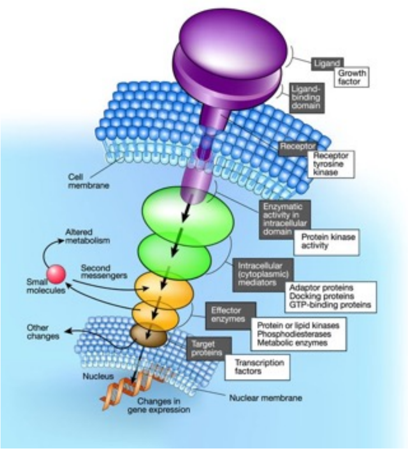
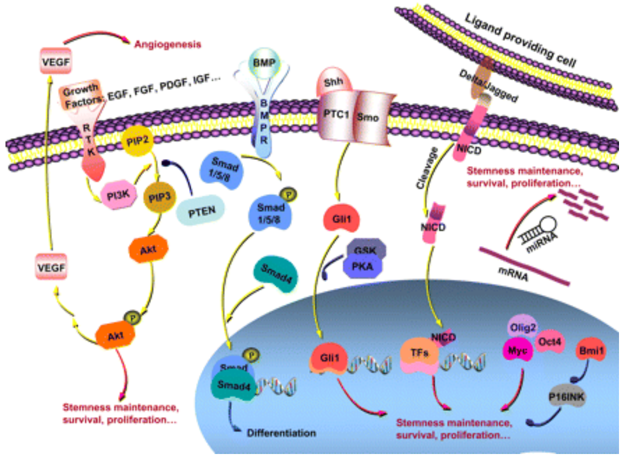




Multiscale modelling, analysis and simulations of intercellular signalling processes in biological tissues

Mariya Ptashnyk

joint work with Chandrasekhar Venkataraman

Multiscale Computational Modelling meeting
ICMS 16 May 2018

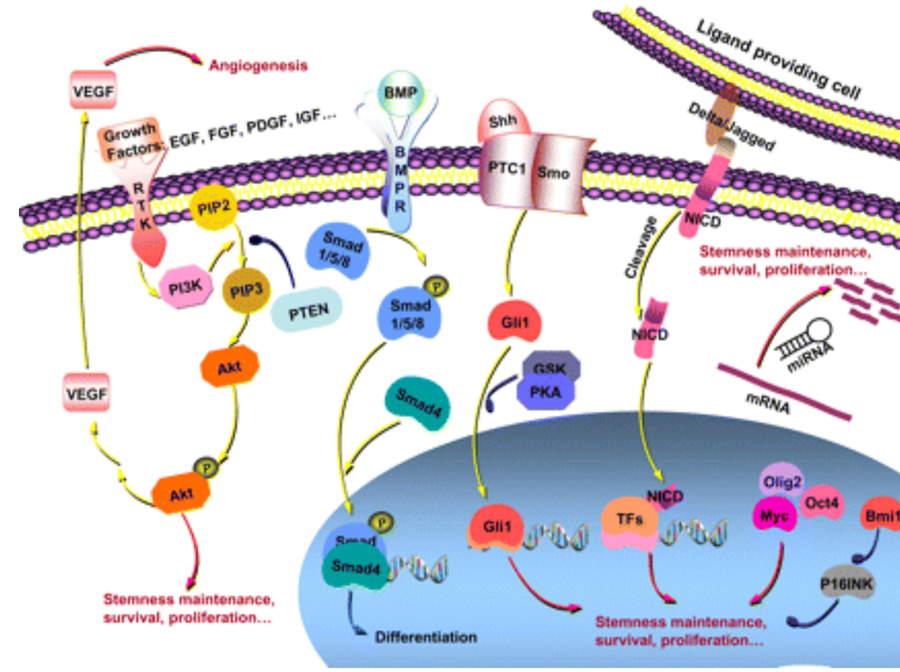
HERIOT WATT UNIVERSITY

Multiscale modelling of transport and signalling processes in biological tissues

Single cell

(intracellular signalling, gene regulatory networks)

(Hes1 gene regulatory network)

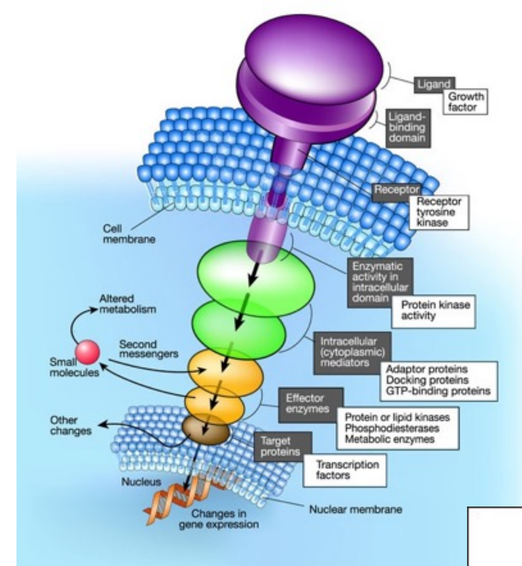


Z. Li et al., J Biol. Chemistry 2009

Collection of cells

(intercellular transport and signalling processes, mechanical interactions between cells)

(receptor-based signalling:
interactions between signalling molecules in the extracellular matrix and cell membrane receptors)

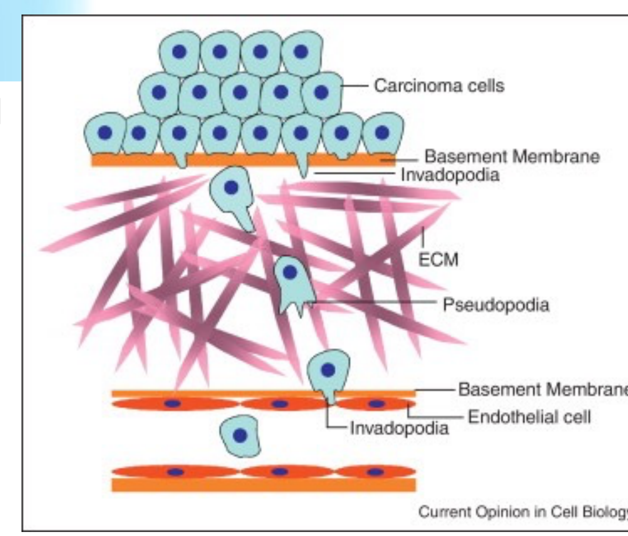


J. Downward, Nature 2001

Tissues and organs

(dynamics of cell populations:
movement, proliferation, mechanical interactions)

(haptotaxis model for cancer cell invasion)



J.J. Bravo-Cordero et al., Curr.Opin.Cell Biol. 2012

Cell signalling

Cell signalling: the ability of cells to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis.

Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, abnormal growth in plants. By understanding cell signalling, diseases may be treated effectively.

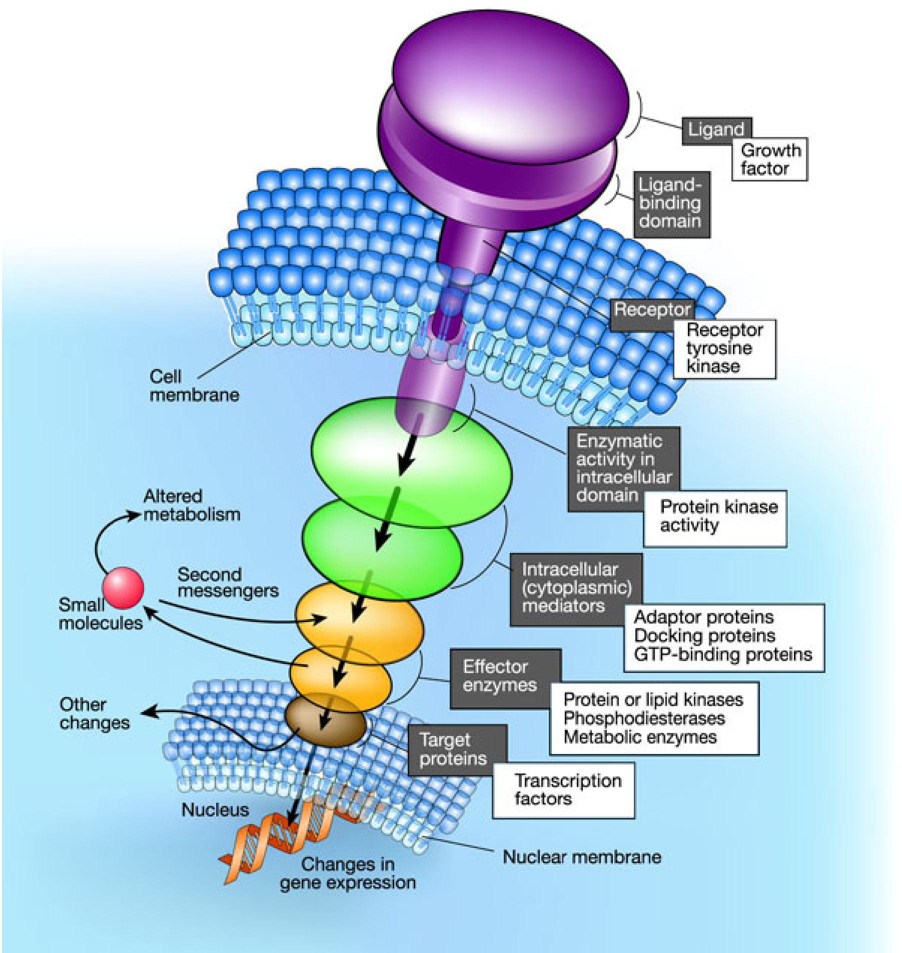
Signaling molecules interact with a target cell as a ligand to cell surface receptors, and/or by entering into the cell through its membrane or endocytosis for intracellular signaling.

