# Heart-on-a-chip

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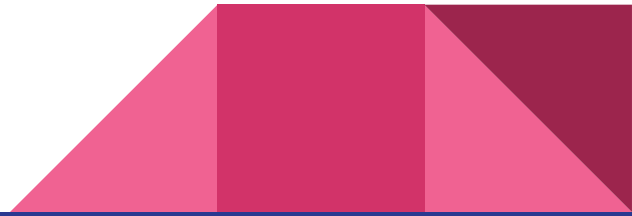
# Outline

- Background - Heart on a chip
  - Current uses - disease states studied - pharmacological studies
  - Technical considerations
- Basic overview of construction
  - Current Technology
  - Specific Parameters
    - Cell concentration, device geometry, etc...
- Proposed improvement
  - Microfluidic Flow
  - Electrophysiology
  - Precise Microenvironmental control
- Summary



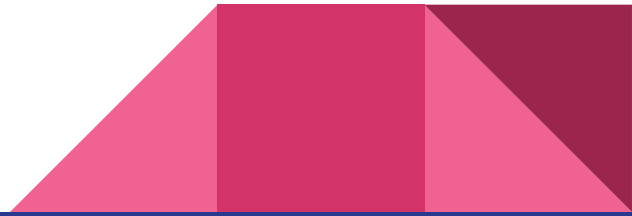
# Background

Current Uses

1. Drug Development
2. Disease Replication

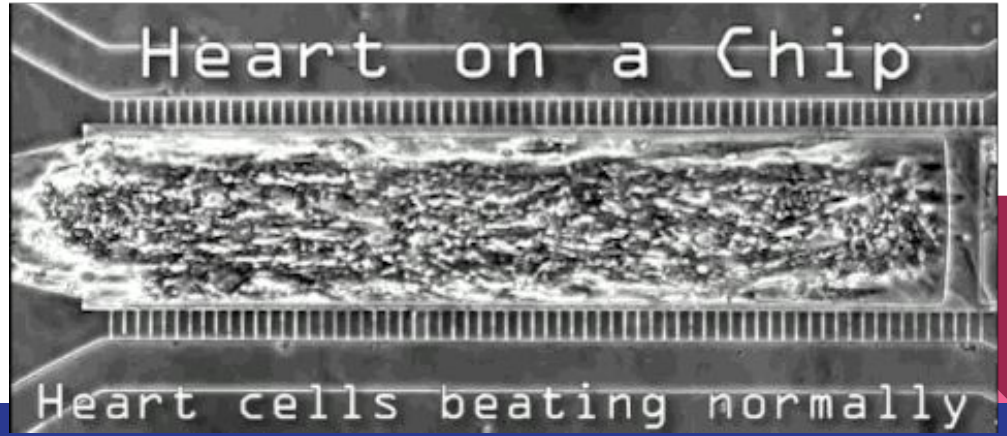
Considerations

1. Seeding Density
2. Hydrogel type
3. Electrical Conditioning Parameters
4. etc...



# Reproducing human physiology

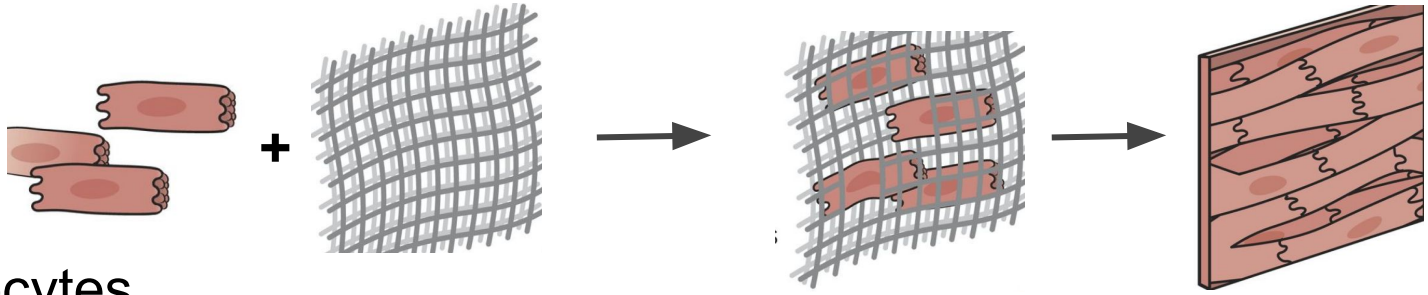
- Multicellular vascular or epithelial interfaces of organs.
  - Blood vessel network
- Tissue-level organization of parenchymal cells.
  - Myocardium and heart



