GTO-on-a-Chip System

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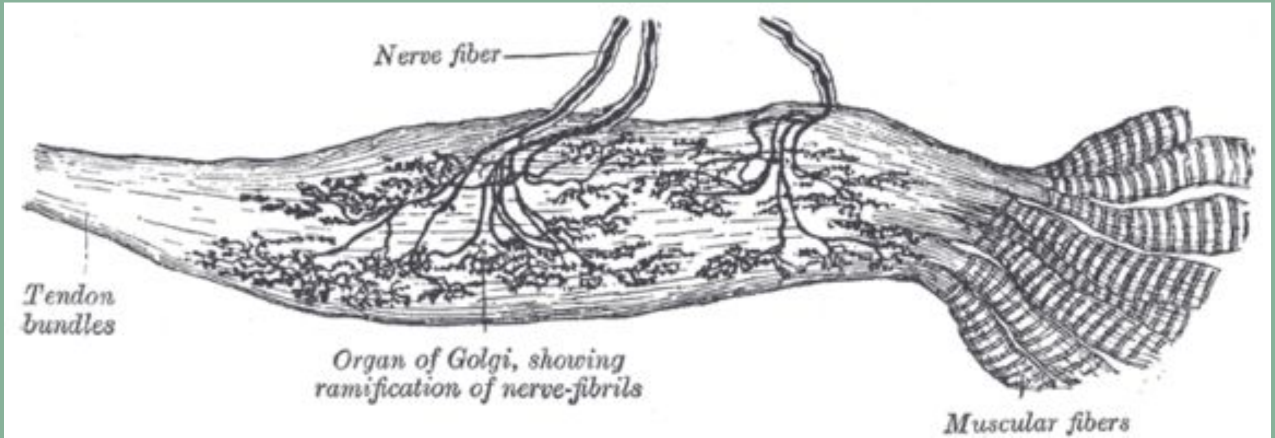
Introduction

The golgi tendon organ (GTO) functions to give the brain proprioception to its skeletal muscles

- Stress Sensitive Cation Channel

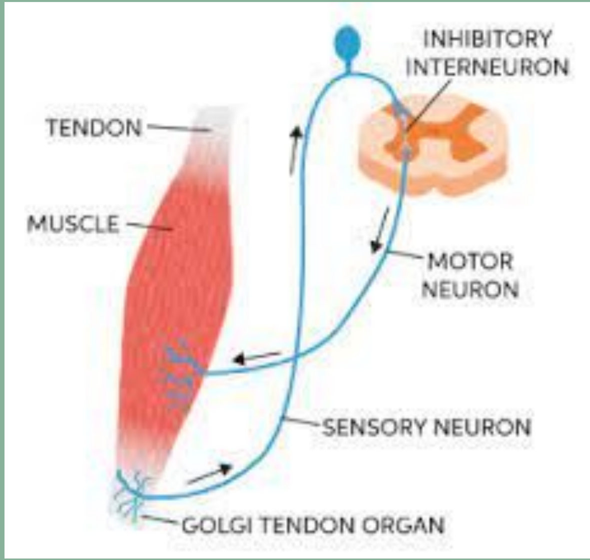


[1]

Introduction

There are key barriers to creating GTO on a chip

- Neurotendinous spindle structure

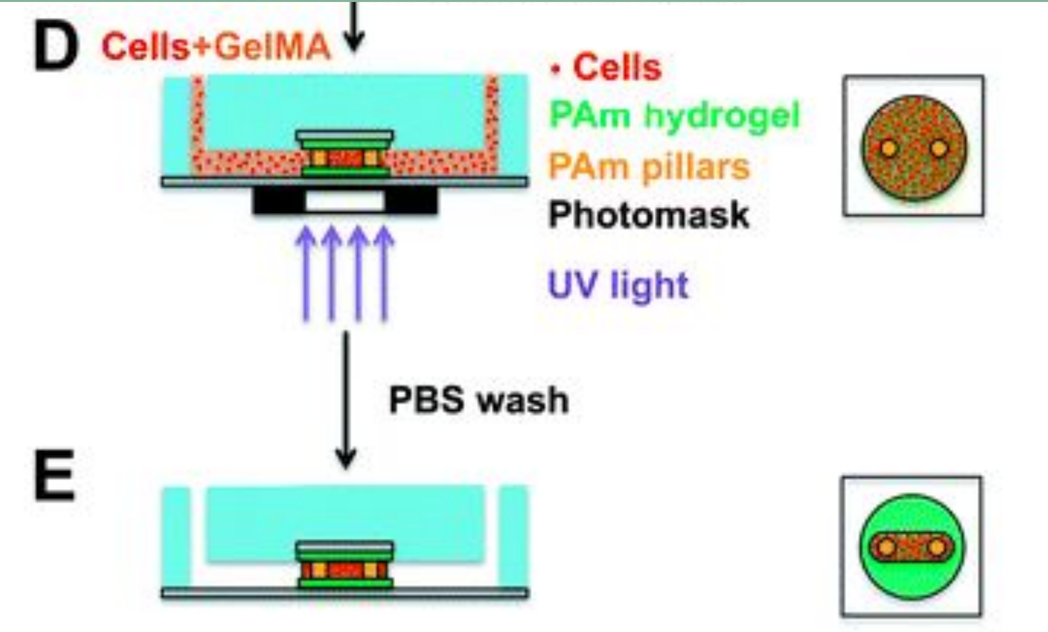


[2]