Wikipedia

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



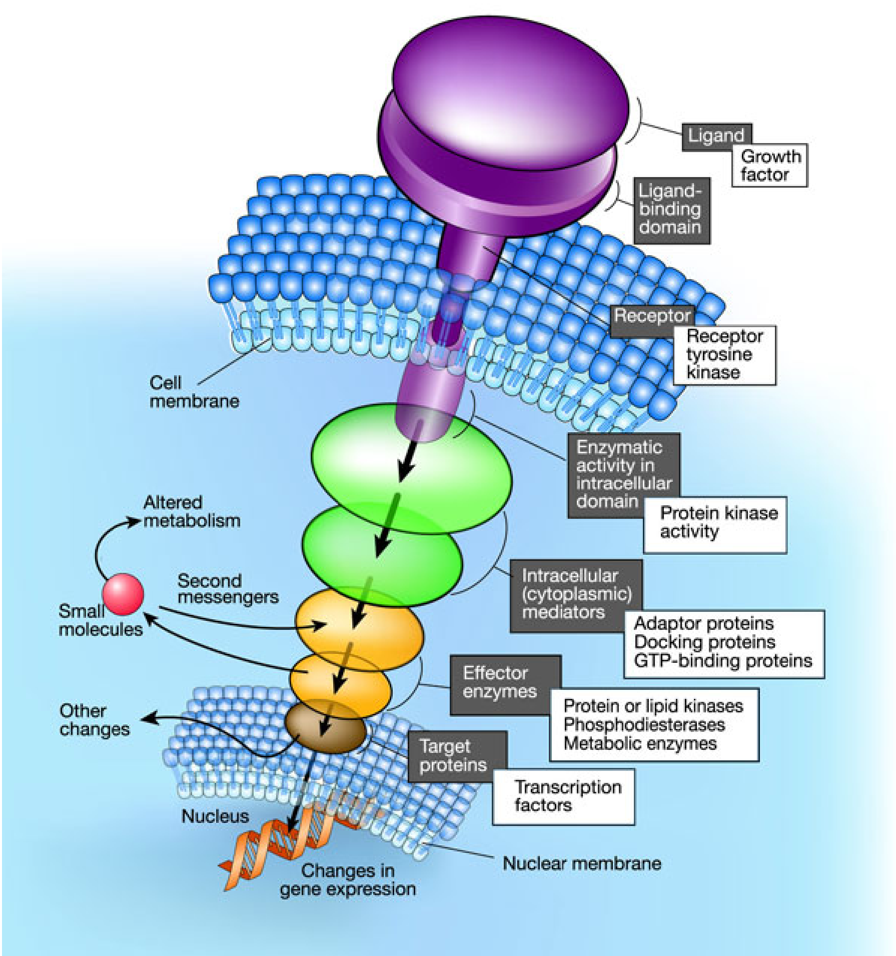
J. Downward, *Nature* 2001

- 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

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



J. Downward, *Nature* 2001

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

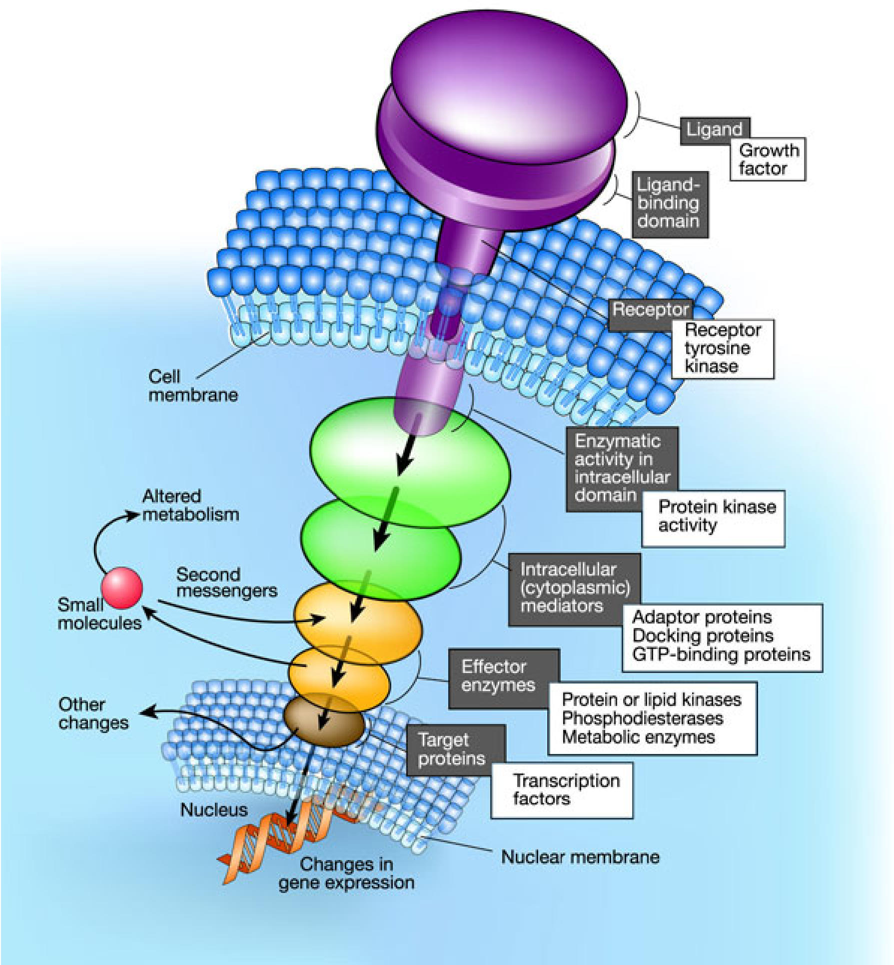
$$R_b + P_d \underset{b_i}{\overset{a_i}{\rightleftharpoons}} P_a \qquad P_a \underset{\kappa_i}{\overset{\gamma_i}{\rightleftharpoons}} S$$

- 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 bind to p_d to activate and produce p_a

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



J. Downward, *Nature* 2001

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

$$R_b + P_d \underset{b_i}{\overset{a_i}{\rightleftharpoons}} P_a$$

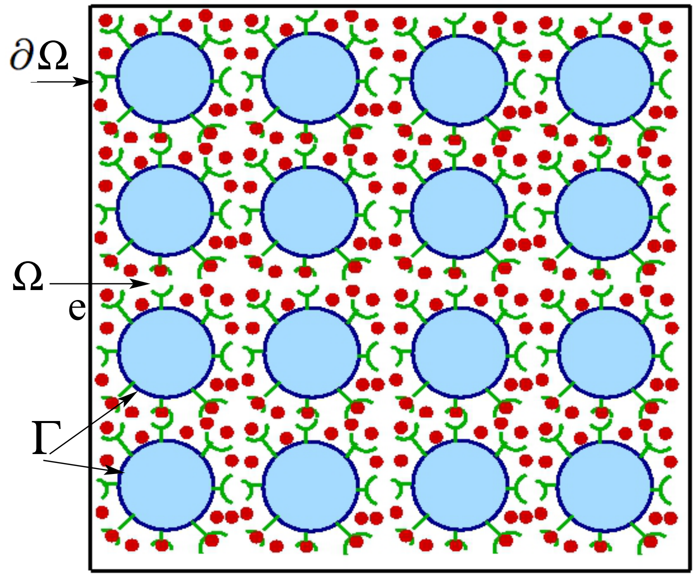
$$P_a \underset{\kappa_i}{\overset{\gamma_i}{\rightleftharpoons}} S$$

- 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 bind to p_d to activate and produce p_a
- Bound receptors r_b dissociate into free receptors r_f and ligands c
- Active co-receptors p_a dissociate into inactive co-receptors p_d and bound receptors r_b

Mathematical model for intercellular signalling

- Diffusion, production and decay of ligands in extracellular space

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



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

- Binding on the cell surfaces

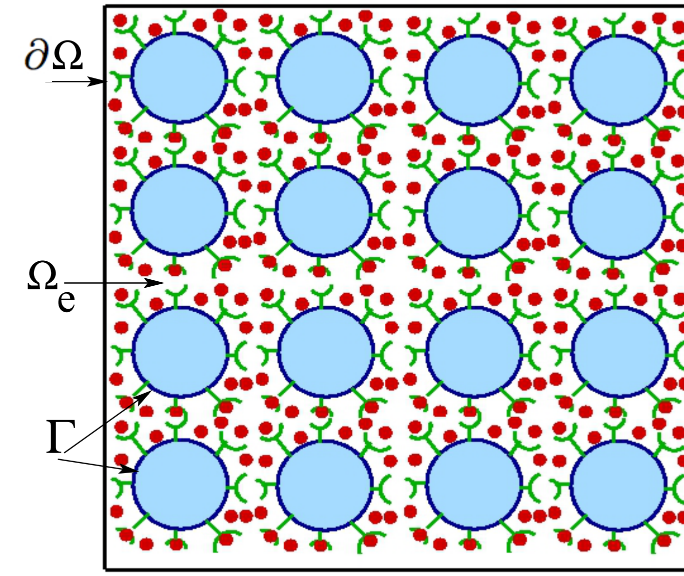
$$D_e(x)\,\nabla c \cdot \nu = -\,a_e(x)\; c\; r_f + b_e(x)\, r_b \qquad \text{on} \quad \Gamma$$

