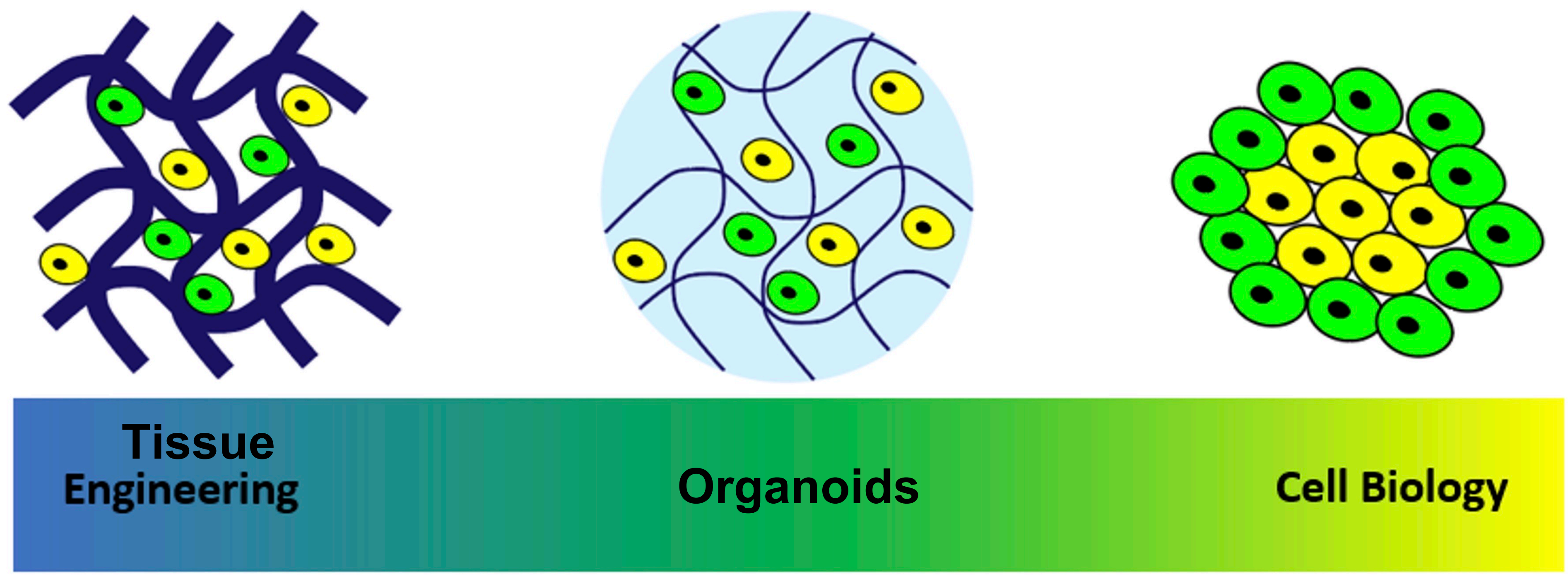


Trophoblast invasion

Advancing Engineering: Cell–Hydrogel Matrix Mechanics







Grand challenges

Measure

R1
Experimental Cellular & Tissue Mechanics

Model

R3
Multiscale Theoretical Mechanics

Properties of pregnancy related cells and tissues

Growth and remodeling

Uterus
Placenta

Properties of pelvic floor cells and tissues

Tissue fracture behavior

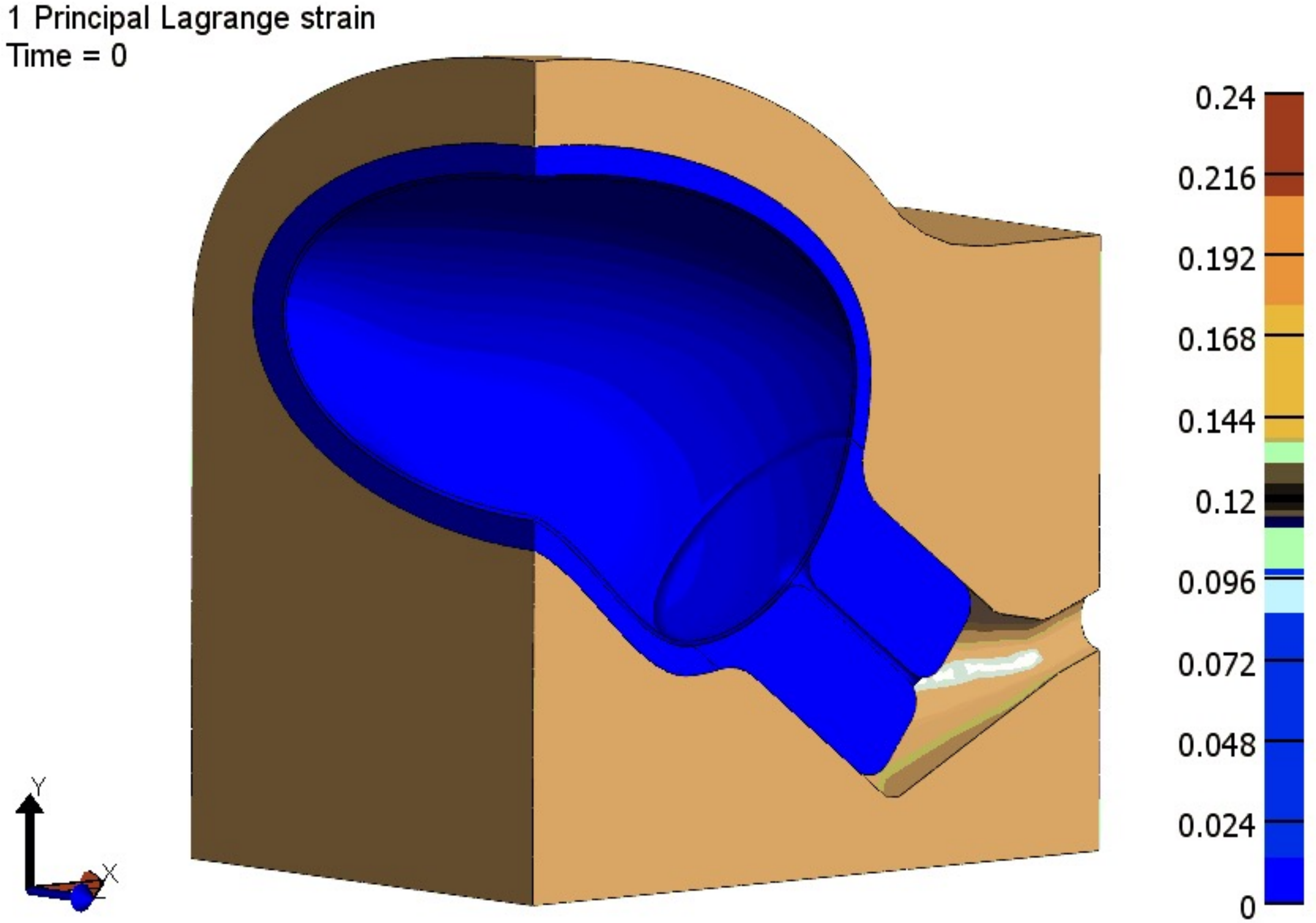
Perineum

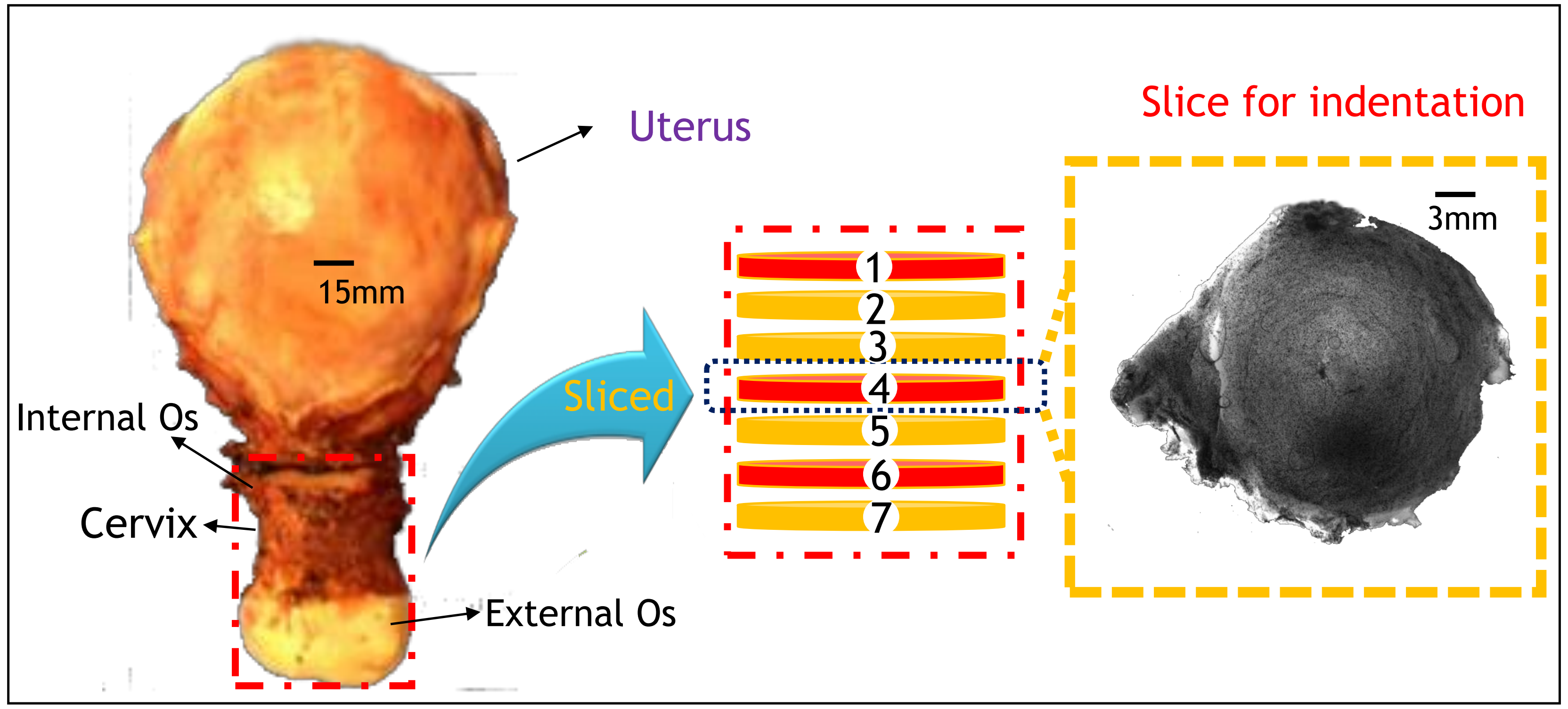
Properties of tissues as a function of hormones

