Towards kinetic theory for multi-scale muscle models

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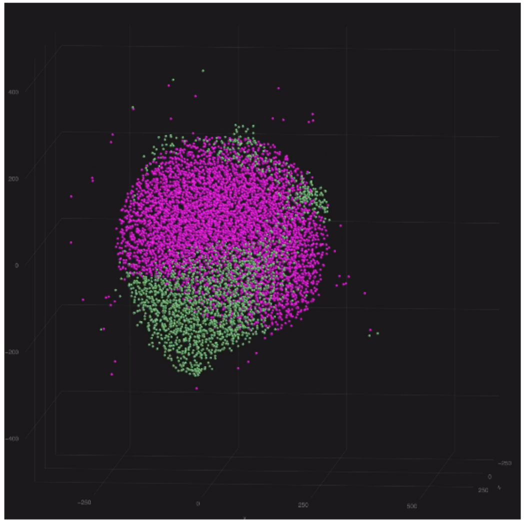
Short self-introduction

Current research in Kyoto Institute for the Advanced Study of Human Biology (ASHBi)

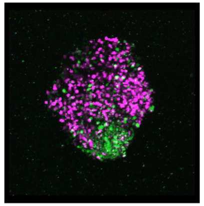
Limb bud morphogenesis

Epithelial-to-mesenchymal transitions

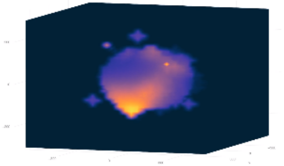
Developmental biology



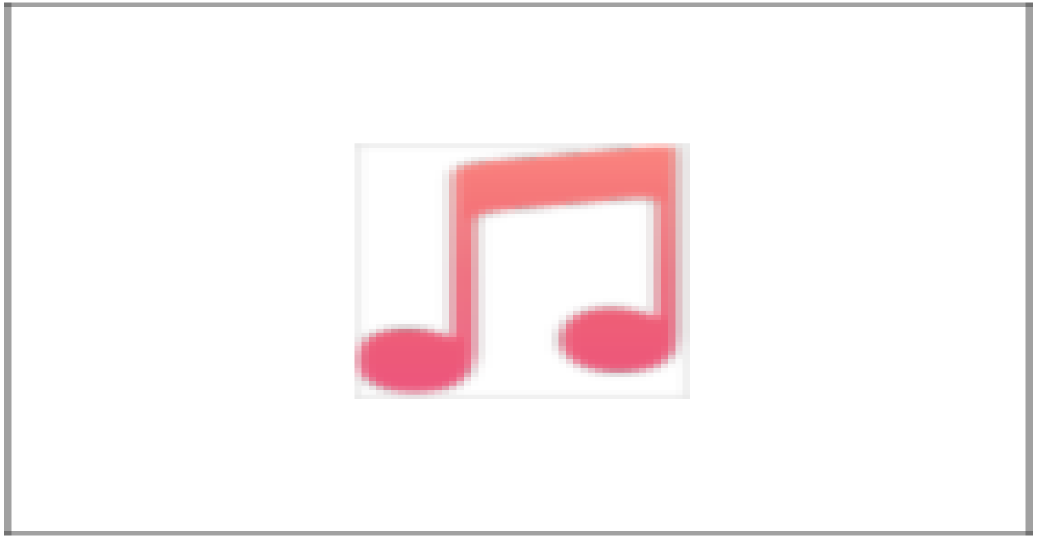
simulation



data



signaling



agent-based model for growing epithelium

Today's talk based on:

[1] S. Plunder, B. Simeon,
The mean-field limit for particle systems with uniform full-rank constraints.
Kinetic and Related Models. (2023)

[2] S. Plunder, B. Simeon,
Coupled Systems of Linear Differential-Algebraic and Kinetic Equations with Application to the Mathematical Modelling of Muscle Tissue.
Conference preceding: Progress Differential-Algebraic Equations II. (2020).

Outline

1. Multi-scale (skeletal) muscle models

2. Abstract "**macro-micro**" model for tissue–cross-bridge coupling

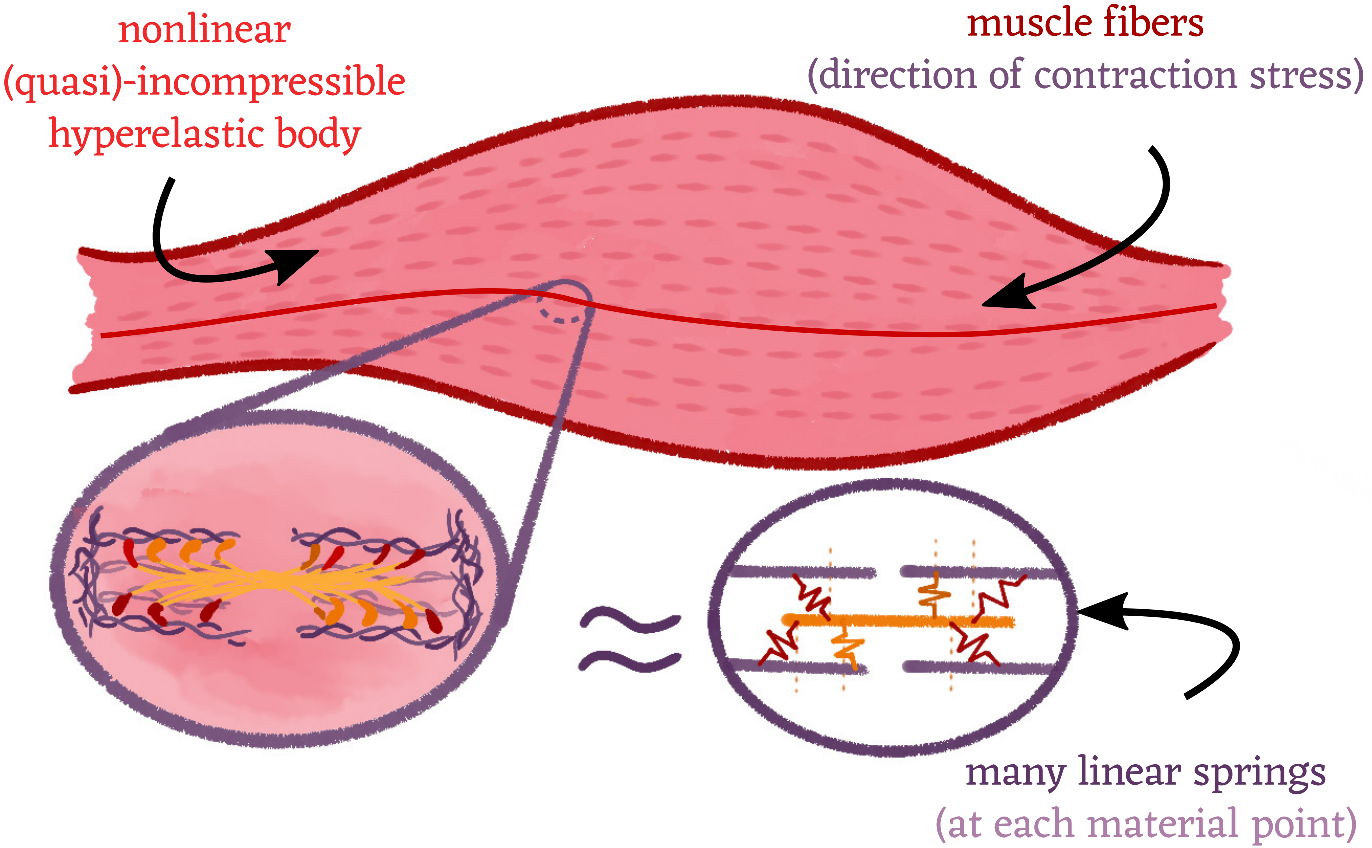
3. Convergence in mean-field limit to "**macro-meso**" model

