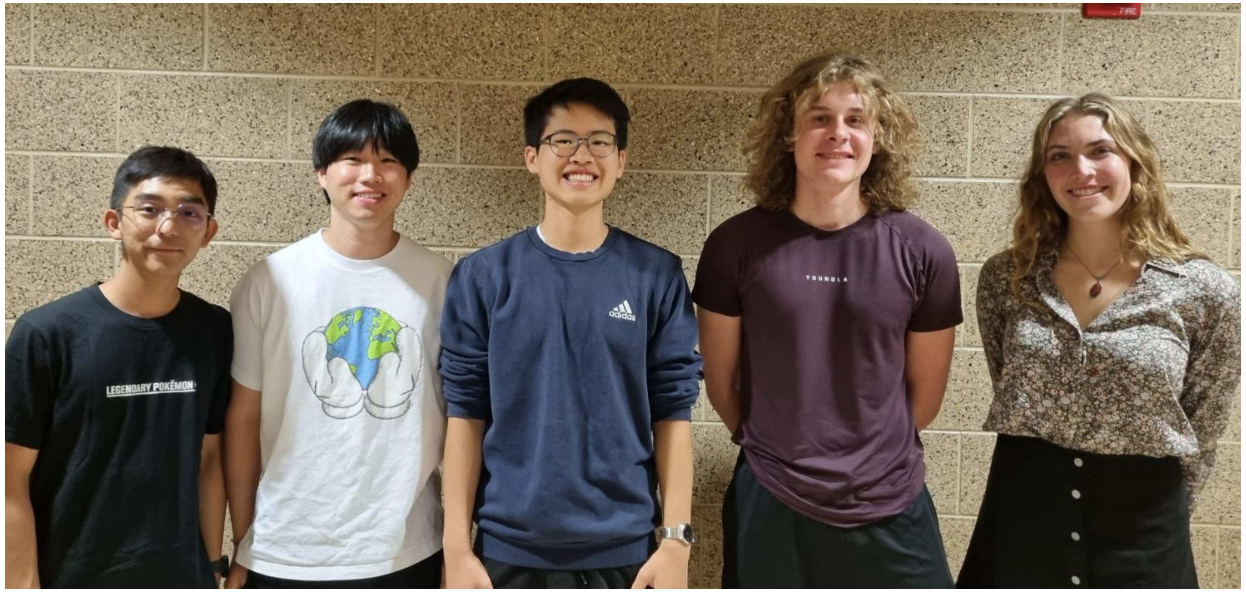
Force-Controlled Cartilage Bioreactor

FC Bioreactor

Project Proposal

10/6

The Team



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Agenda

Introduction

Product Design Specifications

Literature Perspective

Our Approach

Introduction

Overview of Disease in Articular Cartilage

Gap in Literature

Problem Statement & Client Need

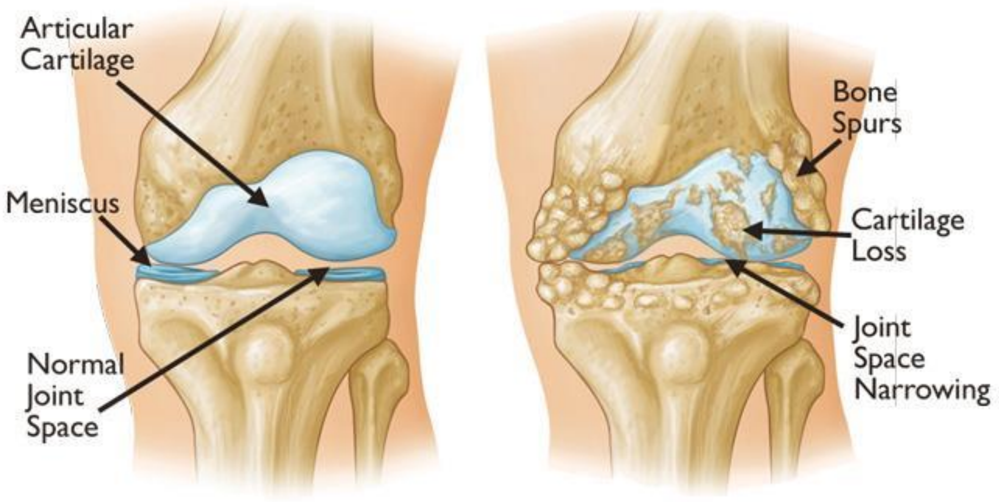
Global Impact

Osteoarthritis (OA) impacts 7% of the global population.