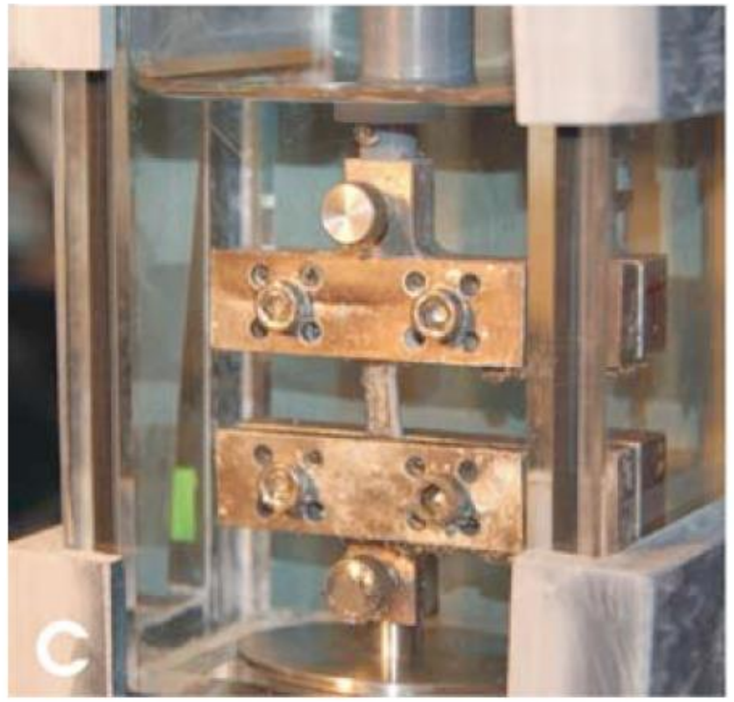
Mechanomics

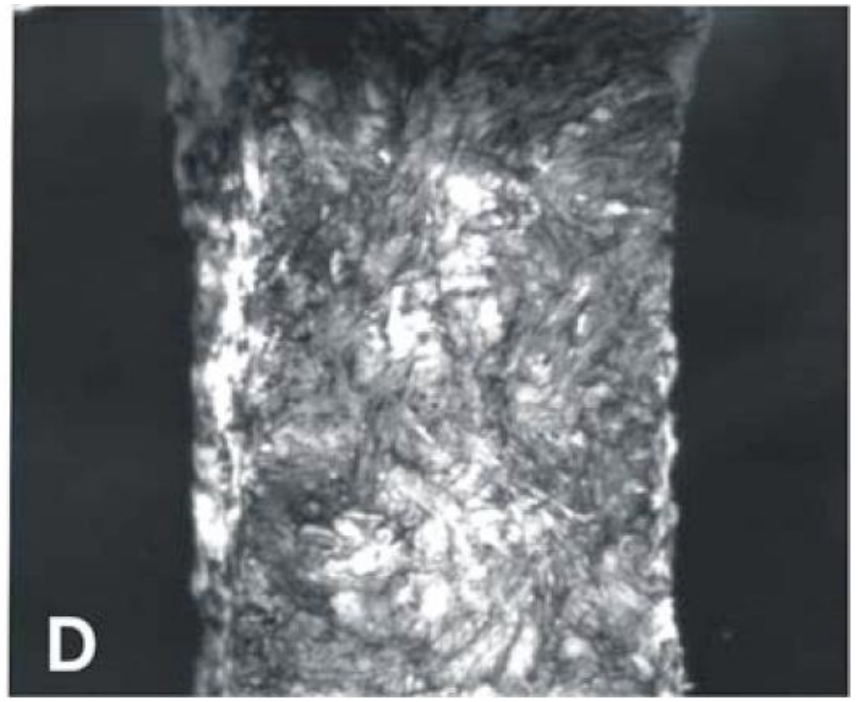
Cardiovascular and musculoskeletal cellular transduction
Hormone effects

