THE UNIVERSITY OF TEXAS AT AUSTIN
Biomedical Engineering

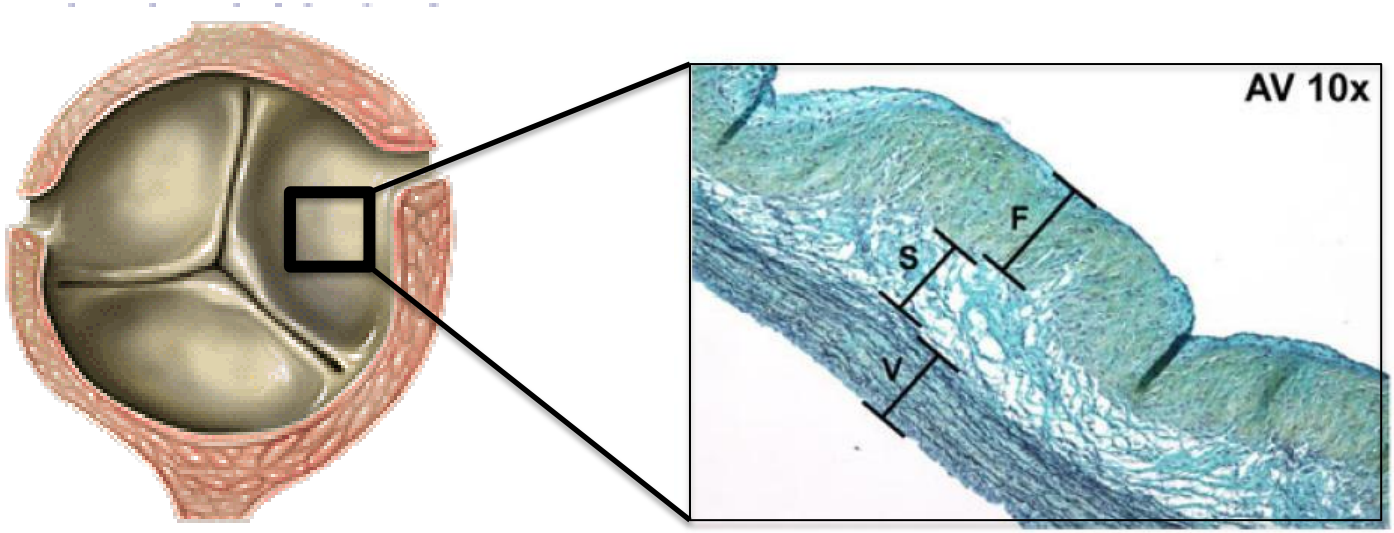
Downscale finite element modeling of aortic valve leaflets for *in situ* estimation of cell level mechanics

Rachel Buchanan, Rong Fan, and Michael Sacks

Excerpt from the Proceedings of the 2012 COMSOL Conference in Boston

Heart Valve Function

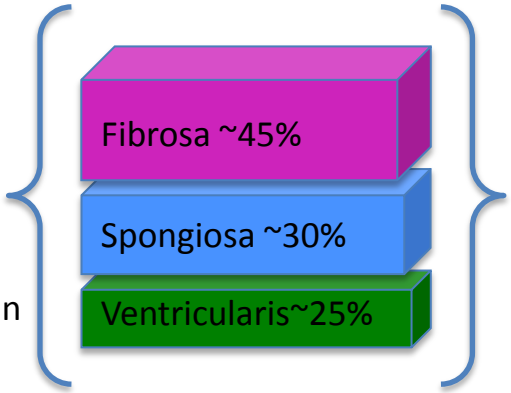
A multi-scale biomechanical problem



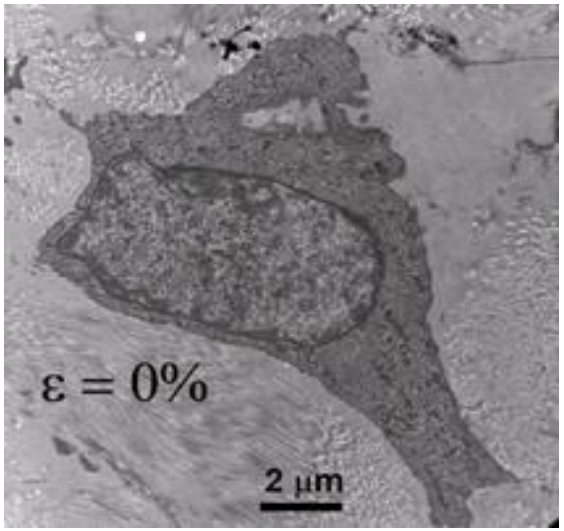
Collagen

GAGs

Collagen, Elastin



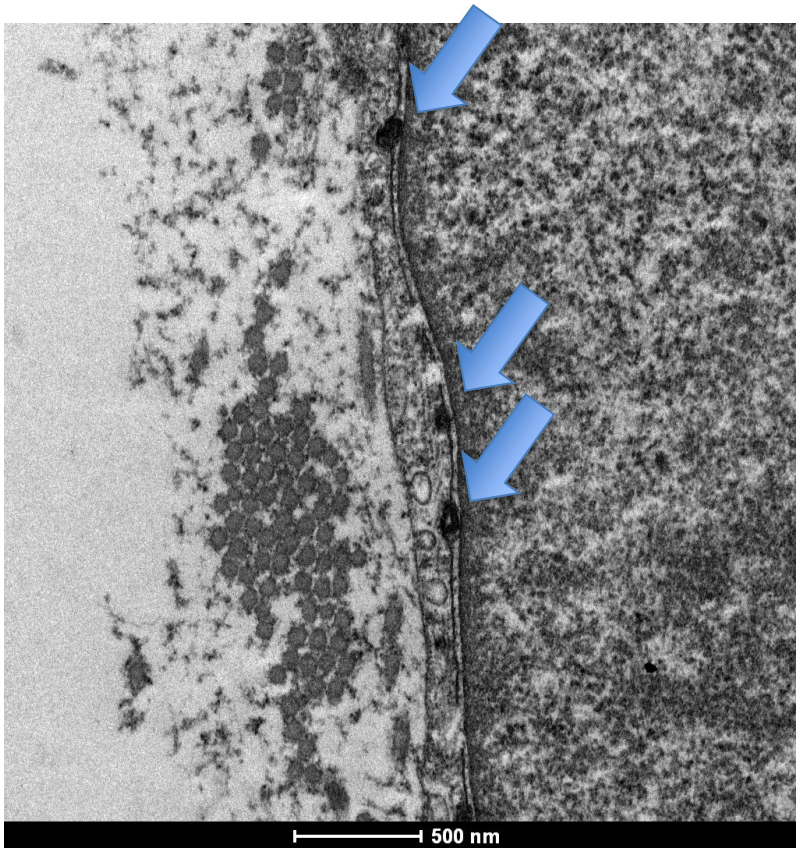
Total Thickness 700 µm



The Valve Interstitial Cell

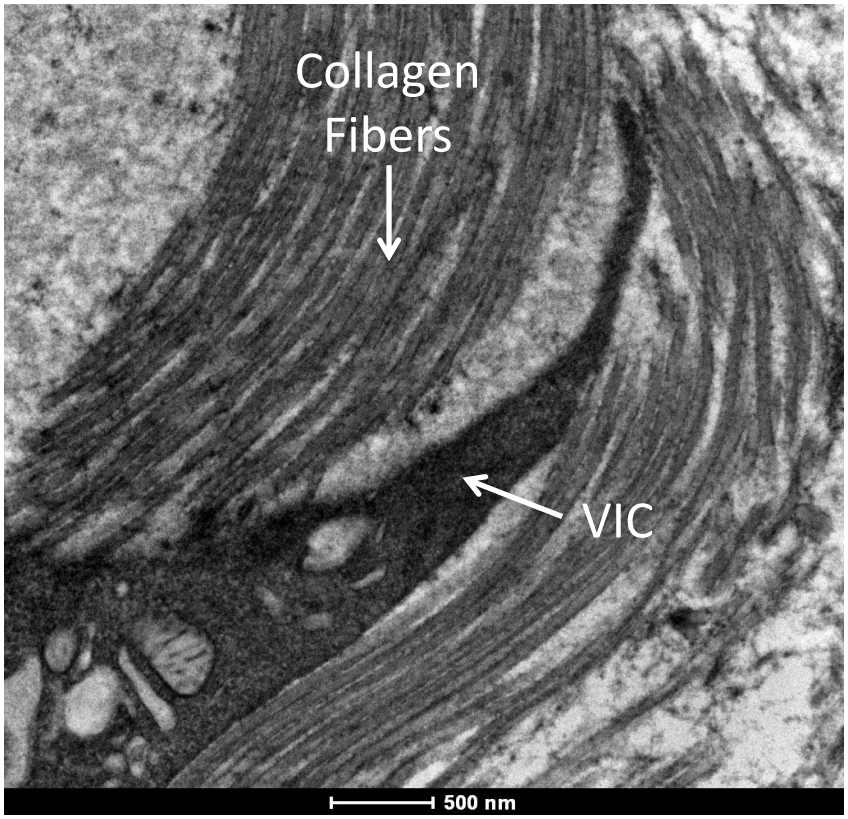
- Mixed fibroblast & smooth-muscle cell phenotype
- Active communicating cell-cell junctions
- Highly “reactive” and contractile
- Maintain the valve ECM homeostasis through protein synthesis and enzyme degradation
- Quiescent during homeostasis & active during growth and disease

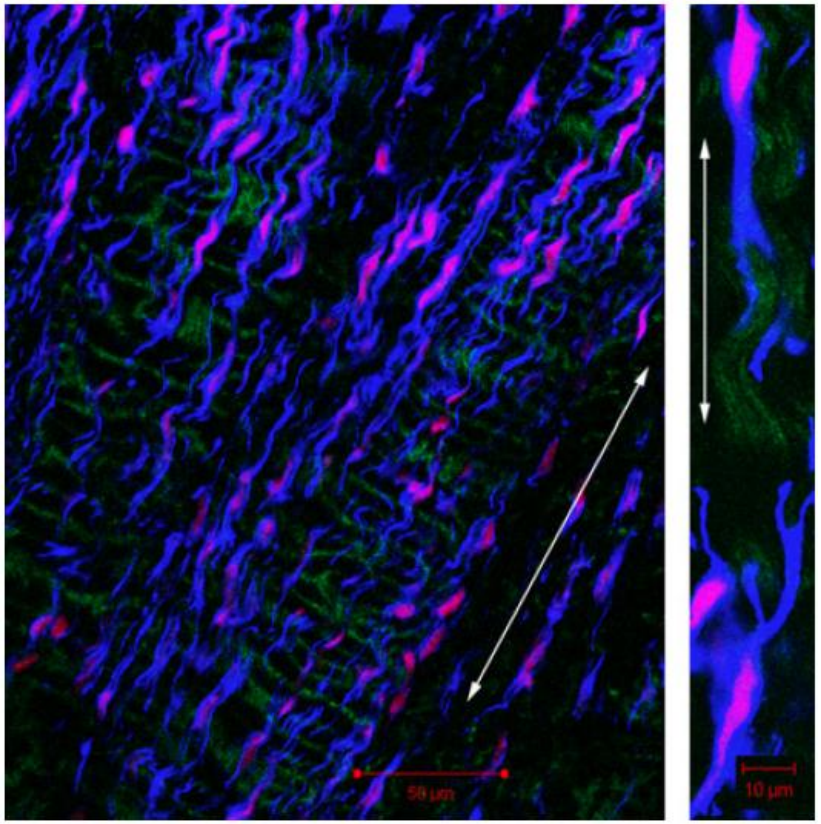
Cell-Cell junctions connecting 2 AVICs



VIC-ECM Coupling: Role in force generation

- VICs align in parallel with the collagen fiber preferred direction
- Integrin mediated contraction/force generation[1]