4. Possible extensions
   - *impossible for me:* adding a jump process for cross-bridge cycling
   - *easier* (?)*:* **global "macro-macro"** model and additive noise,
   - *abstract:* non-full rank constraints

locally macro–micro DAE	locally macro–micro ODE	locally macro–meso mf. char. ODE	locally macro–meso mf. PDE	future	locally macro–macro mf. PDE	global macro–macro mf. PDE

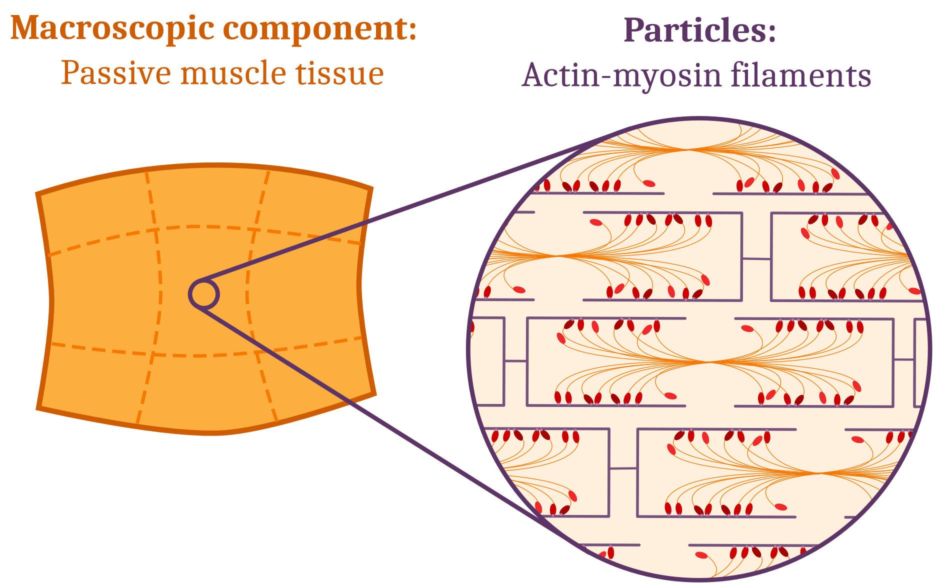
Introduction

Motivation: **Multi-scale muscle models**



Question: **How can we apply kinetic theory to such a system?**

Challenges: **From a kinetic theory perspective**



$$\dot{X}_i = F(X_i, y)$$
$$\dot{y} = G(X_1, \ldots, X_N, y)$$

Each attached cross-bridge is coupled to tissue deformation.
Hence, all particles interact with each other through the tissue!

(However, *once formulated properly*, kinetic theory works out rather well.)

Multi-scale muscle models

... and their lack of perfect physical structure

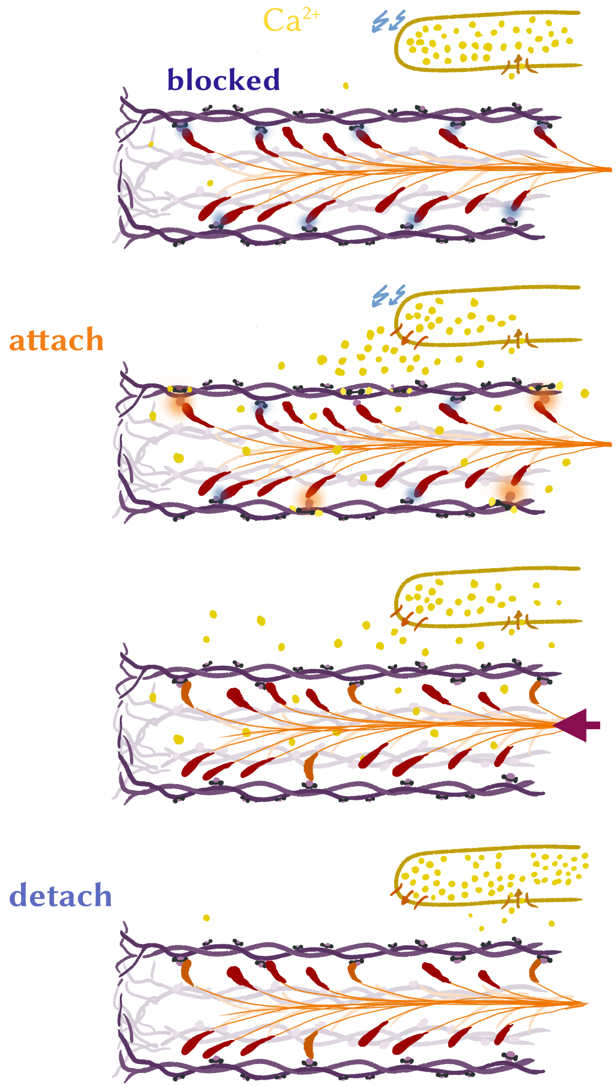
Foundations: **Sliding filament theory**

Huxley's two-state mode:

1. Cross-bridges have two states:
   attached or **detached**.
2. Cross-bridge extension determines transition probabilities between states.
3. Muscle deformation changes cross-bridge extensions

$$\partial_t \rho(x,t) + \mathrm{div}(\rho(x,t)v(t)) = f(x)(1-\rho(x,t)) - g(x)\rho(x,t)$$

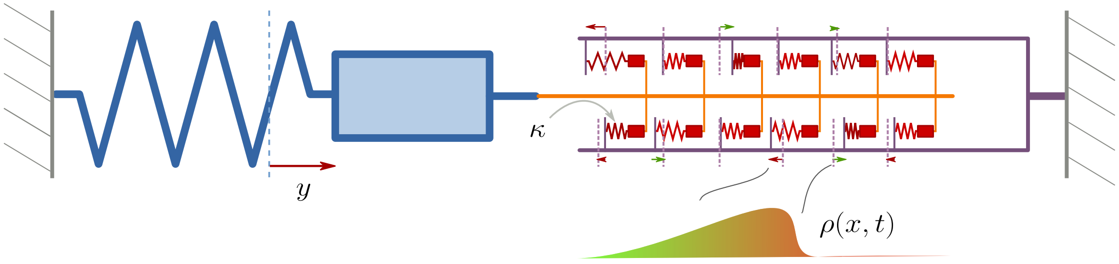
Generated force: $F = -\kappa \int_{\mathbb{R}} x\rho(x,t)\,\mathrm{d}x$



Textbooks: [2009] J. Keener and J. Sneyd [2001] J. Howard

Unilateral *tissue–cross-bridge coupling*

Simplest model:



$$\begin{cases} F_{\mathrm{xb}} = -\kappa \int_{\mathbb{R}} x\rho(x,t)\,\mathrm{d}x \\ m\ddot{y} = F_{\mathrm{passive}} + F_{\mathrm{xb}} \\ \partial_t \rho + \mathrm{div}_x(\rho\,\dot{y}) = 0 \end{cases}$$

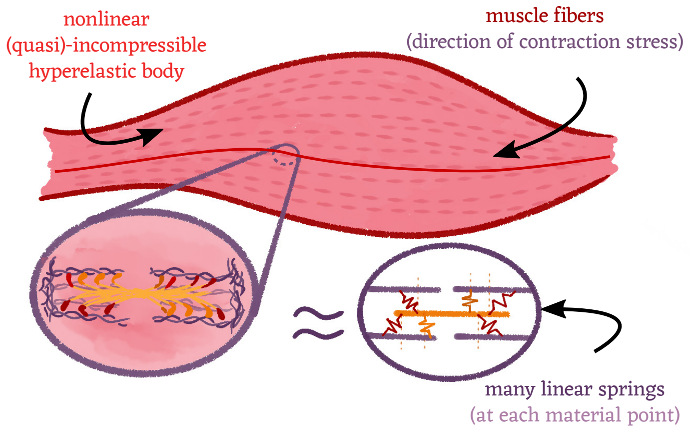
$$\mathcal{W} = \mathcal{W}_{\mathrm{passive}} + \int_{\mathbb{R}} \frac{\kappa}{2} x^2\,\mathrm{d}\rho(x,t) \qquad \mathcal{T} = \frac{m}{2}\|\dot{y}\|^2 + \frac{1}{2}\int_{\mathbb{R}} \|\dot{y}\|^2\,\mathrm{d}\rho(x,t)$$

Potential issues:

- This type of coupling ignores cross-bridge momentum.