Modeling Needs

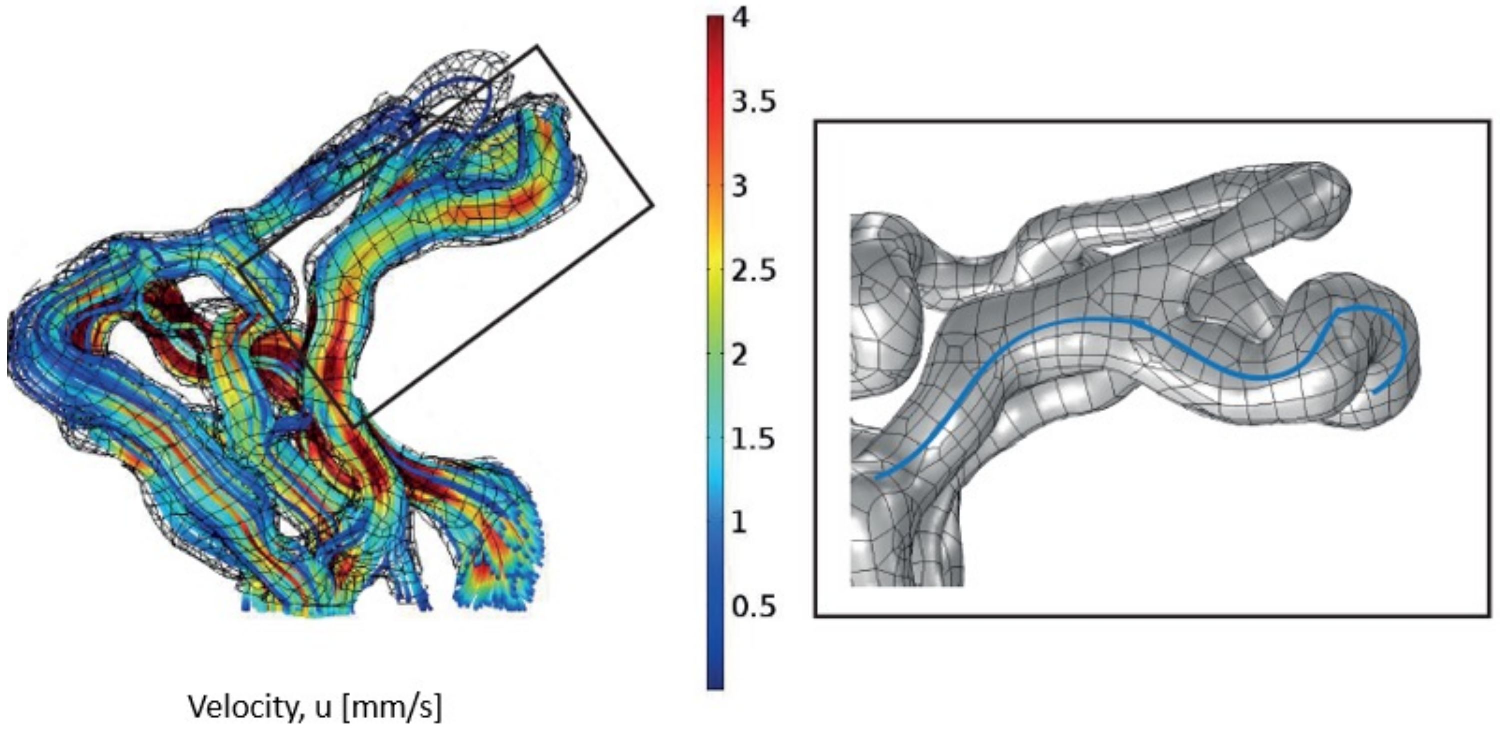


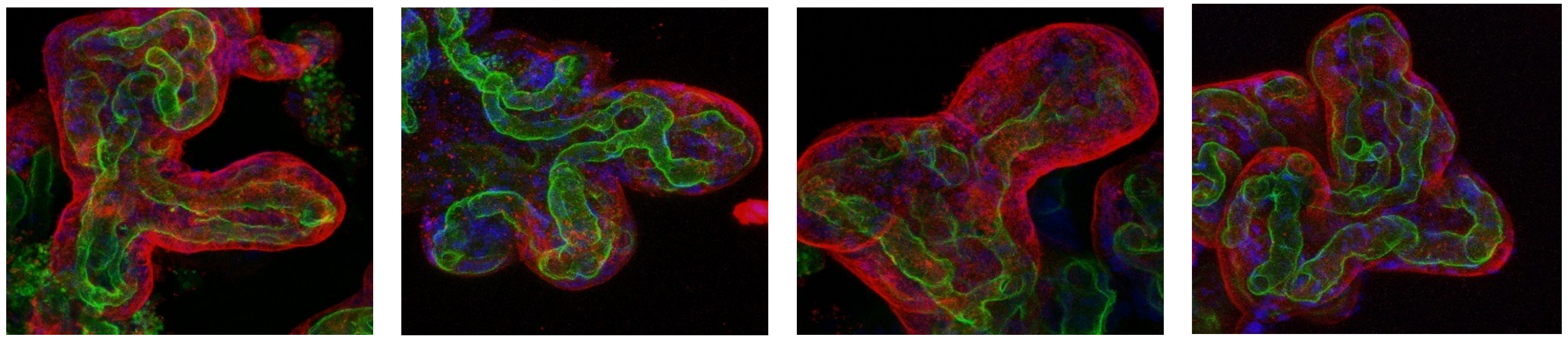


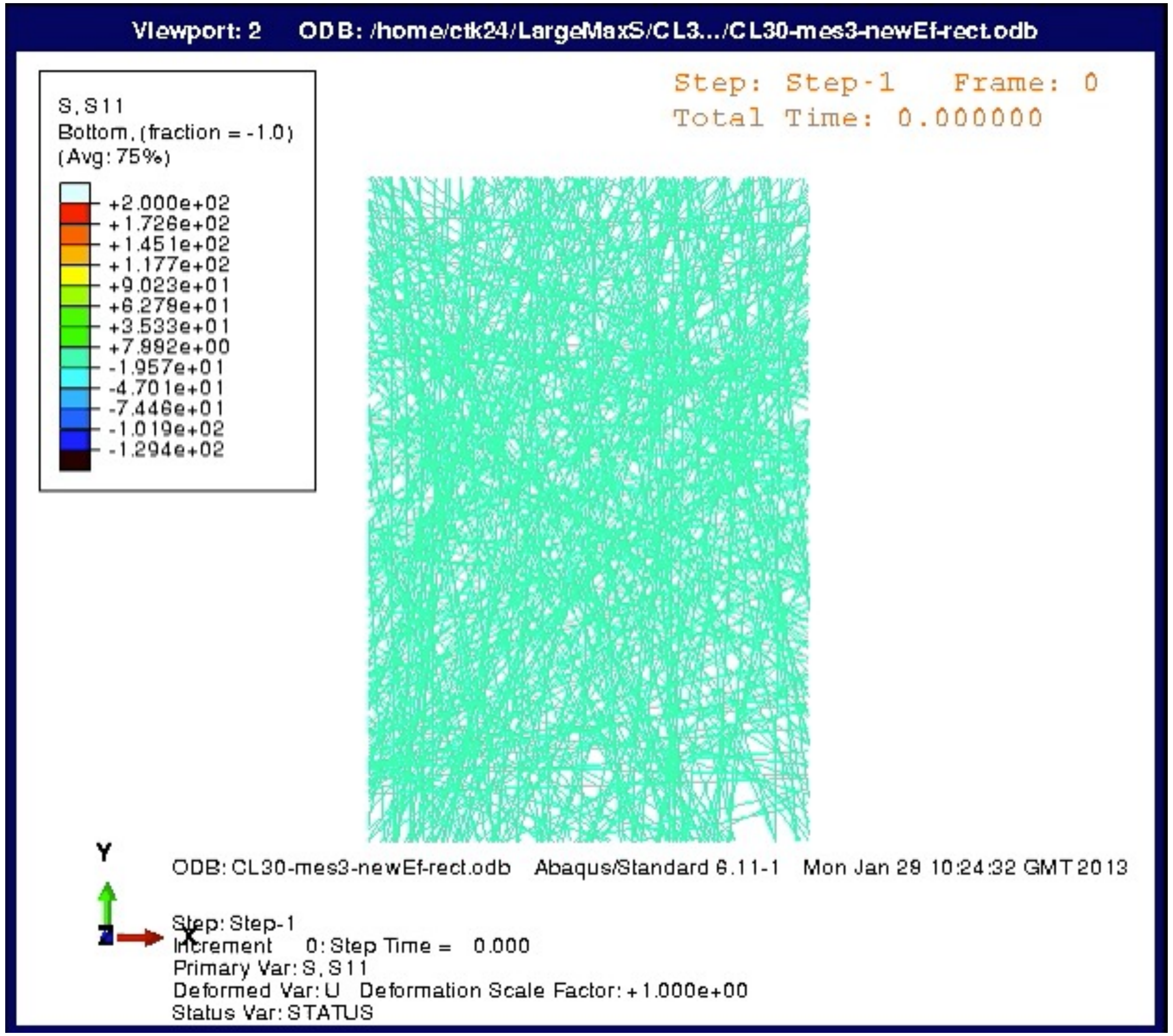




Modeling Needs

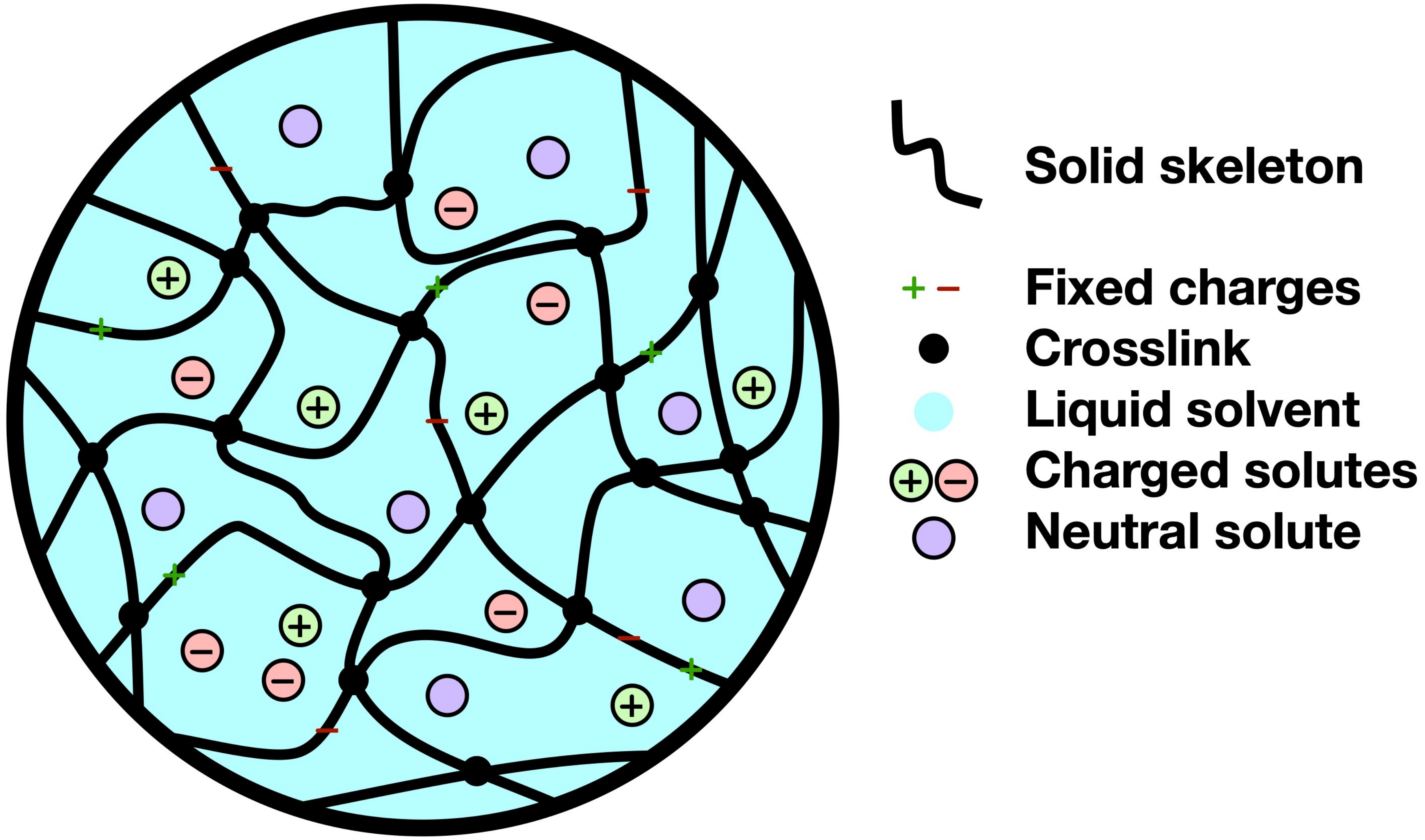






Multiscale Theoretical Framework

- Any number of constituents
  - Fluid solvent
  - Solutes
    - Ions, nutrients, cytokines, growth factors, hormones
  - Solid
    - Extracellular matrix
    - Intracellular cytoskeletal and nuclear structures
  - Electrically neutral or charged
    - Fixed-charge density on ECM
    - Ionic solutes



Mixture Theory Equations

- Mass balance

$$\frac{D^\alpha \rho^\alpha}{Dt} + \rho^\alpha \operatorname{div} \boldsymbol{v}^\alpha = \hat{\rho}^\alpha$$

- Reactions

$$\sum_\alpha \nu_R^\alpha \mathcal{E}^\alpha \rightarrow \sum_\alpha \nu_P^\alpha \mathcal{E}^\alpha$$

- Momentum balance

$$\rho^\alpha \frac{D^\alpha \boldsymbol{v}^\alpha}{Dt} = \operatorname{div} \boldsymbol{\sigma}^\alpha + \rho^\alpha \boldsymbol{b}^\alpha + \hat{\boldsymbol{p}}^\alpha$$

- Constituents
  - Solid-bound molecules $\alpha \rightarrow \sigma$ constrained to move together ($\boldsymbol{v}^\sigma = \boldsymbol{v}^s$)
  - Solvent $\alpha \rightarrow w$, solutes $\alpha \rightarrow \iota$

- Electroneutrality

$$\sum_\alpha z^\alpha \rho^\alpha / M^\alpha = 0$$

- State variables for free energy density

$$\Psi_r^I = \Psi_r^I(\boldsymbol{F}^s, \rho_r^\sigma, \rho_r^\iota, \boldsymbol{u}^\iota, \boldsymbol{u}^w)$$

- Law of mass action

$$\hat{\rho}^\alpha = \nu^\alpha M^\alpha \hat{\zeta}$$

$$\hat{\zeta} = k_F(\boldsymbol{F}^s, \rho_r^\sigma) \prod_\alpha (\rho^\alpha / M^\alpha)^{\nu_R^\alpha}$$

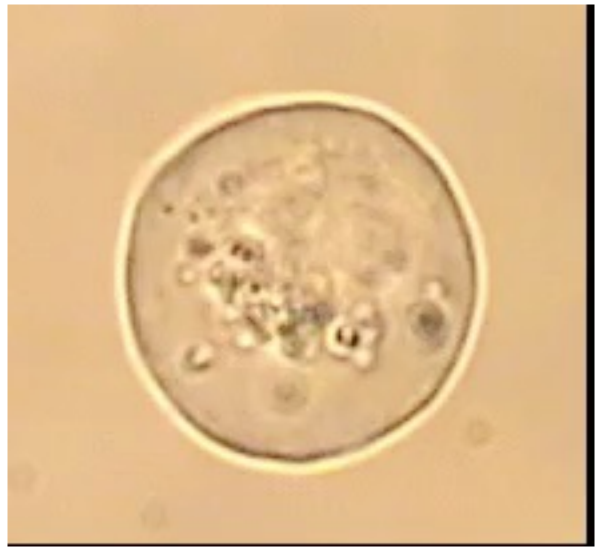
- Stretch or voltage activated channels

  $\rho^\alpha / M^\alpha \rightarrow \tilde{\mu}^\alpha$ (electrochemical potential)

