Multiscale modelling, analysis and simulations of plant biomechanics and cellular signalling processes

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Women in Applied and Computational Mathematics

May 9-11, 2018, GSSI Gran Sasso Science Institute, L'Aquila

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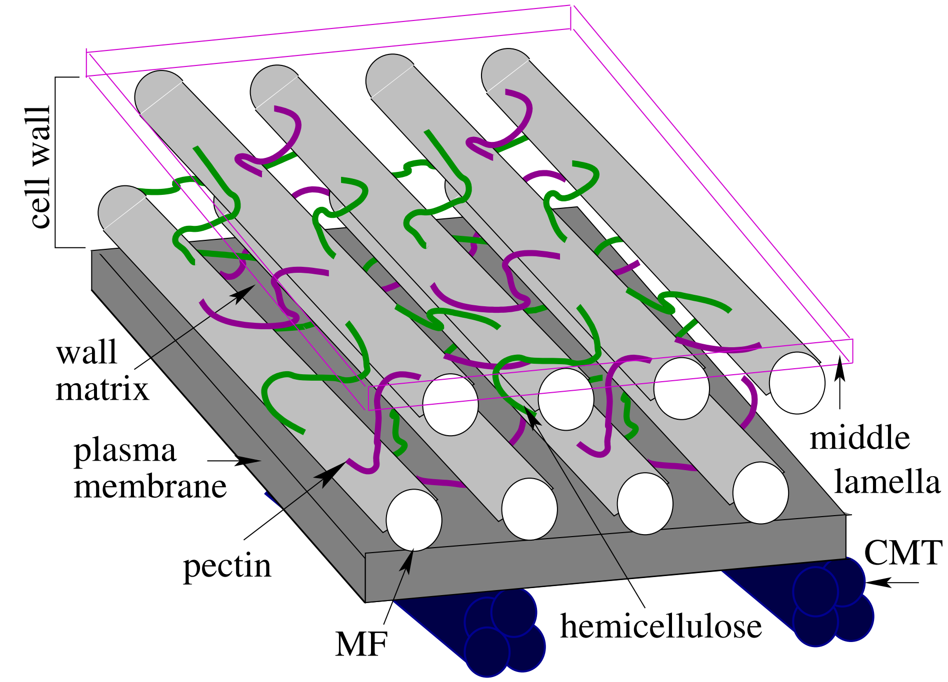
Plant cell walls: microstructure, mechanics & chemistry

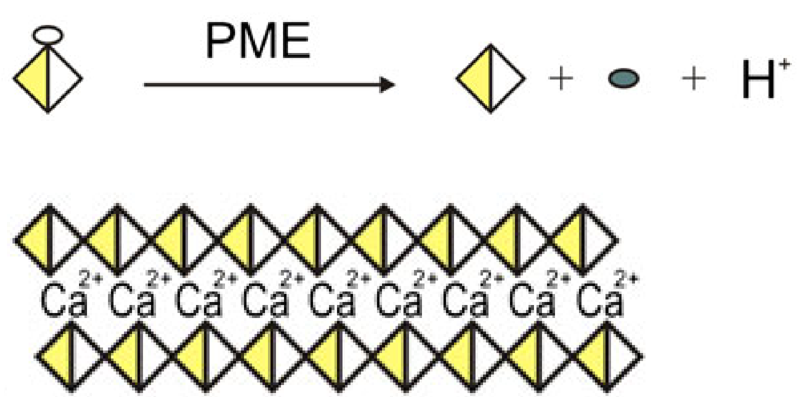


Microscopic structure of plant cell walls

- cellulose microfibrils
- cell wall matrix of pectin, hemicellulose, water, enzymes
- allows for anisotropic cell expansion

Interactions between mechanics and chemistry

- mechanical forces can break load-bearing cross-links
- dynamics of cross-links influences mechanical properties of plant cell wall matrix



Wolf, Greiner, Protoplasma 2012

- Pectin is deposited into cell walls from Golgi apparatus in a methylesterified form
- enzyme PME interacts with methylestrified pectin to form demethylestrified pectin
- Demethylestrified pectin and calcium ions form calcium-pectin cross-links

Mechanics (hyperelastic material)

$$\operatorname{div}\mathbf{T} = 0, \qquad \mathbf{T} = J_e^{-1}\mathbf{F}_e \frac{\partial W(\mathbf{F}_e)}{\partial \mathbf{F}_e} \quad \text{or} \quad \mathbf{T} = \mathbf{F}_e \frac{\partial W(\mathbf{F}_e)}{\partial \mathbf{F}_e} - p\mathbf{I}$$

+ boundary conditions

$\mathbf{F} = \mathbf{I} + \nabla\mathbf{u}$ deformation gradient

$\mathbf{F} = \mathbf{F}_e\mathbf{F}_g$ decomposition in elastic & growth

$J_e = \det(\mathbf{F_e}),\ J_g = \det(\mathbf{F}_g)$

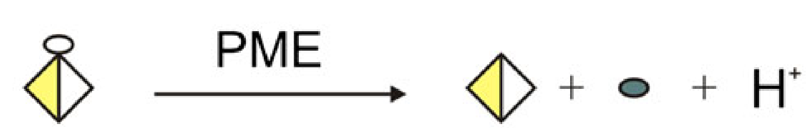
Ogden, *Nonlinear elastic deform.* 1984
Rodriguez, Hoger, McCulloch, *J Biomech.* 1994
Goriely, Moulton, Vandiver, *EPL* 2010
Goriely, Ben Amar, *J Mech.Phys.Solids* 2005
Goriely, Ben Amar, *Biomech.Model.Mechan.* 2007
Huang, Becker, Jones, *J Mech.Phys.Solids* 2012

Calcium-pectin chemistry

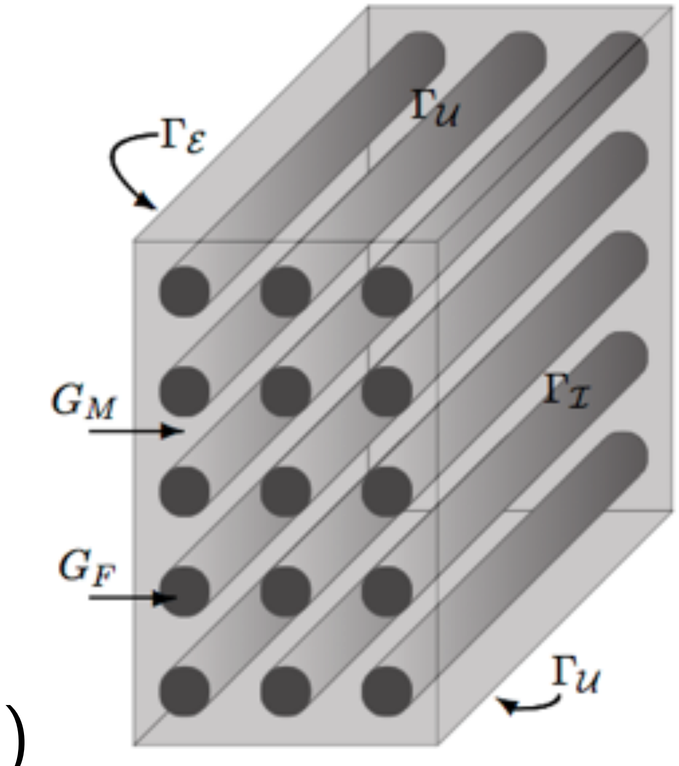
- methylestrified pectin: b_1
- demethylestrified pectin: b_2
- pectin-calcium cross links: b_3
- enzyme PME: p
- calcium ions: c

$$\partial_t n - \operatorname{div}(D_n \nabla n) = g(n, \nabla\mathbf{u})$$

$$n \in \{b_1, b_2, b_3, p, c\}$$



Plant cell walls: mechanics & chemistry



Linear elasticity or viscoelasticity

$$\operatorname{div} \mathbf{T} = 0 \quad \text{in} \quad G, \qquad \mathbf{T}\cdot\mathbf{n} = -P\mathbf{n} \quad \text{on} \quad \partial G$$

$$\mathbf{T} = \left(\mathbb{E}_M(b_3)\chi_{G_M} + \mathbb{E}_F\chi_{G_F}\right)\mathbf{e}(\mathbf{u}_e)$$

$$\mathbf{T} = \left(\mathbb{E}_M(b_3)\,\mathbf{e}(\mathbf{u}_e) + \mathbb{V}_M(b_3)\,\mathbf{e}(\partial_t \mathbf{u}_e)\right)\chi_{G_M} + \mathbb{E}_F\chi_{G_F}\,\mathbf{e}(\mathbf{u}_e)$$

$$\mathbf{e}(\mathbf{u}_e)_{ij} = \tfrac{1}{2}(\partial_{x_i}\mathbf{u}_{e,j} + \partial_{x_j}\mathbf{u}_{e,i})$$

Reaction-diffusion equations for chemical reactions

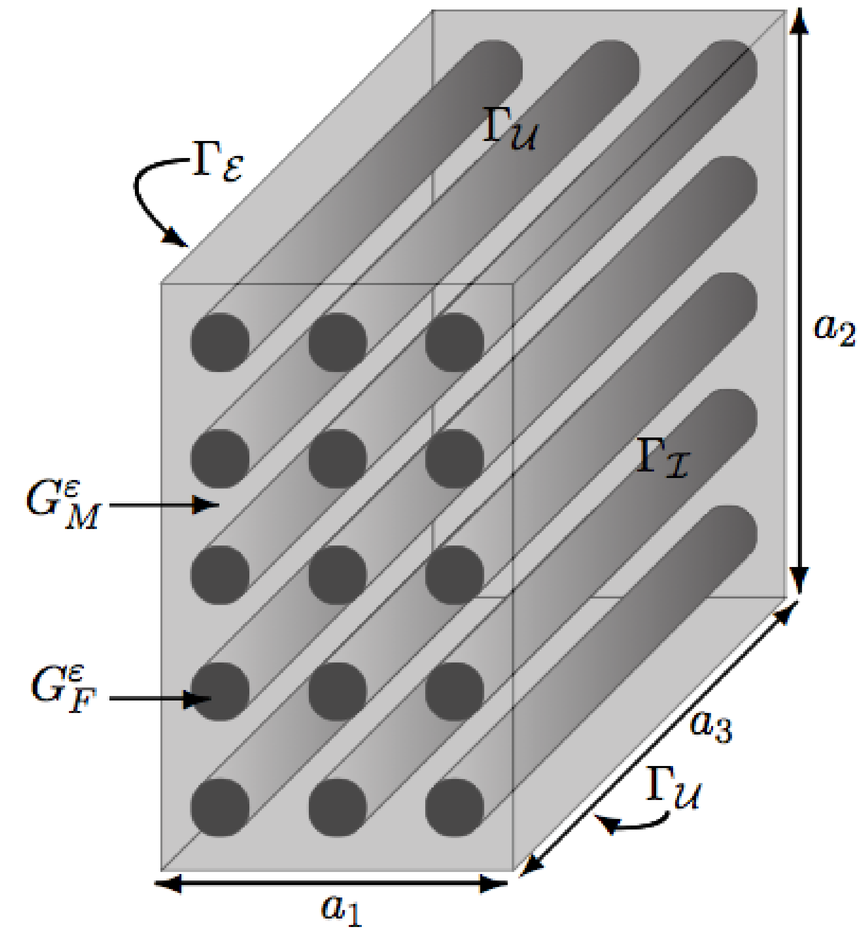
$$\partial_t n - \operatorname{div}(D_n \nabla n) = g_n(n, \mathcal{R}(\mathbf{e}(\mathbf{u}_e)))\,, \qquad n \in \{b_1, b_2, b_3, p, c\}$$

