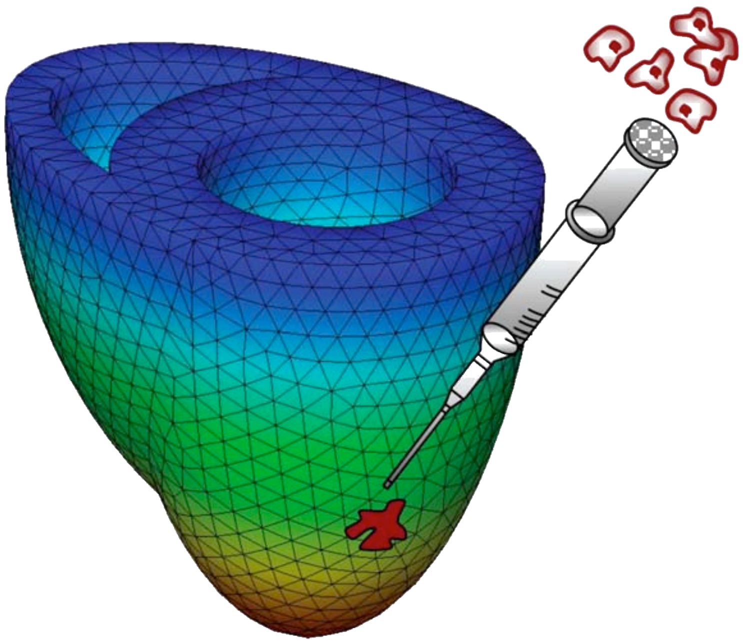
the virtual heart

a hierarchical continuum approach towards computational cardiology



- cardiac disease
- acute ◦ excitation-contraction
- chronic ◦ dilation-hypertrophy
- cardiac repair

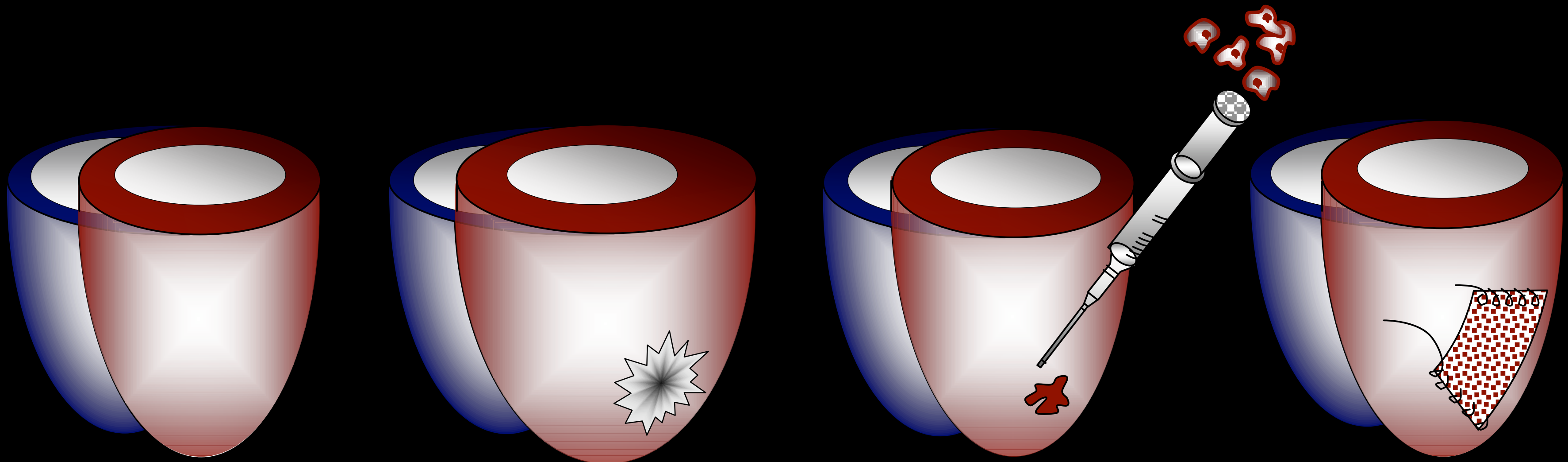
http://biomechanics.stanford.edu

- heart disease is primary cause of death in industrialized nations
- 80 million americans, one in three, suffer from cardiovascular disease
- health care cost in excess of $430 billion
- damaged cardiac tissue does not self regenerate
- novel stem cell therapies offer the potential to restore cardiac function

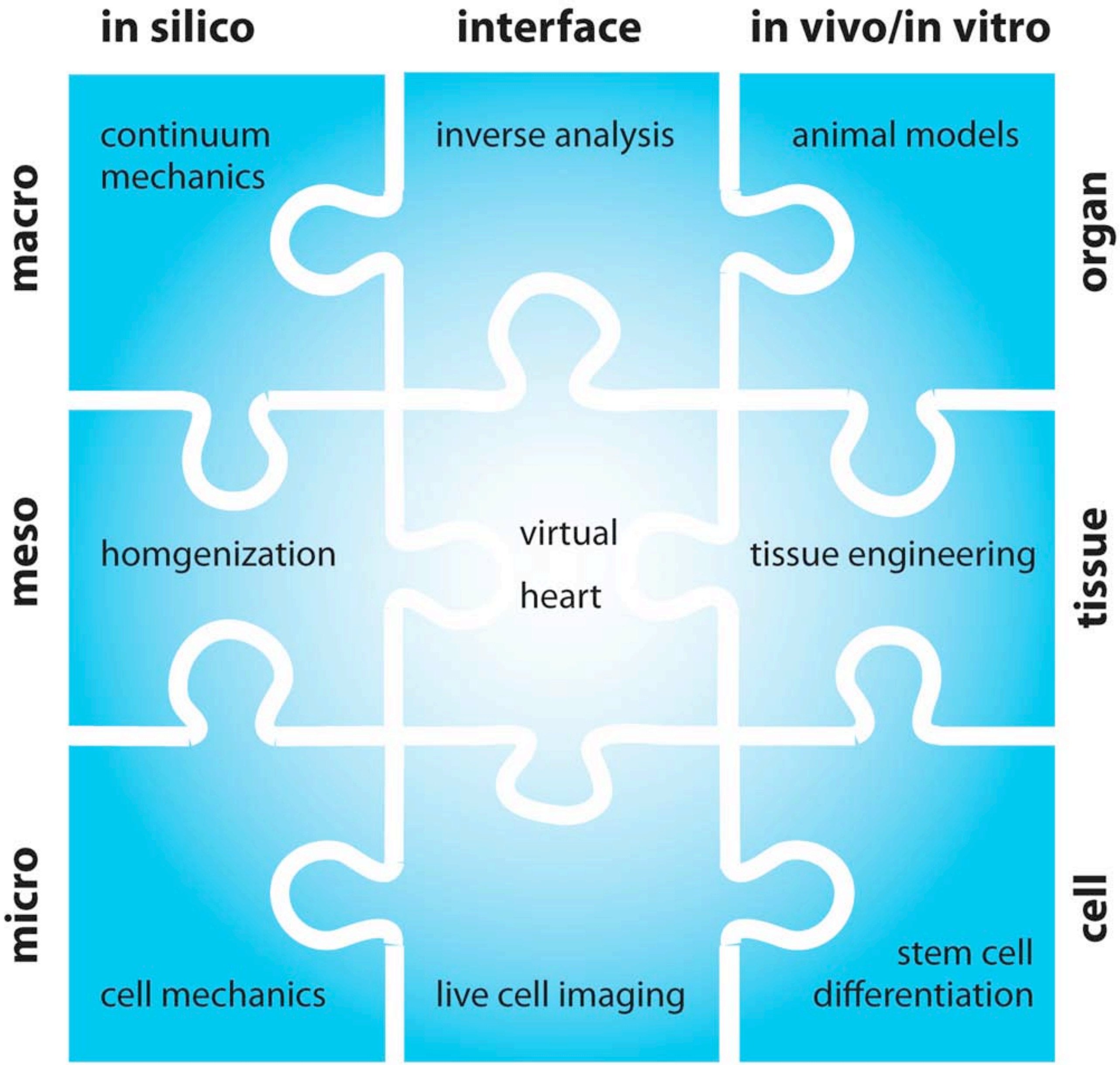
robbins & cotran [2005]

facts & figures

based on active adaptive continuum theories and modern finite element technologies, we want to develop a tool for the computationally guided patient specific design of novel stem-cell based post infarction therapies



the vision



in silico
interface
in vivo/in vitro
macro
meso
micro
organ
tissue
cell
continuum mechanics
inverse analysis
animal models
homgenization
virtual heart
tissue engineering
cell mechanics
live cell imaging
stem cell differentiation

in silico

macro

mechanics of cardiac disease

challenge bridging the time scales

- cardiac cycle ~1 sec
- tissue adaptation ~ weeks/months

scale separation acute vs chronic

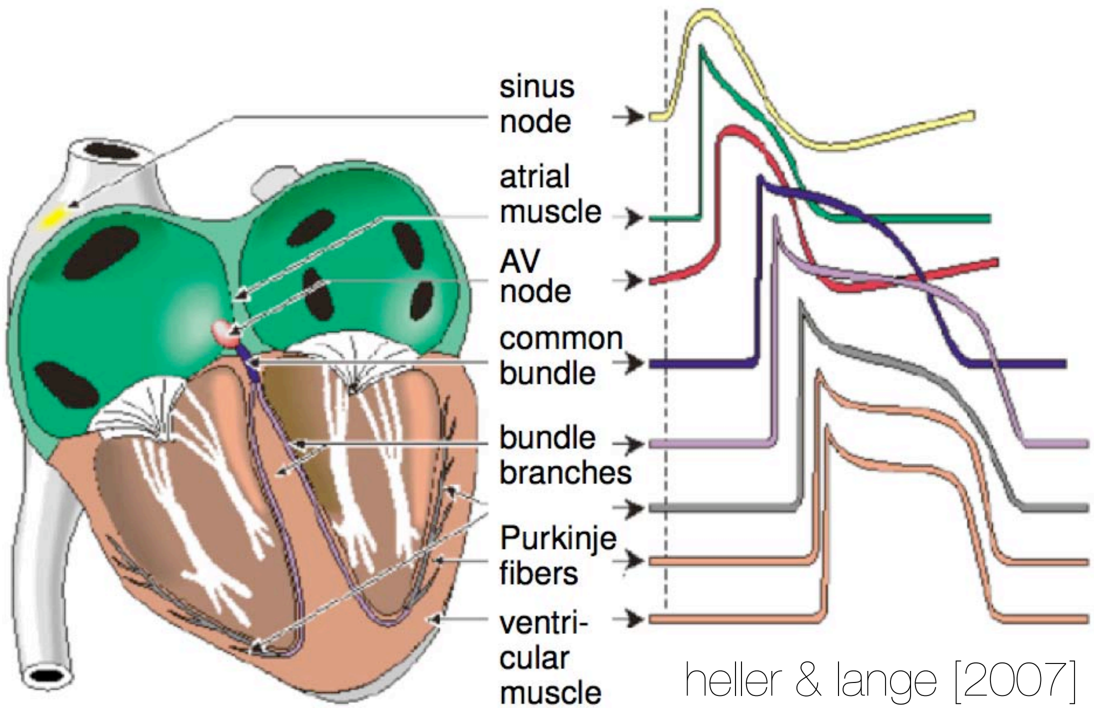
time	phase	cause and mechanical effect
hours	acute ischemia	local loss of **active** contractile properties
days	necrotic phase	pressure overload induced **adaptive** growth
weeks	fibrotic phase	collagen induced **adaptive** anisotropy changes
months	remodeling phase	crosslinking induced material stiffness changes

timeline of myocardial infarction

macro

continuum mechanics

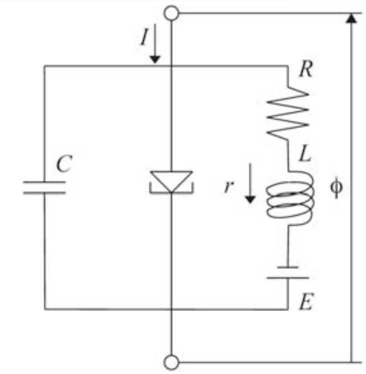
- **acute** changes
- passive vs **active** stress $\boldsymbol{\sigma} = \boldsymbol{\sigma}^{\text{pas}} + \boldsymbol{\sigma}^{\text{act}}$
- excitation contraction $\boldsymbol{\sigma}^{\text{act}} = \sigma^{\text{act}}(\phi)\, \boldsymbol{n}^{\text{fib}} \otimes \boldsymbol{n}^{\text{fib}}$
- atrial/ventricular fibrillation



heller & lange [2007]

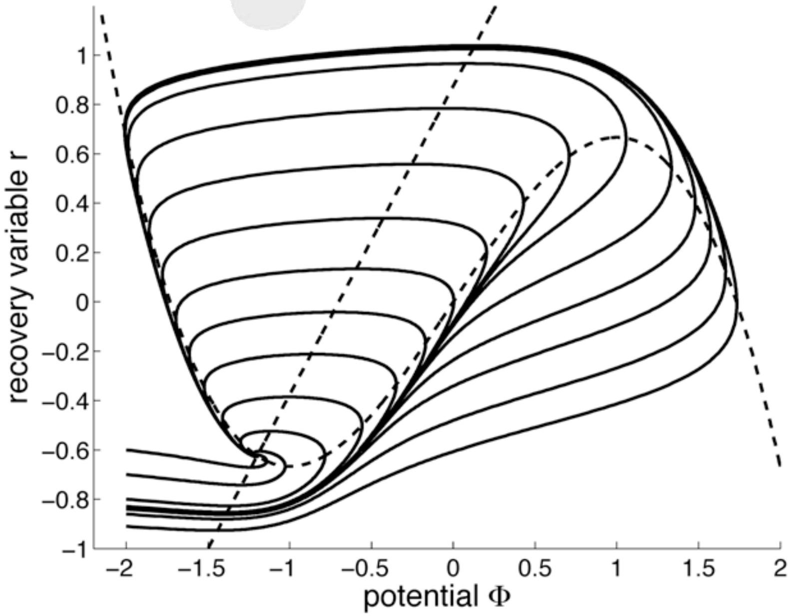
mechanics of excitation contraction

motivation - nerve cells



bonhoeffer-van der pol oscillator

$$\ddot{\phi} + k\,\dot{\phi} + \phi = 0 \qquad k = c[\,\phi^2 - 1\,]$$



fitzhugh-nagumo equation

$$\mathrm{d}_t\phi = f^{\phi}(\phi, r) + \mathrm{div}(\boldsymbol{q}) \qquad \text{potential}$$

$$\mathrm{d}_t r \;= f^{r}(\phi, r) \qquad \text{repolarization}$$

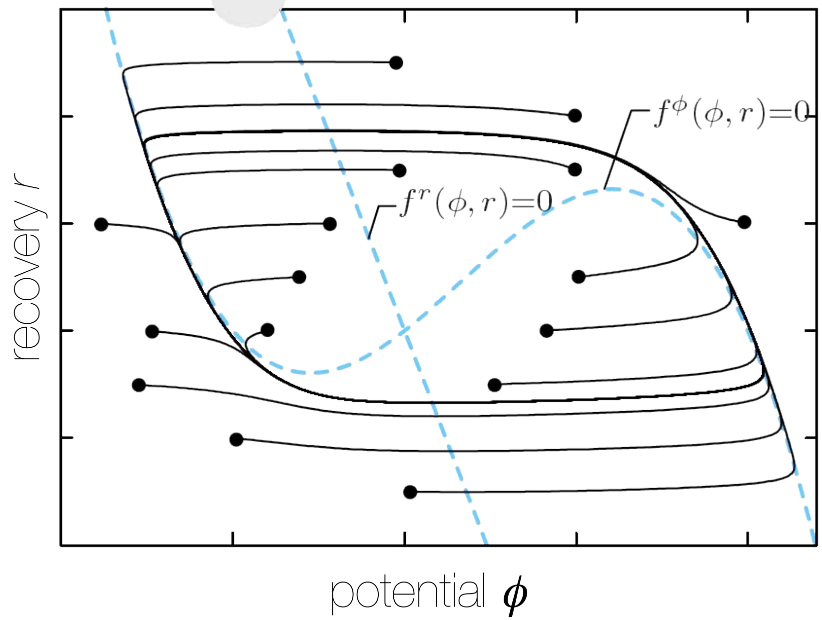
$$\boldsymbol{q} \;= [\,c^{\text{iso}}\boldsymbol{I} + c^{\text{ani}}\boldsymbol{n}\otimes\boldsymbol{n}\,]\cdot\nabla\phi$$

van der pol [1926], hodgkin & huxley [1952], fitzhugh [1961], nagumo et al. [1962]

