Institut für
Kontinuumsmechanik

Leibniz
Universität
Hannover

Invited Seminar @ University of Pisa

05 April 2019 – Pisa, Italy

Computational Modelling of Hydrogels Chemomechanics

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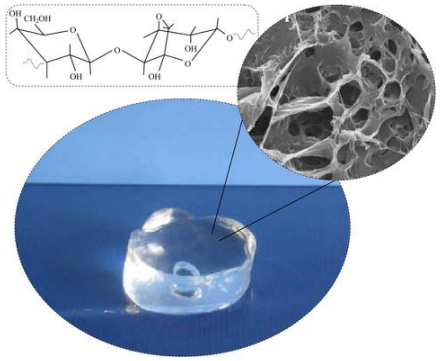
In collaboration with: **Aidin Hajikhani, Jorge U Urrea Quintero, Peter Wriggers**

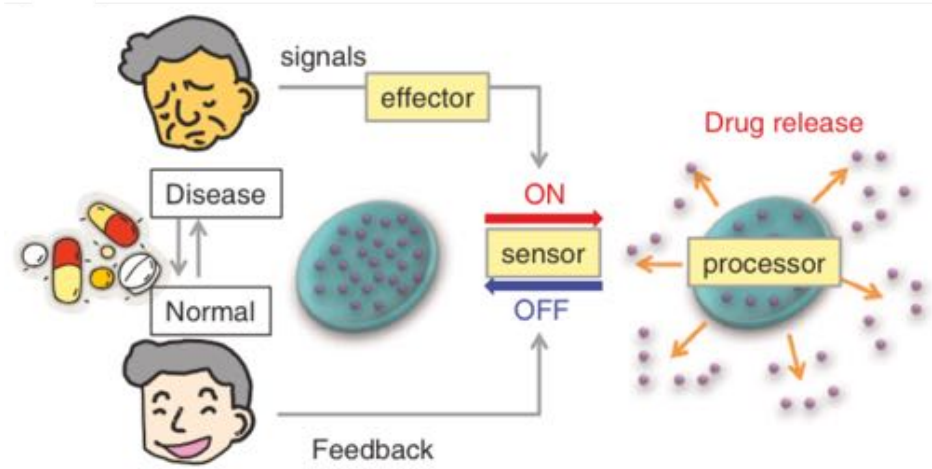
Introduction



Hydrogels: three-dimensional, hydrophilic, polymeric networks capable of absorbing large amounts of water or biological fluids

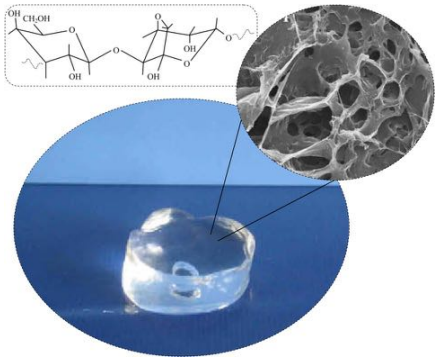
Applications:

- Drug delivery: controlled release



[Ebara et al., Smart Biomaterials 2014]

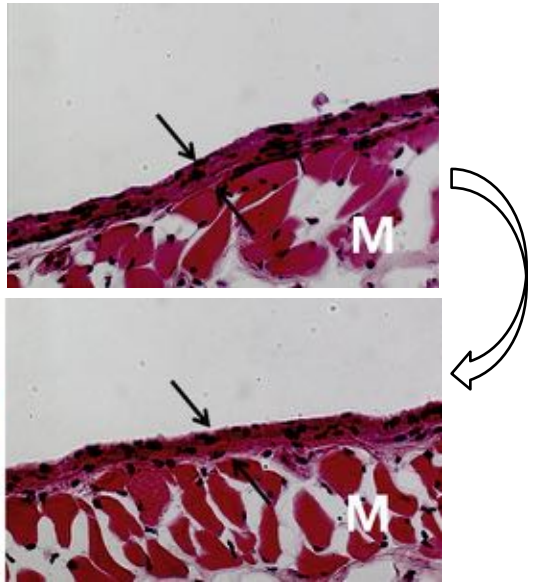
Introduction



Hydrogels: three-dimensional, hydrophilic, polymeric networks capable of absorbing large amounts of water or biological fluids

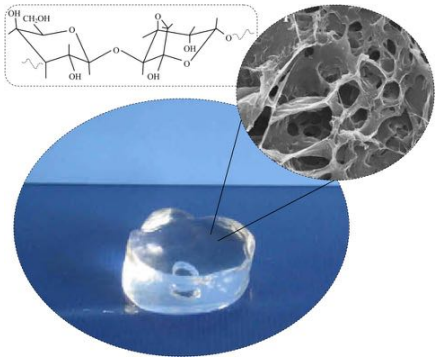
Applications:

- Drug delivery: controlled release
- Wound dressing: maintenance of moisture concentration for minimizing bacterial infection and facilitate wound healing



[Lee and Mooney, Progress Pol Science 2012]

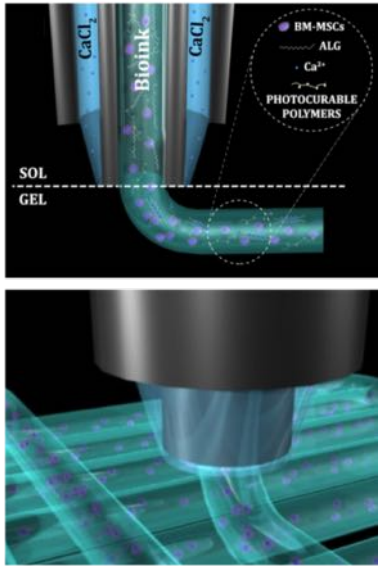
Introduction



Hydrogels: three-dimensional, hydrophilic, polymeric networks capable of absorbing large amounts of water or biological fluids

Applications:

- Drug delivery: controlled release
- Wound dressing: maintenance of moisture concentration for minimizing bacterial infection and facilitate wound healing
- Bioprinting: optimal material for tissue engineering scaffolds