More than 22% of adults older than 40 are estimated to have knee OA.

While symptom-based treatment exists, a definitive treatment for the disease itself has yet to be discovered.

OA involves the gradual degradation of cartilage over time, resulting in painful bone-on-bone friction & bone spurs.



A general depiction of cartilage degradation in knee OA.

Image reproduced from: https://orthoinfo.aaos.org/en/diseases--conditions/arthritis-of-the-knee/

[1]

Cartilage Disease State & Metabolic Dysregulation

Metabolism: Generation of cellular energy (ATP) via glycolysis and/or oxidative phosphorylation.

Metabolic dysregulation plays a significant role in OA.

Osteoarthritic cartilage demonstrates higher glycolytic production and lower oxidative phosphorylation activity than healthy cartilage.

Mechanical overloading has been shown to induce metabolic dysregulation in cartilage.

Mechanical overloading is implicated in osteoarthritis.

[2, 3, 4]

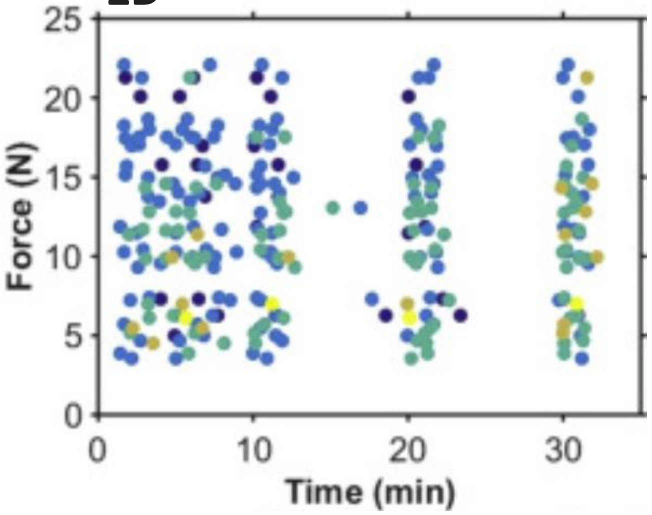
The long-term metabolic response of cartilage to mechanical overloading has not been characterized

Metabolic response (redox imbalance) to short-term (0.5 hr) mechanical loading has been characterized via microscopy techniques.

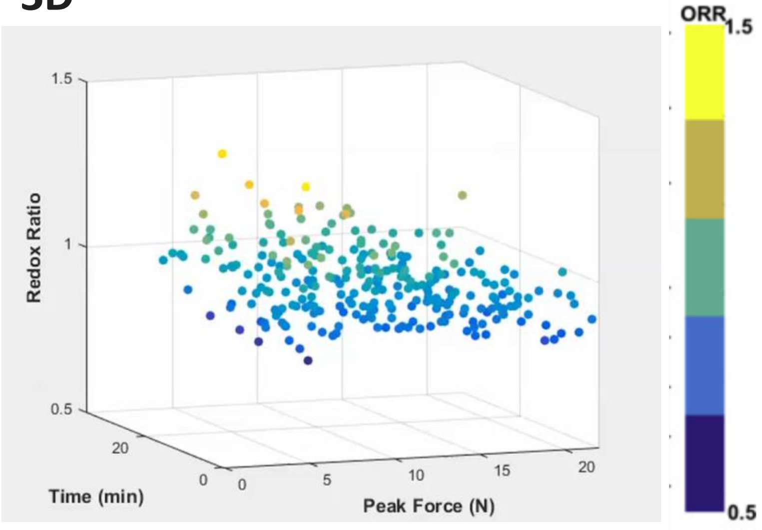
While useful in extracting meaningful metabolic dysregulatory behavior, long-term imaging results in sample damage due to photobleaching, preventing meaningful analysis.