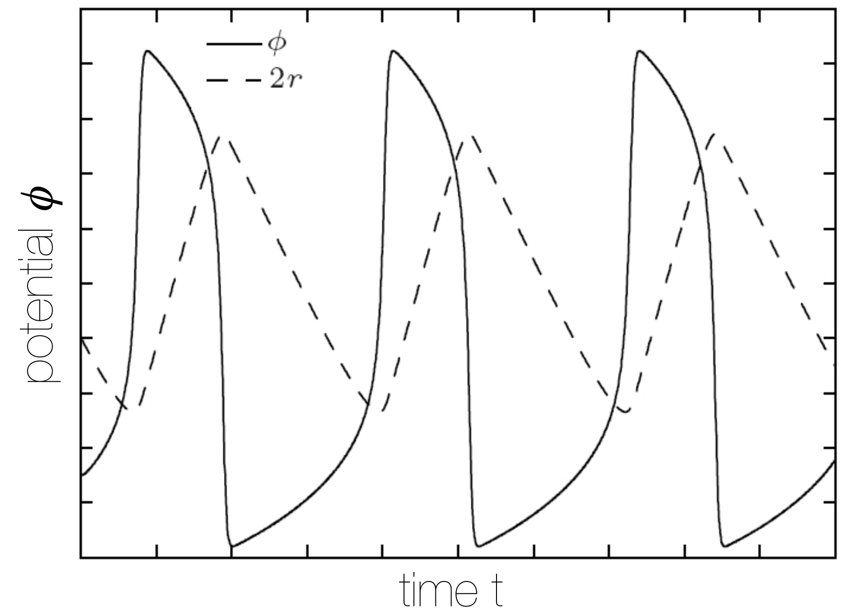
continuum mechanics

pacemaker cells - oscillatory

$$f^{\phi} = -c\,\phi\,[\phi - a][\phi - 1] - c\,r$$
$$f^{r} = \phi - b\,r + a$$



spontaneous re-excitation



hodgkin & huxley [1952], fitzhugh [1961], noble [1962], beeler & reuter [1977], luo & rudy [1991]

in silico

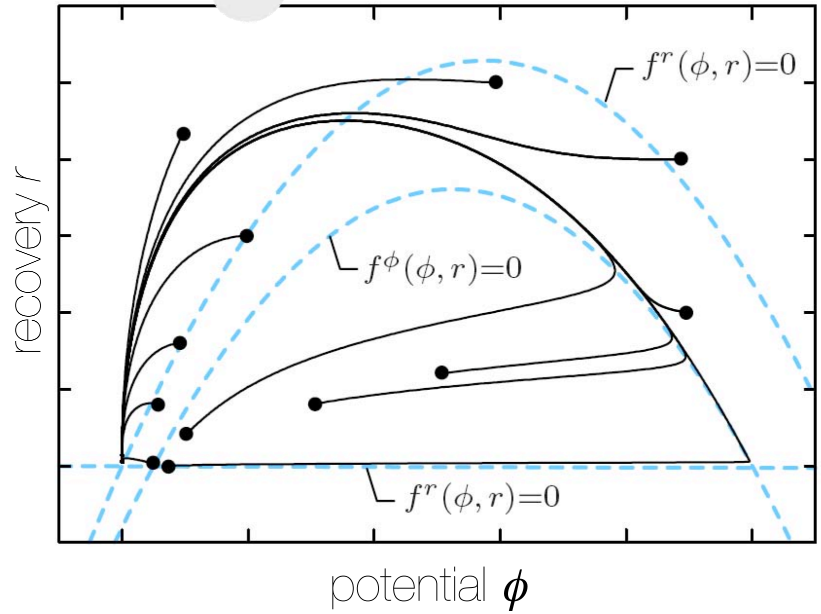
macro

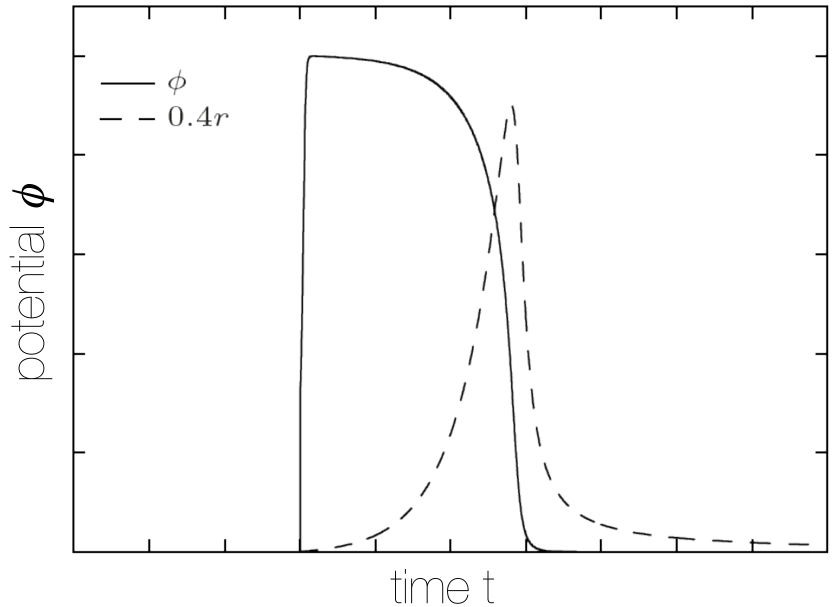
continuum mechanics

ventricular muscle cells - stable

$$f^\phi = -c\,\phi\,[\phi - a][\phi - 1] - r\phi$$
$$f^r = [\gamma + \frac{\mu_1\, r}{\mu_2 + \phi}][-r - c\,\phi[\phi - b - 1]]$$

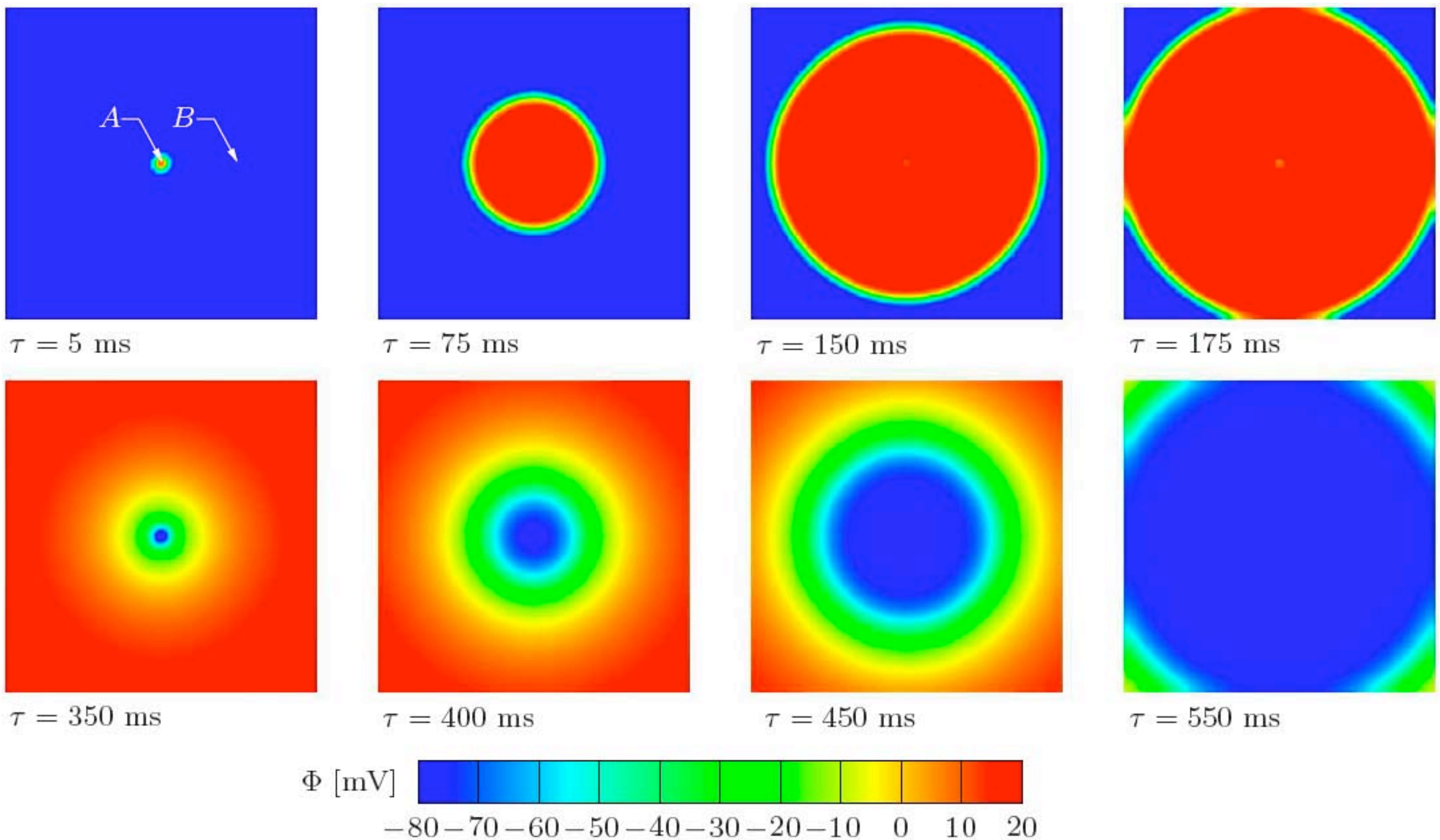
stable resting potential





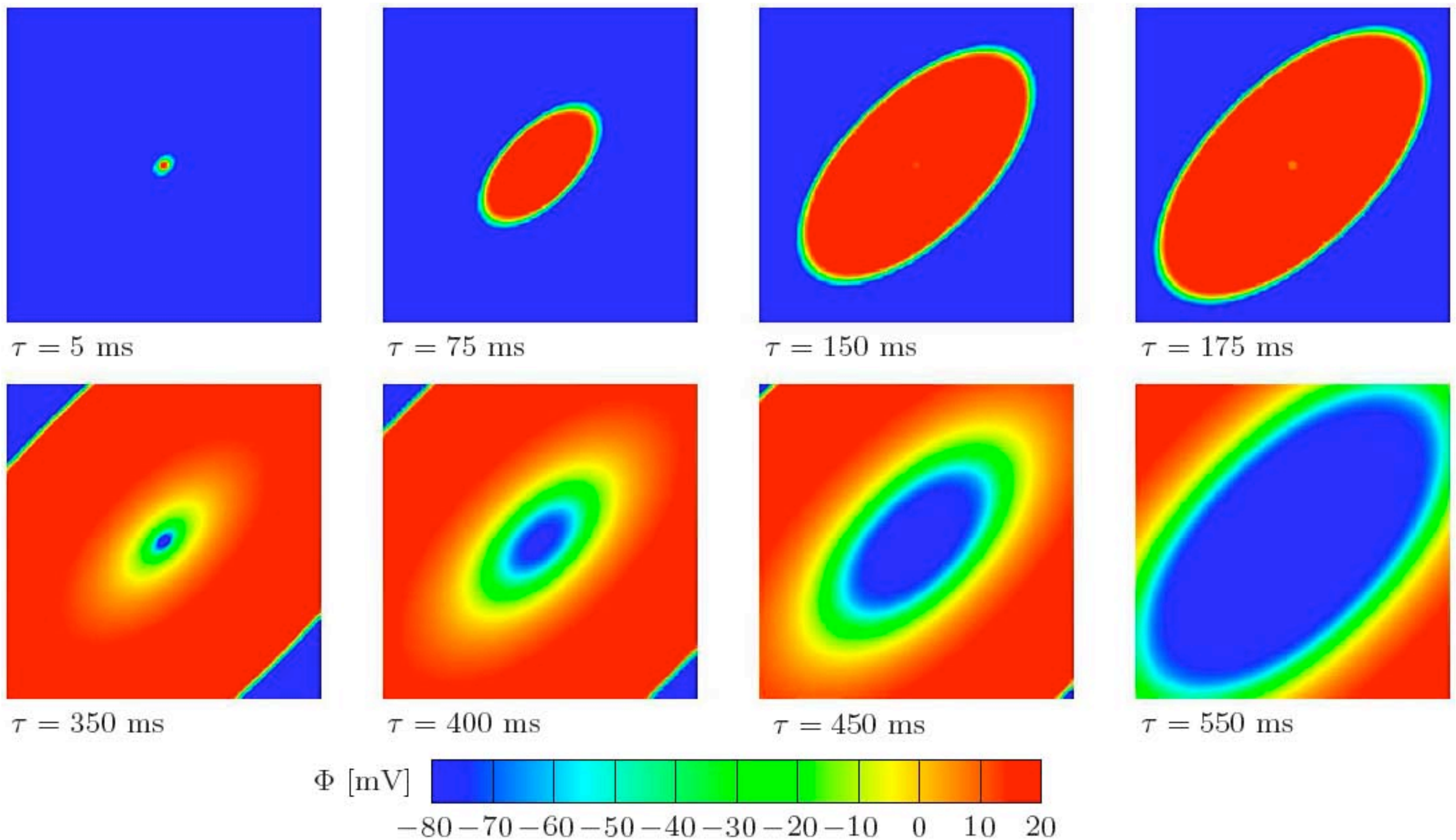
aliev & panfilov [1996], rogers & mc culloch [1994], nash & panfilov [2004]

single pacemaker in isotropic muscle tissue



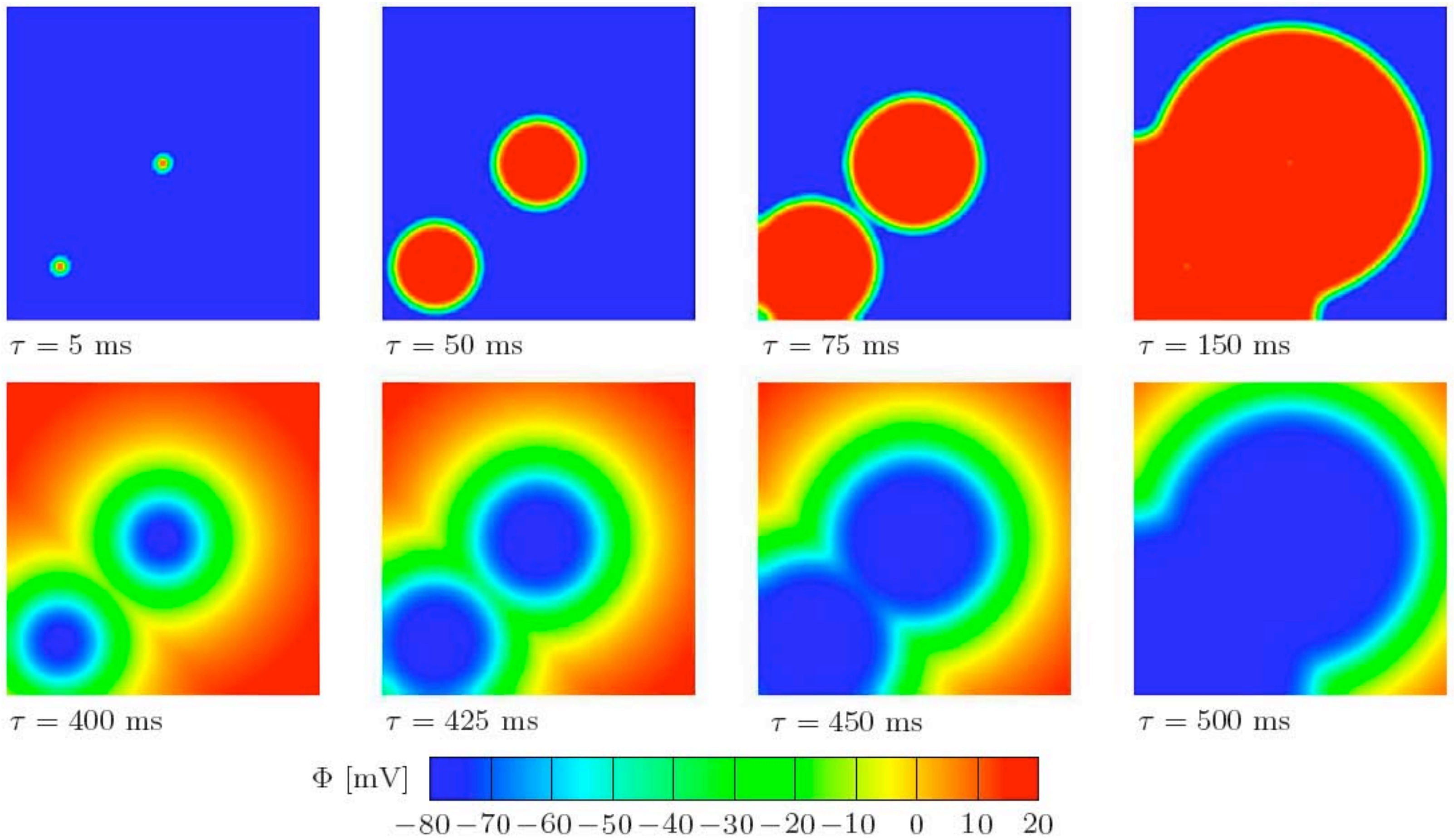
goktepe & kuhl [2008]

single pacemaker in anisotropic muscle tissue



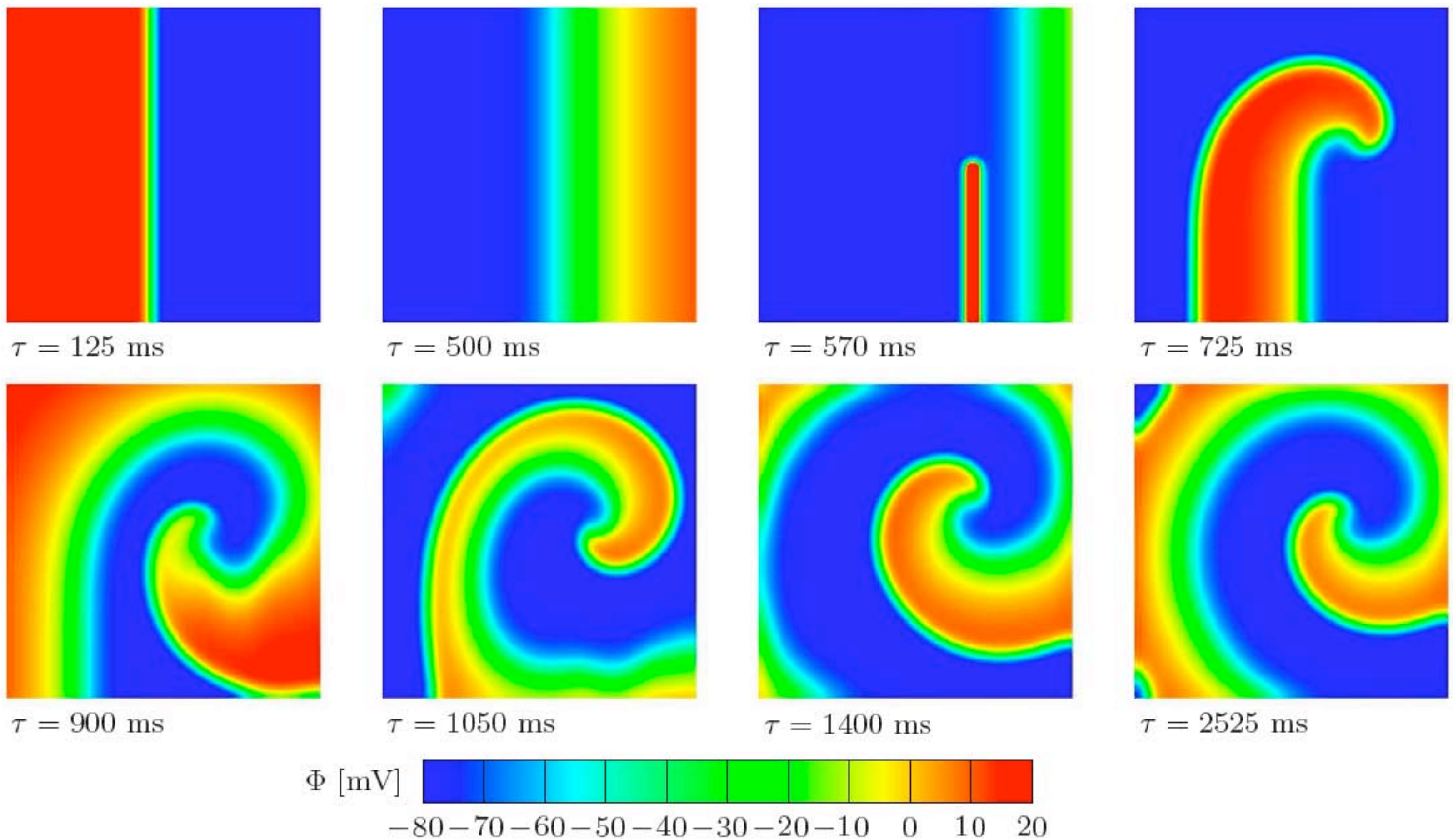
goktepe & kuhl [2008]