# Current Uses

- Cardiotoxicity
  - Heart electrophysiology dysfunction & myocardial damage
  - No suitable in vitro models for pharmaceutical studies
- Heart-on-a-chip + microfluidics
  - Use less cardiomyocytes for high-throughput experiments

# Materials

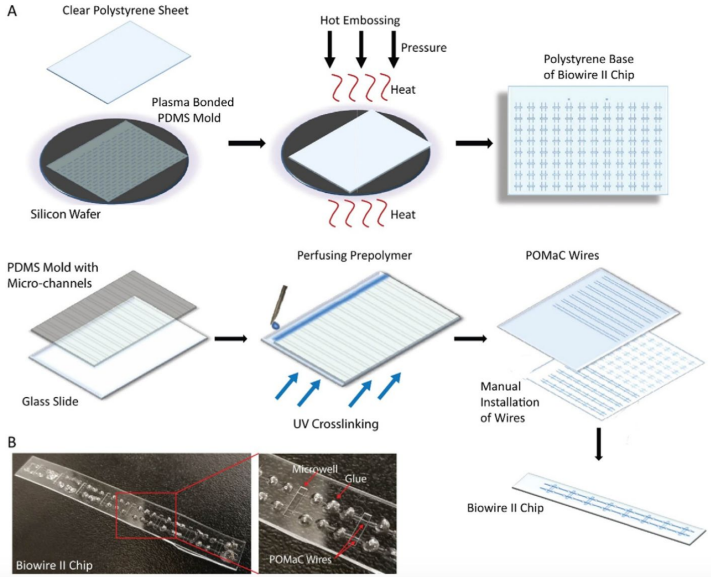


- Cardiomyocytes
  - Human pluripotent stem cell derived cardiomyocytes
  - Animal cells
- Polydimethylsiloxane (PDMS)
  - Highly compliant and deformable
  - Great for building structures
- Poly(octamethylene maleate (anhydride) citrate) (POMaC)
  - Elastic and moldable - good cardiac cell attachment
  - Biocompatible - decreased foreign body response

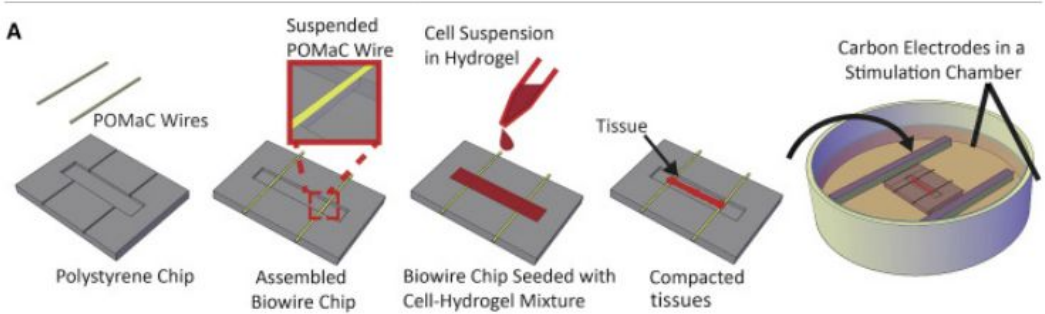
# Overview of Current Technology - Biowire Design