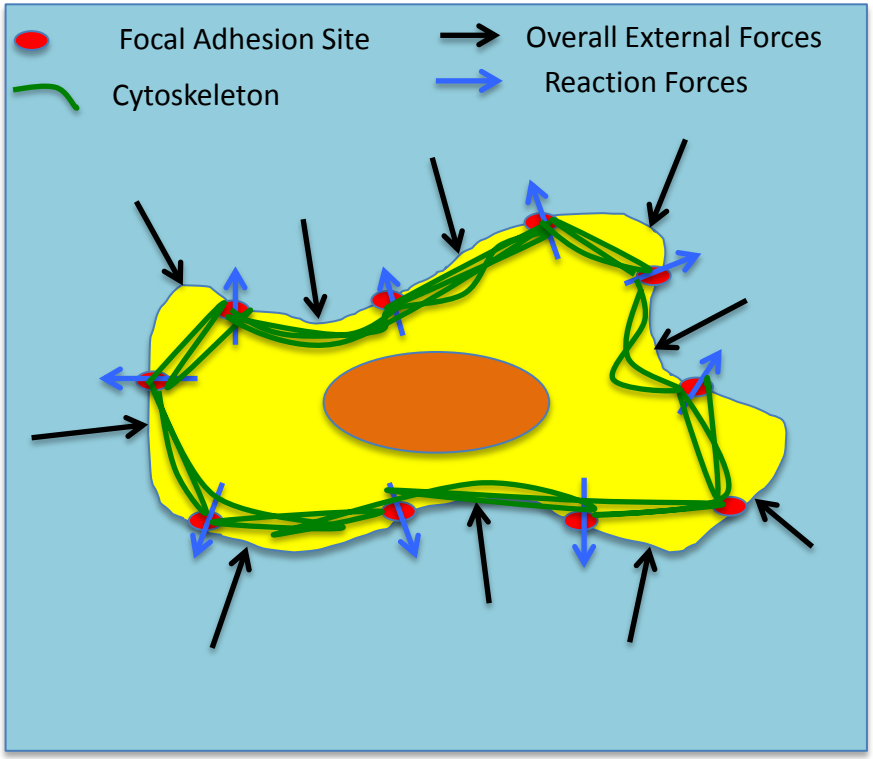
[1]Stephens, E.H., et al., Cellular and Molecular Bioengineering, 2010

VIC Stiffness/Contraction

- Decoupling of stiffness and contraction
- VICs balance forces via contraction to maintain valve homeostasis
- Role of VIC contraction in valve function is poorly understood
- Contraction effects:

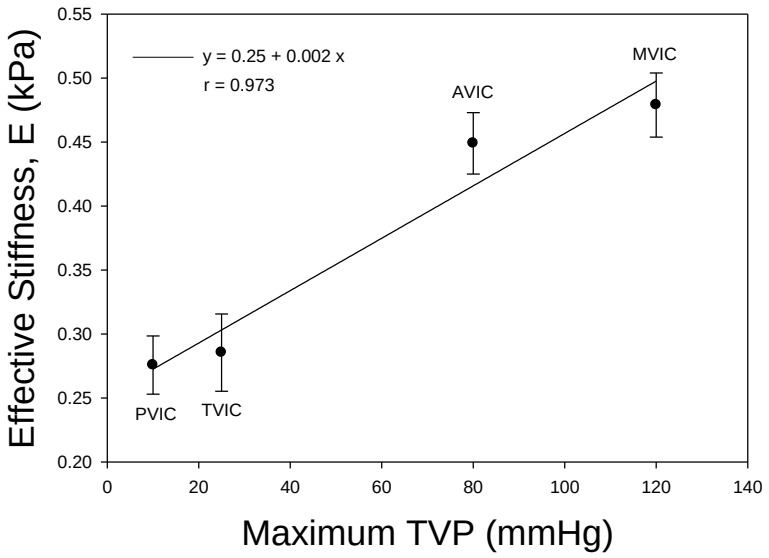
  Short Term → Increased stiffness

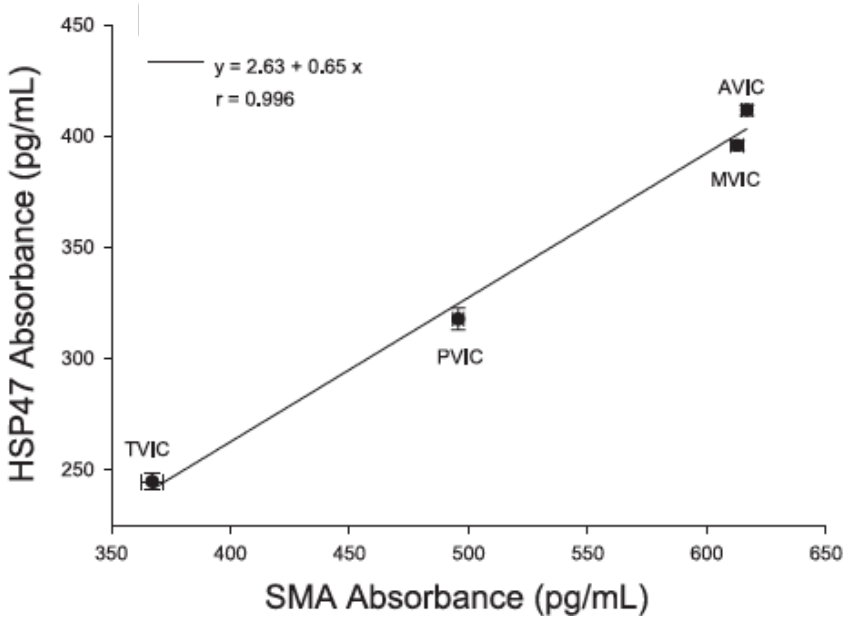
  Long Term → Activation of mechanochemical signaling



External Stress→ Contraction→ Increased cell stiffness→ Mechanotransduction

Mechanotransduction





VIC Stiffness

SMA expression

ECM biosynthesis

- Increased transvalvular pressure positively correlates with higher effective stiffness in VICs[1]
- Strong relation of SMA and HSP47 indicating VICs response to mechanical stimuli in an attempt to maintain valve homeostasis
- Similar trends were found in *in situ* studies

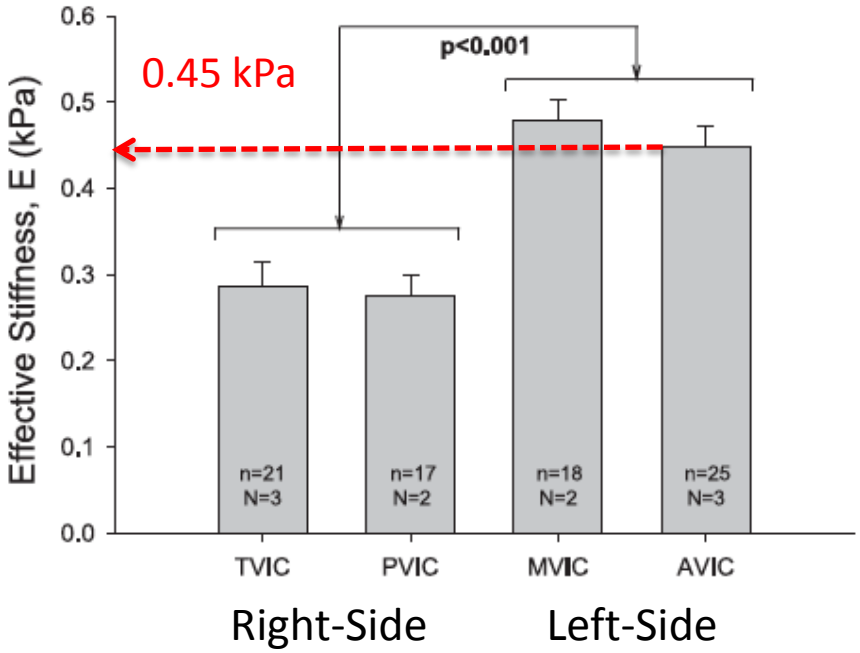
[1]Merryman, W.D., et al., American Journal of Physiology-Heart and Circulatory Physiology, 2006.

Limitations of Ex-vivo methods

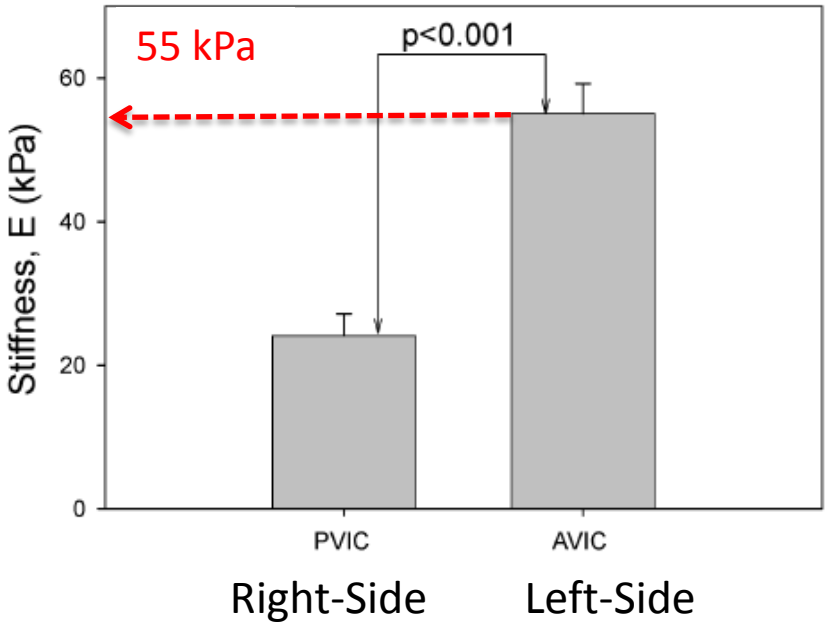
Discrepancy greater than 100-fold[1,2]

- Proportional changes consistent, yet vary in magnitude

Micropipette Aspiration



Atomic Force Microscopy



[1]Merryman, W.D., et al., American Journal of Physiology-Heart and Circulatory Physiology, 2006.