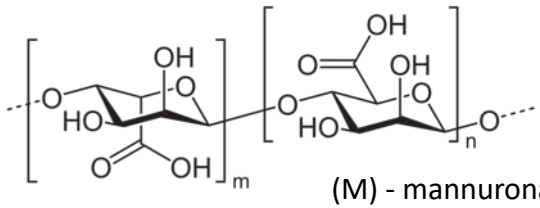


[Costantini et al., Biofabrication 2016]

Due to its biocompatibility, low toxicity, low costs and slight gelling, **alginate** is a polymer widely used for producing hydrogels, especially in biomedical applications

Calcium Alginate

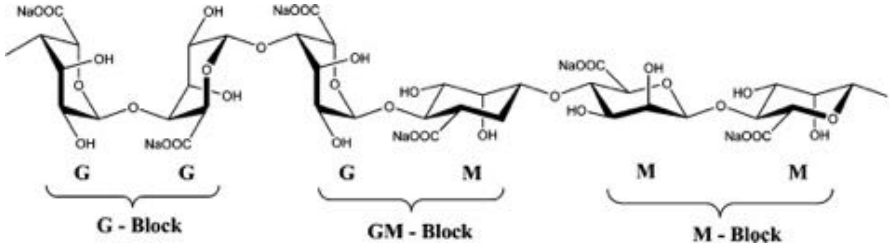
Alginic acid:



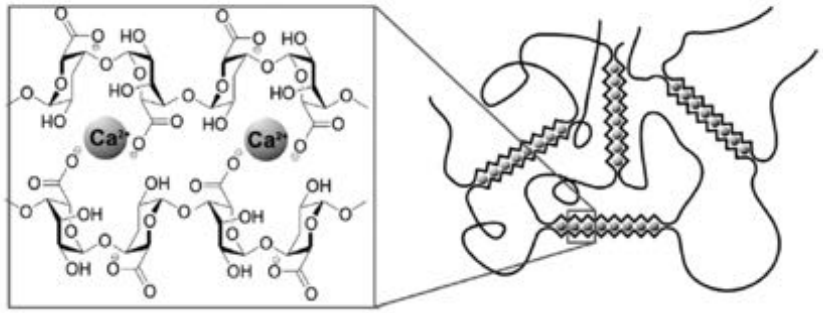
(G) - gluronate

(M) - mannuronate

Alternating sequences of G, M and GM blocks:



Ca^{2+} ⇩ **Calcium-induced chemical crosslinking**



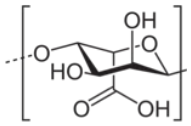
Egg-box

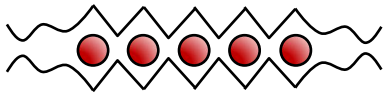
Kim et al, J Int Soc Simul Surg 3:49-59, 2016; Daemi et al, Int J Biol Macromol 66:212-220, 2014

Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

$$\text{alginate} + N_c \text{Ca}^{2+} \rightarrow \text{gel (Ca-alginate)}$$





$c_a = \text{concentration alginate}$

$c_c = \text{concentration } \text{Ca}^{2+}$

$c_g = \text{concentration gel (Ca-alginate)}$

$$\frac{\partial c_a}{\partial t} = \nabla \cdot (D_a \nabla c_a) - \frac{\partial c_g}{\partial t}$$

$$\frac{\partial c_c}{\partial t} = \nabla \cdot (D_c \nabla c_c) - N_c \frac{\partial c_g}{\partial t}$$

$$\frac{\partial c_g}{\partial t} = \underbrace{\nabla \cdot (D_g \nabla c_c)}_{\text{diffusion}} + \underbrace{r_g(c_a, c_c, c_g)}_{\text{reaction}} \longrightarrow$$

assuming $D_g \approx 0$ ⇨ $\dfrac{\partial c_g}{\partial t} = r_g(c_a, c_c, c_g)$

with $k_{11} = k_{1g} = k$ ⇨ $\underbrace{k c_a c_c (c_a + c_g)}_{k_{11} c_c c_a c_a + k_{1g} c_c c_a c_g}$

$$\begin{cases} k_{11} = \text{reaction rate of two alginate monomers} \\ k_{1g} = \text{mean reaction rate of an alginate monomer with gel} \end{cases}$$

Reactions between alginate polymers are neglected

Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

Full ME model:

$$\begin{cases} \dfrac{\partial c_a}{\partial t} = \nabla \cdot (D_a \nabla c_a) - \dfrac{\partial c_g}{\partial t} \\ \dfrac{\partial c_c}{\partial t} = \nabla \cdot (D_c \nabla c_c) - N_c \dfrac{\partial c_g}{\partial t} \\ \dfrac{\partial c_g}{\partial t} = k c_a c_c (c_a + c_g) \end{cases}$$

Reduced ME model: Negligible free-alginate diffusion $D_a \ll D_c$

$$\Rightarrow \quad \frac{\partial c_a}{\partial t} \approx -\frac{\partial c_g}{\partial t} \quad \Rightarrow \quad \frac{\partial (c_a + c_g)}{\partial t} \approx 0 \quad \Rightarrow \quad (c_a + c_g) \text{ is constant in time: } (c_a + c_g) \approx c_a|_{t=0} = c_A$$

Gelation degree: $\alpha = \dfrac{c_g}{c_A}$ Resulting $\dfrac{c_a + c_g}{c_A} = \dfrac{c_a}{c_A} + \alpha \approx 1$ with $\alpha \in [0, 1]$

$$\Rightarrow \quad \frac{1}{c_A}\frac{\partial c_g}{\partial t} = k c_a c_c \left(\frac{c_a + c_g}{c_A}\right) \approx \overbrace{k c_A^2}^{K} \frac{c_c}{c_A}\frac{c_a}{c_A} = K \frac{c_c}{c_A}(1 - \alpha) \quad \Rightarrow \quad \frac{\partial \alpha}{\partial t} = K \frac{c_c}{c_A}(1 - \alpha)$$

Calcium Alginate

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$$\begin{cases} \dfrac{\partial c_c}{\partial t} = \nabla \cdot (D_c \nabla c_c) - N_c K c_c \, (1 - \alpha) \\ \dfrac{\partial \alpha}{\partial t} = K \dfrac{c_c}{c_A} \, (1 - \alpha) \end{cases}$$