two pacemaker sites / biventricular pacing



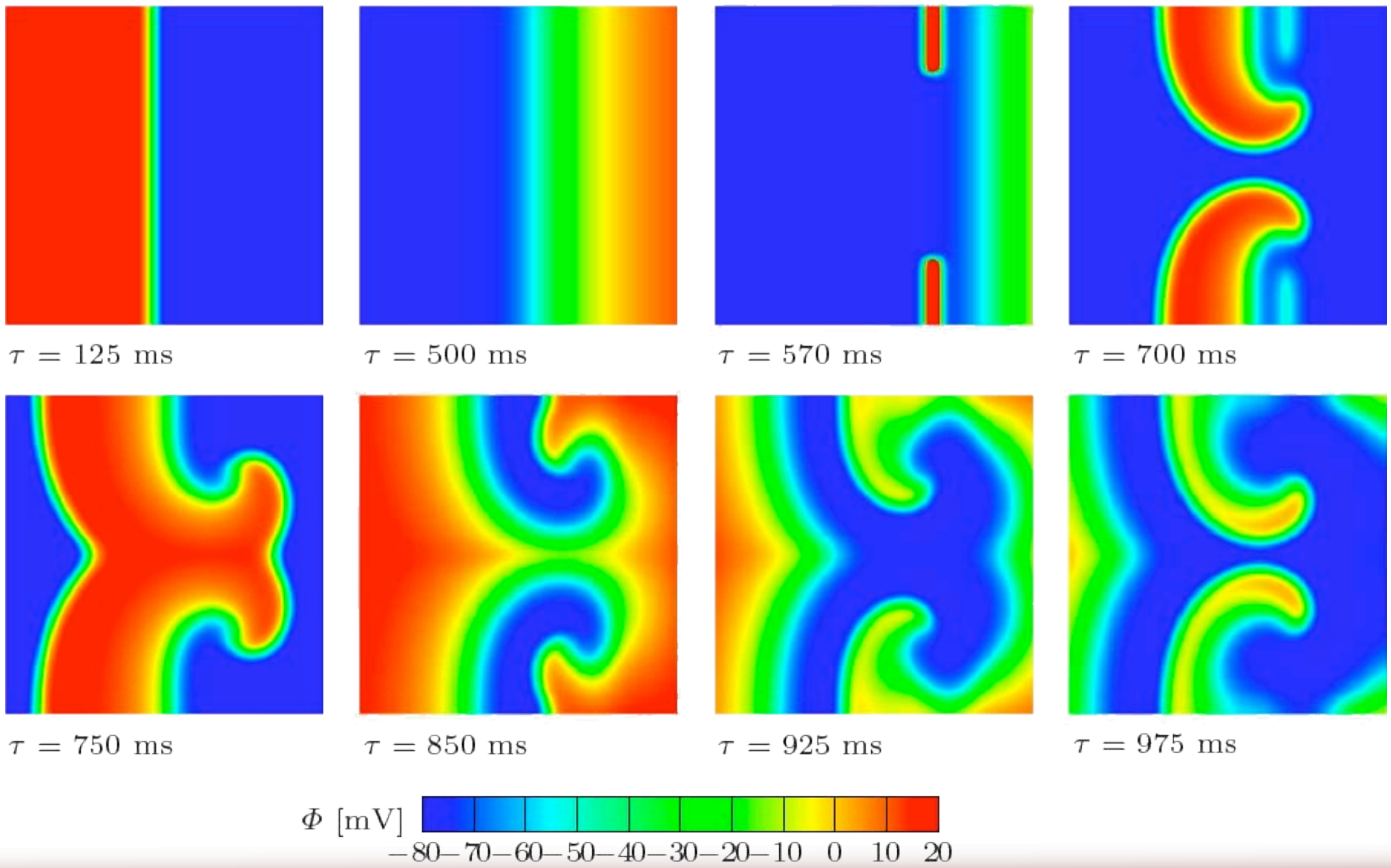
goktepe & kuhl [2008]

spiral waves / re-entry and ventricular fibrillation

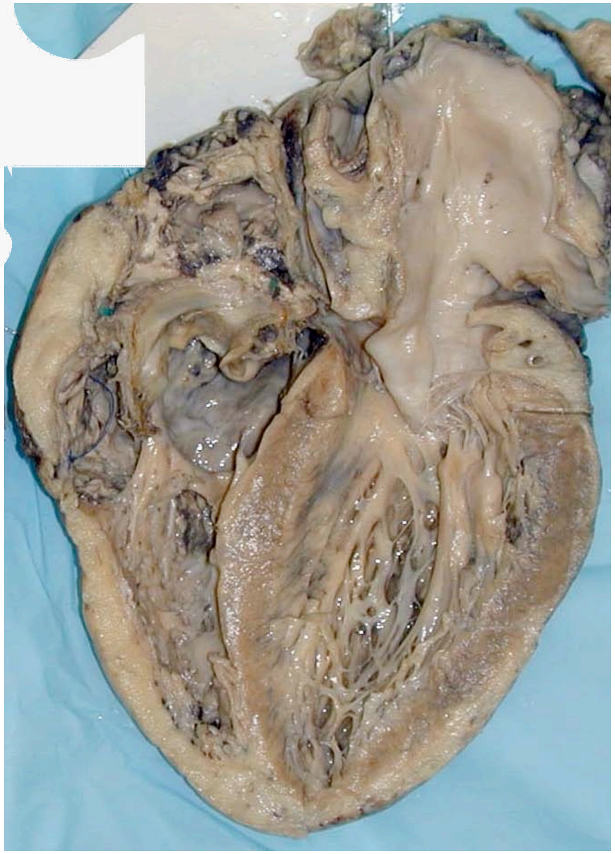


goktepe & kuhl [2008]

spiral waves / re-entry and ventricular fibrillation



excitation of a human heart



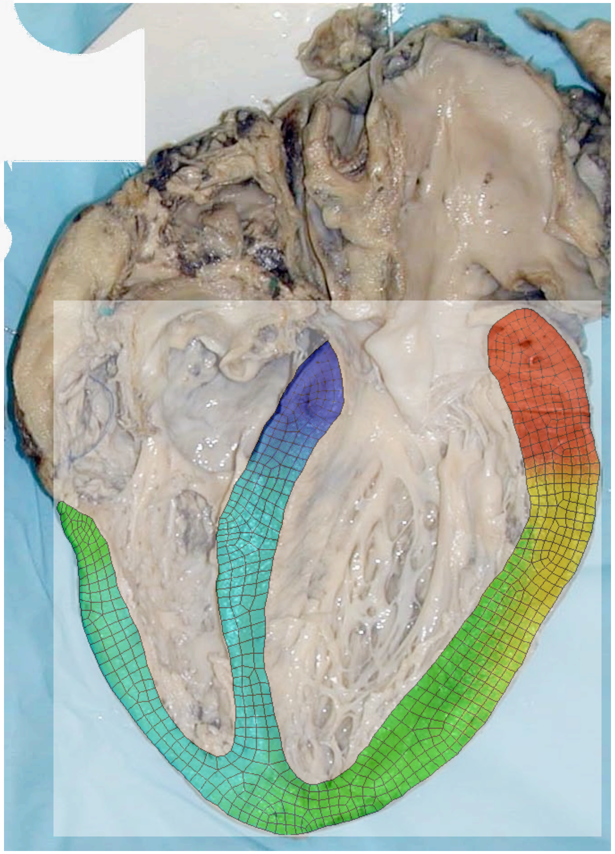
by courtesy of chengpei xu

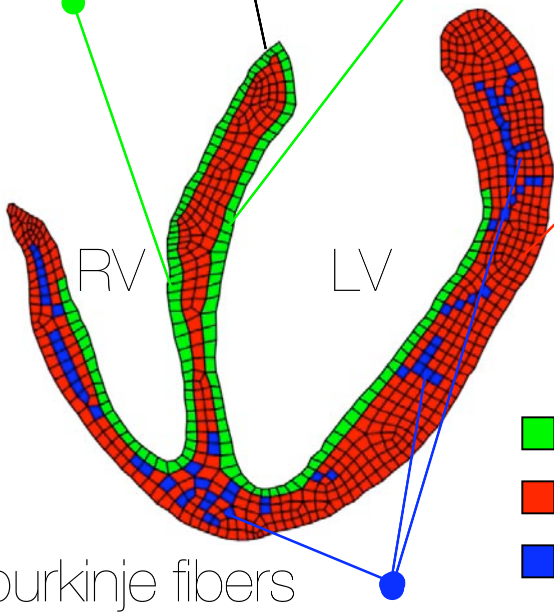
in silico

macro

continuum mechanics

excitation of a human heart





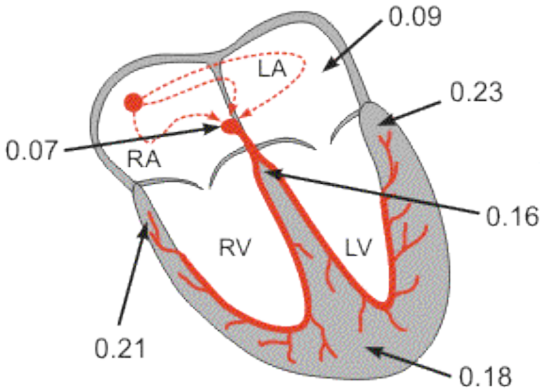
by courtesy of chengpei xu

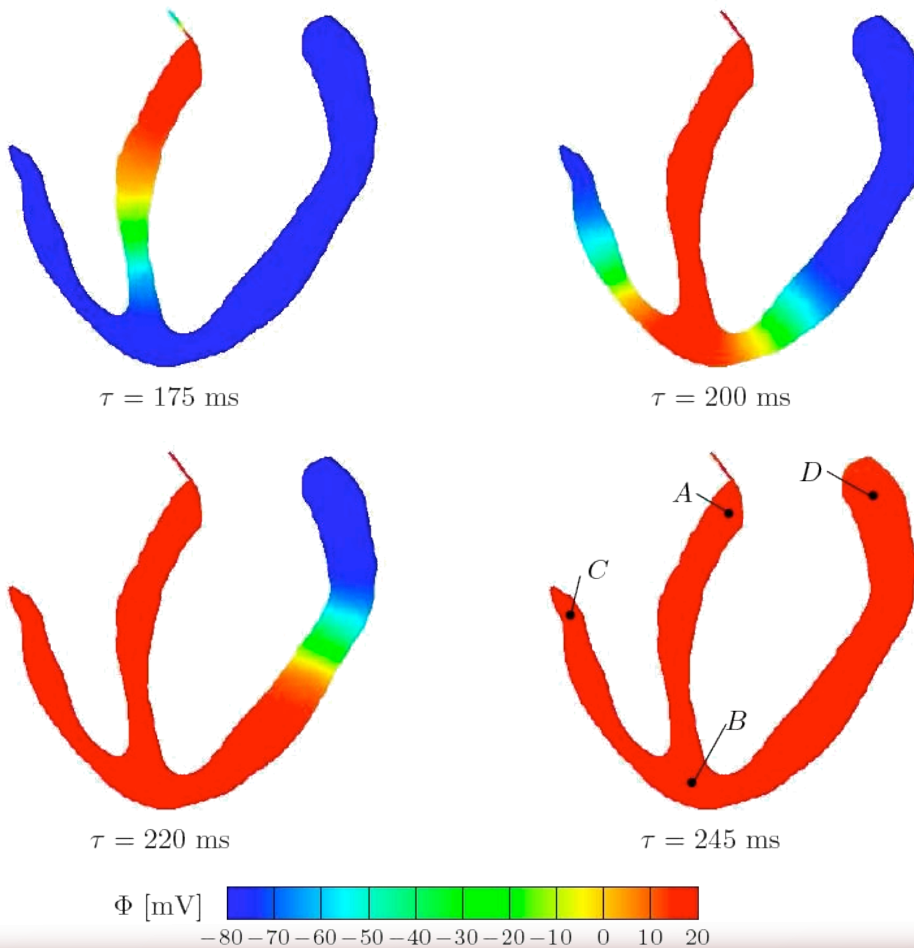
electrophysiology

cardiac activation times

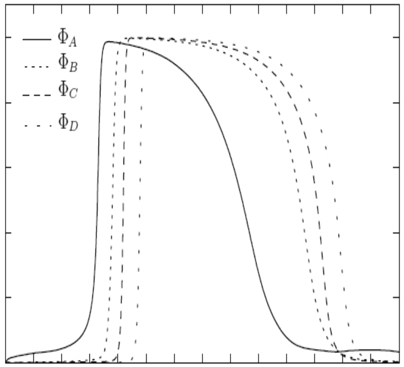
activation delay 15ms

cardiac activation times





action potential @A-D

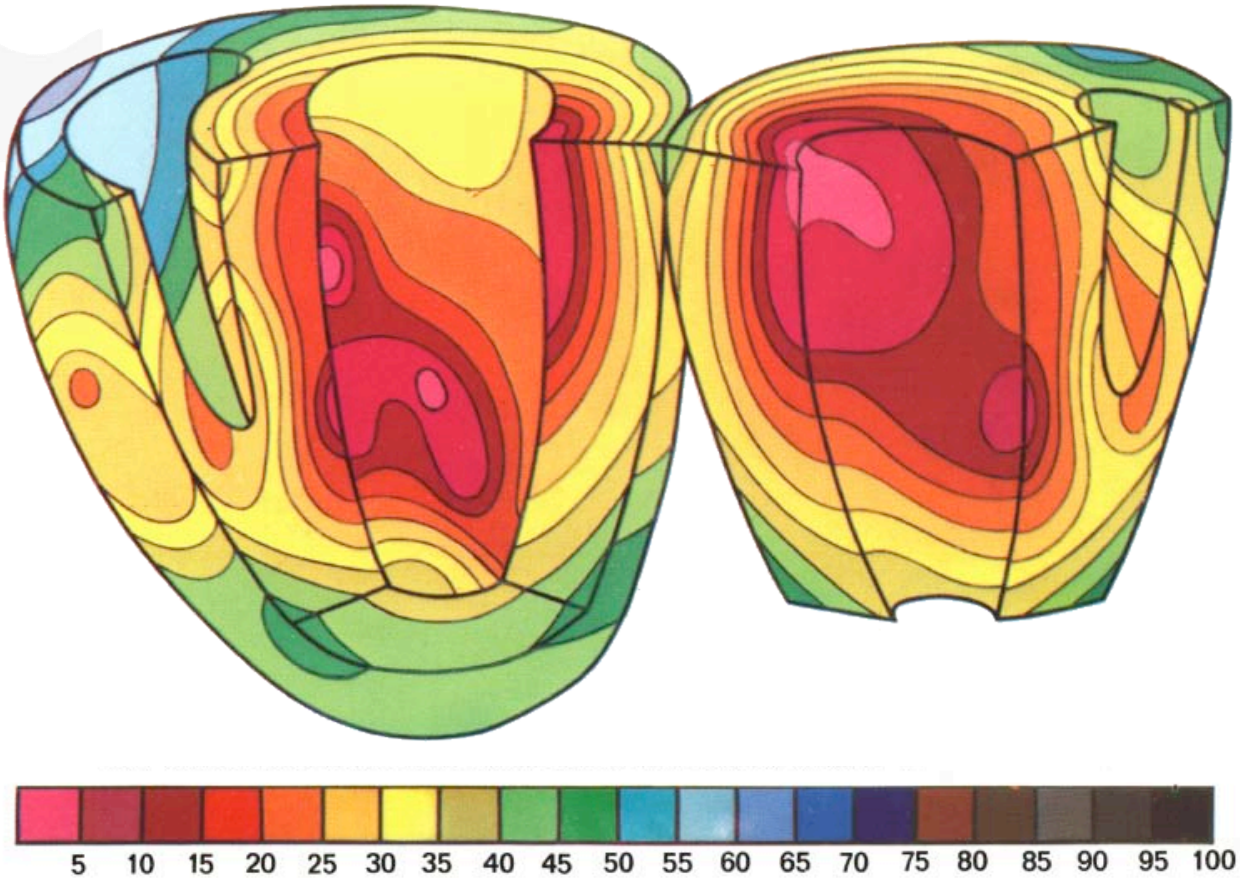


in silico

macro

continuum
mechanics

cardiac activation times

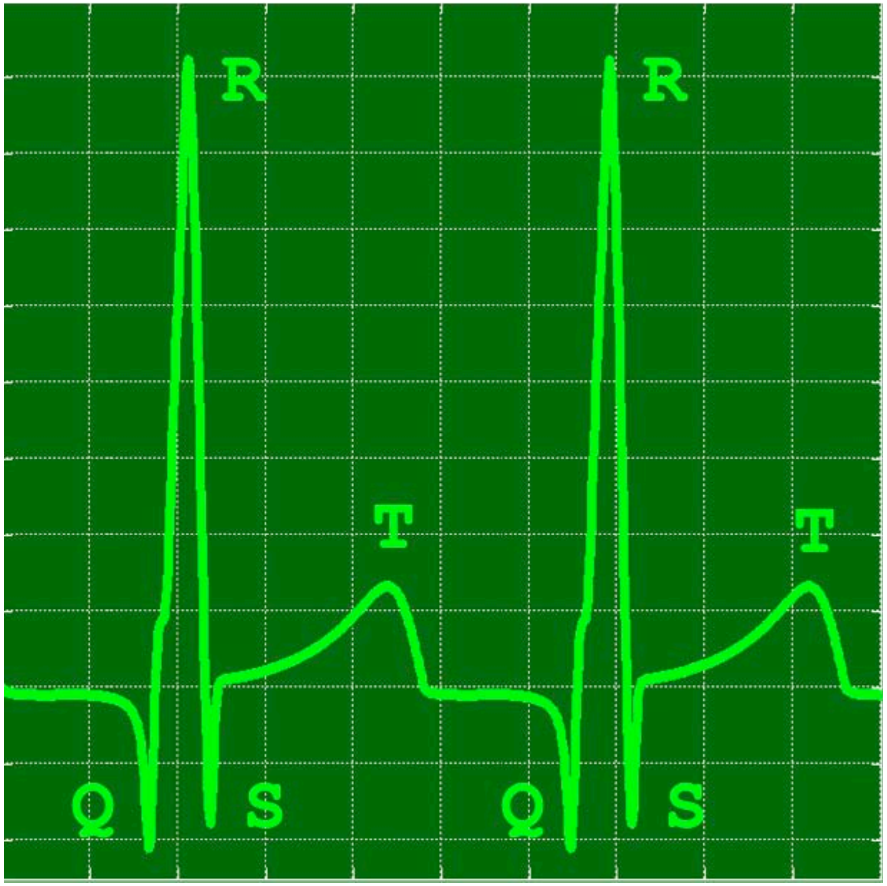


durrer, van dam, freud, janse, meijler, arzbaecher [1970]

electrophysiology

heart vector - in silico EKG

$$\dot{\phi} = \mathrm{div}\, \boldsymbol{q} + f^{\phi}$$



$$\boldsymbol{q}^{\mathrm{heart}} = \int \boldsymbol{q}\, \mathrm{d}V$$

$$\boldsymbol{q} = d^{\mathrm{iso}}\, \boldsymbol{I} + d^{\mathrm{ani}}\, \boldsymbol{n}^{\mathrm{myo}} \otimes \boldsymbol{n}^{\mathrm{myo}}$$

in silico

macro

- primary field variables

$$\boldsymbol{\varphi}, \phi$$

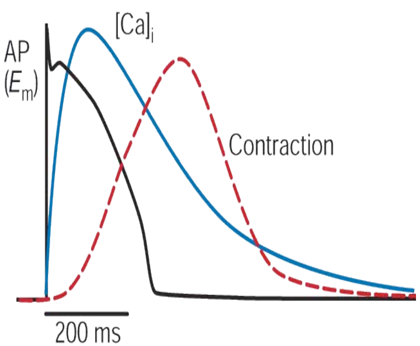
- differential equations

$$\mathbf{0} = \mathrm{Div}(\boldsymbol{P}) + F^{\varphi}$$
$$\mathrm{D}_t \phi = \mathrm{Div}(\boldsymbol{Q}) + F^{\phi}$$