- demethyl-esterification of pectin by PME $\quad \dfrac{\kappa}{1+\beta b_2} b_1\, p$
- demethyl-esterified pectin can decay
- formation and destruction of calcium-pectin cross-links $\quad -2g(c)b_2 + 2\kappa\, b_3\, \mathcal{R}(\mathbf{e}(\mathbf{u}_e))$

$$\mathcal{R}(\mathbf{e}(\mathbf{u}_e)) = \Big(\operatorname{tr}\left(\mathbb{E}_M(b_3)\chi_{G_M} + \mathbb{E}_F\chi_{G_F}\right)\mathbf{e}(\mathbf{u}_e)\Big)^+ \quad \text{or} \quad \mathcal{R}(\mathbf{e}(\mathbf{u}_e)) = (\operatorname{tr}\,\mathbf{e}(\mathbf{u}_e))^+$$

MP, B. Seguin, *ESAIM M2AN*, 2016

Microscopic Model



In $(0,T)\times G$

$$\mathrm{div}(\mathbb{E}^{\varepsilon}(b_3^{\varepsilon},x)\mathbf{e}(\mathbf{u}_e^{\varepsilon}))=\mathbf{0}$$

or

$$\mathrm{div}(\mathbb{E}^{\varepsilon}(b_3^{\varepsilon},x)\mathbf{e}(\mathbf{u}_e^{\varepsilon})+\mathbb{V}^{\varepsilon}(b_3^{\varepsilon},x)\mathbf{e}(\partial_t\mathbf{u}_e^{\varepsilon}))=\mathbf{0}$$

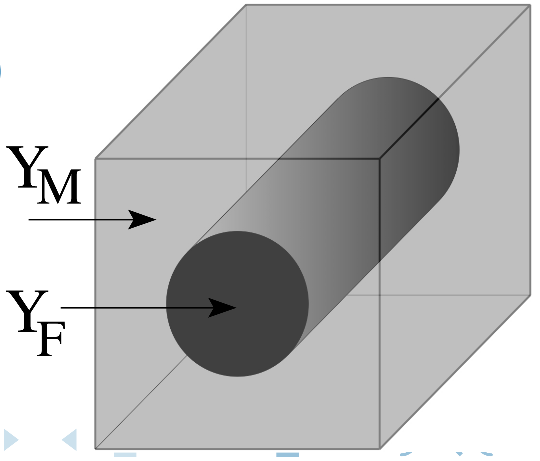
$\mathbb{E}^{\varepsilon}(\xi,x)=\mathbb{E}(\xi,\hat{x}/\varepsilon),\quad \mathbb{V}^{\varepsilon}(\xi,x)=\mathbb{V}(\xi,\hat{x}/\varepsilon)$, where

$\mathbb{E}(\xi,\hat{y})=\mathbb{E}_M(\xi)\,\chi_{\hat{Y}_M}(\hat{y})+\mathbb{E}_F\,\chi_{\hat{Y}_F}(\hat{y}),\quad \mathbb{V}(\xi,\hat{y})=\mathbb{V}_M(\xi)\,\chi_{\hat{Y}_M}(\hat{y})$ are $\hat{Y}$-periodic,

$\hat{Y}=Y\cap\{x_3=\mathrm{const}\}$

In $(0,T)\times G^{\varepsilon}_M$

$$\begin{aligned}
\partial_t p^{\varepsilon} &= \mathrm{div}(D_p\nabla p^{\varepsilon})\\
\partial_t b_1^{\varepsilon} &= \mathrm{div}(D_{b_1}\nabla b_1^{\varepsilon})-f(b_1^{\varepsilon},b_2^{\varepsilon},p^{\varepsilon})\\
\partial_t b_2^{\varepsilon} &= \mathrm{div}(D_{b_2}\nabla b_2^{\varepsilon})+f(b_1^{\varepsilon},b_2^{\varepsilon},p^{\varepsilon})-2g(c^{\varepsilon})b_2^{\varepsilon}+2\kappa\, b_3^{\varepsilon}\,\mathcal{R}(\mathbf{e}(\mathbf{u}_e^{\varepsilon}))\\
\partial_t c^{\varepsilon} &= \mathrm{div}(D_c\nabla c^{\varepsilon})-g(c^{\varepsilon})b_2^{\varepsilon}+\kappa\, b_3^{\varepsilon}\,\mathcal{R}(\mathbf{e}(\mathbf{u}_e^{\varepsilon}))\\
\partial_t b_3^{\varepsilon} &= \mathrm{div}(D_{b_3}\nabla b_3^{\varepsilon})+g(c^{\varepsilon})b_2^{\varepsilon}-\kappa\, b_3^{\varepsilon}\,\mathcal{R}(\mathbf{e}(\mathbf{u}_e^{\varepsilon}))
\end{aligned}$$



Existence of solutions of the model for the cell wall

- For $b^\varepsilon \in L^\infty(0, T; L^\infty(G_M^\varepsilon))$ with $b^\varepsilon \geq 0$

$\exists$ $\mathbf{u}_e^\varepsilon \in L^\infty(0, T; \mathcal{W}(G))$ satisfying elasticity or viscoelasticity problem

$$\|\mathbf{e}(\mathbf{u}_e^{\varepsilon,1} - \mathbf{u}_e^{\varepsilon,2})\|^2_{L^\infty(0,T;L^2(G))} \leq C\|b^{\varepsilon,1} - b^{\varepsilon,2}\|^2_{L^\infty(0,T;L^\infty(G_M^\varepsilon))}$$

- For $\mathbf{u}_e^\varepsilon \in L^\infty(0, T; \mathcal{W}(G))$ such that

$$\|\mathbf{u}_e^\varepsilon\|_{L^\infty(0,T;\mathcal{W}(G))} \leq C,$$

$\exists$ non-negative unique weak solution $(b^\varepsilon, c^\varepsilon)$ such that

$$\|b^{\varepsilon,1} - b^{\varepsilon,2}\|^2_{L^\infty(0,\tilde{T};L^\infty(G_M^\varepsilon))} \leq C\,\tilde{T}\,\|\mathbf{e}(\mathbf{u}_e^{\varepsilon,1} - \mathbf{u}_e^{\varepsilon,2})\|^2_{L^\infty(0,\tilde{T};L^2(G))}, \qquad \tilde{T} \in (0, T]$$

- $\mathcal{K} : L^\infty(G^\varepsilon_{M,\tilde{T}}) \to L^\infty(G^\varepsilon_{M,\tilde{T}})$ by $\mathcal{K}(\tilde{b}^\varepsilon) = b^\varepsilon$

$$\mathcal{W}(G) = \left\{\mathbf{u} \in H^1(G;\mathrm{IR}^3) \;\Big|\; \int_G \mathbf{u}\, dx = \mathbf{0},\ \int_G [(\nabla\mathbf{u})_{12} - (\nabla\mathbf{u})_{21}]dx = \mathbf{0},\ \mathbf{u} \text{ periodic in } x_3\right\}$$

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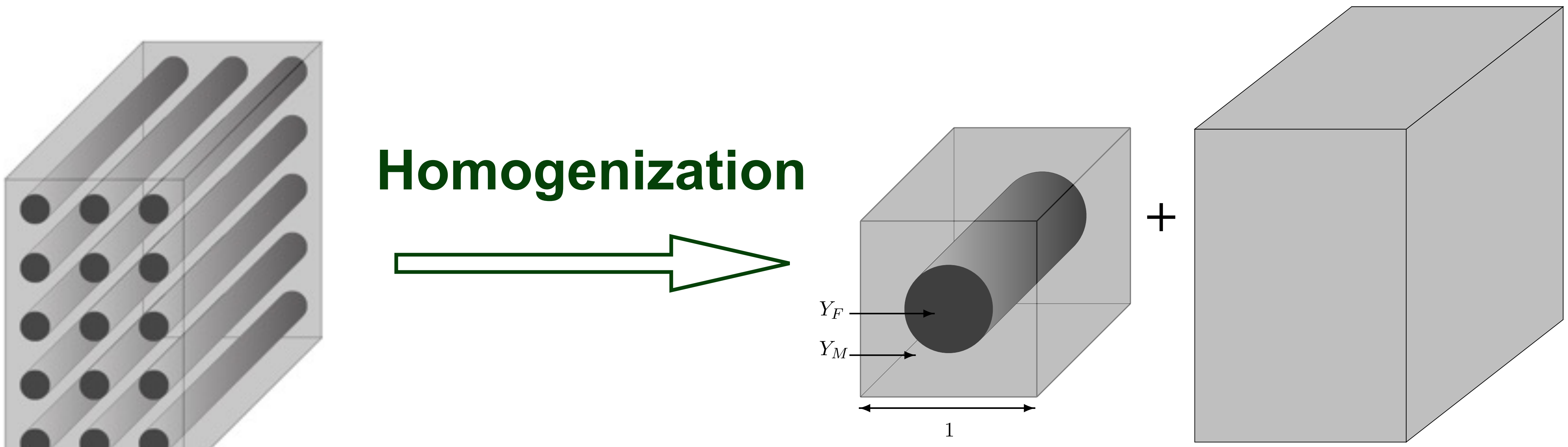
- $\mathcal{K} : L^\infty(G^\varepsilon_{M,\tilde{T}}) \to L^\infty(G^\varepsilon_{M,\tilde{T}})$ by $\mathcal{K}(\tilde{b}^\varepsilon) = b^\varepsilon$