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

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

$$\partial_t c = \nabla \cdot (D_e^\varepsilon(x) \nabla c) + F_e(c) \qquad \text{in } \Omega_e^\varepsilon, \; t > 0$$

$$\partial_t s = \varepsilon^2 \nabla \cdot (D_i^\varepsilon(x) \nabla s) + F_i(s) \qquad \text{in } \Omega_i^\varepsilon, \; t > 0$$

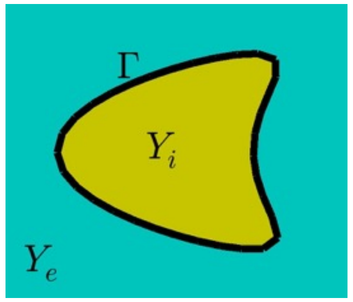
- Equations for the receptors /proteins on the cell surface Γ^ε, $\quad t > 0$

$$\partial_t r_f = \varepsilon^2 D_f \Delta_\Gamma r_f - G_e(c, r_f, r_b) + F_r(r_f, r_b) - d_f \, r_f$$

$$\partial_t r_b = \varepsilon^2 D_b \Delta_\Gamma r_b + G_e(c, r_f, r_b) - G_d(r_b, p_d, p_a) - d_b \, r_b$$

$$\partial_t p_d = \varepsilon^2 D_d \Delta_\Gamma p_d - G_d(r_b, p_d, p_a) + F_d(p_d) - d_d \, p_d$$

$$\partial_t p_a = \varepsilon^2 D_a \Delta_\Gamma p_a + G_d(r_b, p_d, p_a) - G_i(p_a, s) - d_a \, p_a$$



- Binding on the cell surfaces Γ^ε

$$D_e^\varepsilon(x) \nabla c \cdot \nu = -\varepsilon \, G_e(c, r_f, r_b) \qquad \text{on } \Gamma^\varepsilon, \; t > 0$$

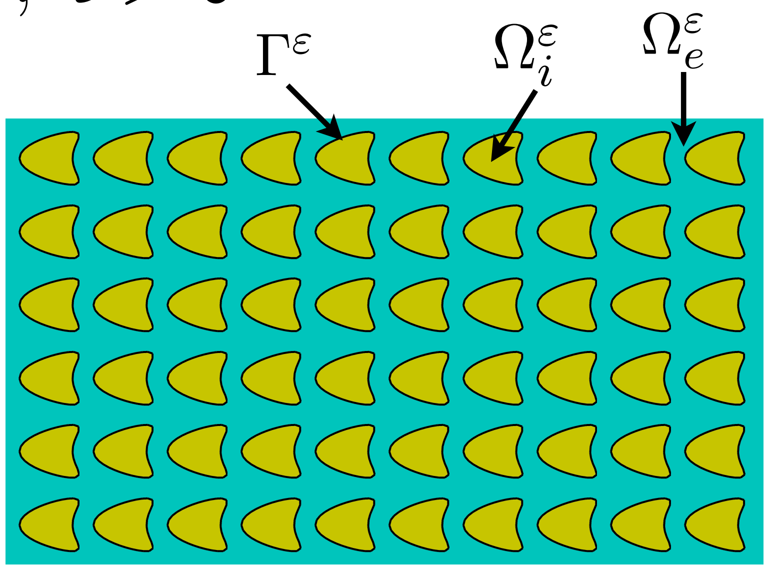
$$\varepsilon^2 D_i^\varepsilon(x) \nabla s \cdot \nu = \varepsilon \, G_i(p_a, s) \qquad \text{on } \Gamma^\varepsilon, \; t > 0$$

- Binding reactions

$$G_e(c, r_f, r_b) = a_e \, c \, r_f - b_e \, r_b$$

$$G_d(r_b, p_d, p_a) = a_i \, r_b \, p_d - b_i \, p_a$$

$$G_i(p_a, s) = \gamma_i \, p_a - \kappa_i \, s$$



Multiscale Analysis

- The aim of homogenization is to derive the macroscopic properties by taking the microscopic processes into account.
- Macroscopic model are helpful for numerical simulation

Start with a family of operators $\mathcal{A}_\varepsilon$, depending on microscopic structure defined via parameter ε

$$\mathcal{A}_\varepsilon u_\varepsilon = f \qquad \text{in} \ \ \Omega$$

The method of homogenization leads to a macroscopic law

$$\mathcal{A}_0 u_0 = f \qquad \text{in} \ \ \Omega$$

The macroscopic law determines a macroscopic approximation u_0 for u_ε as $\varepsilon \to 0$

Methods to derive macroscopic equations

- Formal asymptotic expansion

$$u^\varepsilon(x) = u_0(x, \frac{x}{\varepsilon}) + \varepsilon u_1(x, \frac{x}{\varepsilon}) + \varepsilon^2 u_2(x, \frac{x}{\varepsilon}) + \dots$$

$u_j(x, y)$ is defined for $x \in \Omega$, $y \in Y$, $u_j(x, \cdot)$ is $Y-$periodic

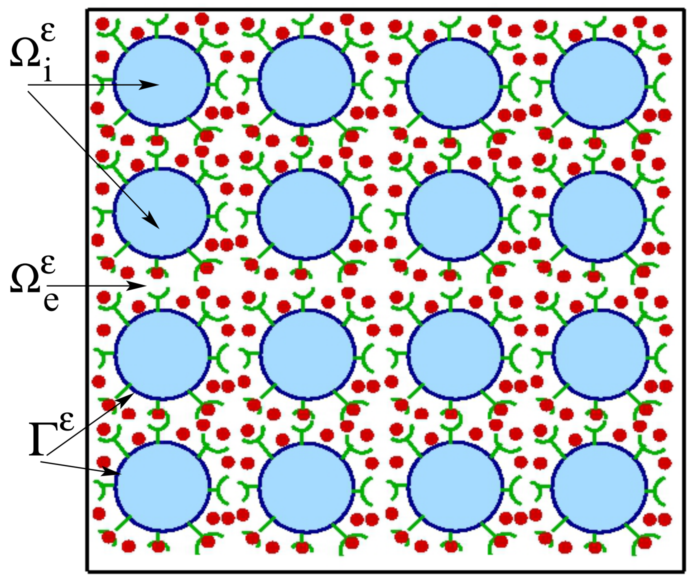
- Energy method: 'oscillating test function' (Tartar, ...)
- Γ-convergence: abstract notion of functional convergence (calculus of variations) (Braides, Müller, ...)
- G-convergence: for symmetric elliptic operators (De Giorgi, Spagnolo,...)

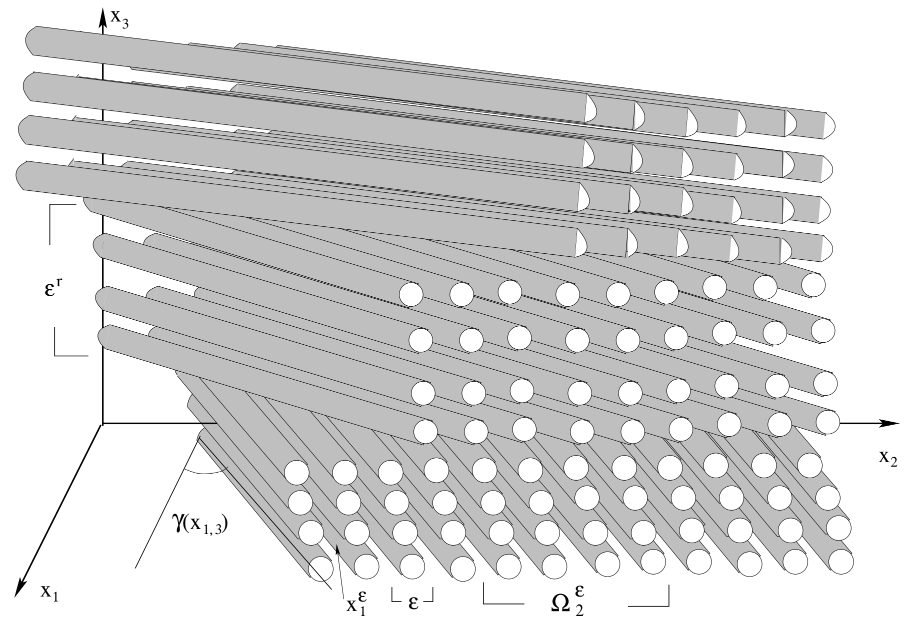
  H - convergence: generalization of G-convergence for non-symmetric problems (Murat, Tartar, ...)