- constitutive equations

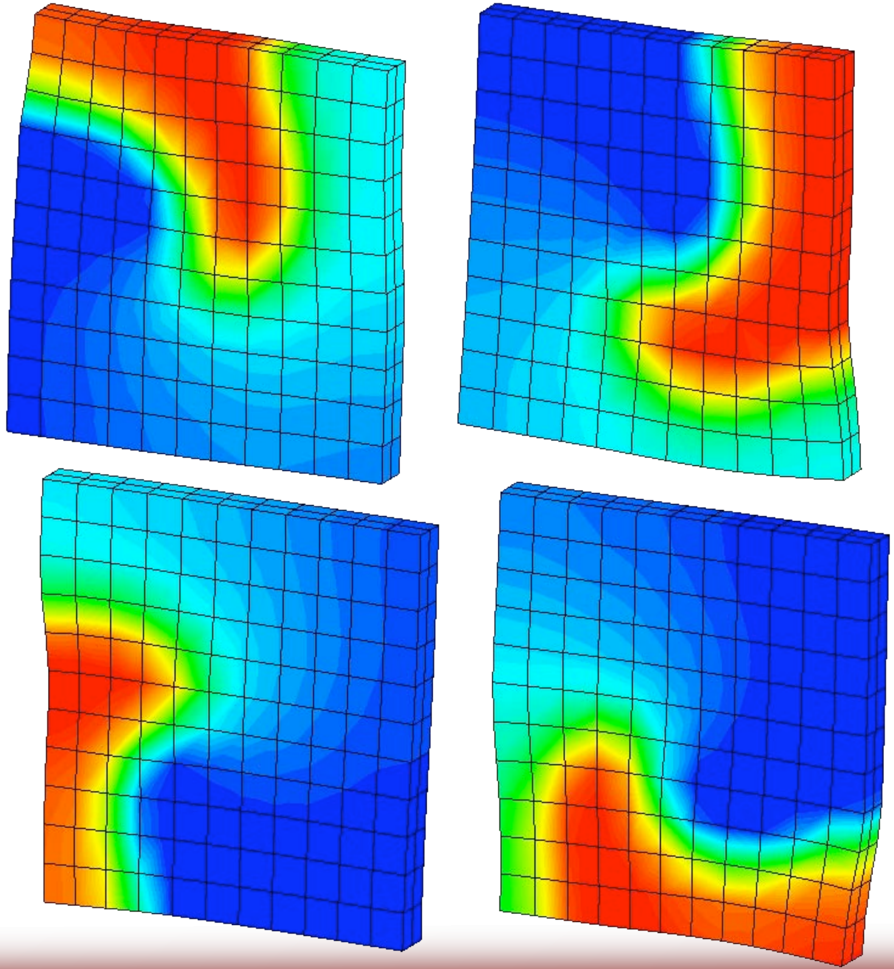
$$\boldsymbol{P} = \boldsymbol{P}^{\mathrm{pas}}(\nabla_{\boldsymbol{X}} \boldsymbol{\varphi}) + P^{\mathrm{act}}(\nabla_{\boldsymbol{X}} \boldsymbol{\varphi}, \phi)\, \boldsymbol{n}^{\mathrm{myo}} \otimes \boldsymbol{n}^{\mathrm{myo}}$$

$$\boldsymbol{Q} = \boldsymbol{D}(\nabla_{\boldsymbol{X}} \boldsymbol{\varphi}) \cdot \nabla_{\boldsymbol{X}} \phi$$



aliev & panfilov [1996], rogers & mc culloch [1994], tentusscher & panfilov [2008]

spiral waves / re-entry and ventricular fibrillation



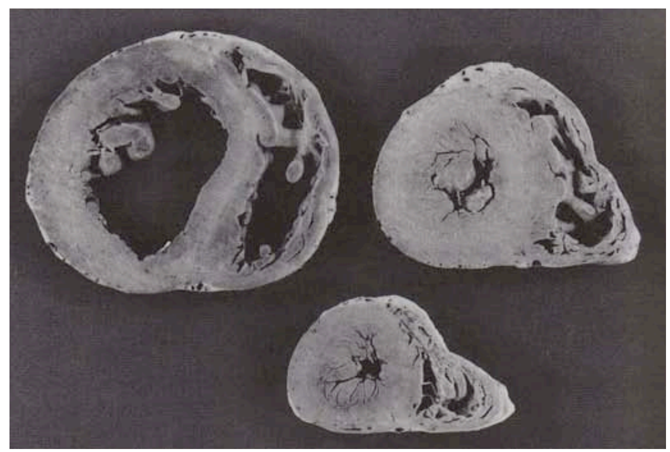
in silico

macro

- **chronic** changes
- **adaptive** geometries
- pressure overload / hypertrophy
- volume overload / dilation

$$\boldsymbol{F} = \boldsymbol{F}^{\mathrm{e}} \cdot \boldsymbol{F}^{\mathrm{g}}$$

kinematics of finite growth

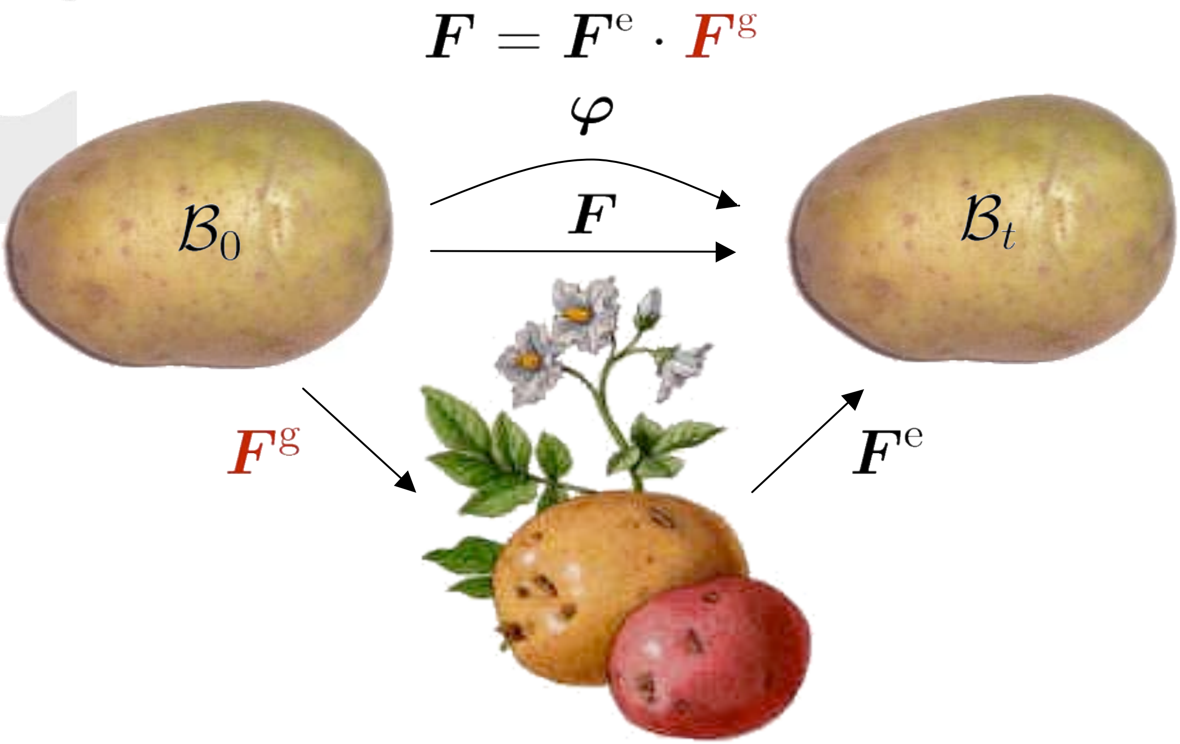


fung [1990]

lee [1969],rodriguez,hoger & mc culloch [1994], taber[1995], epstein&maugin [2000], humphrey[2002] ambrosi & mollica [2002], garikipati, arruda, grosh, narayanan & calve [2004], ben amar & goriely [2005]

mechanics of growth

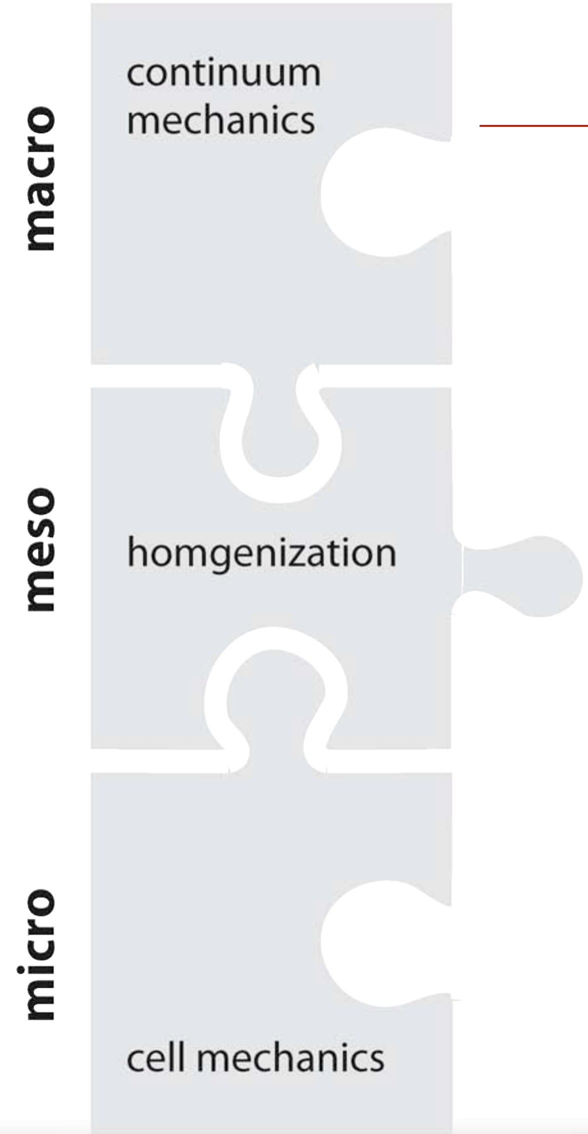
kinematics of finite growth



concept of incompatible growth configuration

lee [1969],rodriguez,hoger & mc culloch [1994], taber[1995], epstein&maugin [2000], humphrey[2002]
ambrosi & mollica [2002], garikipati, arruda, grosh, narayanan & calve [2004], ben amar & goriely [2005]

in silico

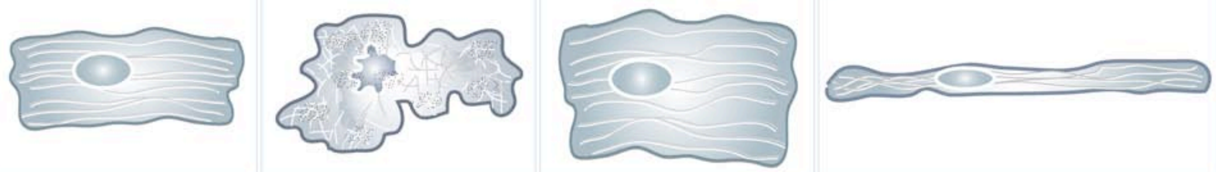


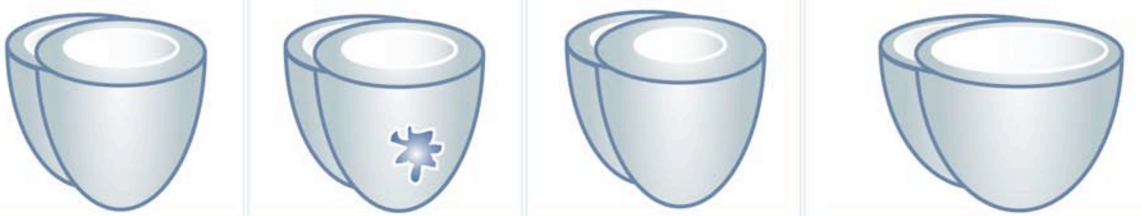
hypertrophy and dilation

$$\boldsymbol{F}^{\mathrm{g}} = \vartheta^{\perp} \boldsymbol{I} + [\vartheta^{||} - \vartheta^{\perp}] \boldsymbol{n}^{\mathrm{myo}} \otimes \boldsymbol{n}^{\mathrm{myo}}$$

hypertrophy dilation

healthy cardiomyocyte	cardiomyocyte death	concentric hypertrophy	eccentric hypertrophy
physiological loading	heart attack	pressure overload	volume overload
p, λ^{myo}	E^{myo}	$\vartheta^{\perp}(p)$	$\vartheta^{\vert\vert}(\lambda^{\mathrm{myo}})$
healthy heart	heart failure	wall thickening	dilation





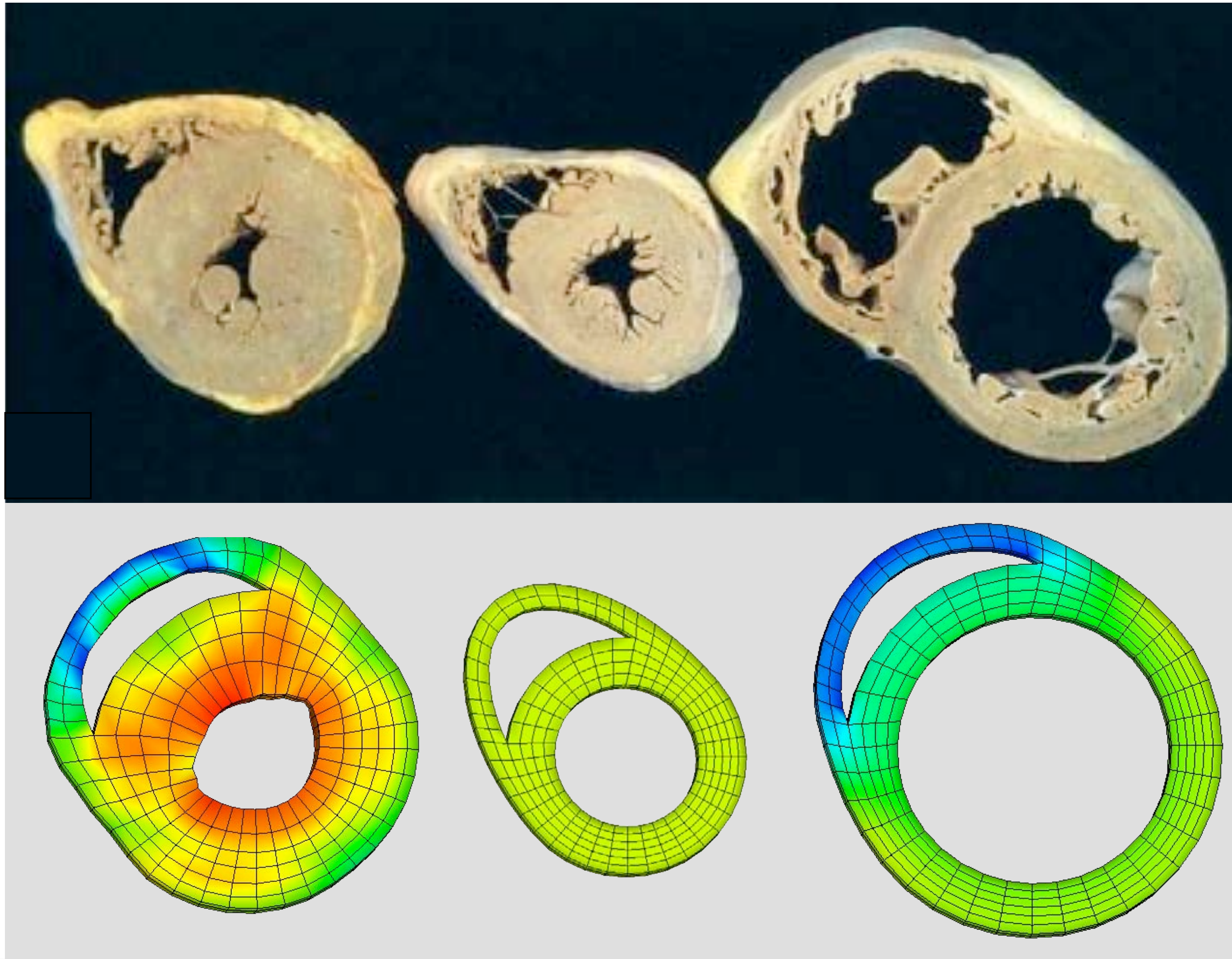
in silico

macro

continuum
mechanics

$$\boldsymbol{F} = \boldsymbol{F}^{\mathrm{e}} \cdot \boldsymbol{F}^{\mathrm{g}}$$

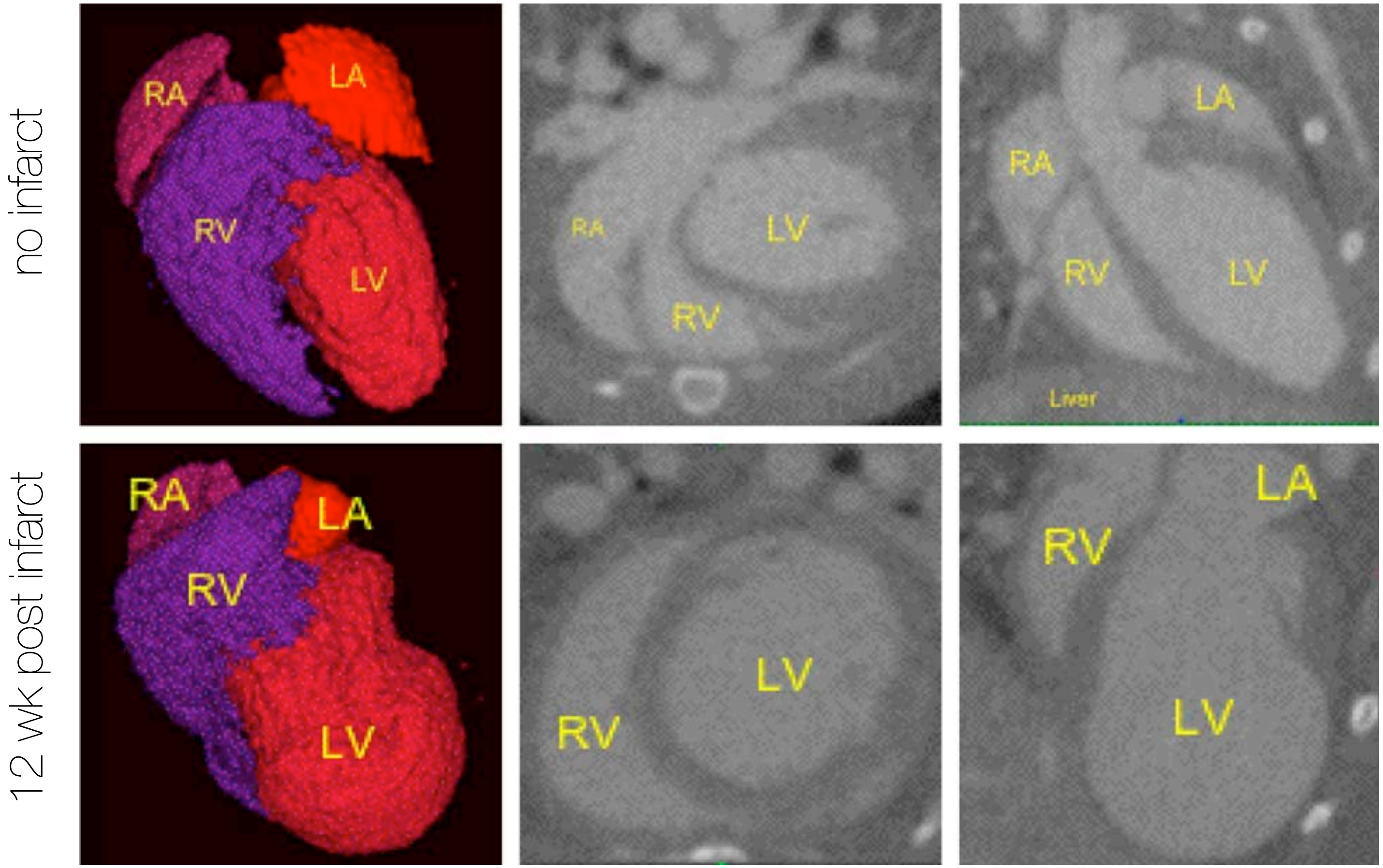
hypertrophied, normal and dilated heart



robbins & cotran [2005]