- Ideally, the system should be conservative (no-cross bridge cycling, but it isn't exactly)...
  Not clearly a Lagrangian system/Euler-Lagrange equation?

Typical multi-scale models*



Quasi-incompressible hyperelasiticity (for muscle tissue)

$$\partial_t \varphi = \mathrm{Div}(P_{\text{passive}} + P_{\text{active}} + pG)$$

$$\det(\partial\varphi) = 1 + \frac{p}{\kappa}$$

Cross-bridge model enters via active stress term:

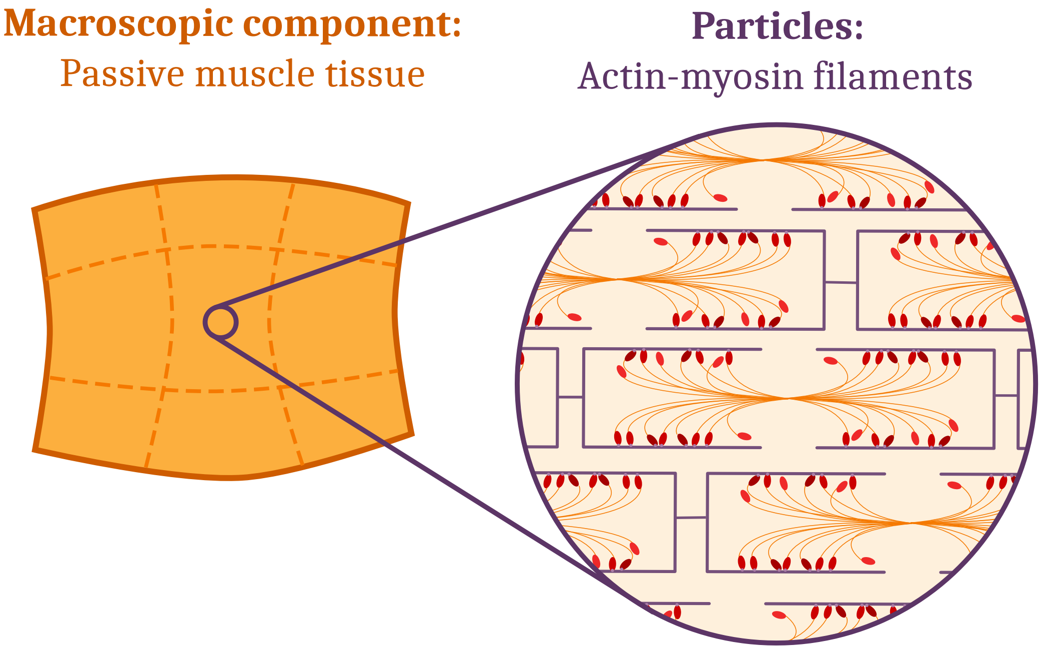
$$P_{\text{active}} = -\frac{\partial \mathcal{W}_{\text{active}}}{\partial \mathrm{D}\varphi} \qquad \mathcal{W}_{\text{active}} = \left(\kappa \int x \, \mathrm{d}\rho(x,t)\right) \cdot \text{“stress tensor in fiber direction”}$$

some equation to approximate $\partial_t \rho + \mathrm{div}_x(\rho \, v_{\mathrm{xb}}) = 0$ *(e.g. distributed moment method).*

The system doesn't seem to be a direct Euler-Lagrange equation.

* *Very non-comprehensive list*: [2008] M. Böl, S. Reese [2016] T. Heidlauf, O. Röhrle [2017] Herzog, W. [2022] M. H. Gfrerer; B. Simeon

The microscopic dynamics are governed by the macroscopic scale

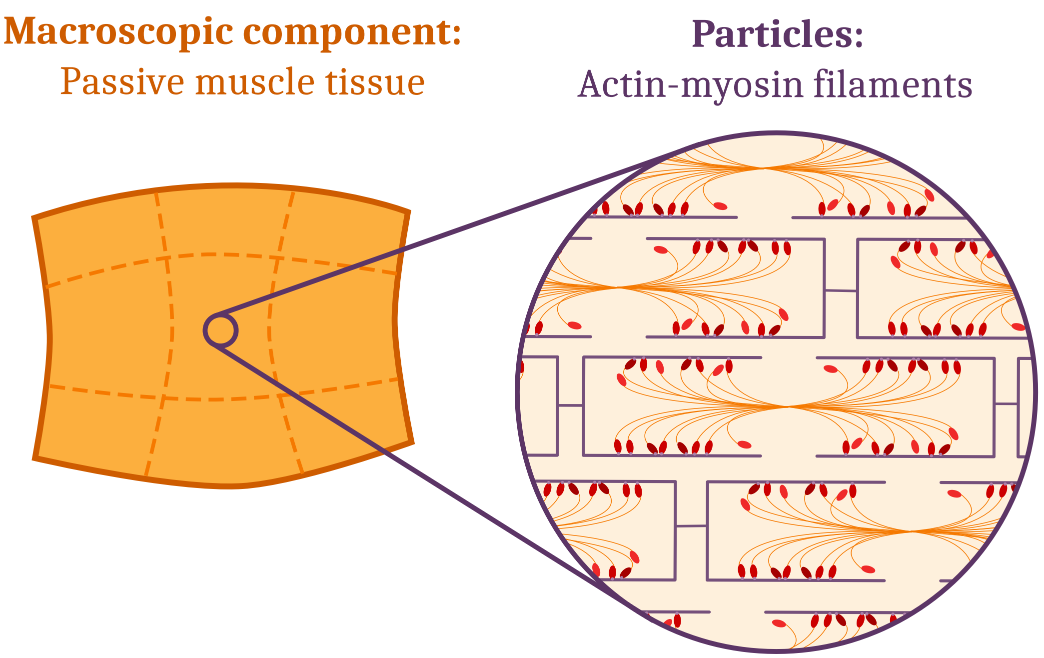


"Unilateral" coupling:

Actin-myosin contractions accumulate to macroscopic stress.