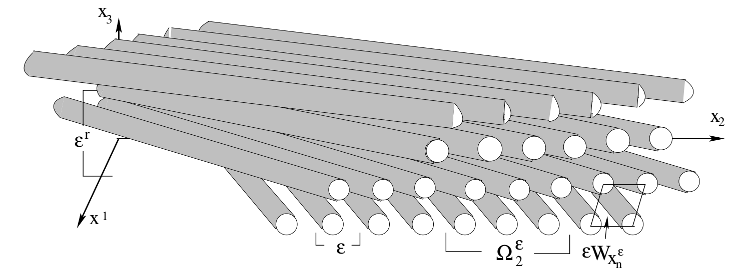
  $\Rightarrow$ Construct a matrix A^0 such that $A^\varepsilon \overset{H}{\rightharpoonup} A^0$, i.e.
  $u^\varepsilon \rightharpoonup u^0$ in $H^1(\Omega)$ and $A^\varepsilon \nabla u^\varepsilon \rightharpoonup A^0 \nabla u^0$ in $L^2(\Omega)$.
- Two-scale convergence and unfolding method for periodic and localy-periodic homogenization (Nguetseng, Allaire, Neuss-Radu, Cioranescu, Damlamian, Griso, MP ...)

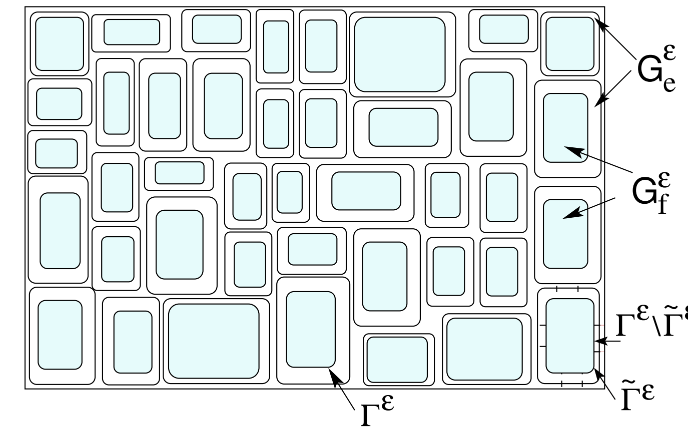
  stochastic two-scale convergence (Bourgeat, Heida, Mikelić, Piatnitski,Wrigit, ...)

Multiscale modelling and analysis









Distribution of cells or microstructure

- Periodic
- Locally periodic
- Random

Homogenization techniques

- Periodic two-scale convergence, unfolding method, two-scale convergence on the surface of periodic microstructures
- Locally-periodic two-scale convergence, unfolding method, two-scale convergence on the surface of locally-periodic microstructures
- Stochastic two-scale convergence, Palm measure

Two-scale convergence

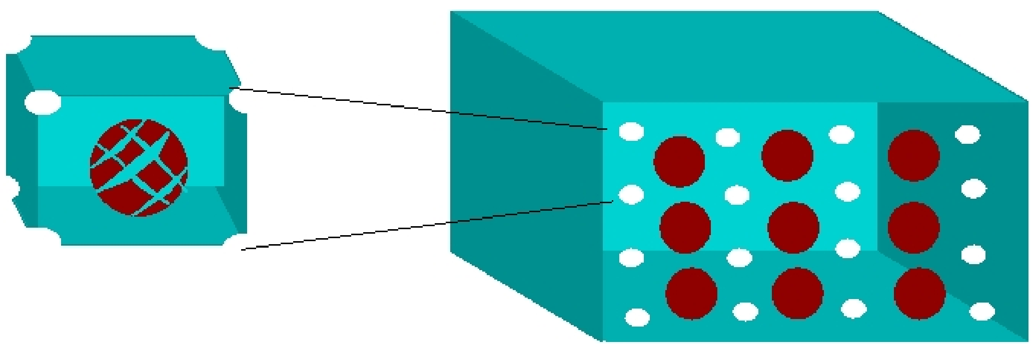
- A special type of convergence in L^p, $1 < p < \infty$ and $1/p + 1/q = 1$

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

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

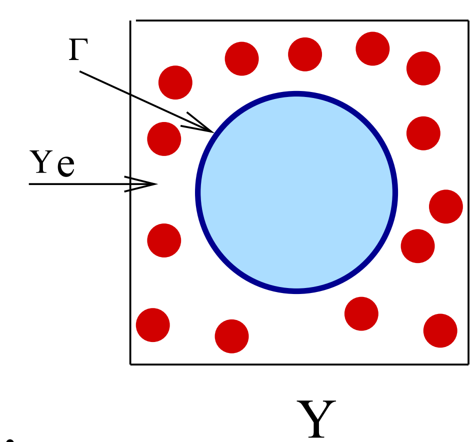
Notice:

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



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

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



Compactness theorems for two-scale conv.

Theorem. *Let* $\{u^\varepsilon\}$ *be a bounded sequence in* $L^p(\Omega)$, $p \in (1,\infty)$.
Then, there exists $u \in L^p(\Omega \times Y)$ *s.t. (up to a subsequence)*

$$u^\varepsilon \quad \textit{two-scale} \quad \textit{converges to} \quad u \qquad \textit{for } \varepsilon \to 0.$$

Theorem. *Let* $\{u^\varepsilon\}$ *be bounded in* $W^{1,p}(\Omega)$ *s.t.*

$$u^\varepsilon \rightharpoonup u \quad \textit{in} \quad W^{1,p}(\Omega).$$

Then there exists $u_1 \in L^p(\Omega; W^{1,p}_{per}(Y)/\mathbb{R})$ *s.t. (up to a subseq.)*

$$u^\varepsilon \qquad \textit{two-scale converges to} \quad u$$

$$\nabla u^\varepsilon \quad \textit{two-scale converges to} \quad \nabla_x u + \nabla_y u_1 \qquad \textit{for } \varepsilon \to 0.$$

$\Omega = (0,1)$, $Y = (0, 2\pi)$

- $u^\varepsilon(x) = x + \varepsilon \sin\left(\frac{x}{\varepsilon}\right)$
- $\frac{du^\varepsilon}{dx}(x) = 1 + \cos\left(\frac{x}{\varepsilon}\right)$

- u^ε strongly converges to x
- $\frac{du^\varepsilon}{dx}$ weakly converges to 1
- $\frac{du^\varepsilon}{dx}$ two-scale converges to $1 + \cos(y)$

Compactness theorems for two-scale converg.

Theorem. *Let* $\{u^\varepsilon\}$ *be a bounded sequence in* $L^2(\Omega)$.
Then, there exists $u \in L^2(\Omega \times Y)$ *s.t. (up to a subsequence)*

$$u^\varepsilon \quad \text{two-scale converges to} \quad u \qquad \text{for } \varepsilon \to 0.$$

Theorem. *Let* $\{u^\varepsilon\}$ *be bounded in* $H^1(\Omega)$ *s.t.*

$$u^\varepsilon \rightharpoonup u \quad \text{in} \quad H^1(\Omega).$$

Then there exists $u_1 \in L^2(\Omega; H^1_{per}(Y)/\mathbb{R})$ *s.t. (up to a subseq.)*

$$u^\varepsilon \qquad \text{two-scale converges to} \quad u$$

$$\nabla u^\varepsilon \qquad \text{two-scale converges to} \quad \nabla_x u + \nabla_y u_1 \qquad \text{for } \varepsilon \to 0.$$

Lemma (Strong two-scale convergence)
Let $\{v^\varepsilon\} \subset L^2(\Omega)$ *two-scale converge to* $v_0 \in L^2(\Omega \times Y)$ *and*

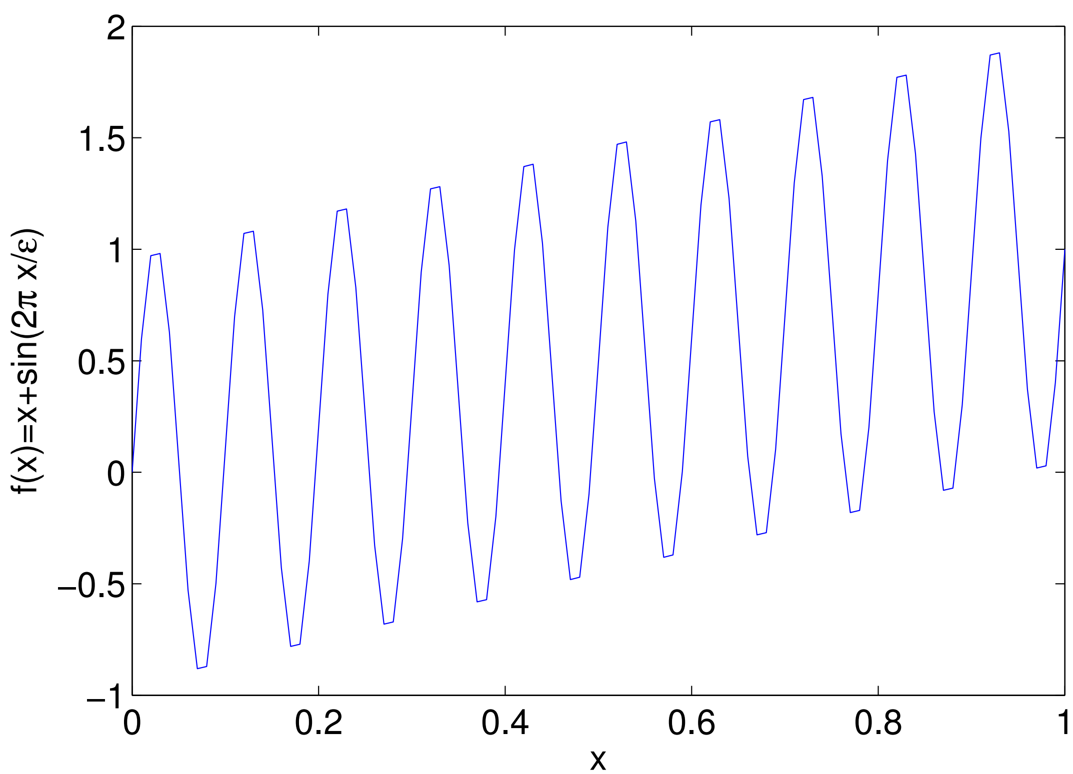
$$\lim_{\varepsilon \to 0} \int_\Omega [v^\varepsilon(x)]^2 \, dx = \int_\Omega \fint_Y [v_0(x,y)]^2 \, dydx.$$