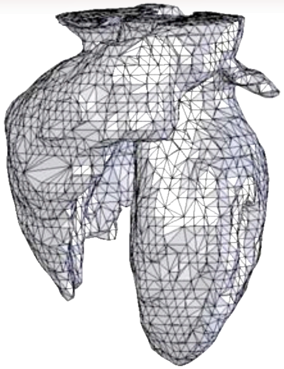
micromechanically motivated growth

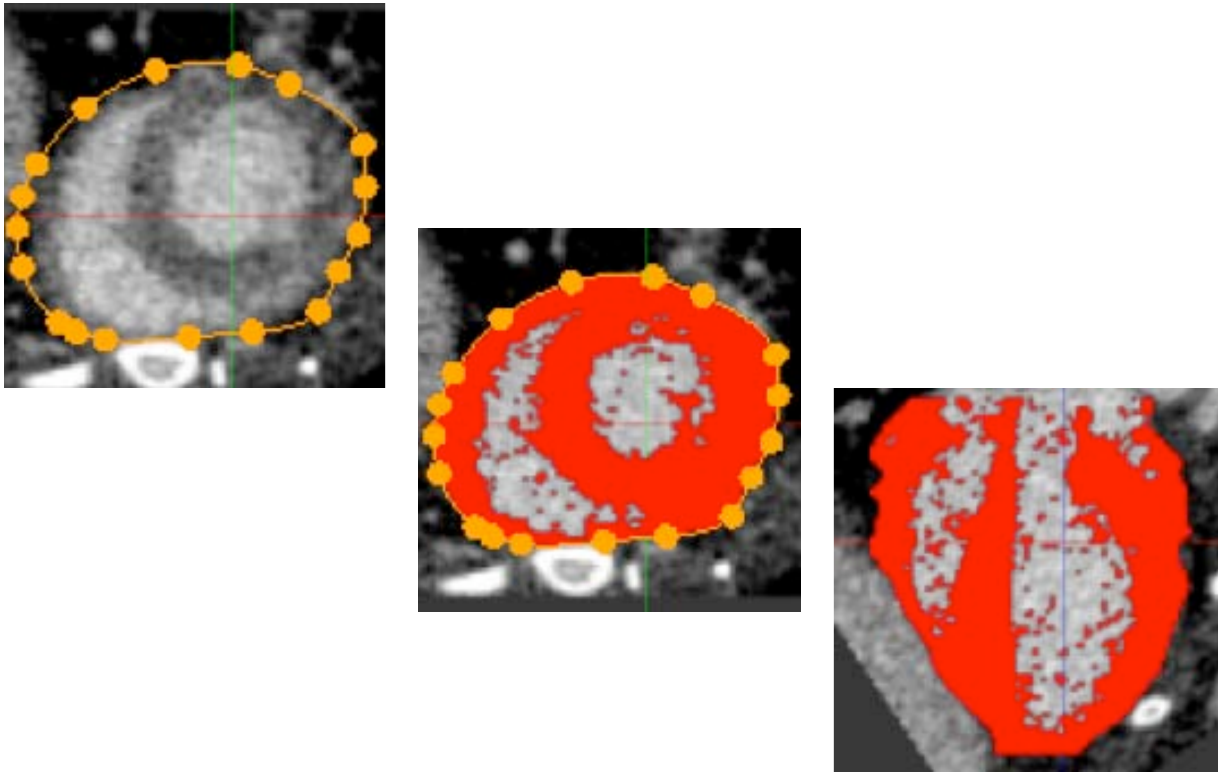
volume overload-induced dilation

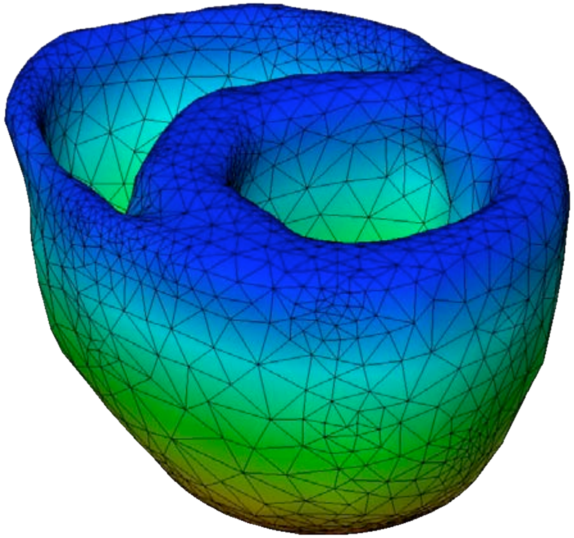


doyle, sheikh, sheikh, cao, yang, robbins, wu [2007]

volume overload-induced dilation



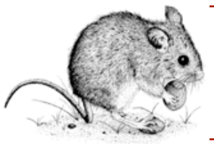




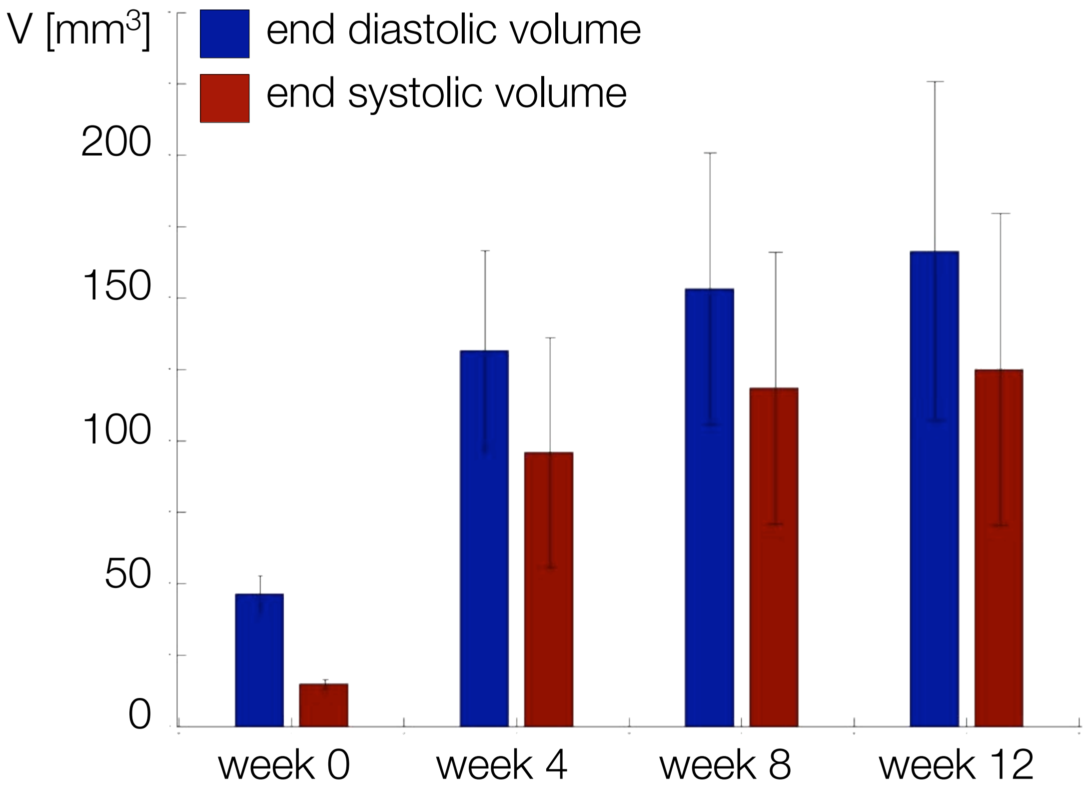
from μct to finite element model

rebecca taylor & anton dam

mouse infarct models - non-invasive



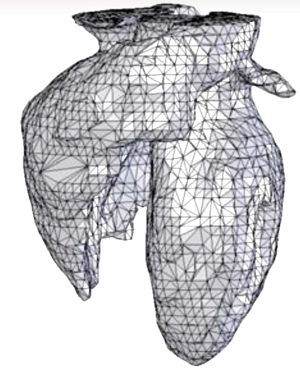
volume overload-induced dilation

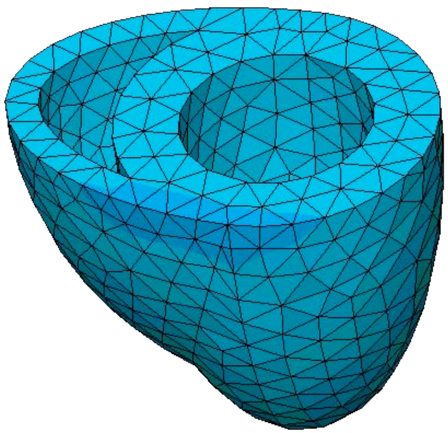


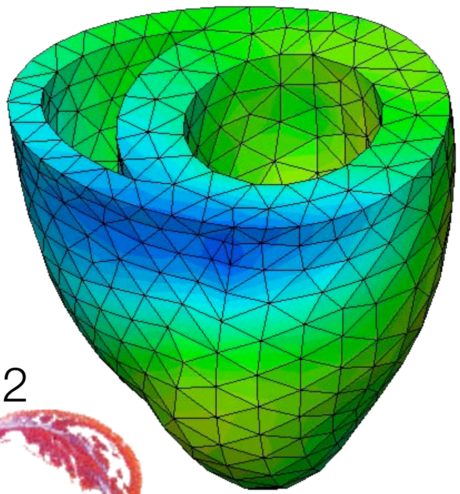
ejection fraction ↓ from 68.16% to 23.33%

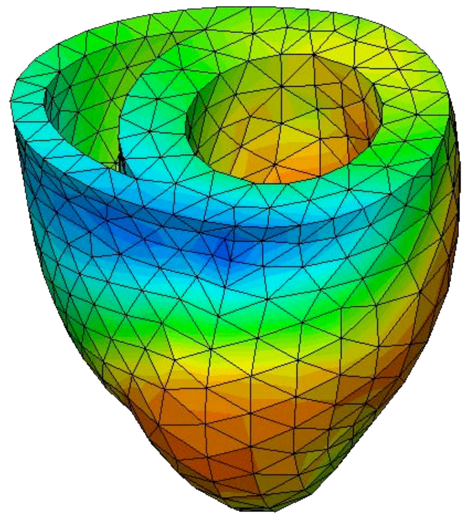
doyle, sheikh, sheikh, cao, yang, robbins, wu [2007]

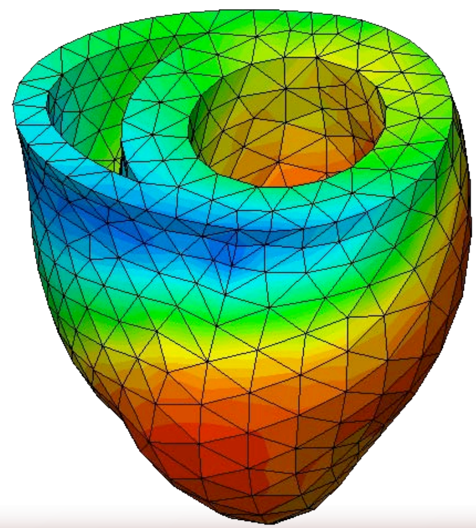
volume overload-induced dilation



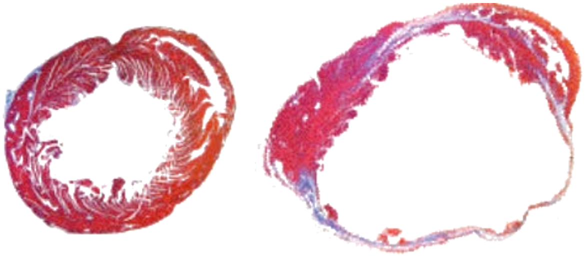








week 0 week 12

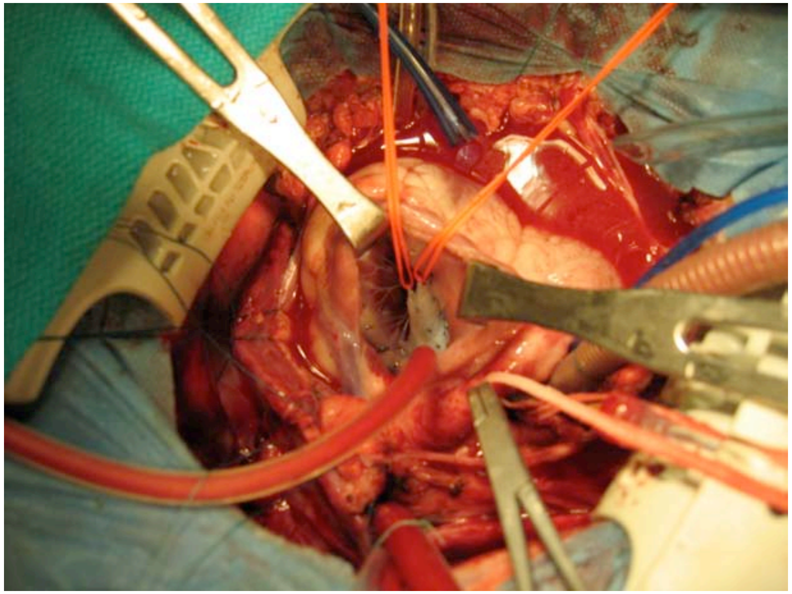


ejection fraction ↓ from 68.16% to 23.33%

end-diastolic volume ↑ from 37.12mm^3 to 133.16mm^3

mouse infarct models - non-invasive

videofluoroscopic markers



surgically implanted epicardial markers and transmural bead set

4d coordiantes from in vivo biplane videofluoroscopic marker images

krishnamurthy, ennis, itoh, bothe, swansons-birchill, langer, rodriguez, criscione, miller, ingels

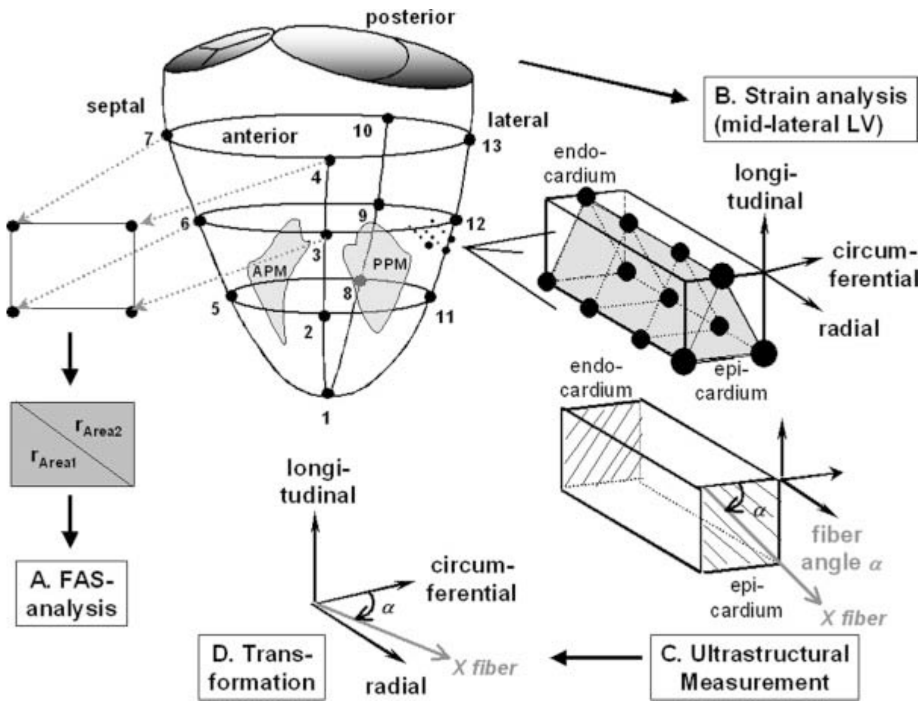
ovine infarct models - invasive

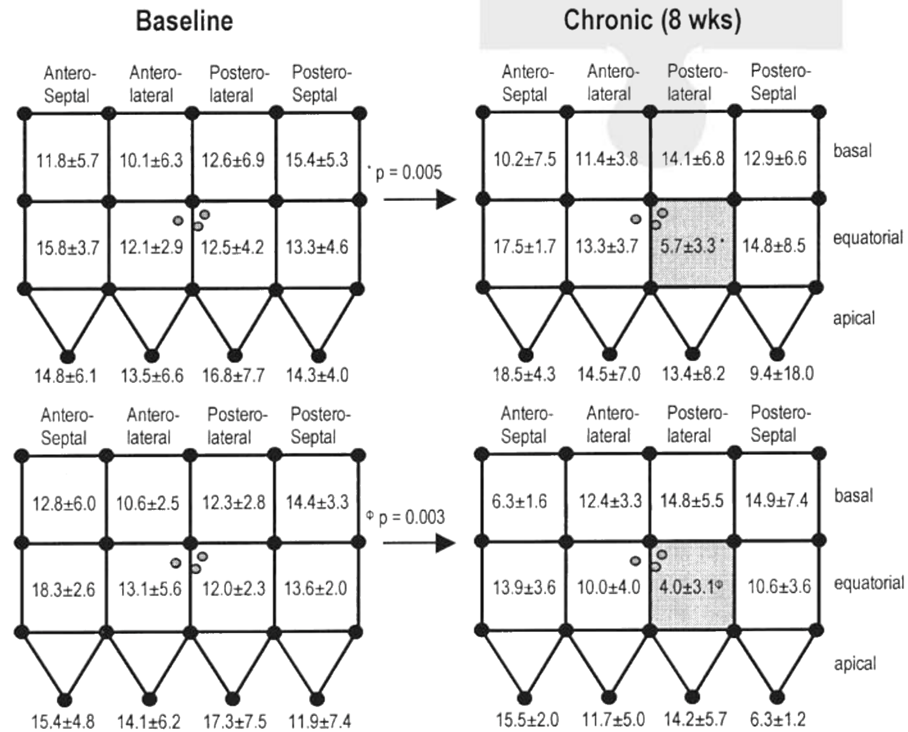
in vivo/in vitro

animal models

infarct-induced stiffening

tissue stiffness **infarcted > healthy**





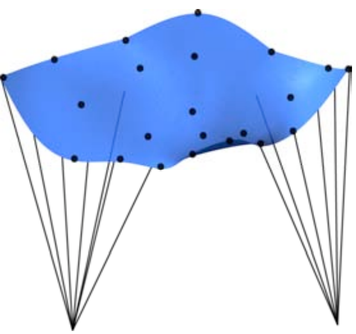
nguyen, cheng, langer, rodriguez, oakes, itoh, ennis, liang, daughters, ingels, miller [2007]

ovine infarct models - invasive

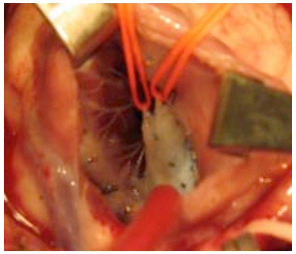
in silico	interface	in vivo/in vitro
continuum mechanics	inverse analysis	animal models

macro

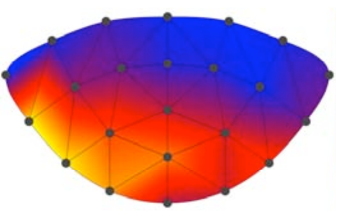
organ



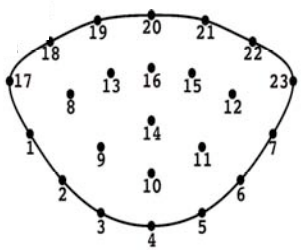
$$\Phi(\boldsymbol{\kappa}) = \frac{1}{2} \sum_{n=1}^{n_{\mathrm{mrk}}} || \boldsymbol{x}_n^{\mathrm{fem}}(\boldsymbol{\kappa}) - \boldsymbol{x}_n^{\mathrm{exp}} ||^2 \rightarrow \min$$