## Device Production Steps:

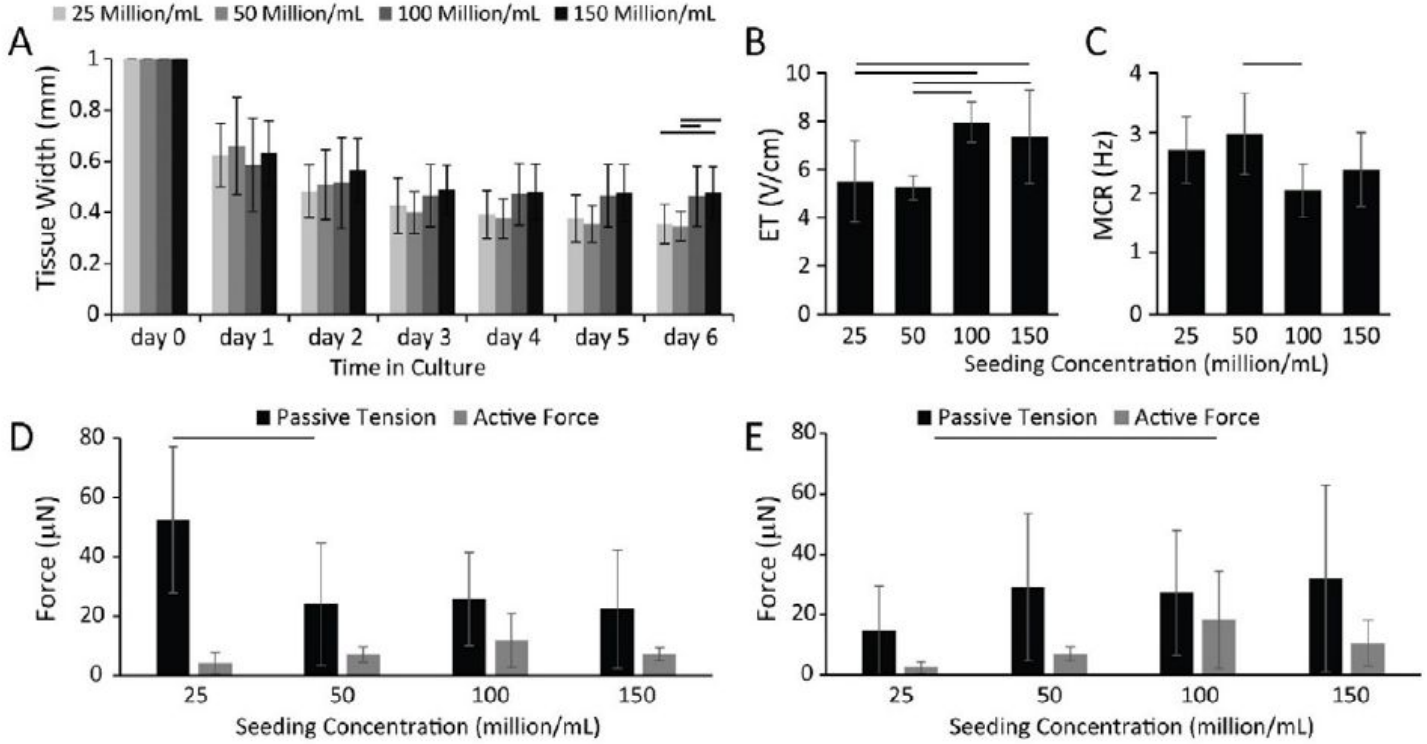
1. Polymer Base & POMaC wire Formation




2. Cell Population

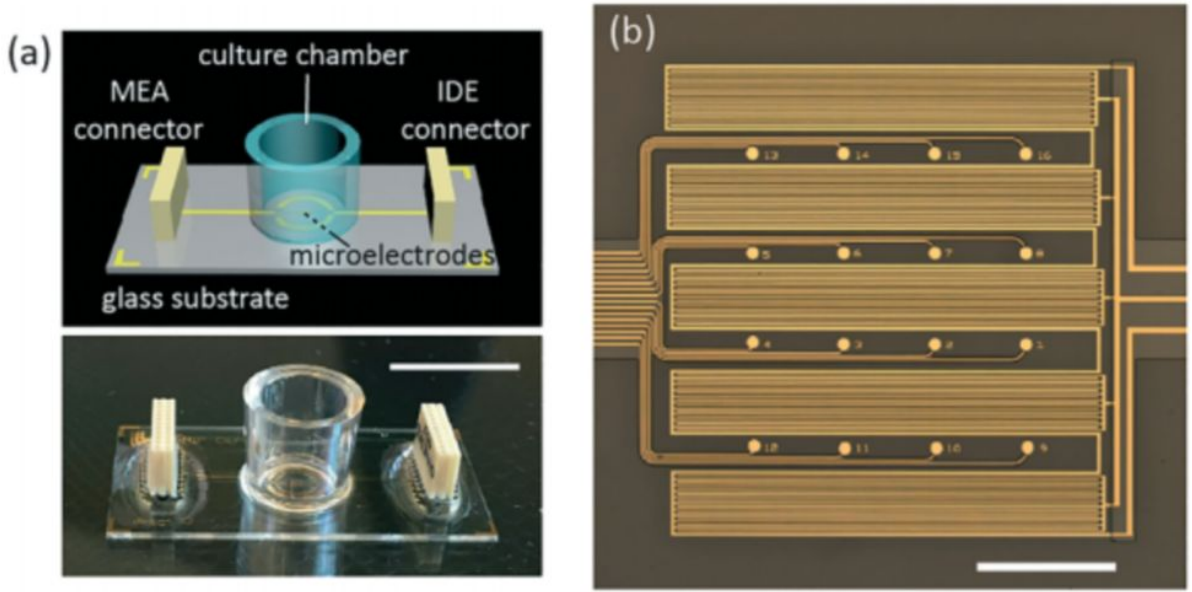