Introduction

Muscle on a chip models have been previously developed

- GTO behavior not isolated

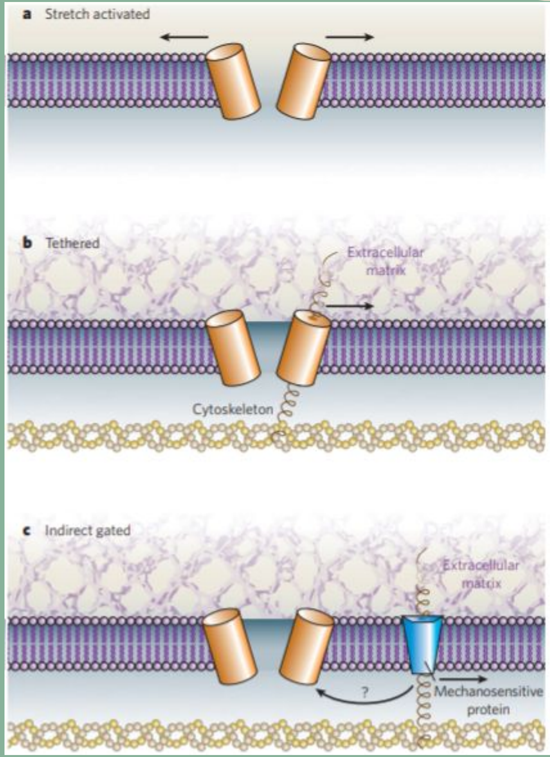


[3]

Introduction

Stress activated channels are applicable to approximations of other bodily systems:

- Inner ear
- Lungs
- Bladder

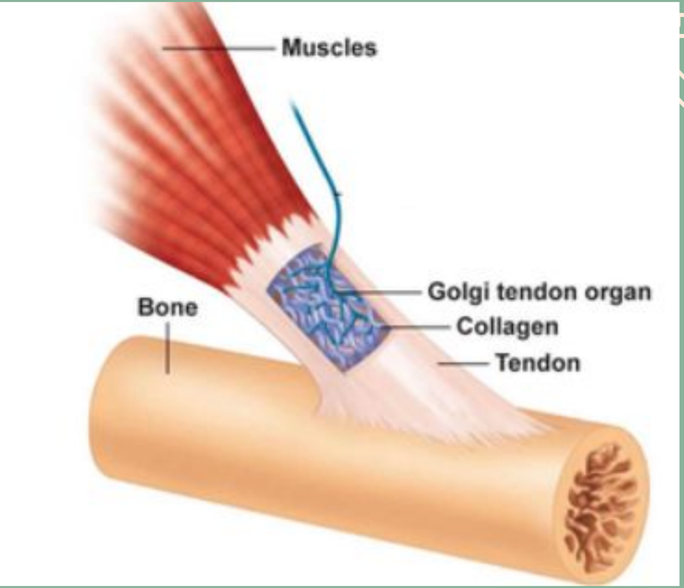


[4]

Introduction

There are diseases associated with muscle function that can be more easily studied with muscle on a chip models

- Cachexia
- Sarcopenia

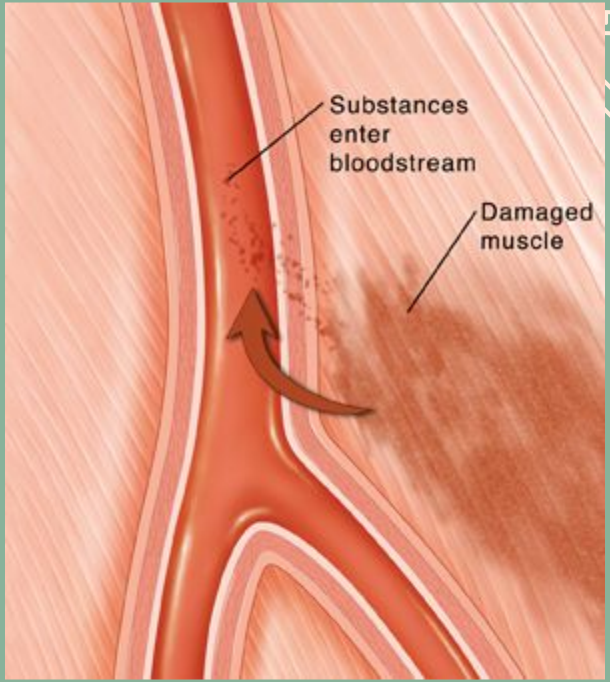


[5]

Introduction

Various drug side effects on muscle tissue could be more accurately studied with muscle on a chip systems that contained GTOs.

- Metformin (treats diabetes)
- Statin (treats high cholesterol)