Gelation degree: $\alpha = \dfrac{c_g}{c_A}$

⇨ Time-discretization (Backward Euler)

$$\left. \frac{\partial f}{\partial t} \right|_{t=t_n} = \frac{f_n - f_{n-1}}{\Delta t}$$

Calcium Alginate

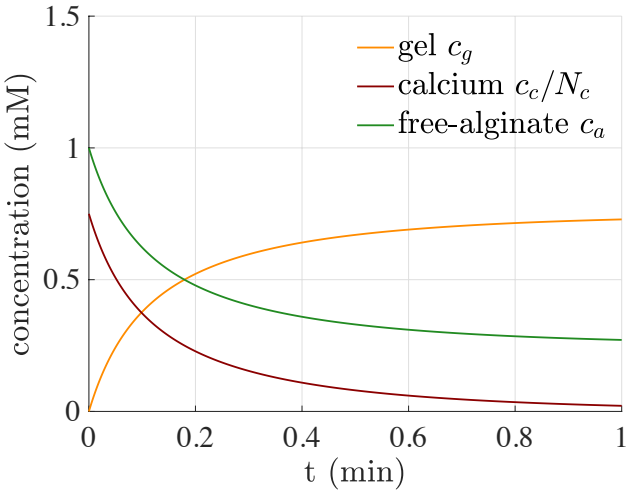
Chemical gelation process: Mikkelsen-Elgsaeter model

Reduced ME model: Toy example: one material point (no Calcium diffusion)

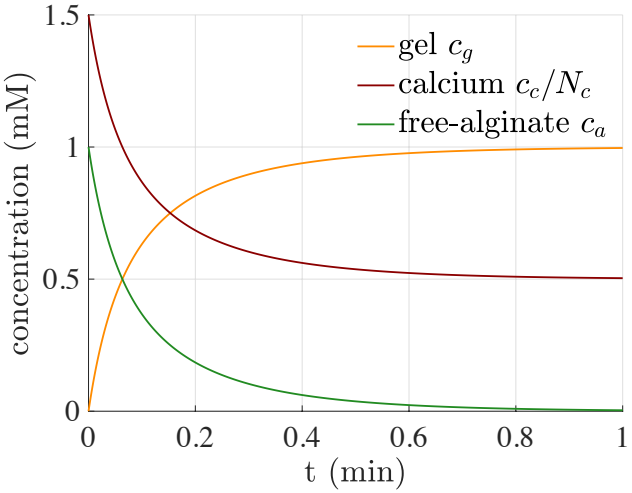
$$\begin{cases} \dfrac{\partial c_c}{\partial t} = -N_c K c_c (1-\alpha) \\ \dfrac{\partial \alpha}{\partial t} = K \dfrac{c_c}{c_A} (1-\alpha) \end{cases} \quad \text{(ODE)}$$

- Relationship between initial Calcium concentration and stoichiometric coefficient

$c_c|_{t=0} < N_c c_A$



$c_c|_{t=0} > N_c c_A$



Calcium Alginate

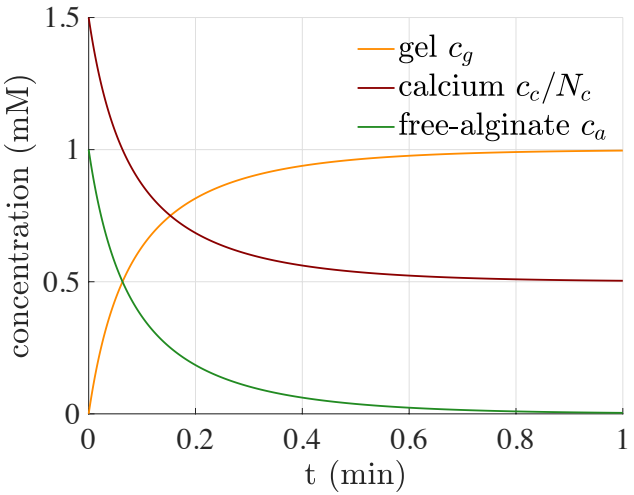
Chemical gelation process: Mikkelsen-Elgsaeter model

Reduced ME model: Toy example: one material point (no Calcium diffusion)

$$\begin{cases} \dfrac{\partial c_c}{\partial t} = -N_c K c_c (1-\alpha) \\ \dfrac{\partial \alpha}{\partial t} = K \dfrac{c_c}{c_A} (1-\alpha) \end{cases} \quad \text{(ODE)}$$

- Effect of reaction rate constant $K = k c_A^2$

$k = 5 \cdot 10^3 \mathrm{M}^{-2} s^{-1}$



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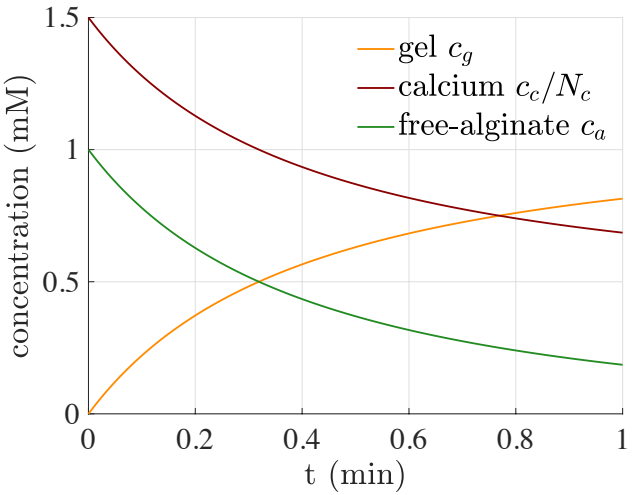