[2]Merryman, W.D., et al., Tissue Engineering, 2007.

Goals

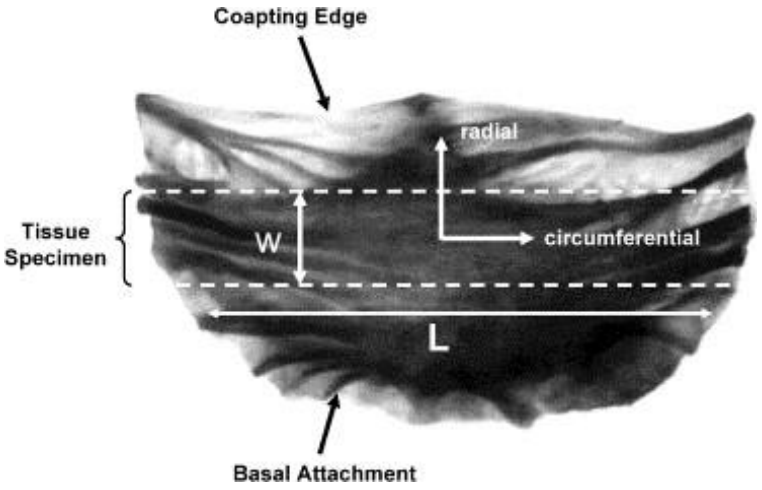
- Develop an integrated computational-experimental tool to assess AVIC physical state in the *in situ* environment (low and high force regions)

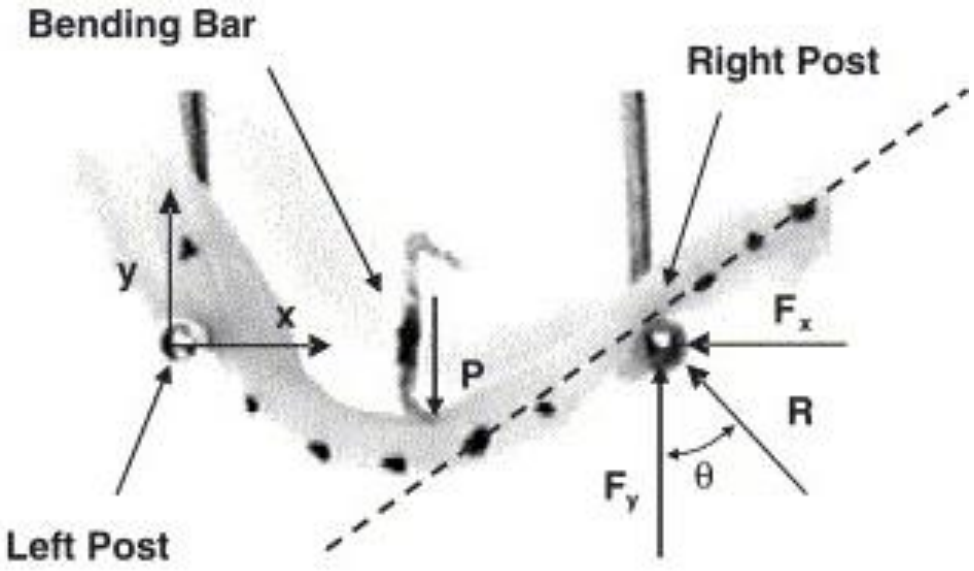
- Ultimately a true multi-scale model based on high-fidelity 3D tissue micromorphology

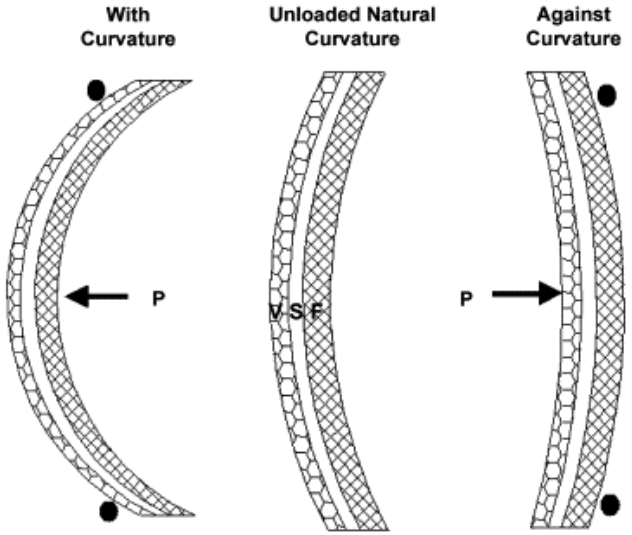
- Accurately address layer and regional differences
  (belly region, coaptation, commissure, basal attachment)

Current experimental methods: Flexure testing[1]

- Physiologically relevant deformation
- Low force measurements *in situ*
- Probe transmural effects



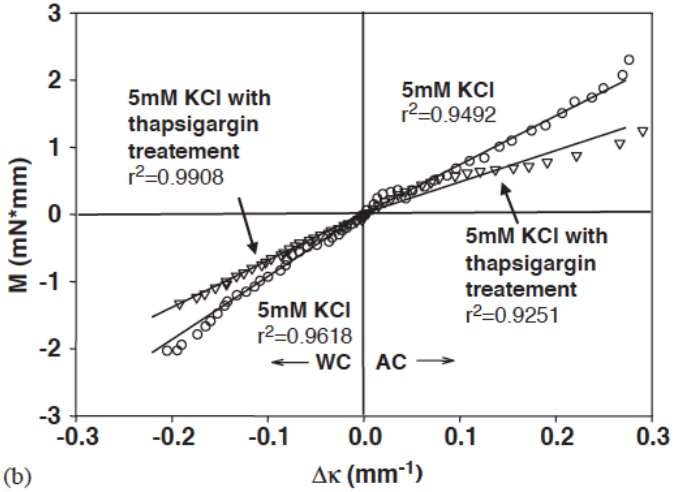


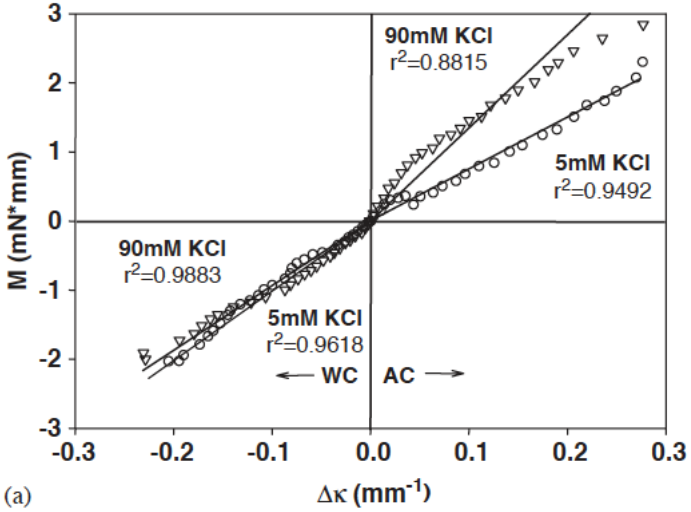


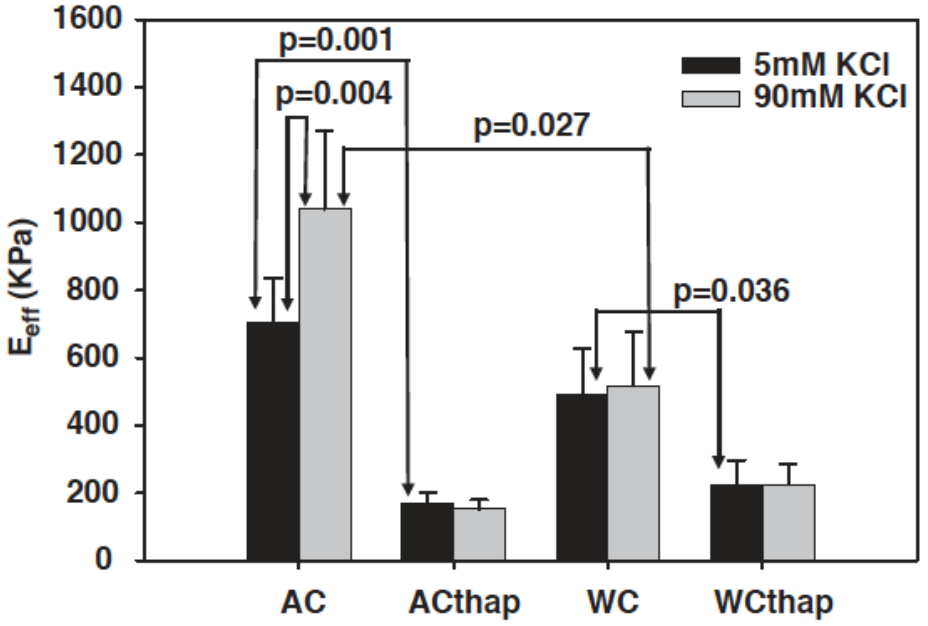
[1]Merryman, W.D., et al.,. Journal of Biomechanics, 2006

Flexure Experimental Results

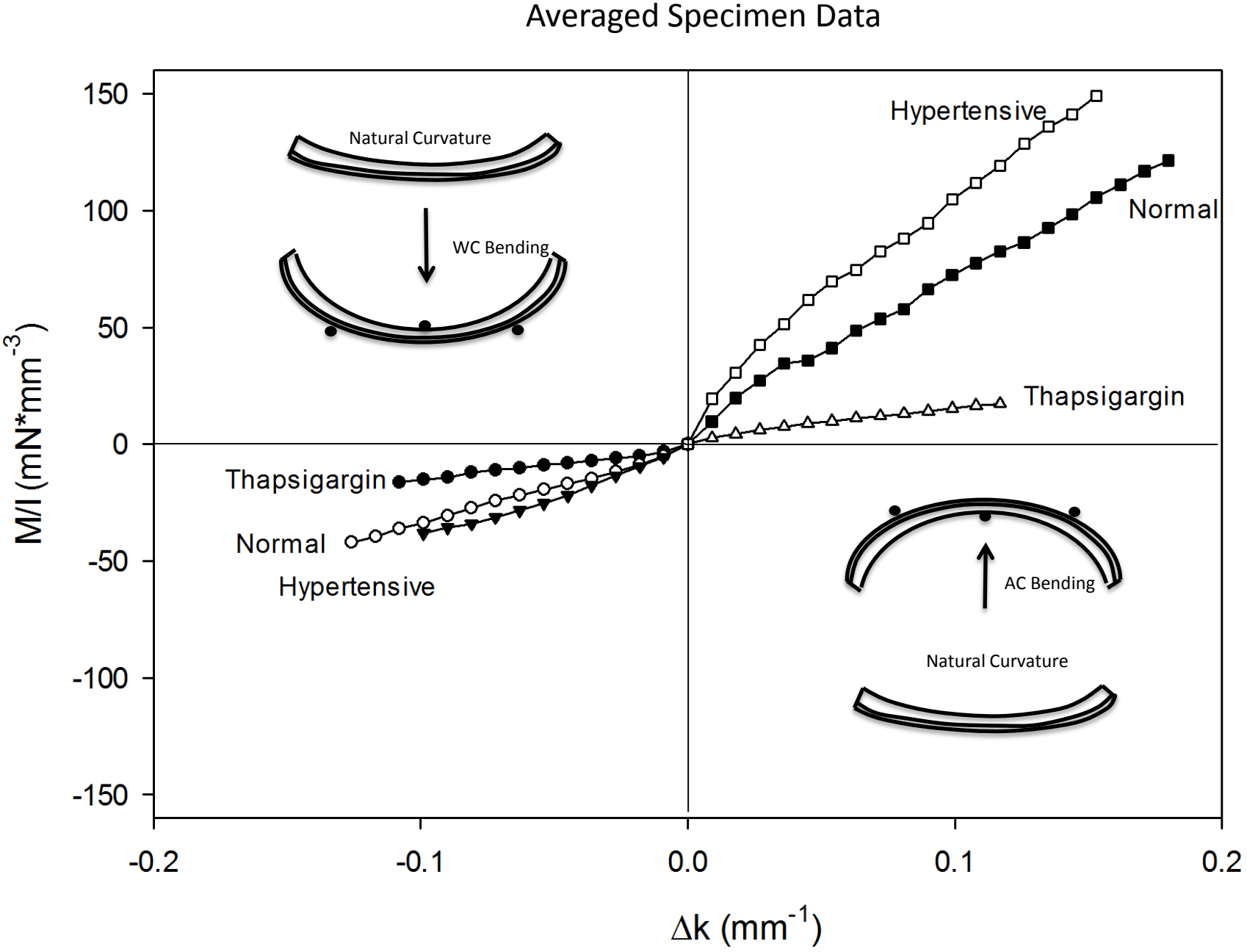
Bi-directional linearity of M vs. Δk^1 suggest linear material model