Tissue deformation ***determines*** *cross-bridge dynamics.*

Focus today on **bilateral coupling** *for multi-scale model*



Both levels impact each other equally:

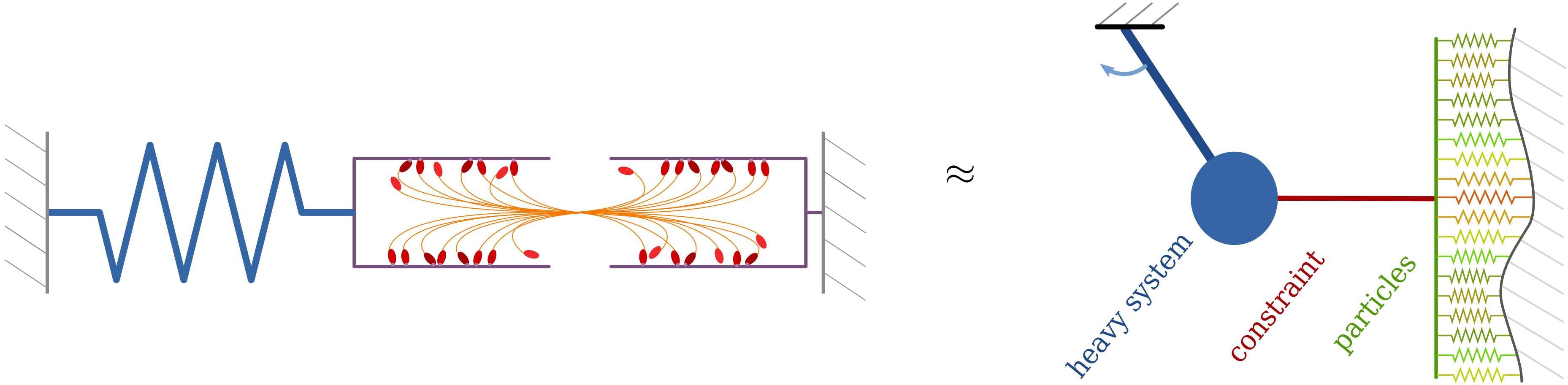
Actin-myosin contraction
accumulates
to macroscopic force.

Tissue deformation
pulls or pushes *cross-bridges.*

Disclaimer: *In terms of physical units, the concrete changes we discuss today are often insignificantly small!*

This talk is about the math of these models, with the hope get insights into the structure of the systems.

Abstract “**macro-micro**” model for **tissue–cross-bridge** coupling



locally macro–micro DAE | locally macro–micro ODE | locally macro–meso mf. char. ODE | locally macro–meso mf. PDE | future | locally macro–macro mf. PDE | global macro–macro mf. PDE

Very short recall of **differential-algebraic equations** (DAEs)

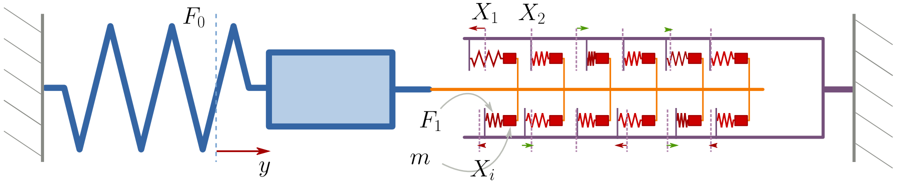
$$\dot{x} = f(x) \qquad \text{such that} \qquad g(x) = 0$$

can be implemented with Lagrangian multipliers via

$$\begin{aligned} \dot{x} &= f(x) + \partial_x g(x)^T \lambda, \\ g(x) &= 0. \end{aligned}$$

Abstract "**macro-micro**" system

$$\ddot{y} = F_0(y) + \frac{1}{N}\sum_{j=1}^{N} \partial_y g(X_j, y)^T \lambda_j,$$



$$mX_i = F_1(X_i) + \partial_{X_i} g(X_i, y)^T \lambda_i + \frac{1}{N}\sum_{j=1}^{N} K(X_j, X_i),$$

$$g(X_i, y) = g(X_i^{\text{init}}, y^{\text{init}}) \qquad \forall 1 \leq i \leq N.$$

$g : \mathbb{R}^{n_x} \times \mathbb{R}^{n_y} \to \mathbb{R}^{n_x}$ Constraints

$\lambda_1, \ldots, \lambda_N \in \mathbb{R}^{n_x}$ Lagrangian multipliers

$$\left.\begin{aligned} F_0(y) &= -\nabla_y \mathcal{W}_0(y) \\ F_1(X) &= -\nabla_X \mathcal{W}_1(X) \end{aligned}\right\} \text{Forces}$$

$K(X_j, X_i) = -\nabla_{X_i} \mathcal{V}(X_j - X_i)$ Interaction forces

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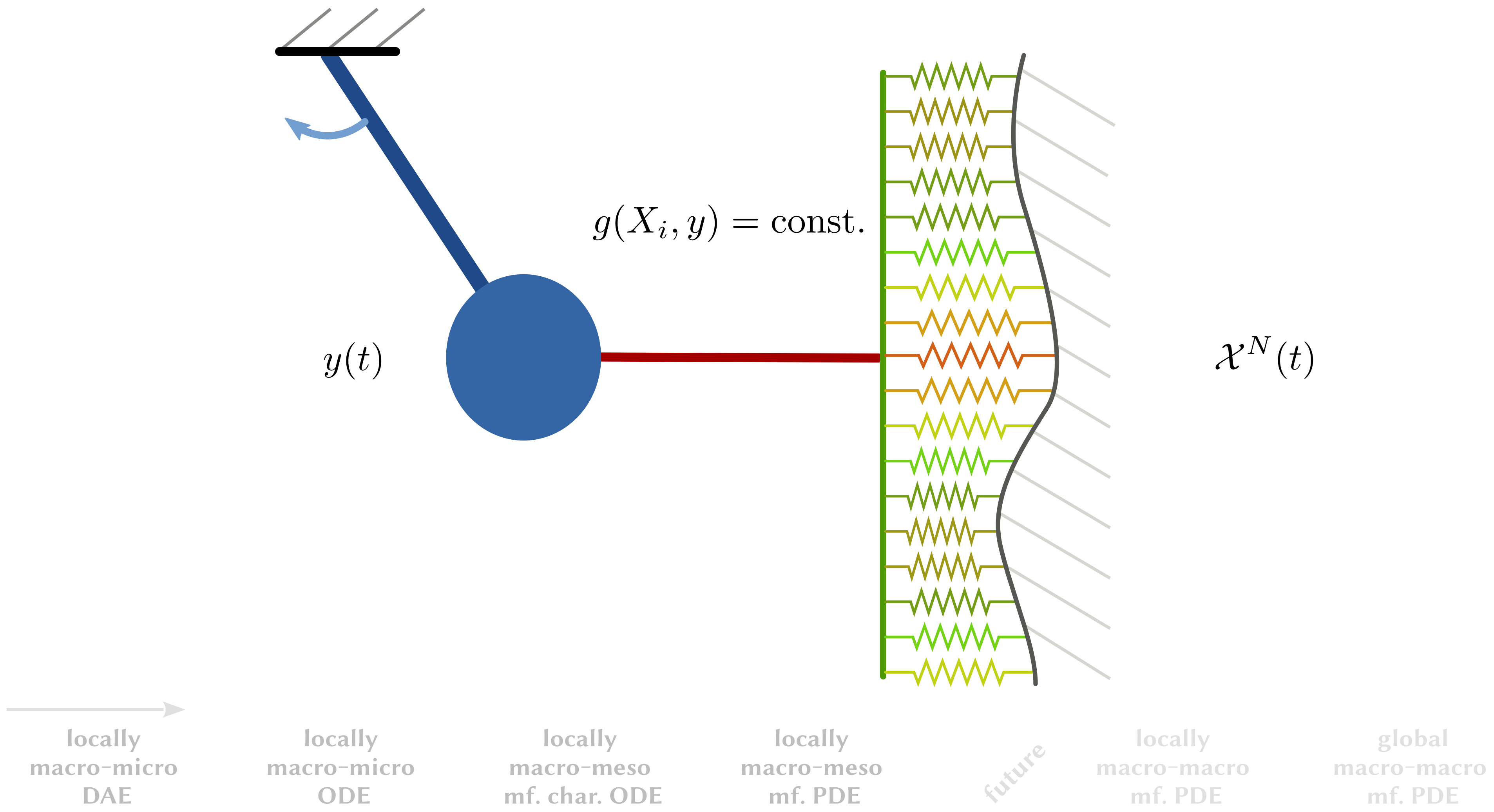