As metabolic response is a function of time, greater loading timescales (> 1 hr) must be investigated to acquire the full redox imbalance profile and its relation to cartilage disease state.

2D



3D



<u>Cartilage redox balance</u>, or optical redox ratio (ORR), <u>is a function of applied mechanical load **and** *time*.</u>

Figures depict the same data; visualized in 2D & 3D.

Figures sourced from: Walsh, S. K., Skala, M. C. & Henak, C. R. Real-time optical redox imaging of cartilage metabolic response to mechanical loading. Osteoarthritis and Cartilage 27, 1841–1850 (2019).

[2, 3]

A Force-Controlled Bioreactor as a Solution

Larger loading timescales than those supported by current methods are required to investigate the relation between mechanical loading, cartilage metabolism, and disease state.

To meet this need, our client, Dr. Henak, has requested the fabrication of an incubator-housed device capable of applying a force-controlled mechanical load over long (> 1 hr to 1 day) timescales.

Product Design Specifications

Device Functions

Incubator and Environment

Additional Modifications

Device Functions

- Induce 20% strain via uniaxial compressive stress
    - Device capable of creating 25N to deliver calculated 5.65N to an approximate 6 [mm] diameter, 2 [mm] height cylindrical cartilage sample
    - Factors in weight of actuator and includes a factor of safety (TBD)
- Actuates enough to allow easy sample removal
- Interface with sample is as frictionless as possible
    - Looking into quantifying this

$$\boldsymbol{\sigma} = \begin{matrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \sigma_z \end{matrix}$$

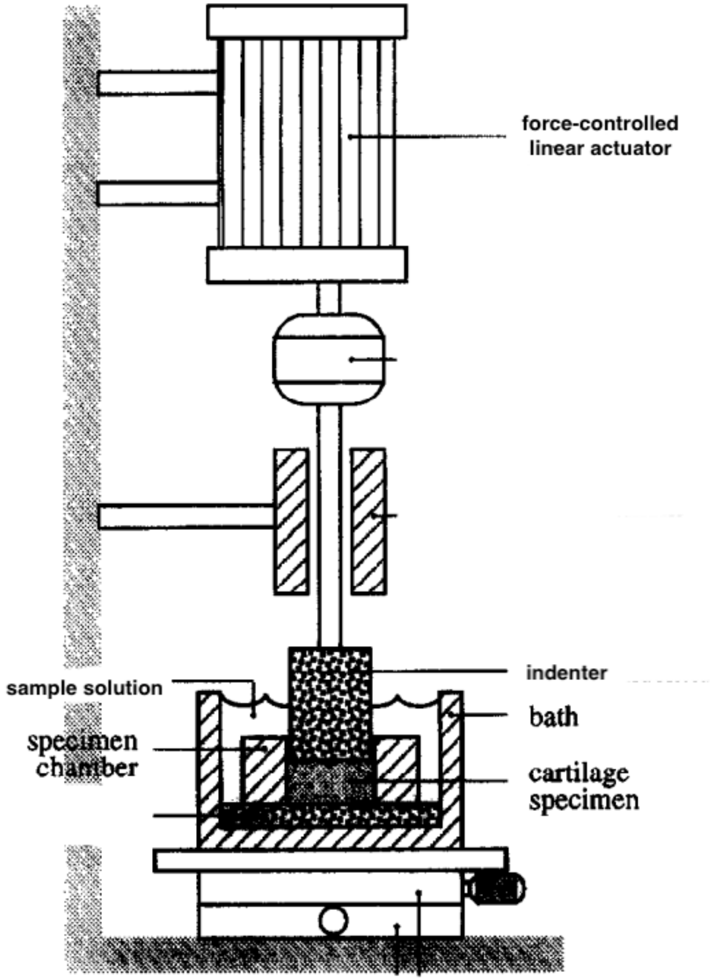
$$\boxed{\boldsymbol{\sigma} = \frac{\boldsymbol{P}}{\boldsymbol{A}} = \boldsymbol{E\varepsilon}}$$

$$E = 1\ [MPa]$$

$$\varepsilon = 0.2$$

$$A = \frac{\pi}{4}(6\ mm)^2$$

Cartilage roughly approximated as linear elastic to estimate force order of magnitude.