[1]Merryman, W.D., et al.,. Journal of Biomechanics, 2006


Averaged Specimen Data
150
100
50
0
-50
-100
-150
M/I (mN*mm-3)
-0.2
-0.1
0.0
0.1
0.2
Δk (mm-1)
Natural Curvature
WC Bending
Hypertensive
Normal
Thapsigargin
Thapsigargin
Normal
Hypertensive
AC Bending
Natural Curvature

Isotropic Hyperelastic Material Model

- Bimodular Ogden (N=1):

$$W^{\pm} = \frac{\mu^{\pm}}{\alpha}\left(\lambda_1^{\alpha} + \lambda_2^{\alpha} + \lambda_3^{\alpha} - 3\right)$$

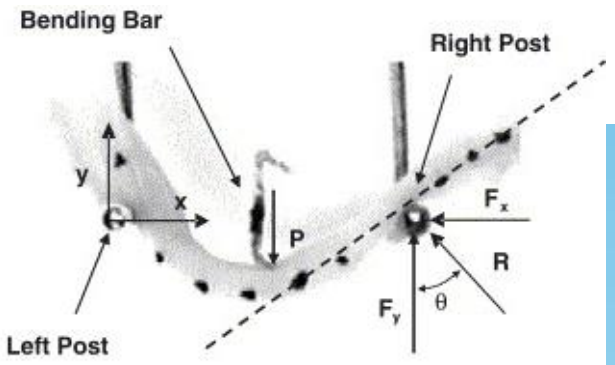
- Incompressibility Assumption:

$$W^{\pm} = \frac{\mu^{\pm}}{\alpha}\left(\lambda_1^{\alpha} + \lambda_2^{\alpha} + \lambda_1^{-\alpha}\lambda_2^{-\alpha} - 3\right)$$

- When α= 2 becomes a Bimodular Neo-Hookean material model

$$W^{\pm} = \frac{\mu^{\pm}}{2}\left(\lambda_1^{2} + \lambda_2^{2} + \lambda_1^{-2}\lambda_2^{-2} - 3\right)$$

Macro-Model



Left Post (pin)

Load Post

Right Post (roller)

y

z

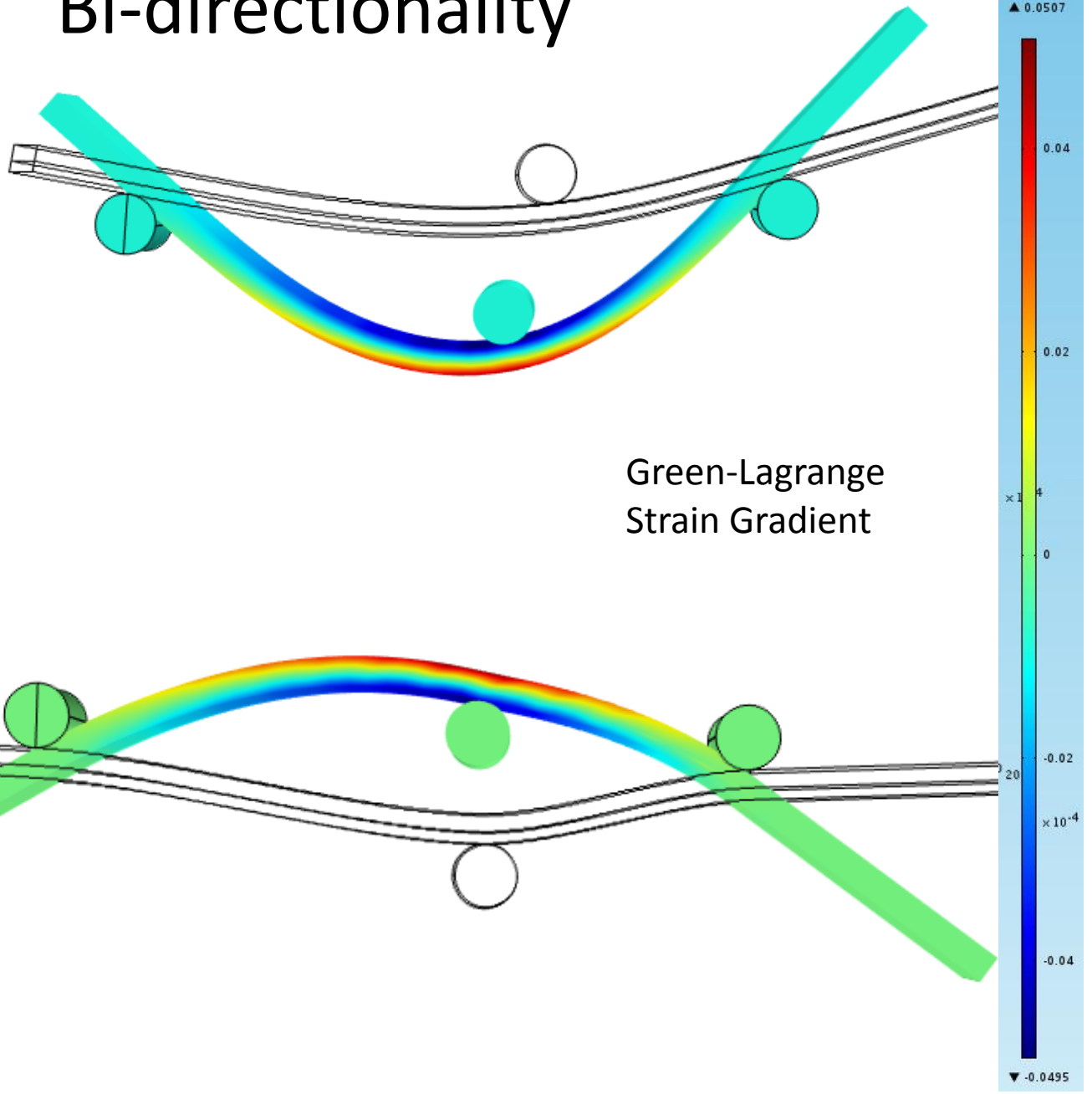
x

Bi-directionality

With Curvature

F

V



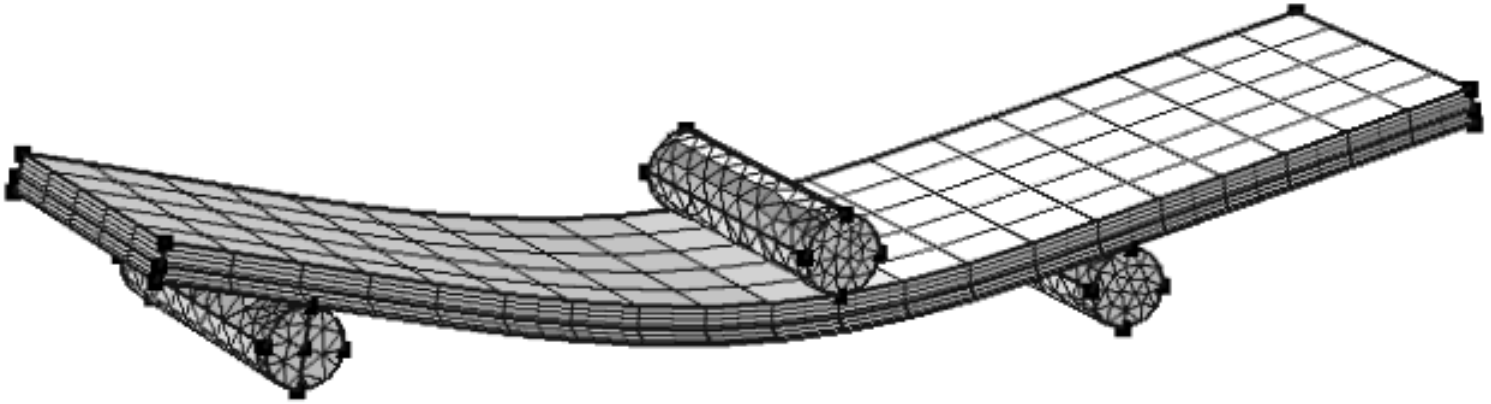
Green-Lagrange
Strain Gradient

Against Curvature

F

V

Comsol Model Details



- Isotropic incompressible hyperelastic model
- 4 assigned shear moduli (bilayer/bimodular)
  - $\mu_{Fibrosa}^{+/-}$ $\mu_{Venticularis}^{+/-}$
  - Stiffer in compression similar to bending of rubber
- Brick element mesh
- Study Extension (Continuation)
- Direct Solver

Justification/Uniqueness

1. Neo-Hookean Bilayer
   -captures thapsigargin state only
   -unable to capture the M/I vs. curvature relation (normal and hyper
   -unable to capture the bidirectionality