$g(X_i, y) = \text{const.}$
$y(t)$
$\mathcal{X}^N(t)$
locally
macro-micro
DAE
locally
macro-micro
ODE
locally
macro-meso
mf. char. ODE
locally
macro-meso
mf. PDE
future
locally
macro-macro
mf. PDE
global
macro-macro
mf. PDE

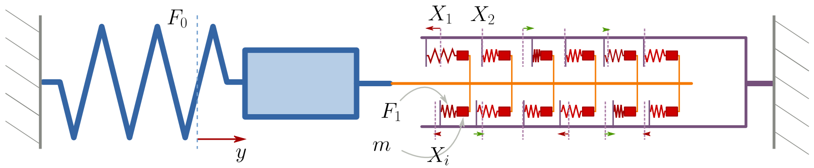
This is a classical **Lagrangian system**

$$\mathcal{L}(y, \mathcal{X}^N, \Lambda^N) = \frac{1}{2}\|\dot{y}\|^2 - \mathcal{W}_0(y) + \frac{1}{N}\sum_{i=1}^{N}\Big(\frac{m}{2}\|\dot{X}_i\|^2 - \lambda_i\left(g(X_i, y) - g(X_i^{\text{init}}, y^{\text{init}})\right) - \mathcal{W}_1(X_i) - \frac{1}{2N}\sum_{j=1}^{N}\mathcal{V}(X_j - X_i)\Big)$$

$\longrightarrow$ conservation of energy

$\longrightarrow$ scaling factors picked such that total energy remains of order one in the limit $N \longrightarrow \infty$.

Examples (linear constraints)



Consider $g(X_i, y) = X_i - Gy = \text{const}$ $\qquad G \in \mathbb{R}^{n_x \times n_y}$

Time derivative of constraint:

$$\Rightarrow \quad \boxed{\dot{X}_i = G\dot{y}}$$

$$\Rightarrow \quad F_1(X_i) + \partial_{X_i} g(X_i, y)^T \lambda_i = \boxed{m\ddot{X}_i = mG\ddot{y}}$$

$$\Rightarrow \quad \lambda_i = mG\ddot{y} - F_1(X_i)$$

$$\Rightarrow \quad \ddot{y} = F_0(y) + \frac{1}{N}\sum_{j=1}^{N} G^T \left(mG\ddot{y} - F_1(X_j)\right)$$

$$\Rightarrow \quad (1 + mG^T G)\ddot{y} = F_0(y) - \frac{1}{N}\sum_{j=1}^{N} G^T F_1(X_j)$$

$$\rightsquigarrow \quad \partial_t \rho = -\mathrm{div}_x(\rho\, G\dot{y})$$

$$\rightsquigarrow \quad m_{\text{eff}}\ddot{y} = F_0(y) - \int_{\mathbb{R}} G^T F_1(x)\rho(x,t)\,\mathrm{d}x = F_{\text{eff}}(y, \rho)$$

locally macro–micro DAE

locally macro–micro ODE

locally macro–meso mf. char. ODE

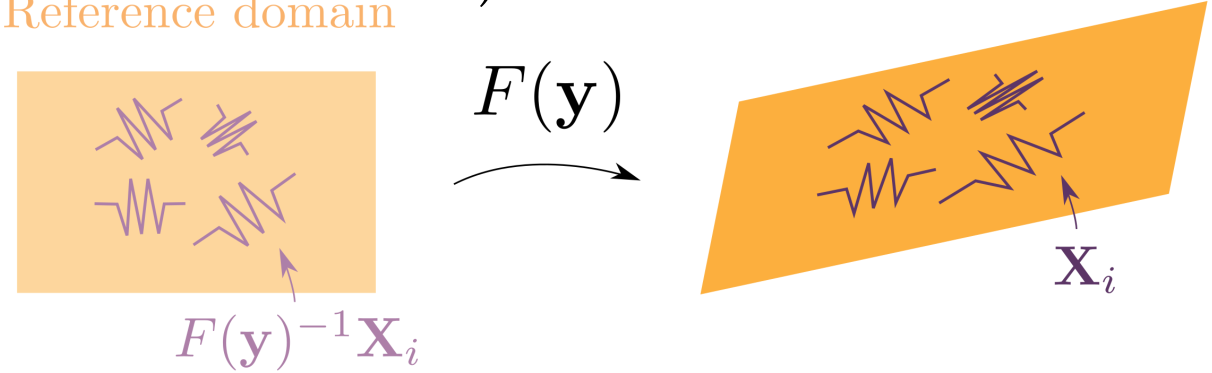
locally macro–meso mf. PDE

future

locally macro–macro mf. PDE

global macro–macro mf. PDE

Examples (nonlinear constraint)



Consider linear deformations of a finite element (e.g. rotation, stretching, **shearing**, ...)

$$g(X_i, y) = F(y(t))^{-1} X_i = \text{const} \quad (= X_i^{\text{in}})$$

Cp. [1996] G. I. Zahalak. *Non-axial Muscle Stress and Stiffness.* Journal of Theoretical Biology

In our framework, we can directly derive resulting active stress component from given constraints.

Strategy towards a mean-field description

$$\begin{tikzcd}[column sep=huge, row sep=huge]
\text{DAE model} \arrow[r, dashed] \arrow[d, "\text{Index reduction + multiplier elimination}"] & \text{Mean-field PDAE system} \arrow[d, dashed] \\
\text{ODE model} \arrow[r, "\text{Mean-field limit}"'] & \text{Mean-field PDE system}
\end{tikzcd}$$

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On this slide: $g_x := \dfrac{\partial g}{\partial X}(X_i, y)$ etc.

Index reduction

Index-3 DAE $\mathcal{M} = g^{-1}(\{0\})$

$$g(X_i, y) = 0$$

Index-2 DAE $T_{(X_i,y)}\mathcal{M}$

$$g_X[\dot{X}_i] + g_y[\dot{y}] = 0$$

$$\Rightarrow \quad \dot{X}_i = -g_x^{-1}[g_y[\dot{y}]]$$

$$\dot{X}_i = \Phi(X_i, y)[\dot{y}]$$

Index-1 DAE $T_{(\dot{X}_i,\dot{y},X_i,y)}T\mathcal{M}$

$$g_x[\ddot{X}_i] + g_{xx}[\dot{X}_i, \dot{X}_i] + 2g_{xy}[\dot{X}_i, \dot{y}] + g_y[\ddot{y}] + g_{yy}[\dot{y}, \dot{y}] = 0$$

$$\ddot{X} = \Phi(X, y)[\ddot{y}] + \Omega(X, y)[\dot{y}, \dot{y}]$$

Assume:

$\partial_{X_i} g(X_i, y) \in \mathbb{R}^{n_x \times n_x}$

is always invertible

$$\Omega = -g_x^{-1}\left(g_{xx}[\Phi\dot{y}, \Phi\dot{y}] + 2g_{xy}[\Phi\dot{y}, \dot{y}] + g_{yy}[\dot{y}, \dot{y}]\right)$$

Elimination of multipliers (uses special structure of system!)

$$m\ddot{X}_i = F_1 + \frac{1}{N}\sum_j K_{ij} + g_x^T \lambda_i = m\Phi[\ddot{y}] + m\Omega[\dot{y}, \dot{y}]$$

$$\Rightarrow \quad \lambda_i = -g_x^{-1}\left(F_1 + \frac{1}{N}\sum K_{ij} - m\Phi[\ddot{y}] - m\Omega[\dot{y}, \dot{y}]\right)$$

The equivalent **ODE model**

$$\ddot{y} = F_0 + \frac{1}{N}\sum_{j=1}^{N} g_y^T \lambda_j \qquad \lambda_i = -g_x^{-1}\left(F_1 + \frac{1}{N}\sum K - m\Phi[\ddot{y}] - m\Omega[\dot{y},\dot{y}]\right)$$

$$\overbrace{\left(1 + \frac{1}{N}\sum_{j=1}^{N} m\Phi^T\Phi\right)}^{m_{\text{eff}}(\mathcal{X}^N, y)}\ddot{y} = \overbrace{\frac{1}{N}\sum_{j=1}^{N}\left(F_0 + \Phi^T\left(F_1 - m\Omega[\dot{y},\dot{y}] + \frac{1}{N}\sum_{k=1}^{N} K\right)\right)}^{F_{\text{eff}}(\mathcal{X}^N, y)}$$

$$\dot{X}_i = \Phi[\dot{y}]$$

Each solution of the DAE model solves the ODE mode, and vice versa.

