A continuum model for the active mechanical response of the myocardium

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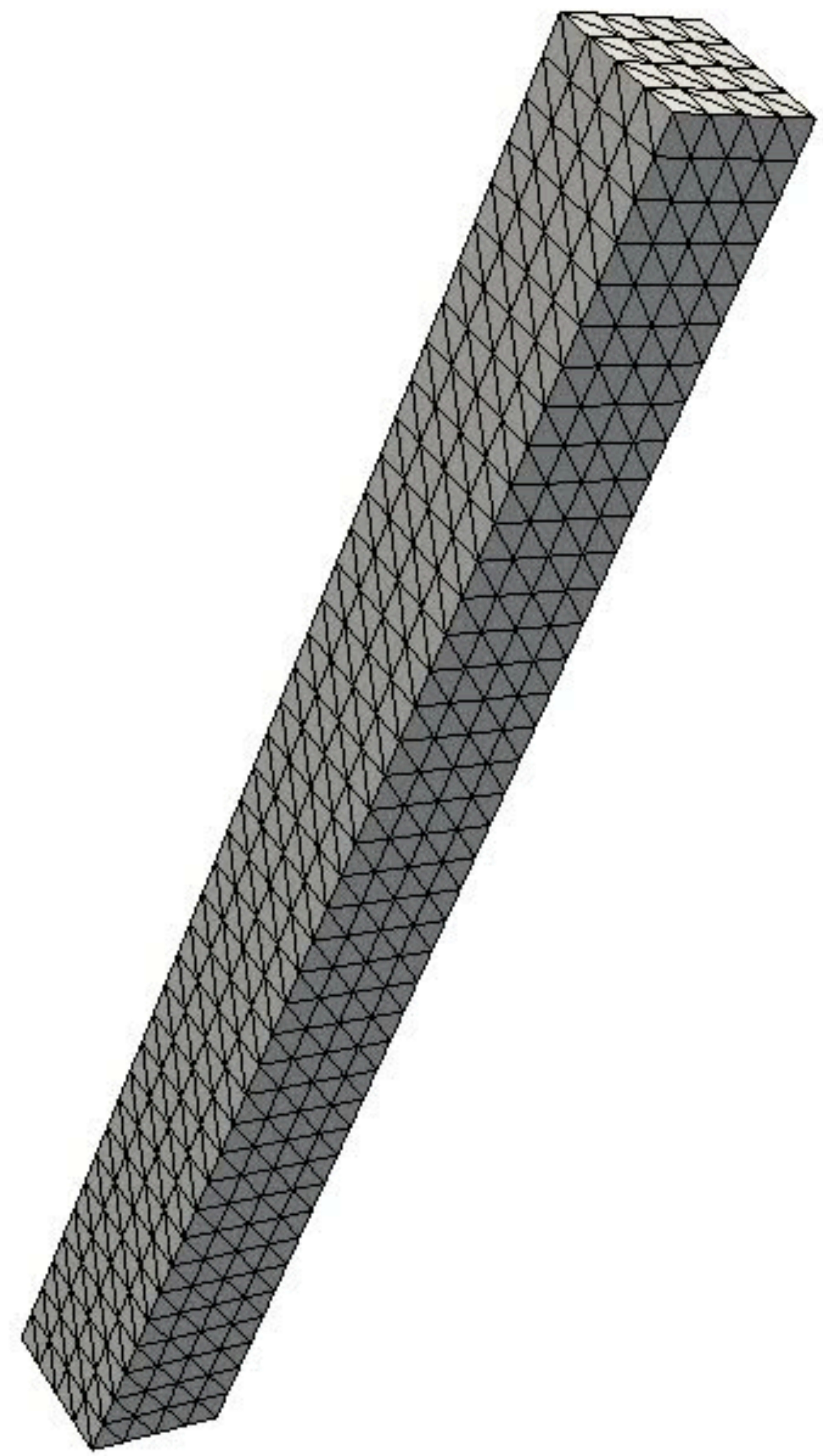
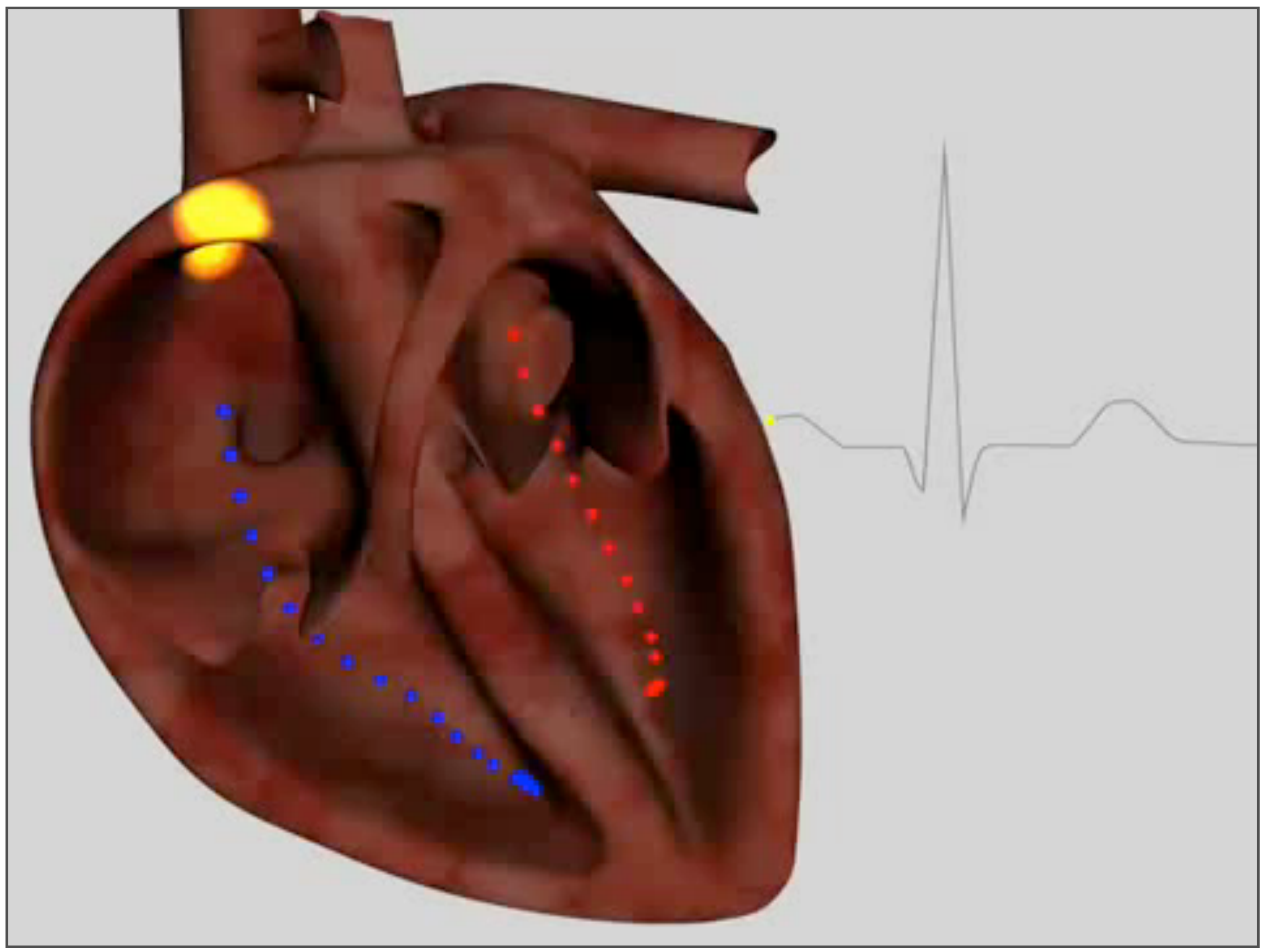


Constitutive modelling of the myocardium is a key step in understanding the coupled behaviour of the heart



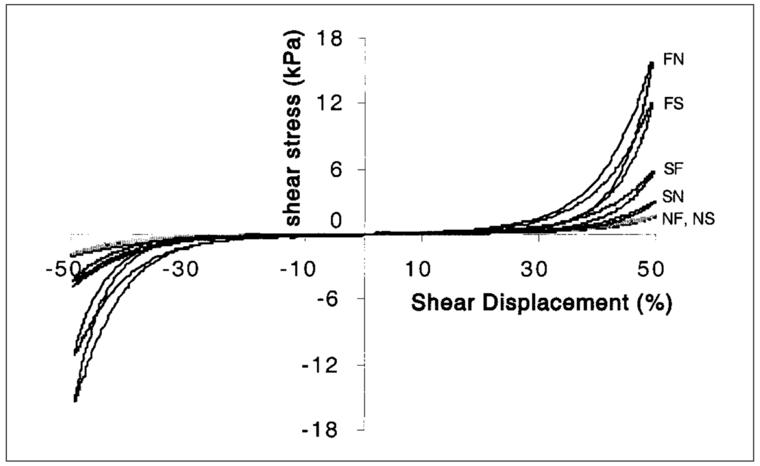
The multi-physics of a beating heart

http://youtu.be/8aLufvkRw-k

Cardiac mechanics:

- involve complex geometry, boundary conditions and heterogeneous material properties
- are anisotropic, nonlinear and viscoelastic
- include active contributions due to fibre contraction, which are coupled to electro-chemical mechanisms

We are going to approach this in three steps

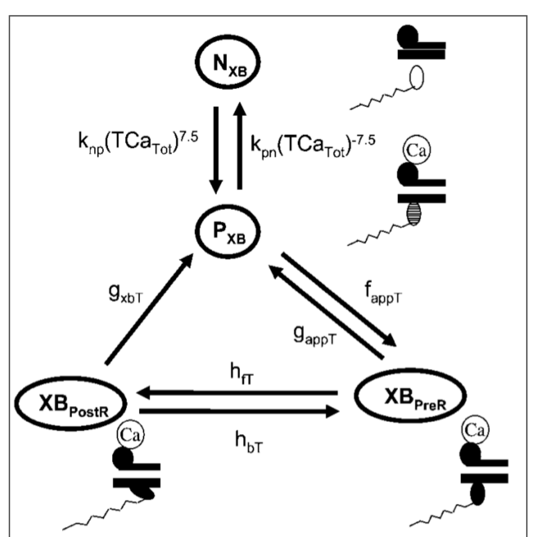


Look at experimental data to motivate a model for the *passive response* of the myocardium

$$\boldsymbol{P} = \frac{\partial \psi}{\partial \boldsymbol{F}} + \boldsymbol{P}_{\mathrm{a}}$$

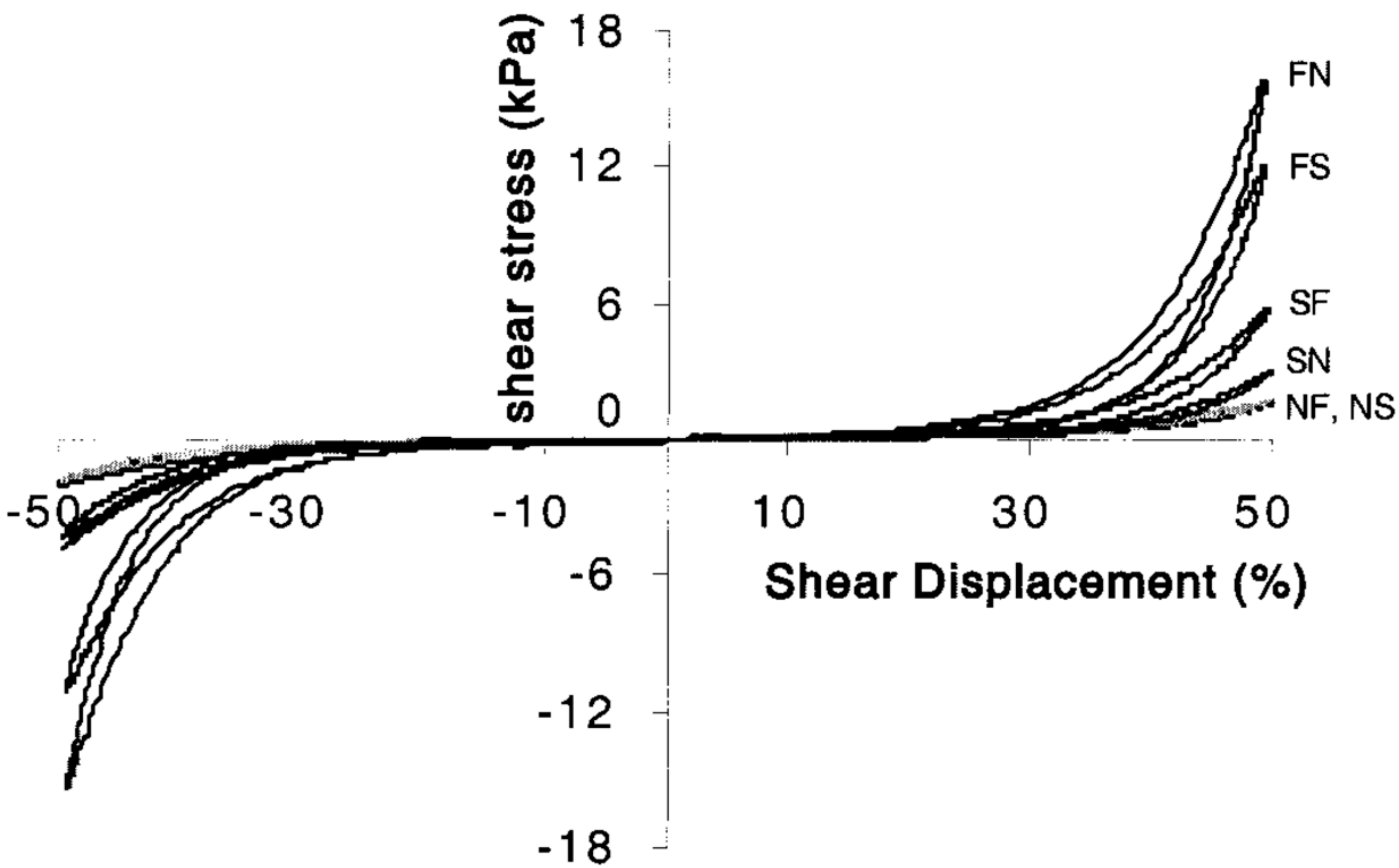
$$\boldsymbol{P} = \det(\boldsymbol{F}_{\mathrm{a}}) \frac{\partial \psi}{\partial \boldsymbol{F}_{\mathrm{e}}} \boldsymbol{F}_{\mathrm{a}}^{-\mathrm{T}}$$

Consider two ways of introducing the *active response* due to cardiomyocyte contraction



Relate the active contraction to the underlying *crossbridge kinetics*

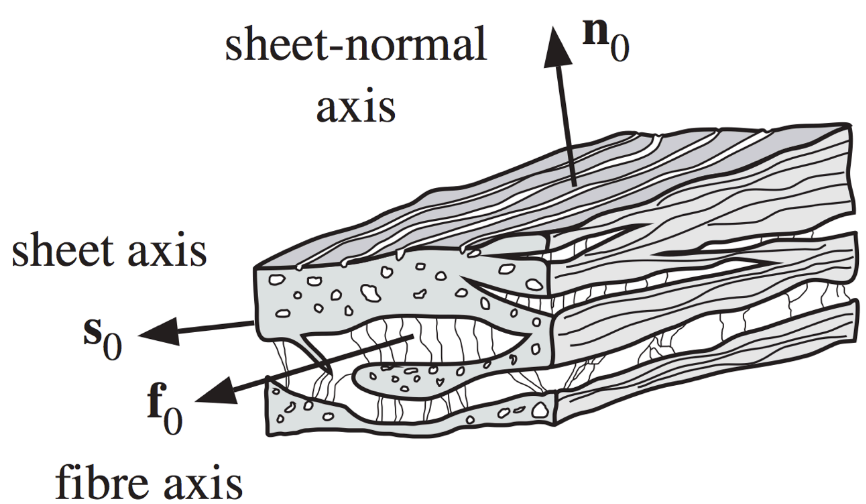
The mechanical behaviour of passive myocardium is nonlinear, orthotropic and viscoelastic



Response of a typical pig myocardial specimen to simple shear

Dokos et al., 2002

Motivated by this data, we begin with a state-of-the-art hyperelastic passive myocardium model



Orthonormal coordinate system

$$I_1 = \mathrm{tr}(\boldsymbol{C})$$
$$I_2 = \frac{1}{2}\left[I_1^2 - \mathrm{tr}\left(\boldsymbol{C}^2\right)\right]$$
$$I_{4f} = \boldsymbol{f}_0 \cdot (\boldsymbol{C}\boldsymbol{f}_0)$$
$$I_{4s} = \boldsymbol{s}_0 \cdot (\boldsymbol{C}\boldsymbol{s}_0)$$
$$I_{8fs} = \boldsymbol{f}_0 \cdot (\boldsymbol{C}\boldsymbol{s}_0)$$

(Pseudo) Invariants of the right Cauchy-Green tensor

$$\psi = \frac{a}{2b}\exp[b(I_1 - 3)] + \sum_{\iota=f,s}\frac{a_\iota}{2b_\iota}\{\exp\left[b_\iota\left(I_{4\iota} - 1\right)^2\right] - 1\} + \frac{a_{fs}}{2b_{fs}}\left[\exp\left(b_{fs}I_{8fs}^2\right) - 1\right]$$