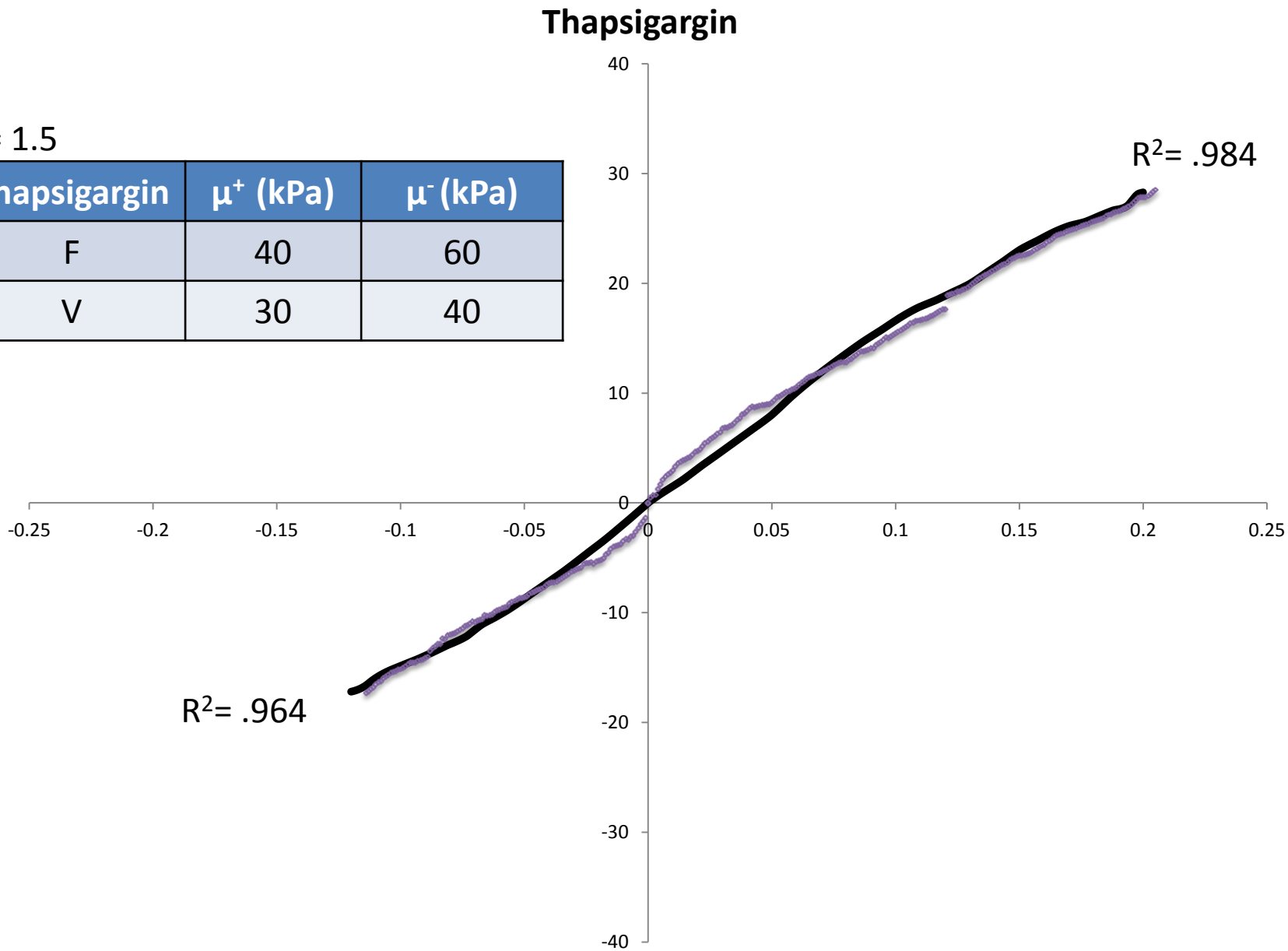
2. Ogden Bilayer
   -captures the M/I vs. curvature relation for all 3 states
   -unable to capture the bidirectionality

3. **Ogden Bilayer /Bimodular**
   -captures the M/I vs. curvature relation and bidirectionality for all 3 states

Results

α= 1.5

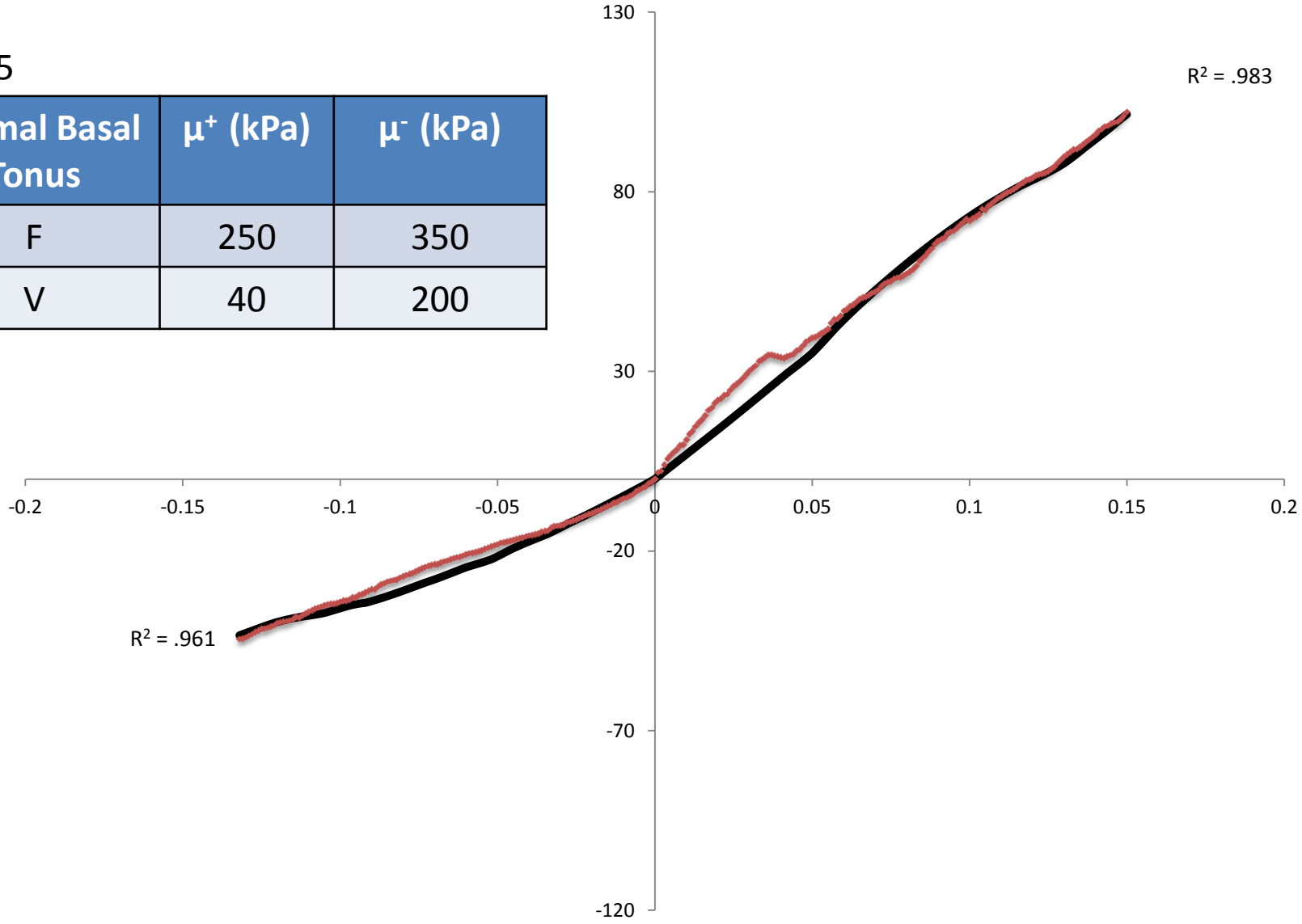
Thapsigargin	μ^+ (kPa)	μ^- (kPa)
F	40	60
V	30	40



Normal Basal Tonus

$\alpha = 1.5$

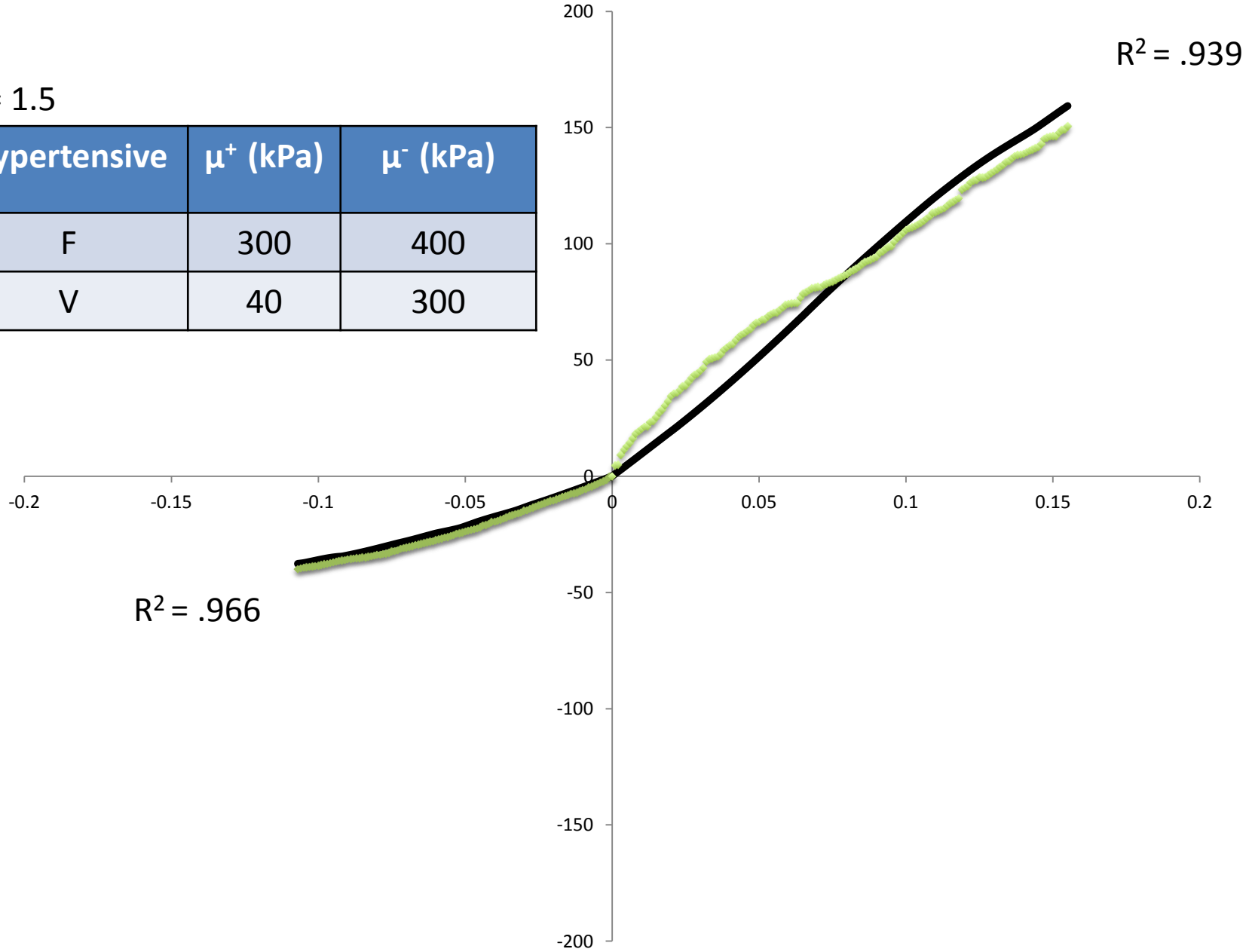
Normal Basal Tonus	μ^+ (kPa)	μ^- (kPa)
F	250	350
V	40	200