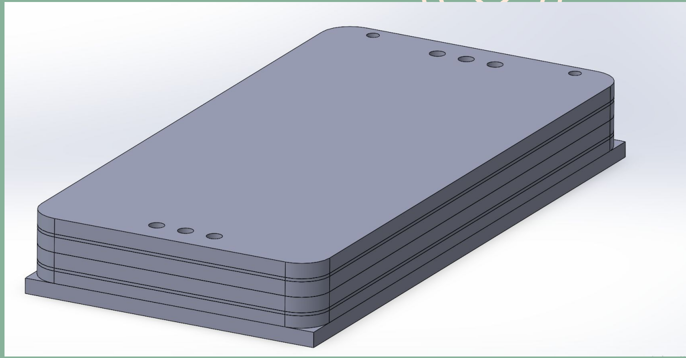


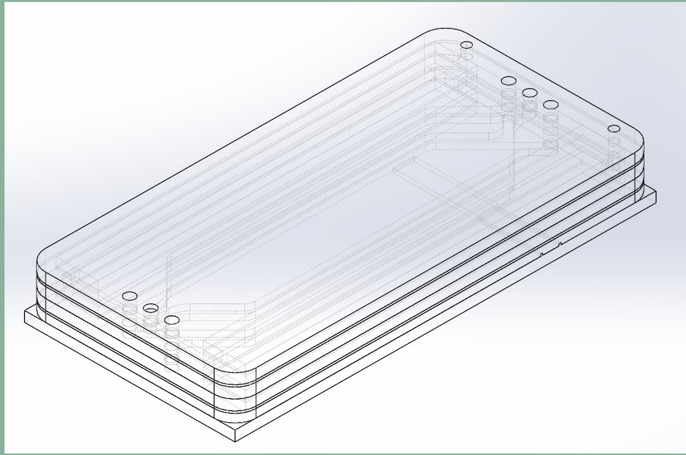
[6]

Device

- Simulate GTO operation
- Inspired by pulmonary and muscle specific BioMEMS devices

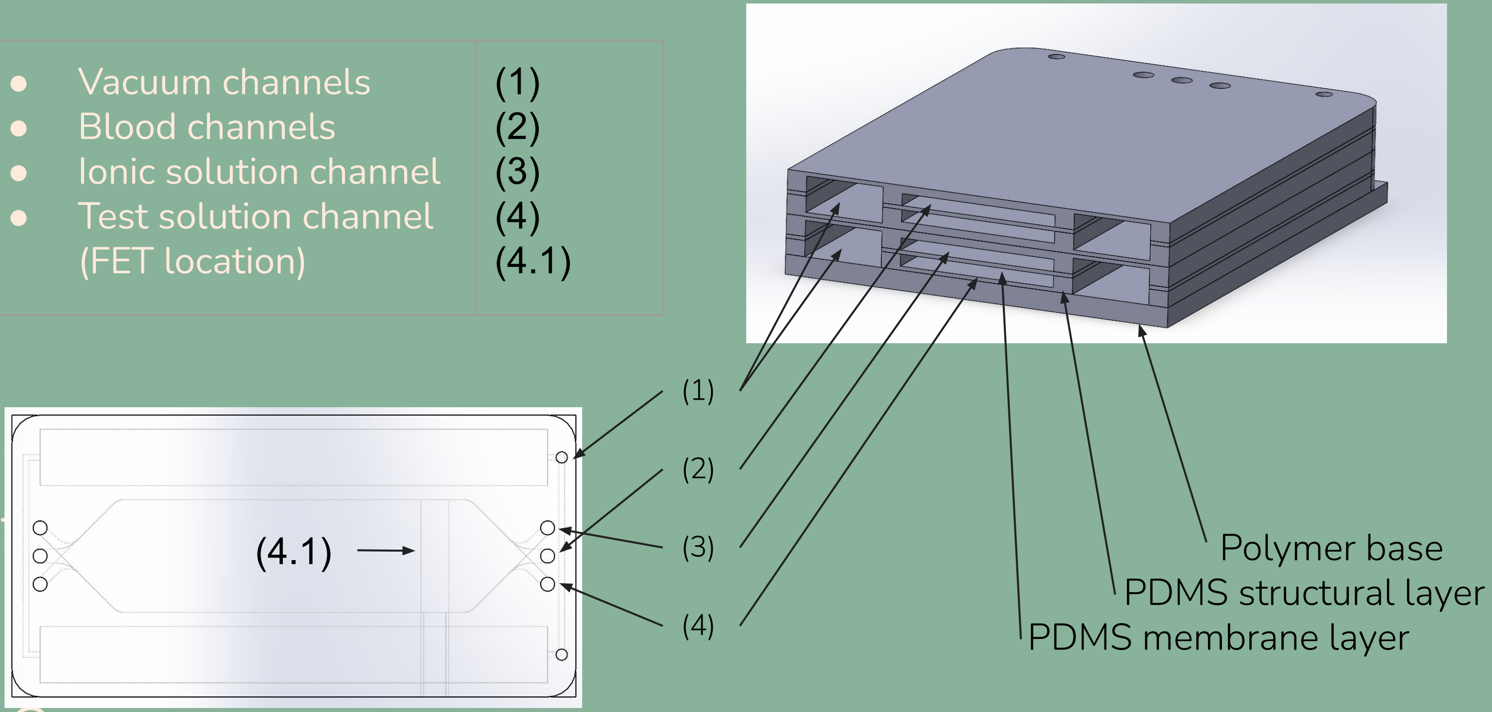
- All-in-one design
  - Cell culture
  - Cell stretching
  - Golgi tendon simulation
- Open or closed-loop feedback operation
  - Calibration
  - Comparison