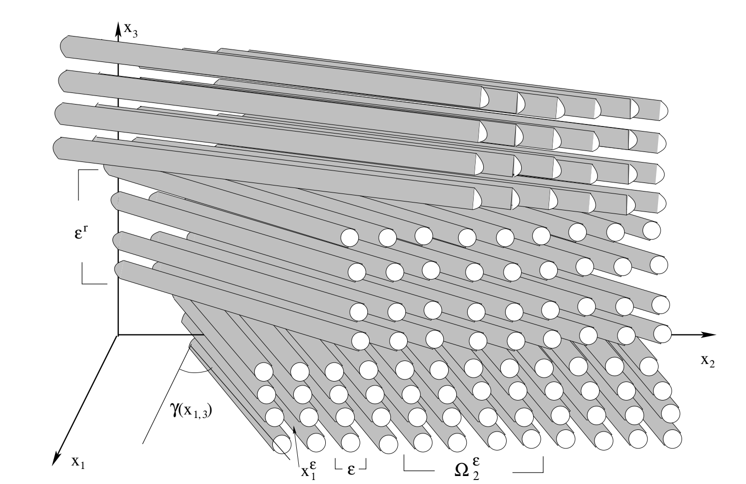
- Main tools: Gagliardo-Nirenberg inequality & Moser-Alikakos iteration technique

Multiscale analysis

Aim of multiscale analysis:

to defined macroscopic behaviour of a biological or physical system by taking microscopic processes and microstructure into account



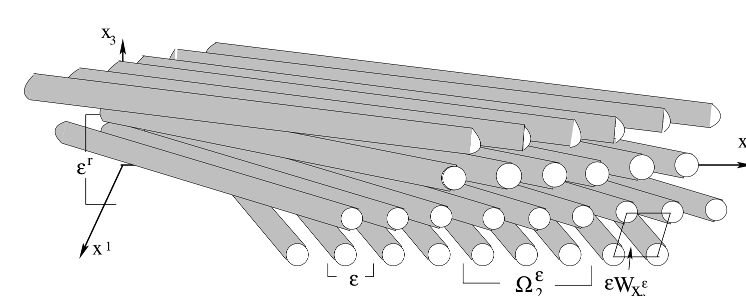


Microstructures:

- Periodic or locally-periodic microstructures
- Stochastic microstructures

Methods:

- formal asymptotic expansion
- two-scale convergence
- H- , Γ- , and G- convergences
- periodic and locally-periodic unfolding operators



Two-scale convergence

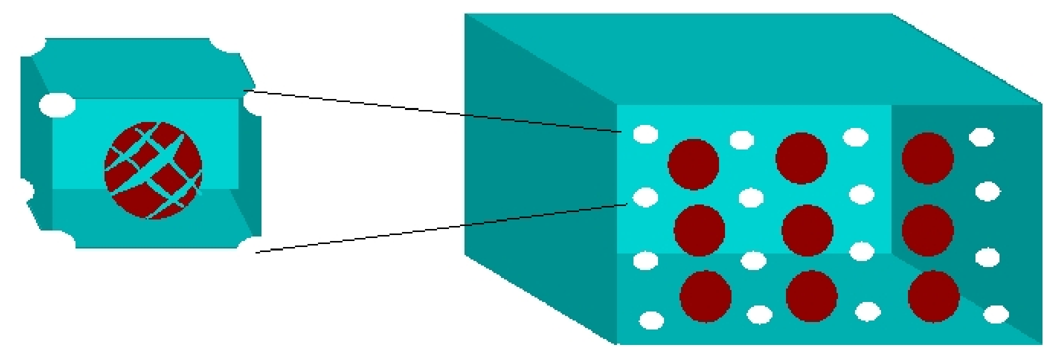
- A special type of convergence in L^p, $1 < p < \infty$ and $1/p + 1/q = 1$

Definition. $\{u^\varepsilon\} \subset L^p(\Omega)$ two-scale converge to u, $u \in L^p(\Omega \times Y)$ iff for any $\phi \in L^q(\Omega, C_{per}(Y))$

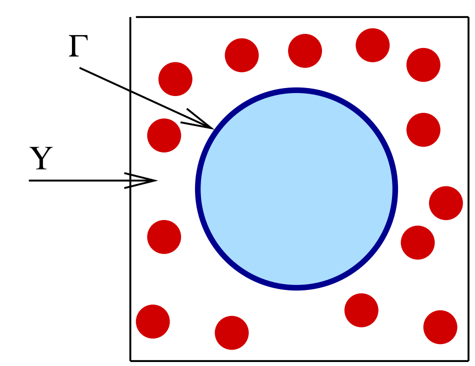
$$\lim_{\varepsilon \to 0} \int_\Omega u^\varepsilon(x)\phi\left(x, \frac{x}{\varepsilon}\right) dx = \int_\Omega \fint_Y u(x,y)\phi(x,y)dxdy.$$

Notice:

$$u^\varepsilon \rightharpoonup \fint_Y u(\cdot, y)dy \quad \text{weakly in} \quad L^p(\Omega)$$



Definition. $\{u^\varepsilon\} \subset L^2(\Gamma^\epsilon)$ two-scale converge to u, $u \in L^2(\Omega \times \Gamma)$ iff for $\psi \in C(\overline{\Omega}, C_{per}(Y))$:



$$\lim_{\varepsilon \to 0} \varepsilon \int_{\Gamma^\varepsilon} u^\epsilon(x)\psi(x, x/\varepsilon)d\gamma_x = \frac{1}{|Y|}\int_\Omega \int_\Gamma u(x,y)\psi(x,y)dxd\gamma_y.$$

Convergence results

$$b, c \in L^2(0,T;H^1(G)), \qquad c^1, b^1 \in L^2(G_T;H^1_{\mathrm{per}}(\hat{Y}))$$

$$\mathbf{u}_e \in L^\infty(0,T;\mathcal{W}(G)), \qquad \mathbf{u}_e^1 \in L^2(G_T;H^1_{\mathrm{per}}(\hat{Y}))$$

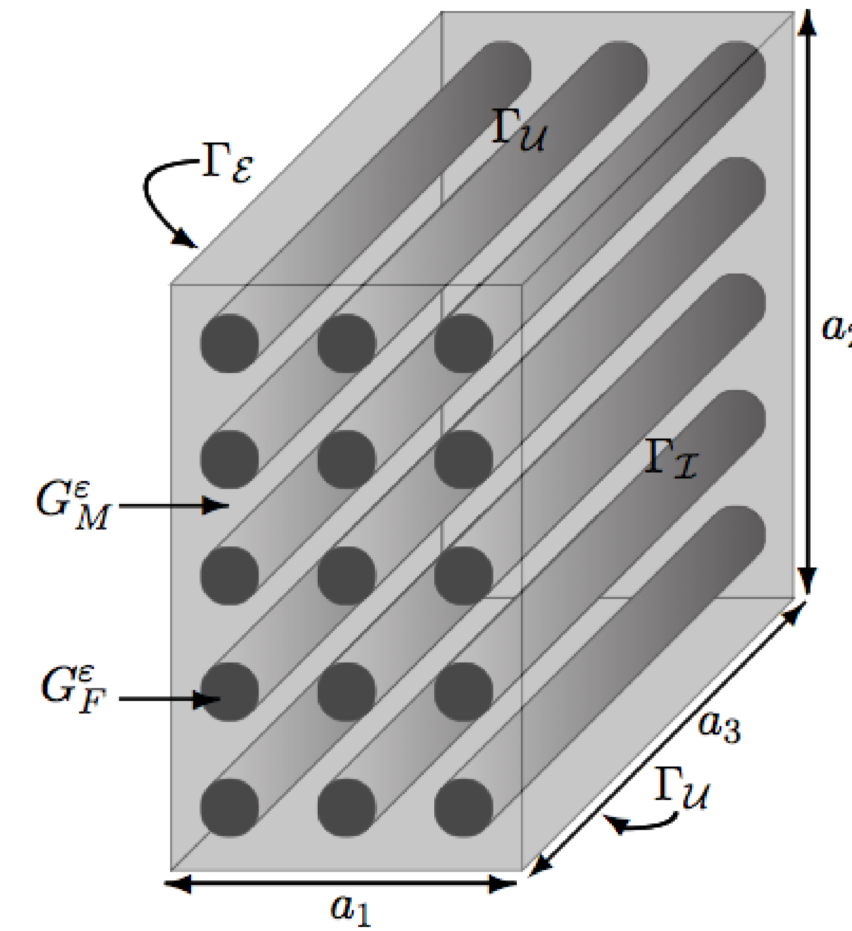
$$\begin{array}{ll} b^\varepsilon \rightharpoonup b, \quad c^\varepsilon \rightharpoonup c & \text{weakly in } L^2(0,T;H^1(G)) \\ \nabla b^\varepsilon \rightharpoonup \nabla b + \hat{\nabla}_y b^1, \quad \nabla c^\varepsilon \rightharpoonup \nabla c + \hat{\nabla}_y c^1 & \text{weakly two-scale} \\ b^\varepsilon \to b, \quad c^\varepsilon \to c & \text{strongly in } L^2(G_T) \end{array}$$

$$\begin{array}{ll} \mathbf{u}_e^\varepsilon \rightharpoonup \mathbf{u}_e & \text{weakly}^* \text{ in } L^\infty(0,T;\mathcal{W}(G)) \\ \nabla \mathbf{u}_e^\varepsilon \rightharpoonup \nabla \mathbf{u}_e + \hat{\nabla}_y \mathbf{u}_e^1 & \text{weakly two-scale} \end{array}$$

$$\mathbf{e}(\mathbf{u}_e^\varepsilon) \to \mathbf{e}(\mathbf{u}_e) + \mathbf{e}_y(\mathbf{u}_e^1) \qquad \text{strongly two-scale}$$

$$\hat{Y} = Y \cap \{x_3 = \mathrm{const}\}, \qquad G_T = (0,T) \times G$$

Microscopic Model



In $(0, T) \times G$

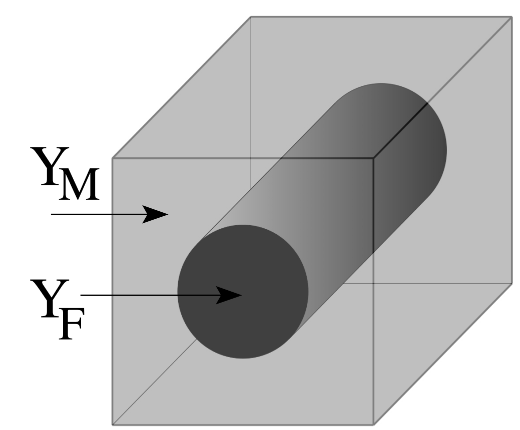
$$\operatorname{div}(\mathbb{E}^\varepsilon(b^\varepsilon, x)\mathbf{e}(\mathbf{u}_e^\varepsilon)) = \mathbf{0}$$

or

$$\operatorname{div}(\mathbb{E}^\varepsilon(b^\varepsilon, x)\mathbf{e}(\mathbf{u}_e^\varepsilon) + \mathbb{V}^\varepsilon(b^\varepsilon, x)\mathbf{e}(\partial_t \mathbf{u}_e^\varepsilon)) = \mathbf{0}$$