Confined compression cartilage bioreactor from Ateshian et. al. 1997 (modifications were made to the figure)

Figures sourced from: Ateshian et. al., "Finite deformation biphasic material properties of bovine articular cartilage from confined compression experiments," J Biomech, 1997

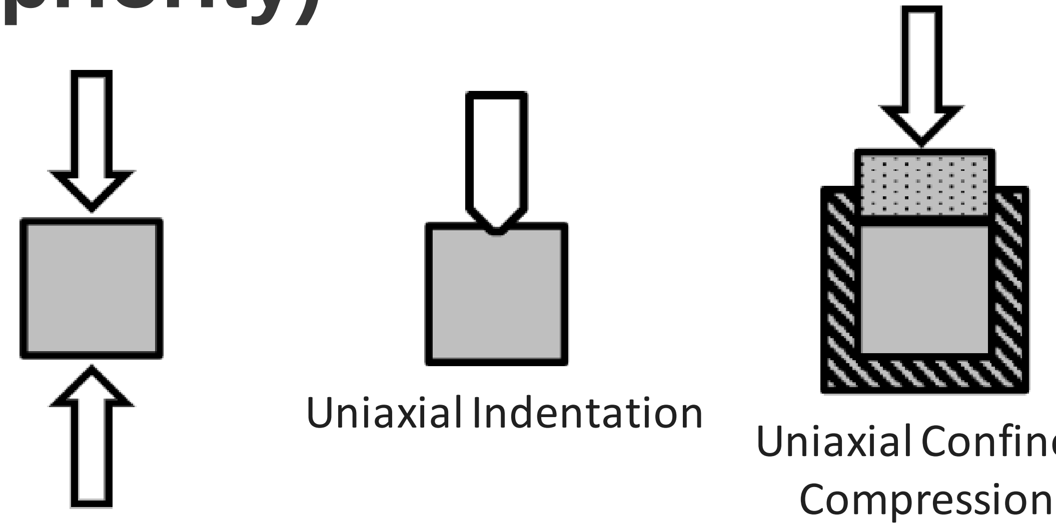
Incubator and Environment

- Fits inside Dr. Henak's incubator
  - 20x21x25 [in]
- Withstands:
  - Incubator environment
  - Lab-grade sanitation procedures
- External power sources are accessible

Henak lab incubator to house the force-controlled bioreactor.

Additional Modifications (lower priority)

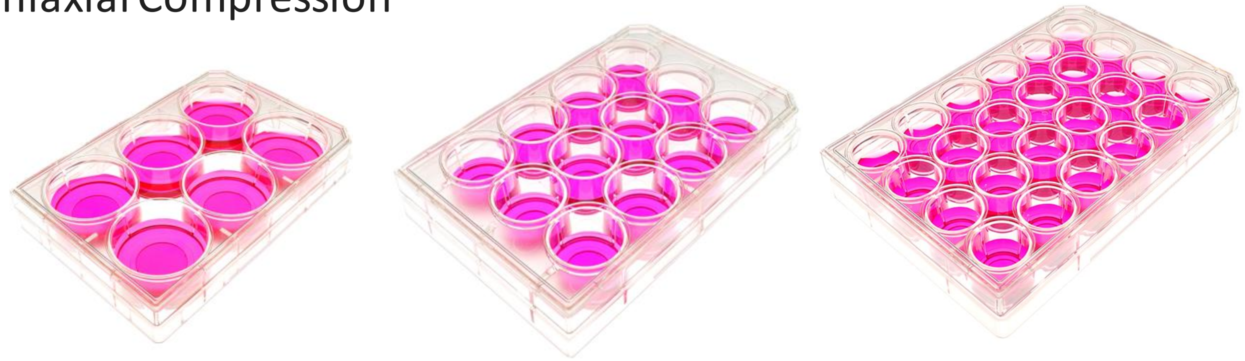
- Modular elements
  - Larger or smaller-sized well plate compatibility
  - Different sizes/shapes of compressive pillars (e.g. for indentation testing)
- Re-feeding mechanism
  - Sample media monitoring and refreshment