Dealing with the **non-constant mean-field mass**

ODE model $\quad m_{\text{eff}}^N(\mathcal{X}^N, y)\,\ddot{y} = F_{\text{eff}}^N(\mathcal{X}^N, y, \dot{y}) \qquad \dot{X}_i = \Phi(X_i, y)[\dot{y}]$

“Remember”: $\quad \dfrac{\mathrm{d}}{\mathrm{d}z}\dfrac{f(z)}{m(z)} = \dfrac{f'(z)m(z) - f(z)m'(z)}{m(z)^2}$

We need that mass is bounded from below...

Lemma: Assume $g : \mathbb{R}^{n_x} \times \mathbb{R}^{n_y} \to \mathbb{R}^{n_x}$ is twice continuously differentiable and $g, \mathrm{D}g, \mathrm{D}^2 g$ are all bounded and Lipschitz and the Jacobian is uniformly elliptic, i.e.

$$\inf_{v \in \mathbb{R}^{n_x}} v^T \partial_{X_i} g(X_i, y) v \geq \delta \|v\|^2 \quad \forall X_i \in \mathbb{R}^{n_x}, y \in \mathbb{R}^{n_y},$$

then Φ, Ω and m_{eff}^N are well-defined, bounded and Lipschitz continuous.

Full list of mathematical assumptions

$$F_0(y) = -\nabla_y \mathcal{W}_0(y), \qquad F_1(X_i) = -\nabla_{X_i} \mathcal{W}_1(X_i), \qquad K(X_j, X_i) = -\nabla_{X_i} \mathcal{V}(X_j - X_i)$$

$F_0, F_1, K, g, \mathrm{D}g, \mathrm{D}^2 g \in BL$ $\qquad$ $BL =$ "bounded and Lipschitz continuous functions"

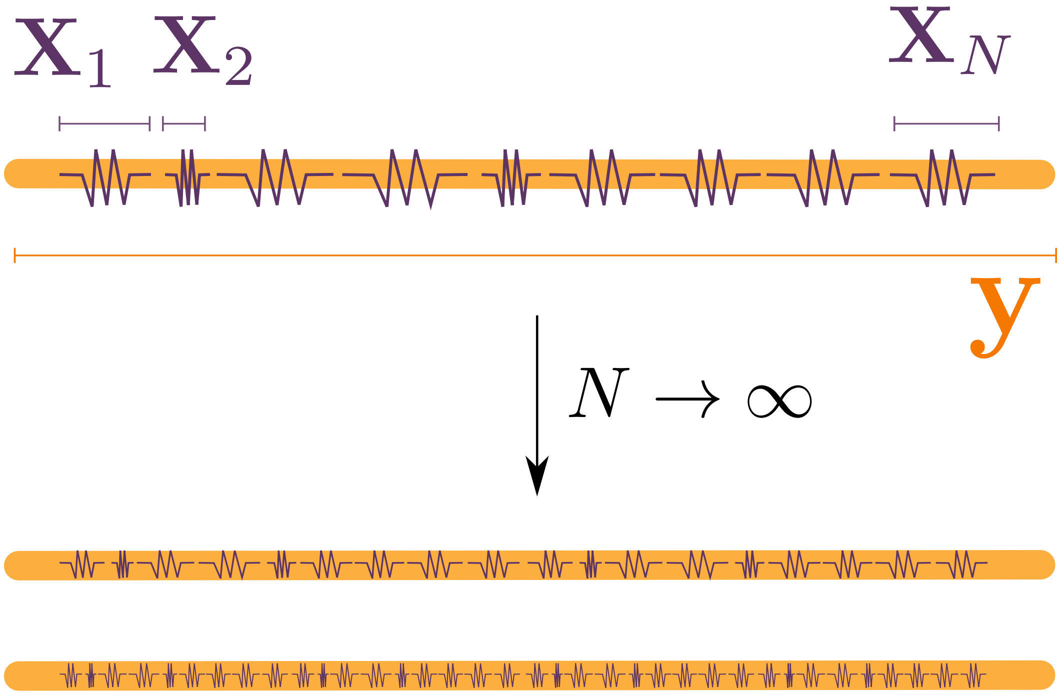
$$\inf_v v^T g(x,y) v \geq \delta \|v\|^2 \quad \forall v, x, y$$

Lemma: The ODE model is well-posed and for any constant $M_v > 0$ the map

$$(y, v, \mathcal{X}^N) \mapsto \left(1 + \frac{1}{N} \sum_{j=1}^N m \Phi^T \Phi\right)^{-1} \left(\frac{1}{N} \sum_{j=1}^N \left(F_0 + \Phi^T \left(F_1 - m\Omega[v,v] + \frac{1}{N} \sum_{k=1}^N K\right)\right)\right)$$

is bounded and Lipschitz on $\mathbb{R}^{n_y} \times B_{M_v}^{\mathbb{R}^{n_y}}(0) \times (\mathbb{R}^{n_x})^N$.

The mean-field limit



Formal transition from **macro-micro** to **macro-meso**...

ODE model

$$m_{\text{eff}}^N(\mathcal{X}^N, y)\,\ddot{y} = F_{\text{eff}}^N(\mathcal{X}^N, y, \dot{y})$$
$$\dot{X}_i = \Phi(X_i, y)[\dot{y}]$$

Define empirical measure as:

$$\mu_{\mathcal{X}^N}^{\text{emp}} = \frac{1}{N}\sum_{i=1}^N \delta_{X_i}.$$

Mean-field characteristic flow:

$$m_{\text{eff}}(\mu^t, y)\,\ddot{y} = F_{\text{eff}}(\mu^t, y, \dot{y}),$$
$$\partial_t X^t(x^{\text{in}}) = \Phi(X^t(x^{\text{in}}), y)[\dot{y}] \quad \forall x^{\text{in}} \in \mathbb{R}^{n_x},$$
$$\mu^t(A) \coloneqq \mu_{\mathcal{X}_N^{\text{in}}}^{\text{emp}}((X^t)^{-1}(A)).$$

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Mean-field PDE

For particle densities $\rho(x,t)\,\mathrm{d}x = \mathrm{d}\mu^t(x)$ where $X_i \sim \mu^N(x,t)\mathrm{d}x$ and $\mu^N \to \mu$.