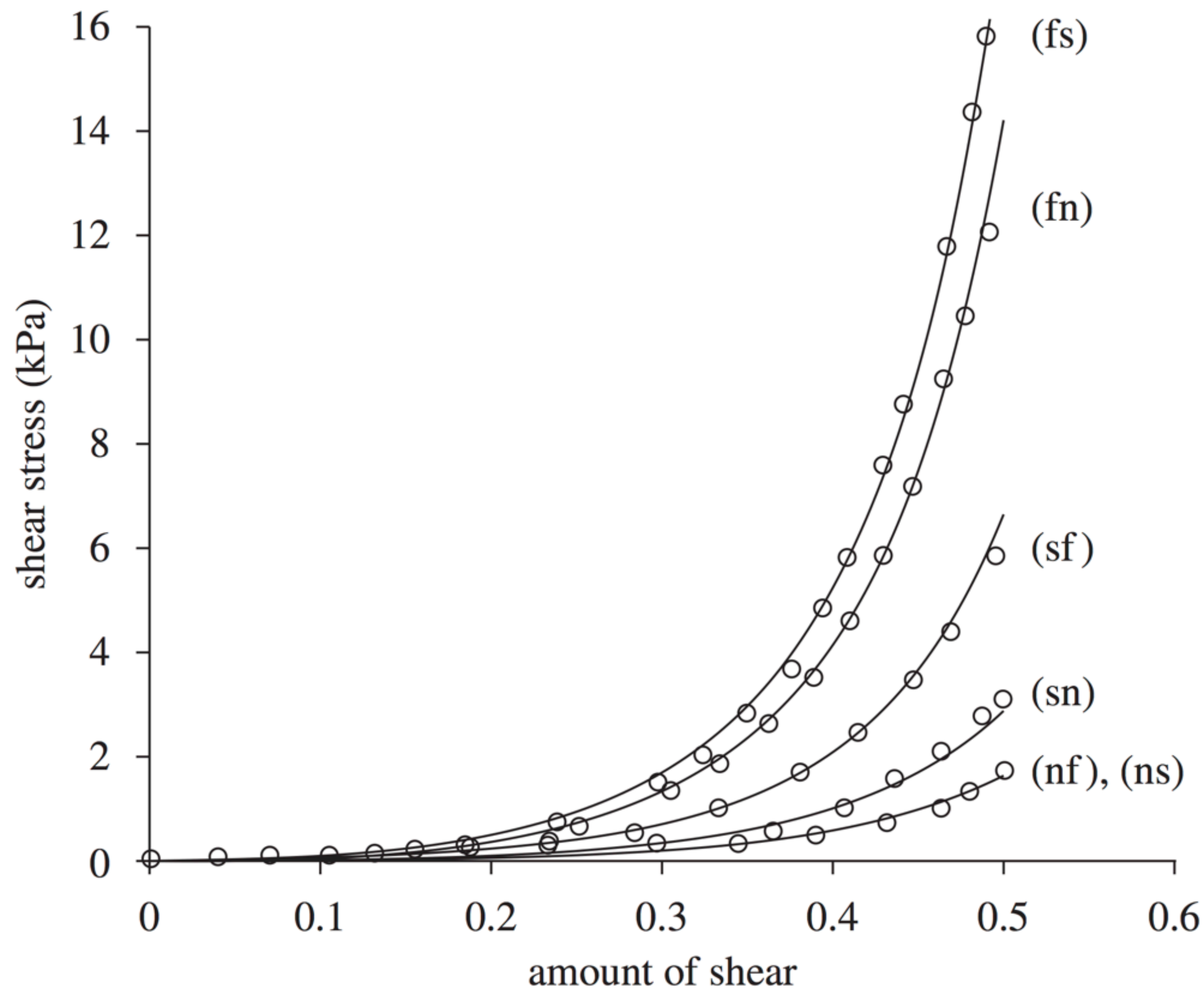
Strain-energy function

$$\boldsymbol{S} = 2\left(\frac{\partial\psi}{\partial I_1} + \frac{\partial\psi}{\partial I_2}I_1\right)\mathbf{1} - 2\frac{\partial\psi}{\partial I_2}\boldsymbol{C} - p\boldsymbol{C}^{-1}$$
$$+ 2\frac{\partial\psi}{\partial I_{4f}}\boldsymbol{f}_0 \otimes \boldsymbol{f}_0 + 2\frac{\partial\psi}{\partial I_{4s}}\boldsymbol{s}_0 \otimes \boldsymbol{s}_0 + \frac{\partial\psi}{\partial I_{8fs}}\left(\boldsymbol{f}_0 \otimes \boldsymbol{s}_0 + \boldsymbol{s}_0 \otimes \boldsymbol{f}_0\right)$$

Second Piola–Kirchhoff stress tensor

Holzapfel and Ogden, 2009

The Holzapfel-Ogden model fits the loading curve of the experiments closely using eight parameters



Holzapfel-Ogden model fit to experimental data

Holzapfel and Ogden, 2009

To capture the unload curve as well, we extend this model to include viscous effects

$$\overline{\boldsymbol{C}} = J^{-\frac{2}{3}}\boldsymbol{C},\ \overline{I}_\iota = \mathrm{Invariants}(\overline{\boldsymbol{C}})$$

Volumetric-isochoric decomposition

$$\psi = \psi^{\infty}_{\mathrm{vol}}(J) + \psi^{\infty}_{\mathrm{iso}}(\overline{\boldsymbol{C}}) + \sum_{\alpha=1}^{m} \gamma_\alpha(\overline{\boldsymbol{C}}, \boldsymbol{\Gamma}_\alpha)$$

Decoupled representation of the free-energy function

$$\boldsymbol{S} = \boldsymbol{S}^{\infty}_{\mathrm{vol}} + \boldsymbol{S}^{\infty}_{\mathrm{iso}} + \sum_{\alpha=1}^{m} \boldsymbol{Q}_\alpha$$

$$\boldsymbol{S}^{\infty}_{\mathrm{vol}} = J\frac{\partial \psi^{\infty}_{\mathrm{vol}}(J)}{\partial J}\boldsymbol{C}^{-1}$$

$$\boldsymbol{S}^{\infty}_{\mathrm{iso}} = J^{-\frac{2}{3}}\,\mathrm{Dev}\left(2\frac{\partial \psi^{\infty}_{\mathrm{iso}}(\overline{\boldsymbol{C}})}{\partial \overline{\boldsymbol{C}}}\right)$$

Elastic and viscoelastic contributions to the stress

$$\dot{\boldsymbol{Q}}_\alpha + \frac{\boldsymbol{Q}_\alpha}{\tau_\alpha} = \beta_\alpha \dot{\boldsymbol{S}}^{\infty}_{\mathrm{iso}}(\overline{\boldsymbol{C}}), \quad \boldsymbol{Q}_\alpha|_{t=0} = \boldsymbol{0}$$