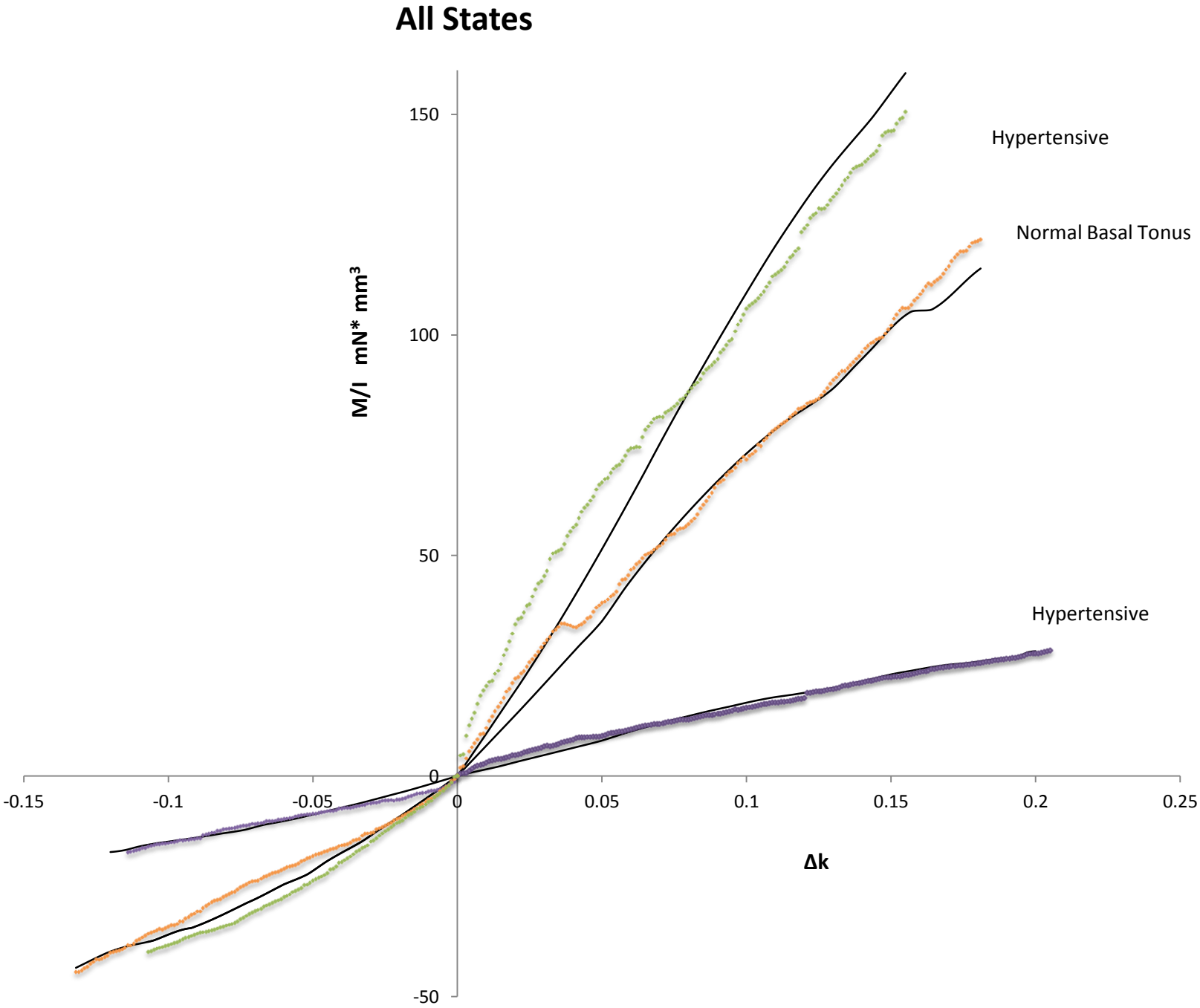


Hypertensive

α= 1.5

Hypertensive	μ^+ (kPa)	μ^- (kPa)
F	300	400
V	40	300




All States
150
100
50
0
-50
M/I mN* mm³
-0.15
-0.1
-0.05
0
0.05
0.1
0.15
0.2
0.25
Δk
Hypertensive
Normal Basal Tonus
Hypertensive

Ogden Bilayer/Bimodular/Bidirectional

$$W^{\pm} = \frac{\mu^{\pm}}{\alpha}(\lambda_1^{\alpha} + \lambda_2^{\alpha} + \lambda_1^{-\alpha}\lambda_2^{-\alpha} - 3)$$

α= 1.5

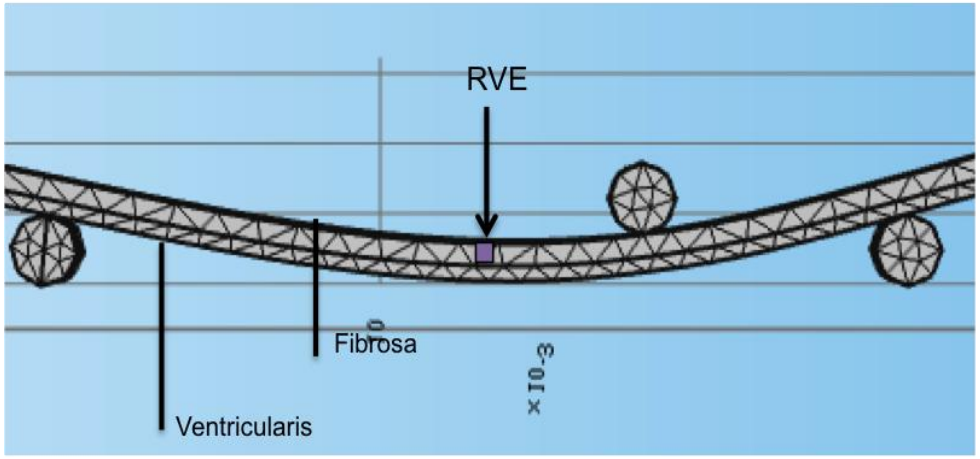
Thapsigargin	μ^+ (kPa)	μ^- (kPa)
F	40	60
V	30	40