In $(0, T) \times G_M^\varepsilon$

$$\partial_t b^\varepsilon = \operatorname{div}(D_b \nabla b^\varepsilon) + g_b(b^\varepsilon, c^\varepsilon, \mathcal{R}(\mathbf{e}(\mathbf{u}_e^\varepsilon)))$$
$$\partial_t c^\varepsilon = \operatorname{div}(D_c \nabla c^\varepsilon) + g_c(b^\varepsilon, c^\varepsilon, \mathcal{R}(\mathbf{e}(\mathbf{u}_e^\varepsilon)))$$



$$\mathcal{R}(\mathbf{e}(\mathbf{u}_e^\varepsilon)) = \Big(\operatorname{tr}\left(\mathbb{E}_M(b^\varepsilon)\chi_{G_M} + \mathbb{E}_F\chi_{G_F}\right)\mathbf{e}(\mathbf{u}_e^\varepsilon)\Big)^+ \quad \text{or} \quad \mathcal{R}(\mathbf{e}(\mathbf{u}_e^\varepsilon)) = (\operatorname{tr}\,\mathbf{e}(\mathbf{u}_e^\varepsilon))^+$$

Numerical simulations for plant cell wall model

Macroscopic model for plant cell wall biomechanics

$$\mathrm{div}(\mathbb{E}_{\mathrm{hom}}(b_3)\,\mathbf{e}(\mathbf{u}_e)) = \mathbf{0} \qquad \text{in } G_T$$

$$\begin{aligned} \partial_t b &= \mathrm{div}(\mathcal{D}_b \nabla b) + g_b(b, c, R(\mathbf{e}(\mathbf{u}_e))) \qquad &\text{in } G_T \\ \partial_t c &= \mathrm{div}(\mathcal{D}_c \nabla c) + g_c(b, c, R(\mathbf{e}(\mathbf{u}_e))) \qquad &\text{in } G_T \end{aligned}$$

$$R(\mathbf{e}(\mathbf{u}_e)) = \Big(\mathrm{tr}\big(\mathbb{E}_{\mathrm{hom}}(b_3)\,\mathbf{e}(\mathbf{u}_e)\big)\Big)^+ \quad \text{or} \quad \big(\mathrm{tr}\,\mathbf{e}(\mathbf{u}_e)\big)^+$$

$$\mathcal{D}_{\alpha,j3} = \mathcal{D}_{\alpha,3j} = D_\alpha \delta_{3j}, \quad \mathcal{D}_{\alpha,ij} = D_\alpha \fint_{\hat{Y}_M} \big[\delta_{ij} + \partial_{y_j} v_\alpha^i(y)\big]\,dy,$$

$$\alpha = b_1, b_2, b_3, c$$

$$\mathbb{E}_{\mathrm{hom},ijkl}(b_3) = \fint_Y \big[\mathbb{E}_{ijkl}(b_3, y) + \big(\mathbb{E}(b_3, y)\mathbf{e}_y(\mathbf{w}^{ij})\big)_{kl}\big]\,dy$$

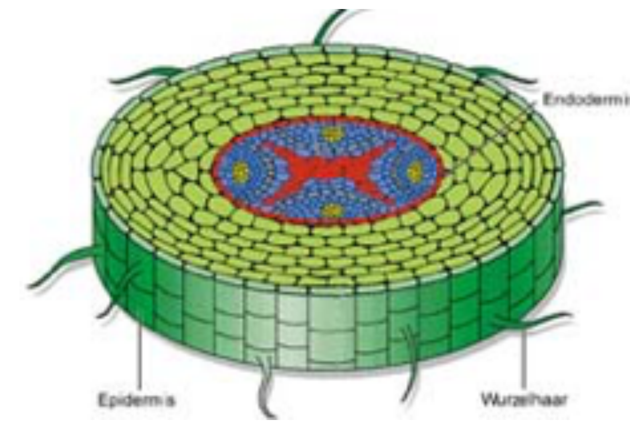
MP, B. Seguin, *ESAIM M2AN*, 2016

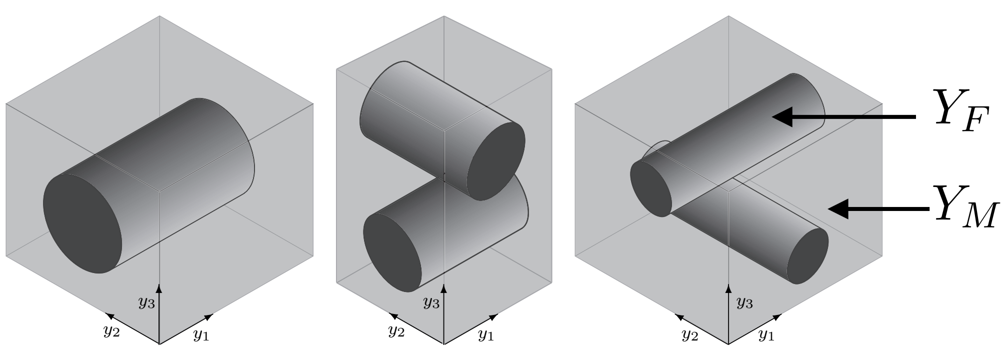
Macroscopic elasticity tensor

$$\mathbb{E}_{\mathrm{hom},ijkl}(x,b_3) = \fint_Y \left[\mathbb{E}_{Y,ijkl}(b_3,y) + \mathbb{E}_{Y,ijpq}(b_3,y)\mathbf{e}_y(\mathbf{w}^{kl})_{pq}(y)\right] dy$$

$$\mathrm{div}_y\big(\mathbb{E}_Y(b_3,y)(\mathbf{e}_y(\mathbf{w}^{kl}) + \mathbf{b}^{kl})\big) = \mathbf{0} \qquad \text{in } Y$$

$$\int_Y \mathbf{w}^{kl}\, dy = \mathbf{0}, \qquad \mathbf{w}^{kl} \text{ is } Y\text{-periodic}$$



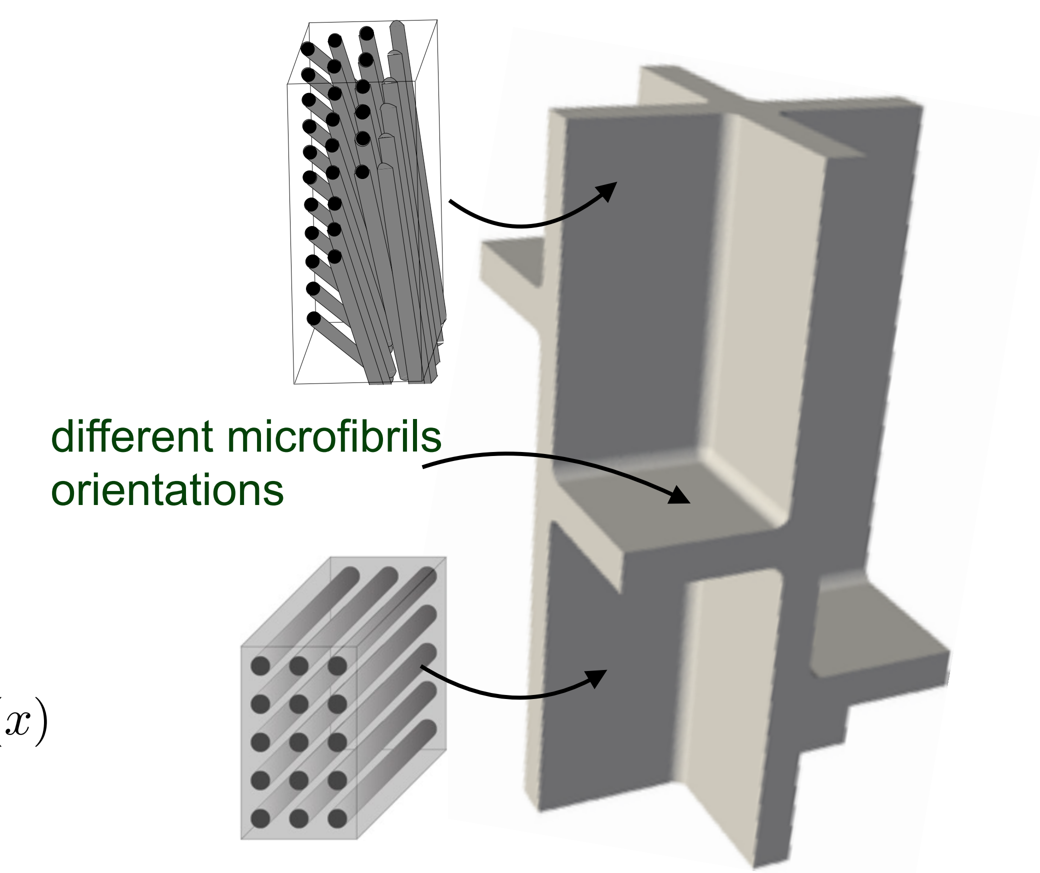


$$\mathbb{E}_Y(b_3,y) = \begin{cases} \mathbb{E}_M(b_3) & \text{if } y \in Y_M \\ \mathbb{E}_F & \text{if } y \in Y_F \end{cases}$$

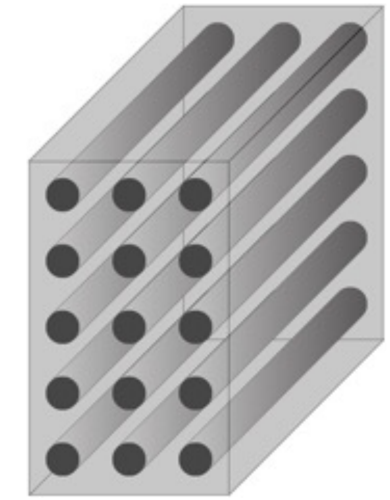
Continuous rotation of microfibrils in cell walls