Evolution equation for the internal stress variables

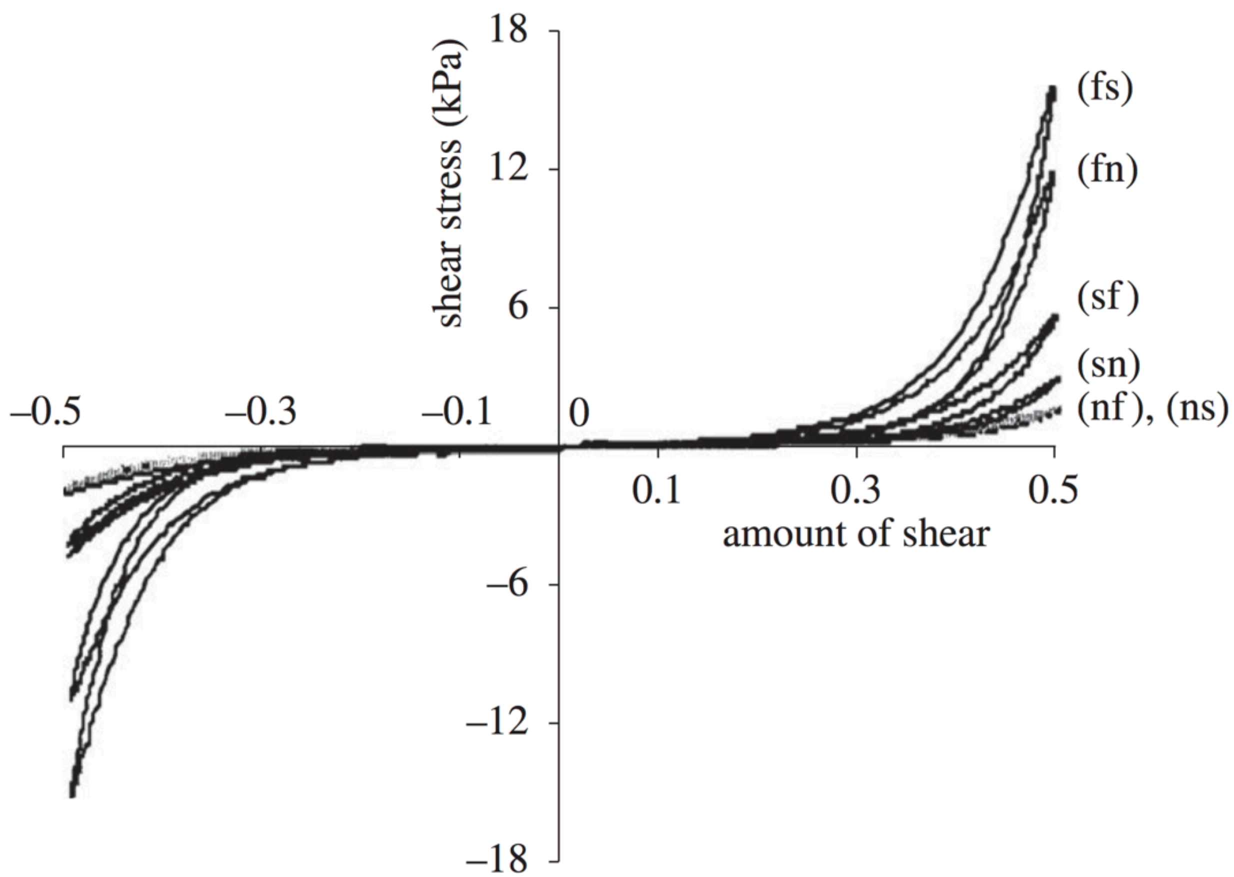
$$\begin{aligned}\psi^{\infty}_{\mathrm{iso}} &= \frac{a}{2b}\exp[b(\overline{I}_1 - 3)] \\ &+ \sum_{\iota=f,s} \frac{a_\iota}{2b_\iota}\{\exp\left[b_\iota\left(\overline{I}_{4\iota} - 1\right)^2\right] - 1\} \\ &+ \frac{a_{fs}}{2b_{fs}}\left[\exp\left(b_{fs}\overline{I}^2_{8fs}\right) - 1\right]\end{aligned}$$

$$\psi^{\infty}_{\mathrm{vol}} = \kappa\left[\frac{1}{\beta^2}\left(\beta \ln J + \frac{1}{J^\beta} - 1\right)\right]$$

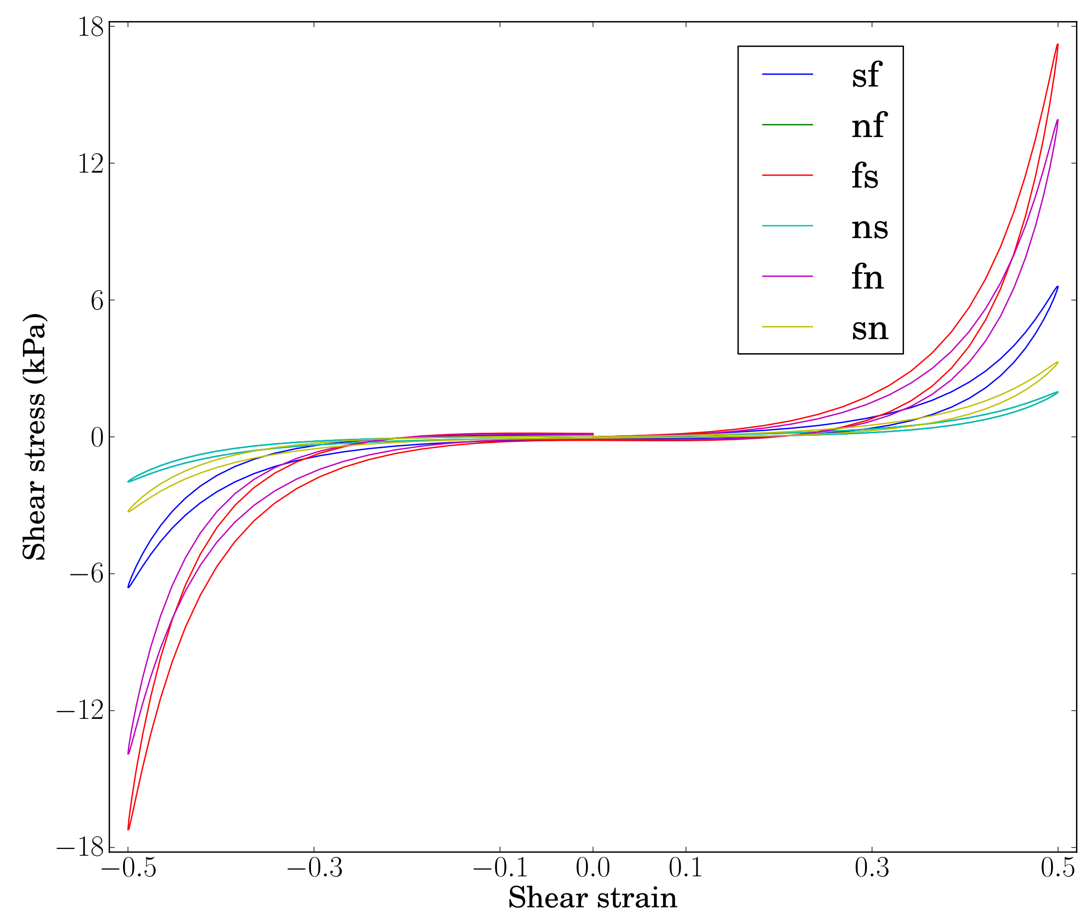
Specific forms for the strain energy functions

Simo, 1987

With two additional parameters related to viscoelasticity, our model further captures the data



Experimental data from Dokos et al., 2002



Our viscoelastic model with τ_1 = 1.5 s, β_1 = 0.25

The *active stress* approach is an intuitive way of incorporating cardiomyocyte contraction

$$\boldsymbol{P} = \boldsymbol{P}_{\mathrm{p}} + \boldsymbol{P}_{\mathrm{a}} = \frac{\partial \psi}{\partial \boldsymbol{F}} + \boldsymbol{P}_{\mathrm{a}}$$

Additional active contribution to the stress

$$\boldsymbol{P}_{\mathrm{a}} = T_{\mathrm{a}}\, \boldsymbol{F}\boldsymbol{C}^{-1}$$

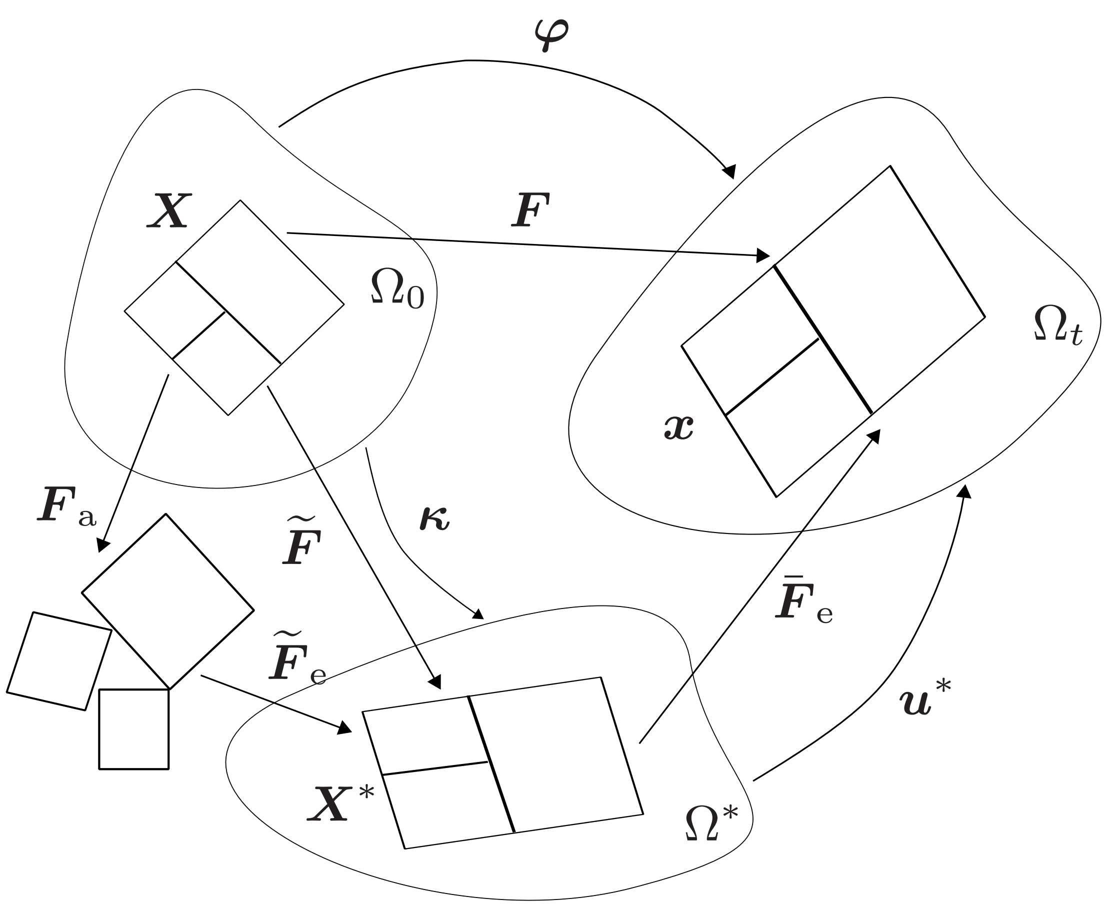
$$\boldsymbol{P}_{\mathrm{a}} = T_{\mathrm{a}}\, \boldsymbol{F}\boldsymbol{f}_0 \otimes \boldsymbol{f}_0$$