Uniaxial Compression

Uniaxial Indentation

Uniaxial Confined Compression

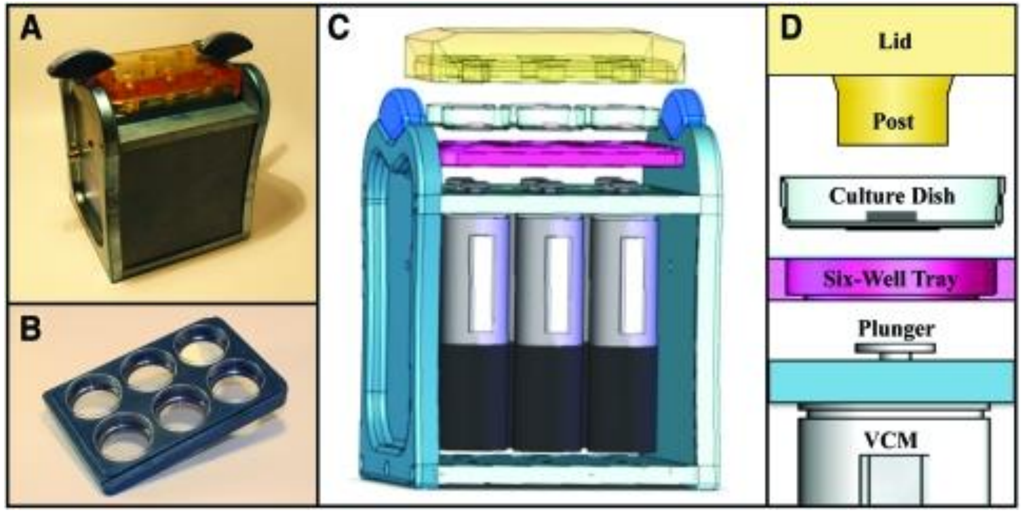


6, 12, and 24 sample well plates

Above figures sourced from: Dr. Corinne Henak, BME 615 (Tissue Mechanics) Lecture Slides
Below figures sourced from: MATTEK Life Sciences, 6, 12, 24 well plates.

Force Control via Voice Coil Motor

- Uses an electromagnetic actuator
  - Stroke of 15 mm
  - Oscillate at velocities up to 1.5 m/s
  - Peak force of 18N, continuous forces of 10 N
- Programmable with LabView
- Static Loads
  - Low Magnitude 0.1-1.0N
  - High Magnitude 1.0-10.0N
- Dynamic Testing
  - Linear spring of 10N/mm
  - Variable sinusoidal amplitude ranging 0.1-10.0N at (1,10) Hz



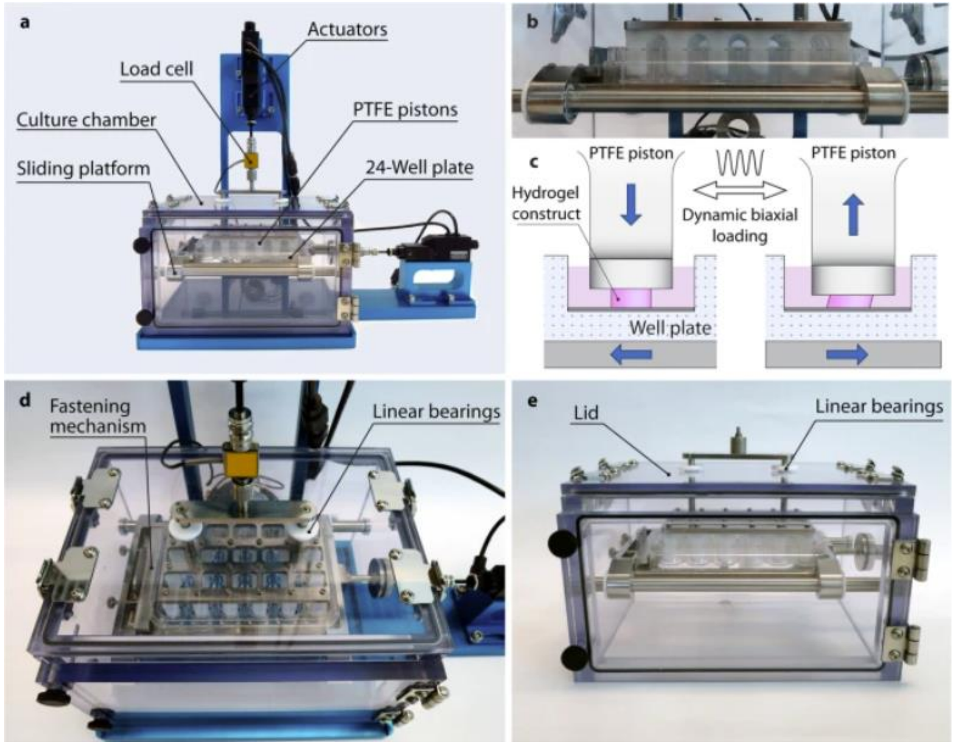
Schematic breakdown of compressive bioreactor utilizing electromagnetic actuation.