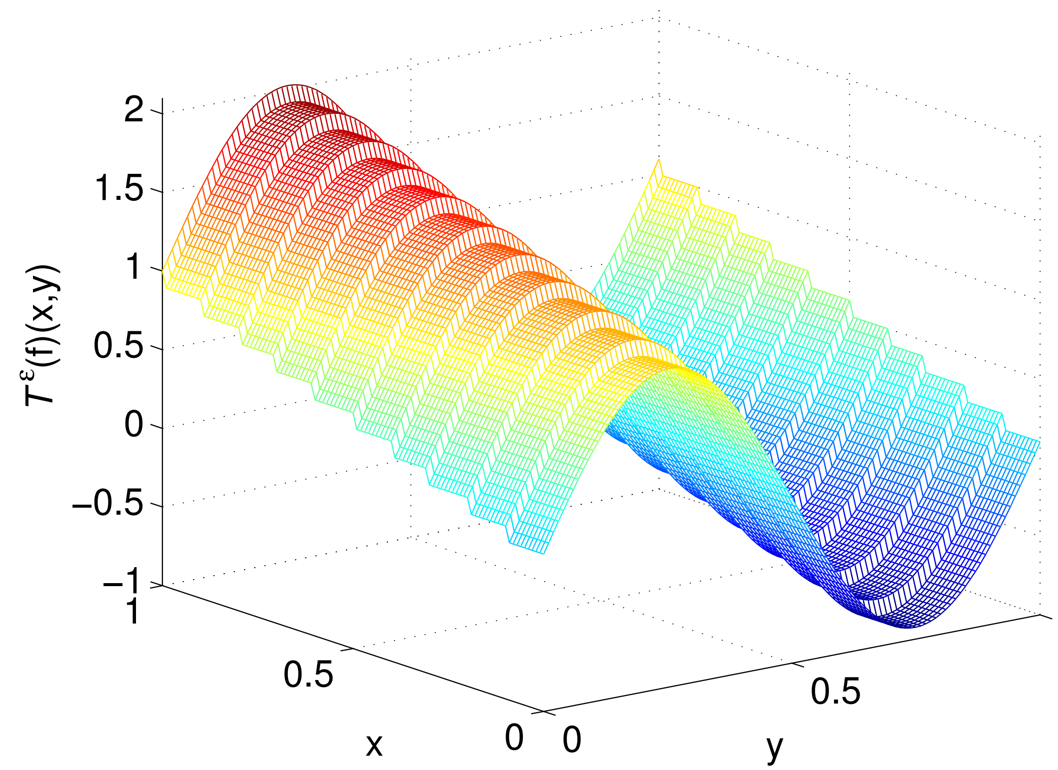
Then, for $\{w^\varepsilon\}$ *that two-scale converg. to* $w_0 \in L^2(\Omega \times Y)$:

$$v^\varepsilon w^\varepsilon \to \fint_Y v_0(\cdot, y) w_0(\cdot, y) \, dy \quad \text{in} \quad \mathcal{D}'(\Omega).$$

Unfolding operator

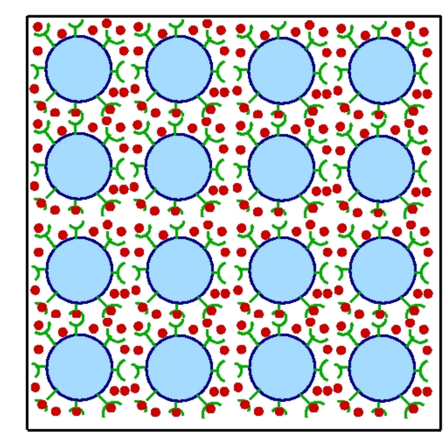
maps functions defined on the varying perforated domains into functions defined on a fixed domain





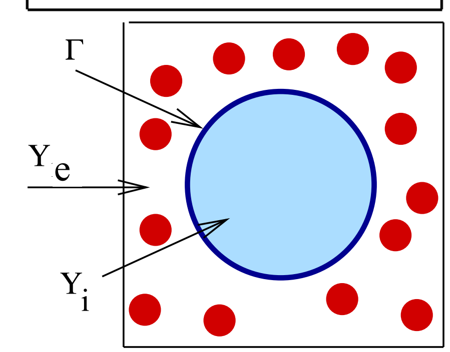
For ϕ Lebesgue-measurable on Ω_e^ε:

$$\mathcal{T}_{Y_e}^{\varepsilon}(\phi)(x,y) = \phi(\varepsilon \left[\frac{x}{\varepsilon}\right]_Y + \varepsilon y) \qquad \text{for a.e.} \quad y \in Y_e, \;\; x \in \Omega$$



For ϕ Lebesgue-measurable on Γ^ε:

$$\mathcal{T}_{\Gamma}^{\varepsilon}(\phi)(x,y) = \phi(\varepsilon \left[\frac{x}{\varepsilon}\right]_Y + \varepsilon y) \qquad \text{for a.e.} \quad y \in \Gamma, \;\; x \in \Omega$$



Properties of the unfolding operator

- For $u \in L^2(\Omega^\varepsilon)$:

$$||\mathcal{T}^\varepsilon_{Y_j}(u)||_{L^2(\Omega\times Y_j)} \le |Y_j|^{\frac{1}{2}}||u||_{L^2(\Omega^\varepsilon)}, \qquad j = e, i$$

- If $u \in L^2(\Omega)$:

$$\mathcal{T}^\varepsilon_{Y_j}(u) \to u \quad \text{strongly in} \quad L^2(\Omega\times Y_j) \quad \text{as} \ \ \varepsilon \to 0$$

- For $u \in L^2(\Gamma^\varepsilon)$:

$$||\mathcal{T}^\varepsilon_{\Gamma}(u)||_{L^2(\Omega\times\Gamma)} \le \sqrt{\varepsilon}\,|Y_j|^{\frac{1}{2}}\,||u||_{L^2(\Gamma^\varepsilon)}.$$

- $\mathcal{T}^\varepsilon_{Y_j}(u^\varepsilon) \rightharpoonup u^*$ in $L^2(\Omega\times Y_j)$, $\qquad u^\varepsilon \to u$ two-scale, then

$$u^* = u \quad \text{a.e. in} \quad \Omega\times Y_j$$

- $\mathcal{T}^\varepsilon_{Y_j} : W^{1,p}(\Omega^\varepsilon) \to L^p(\Omega, W^{1,p}(Y_j))$ and

$$\varepsilon\,\mathcal{T}^\varepsilon_{Y_j}(\nabla_x u) = \nabla_y \mathcal{T}^\varepsilon_{Y_j}(u)$$

- Let $\{u^\varepsilon\}$ converges weakly in $W^{1,p}_0(\Omega)$ to u, then

$$\mathcal{T}^\varepsilon_{Y_e}(u^\varepsilon) \to u \qquad \text{stongly in} \ \ L^p(\Omega; W^{1,p}(Y_e))$$

$$\mathcal{T}^\varepsilon_{Y_e}(\nabla u^\varepsilon) \rightharpoonup \nabla u + \nabla_y u_1 \quad \text{weakly in} \ \ L^p(\Omega\times Y_e)$$

Macroscopic equations

- Macroscopic concentrations

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

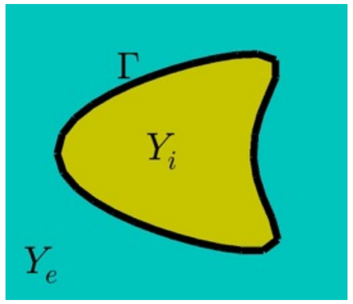
$$\partial_t s - \nabla_y \cdot (D_i(y) \nabla_y s) = F_i(s) \qquad \text{in } \Omega_T \times Y_i$$