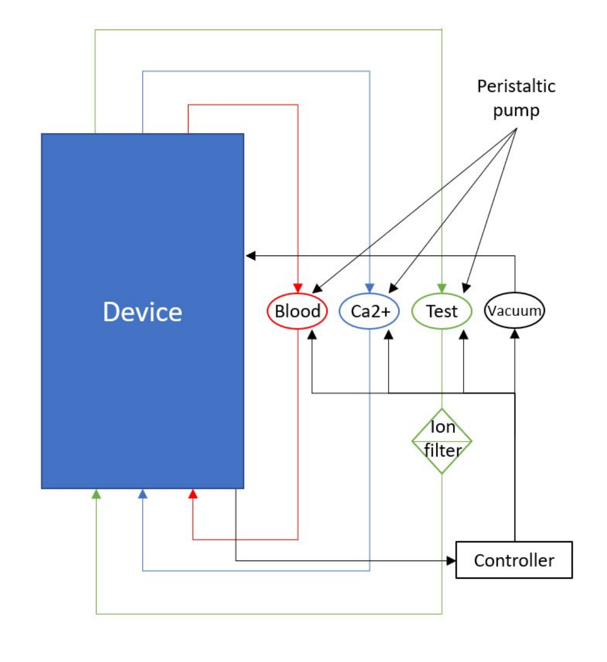
Layout

• Vacuum channels	(1)
• Blood channels	(2)
• Ionic solution channel	(3)
• Test solution channel	(4)
(FET location)	(4.1)

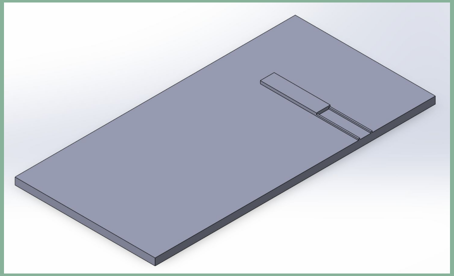


System

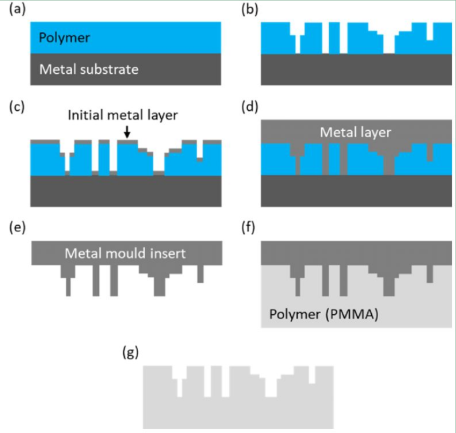
- 1 Controller
- 3 Peristaltic pumps
- 2 Vacuum pumps
- 3 independent circuits
  - Oxygen rich blood
  - High concentration ion solution
  - Test solution (filtered)
- FET and Capacitive pressure sensor feedback



Base Plate Fabrication



- Silicon Surface Micromachining
  - Fully compatible with microfluidic sensors
  - Low Cost

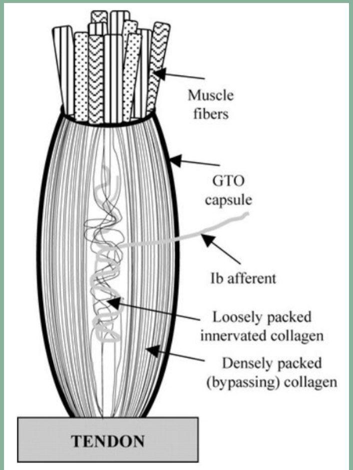


- LIGA
  - Constructs microstructures made of polymers, ceramics, metals, etc.
  - Easily integratable with biomimetic sensors
    - Force/pressure changes resistivity of conductive polymers
    - Can act as actuator between systems

[7]

Membrane Fabrication

- Needs to behave similar to a GTO
- Stretching activated by two collagen sections
  - Innervated collagen near center of structure
    - Packed with GTO afferents
    - Stretches and aligns when activated
  - Dense collagen forming capsule surface
    - Don’t interact with afferent
  - Packed tighter near ends of GTO
- Create similar collagen network without muscle fibers, tendon, of afferent



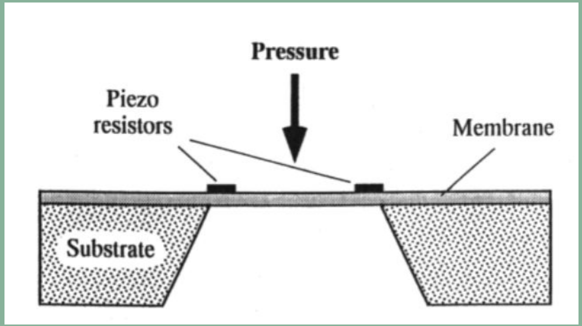
[8]

$$T^{col} = K^{col} \times A^{col} \times \text{sign}\,(x - x_{rest}) \times \left\{ \left[\frac{\text{abs}\,(x - x_{rest}) + x_{rest}}{x_{rest}} - 0.99 \right]^3 - 10^{-6} \right\}$$

[8]

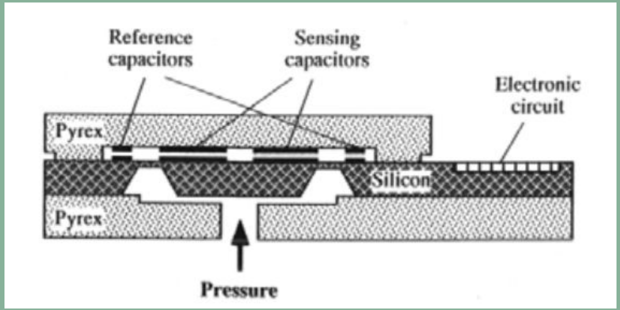
Biomimetic Membrane Sensors

- Piezoelectric Pressure Sensor
  - Used on small, deflectable membranes
  - Deflection→Change in resistance



[9]