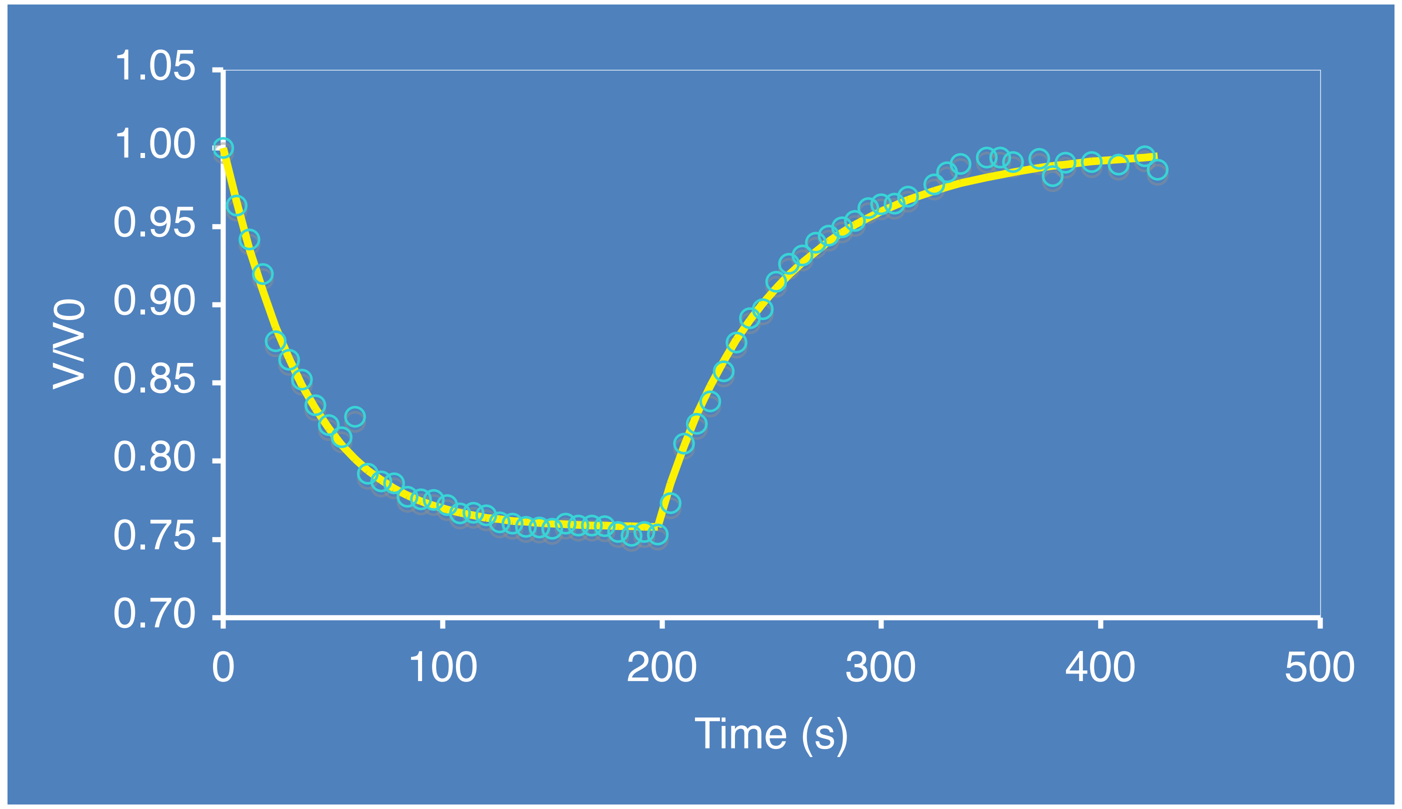
- Bond-breaking-and-reforming

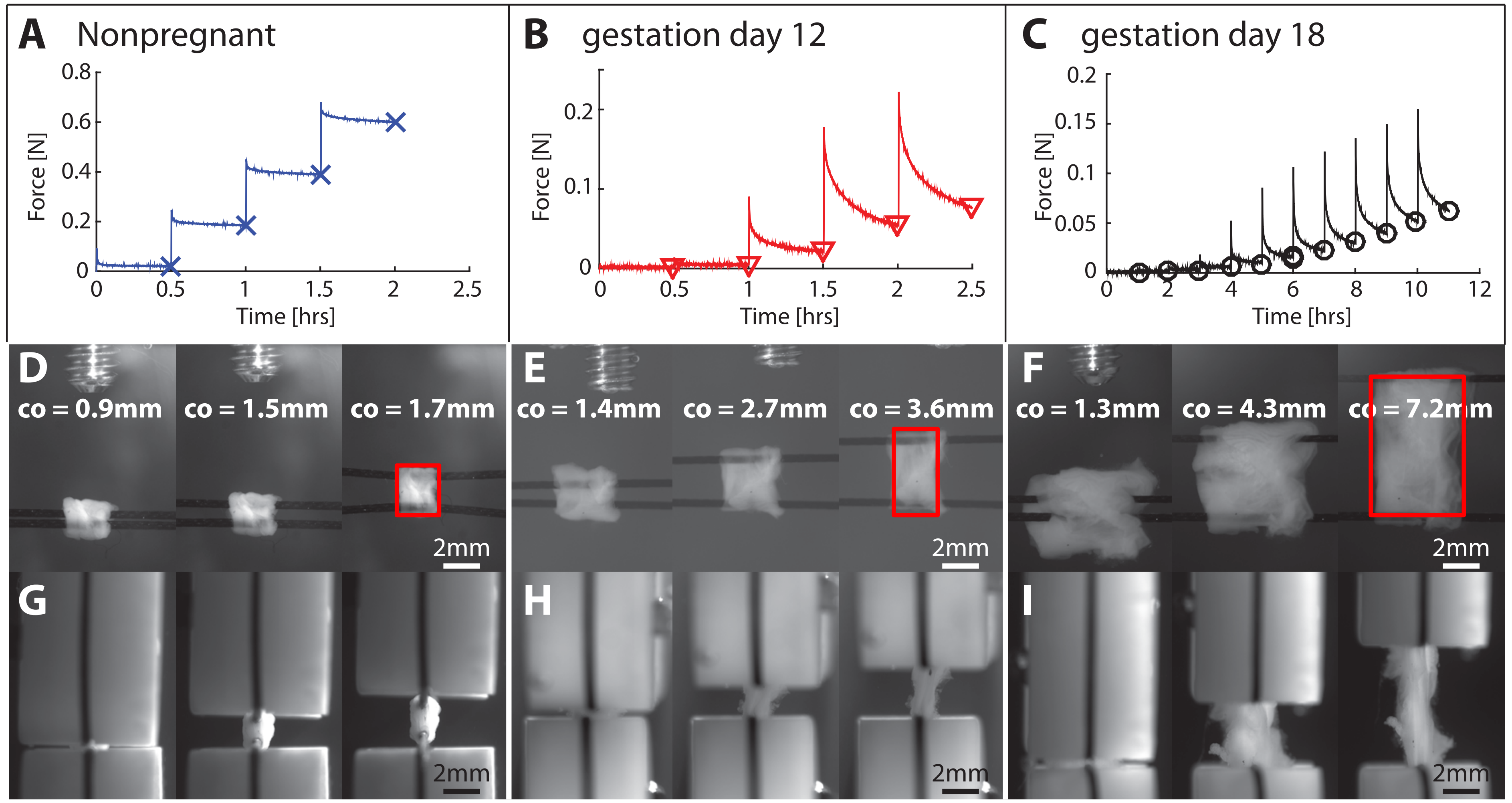
  $\boldsymbol{F}^s = \boldsymbol{F}^\alpha \cdot \boldsymbol{F}^{\alpha s}$, $\boldsymbol{F}^{\alpha s} = \partial \boldsymbol{X}^\alpha / \partial \boldsymbol{X}^s$

Mixture Theory: Mechanics and Transport



Osmotic loading of cell with NaCl

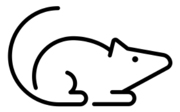


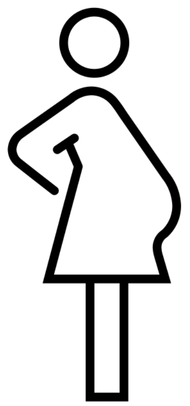


Mechanical testing of pregnant mouse cervix

Workflow and Milestones

YEARS 1–2	YEARS 3–5	YEARS 5–10



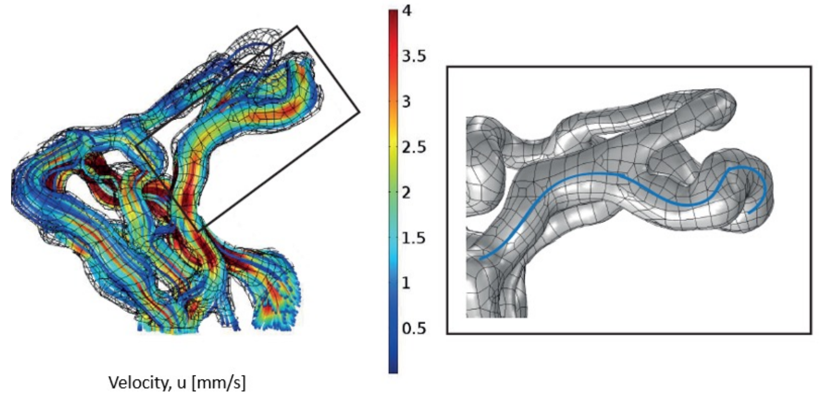


Measure tissue properties:
Uterus and cervix
Fetal membrane and placenta
Pelvic floor and perineum
Cell migration/invasion
Hormone effects on cardiovascular and musculoskeletal tissues