- 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

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

where

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

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

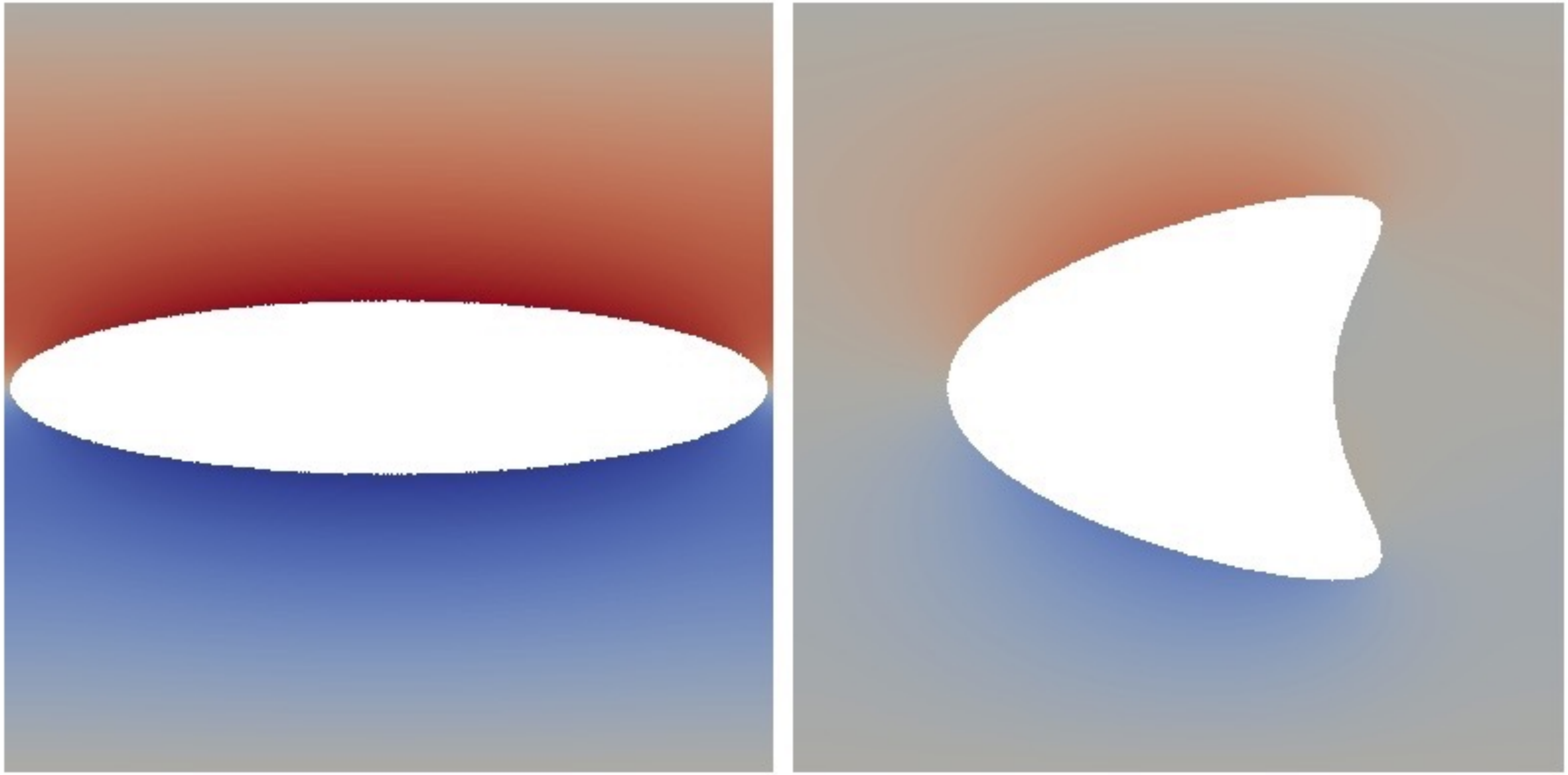
$\Omega_T = (0, T) \times \Omega$

MP, C. Venkataraman, *arXiv* 2018

Multiscale numerical simulations

$$\mathrm{div}_y(D_e^*(\nabla_y w^j + e_j)) = 0 \quad \text{in } Y_e, \quad \int_{Y_e} w^j(y)dy = 0,$$

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

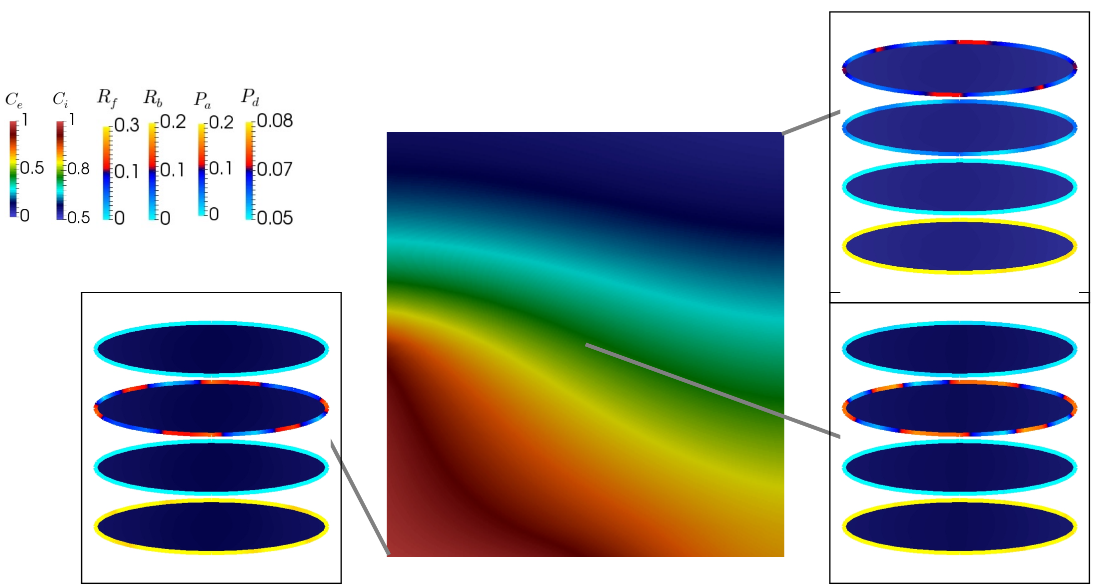


$$D_{h,e}^{\mathrm{hom}} = \begin{bmatrix} 8.167\cdot 10^{-3} & 0 \\ 0 & 1.841\cdot 10^{-3} \end{bmatrix} \qquad D_{h,e}^{\mathrm{hom}} = \begin{bmatrix} 6.556\cdot 10^{-3} & 0 \\ 0 & 6.149\cdot 10^{-3} \end{bmatrix}$$

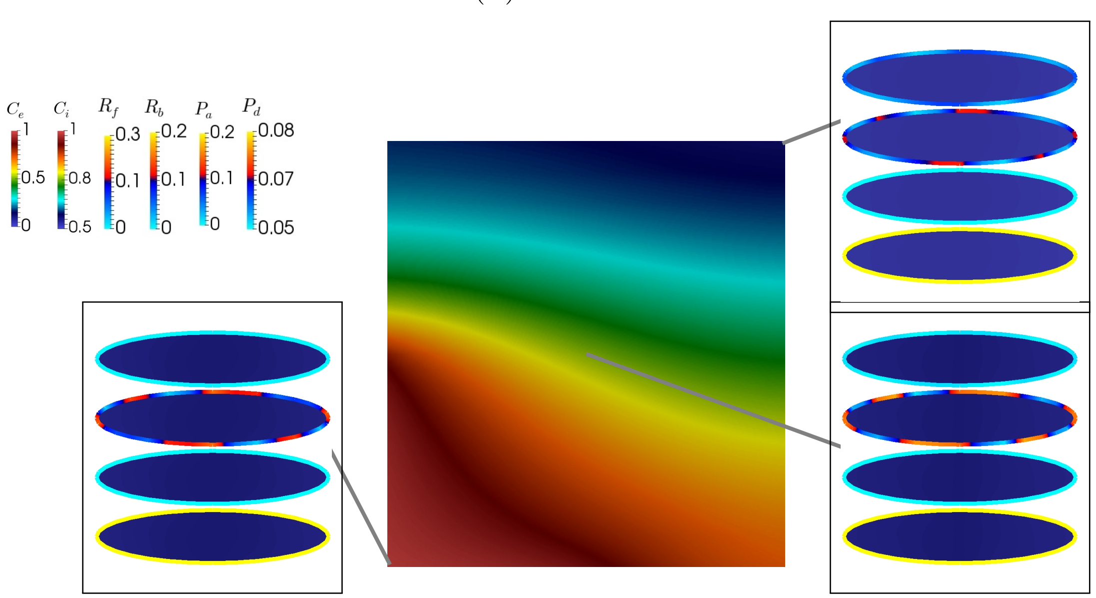
$D_e^* = 10^{-2}, \quad D_i^* = 10, \quad D_f^* = D_b^* = D_d^* = D_a^* = 10^{-2}.$