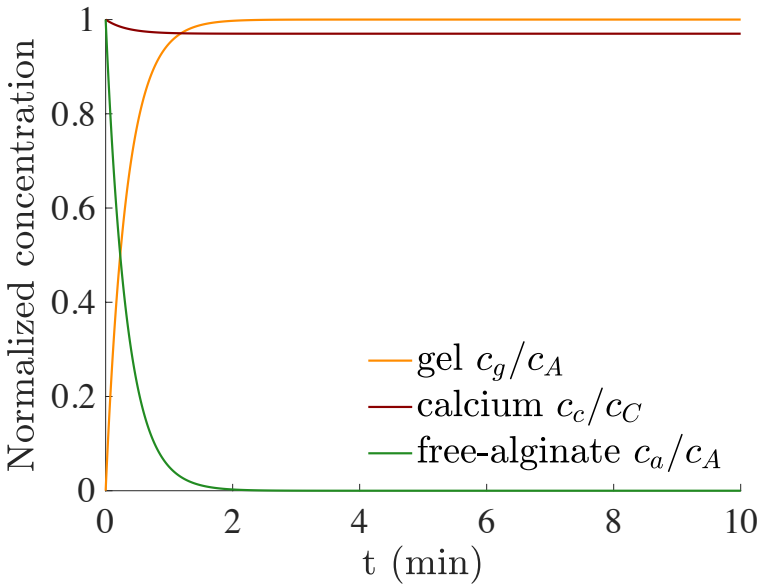
Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

Reduced ME model: Toy example: one material point (no Calcium diffusion)

$$\begin{cases} \dfrac{\partial c_c}{\partial t} = -N_c K c_c (1-\alpha) \\ \dfrac{\partial \alpha}{\partial t} = K \dfrac{c_c}{c_A} (1-\alpha) \end{cases} \quad \text{(ODE)}$$

- For $N_c = 0.3$ and $c_c|_{t=0} = c_C = 10 c_A > c_A$



⇨ **Full transformation at almost constant Calcium concentration**

- Reaction term plays a minor role:

$$- N_c K c_c (1-\alpha) \approx 0$$

- Time evolution depends almost exclusively on the diffusion term:

$$\frac{\partial c_c}{\partial t} \approx \nabla \cdot (D_c \nabla c_c)$$

Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

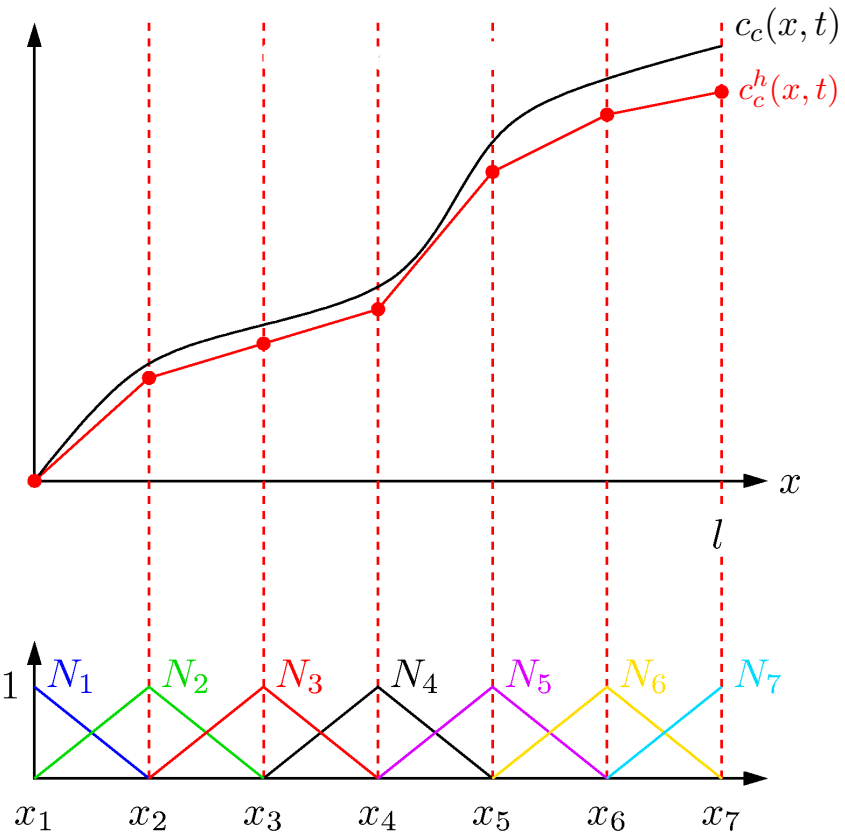
Reduced ME model: (only diffusion)

$$\begin{cases} \dfrac{\partial c_c}{\partial t} = \nabla \cdot (D_c \nabla c_c) \\ \dfrac{\partial \alpha}{\partial t} = K \dfrac{c_c}{c_A} (1 - \alpha) \end{cases} \quad \text{(PDE)}$$

Finite element discretization:

$$c_c(x,t) \approx c_c^h(x,t) = \sum_{i=1}^{n_{nodes}} N_i(x) c_i(t) \Big\} \; c_i(t_n) = c_{i,n}$$

$$\left.\begin{aligned} K_{ji,n} &= \int_0^l \left[D_c \frac{\partial N_i}{\partial x} \frac{\partial N_j}{\partial x} + \frac{1}{\Delta t} N_i N_j \right] dx \\ f_{j,n} &= \sum_{i=1}^{n_{nodes}} \left(\int_0^l \frac{1}{\Delta t} N_i N_j dx \right) c_{i,n-1} \end{aligned}\right\} \; \boldsymbol{K}_n \boldsymbol{c}_n = \boldsymbol{f}_n$$



Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

Reduced ME model: (only diffusion)