$$\begin{aligned}\boldsymbol{P}_{\mathrm{a}} = {} & T_{\mathrm{a_{ff}}}\, \boldsymbol{F}\boldsymbol{f}_0 \otimes \boldsymbol{f}_0 \\ & + T_{\mathrm{a_{ss}}}\, \boldsymbol{F}\boldsymbol{s}_0 \otimes \boldsymbol{s}_0 \\ & + T_{\mathrm{a_{nn}}}\, \boldsymbol{F}\boldsymbol{n}_0 \otimes \boldsymbol{n}_0\end{aligned}$$

Examples of the active stress tensor

Smith et al., 2004; Panfilov et al., 2005; Niederer and Smith, 2008; Pathmanathan et al., 2010

The *active strain* approach is another way of incorporating cardiomyocyte contraction



$$\boldsymbol{F}_\mathrm{a} = \mathbf{1} + \gamma_\mathrm{f} \boldsymbol{f}_0 \otimes \boldsymbol{f}_0$$

$$\boldsymbol{F}_\mathrm{a} = \mathbf{1} + \gamma_\mathrm{f} \boldsymbol{f}_0 \otimes \boldsymbol{f}_0 + \gamma_\mathrm{s} \boldsymbol{s}_0 \otimes \boldsymbol{s}_0$$

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Examples of the active tensor (not necessarily a gradient)

$$\boldsymbol{P} = \det(\boldsymbol{F}_\mathrm{a}) \frac{\partial \psi}{\partial \boldsymbol{F}_\mathrm{e}} \boldsymbol{F}_\mathrm{a}^{-\mathrm{T}}$$

First Piola-Kirchhoff stress tensor

$$\boldsymbol{F} = \bar{\boldsymbol{F}}_\mathrm{e} \widetilde{\boldsymbol{F}}_\mathrm{e} \boldsymbol{F}_\mathrm{a} = \boldsymbol{F}_\mathrm{e} \boldsymbol{F}_\mathrm{a}$$

Introducing some intermediate configurations

Cherubini et al., 2010; Ambrosi et al., 2011; Nobile et al., 2012; Rossi et al., 2012

The active strain approach inherits the convexity of the passive model, active stress does not

The equilibrium equation reads: $\mathrm{Div}(\boldsymbol{P}) = \boldsymbol{0}; \quad \boldsymbol{P} = \dfrac{\partial \psi}{\partial \boldsymbol{F}}$

To guarantee existence and uniqueness of the solution, we require $\forall \boldsymbol{F} \in \mathbb{L}\mathrm{in}^+, \ \forall \boldsymbol{H} \neq \boldsymbol{0}$:

$$\boldsymbol{H} : \frac{\partial^2 \psi}{\partial \boldsymbol{F} \partial \boldsymbol{F}} : \boldsymbol{H} + \boldsymbol{H} : \frac{\partial \boldsymbol{P}_\mathrm{a}}{\partial \boldsymbol{F}} : \boldsymbol{H} > 0$$

Rank-one convexity condition for the active stress approach

$$\boldsymbol{H} : \frac{\partial^2 \psi}{\partial \boldsymbol{F} \partial \boldsymbol{F}} : \boldsymbol{H} = \boldsymbol{H} : \frac{\partial^2 \psi(\boldsymbol{F}\boldsymbol{F}_\mathrm{a}^{-1})}{\partial \boldsymbol{F} \partial \boldsymbol{F}} : \boldsymbol{H} = \boldsymbol{H}\boldsymbol{F}_\mathrm{a}^{-1} : \frac{\partial^2 \psi}{\partial \boldsymbol{F} \partial \boldsymbol{F}} : \boldsymbol{H}\boldsymbol{F}_\mathrm{a}^{-1} > 0$$

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Ambrosi and Pezzuto, 2011

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Rank-one convexity condition for the active strain approach

Ambrosi and Pezzuto, 2011

What does the convexity argument mean for the orthotropic Holzapfel-Ogden model in particular?

Form of the active strain: $\boldsymbol{F}_{\mathrm{a}} = \mathbf{1} + \gamma_{\mathrm{f}} \boldsymbol{f}_0 \otimes \boldsymbol{f}_0 + \left(\frac{1}{\sqrt{1+\gamma_{\mathrm{f}}}} - 1 \right) [\boldsymbol{s}_0 \otimes \boldsymbol{s}_0 + \boldsymbol{n}_0 \otimes \boldsymbol{n}_0]$

The isotropic term, $\frac{a}{2b} \exp[b(I_1^{\mathrm{E}} - 3)]$, is strongly elliptic for all $-1 < \gamma_{\mathrm{f}} \leq 0$.

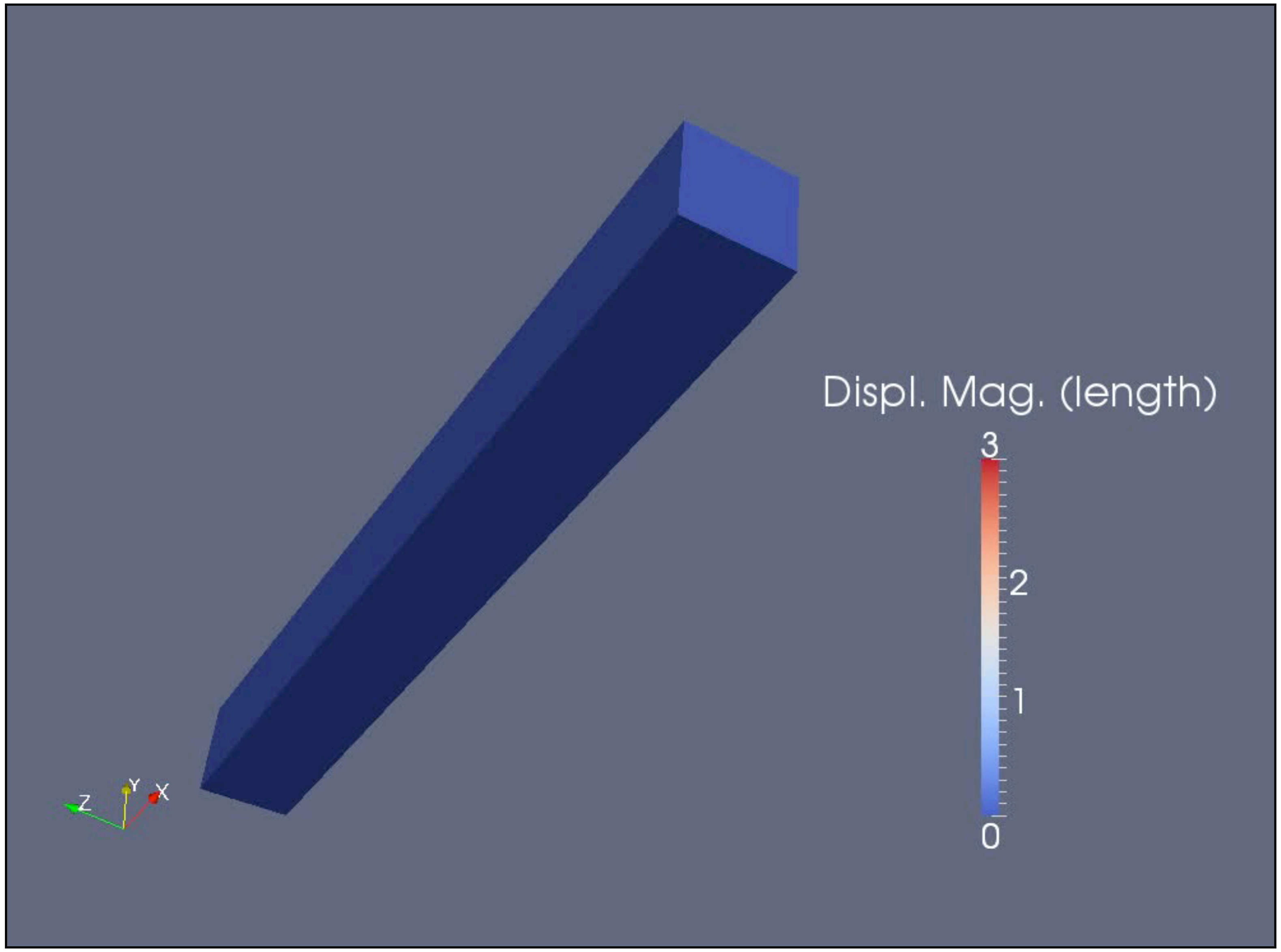
Anisotropic terms *are not* strongly elliptic in general, e.g. for $\frac{a_{\mathrm{f}}}{2b_{\mathrm{f}}} \{\exp\left[b_{\mathrm{f}} \left(I_{4\mathrm{f}}^{\mathrm{E}} - 1\right)^2\right] - 1\}$,