Figure sourced from: T. J. Lujan, K. M. Wirtz, C. S. Bahney, S. M. Madey, B. Johnstone, and M. Bottlang, "A Novel Bioreactor for the Dynamic Stimulation and Mechanical Evaluation of Multiple Tissue-Engineered Constructs," *Tissue Eng Part C Methods*, vol. 17, no. 3, pp. 367–374, Mar. 2011, doi: 10.1089/ten.tec.2010.0381.

[5]

Force Control via Closed-Loop Control

- Uses a linear force actuator
  - Motion velocity from 0.00022 mm/s to 8 mm/s
  - Continuous force of 50N
  - Capable of generating uni-axial and biaxial force
  - Load cell attached in series allows for closed-loop control of applied force
- Programmable using LabView
- Chamber and interior components are autoclavable

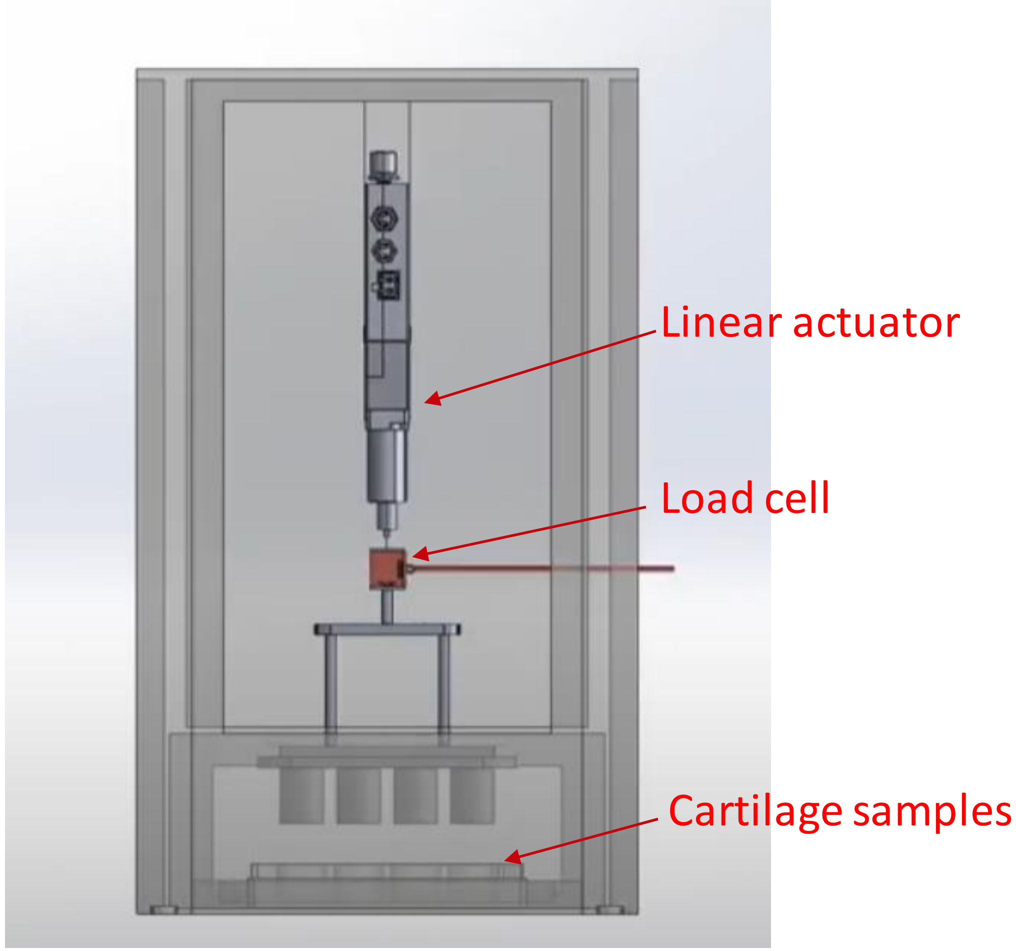


Breakdown of bioreactor controlled via a closed-loop system.

Figure sourced from: C. Meinert, K. Schrobback, D. W. Hutmacher, and T. J. Klein, "A novel bioreactor system for biaxial mechanical loading enhances the properties of tissue-engineered human cartilage," *Sci Rep*, vol. 7, no. 1, Art. no. 1, Dec. 2017, doi: 10.1038/s41598-017-16523-x.

Potential Designs: Linear actuator (Design 1)

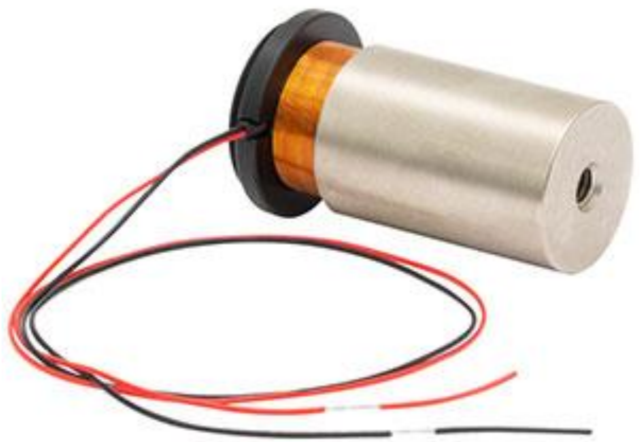
- Force application and control
  - Closed-loop PID control (implemented externally in LabVIEW)
- Drawbacks
  - Time and difficulty to implement PID and tune parameters
  - Cost: linear actuator, load cell, actuator software (~$3000 total)



Preliminary conceptual CAD design using linear actuator

Potential Designs: Voice coil actuator (Design 2)

- Force application and control
  - Electrical current is applied to generate magnetic field and force
  - Open-loop control (no feedback control necessary)
- Advantages