Measure

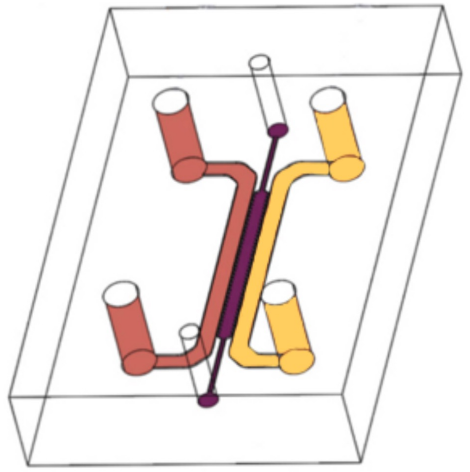
Incorporate measured properties into novel *in silico* engineering models, both theoretical and computational:

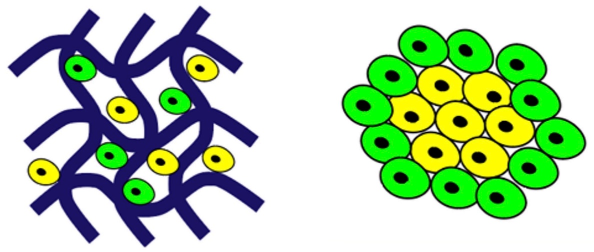
Growth and remodeling; fracture mechanics; cellular mechanomics



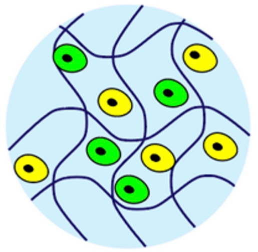
Model

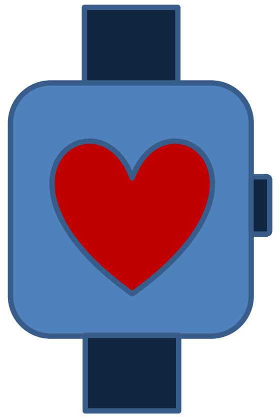
Create and expand on novel *in vitro* organ-on-a-chip devices





Create new hydrogel-based tissue engineered and organoid systems

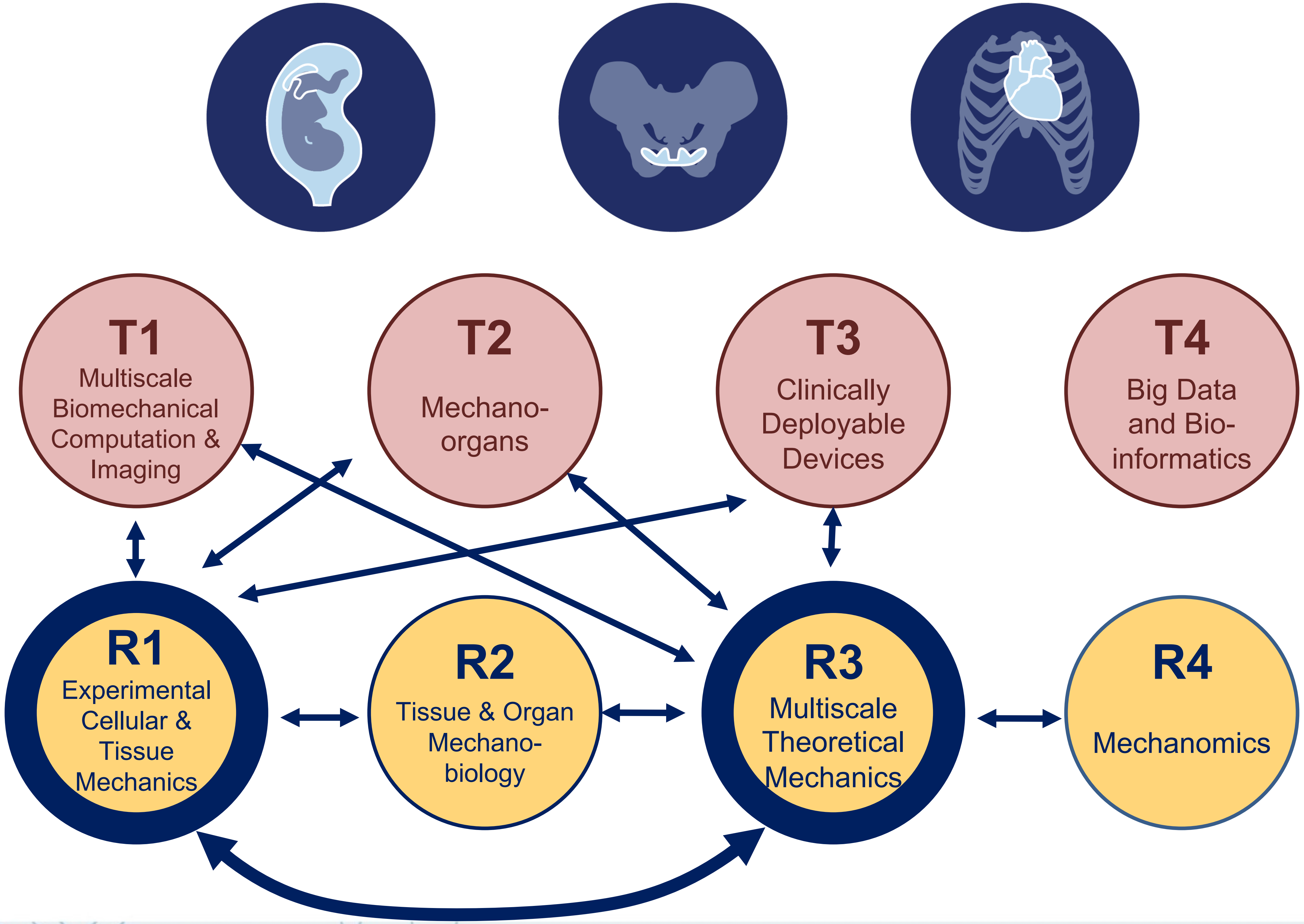




Create and test novel wearables for maternal and fetal monitoring

Make

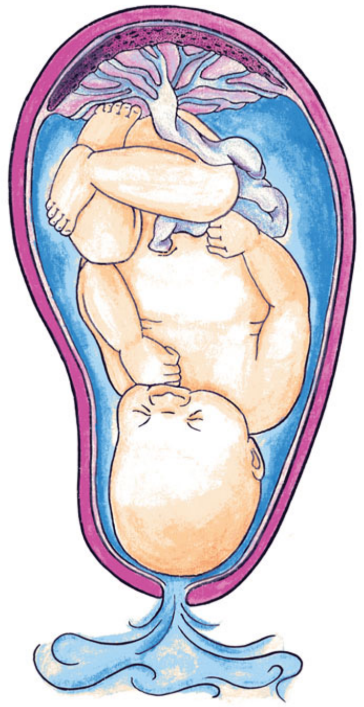
Convergence (R1+R3)