$\boldsymbol{x}_n^{\mathrm{fem}}(\boldsymbol{\kappa})$



$\boldsymbol{x}_n^{\mathrm{exp}}$



- cardiac tissue stiffness **in vivo > in vitro**
- **electric stimulation** increases stiffness

krishnamurthy, ennis, itoh, bothe, swanson-birchilll, karlsson, kuhl, miller, ingels [2008]

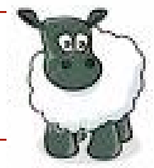
ovine infarct models - invasive

in silico

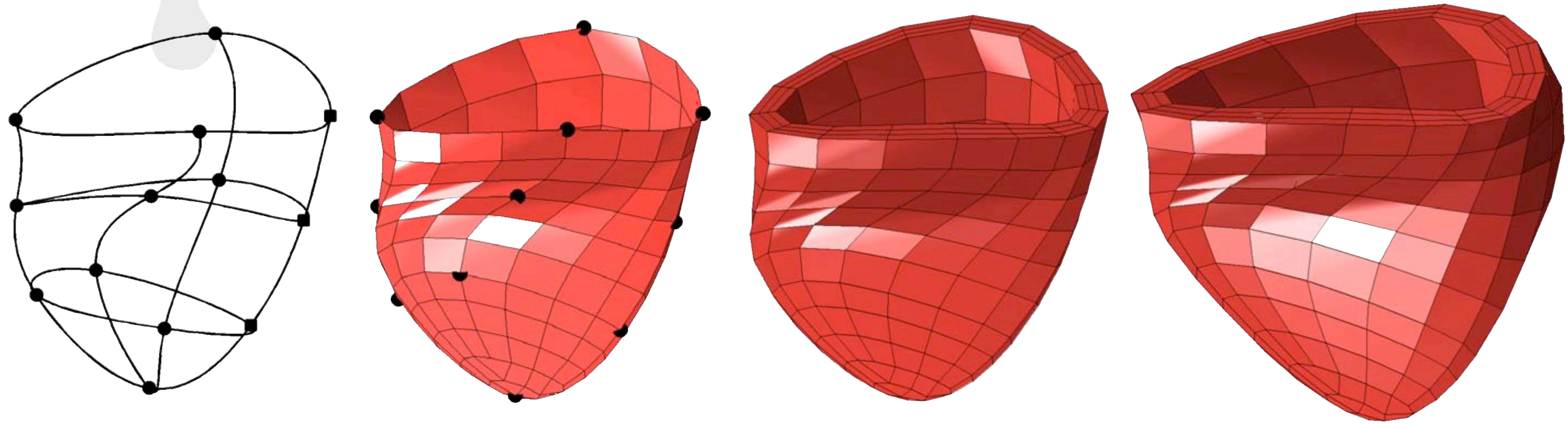
macro

continuum mechanics

infarct-induced dilation



ventricular markers | surface mesh | week 1 pre-infarct | week 8 post-infarct



end-diastolic volume ↑ by 22±10%, sphericity ↓ by 5%

cheng, nguyen, malinowski, langer, liang, daughtes,ingels, miller [2006]

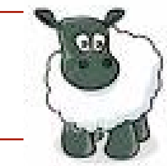
ovine infarct models - invasive

in silico

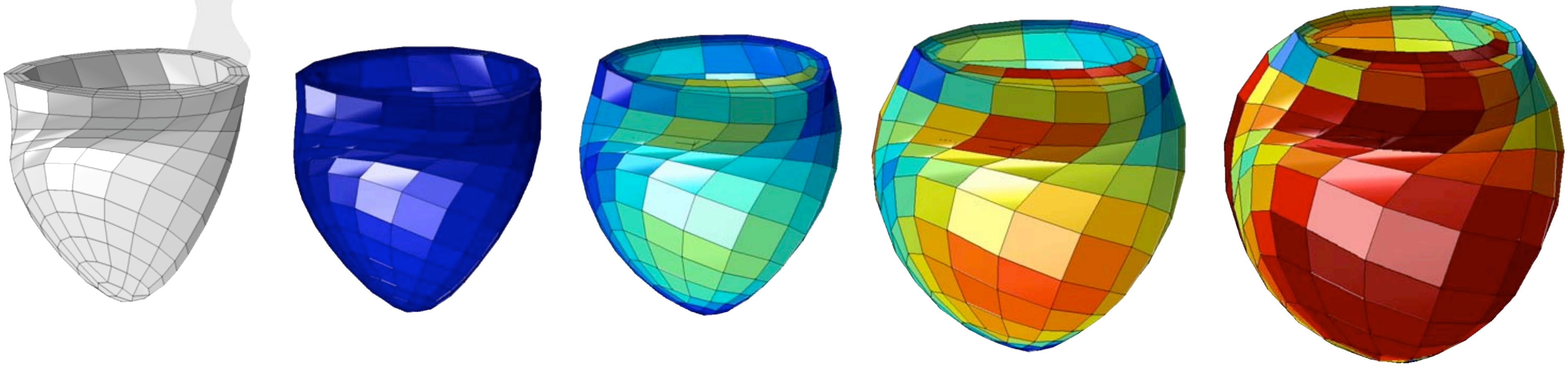
macro

continuum
mechanics

infarct-induced dilation



$$\boldsymbol{F}^{\rm g} = \vartheta\, \boldsymbol{I} \qquad {\rm D}_t \vartheta = k_\vartheta(\vartheta)\; {\rm tr}(\boldsymbol{C}^{\rm e} \cdot \boldsymbol{S}^{\rm e})$$

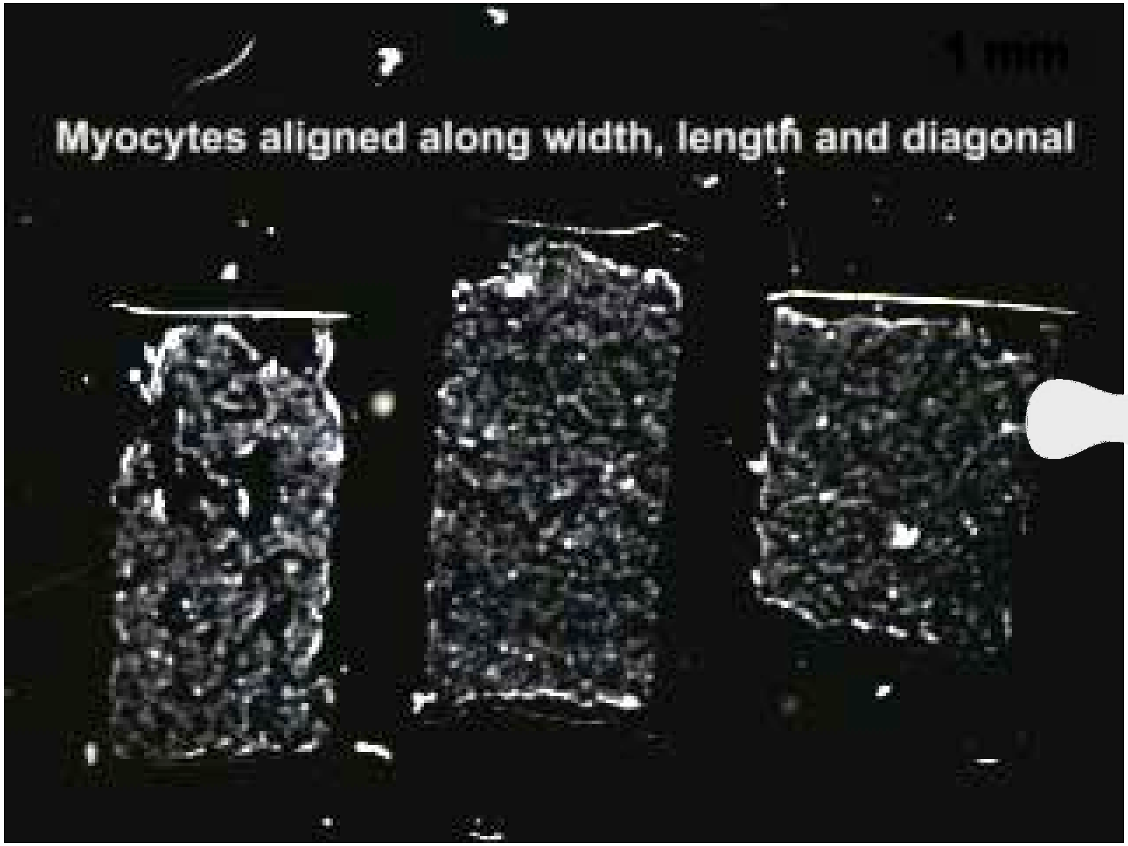


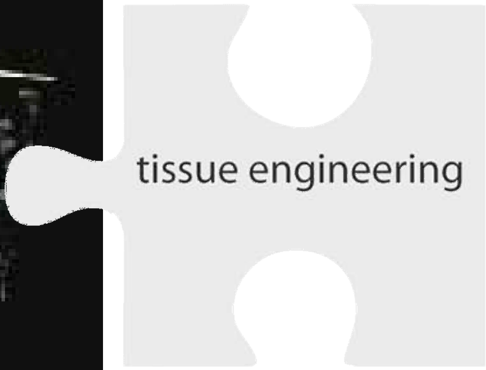
$t = 0\ t_0$ $t = 16\ t_0$ $t = 32\ t_0$ $t = 64\ t_0$ $t = 128\ t_0$

end-diastolic volume ↑ and sphericity ↓

ovine infarct models - invasive

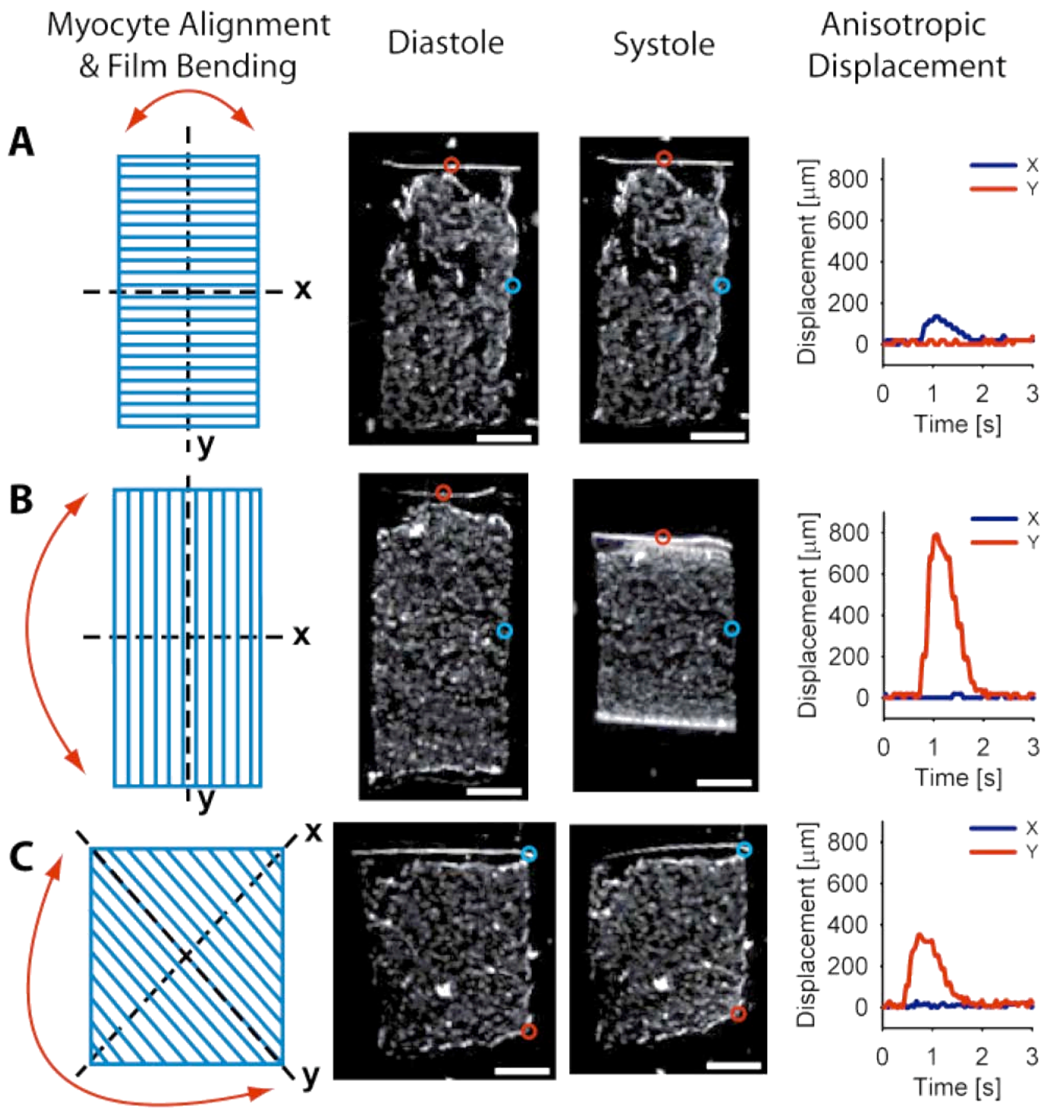
PDMS base layer seeded with
synchronously contracting neonatal rat ventricular cardiomyocytes





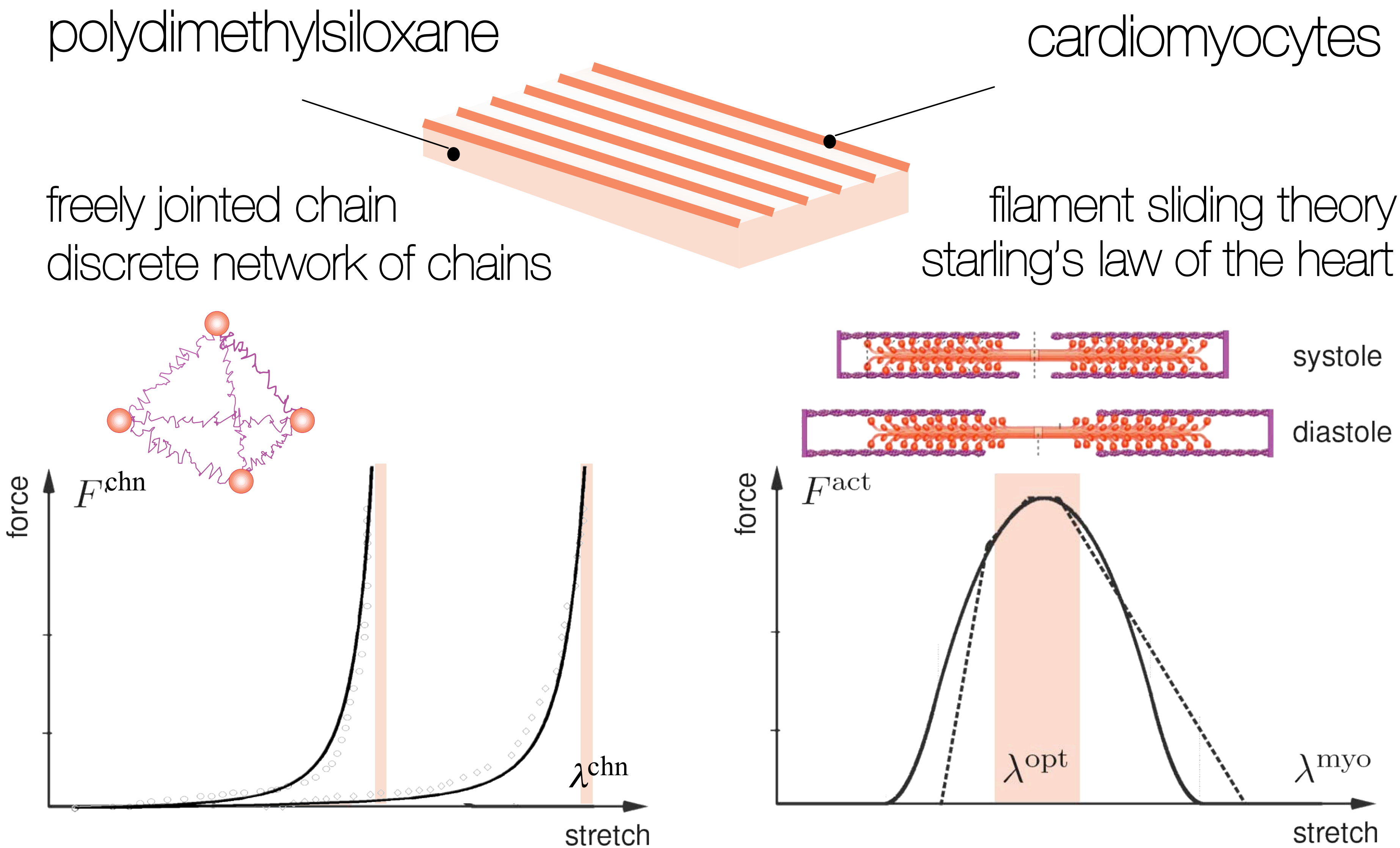
feinberg, feigel, shevkoplyas, sheehy, whitesides, parker [2007]

muscular thin films for cardiac repair



feinberg, feigel, shevkoplyas, sheehy, whitesides, parker [2007]