  - Cost: cheaper (~$300 per actuator)
- Drawbacks
  - No feedback control of force; need to directly correlate current with force applied to cartilage



Depiction of a voice coil motor (i.e., electromagnetic actuator)

Image sourced from: www.thorlabs.com/thorproduct.cfm?partnumber=VC250/M

Conclusion

- **Why a solution is needed:** apply loading to correlate long-term mechanical stimuli with cartilage metabolic response and disease state
- Empathy plan
- Current approaches used in literature
- Potential design approaches for our specific client need

Acknowledgements

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Thank you!
Questions are now welcome.

References

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[2] Walsh, S. K., Skala, M. C. & Henak, C. R. Real-time optical redox imaging of cartilage metabolic response to mechanical loading. Osteoarthritis and Cartilage 27, 1841–1850 (2019).

[3] Walsh, S. K., Soni, R., Arendt, L. M., Skala, M. C. & Henak, C. R. Maturation- and degeneration-dependent articular cartilage metabolism via optical redox ratio imaging. Journal of Orthopaedic Research 40, 1735–1743 (2022).

[4] Han, S.-K., Wouters, W., Clark, A. & Herzog, W. Mechanically induced calcium signaling in chondrocytes in situ. Journal of Orthopaedic Research 30, 475–481 (2012).

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[6] C. Meinert, K. Schrobback, D. W. Hutmacher, and T. J. Klein, “A novel bioreactor system for biaxial mechanical loading enhances the properties of tissue-engineered human cartilage,” *Sci Rep*, vol. 7, no. 1, Art. no. 1, Dec. 2017, doi: 10.1038/s41598-017-16523-x.

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