Predictive Modeling of Heart Failure using Chamber-Specific Engineered Heart Tissue

Team #32: Kylie Chan, Megan Chavez, Justin Liu, Alexa Roa, Tiffany Zhang

Dr. Christopher Anderson, PhD, Dr. Andrew D. McCulloch, PhD, Cardiac Mechanics Research Group

Department of Bioengineering, University of California San Diego, La Jolla, CA, USA

UC San Diego
JACOBS SCHOOL OF ENGINEERING
Shu Chien-Gene Lay Department of Bioengineering

Background & Motivation

Problem

Disease progression of **heart failure exhibits chamber-specific variation**. Current cardiac models treat the heart as a generalized system, limiting the ability to capture chamber-specific mechanisms.

Objective

Develop a **lineage-specific network model** to investigate how left and right heart chambers respond differently to mechanical stress and contribute to chamber-specific variations in heart failure.

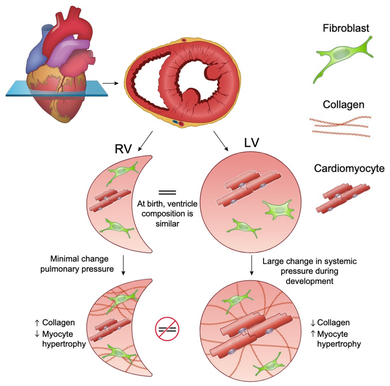
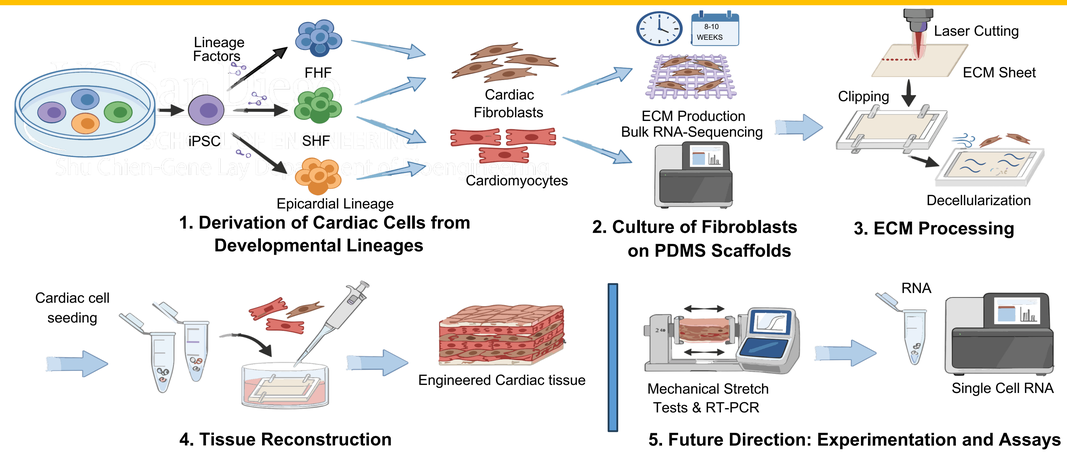


Figure 1. Developmental differences in right and left ventricular cellular composition. Taken from [1].

Culture and Differentiation of Chamber-Specific Cardiac Tissues



1. Derivation of Cardiac Cells from Developmental Lineages

2. Culture of Fibroblasts on PDMS Scaffolds

3. ECM Processing

4. Tissue Reconstruction

5. Future Direction: Experimentation and Assays

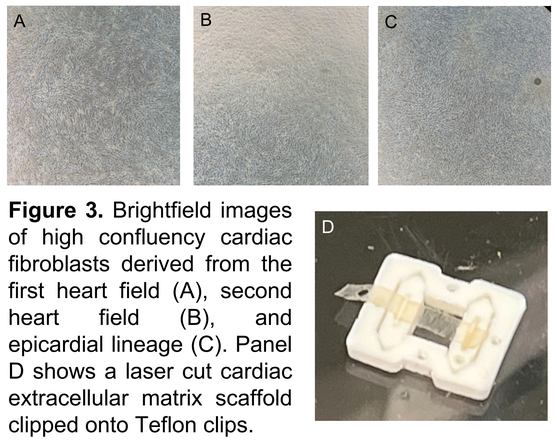
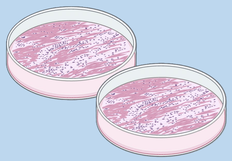


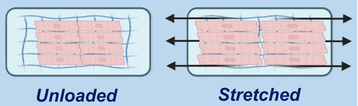
Figure 3. Brightfield images of high confluency cardiac fibroblasts derived from the first heart field (A), second heart field (B), and epicardial lineage (C). Panel D shows a laser cut cardiac extracellular matrix scaffold clipped onto Teflon clips.