# Overview of Current Technology - Biowire Design



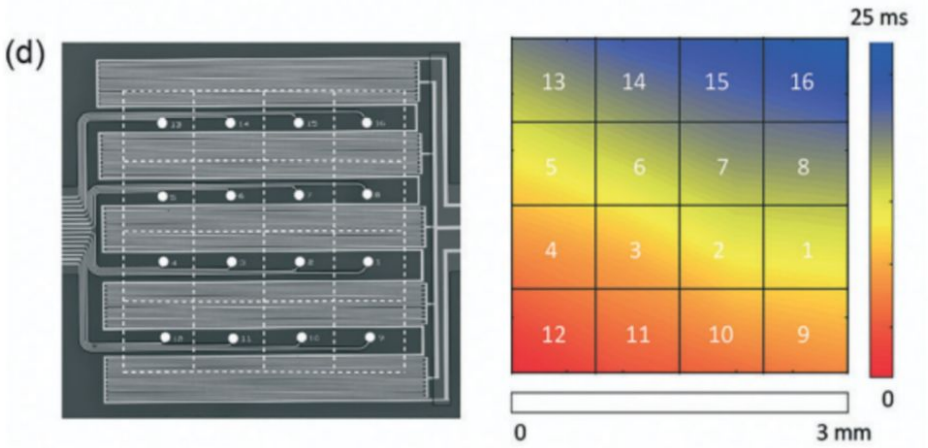
# Overview of Current Technology - Electrical Recordings for heart-on-a-chip