Normal Basal Tonus	μ^+ (kPa)	μ^- (kPa)
F	250	350
V	40	200

Hypertensive	μ^+ (kPa)	μ^- (kPa)
F	300	400
V	40	300

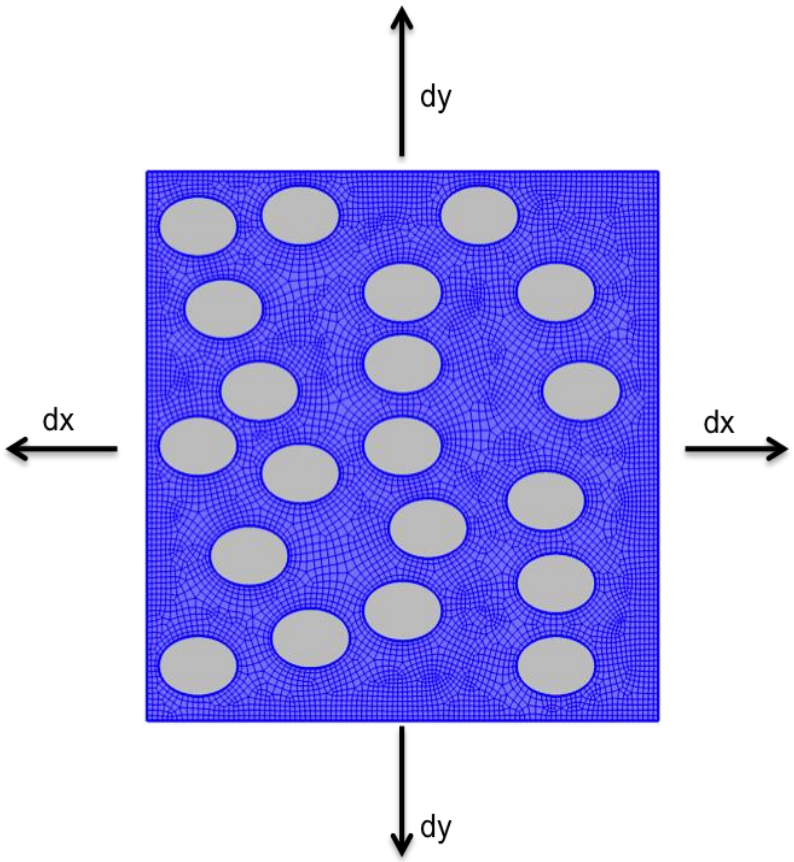
Model Coupling

Macro-Scale



Displacements calculated at the Macro-Scale

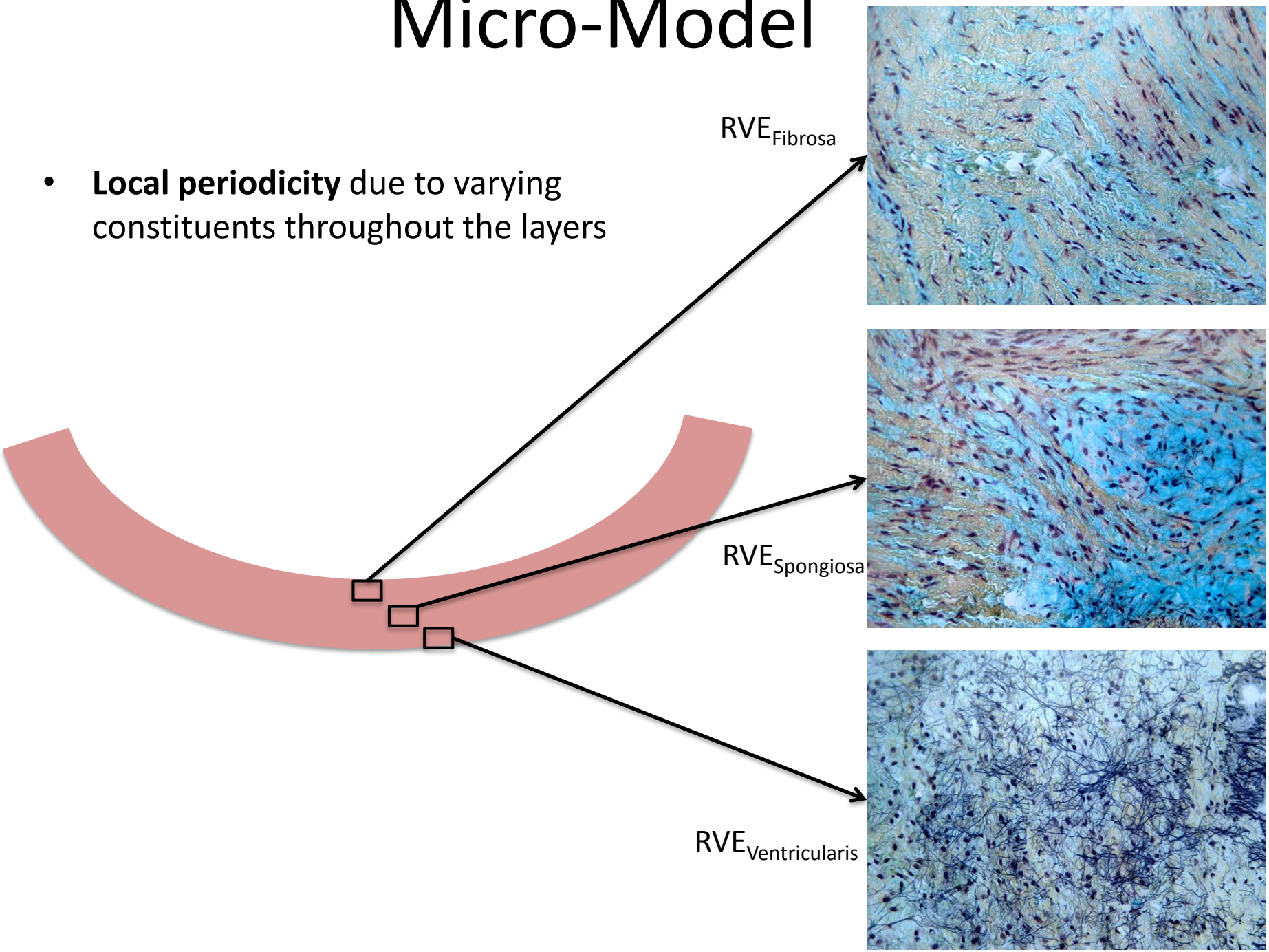
Micro-Scale



Macro displacements mapped to boundary nodes of the micro-scale

Micro-Model

- **Local periodicity** due to varying constituents throughout the layers



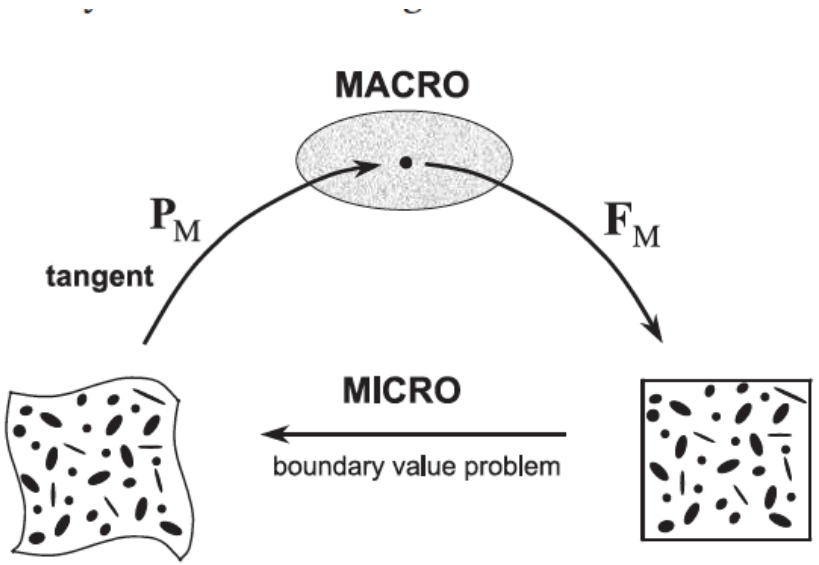
First-order computational homogenization method

1. Localization: Macro scale displacements (F_M) mapped to the boundary nodes of the RVEs

1. Homogenization: Classical 1st order homogenization procedure (average stress over RVE)

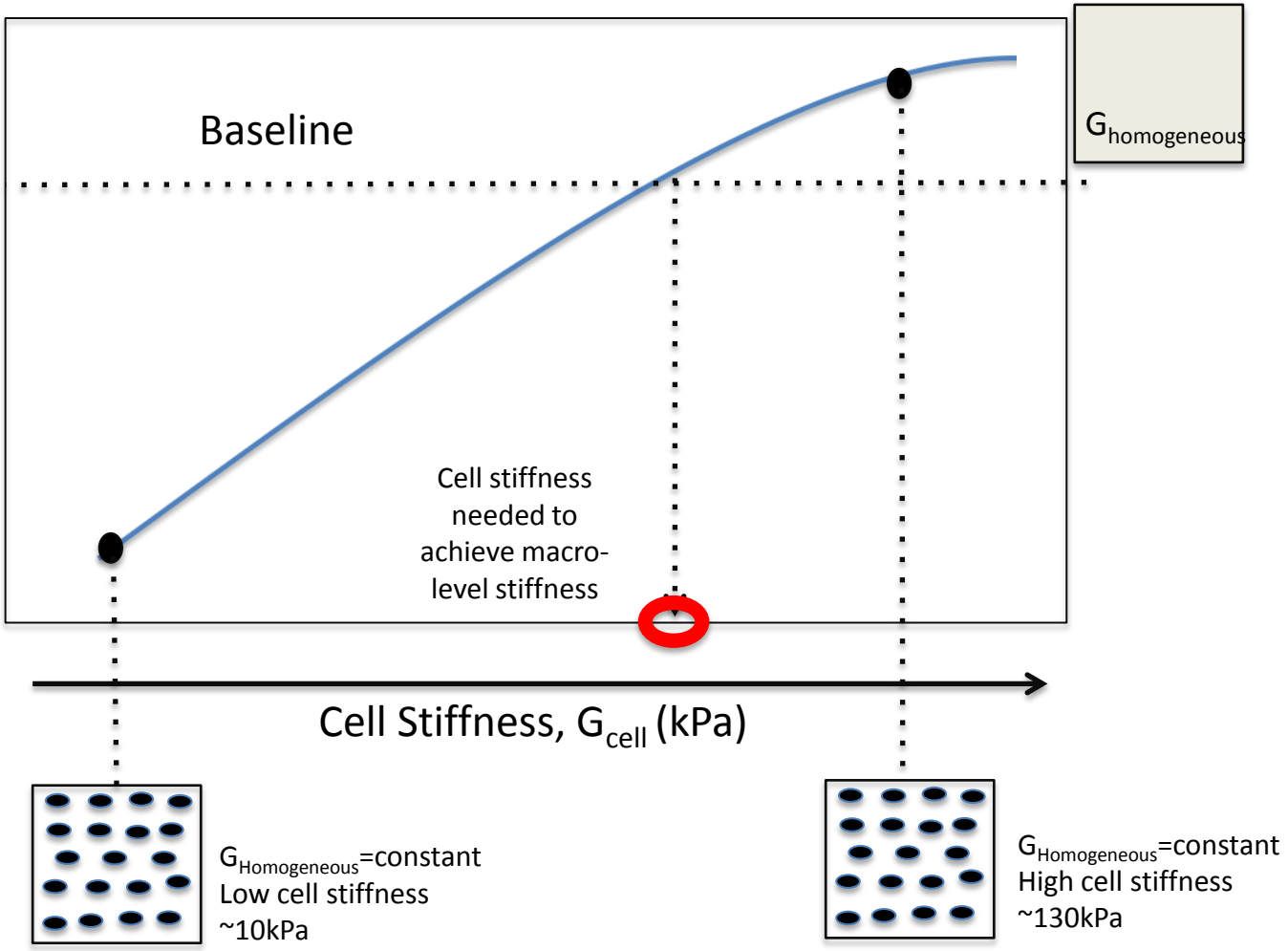
$$\overline{\sigma} = \frac{1}{V}\int \sigma(\hat{x})dV$$

1. Becomes the baseline stress value of the "homogeneous" tissue

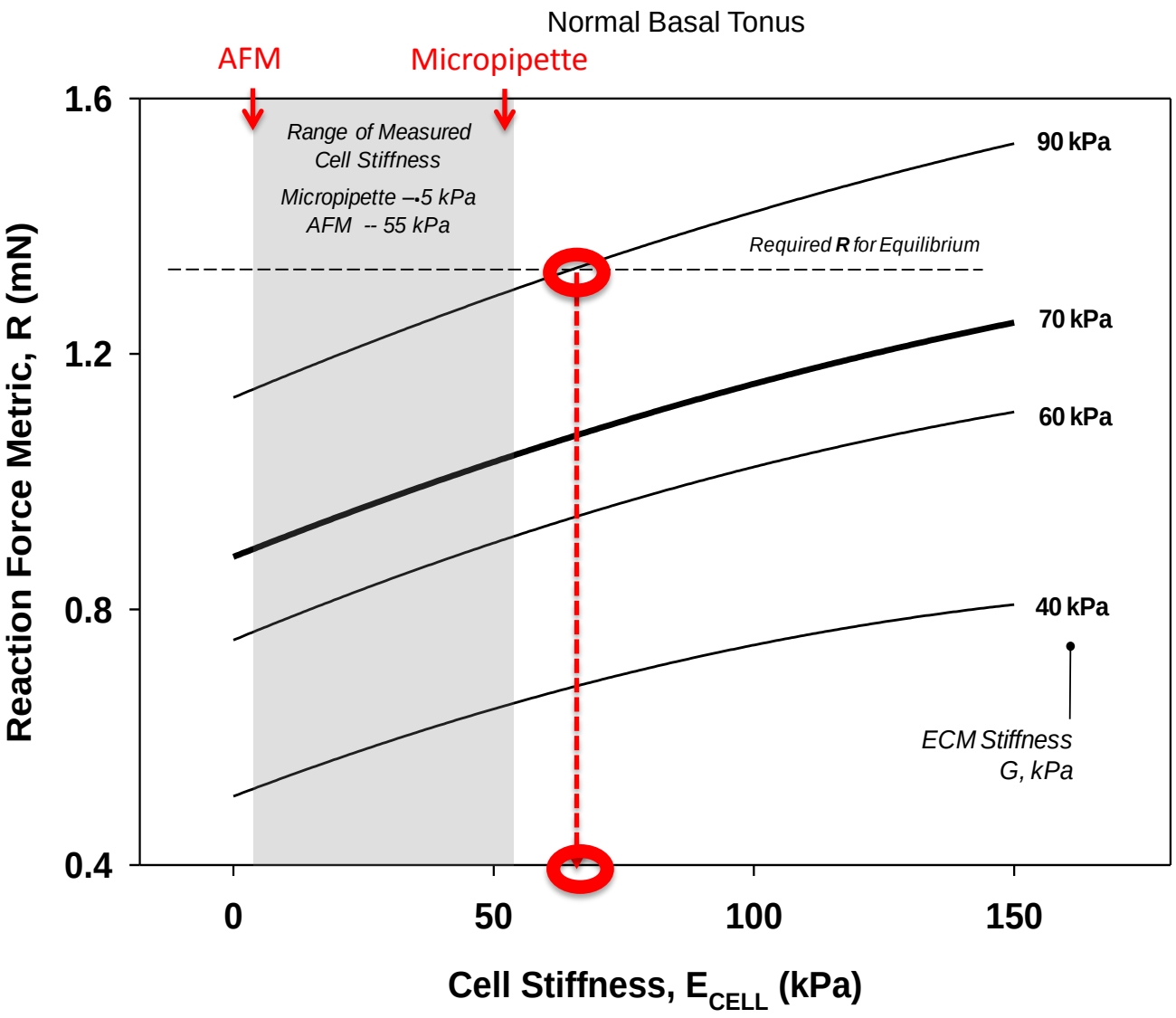


[1]Kouznetsova, V.G. "Computational homogenization for the multi-scale analysis of multi-phase materials".Ph.D. dissertation, Technische Universiteit Eindhoven, 2002.