Project Overview

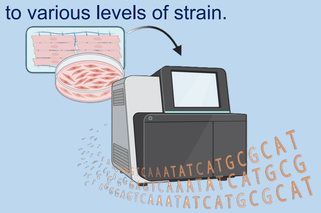
Experimental



1. Derive Engineered Cardiac Tissue from different developmental lineages.

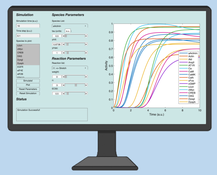


2. Stretch Engineered Cardiac Tissue to various levels of strain.

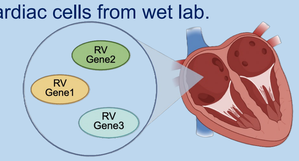


3.RNA-sequence Engineered Cardiac Tissue.

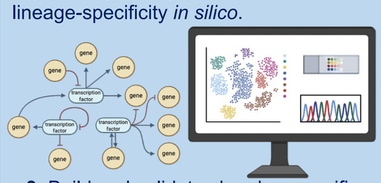
Computational



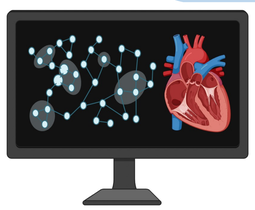
1. Analyze RNA-sequenced data of cardiac cells from wet lab.



2. Use RNA-sequenced data to identify chamber-specific parameters to simulate lineage-specificity *in silico*.



3. Build and validate chamber-specific signaling networks for 3 cardiac cell types.



Chamber-Specific Predictive Network Model for Gene Expression Under Mechanical Stress

Network Model for Predicting Stretch-Induced Gene Expression

Model Characteristics

Model Type	Total Nodes	Chamber-Specific Nodes
Cardiomyocyte [2]	878	23
Fibroblast [3]	91	24
Macrophage [4]	137	19

Desired Features of Chamber Models

Left Ventricle	Strong mechano-transduction
Right Ventricle	Strong fibrotic program (ECM)
Left Atrial	Suppressed across categories
Right Atrial	Moderate and balanced

- Chamber-specific initialization makes the model more responsive to perturbations
- Adding physiological context meaningfully altered network behavior

Sensitivity Analysis

Sensitivity: number of times a node's steady-state activation changes >25% during all other node knockout simulations

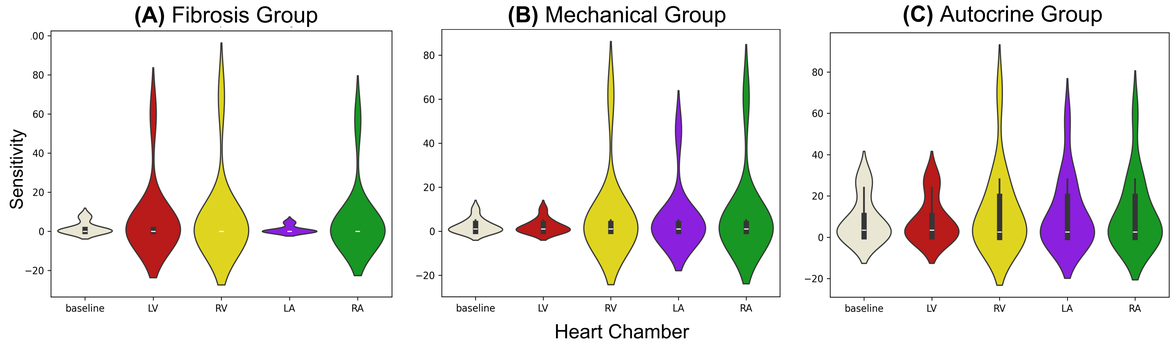


Figure 4. Sensitivity analysis of cardiac fibroblast models across heart chambers. Violin plots show sensitivity score distributions for fibrosis (A), mechanical (B), and autocrine signaling (C) groups, with baseline shown in beige.

Conclusion

Experimental

- Derived **cardiac cells** from different **developmental lineages**
- Produced cardiac **ECM sheets**, decellularize then laser cut into tissue scaffold
- Performed various **experiments and bioassays** to validate cardiac tissue model

Computational

- Experimentally derived priors produced **ventricle-specific variations** in stress response and signaling propagation.
- Applicability to human cells is limited due to **mouse-derived base models.**

Together, these workflows create an experimental-computational platform for predicting **lineage-specific cardiac remodeling responses**.

Future Work & Recommendations

1. Characterize engineered cardiac tissue function through experimental assays to **confirm tissue lineage-specificity**.
2. Compare engineered cardiac tissue against native heart tissue to **assess maturity and biological relevance.**
3. **Validate computational predictions with engineered cardiac tissue data** to strengthen model's biological accuracy.
4. **Incorporate stretch** in model validation to evaluate chamber-specific remodeling.
5. Expand tissue and computational model with **additional cell types such as macrophages and vascular cells** to capture broader remodeling interactions.

Acknowledgements and References

The team would like to thank Dr. Christopher Anderson, Dr. Andrew McCulloch, Dr. Jeffrey Saucerman, Dimitry Major, Dr. Alyssa Taylor-Amos, Sri-Veda Chidaraboyina, Iris Zaretzki, and Yashwin Madakamutil for all their support and contributions throughout this project.