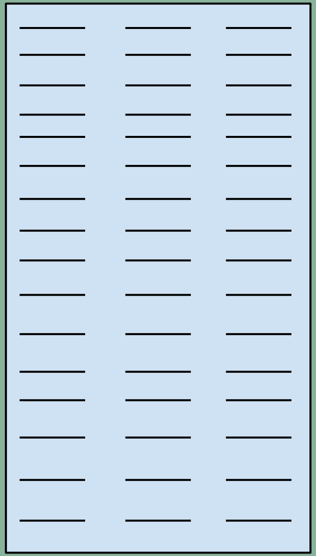
- Capacitive pressure sensor
  - Uses change in capacitance between two metal plates
  - Higher linearity, sensitivity, and stability
  - Higher production cost and less effective for complex signals

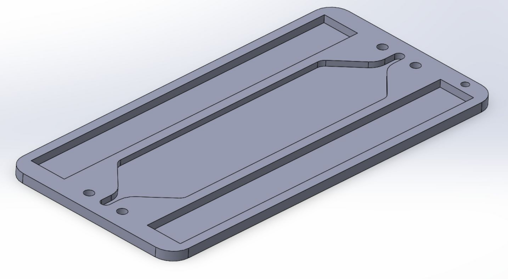
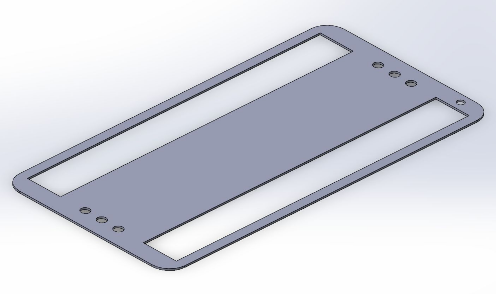
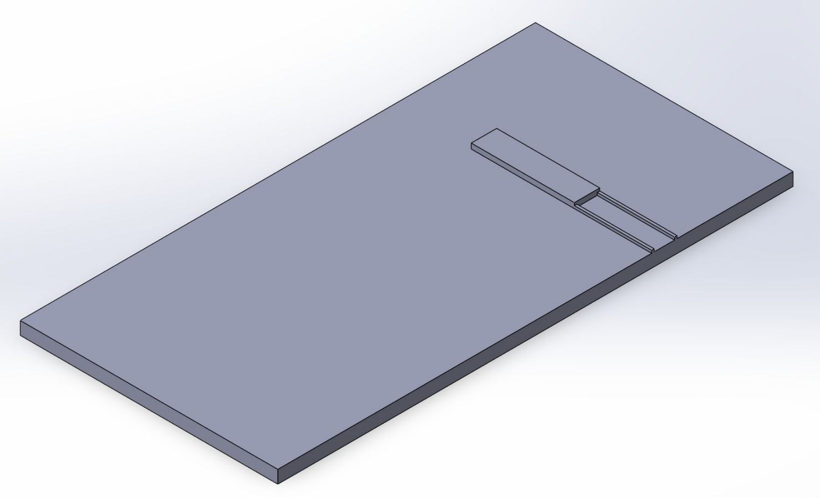


[9]

Ion Membrane Fabrication

- Pores open via vacuum stretching
  - Activated when capacitor displacement is detected
- PDMS layer
  - Highly flexible to deform with the vacuum
- Fluorine based Reactive Ion Etching
  - Complements molding with SU-8 photoresist



Biocompatibility

External device with no body contact:

- No ISO of FDA requirements

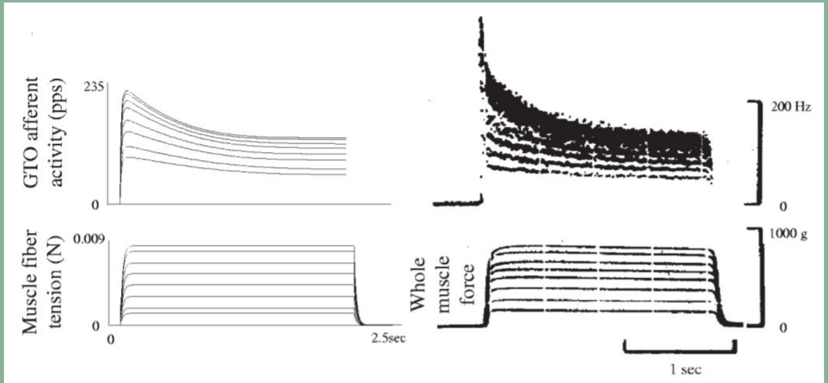
Material requirements:

- Membrane
  - Skeletal muscle growth
  - Channel geometry for ion transfer
- Channel structure
  - Limiting ion absorption and diffusion
- Effective ion filters for FET unsaturation

Testing (1)

Golgi Tendon Property

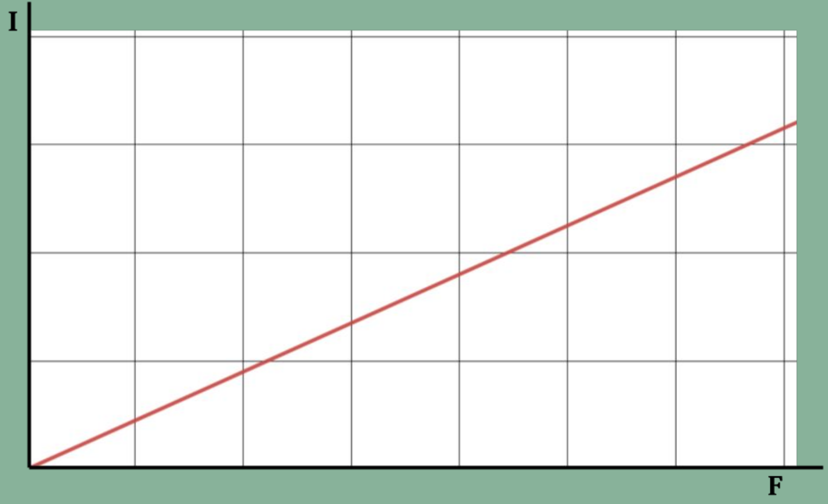
Tension Proportionality (*Steady State* GTO Activation is Linearly Proportional to Muscle Tension) [10]