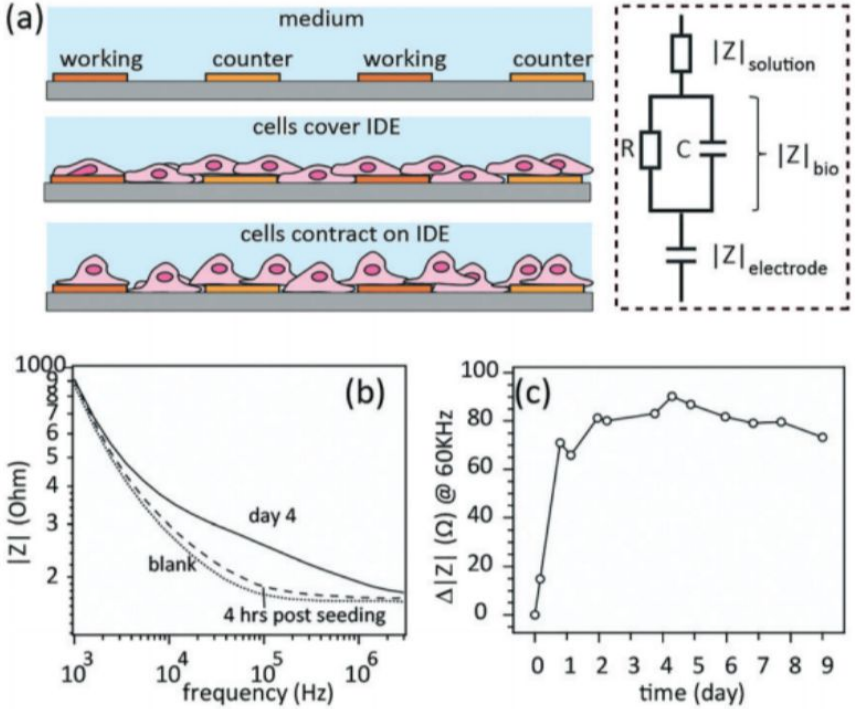
- Interpenetrating MEA and IDE geometries for measuring electrophysiology and contraction simultaneously



# Overview of Current Technology - Electrical Recordings for heart-on-a-chip

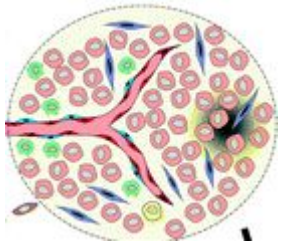
$$K = 2^3 \sqrt{\frac{S}{W}/\left[L(N-1)\right]}$$

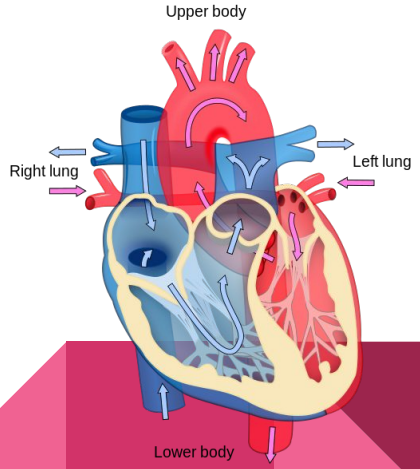


# Issue with Past Systems

- Biowire system has no microfluidic components to study contractile flow
- Biowire system lacks precise electrophysiologic measurement
- Qian et. al. chip lacks microfluidic components to study contractile flow
- Qian et. al. chip lacks precise microenvironment controls