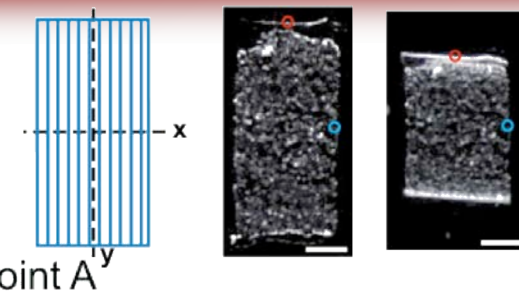
muscular thin films - in vitro

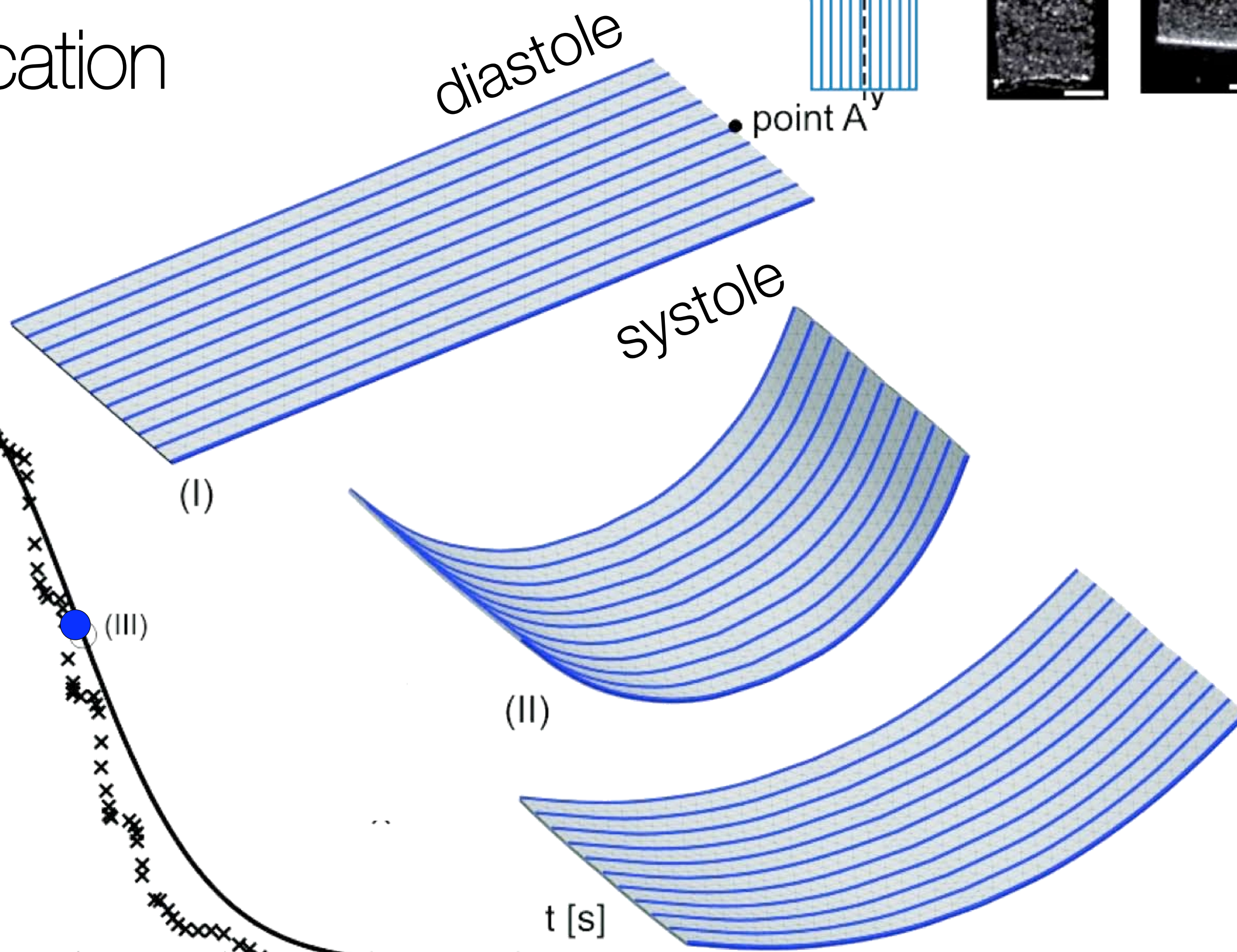


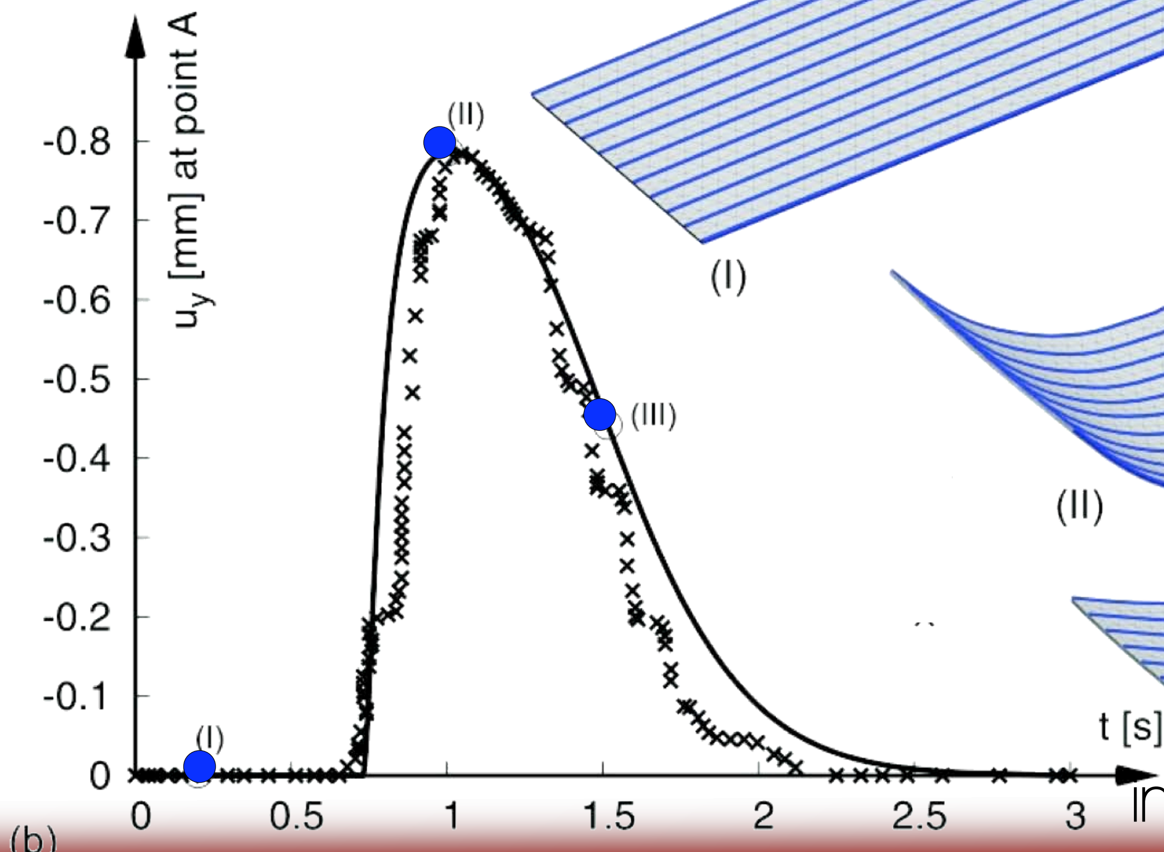
böl, reese, parker, kuhl [2008]