Determine cell stiffness contribution

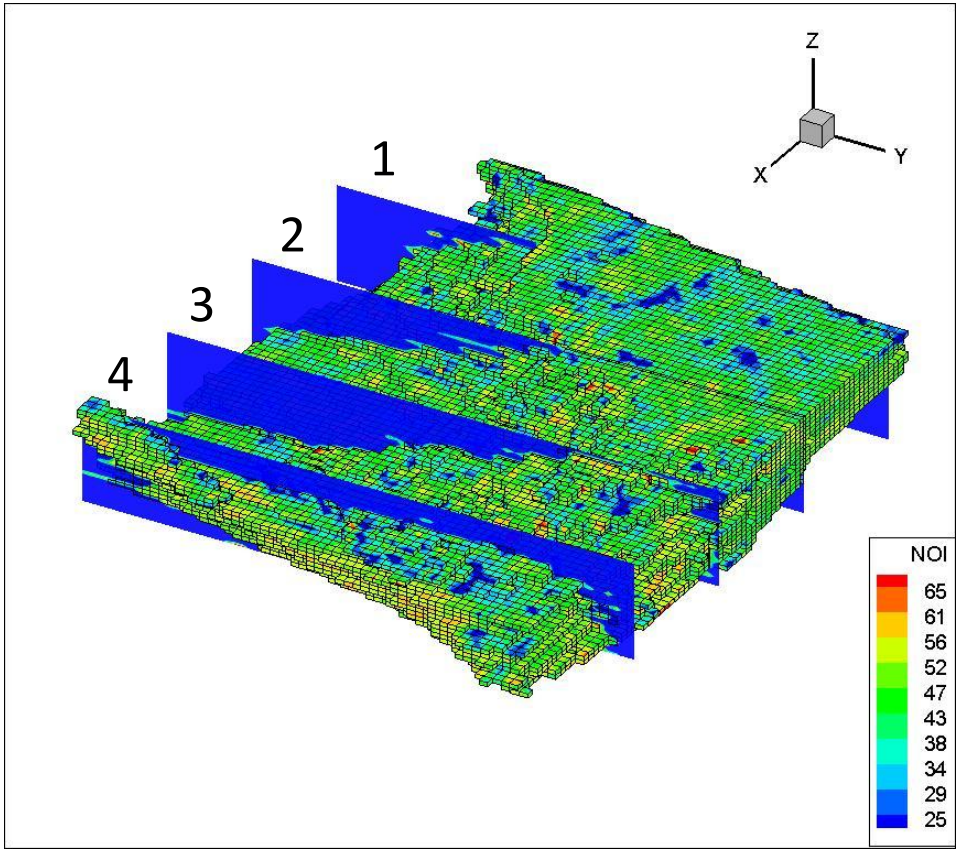


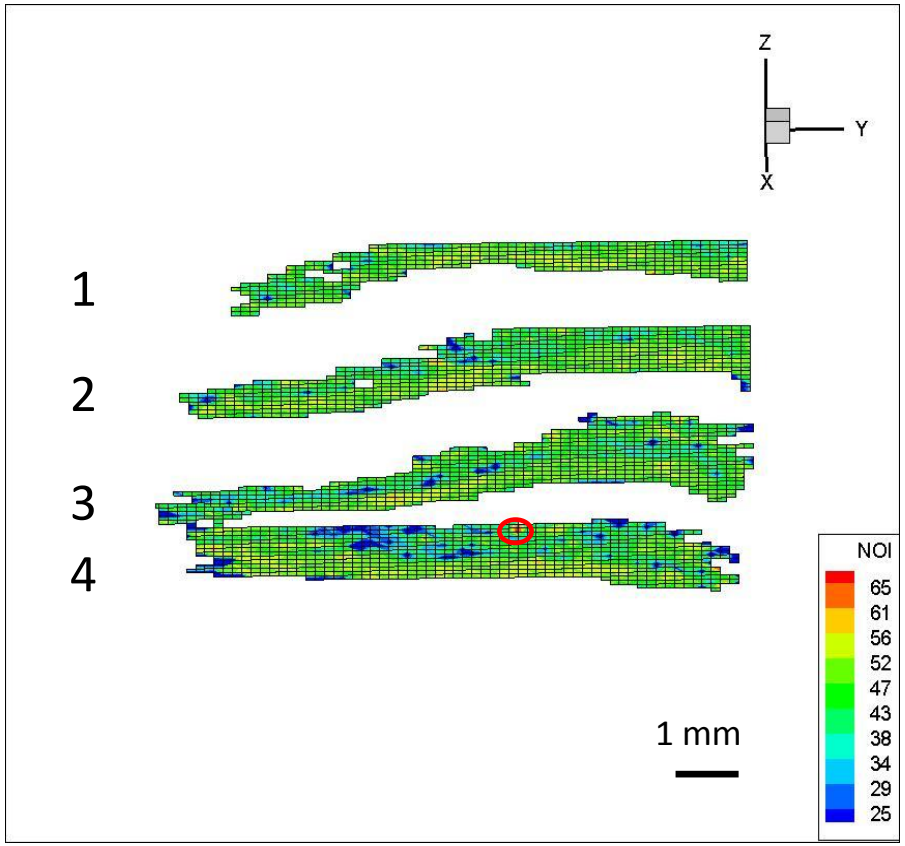
Influence of ECM and Cell Stiffness on Tissue Properties



3D micromorphology Integration

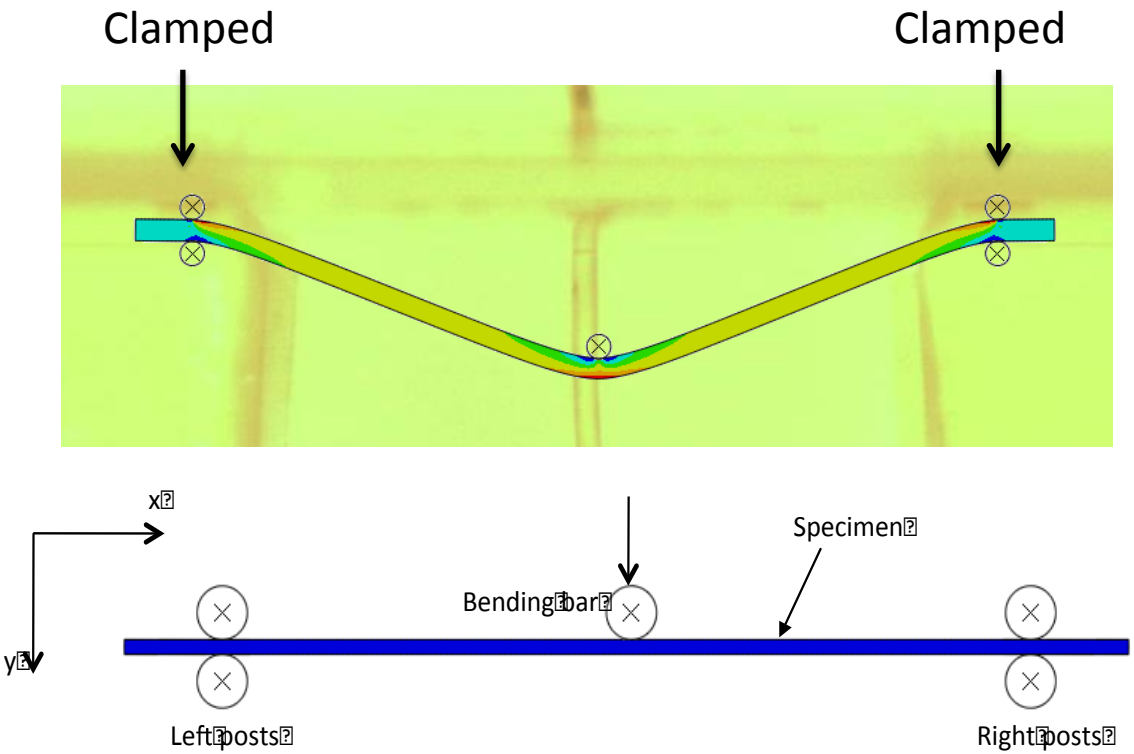
- Developing a more realistic model that incorporates recent micro-morphology data relating to layer varying properties

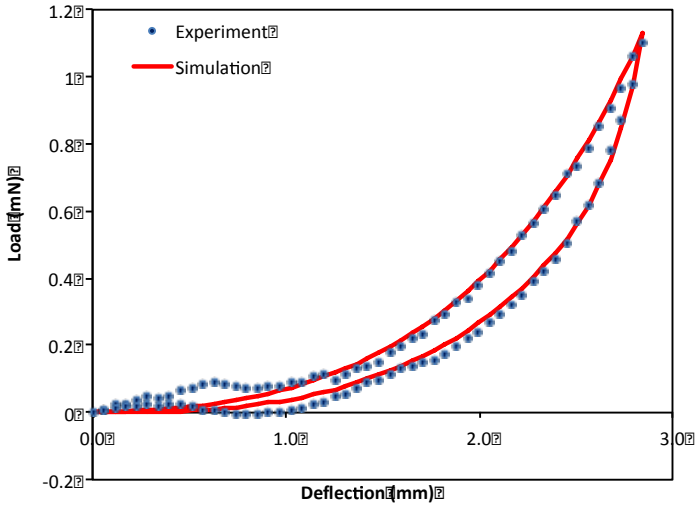




Combining flexure and low level stretch

Physiologically relevant testing capable of investigating **small level forces** that represent residual stresses known to be present[1]





[1]Amini, R, et al., Annals of Biomedical Engineering, 2012.

Conclusions

- Multi-scale approaches can provide a sensitive method to estimate individual cell behavior *in situ* from tissue level measurements
- A bilayer/bimodular hyperelastic model is essential to capture bidirectional effects of tissue response
- Expand existing models to reflect true regional micromorphology of the valve
- Account for full physiological loading conditions
- Use as an investigative tool for VIC state with various agents (e.g. statins).

Acknowledgements

- Funding
  NIH R01 HL-068816 and HL-089750

Thank you!