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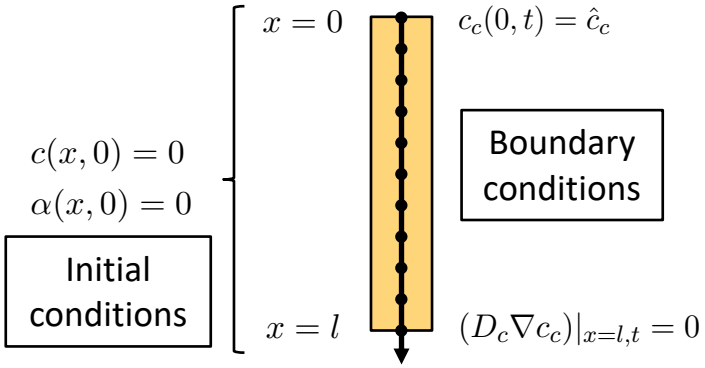
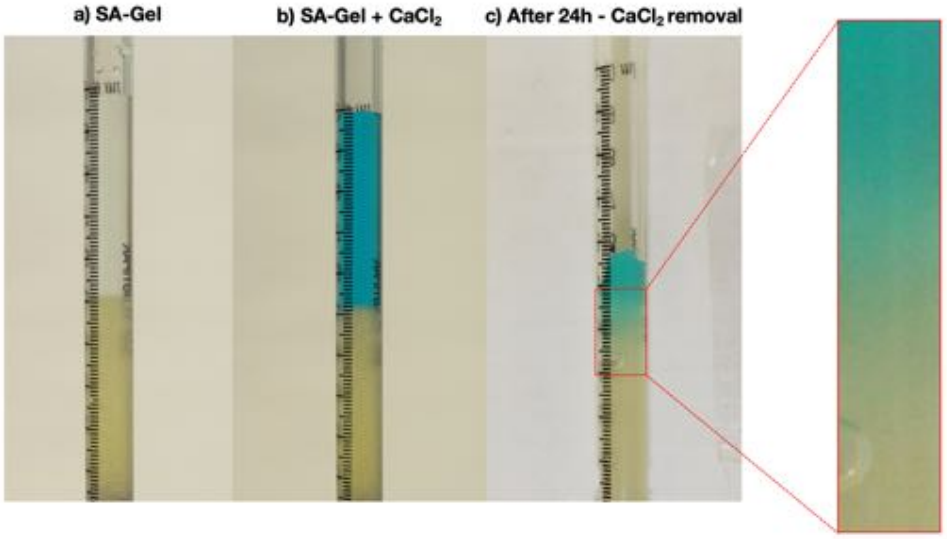


$$V_c(t) = A \int_0^l \frac{c_c(x,t)}{c_A}\, dx$$

Experimental data:

with Michele Conti, Franca Scocozza, Ferdinando Auricchio (Univ. of Pavia)



Total absorbed $CaCl_2$ volume:

Time	2 min	5 min	10 min	15 min	20 min	2 h	24 h	48 h
mean (μl)	2.97	5.13	6.01	7.77	8.95	18.25	53.38	78.65
s.d. (μl)	0.90	0.79	0.82	0.63	1.37	5.01	8.17	8.00

Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

Reduced ME model: (only diffusion)

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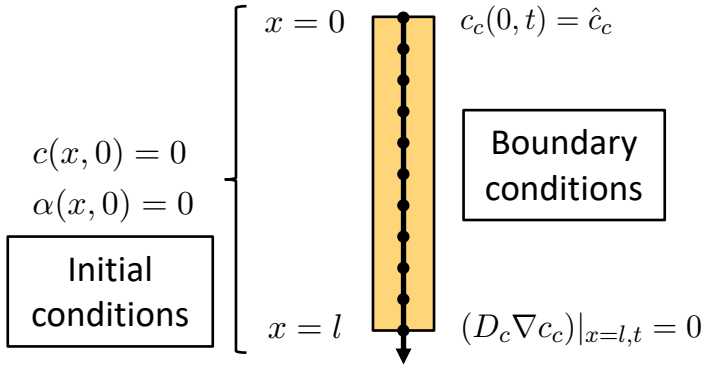


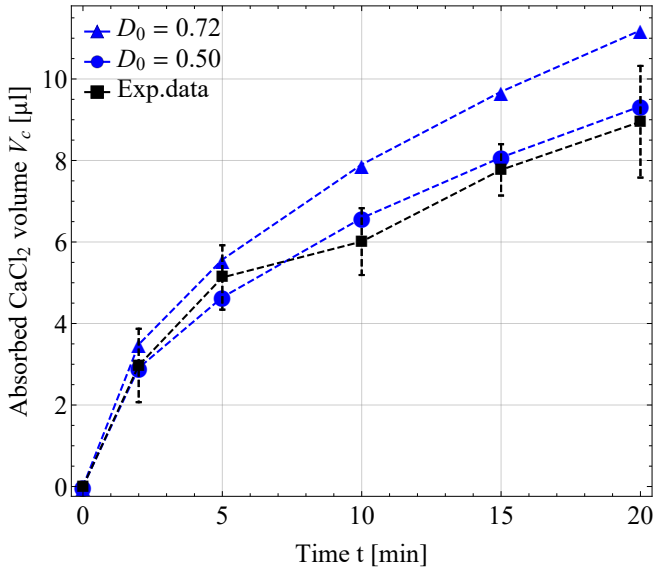
$$V_c(t) = A \int_0^l \frac{c_c(x,t)}{c_A}\, dx$$

Calcium diffusion parameter: D_c

1) Constant diffusion $D_c = D_0 = \text{const}$

$$D_0 \in (0.72 - 0.94) \times 10^{-9} \text{m}^2\text{s}^{-1}$$

Braschler et al, Anal. Chem. 83:2234-2242, 2011



Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

Reduced ME model: (only diffusion)

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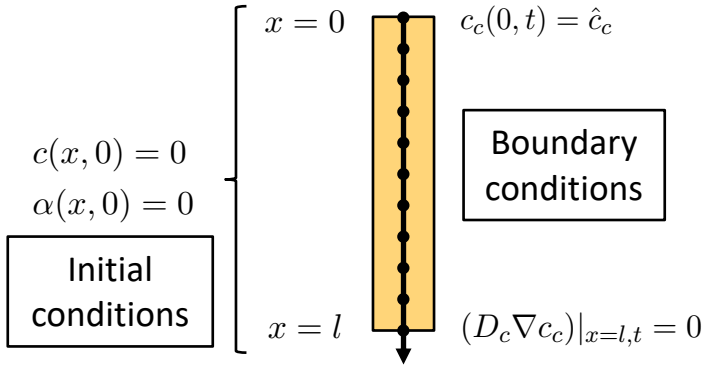

$$V_c(t) = A \int_0^l \frac{c_c(x,t)}{c_A} \, dx$$

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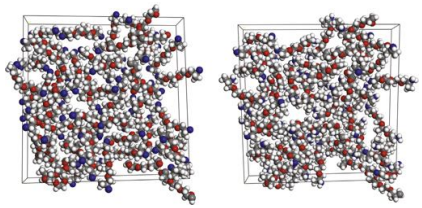
2) Varying diffusion $D_c = D_c(\alpha)$ $\quad \alpha \nearrow \Rightarrow D_c \searrow$