MP, C. Venkataraman, *arXiv* 2018

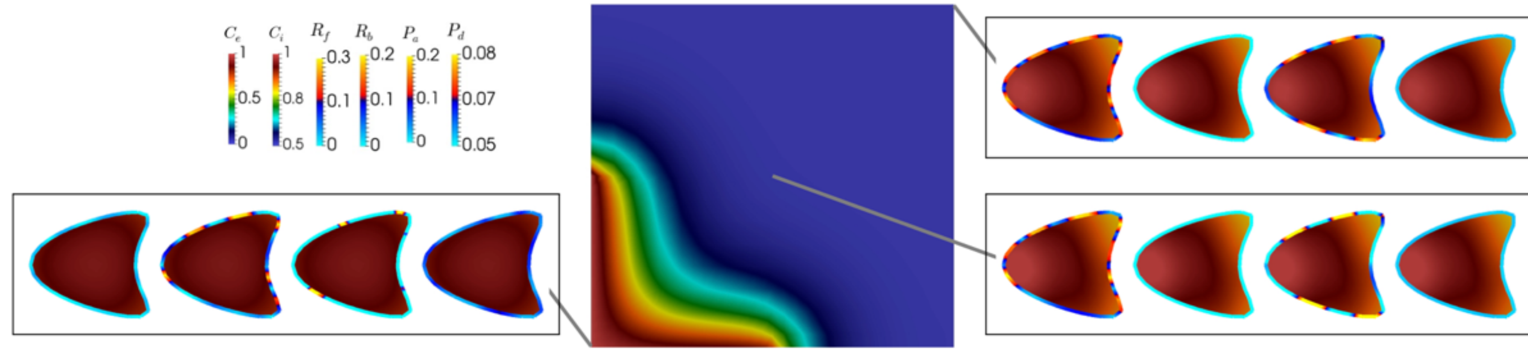
Effect of anisotropic microstructure



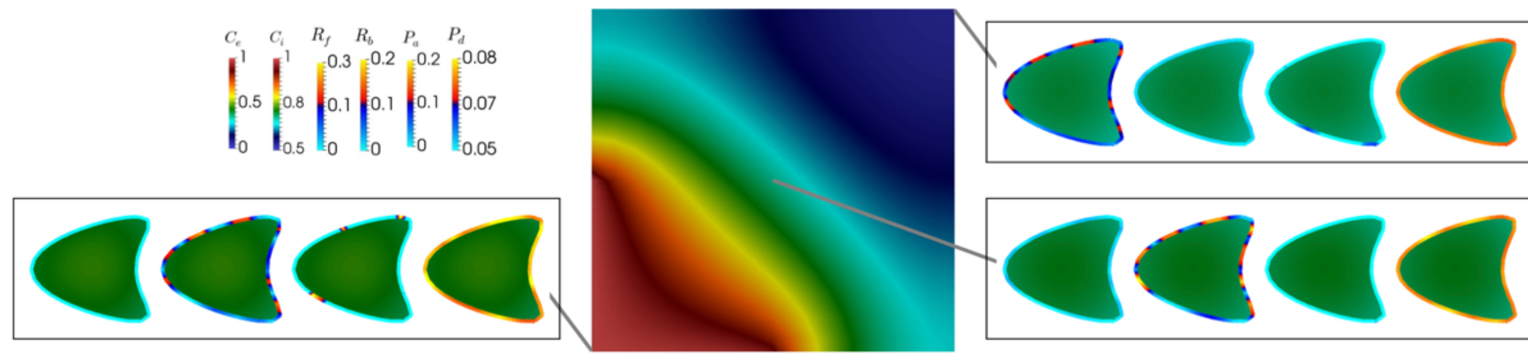
(A) $t = 200$



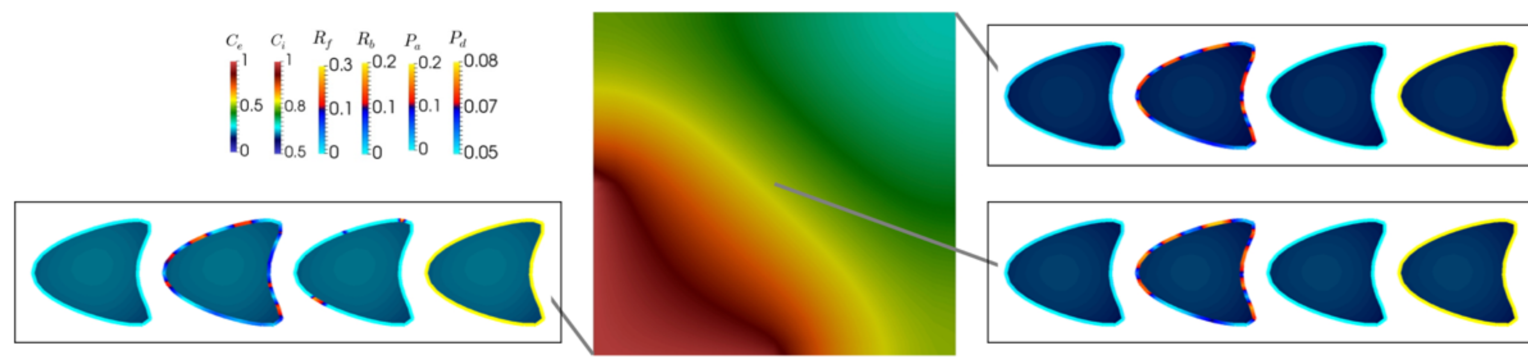
(B) $t = 250$



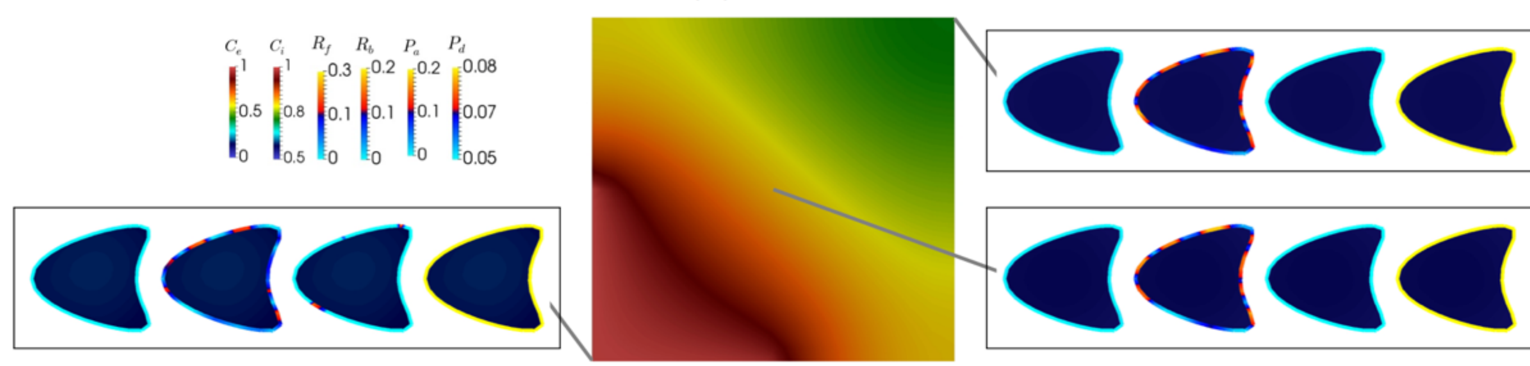
(A) $t = 10$



(B) $t = 100$