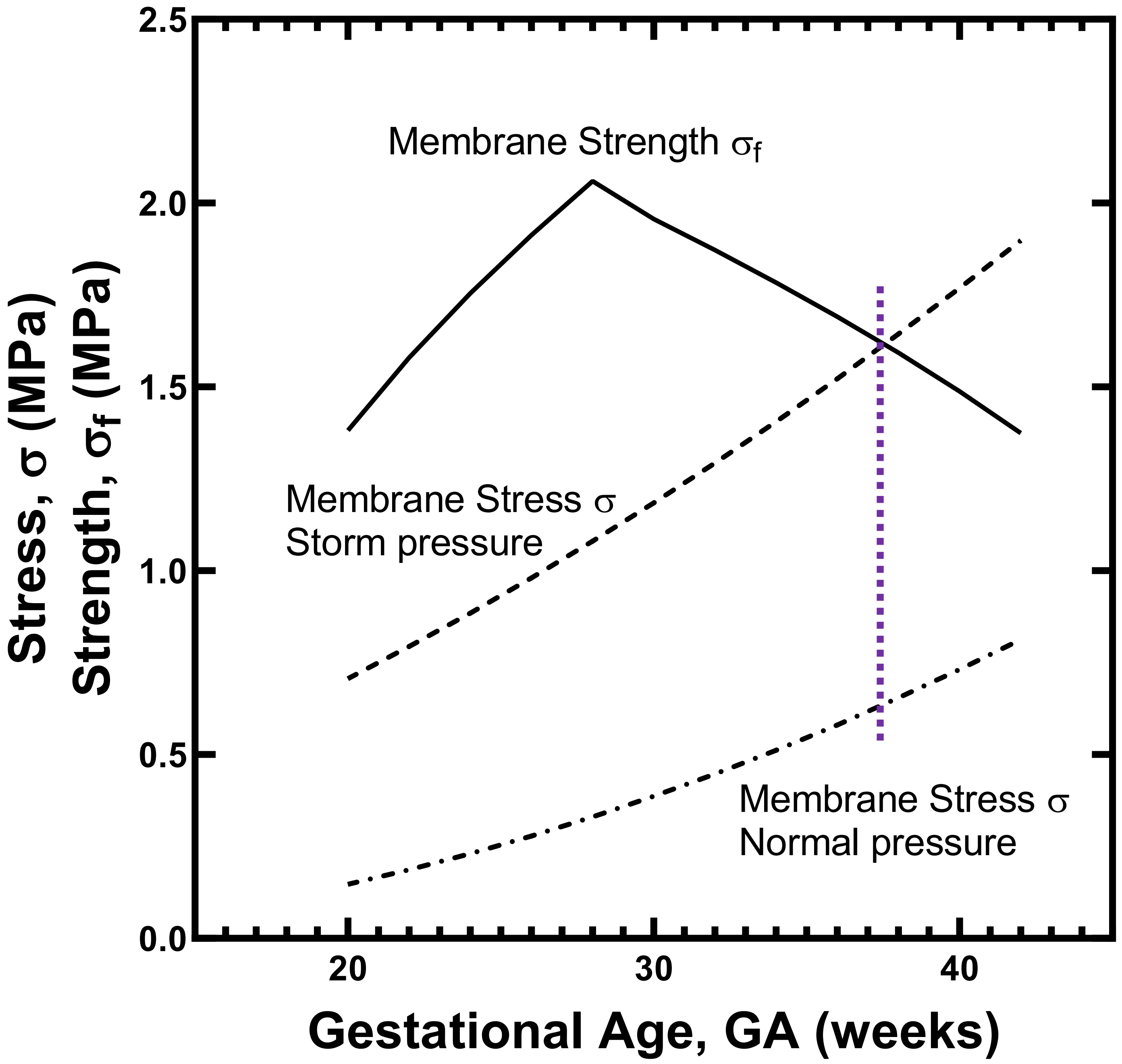


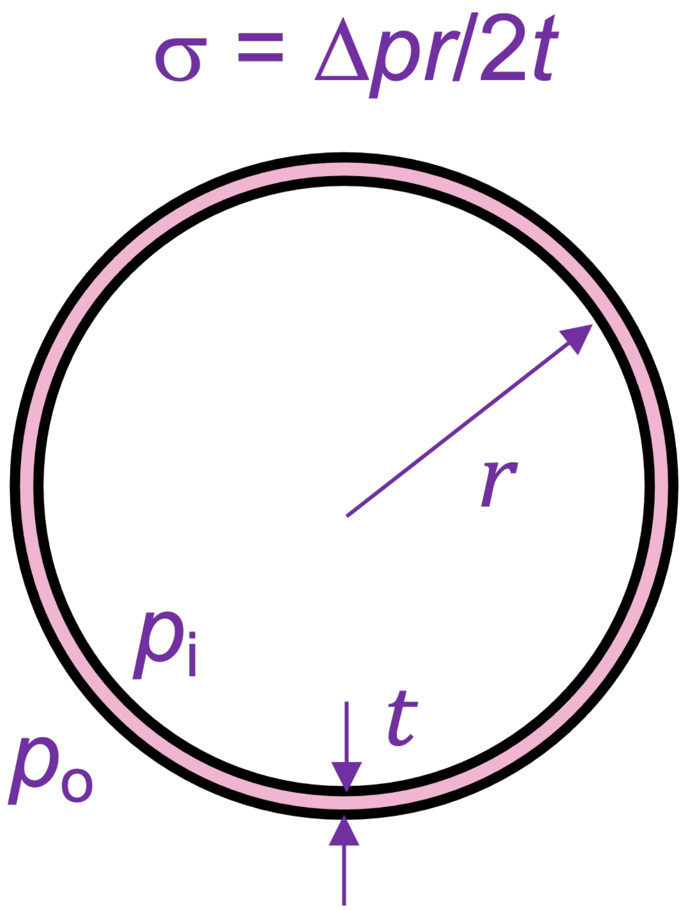
Experimental Cellular and Tissue Mechanics (R1) and **Multiscale Theoretical Mechanics (R3)** are directly linked as the measure–model components of the IMWEL research approach.

- Both R1 and R3 will inform the other two research thrusts **Tissue and Organ Mechanobiology (R2)** and **Mechanomics (R4).**
- Both R1 and R3 will feed experimental and modeling data into **Multiscale Biomechanical Computation & Imaging (T1), Mechano-organs (T2)** and **Clinically Deployable Devices (T3)**