$$\left[\frac{1}{(1+\gamma_{\mathrm{f}})^2} + 2b_{\mathrm{f}} \left(I_{4\mathrm{f}}^{\mathrm{E}} - 1\right)^2\right] (\boldsymbol{u} \cdot \boldsymbol{F} \boldsymbol{f}_0)^2 + \left[\frac{I_{4\mathrm{f}}}{(1+\gamma_{\mathrm{f}})^2} - 1\right] > 0,$$

is the condition that needs to be satisfied.

Rossi et al., 2012

A numerical example where the active strain formulation easily allows for large strains



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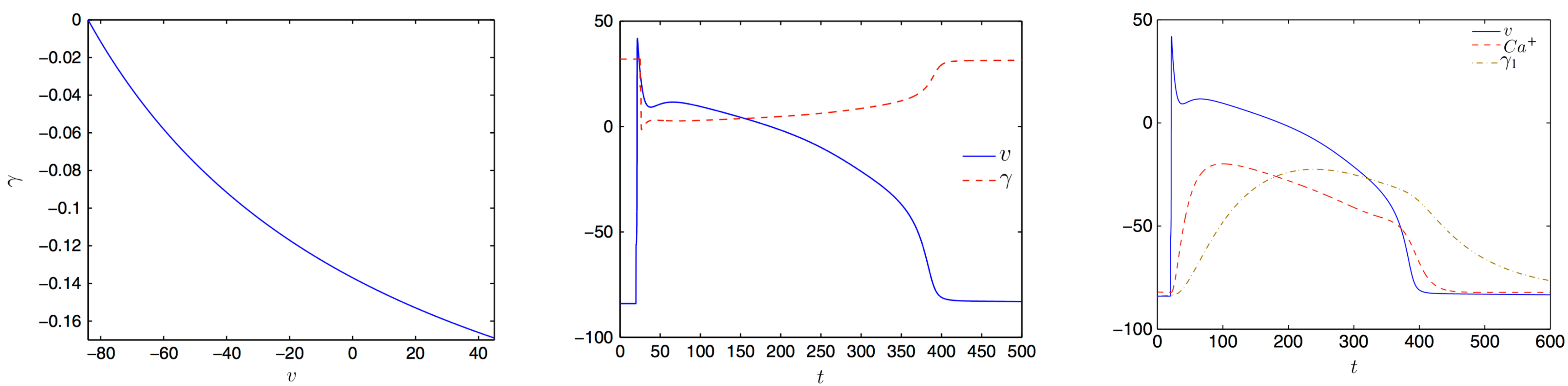
Toy activation function within the physiological range: $\gamma_{\mathrm{f}}(t) = -0.15\,[1 - \sin(t - 3\pi/2)]$

One straightforward way to define the activation function is in terms of known relations to other fields

One recent example, $\boldsymbol{F}_{\mathrm{a}} = \mathbf{1} + \gamma \boldsymbol{f}_0 \otimes \boldsymbol{f}_0 - \frac{\gamma}{1+\gamma} \boldsymbol{s}_0 \otimes \boldsymbol{s}_0$, with the activation function:

$$\gamma = \gamma(v, [Ca^{2+}]) = -\beta \frac{v - v_{\min}}{v_{\max} - v_{\min} + v} + \epsilon_1 \beta \frac{l_0}{1 + \eta([Ca^{2+}])(l_0 - 1)}$$

where, $l_0 = (\eta(c_0^* - \epsilon_1)^{-1}(\eta(c_0^*) - 1)$ and $\eta([Ca^{2+}]) = \frac{1}{2} + \frac{1}{\pi}\arctan(\beta^2 \log([Ca^{2+}]/c_{\mathrm{R}}))$.



Variation of the activation function with other fields

Cherubini et al., 2010; Nobile et al., 2012

We turn to classical continuum thermodynamics to restrict the form of the activation function

$$\boldsymbol{F}_{\mathrm{a}} = \lambda_{\mathrm{a}} \boldsymbol{f}_0 \otimes \boldsymbol{f}_0 + \frac{1}{\sqrt{\lambda_{\mathrm{a}}}} (\boldsymbol{s}_0 \otimes \boldsymbol{s}_0 + \boldsymbol{n}_0 \otimes \boldsymbol{n}_0)$$

Active contraction tensor in terms of the contraction stretch

$$\begin{aligned}
\frac{\partial \rho_0}{\partial t} &= 0 \\
\rho_0 \frac{\partial \boldsymbol{V}}{\partial t} &= \mathrm{Div}(\boldsymbol{P}) + \boldsymbol{b} \\
\rho_0 \frac{\partial e}{\partial t} &= \boldsymbol{P} : \dot{\boldsymbol{F}} + P_{\mathrm{a}} \dot{\lambda}_{\mathrm{a}} + P_{\mathrm{c}} \dot{\beta} \\
\rho_0 \frac{\partial \eta}{\partial t} &\geq 0
\end{aligned}$$

Balance laws and entropy inequality

→

$$\dot{\psi} \leq \boldsymbol{P} : \dot{\boldsymbol{F}} + P_{\mathrm{a}} \dot{\lambda}_{\mathrm{a}} + P_{\mathrm{c}} \dot{\beta}$$

Isothermal dissipation inequality

$$\psi = \psi_1(\boldsymbol{C}, [\boldsymbol{f}_0, \boldsymbol{s}_0, \boldsymbol{n}_0]) + \psi_2(\lambda_{\mathrm{a}}, \boldsymbol{C}_{\mathrm{e}}, [\boldsymbol{f}_0, \boldsymbol{s}_0, \boldsymbol{n}_0], \boldsymbol{\alpha}) + \psi_3(\boldsymbol{\alpha}) + \psi_4(\beta)$$

Free energy decomposed into passive mechanics, chemo-mechanical coupling, chemical kinetics and calcium regulation

Stålhand et al., 2011

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Active contraction tensor in terms of the contraction stretch

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Balance laws and entropy inequality

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Isothermal dissipation inequality

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Free energy decomposed into passive mechanics, chemo-mechanical coupling, chemical kinetics and calcium regulation

Stålhand et al., 2011

Classical arguments are used to arrive at constitutive laws that *a priori* satisfy the dissipation inequality

$$\boldsymbol{P} = -p\boldsymbol{F}^{-T} + 2\boldsymbol{F}\frac{\partial \psi_1}{\partial \boldsymbol{C}} + 2\boldsymbol{F}\boldsymbol{F}_{\mathrm{a}}^{-1}\frac{\partial \psi_2}{\partial \boldsymbol{C}_{\mathrm{e}}}\boldsymbol{F}_{\mathrm{a}}^{-\mathrm{T}}$$

Total stress of the passive tissue and elastic deformation of the cross-bridges

$$C(\boldsymbol{\alpha}, \lambda_{\mathrm{a}}, \boldsymbol{v})\dot{\lambda}_{\mathrm{a}} = P_{\mathrm{a}} - \frac{\partial \psi_2}{\partial \lambda_{\mathrm{a}}} + 2\left(\boldsymbol{F}\boldsymbol{F}_{\mathrm{a}}^{-1}\right)^{\mathrm{T}}\left(\boldsymbol{F}\boldsymbol{F}_{\mathrm{a}}^{-1}\right)\frac{\partial \psi_2}{\partial \boldsymbol{C}_{\mathrm{e}}}\boldsymbol{F}_{\mathrm{a}}^{-T} : \frac{\partial \boldsymbol{F}_{\mathrm{a}}}{\partial \lambda_{\mathrm{a}}}$$