[8]

Method for Testing

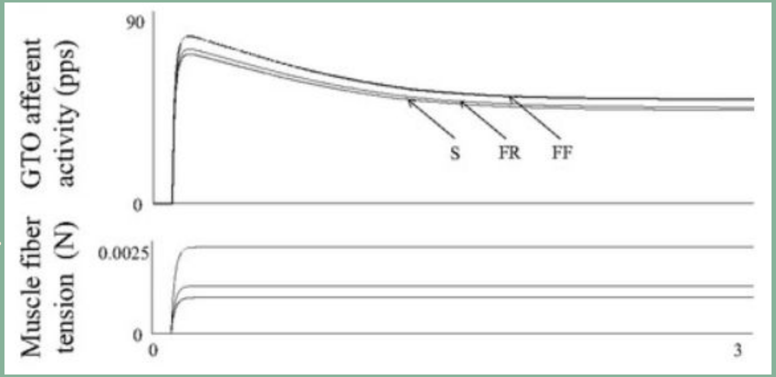
Apply constant voltage to FET, apply range of vacuum pressures in chambers. Graph FET current (as t -> inf) against vacuum pressure:



Testing (2)

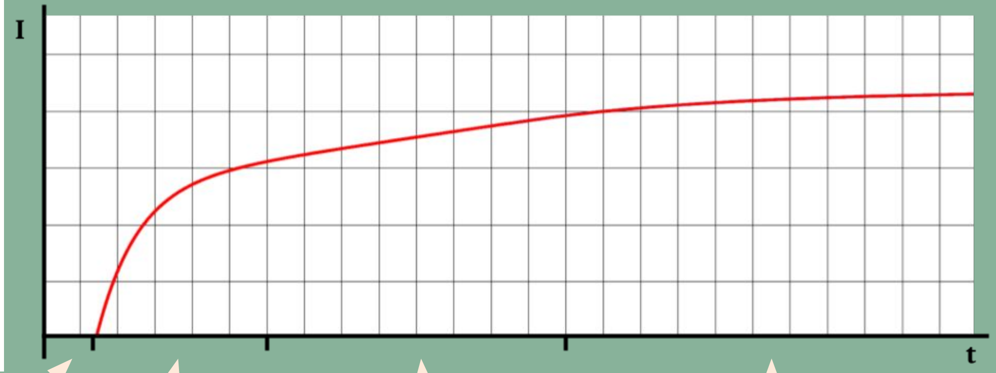
Golgi Tendon Property

Stress Relaxation (GTO Typically modeled as Standard Linear Viscoelastic Solid) [8]



Method for Testing

Apply constant strain in vacuum chambers, apply constant voltage to FET, verify FET current resembles:



Gate Threshold not met

Stress Relaxation Dominates

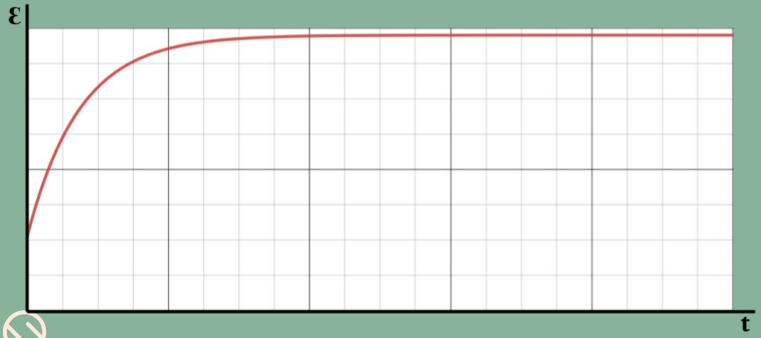
Passive Stress Dominates

Ligand Binding Dominates

Testing (3)