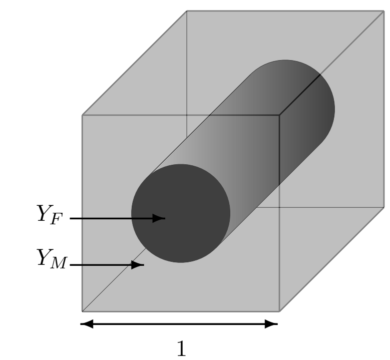
$$\mathbb{E}^{\theta}_{\mathrm{hom},ijkl} = \mathbf{R}^{\theta}_{ip}\mathbf{R}^{\theta}_{jq}\mathbf{R}^{\theta}_{kr}\mathbf{R}^{\theta}_{ls}\mathbb{E}_{\mathrm{hom},pqrs}$$

$$\mathbf{R}^{\theta} = \begin{pmatrix} \cos(\theta) & 0 & \sin(\theta) \\ 0 & 1 & 0 \\ -\sin(\theta) & 0 & \cos(\theta) \end{pmatrix}, \qquad \mathbf{R}^{\theta} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos(\theta) & -\sin(\theta) \\ 0 & \sin(\theta) & \cos(\theta) \end{pmatrix}, \qquad \theta = \theta(x)$$



Macroscopic elasticity tensor for cell wall





$$\mathbb{E}(y,b_3) = \mathbb{E}_M(b_3)\ \chi_{Y_M}(y) + \mathbb{E}_F \chi_{Y_F}(y)$$

Cell wall matrix is assumed to be isotropic

$$\mathbb{E}_M(b_3) = E_M(b_3)\ \mathbb{E}_1 + \mathbb{E}_0 \longrightarrow \mathbb{E}_{\text{hom}}(b_3) = E_M(b_3)\ \mathbb{E}_{\text{hom},1} + \mathbb{E}_{\text{hom},0}$$

$$\mathbb{E}_M \mathbf{A} = 2\mu_M \mathbf{A} + \lambda_M (\operatorname{tr} \mathbf{A})\mathbf{1}$$

Lame moduli μ_M λ_M

$$E_M = \frac{\mu_M(2\mu_M + 3\lambda_M)}{\mu_M + \lambda_M} \quad \text{and} \quad \nu_M = \frac{\lambda_M}{2(\mu_M + \lambda_M)}$$

$E_M(b_3) = 0.775\ b_3 + 8.08$ MPa

(Zsivanovits, MacDougall, Smith, Ring Carbohydrate Research, 2004)

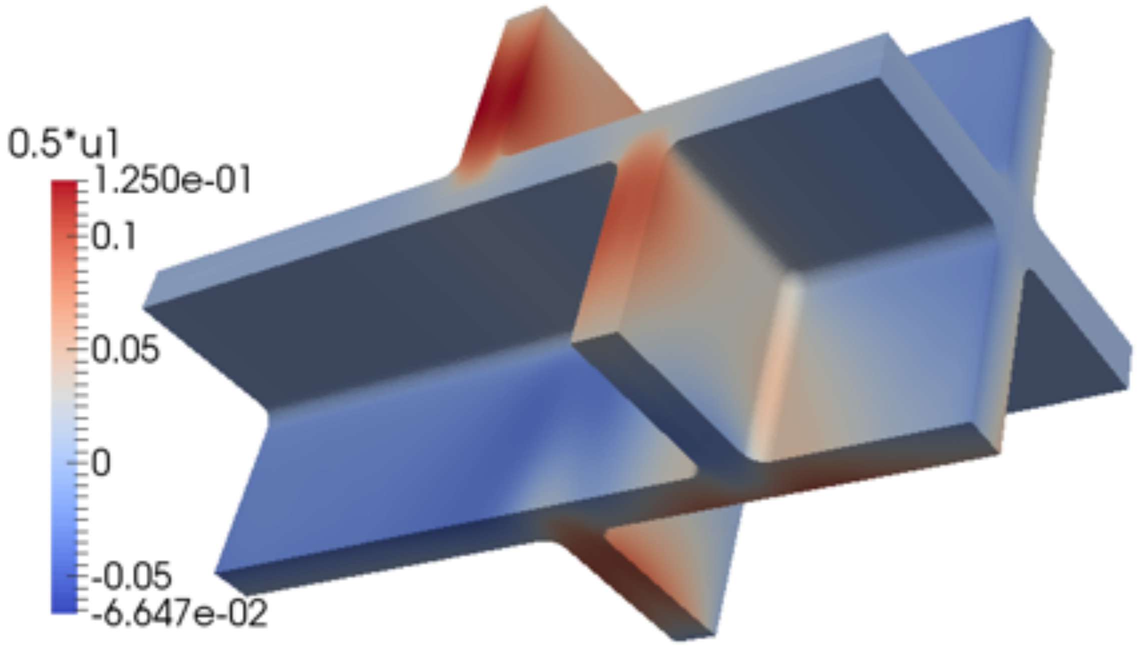
Microfibrils are transversally isotropic

$$\begin{pmatrix} \alpha_2+\alpha_5 & \alpha_2-\alpha_5 & \alpha_3 & 0 & 0 & 0 \\ \alpha_2-\alpha_5 & \alpha_2+\alpha_5 & \alpha_3 & 0 & 0 & 0 \\ \alpha_3 & \alpha_3 & \alpha_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & \alpha_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & \alpha_5 \end{pmatrix} \qquad \begin{pmatrix} 18393 & 6855 & 22277 & 0 & 0 & 0 \\ 6855 & 18393 & 22277 & 0 & 0 & 0 \\ 22277 & 22277 & \underline{259901} & 0 & 0 & 0 \\ 0 & 0 & 0 & 84842 & 0 & 0 \\ 0 & 0 & 0 & 0 & 84842 & 0 \\ 0 & 0 & 0 & 0 & 0 & 5769 \end{pmatrix}$$

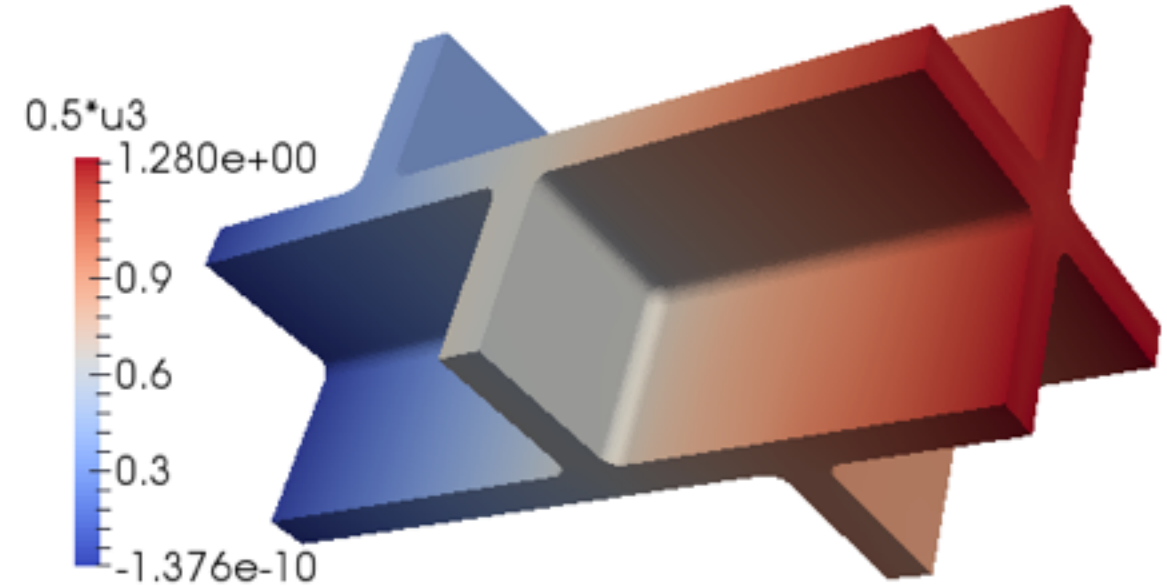
$$E_F = 15{,}000\,\text{MPa},\ \nu_{F1} = 0.3,\ n_F = 0.068,\ \nu_{F2} = 0.06,\ Z_F = 84{,}842\,\text{MPa}.$$

(Robert Moon, Review Wisconsin 2013-2014, Diddens et al., 2008)

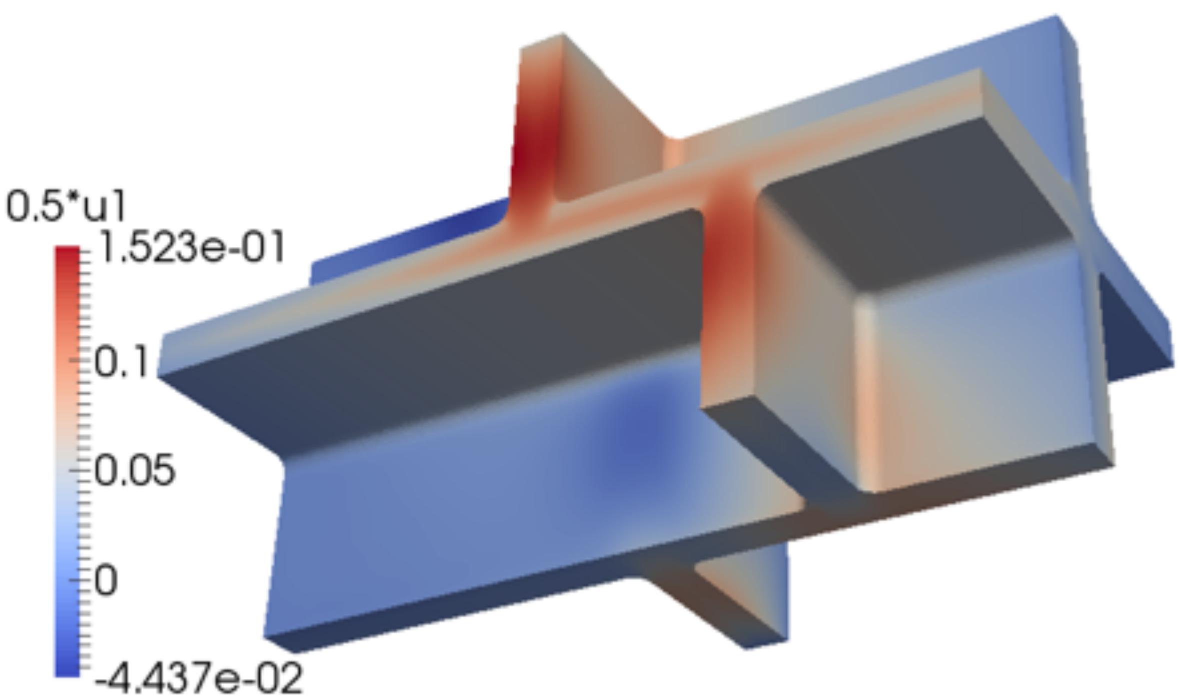
Impact of the orientation of microfibrils