muscular thin films - in silico

vertical fibers
model verification

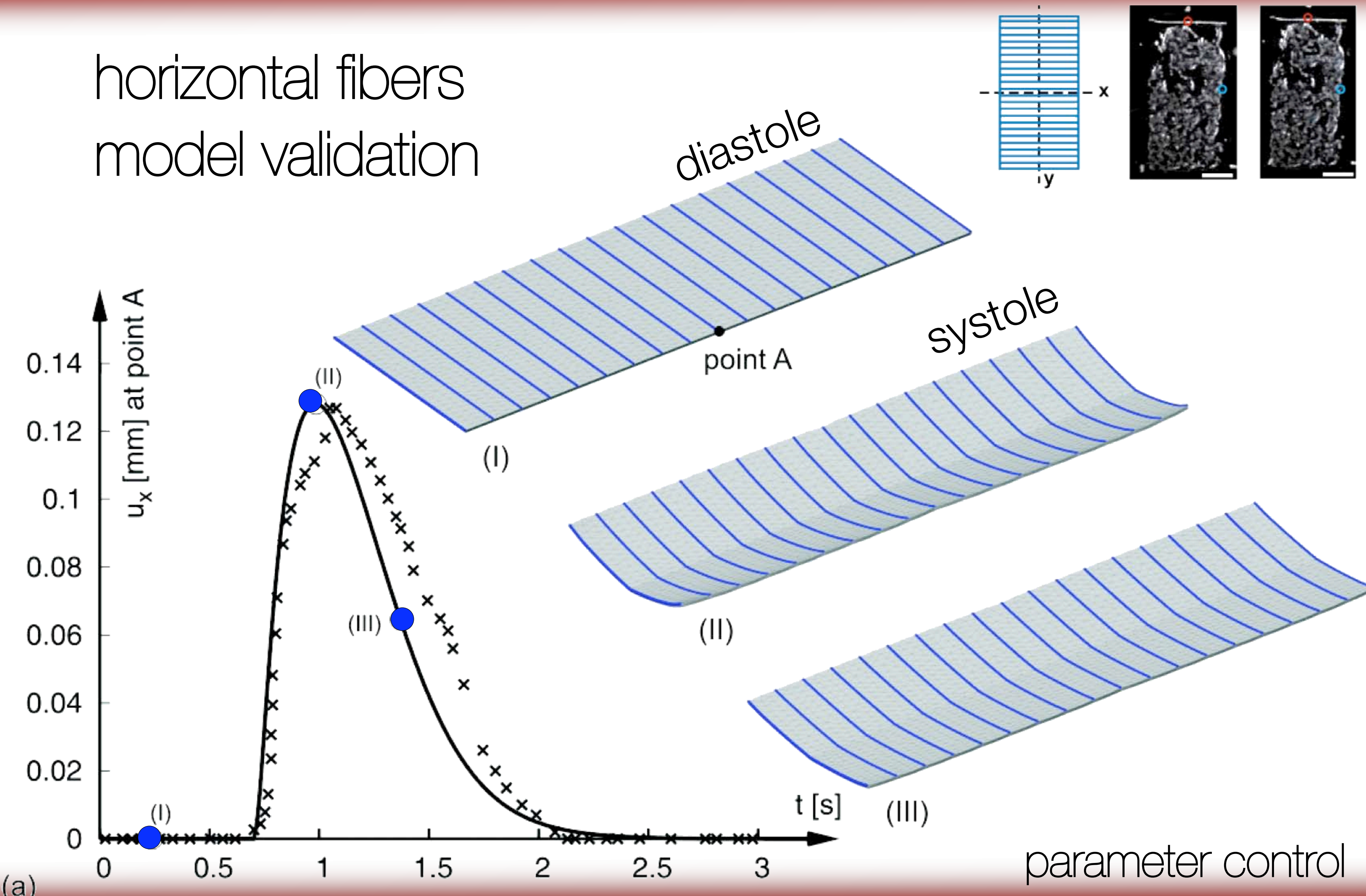






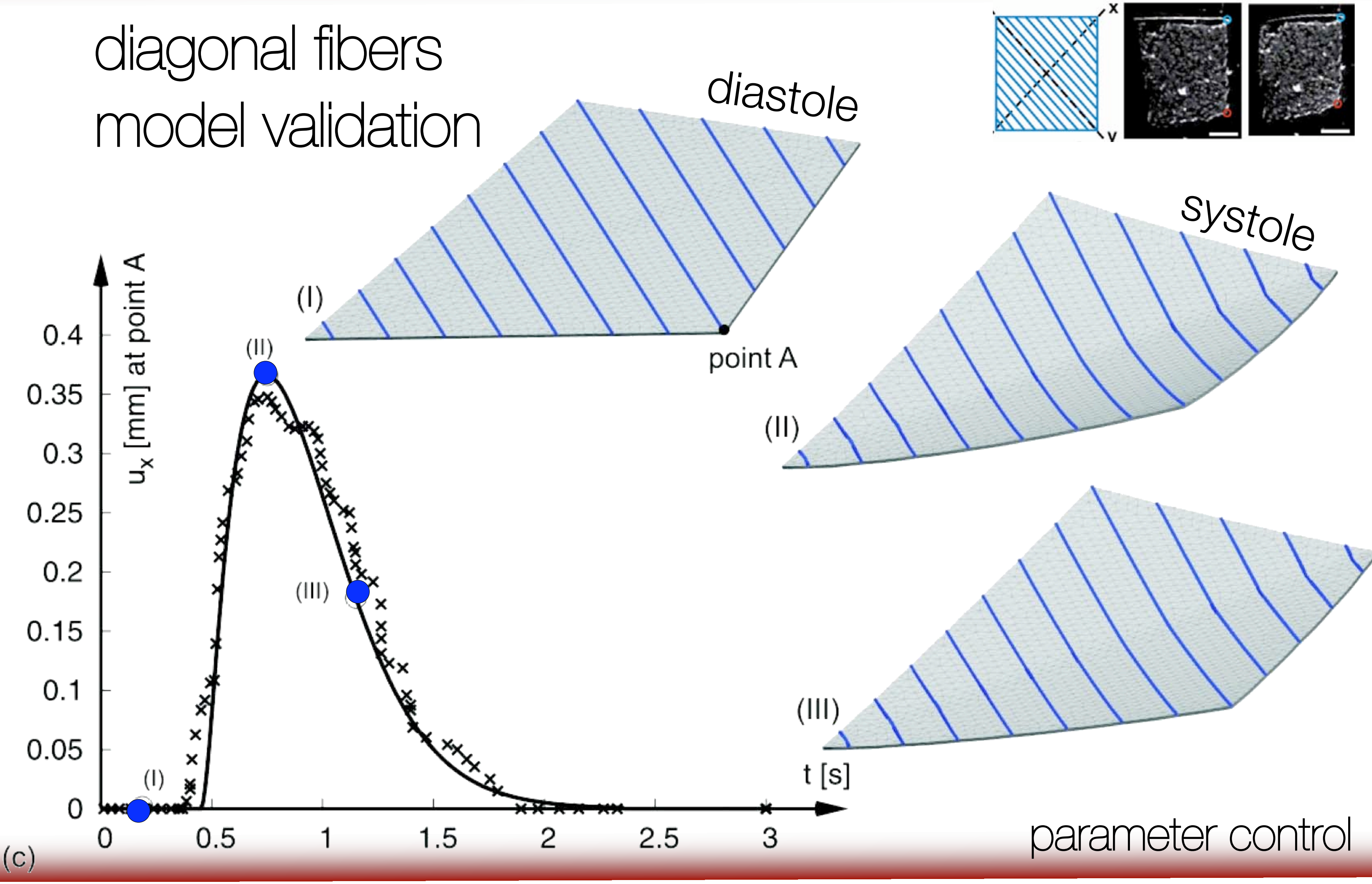
initial (III) parameter calibration

horizontal fibers
model validation



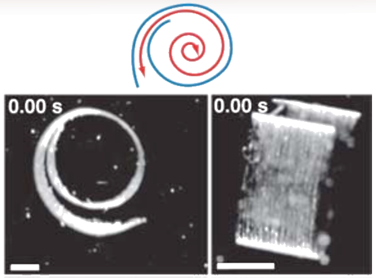
parameter control

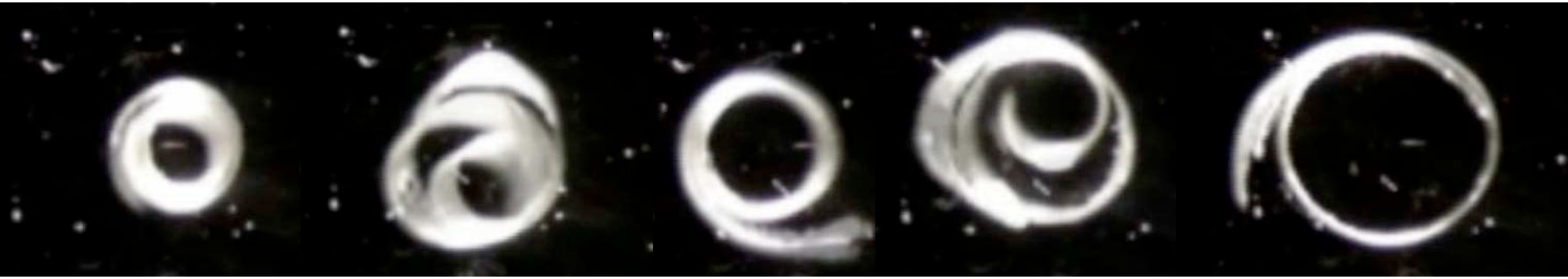
diagonal fibers model validation

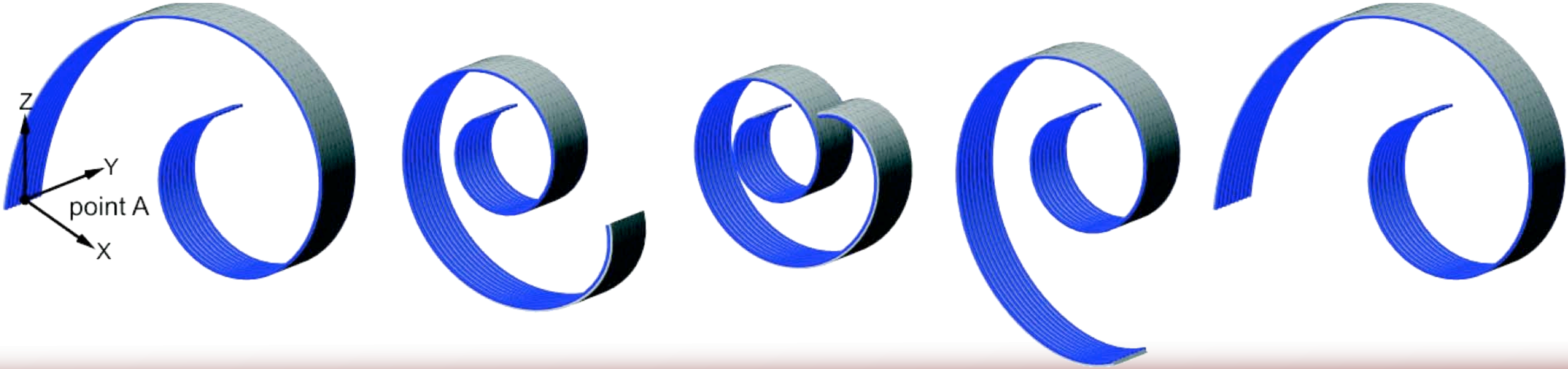


parameter control

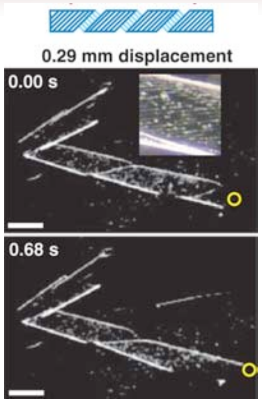
coiling strip
longitudinal fibers

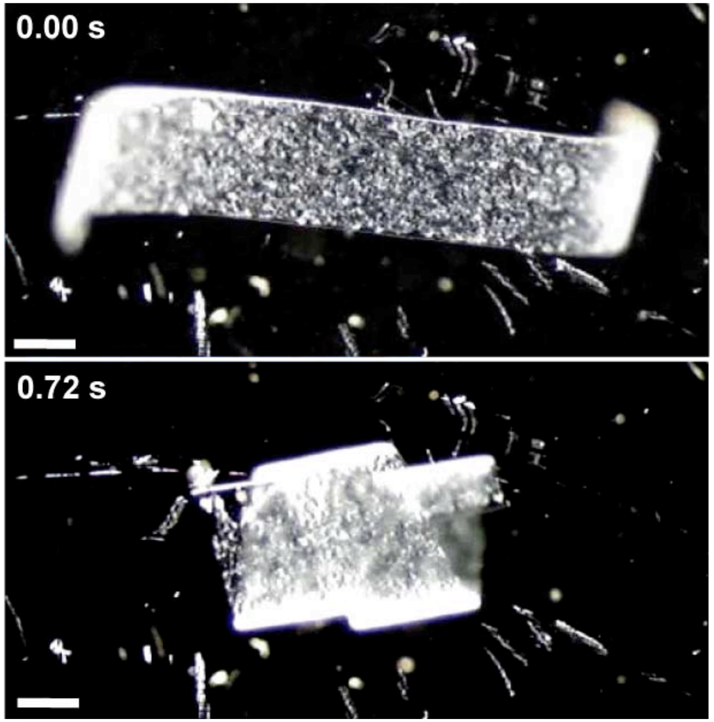


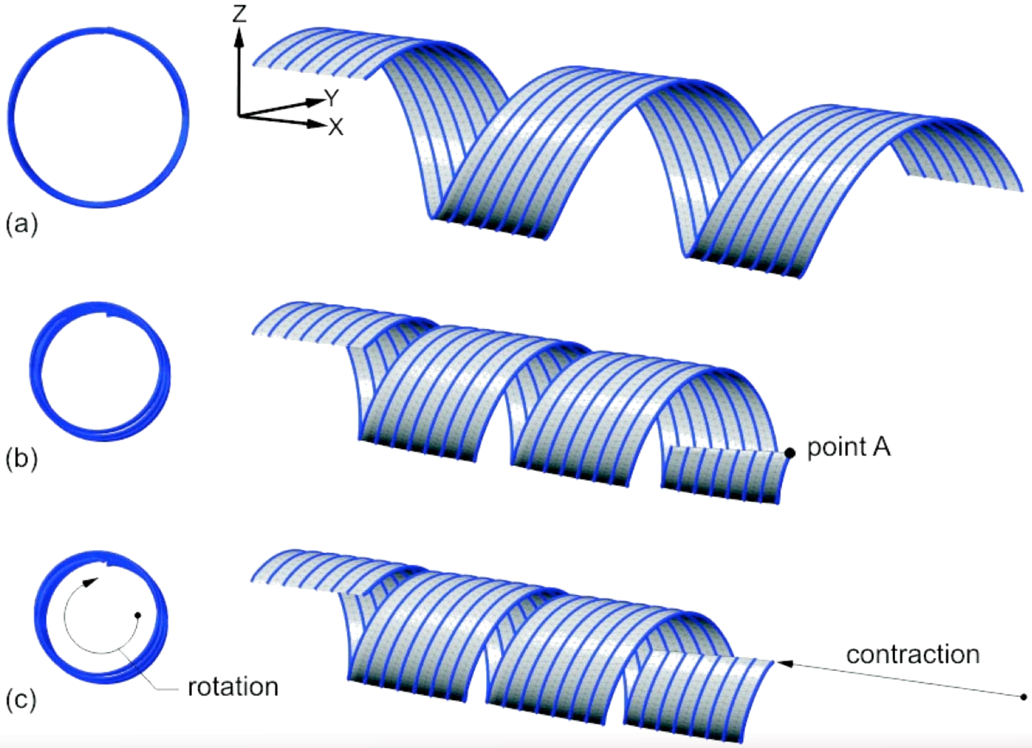




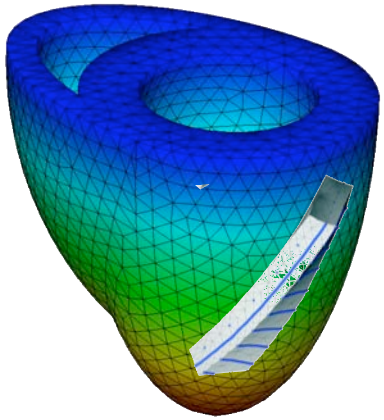
helical actuator
longitudinal fibers

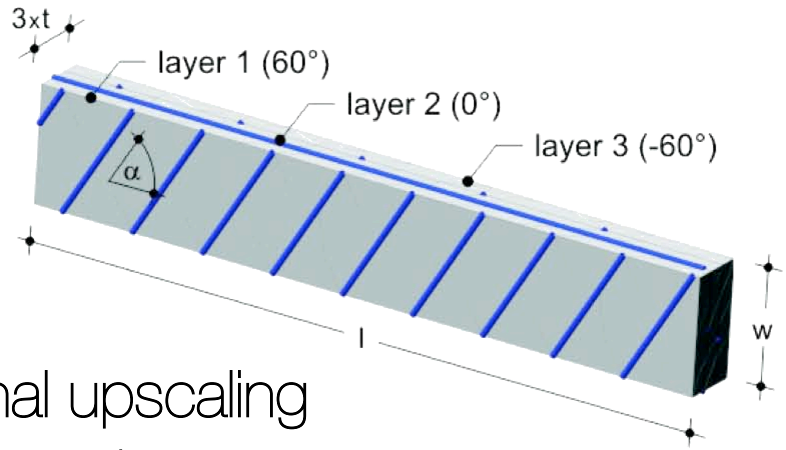




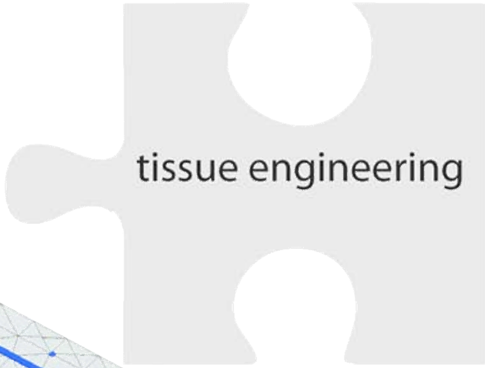


tissue engineered patches for cardiac repair

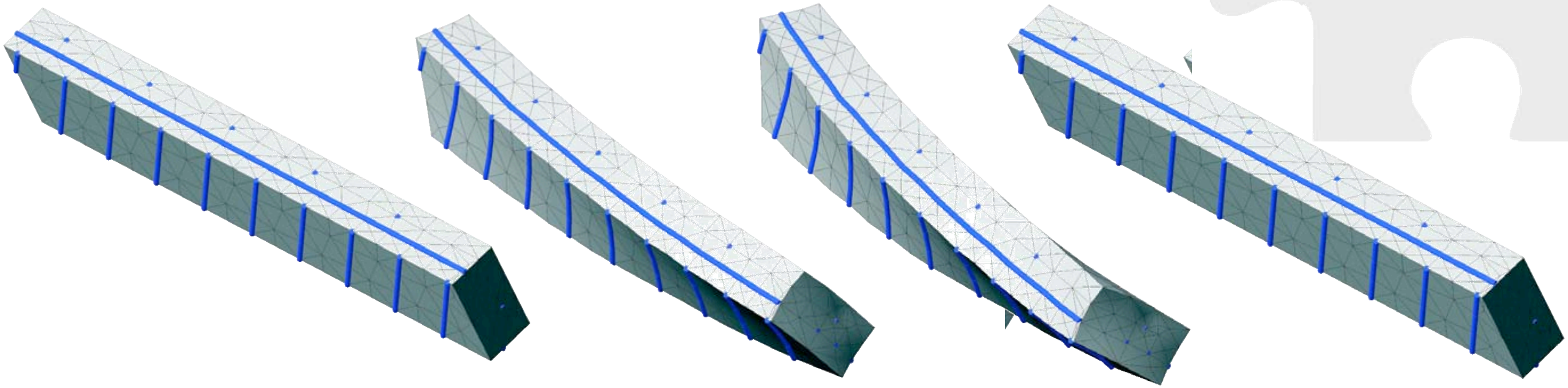




substrate stiffness
fiber orientation
contractility
graft geometry



challenge dimensional upscaling
stackable **fully tunable** sheets



NSF-EFRI engineering of cardiovascular cellular interfaces and tissue constructs
pruitt, heilshorn, kuhl, wu, zarins

muscular thin films for cardiac repair

in silico

macro

continuum mechanics

meso

homgenization

micro

cell mechanics

mechanics of cardiac disease

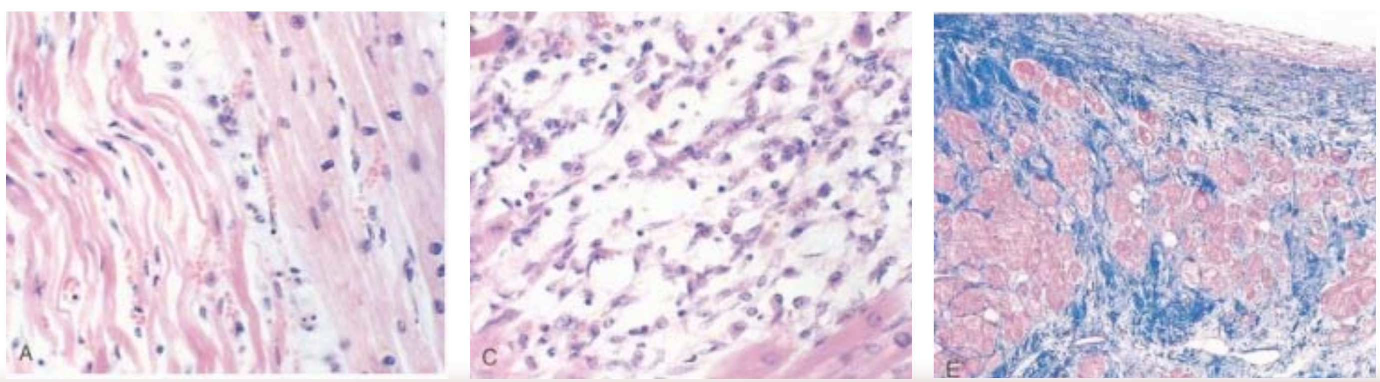
challenge bridging the spatial scales

- micromechanically motivated **active** force

$$\boldsymbol{P}^{\mathrm{act}} = \boldsymbol{P}^{\mathrm{act}}(\boldsymbol{F}^{\mathrm{e}}, \mathrm{Ca}^{2+}, \boldsymbol{n}^{\mathrm{myo}}, t)$$

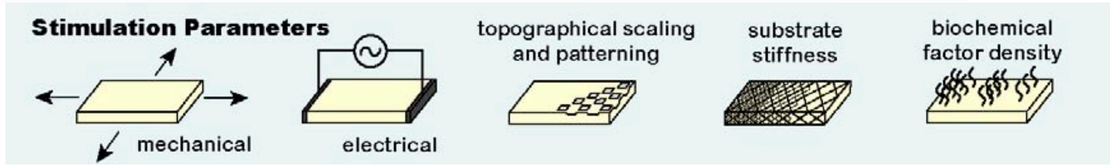
- micromechanically motivated **adaptive** growth

$$\boldsymbol{F}^{\mathrm{g}} = \vartheta^{\perp}\boldsymbol{I} + [\vartheta^{||} - \vartheta^{\perp}]\boldsymbol{n}^{\mathrm{myo}} \otimes \boldsymbol{n}^{\mathrm{myo}}$$

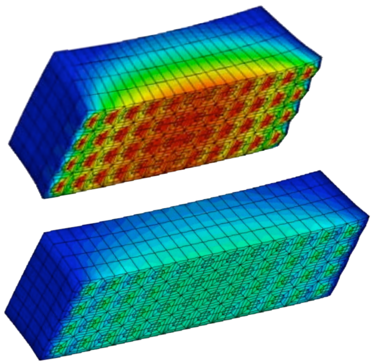


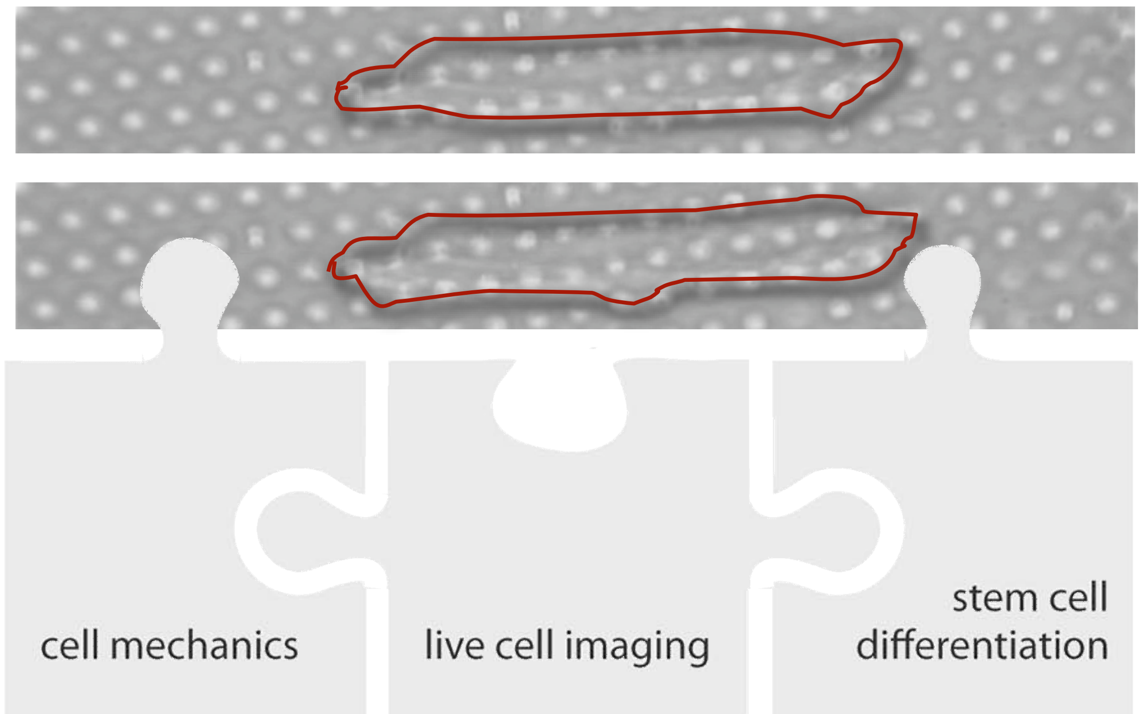
robbins&cotran[2005]

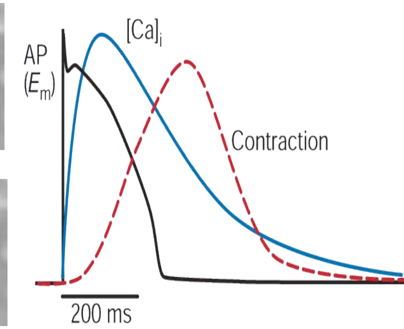
multiscale modeling



neonatal rat cardiomyocytes on force posts







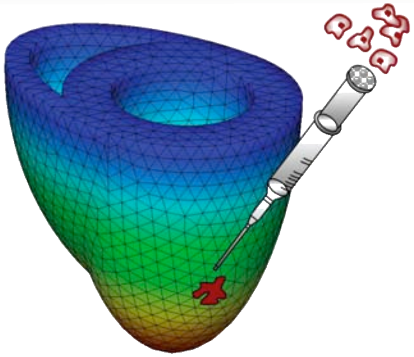
micro

cell

in silico **interface** **in vivo/in vitro**

NSF-EFRI engineering of cardiovascular cellular interfaces and tissue constructs
pruitt, heilshorn, kuhl, wu, zarins

multiscale modeling



... special thanx to

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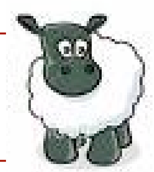
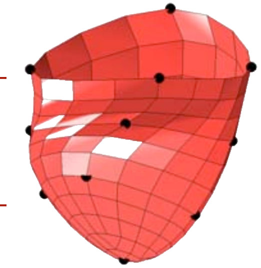
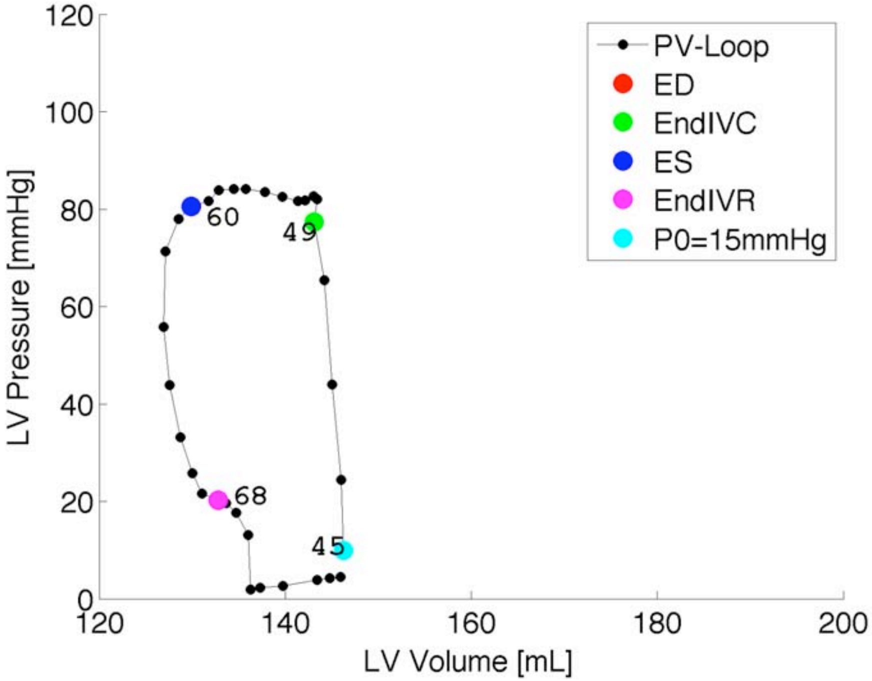
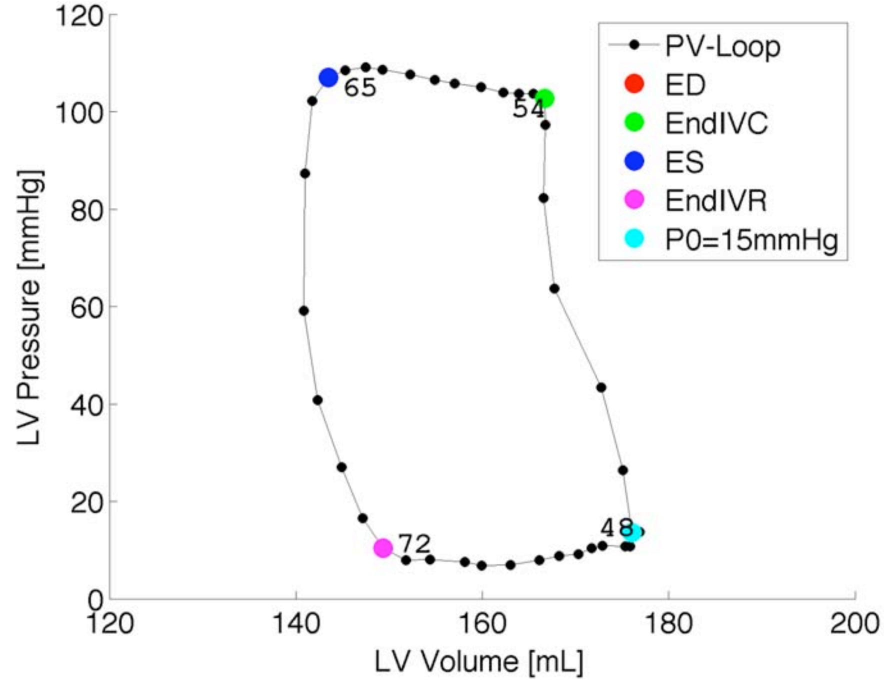
nih simbios simgrowth - a virtual lab for myocardial infarction and restoration of cardiac function, **nsf efri** engineering of cardiovascular cellular interfaces and tissue constructs, **bio-x seed grant** an integrated approach for cardiac repair



infarct-induced dilation







end-diastolic volume ↑ end-systolic volume ↑