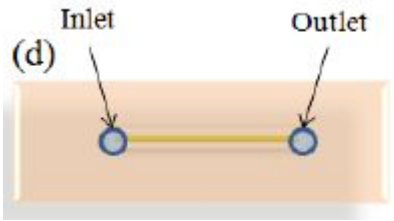


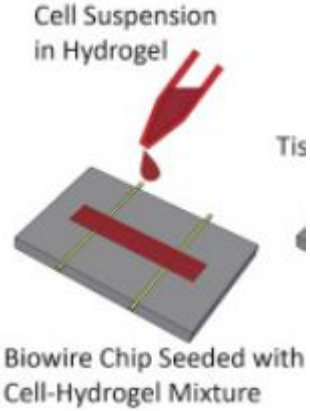
# Proposed Solutions

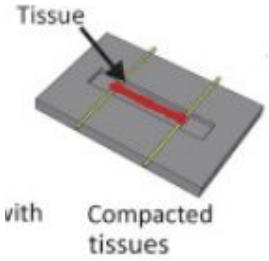
- Microfluidic and electrophysiologic addition to Biowire II Platform to incorporate blood flow with the cardiac myocytes and measure electrophysiology.
- Combination of four variables: cardiac electrophysiology (MEA), cell adhesion, contractility, and **FLOW**
- Introduce a microchannel for blood flow that we could line with the cardiac myocytes
- Stimulator at the inlet to begin the propagation of action potential driven contraction
- 2 layers: Hollow biowire platform with interpenetrating IDE and MEA, cardiac myocytes around wire

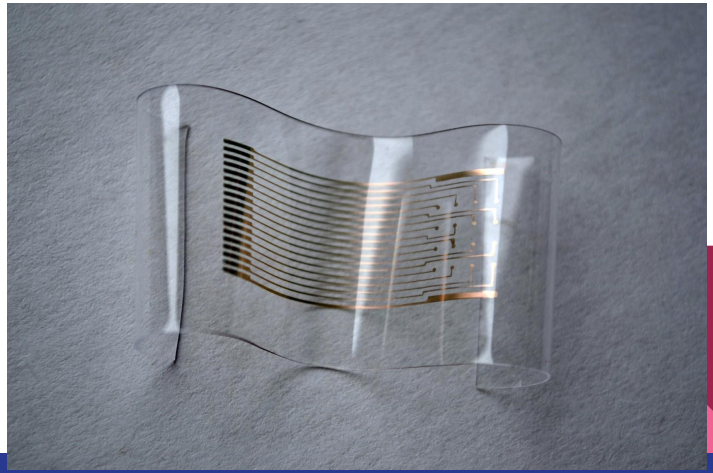
# Device Design

1. Fabricate flexible MEA and IDE on PDMS using standard photolithography and electron beam evaporation for patterning
2. Create polystyrene chip via hot embossing with inlet and outlet
3. Create POMaC wires via PDMS mold and UV crosslinking
4. Manually place POMaC wires
5. Manually form PDMS with MEA and IDE into cylinder and glue to either end of channel with inlet and outlet
6. Seed with cell suspension and culture
7. Electrically stimulate
8. Mimic pressure experienced by myocardium at inlet and outlet with blood



# Improvements

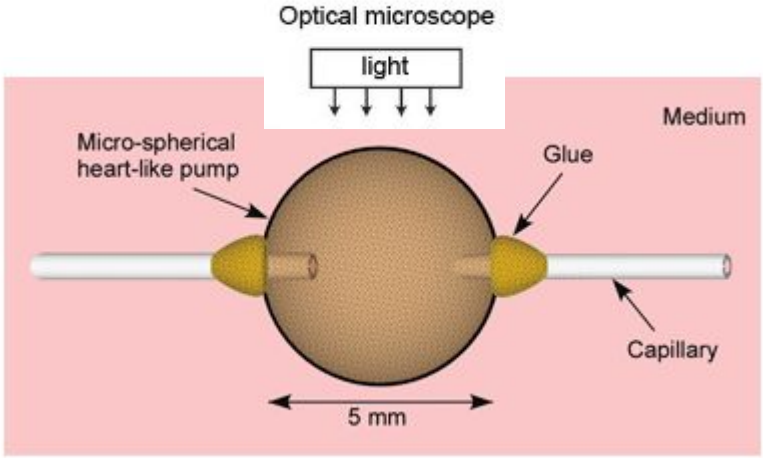
- Precise microenvironment control, cell contractility and electrophysiology measurement in one device
- Visualize cardiac flow in a heart on a chip device