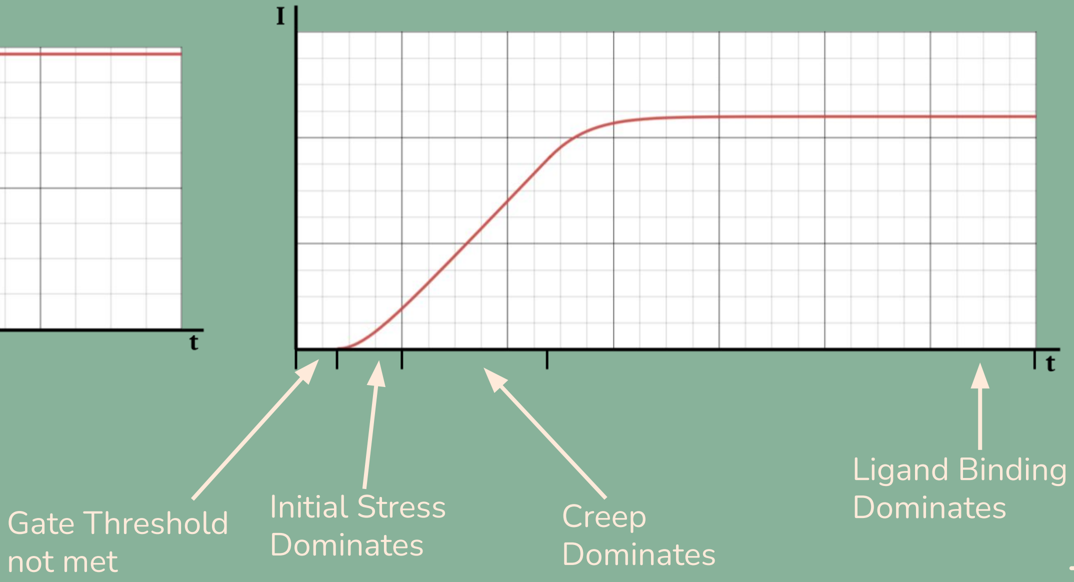
Golgi Tendon Property

Creep (GTO Typically modeled as Standard Linear Viscoelastic Solid) [1]



Method for Testing

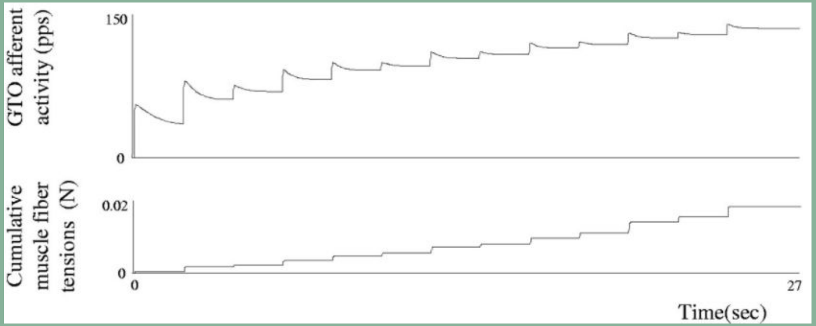
Apply constant stress in vacuum chambers, apply constant voltage to FET, verify FET current resembles:



Testing (3)

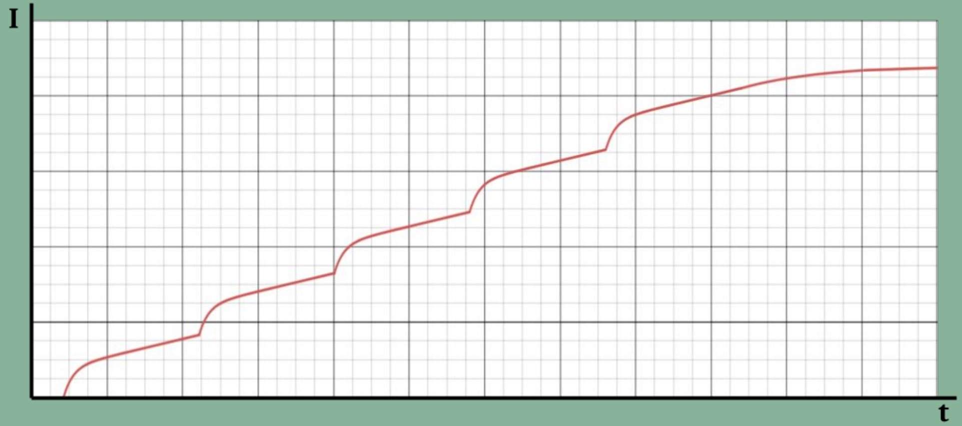
Golgi Tendon Property

Summation Response (GTO Activity increases as more motor units engaged) [8]



Method for Testing

Apply constant voltage to FET, apply vacuum pressure as series of step functions with diminishing amplitude increases. [8] Verify FET current resembles:



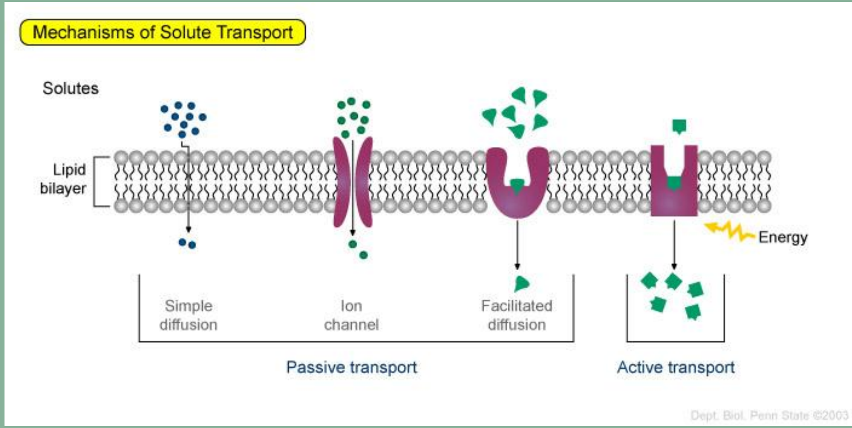
Testing (3)

Golgi Tendon Property	Method for Testing
Ion Selectivity (Stretch Sensitive Ion Channels are only meant to release Ca+)	Repeat stress relaxation test with Na+ in ion chamber:

Testing (4)