The mean-field PDE is

$$\begin{aligned} m_{\text{eff}}(y,\rho)\ddot{y} &= F_{\text{eff}}(y,\dot{y},\rho) \\ \partial_t \rho &= -\mathrm{div}(\rho\,\Phi(x,y)[\dot{y}]) \end{aligned}$$

with

$$\Phi(x,y) = -\left(\partial_x g(x,y)\right)^{-1} \partial_y g(x,y)$$

Macro-micro velocity map

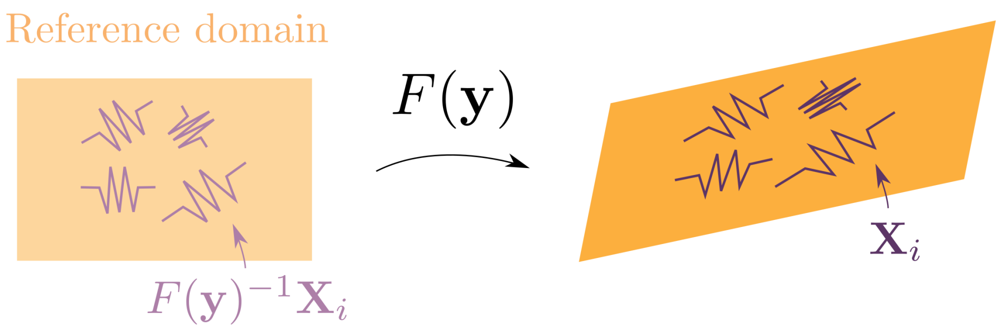
$$m_{\text{eff}} = 1 + m\int \Phi(x,y)^T \Phi(x,y)\rho(x,t)\,\mathrm{d}x$$

“Mean-field” mass

$$F_{\text{eff}} = F_0 - \int \Phi^T \left(F_1(x) + m\Omega(x,y)[\dot{y}] + \int K(x,x')\rho(x',t)\,\mathrm{d}x' \right) \rho(x,t)\,\mathrm{d}x$$

“Mean-field” force

Recall: nonlinear constraint example



Consider linear deformations of a finite element (e.g. rotation, stretching, **shearing**, ...)

$$g(X_i, y) = F(y(t))^{-1} X_i = \text{const} \quad (= X_i^{\text{in}})$$

Resulting **mean-field PDE**

$$\partial_t \rho = -\text{div}_x(\rho F(\dot{y}) F(y)^{-1} x) = -\rho \text{tr}(F(\dot{y}) F(y)^{-1}) - F(\dot{y}) F(y)^{-1} x \cdot (\partial_x \rho)$$

Mathematical setup for **kinetic theory**

$$\mathcal{P}^1(\mathbb{R}^{n_x}) = \{\mu \text{ prob. measure on } \mathbb{R}^{n_x} \mid \int \|x\| \, \mathrm{d}\mu(x) < \infty\}$$

space of probability measures with finite first moment.

$$W_1(\mu, \nu) = \sup_{\phi \in C(\mathbb{R}^{n_x}, \mathbb{R}^{n_x}), \mathrm{Lip}(\phi) < 1} \int \phi(x) \, \mathrm{d}\mu(x) - \int \phi(x) \, \mathrm{d}\nu(x)$$

Wasserstein distance (with exponent 1).

$$\mu^{\mathrm{emp}}_{\mathcal{X}^N} = \frac{1}{N} \sum_{i=1}^{N} \delta_{X_i}$$

empirical measure

Stability estimate [SP, Simeon] Given two solutions $(y_1, \mu_1), (y_2, \mu_2) : [0, T] \to \mathbb{R}^{n_y} \times \mathcal{P}^1(\mathbb{R}^{n_x})$ with initial conditions $y_i(0) = y_i^{\text{in}}, \dot{y}_i(0) = v_i^{\text{in}}$ and $\mu_i^0 = \mu_i^{\text{in}}$ then

$$\begin{aligned} &\|y_1(t) - y_2(t)\| + \|\dot{y}_1(t) - \dot{y}_2(t)\| + W_1(\mu_1^t, \mu_2^t) \\ &\qquad \le C e^{Lt} \left(\|y_1^{\text{in}} - y_2^{\text{in}}\| + \|v_1^{\text{in}} - v_2^{\text{in}}\| + W_1(\mu_1^{\text{in}}, \mu_2^{\text{in}}) \right) \end{aligned}$$

where the constants C and L only depend on the total energy and

$$C_\mu = \max\left(\int 1 + \|x\| \, \mathrm{d}\mu_1^{\text{in}}(x), \int 1 + \|x\| \, \mathrm{d}\mu_2^{\text{in}}(x)\right).$$

Convergence in mean-field limit For any sequence of microscopic initial conditions $(\mathcal{X}_k^{\text{in}})_k$ such that $W_1(\mu^{\text{emp}}_{\mathcal{X}_k^{\text{in}}}, \mu^{\text{in}}) \to 0$ as $k \to \infty$, then $W_1(\mu^{\text{emp}}_{\mathcal{X}_k(t)}, \mu(t)) \to 0$ for all $0 \le t \le T$.

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Outline of the proof (mostly whiteboard)

Ingredients

Mean-field characteristic flow

$$m_{\text{eff}}(\mu^t, y)\,\ddot{y} = F_{\text{eff}}(\mu^t, y, \dot{y})$$

$$\partial_t X^t(x^{\text{in}}) = \Phi(X^t(x^{\text{in}}), y)[\dot{y}] \quad \forall x^{\text{in}} \in \mathbb{R}^{n_x},$$

$$\mu^t(A) := \mu^{\text{in}}((X^t)^{-1}(A)) \quad \forall A \in \mathfrak{B}(\mathbb{R}^{n_x})$$

$$\Leftrightarrow \quad \dot{z} = b(z, \mu^{\text{in}})$$

$$z = (y, \dot{y}, \varphi) \in \mathbb{R}^{n_y} \oplus B_{M_v}^{\mathbb{R}^{n_y}} \oplus Y =: Z_{M_v} \subset Z$$

$$Y = \{\varphi \in C(\mathbb{R}^{n_x}, \mathbb{R}^{n_x}) \mid \sup_{x \in \mathbb{R}^{n_x}} \frac{\|\varphi(x)\|}{1 + \|x\|} < \infty\}$$

$z \mapsto b(z, \mu^{\text{in}})$ is Lipschitz (for limited velocities $\dot{y}$):

$$\|b(z_1, \mu^{\text{in}}) - b(z_2, \mu^{\text{in}})\| \le L_z \|z_1 - z_2\|_Z$$

$\mu \mapsto b(z, \mu)$ is Lipschitz:

$$\|b(z, \mu_1) - b(z, \mu_2)\| \le L_\mu W_1(\mu_1, \mu_2)$$

Fundamental lemma:

$$\dot{z}_i = b(z_i, \mu_i^{\text{in}}), \quad z_i(0) = z_i^{\text{in}} \qquad \text{for } i = 1, 2.$$