Evolution law for the active stretch

$$A(\boldsymbol{F}, \beta)\dot{\boldsymbol{\alpha}} = -\frac{\partial \psi_3}{\partial \boldsymbol{\alpha}} + r\mathbf{1}$$

Evolution law for the chemical state

$$P_{\mathrm{c}} = \frac{\partial \psi_4}{\partial \beta}$$

Thermodynamic force driving calcium ions

Coleman and Noll, 1963; Stålhand, 2011

Classical arguments are used to arrive at constitutive laws that *a priori* satisfy the dissipation inequality

$$\psi_1 = \frac{a}{2b}\exp[b(I_1 - 3)] + \sum_{\iota = f,s} \frac{a_\iota}{2b_\iota}\{\exp\left[b_\iota\left(I_{4\iota} - 1\right)^2\right] - 1\} + \frac{a_{fs}}{2b_{fs}}\left[\exp\left(b_{fs} I_{8fs}^2\right) - 1\right]$$

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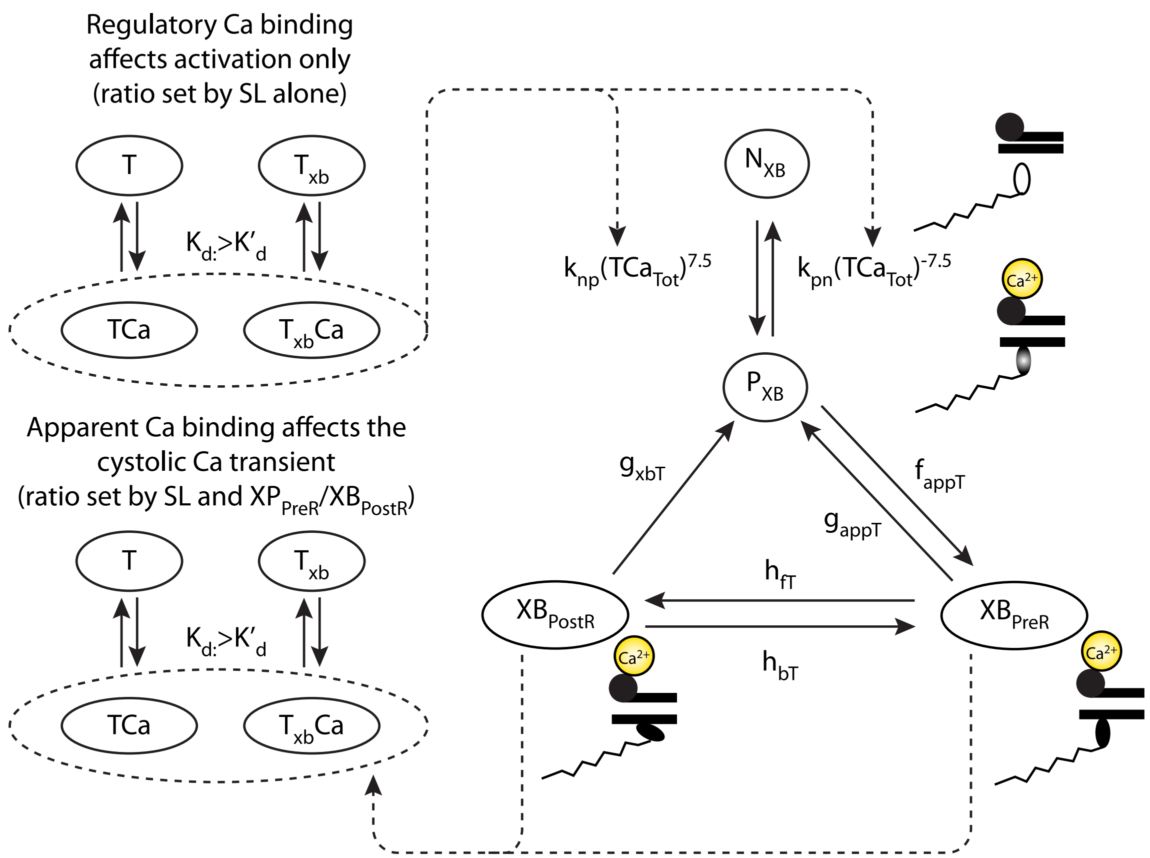
Coleman and Noll, 1963; Stålhand, 2011

But how do these abstract relationships relate to the biochemistry of force-generation at the filament level?



Regulatory unit activation and cross-bridge cycling

$$\frac{d}{dt}N_{\mathrm{XB}} = -k_{\mathrm{n\_pT}}N_{\mathrm{XB}} + k_{\mathrm{p\_nT}}P_{\mathrm{XB}}$$

$$\frac{d}{dt}P_{\mathrm{XB}} = k_{\mathrm{n\_pT}}N_{\mathrm{XB}} - (k_{\mathrm{p\_nT}} + f_{\mathrm{appT}})P_{\mathrm{XB}} + g_{\mathrm{appT}}XB_{\mathrm{PreR}} + g_{\mathrm{xbT}}XB_{\mathrm{PostR}}$$

$$\frac{d}{dt}XB_{\mathrm{PreR}} = f_{\mathrm{appT}}P_{\mathrm{XB}} - (g_{\mathrm{appT}} + h_{\mathrm{fT}})XB_{\mathrm{PreR}} + h_{\mathrm{bT}}XB_{\mathrm{PostR}}$$

$$\frac{d}{dt}XB_{\mathrm{PostR}} = h_{\mathrm{fT}}XB_{\mathrm{PreR}} - (h_{\mathrm{bT}} + g_{\mathrm{xbT}})XB_{\mathrm{PostR}}$$

$$\Updownarrow$$

$$\dot{\boldsymbol{\alpha}} = \boldsymbol{K}\alpha$$

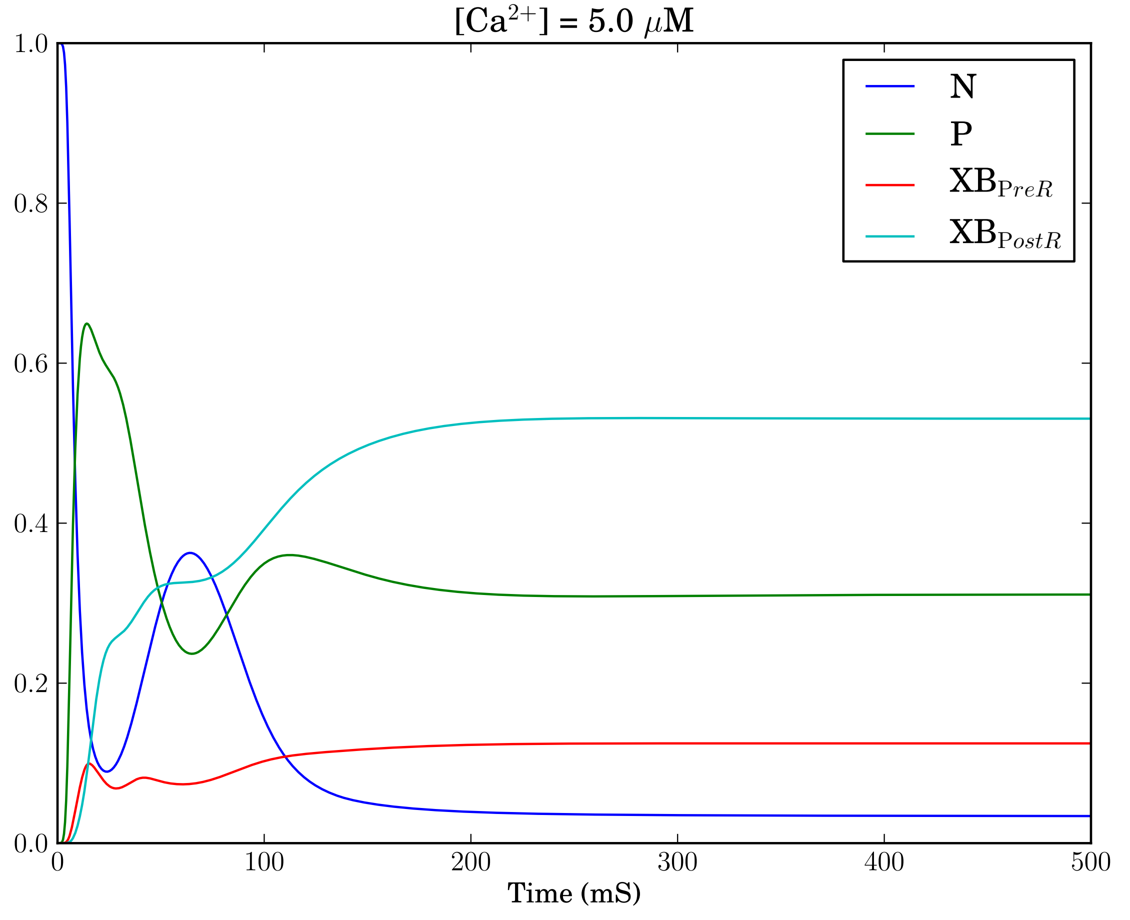
Evolution law for the chemical state

$$\psi_2 = \frac{2}{3}(E_1 XB_{PreR} + E_2 XB_{PostR})\left[I_{4f_e}^{\frac{3}{2}} - \frac{3}{2}I_{4f_e} + \frac{1}{2}\right]$$