Golgi Tendon Property

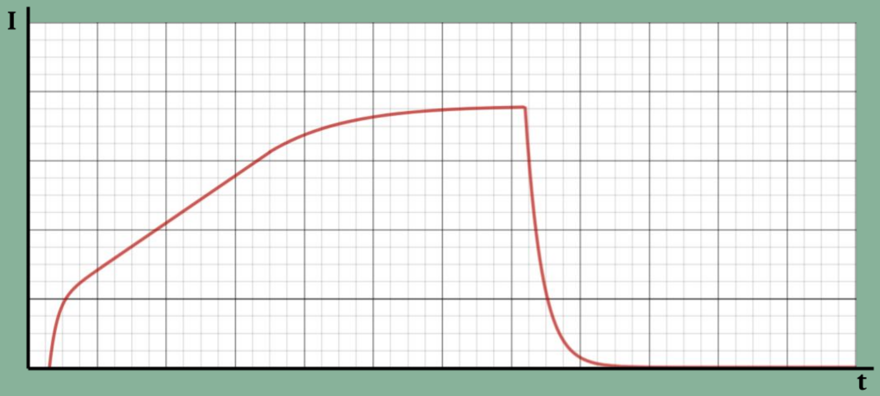
Extracellular Calcium concentration dissipates after Golgi Tendon activation ends



[11]

Method for Testing

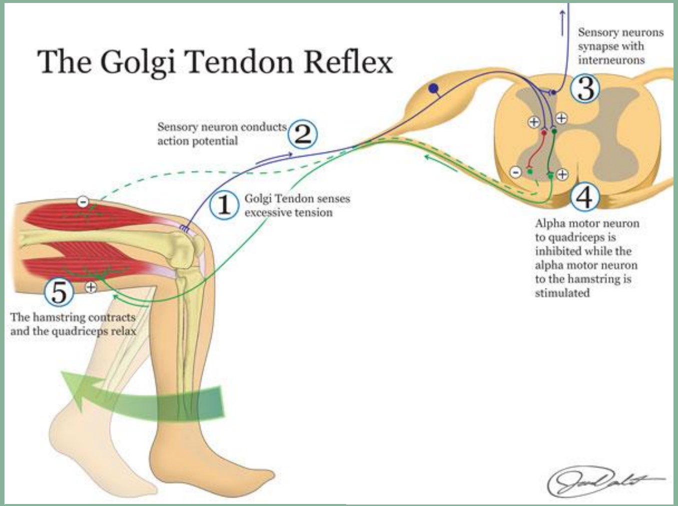
Apply constant isFET voltage and pressure, wait until isFET current reaches steady state, then deactivate pressure chambers:



Testing (5)

Golgi Tendon Property

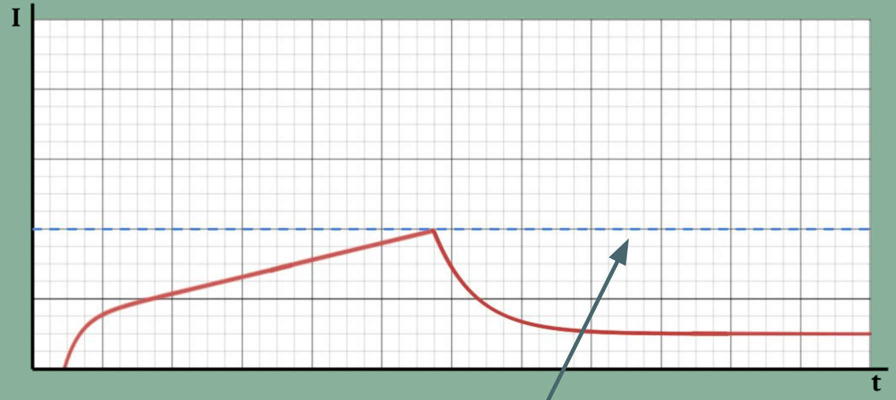
Reflex (GTO works to prevent harmful levels of muscle tension) [12]



[13]

Method for Testing

Apply linearly increasing vacuum pressure, verify GTO feedback downsteps vacuum at set value:



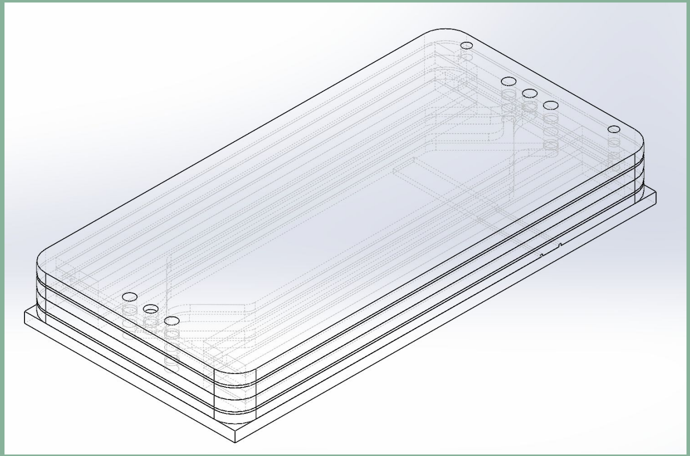
Force Threshold (Current Max Force Levels At)

Limitations

1. No proper modeling of action potential or nerve fibers
2. Only modeling one GTO fiber
3. In a true GTO, passive stretch doesn't cause activation
4. Standard linear elastic solid is an approximation of material properties

Conclusion

- GTO/Muscle on a chip not fully developed
- Device limited to full GTO scale, but models main ion activation behavior
- Future Directions
  - Device dimensioning
  - Test how GTO responds to different drugs
  - Model different disease state responses
  - Apply principles to model other mechanosensitive channels in the body
- Future Improvements/Revisions
  - Populate with true mechanosensitive channels
  - Integrate with nervous system on a chip



Sources

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