Molecular Dynamic Simulations



$D_1 = 0.5 D_0$

(Salahshoora, Rahbar, JMBBM 2014)

$$D(\alpha) = D_0 + (D_1 - D_0) \frac{\exp(-\alpha/\alpha_{\text{gel}}) - 1}{\exp(-1/\alpha_{\text{gel}}) - 1}$$

Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

Reduced ME model: (only diffusion)

$$\begin{cases} \dfrac{\partial c_c}{\partial t} = \nabla \cdot (D_c \nabla c_c) \\ \dfrac{\partial \alpha}{\partial t} = K \dfrac{c_c}{c_A} (1 - \alpha) \end{cases} \quad \text{(PDE)}$$

$c(x,0) = 0$
$\alpha(x,0) = 0$

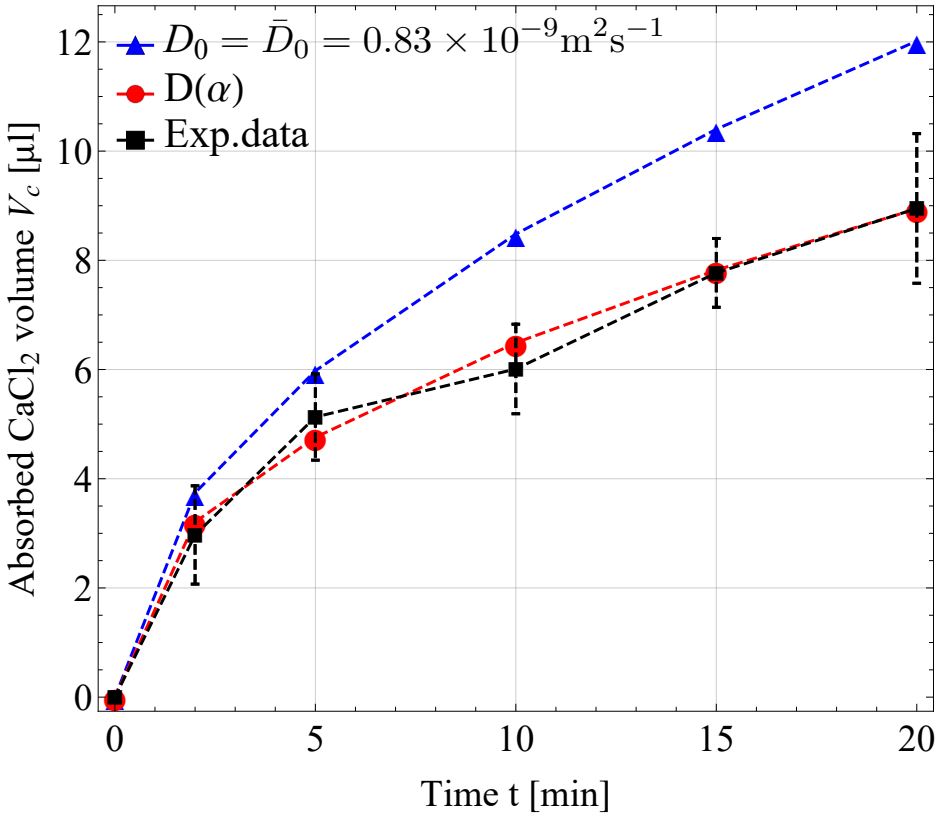
Initial conditions

$x = 0$: $c_c(0,t) = \hat{c}_c$

$x = l$: $(D_c \nabla c_c)|_{x=l,t} = 0$

Boundary conditions

$$V_c(t) = A \int_0^l \frac{c_c(x,t)}{c_A} \, dx$$

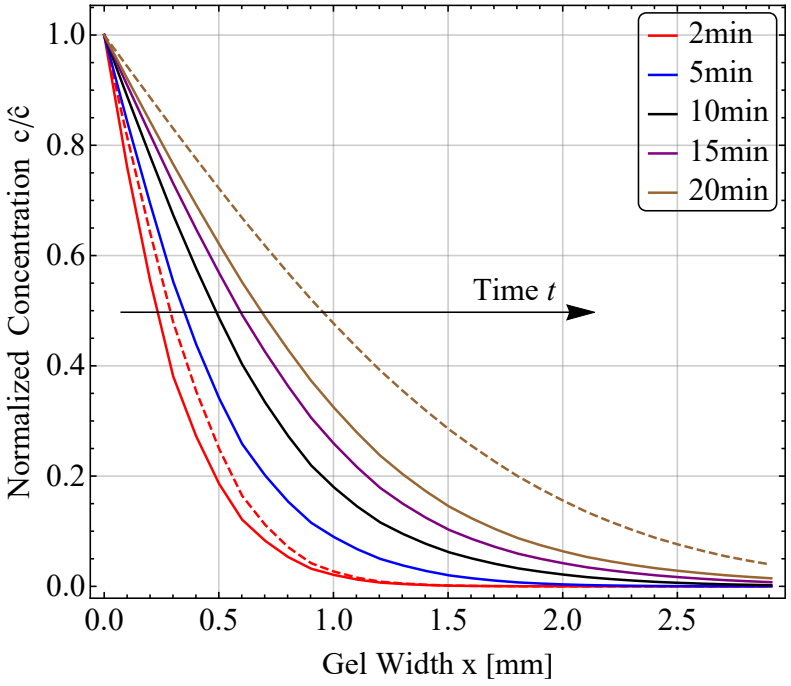