# Precise Microenvironment

- Control environment in well and seeding of wells to obtain optimal cardiomyocyte formation
- Optimal seeding density of 50 million cells/mL
- Collagen hydrogel blended with fibrin
- 10% seeding of cardiac fibroblasts
- Electrical conditioning to induce physiologic function

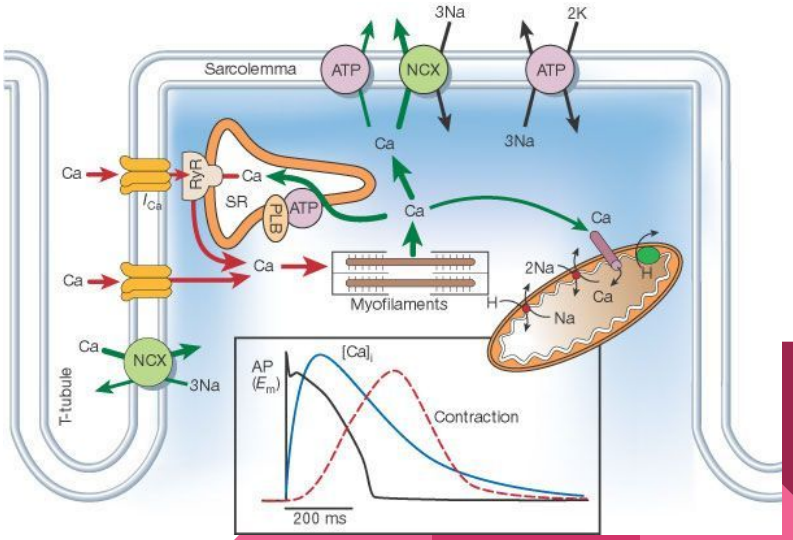
# Microfluidic Flow

- Hollow PDMS tube attached to either side of capillary
- Cardiomyocytes beat causing contraction of PDMS tube and movement of fluid
- Visualize the flow fluorescently



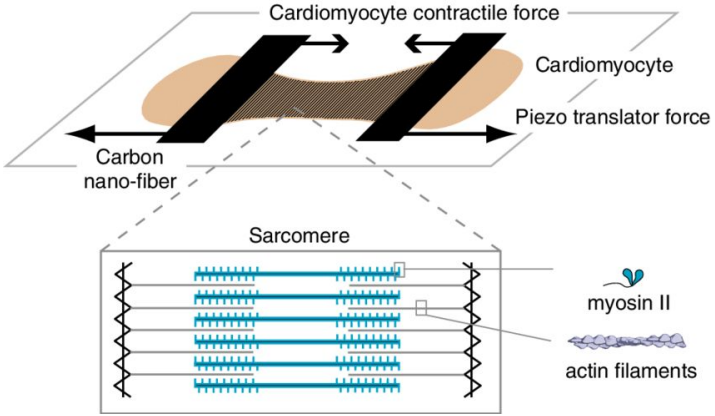
# Precise Electrophysiology

- MEA and IDE interpenetrated concentrically
- Track AP/voltage propagation
- Force-frequency relationship, post-rest potentiation
- Excitation/contraction coupling



# IDE/MEA Process Steps

- How will we introduce the IDE/MEA into the chip?
  - Integrative approach
  - Use standard photolithography and electron beam evaporation for patterning
  - Use bonding techniques to combine Biowire and IDE/MEA components
  - Simple adhesive backing on the IDE/MEA
  - Use UV curable silicone glue - i.e. Loctite SI5240



# Summary

- Improved heart-on-a-chip model for drug discovery and disease replication
- Includes electrophysiology, flow, contractility and precise microenvironment control

# References


1. Qian et. al. *Lab Chip,* 2017, 17, 1732.
2. Tanaka et. al. *Lab Chip*, 2007, 7, 207-212.
3. Zhao et. al. *Matrix Biology,* 2020, 85-96, 189-204.

# Questions?