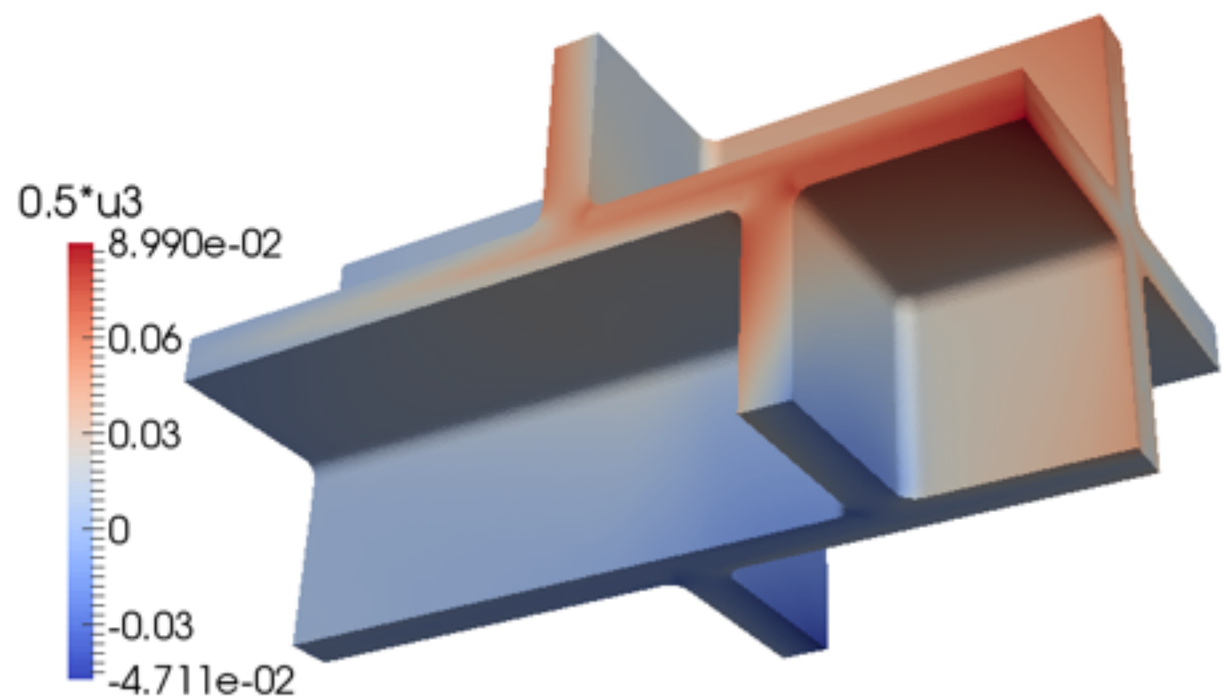
(BC1), (C1), parallel microfibrils



(BC1), (C1), parallel microfibrils



(BC1), (C1), rotating microfibrils



(BC1), (C1), rotating microfibrils

(BC1) Base case: $p = p_{\circ,1} = 0.209$ MPa and $f = 2.938 p_{\circ,1}$ MPa

MP, B. Seguin, *Bull Math Biology*, 2016

Comparison with experimental results on tissue extension and compression

RD	(BC1) parallel MF	(BC1) no shift	(BC1) 4 shifts	(BC1) rotated MF	(BC2)	(BC3)
(C1)	1.06497	1.06396	1.06984	1.00456	1.00683	1.00816
(C2)	1.06452	1.06391		1.00462	1.00671	1.00823
(C3)	1.06234	1.06294	1.06680	1.00379	1.00672	1.00831
(C4)	1.06411	1.06320		1.00497	1.00696	1.00811

Good agreement with experimental data on changes in inner or outer tissue length due to tissue tension elimination, Hejnowicz, Sievers, *J Exp.Botany* 1995:

relative displacement (RD) ranging between 0.38% and 6.98%
versus experimental data: 0.3% - 4.99%

(BC1) Base case: $p = p_{\circ,1} = 0.209$ MPa and $f = 2.938 p_{\circ,1}$ MPa

(BC2) No tensile tractions: $p = p_{\circ,1}$ and $f = 0$

(BC3) Different turgor pressures in neighbouring cells and no tensile tractions: $p_1 = p_4 = p_5 = p_8 = p_\circ$ and $p_2 = p_3 = p_6 = p_7 = 1.3 p_{\circ,1}$, where p_i, for $i = 1, \ldots, 8$, is the pressure in cell i, and $f = 0$

MP, B. Seguin, *Bull Math Biology*, 2016

Intercellular transport of signalling molecules

Signalling molecules interact with cells

- as a ligand for membrane receptors
- and/or by entering into the cell through its membrane or endocytosis

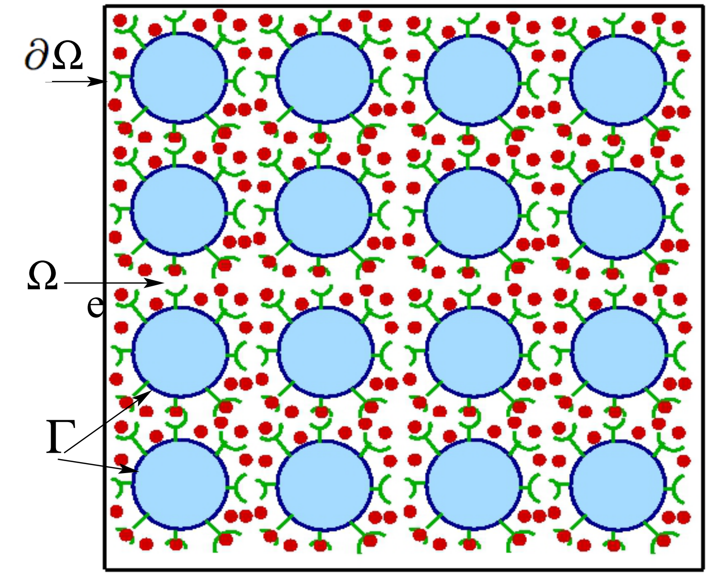
$$C + R_f \underset{a_e}{\overset{b_e}{\rightleftharpoons}} R_b$$

- Diffusion of signalling molecules c and s in the extra- and intracellular spaces
- Diffusion of free and bound receptors r_f and r_b and of active and inactive co-receptors (proteins) p_a and p_d on cell membrane
- Ligands c bind to r_f to produce r_b and s interact with p_a
- Bound receptors r_b dissociate into free receptors and ligands
  Active co-receptors (proteins) p_a dissociate into inactive co-receptors (proteins) and bound receptors

Mathematical model for intercellular signalling

- Diffusion, production and decay of ligands in extracellular space

$$\begin{aligned} &\partial_t c = \nabla \cdot (D_e(x)\nabla c) + F_e(c) && \text{in} \quad \Omega_e, \; t > 0 \\ &D_e(x)\nabla c \cdot \nu = 0 && \text{on} \quad \partial\Omega, \; t > 0 \\ &c(0) = c_0 && \text{in} \quad \Omega_e \end{aligned}$$



- Equations for the receptors on the cell surface Γ

$$\begin{aligned} &\partial_t r_f = D_f \, \Delta_\Gamma r_f + F_r(r_f, r_b) - a_e(x)\, r_f \, c + b_e(x)\, r_b - d_f \, r_f && \text{on} \quad \Gamma, \; t > 0 \\ &\partial_t r_b = D_b \, \Delta_\Gamma r_b + a_e(x)\, r_f \, c - b_e(x)\, r_b - d_b \, r_b && \text{on} \quad \Gamma, \; t > 0 \end{aligned}$$

- Binding on the cell surfaces

$$D_e(x)\, \nabla c \cdot \nu = - a_e(x)\, c\, r_f + b_e(x)\, r_b \qquad \text{on} \quad \Gamma$$

- Activation of an intracellular signalling pathway by r_b

c, r_f, r_b	density of ligands/receptors,	d_f, d_b	rate of decay of ligands/receptors
F_e, F_r	product. of ligands/receptors,	D_e, D_f, D_b	diffusion coefficients

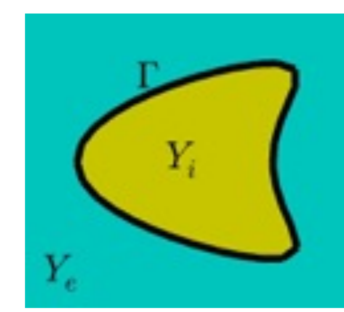
Microscopic model for signalling processes

- Diffusion, production and decay of signalling molecules

$$\begin{aligned} \partial_t c &= \nabla \cdot (D_e^\varepsilon(x)\nabla c) + F_e(c) && \text{in } \Omega_e^\varepsilon,\ t > 0 \\ \partial_t s &= \varepsilon^2 \nabla \cdot (D_i^\varepsilon(x)\nabla s) + F_i(s) && \text{in } \Omega_i^\varepsilon,\ t > 0 \end{aligned}$$

- Equations for the receptors /proteins on the cell surface Γ^ε

$$\begin{aligned} \partial_t r_f &= \varepsilon^2 D_f \Delta_\Gamma r_f - G_e(c, r_f, r_b) + F_r(r_f, r_b) - d_f\, r_f \\ \partial_t r_b &= \varepsilon^2 D_b \Delta_\Gamma r_b + G_e(c, r_f, r_b) - G_d(r_b, p_d, p_a) - d_b\, r_b \\ \partial_t p_d &= \varepsilon^2 D_d \Delta_\Gamma p_d - G_d(r_b, p_d, p_a) + F_d(p_d) - d_d\, p_d \\ \partial_t p_a &= \varepsilon^2 D_a \Delta_\Gamma p_a + G_d(r_b, p_d, p_a) - G_i(p_a, s) - d_a\, p_a \end{aligned}$$