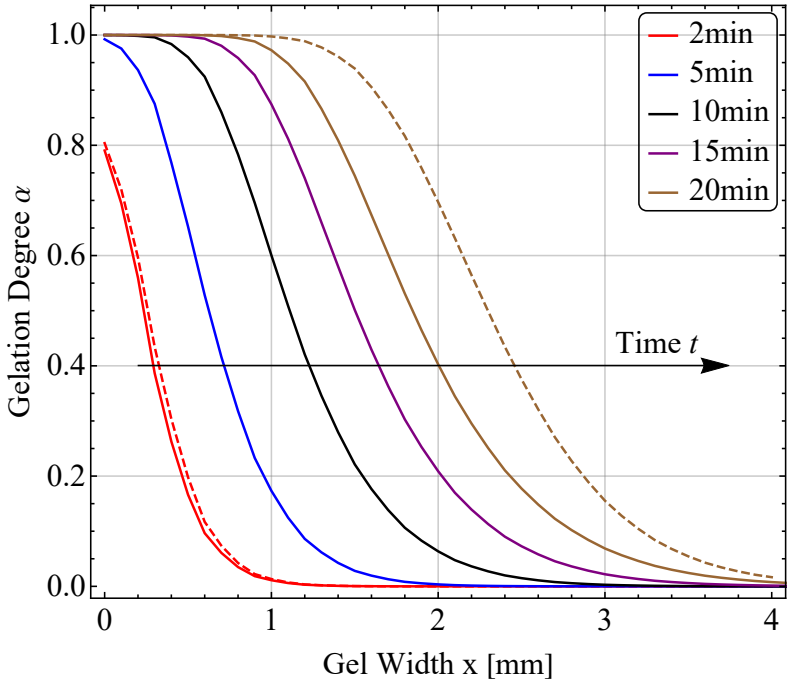
Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

Reduced ME model: (only diffusion)

Continuous lines: $D_c = D_c(\alpha)$ Dashed lines: $D_c = D_0$





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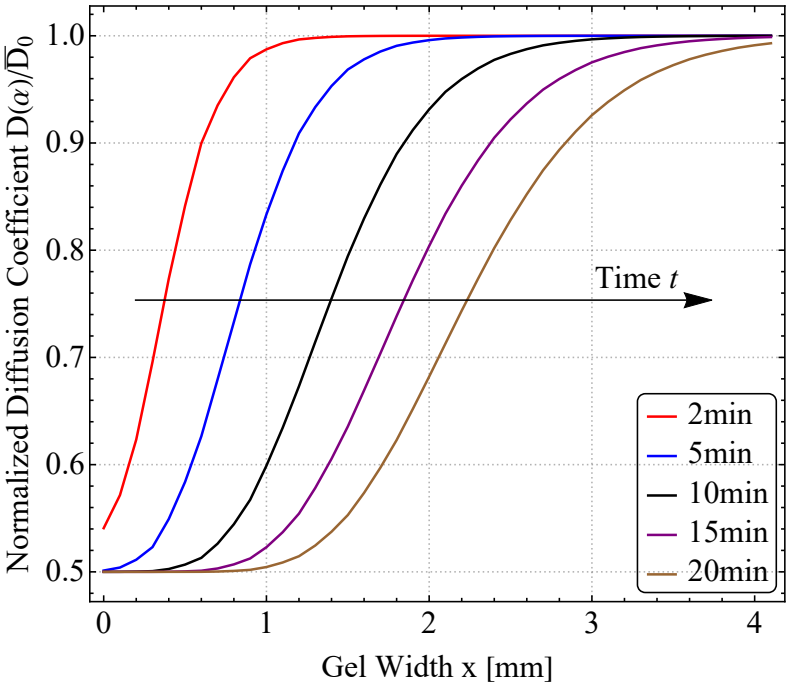

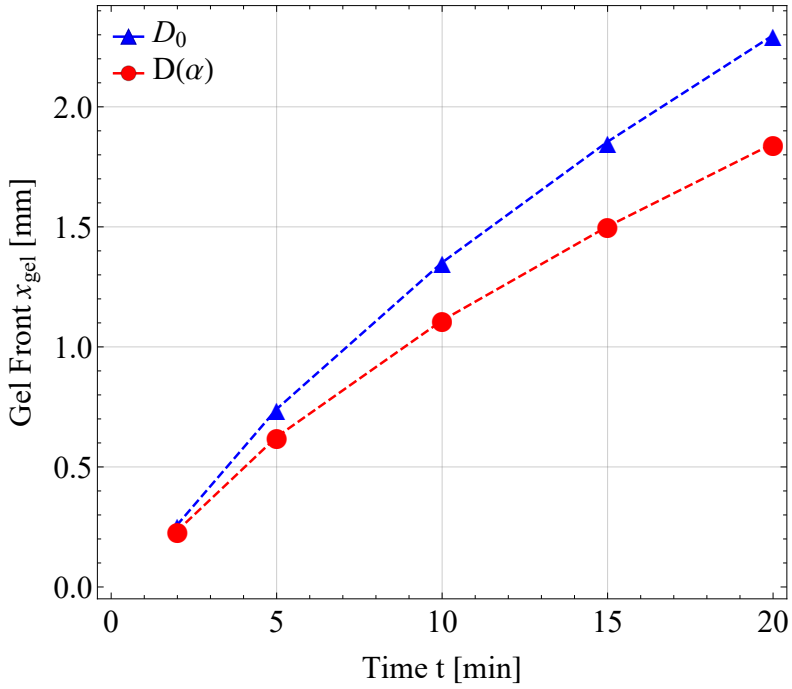

Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

Reduced ME model:

$$\begin{cases} \dfrac{\partial c_c}{\partial t} = \nabla \cdot (D_c \nabla c_c) - N_c K c_c (1-\alpha) \\ \dfrac{\partial \alpha}{\partial t} = K \dfrac{c_c}{c_A} (1-\alpha) \end{cases}$$

Gelation degree: $\alpha = \dfrac{c_g}{c_A}$

- Analysis of Calcium reaction kinetics ✓
- Analysis of Calcium diffusion ✓
- Effects of free-alginate diffusion? ✗