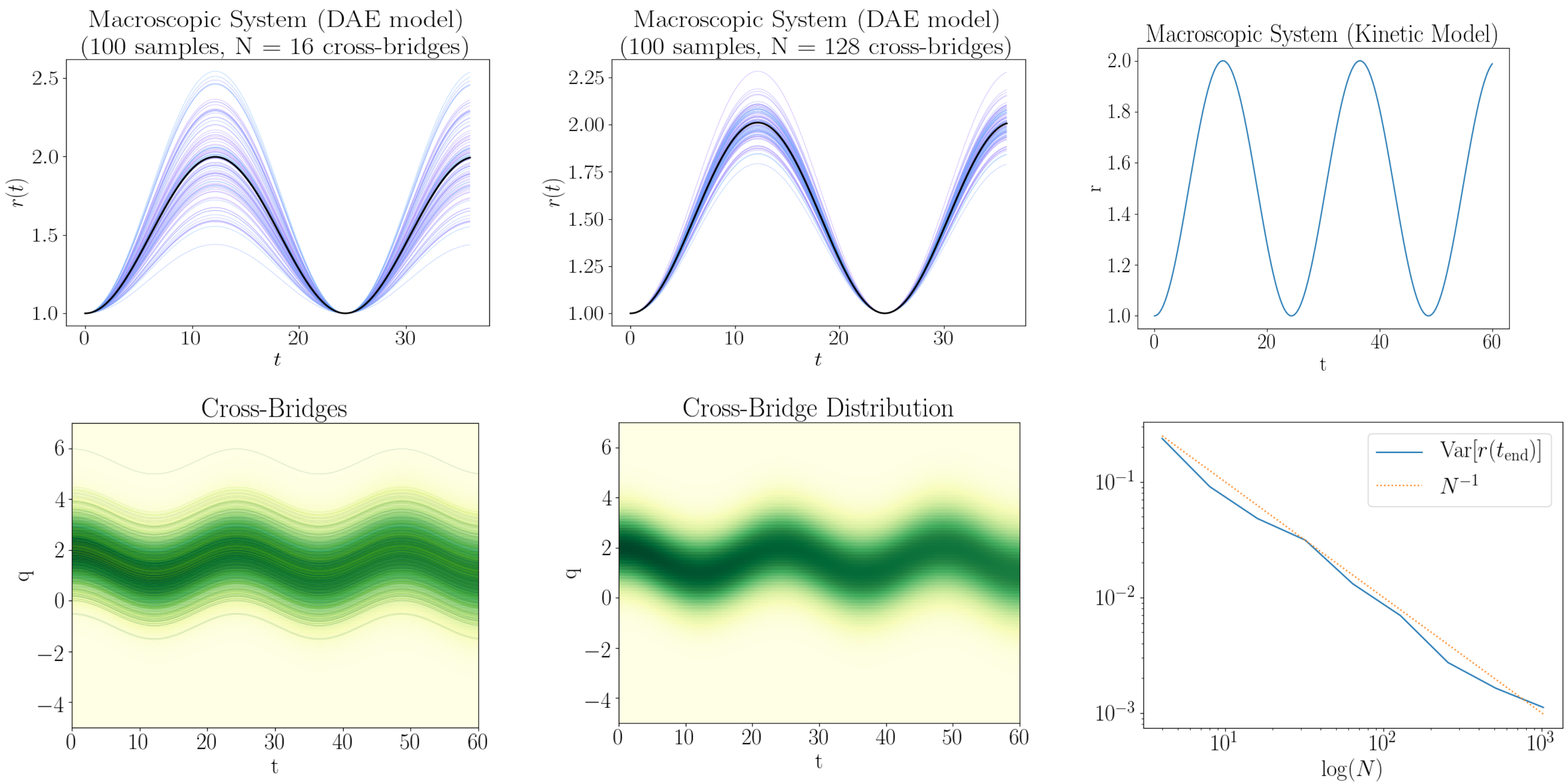
If $\quad \|z_1^{\text{in}} - z_2^{\text{in}}\|_Z \le \varrho,$

$$\|b(z, \mu_1^{\text{in}}) - b(z, \mu_2^{\text{in}})\| \le \varepsilon \quad \forall z \in Z_{M_v}$$

$$\|b(z, \mu_1^{\text{in}}) - b(z', \mu_2^{\text{in}})\| \le L\|z - z'\| \quad \forall z, z' \in Z_{M_v}$$

Then $\|z_1(t) - z_2(t)\| \le \varrho e^{Lt} + \dfrac{\varepsilon}{L}(e^{Lt} - 1).$

Small numerical validation (linear case)



locally
macro–micro
DAE

locally
macro–micro
ODE

locally
macro–meso
mf. char. ODE

locally
macro–meso
mf. PDE

future

locally
macro–macro
mf. PDE

global
macro–macro
mf. PDE

Outlooks

Is there general “**Macro-macro**” system?

Assuming $x^2\rho(x,t)\Phi(x,y) \to 0, \quad \text{as}|x| \to \infty:$

Mean-field PDE

$$m_{\text{eff}}(y,\rho)\ddot{y} = F_{\text{eff}}(y,\dot{y},\rho)$$
$$\partial_t\rho = -\text{div}(\rho\,\Phi(x,y)[\dot{y}])$$

$$\longrightarrow$$

$$\dot{m}(t) = 0 \quad \text{conservation of mass}$$
$$\dot{\nu}(t) = \dot{y}\int \rho(x,t)\Phi(x,y)\,\mathrm{d}x$$
$$\dot{\sigma}(t) \approx 2\dot{y}\int x\rho(x,t)\Phi(x,y)\,\mathrm{d}x$$

$$m(t) = \int \rho(x,t)\,\mathrm{d}x$$
$$\nu(t) = \int x\rho(x,t)\,\mathrm{d}x$$
$$\sigma(t) = \int x^2\rho(x,t)\,\mathrm{d}x$$

To close the system, one might need to use the concrete constraints...

Or approximate "**Macro-macro**" systems?

Mean-field PDE

Distributed moment method?

$$\rho(x,t) := \gamma_t \frac{1}{\sqrt{2\sigma_t^2}} e^{-\frac{x-\mu_t}{2\sigma_t^2}}$$

$$m_{\text{eff}}(y,\rho)\ddot{y} = F_{\text{eff}}(y,\dot{y},\rho)$$
$$\partial_t \rho = -\operatorname{div}(\rho\,\Phi(x,y)[\dot{y}])$$

Find ODE for moments using transport equation...

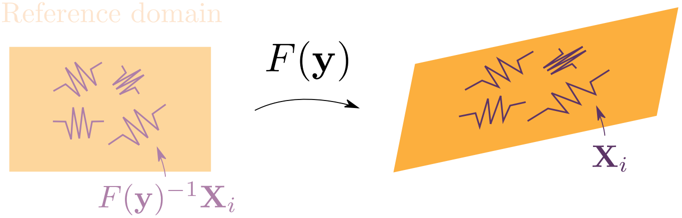
[1981] G. I. Zahalak, A distribution-moment approximation for kinetic theories of muscular contraction.

locally macro-micro DAE	locally macro-micro ODE	locally macro-meso mf. char. ODE	locally macro-meso mf. PDE	future	locally macro-macro mf. PDE	global macro-macro mf. PDE

Adding spacial macroscopic model

Theory might well generalize for cases where the macroscopic system is a PDE:

$$y(t) \in H^1(\Omega_{\text{ref}}, \mathbb{R}^2)$$



Formally, the current framework always supports this:

$$Z_i = (X_i, p) \in \mathbb{R}^{n_x} \times \Omega_{\text{ref}}$$

$$\dot{Z}_i = \begin{pmatrix} F_1(X_i) + \partial_X g(Z_i, y)\lambda_i \\ \partial_p g(Z_i, y) \end{pmatrix} \qquad g(Z_i, y) = \begin{pmatrix} F(y(t, p_i))^{-1} X_i \\ p_i \end{pmatrix} = \text{const.}$$

However, it is probably overly complicated...

locally macro–micro DAE	locally macro–micro ODE	locally macro–meso mf. char. ODE	locally macro–meso mf. PDE	future	locally macro–macro mf. PDE	global macro–macro mf. PDE

Further directions

1. Most obvious current flaw: **Cross-bridge cycling is missing!**

Requires either two population with creation/annihilation:

$$X_i^{\text{attached}} \to X_i^{\text{detached}}$$

Or one could modulate the constraints (but the analysis breaks):

$$Z_i = (X_i, s), \quad g(Z_i, y) = s \cdot (Z_i - y)$$

(I am sure the audience knows better how to integrate cross-bridge cycling.)

2. Relaxing the full rank condition: $\mathrm{rnk}(\partial_X g(X_i, y)) < n_x$?

Thanks