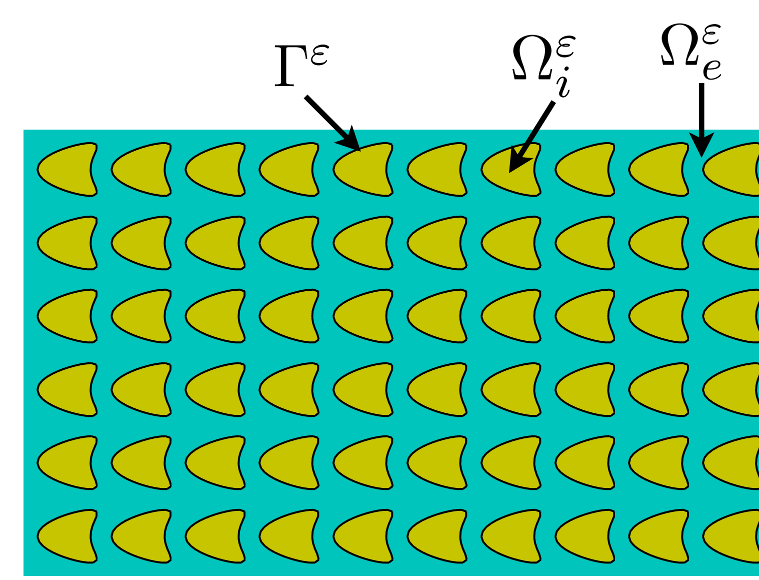


- Binding on the cell surfaces Γ^ε

$$\begin{aligned} D_e^\varepsilon(x)\, \nabla c \cdot \nu &= -\varepsilon G_e(c, r_f, r_b) && \text{on } \Gamma^\varepsilon,\ t > 0 \\ \varepsilon^2 D_i^\varepsilon(x)\, \nabla s \cdot \nu &= \varepsilon G_i(p_a, s) && \text{on } \Gamma^\varepsilon,\ t > 0 \end{aligned}$$

- Binding reactions

$$\begin{aligned} G_e(c, r_f, r_b) &= a_e^\varepsilon(x)\, c\, r_f - b_e^\varepsilon(x)\, r_b \\ G_d(r_b, p_d, p_a) &= a_i(x)\, r_b\, p_d - b_i^\varepsilon(x)\, p_a \\ G_i(p_a, s) &= \gamma_i^\varepsilon(x)\, p_a - \kappa_i^\varepsilon(x)\, s \end{aligned}$$



Macroscopic equations

- Macroscopic concentrations

$$\partial_t c - \nabla \cdot (D_e^{\mathrm{hom}} \nabla c) = F_e(c) - \frac{1}{|Y_e|} \int_\Gamma G_e(c, r_f, r_b)\, d\gamma_y \qquad \text{in } \ \Omega_T$$

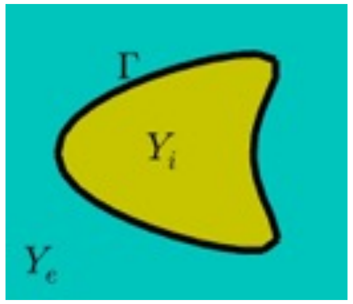
$$\partial_t s - \nabla_y \cdot (D_i(y) \nabla_y s) = F_i(s) \qquad \text{in } \ \Omega_T \times Y_i$$

- Receptors distribution on the cell surface on $\Omega_T \times \Gamma$

$$\partial_t r_f = D_f \Delta_{\Gamma,y} r_f - G_e(c, r_f, r_b) + F_r(r_f, r_b) \quad - d_f\, r_f$$

$$\partial_t r_b = D_b \Delta_{\Gamma,y} r_b + G_e(c, r_f, r_b) - G_d(r_b, p_d, p_a) - d_b\, r_b$$

$$+ \text{ equations for } p_a,\ p_d$$



- Macroscopic coefficients

$$D_{e,ij}^{\mathrm{hom}}(x) = \frac{1}{|Y_e|} \sum_{k=1}^{3} \int_{Y_e} \left(D_{e,ij}(x,y) + D_{e,ik}(x,y) \partial_{y_k} w_j \right) dy$$

where

$$-\nabla_y \cdot (D_e(x,y)(\nabla_y w^j + e_j)) = 0 \text{ in } Y_e,$$

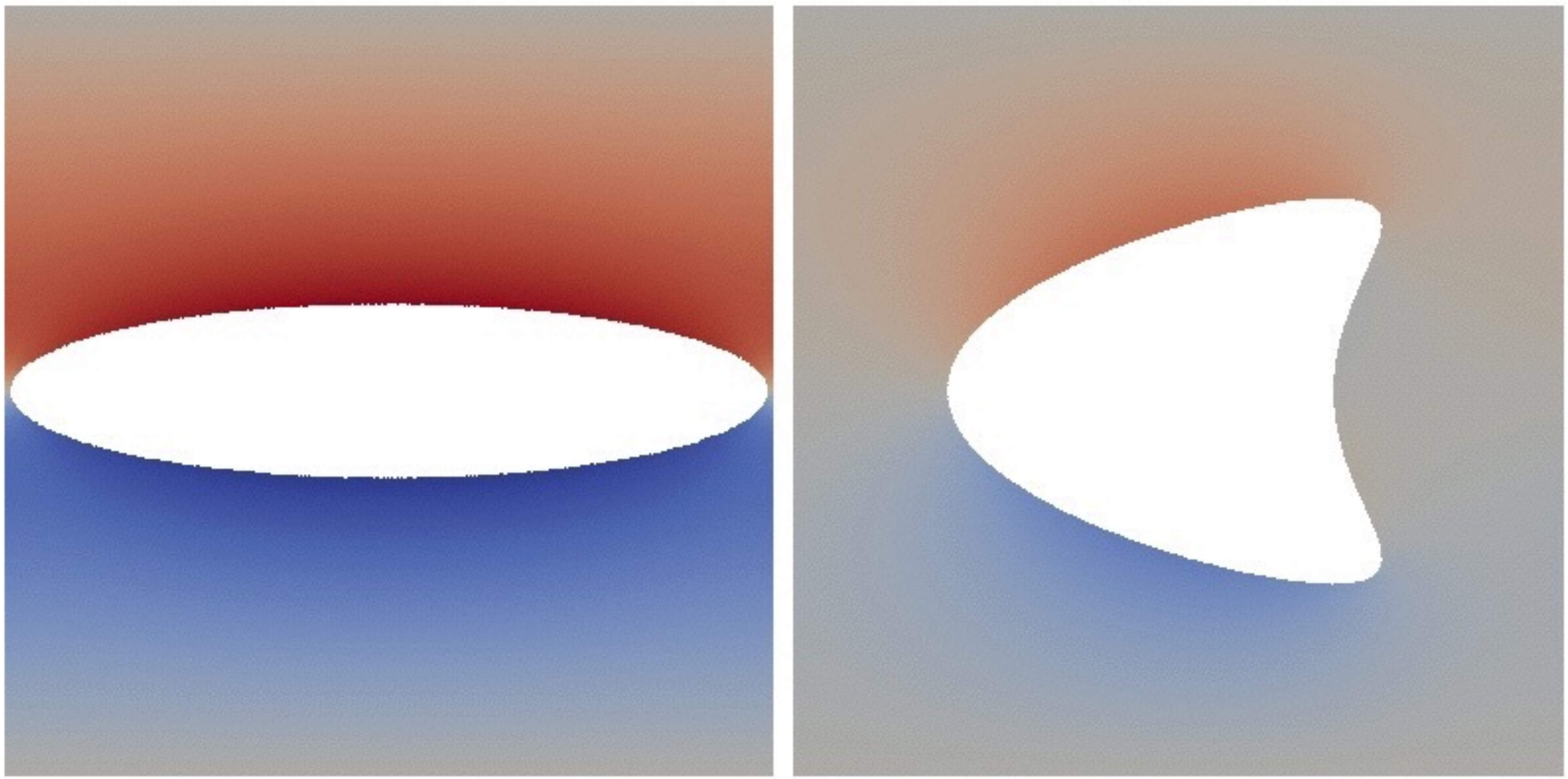
$$-D_e(x,y)(\nabla_y w^j + e_j) \cdot \nu = 0 \text{ on } \Gamma, \quad w^j \quad Y - \text{periodic}$$

$$\Omega_T = (0, T) \times \Omega$$

MP, C. Venkataraman, *arXiv* 2018

Multiscale numerical simulations

$$\mathrm{div}_y(D_e^*(\nabla_y w^j + e_j)) = 0 \quad \text{in } Y_e, \quad \int_{Y_e} w^j(y)dy = 0,$$
$$D_e^*(\nabla_y w^j + e_j)\cdot\nu = 0 \quad \text{on } \Gamma, \quad w^j \quad Y - \text{periodic}$$

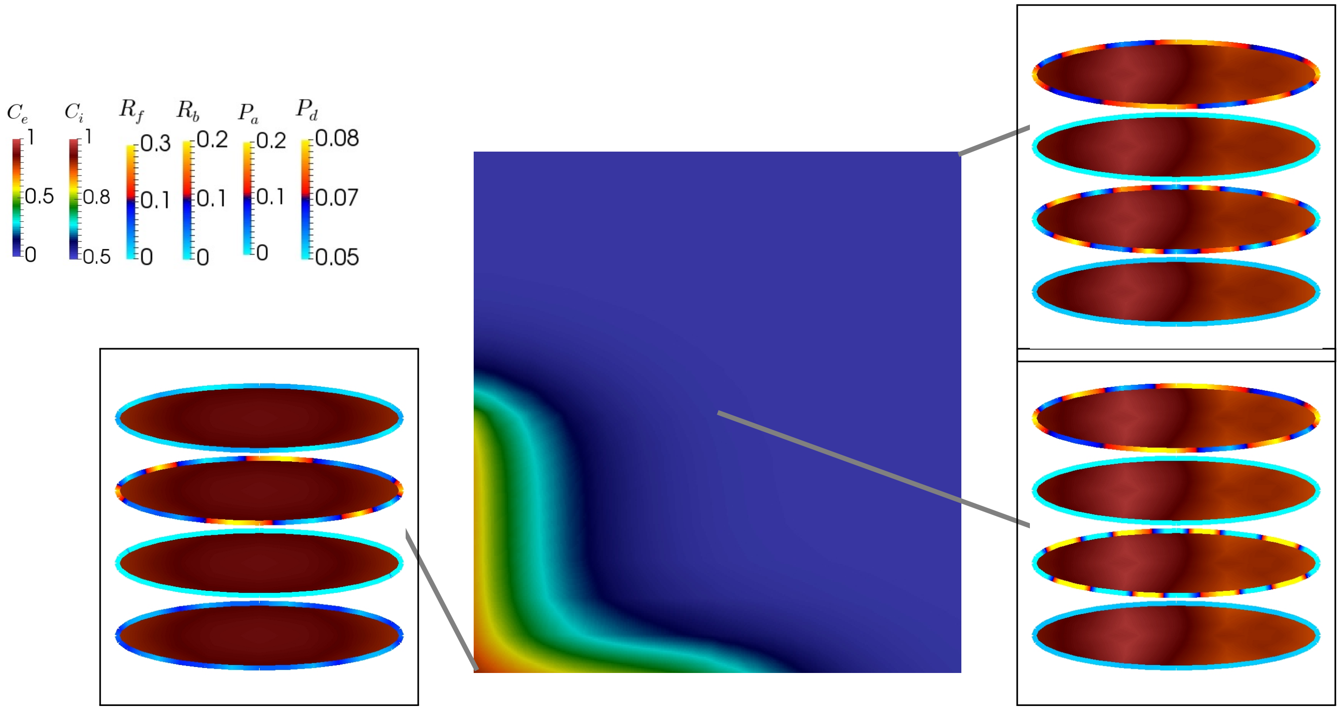


$$D_{h,e}^{\mathrm{hom}} = \begin{bmatrix} 8.167\cdot 10^{-3} & 0 \\ 0 & 1.841\cdot 10^{-3} \end{bmatrix} \qquad D_{h,e}^{\mathrm{hom}} = \begin{bmatrix} 6.556\cdot 10^{-3} & 0 \\ 0 & 6.149\cdot 10^{-3} \end{bmatrix}$$