Integration with Broader Impacts

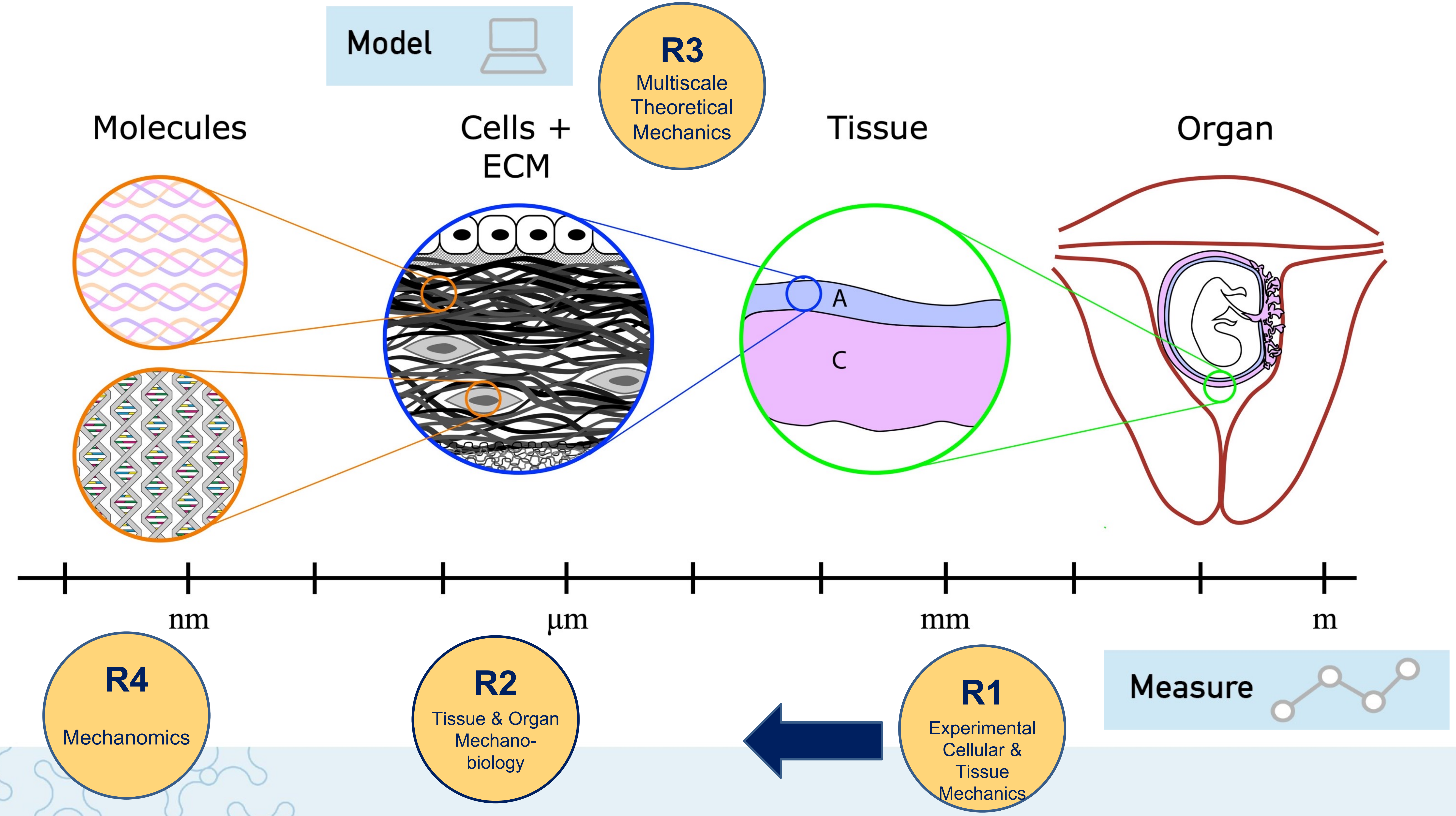




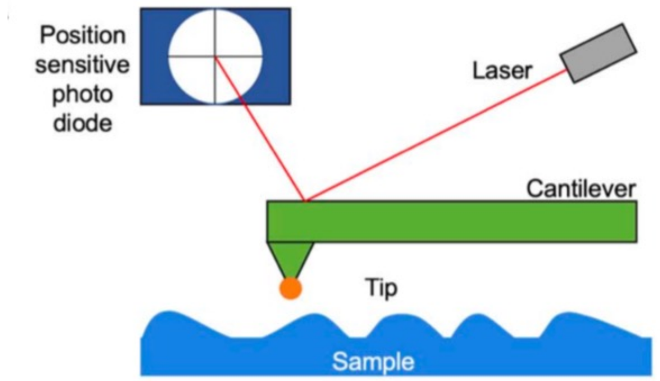


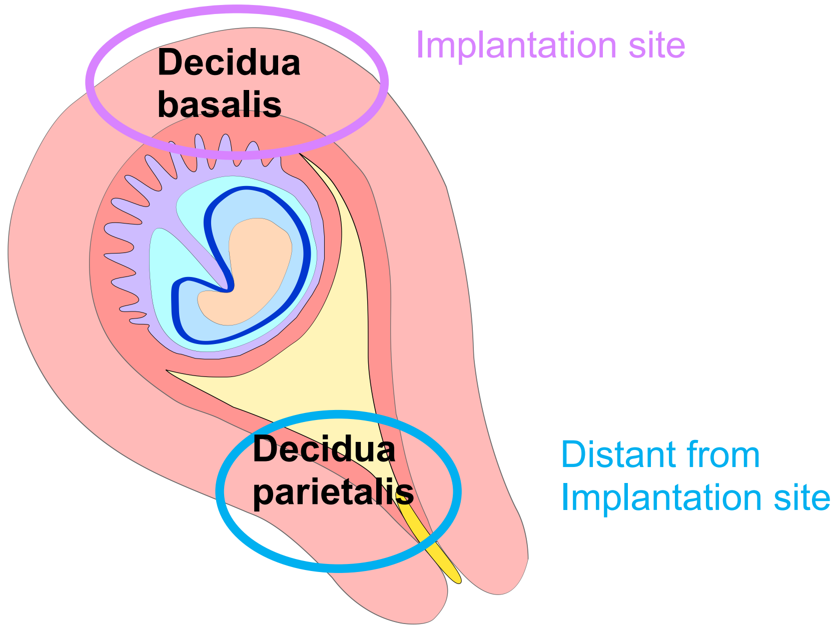
Research Thrusts
Introduction, R1, R3

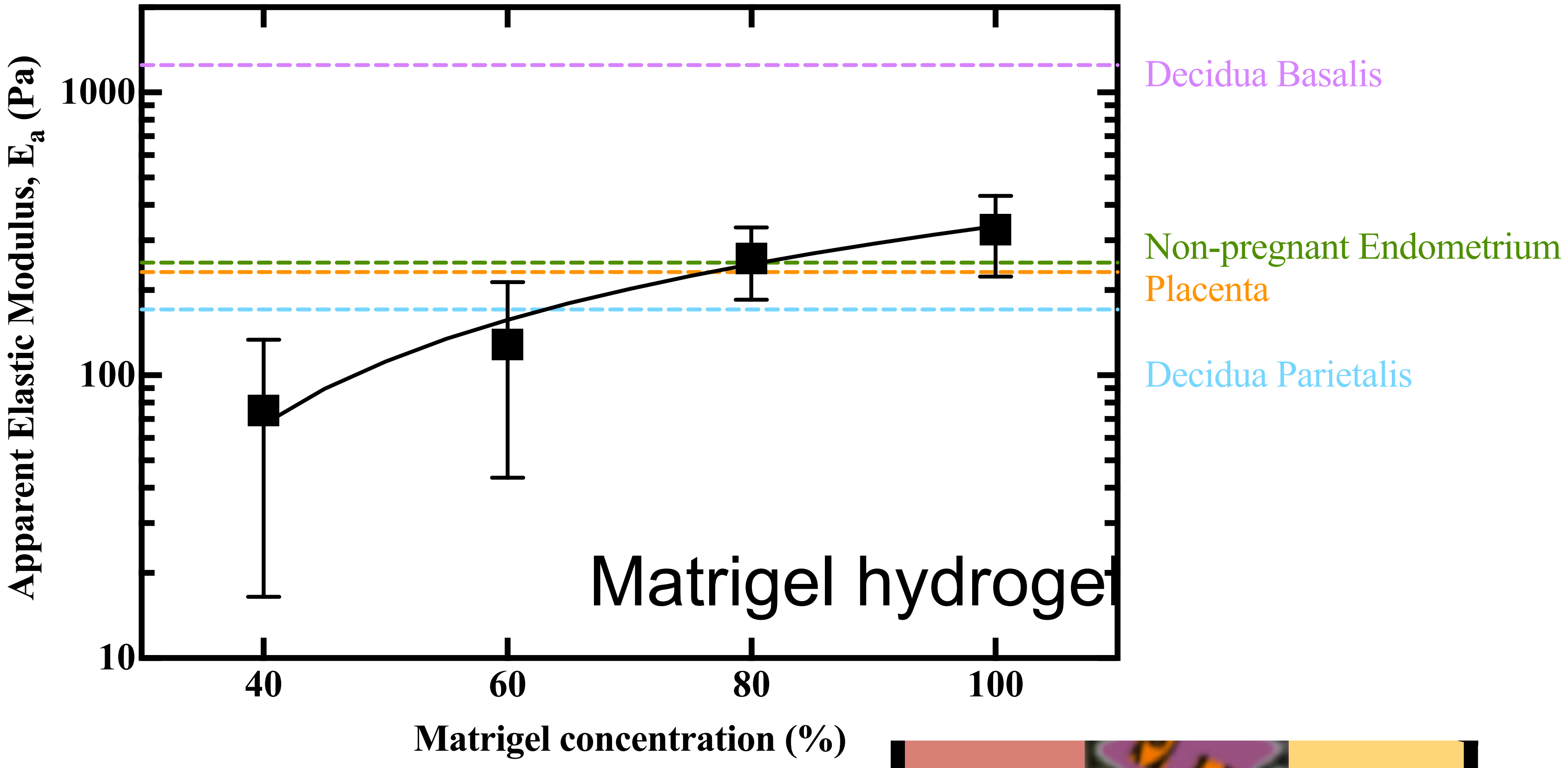
IMWEL Research Emphasis: Multiscale Perspective

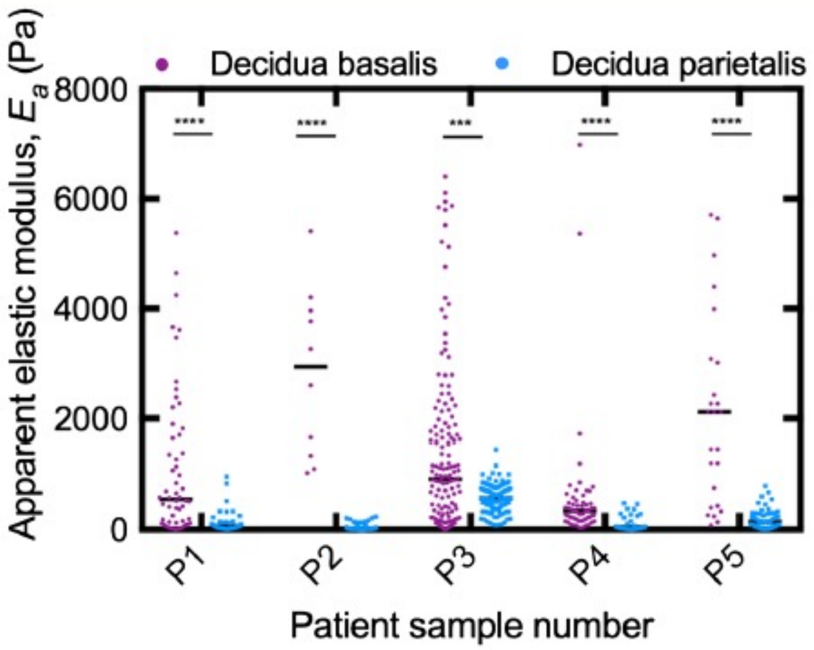


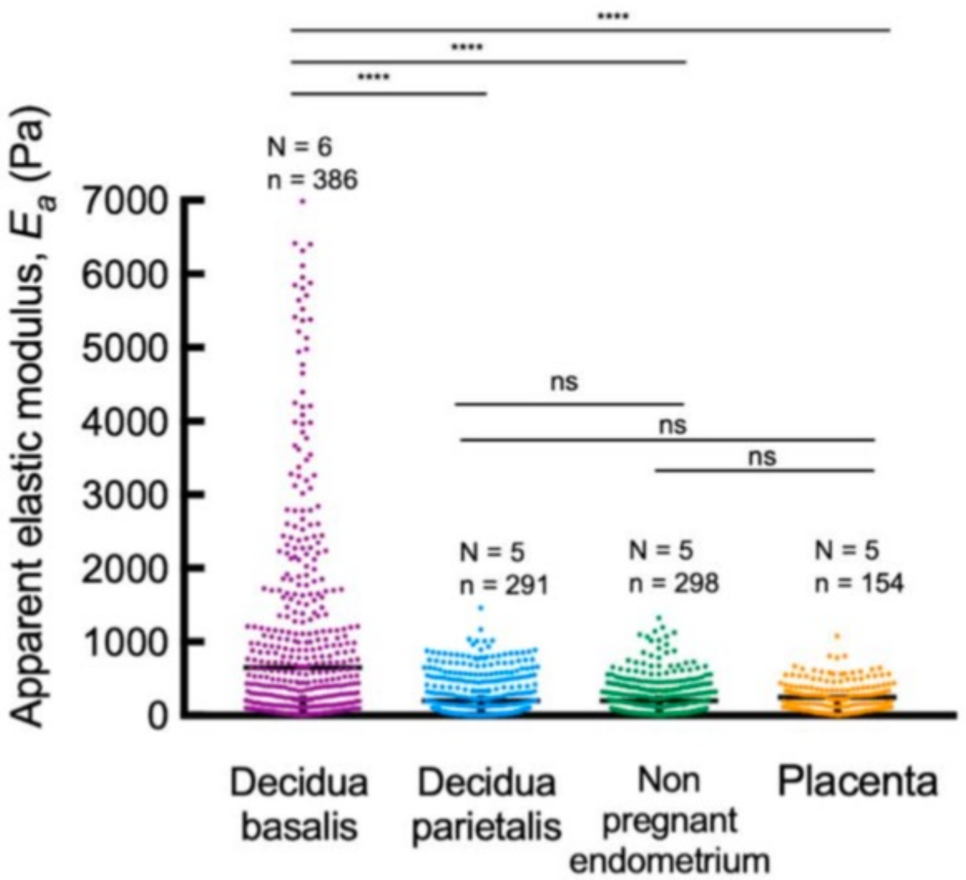
Advancing Engineering: Cell–Hydrogel Matrix Mechanics