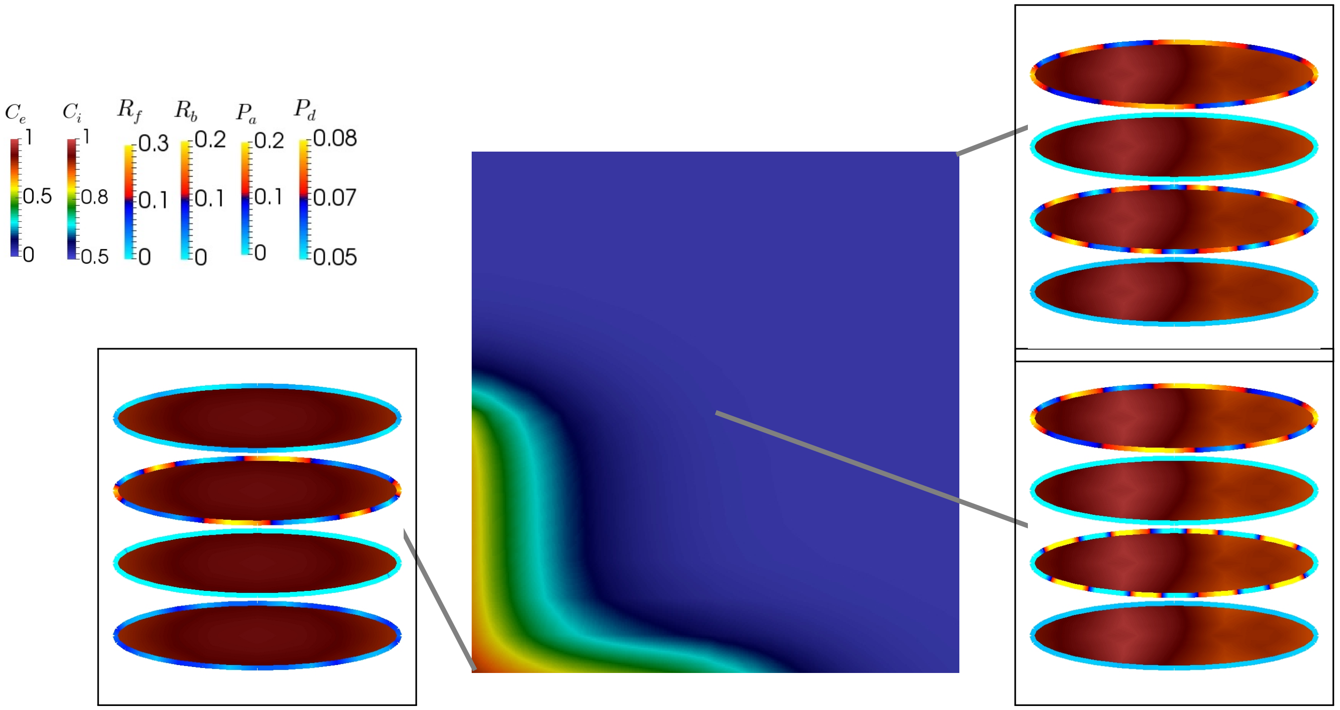


(C) $t = 200$

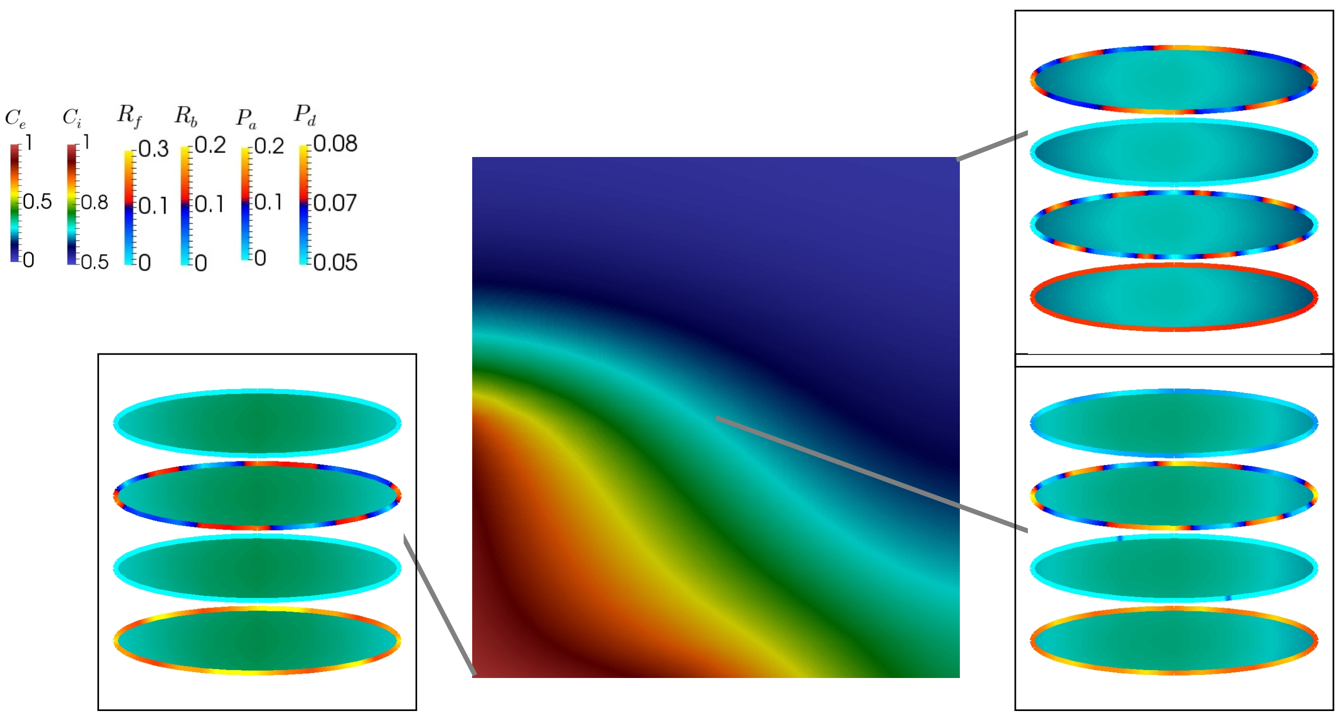


(D) $t = 250$

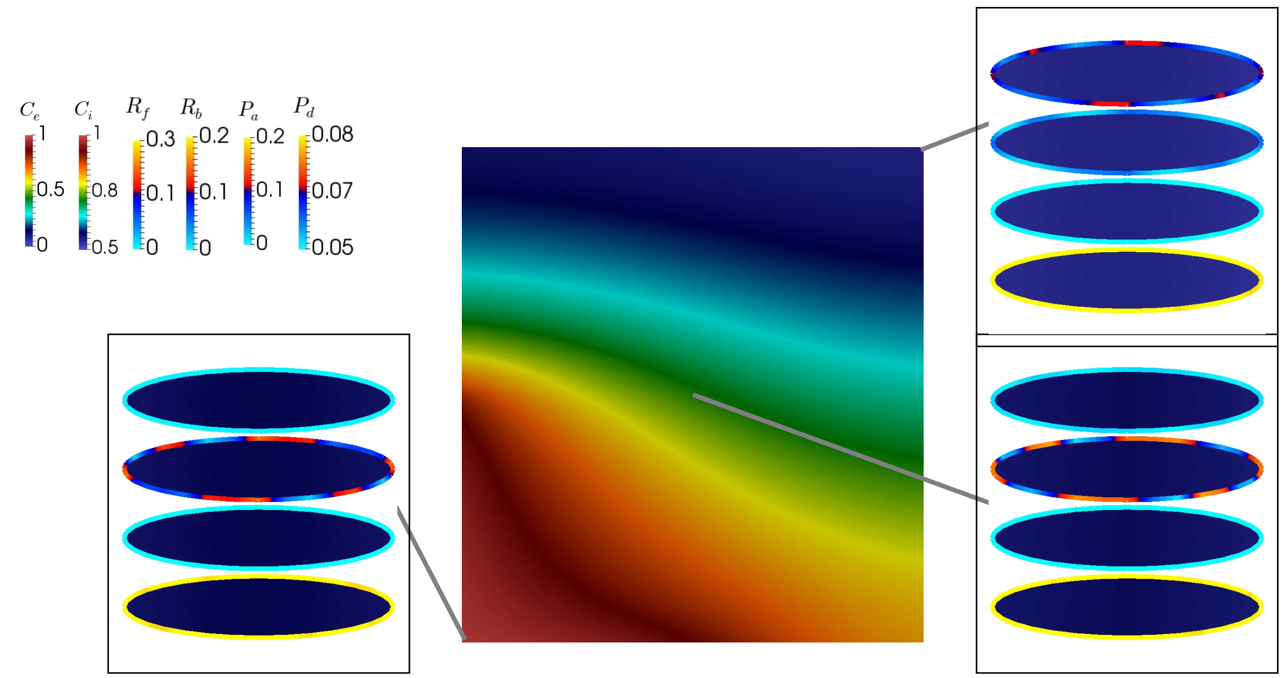
Effect of anisotropic microstructure



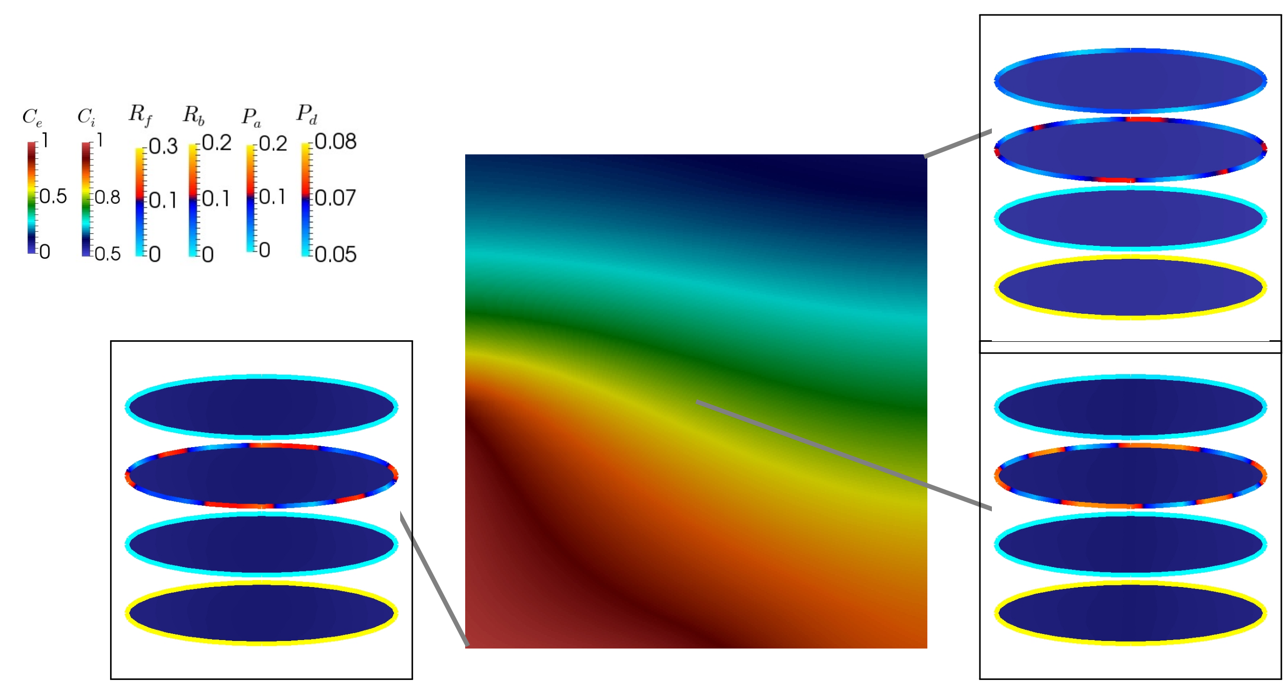
(A) $t = 10$



(B) $t = 100$



(A) $t = 200$



(B) $t = 250$

Thank you very much !

Questions ?