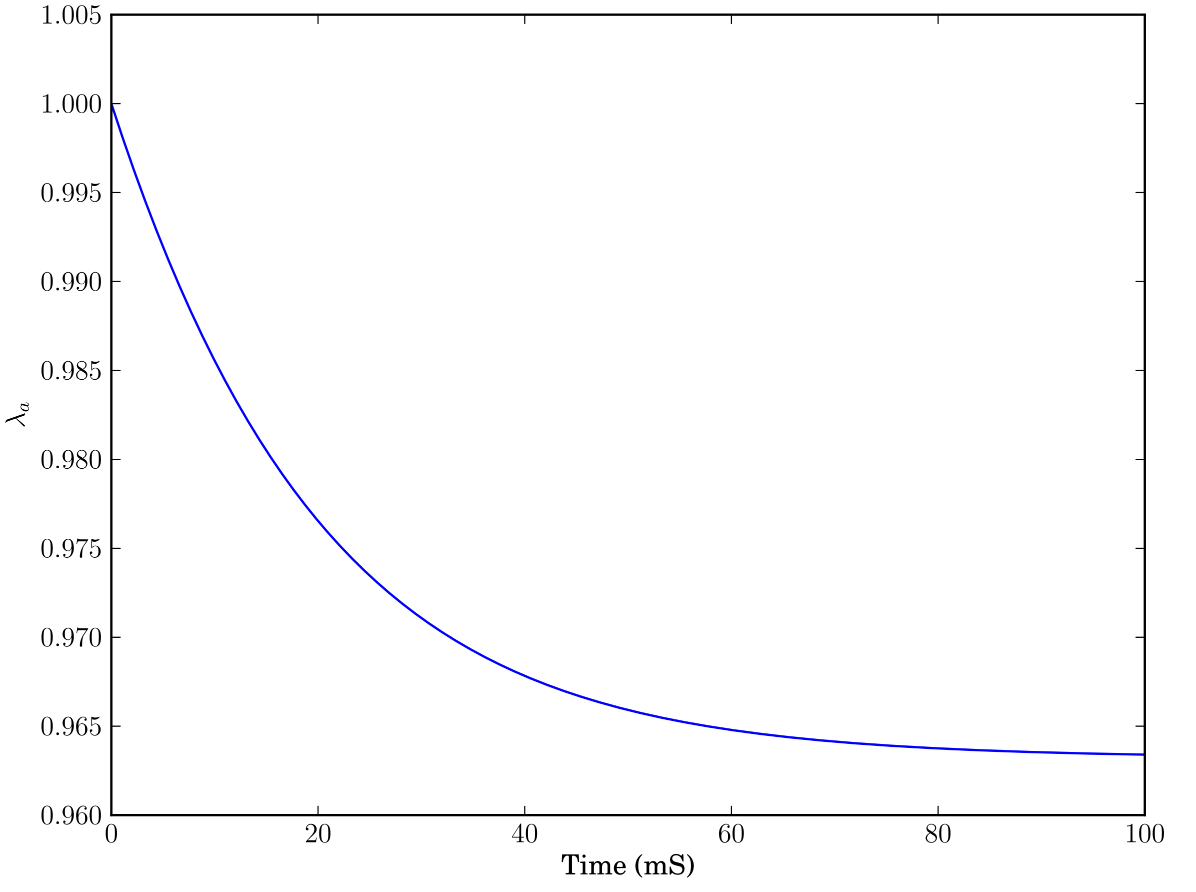
Elastic energy stored in cross-bridges

Rice et al., 2008

A preliminary example demonstrating the coupling between cross-bridge kinetics and the active strain

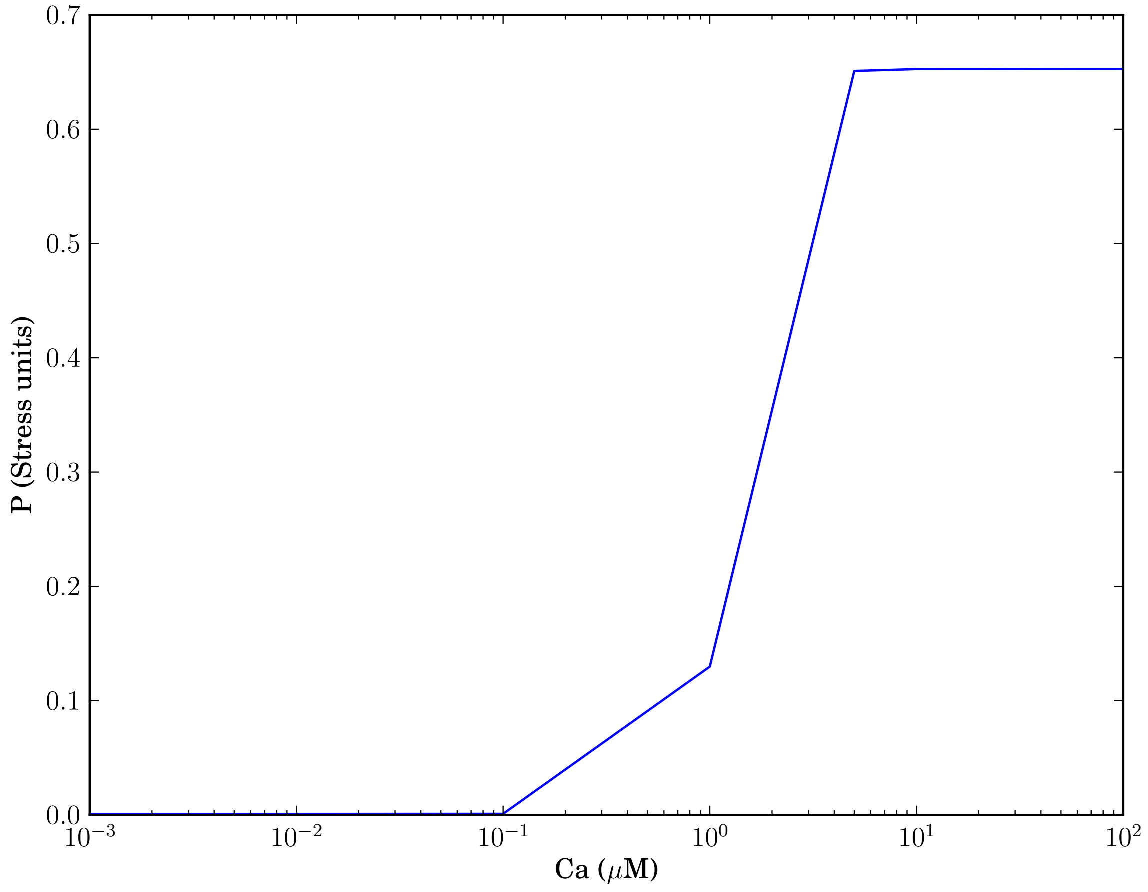


Evolve chemical state at a given stretch and $[Ca^{2+}]$ level



Solve for the active stretch using steady chemical state

A preliminary example demonstrating the coupling between cross-bridge kinetics and the active strain



Steady-state isometric tension at different [Ca^{2+}] levels

Summarising remarks, and some points for discussion

- We are building a chemo-mechanical continuum model for characterising and studying the behaviour of the cardiac myocardium
  - We use a viscoelastic passive model based on a modern hyperelastic law
  - We explored some arguments to choose the active strain approach
  - We use continuum thermodynamics and biophysics to motivate the form of the active strain

Summarising remarks, and some points for discussion

- We are building a chemo-mechanical continuum model for characterising and studying the behaviour of the cardiac myocardium
  - We use a viscoelastic passive model based on a modern hyperelastic law
  - We explored some arguments to choose the active strain approach
  - We use continuum thermodynamics and biophysics to motivate the form of the active strain
- More work is needed in tying the abstract formulation to underlying biophysics
- The importance of viscosity is not clear, but I am exploring its role in energy dissipation and starting to look at whether this helps with numerical stability
- Much of the results you saw today were generated using open source Python code, so ask me for it if you'd like to play too!

http://harishnarayanan.org/