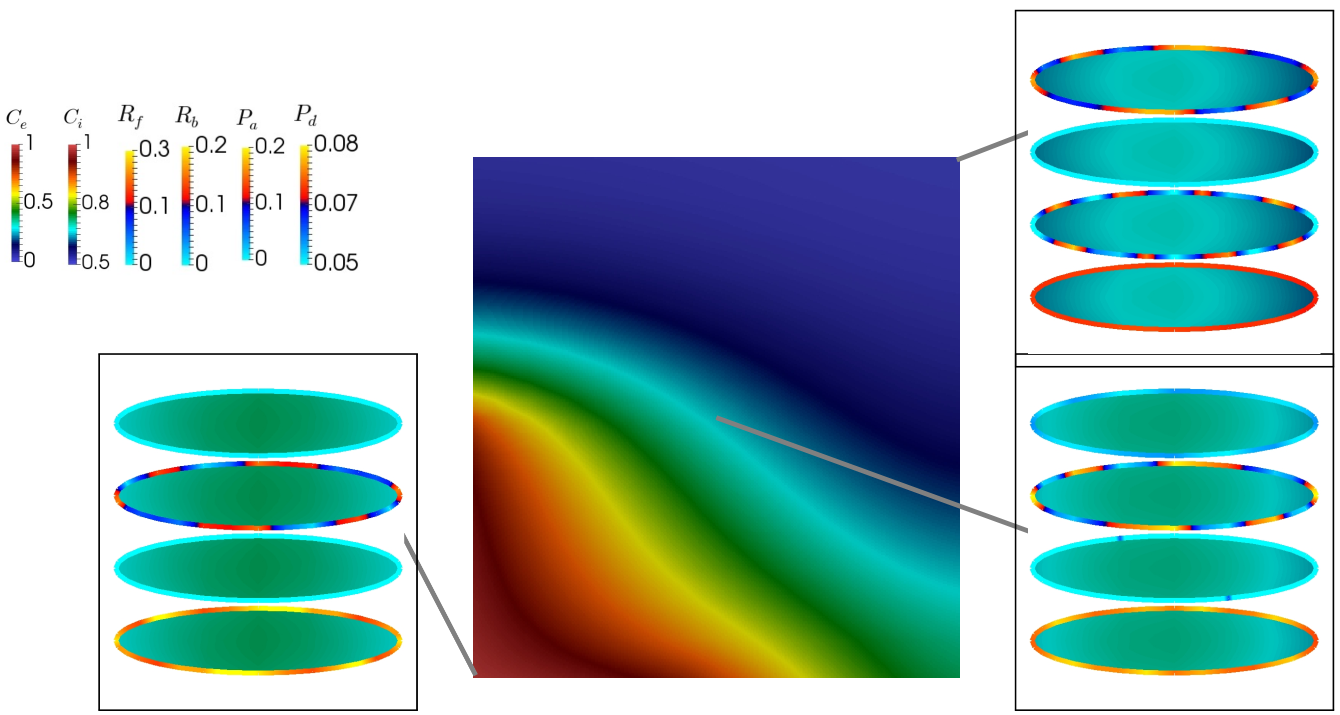
$D_e^* = 10^{-2}, \quad D_i^* = 10, \quad D_f^* = D_b^* = D_d^* = D_a^* = 10^{-2}$

MP, C. Venkataraman, *arXiv* 2018

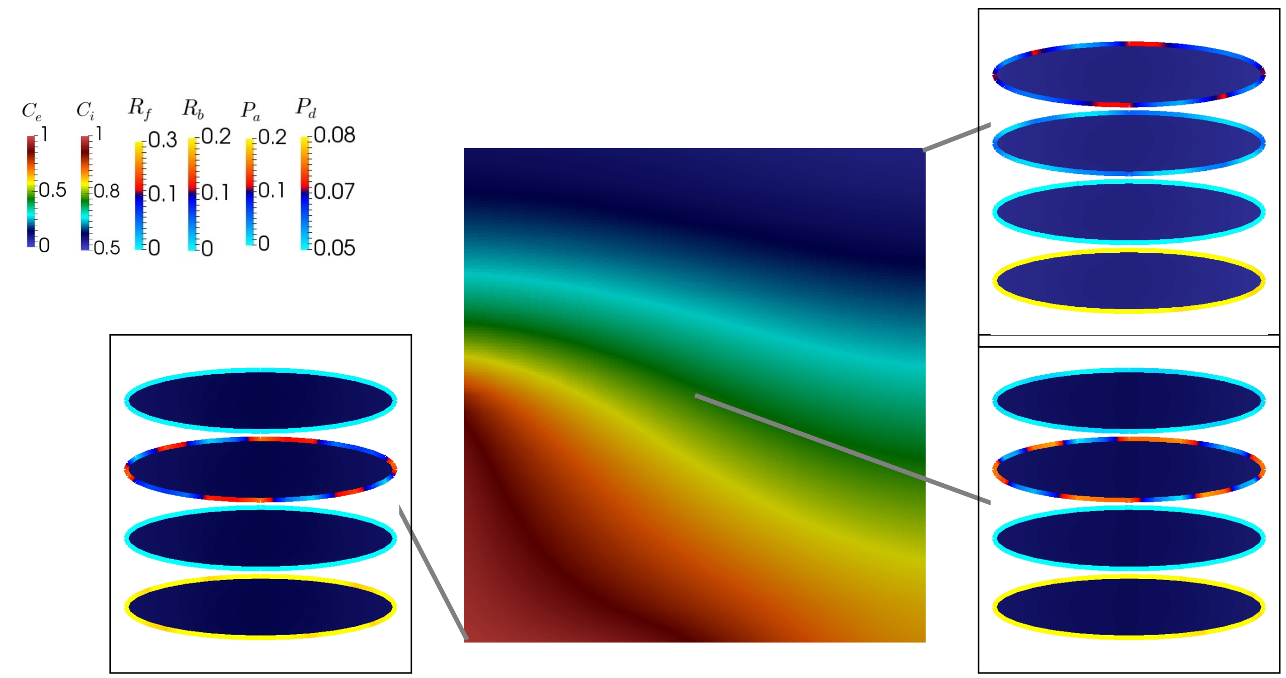
Effect of anisotropic microstructure



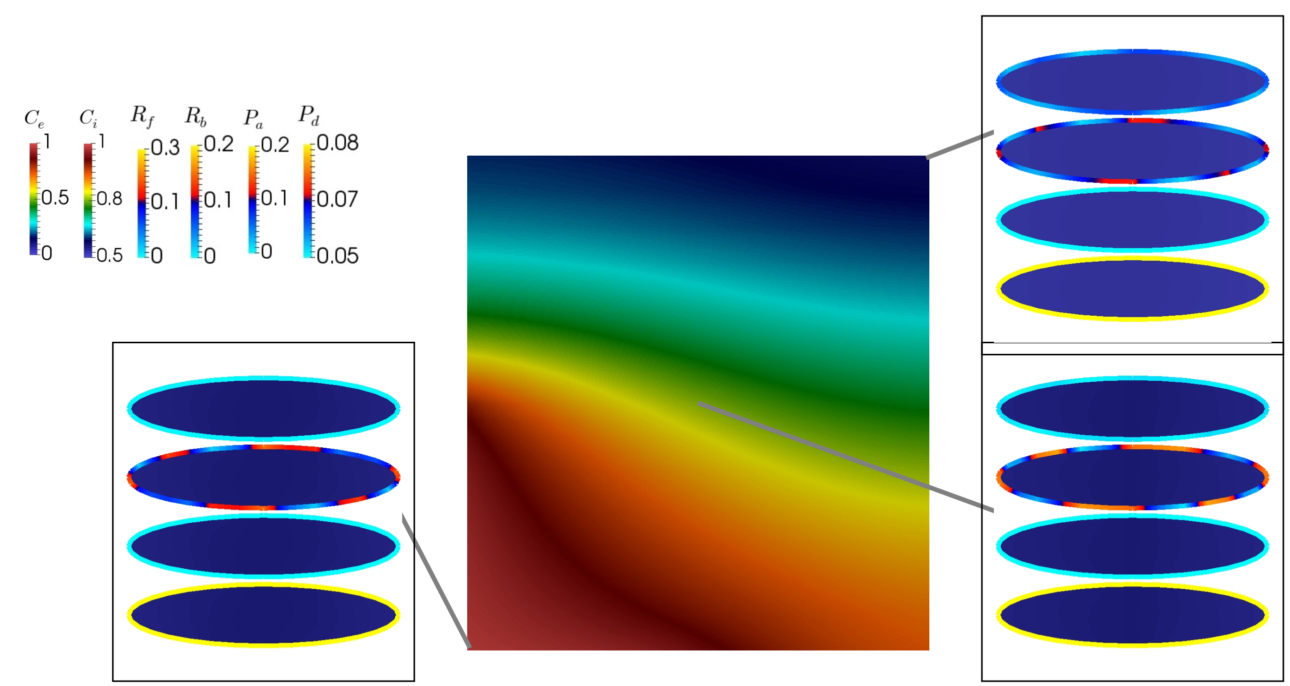
(A) $t = 10$



(B) $t = 100$



(A) $t = 200$



(B) $t = 250$