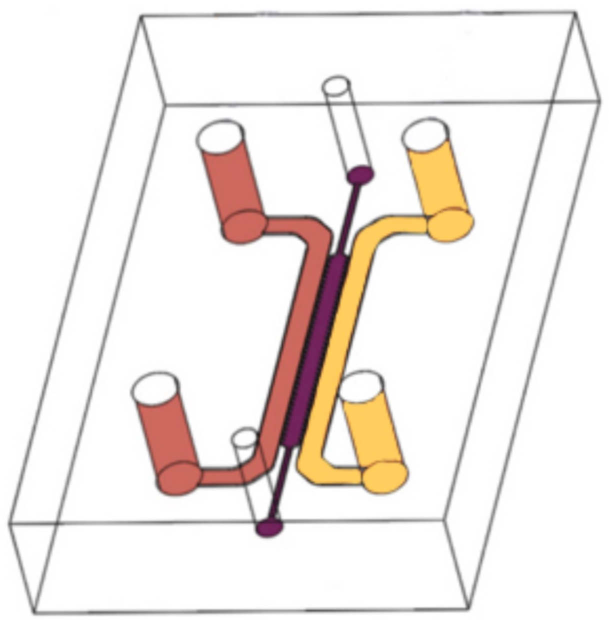


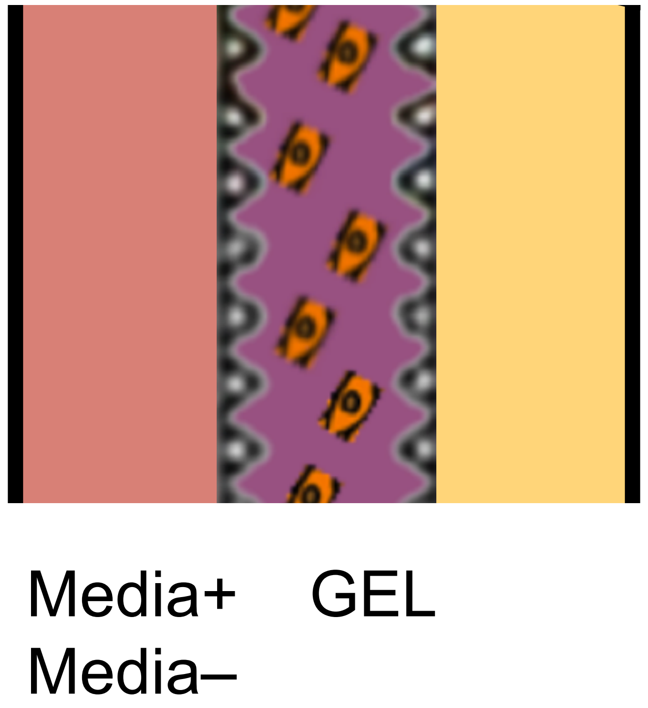












Mixture Theory: Damage Mechanics

- Reaction triggered by loading

  intact bonds $i \rightarrow$ broken bonds b

- Strain energy density

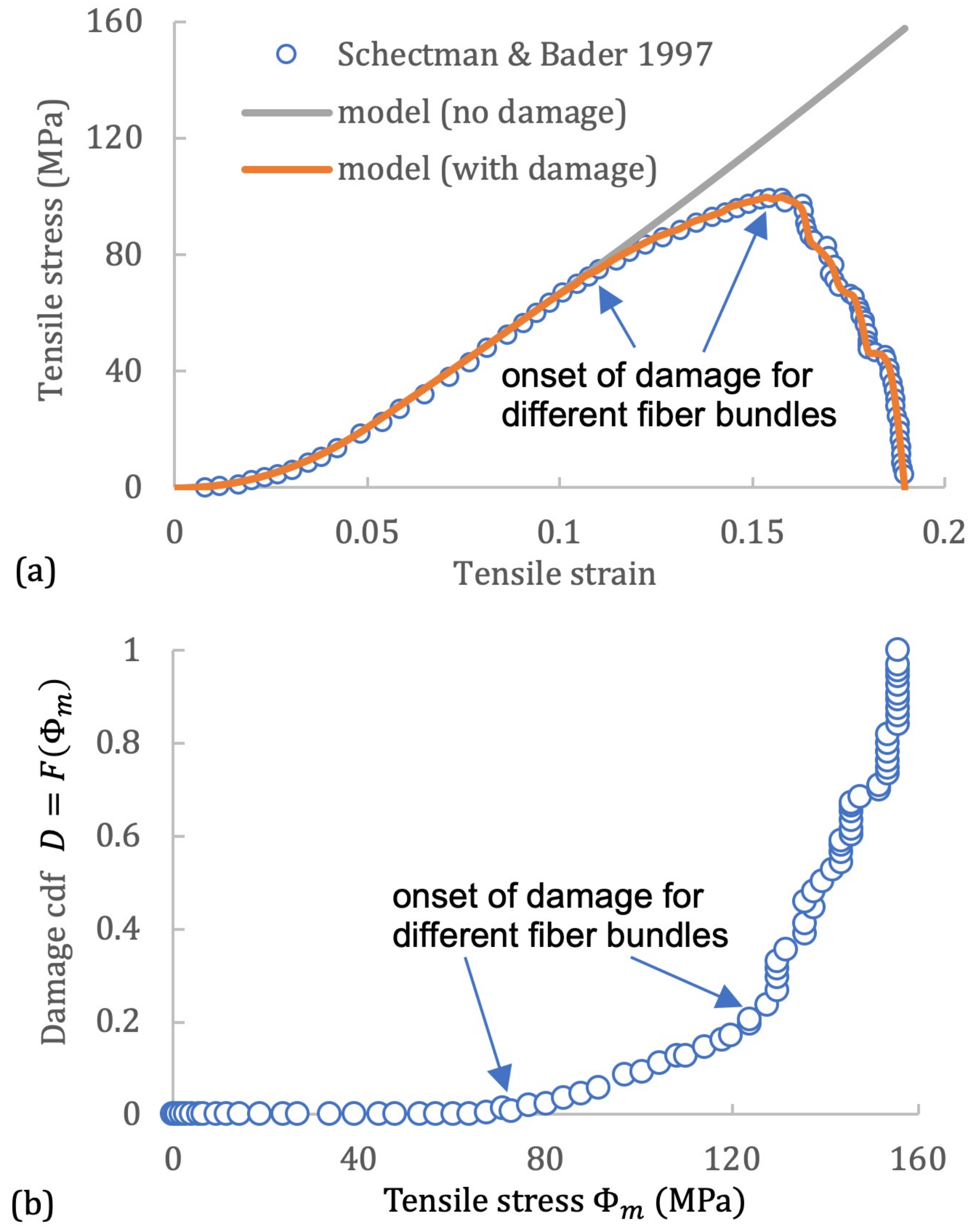
  $$\Psi_r(\rho_r, \boldsymbol{F}^s) = \Psi_r^i(\rho_r^i, \boldsymbol{F}^s) + \Psi_r^b(\rho_r^b, \boldsymbol{F}^s)$$

- Damage is fraction of broken bonds

  $$D = \frac{\rho_r^b}{\rho_r} = \frac{\rho_r^b}{\rho_r^i + \rho_r^b}$$

- Stress

  $$\boldsymbol{\sigma} = \rho_r^i \psi^i(\boldsymbol{F}^s) = (1 - D)\boldsymbol{\sigma}_0(\boldsymbol{F}^s)$$



Human tendon damage

- Reaction triggered by loading

  intact bonds $i \rightarrow$ broken bonds b
- Strain energy density

  $\Psi_r(\rho_r, \boldsymbol{F}^s) = \Psi_r^i(\rho_r^i, \boldsymbol{F}^s) + \Psi_r^b(\rho_r^b, \boldsymbol{F}^s)$
- Damage is fraction of broken bonds

  $D = \frac{\rho_r^b}{\rho_r} = \frac{\rho_r^b}{\rho_r^i + \rho_r^b}$
- Stress

  $\boldsymbol{\sigma} = \rho_r^i \psi^i(\boldsymbol{F}^s) = (1 - D)\boldsymbol{\sigma}_0(\boldsymbol{F}^s)$

Mixture Theory: Nonlinear Viscoelasticity

- Reaction triggered by loading

$$\text{loaded bonds } u \rightarrow \text{stress–free reformed bonds } v$$

- Strain energy density

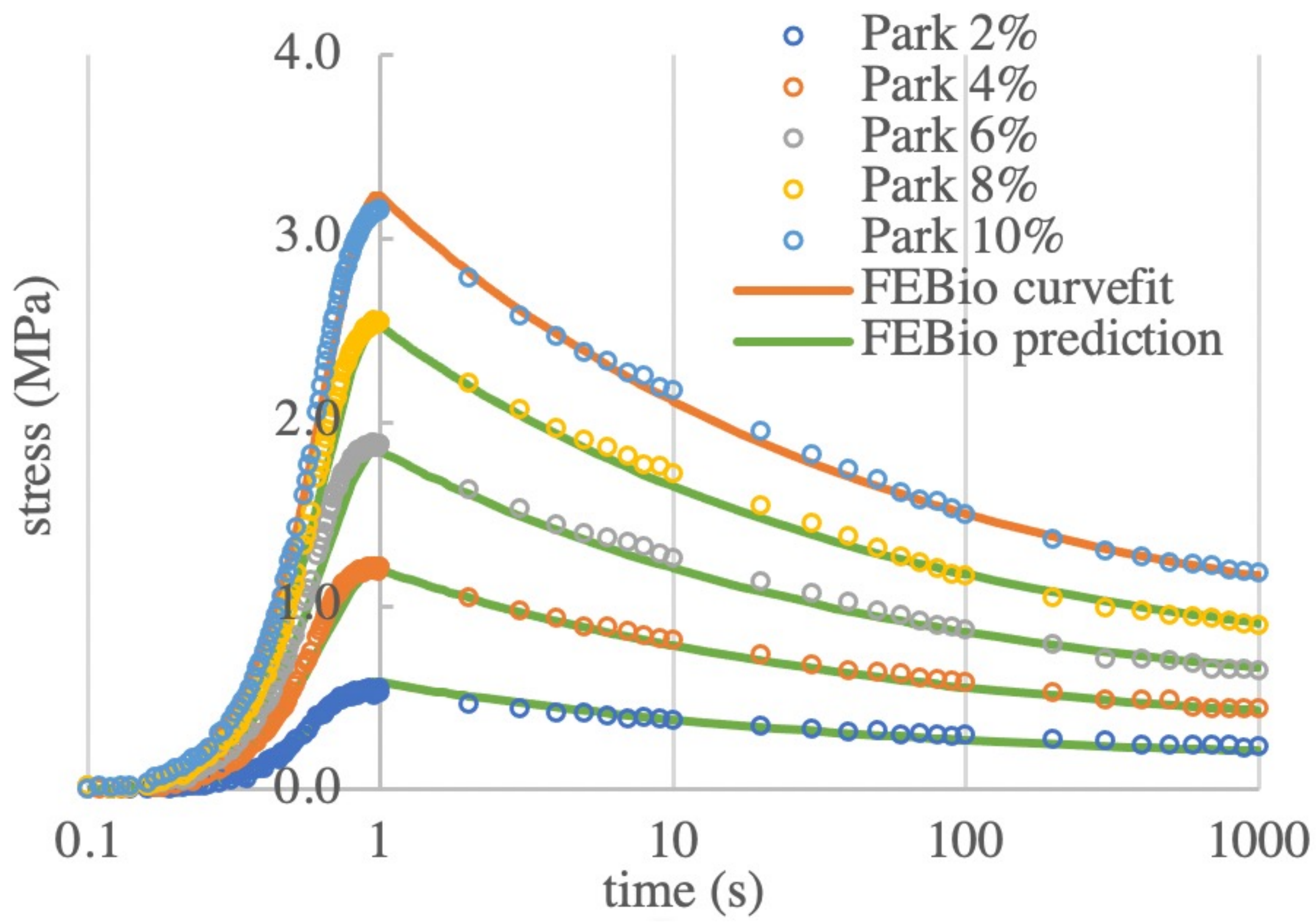
$$\Psi_r(\boldsymbol{F}) = \Psi_r^e(\boldsymbol{F}) + \sum_v w^v \Psi_0^a(\boldsymbol{F}^v)$$

- Reformed bonds are in stress-free state at time v

$$\boldsymbol{F}^v(t) = \boldsymbol{F}(t) \cdot \boldsymbol{U}^{-1}(v)$$

- Stress

$$\boldsymbol{\sigma}(\boldsymbol{F}) = \boldsymbol{\sigma}^e(\boldsymbol{F}) + \sum_v w^v J^{-1}(v) \boldsymbol{\sigma}_0^a(\boldsymbol{F}^v)$$



Bovine cartilage viscoelasticity in tension