Basic hypothesis:
Negligible free-alginate diffusion $D_a \ll D_c$

➡ Need of the use of:

Full ME model:

$$\begin{cases} \dfrac{\partial c_a}{\partial t} = \nabla \cdot (D_a \nabla c_a) - \dfrac{\partial c_g}{\partial t} \\ \dfrac{\partial c_c}{\partial t} = \nabla \cdot (D_c \nabla c_c) - N_c \dfrac{\partial c_g}{\partial t} \\ \dfrac{\partial c_g}{\partial t} = k c_a c_c (c_a + c_g) \end{cases}$$

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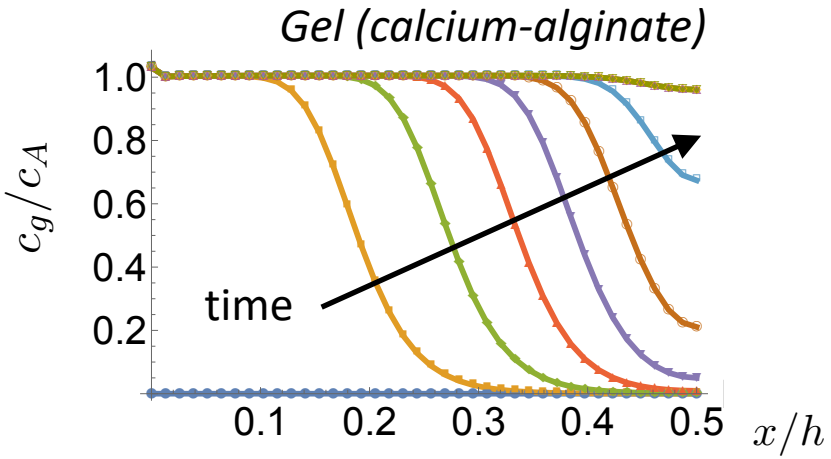
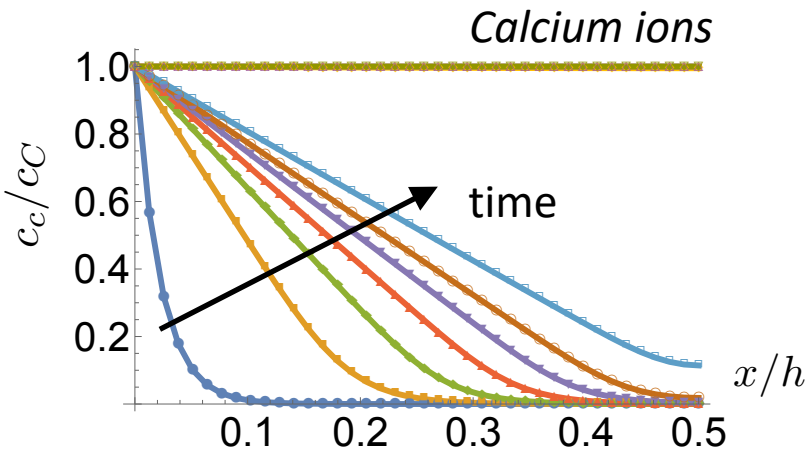
Chemical gelation process: Mikkelsen-Elgsaeter model

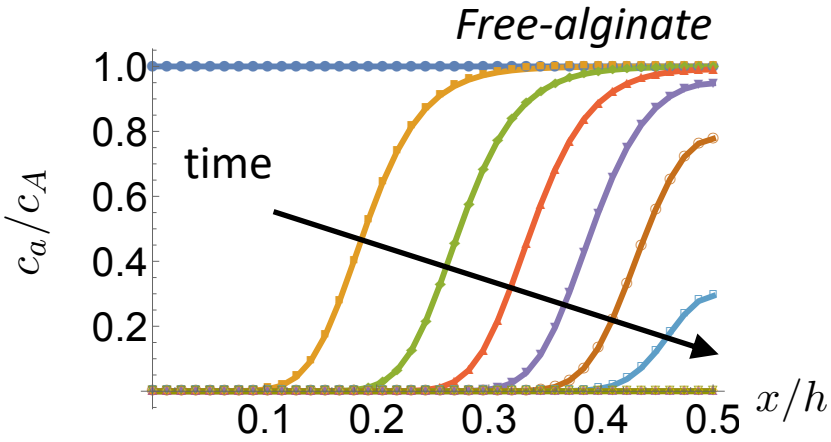
Full ME model:

$$\begin{cases} \dfrac{\partial c_a}{\partial t} = \nabla \cdot (D_a \nabla c_a) - \dfrac{\partial c_g}{\partial t} \\ \dfrac{\partial c_c}{\partial t} = \nabla \cdot (D_c \nabla c_c) - N_c \dfrac{\partial c_g}{\partial t} \\ \dfrac{\partial c_g}{\partial t} = k c_a c_c (c_a + c_g) \end{cases}$$

- **Low** free-alginate diffusion: $D_a = 0.0001 D_c$





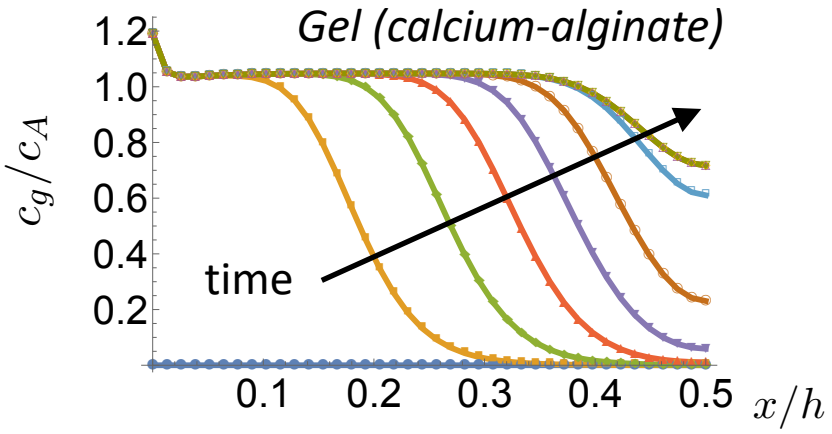


Calcium Alginate

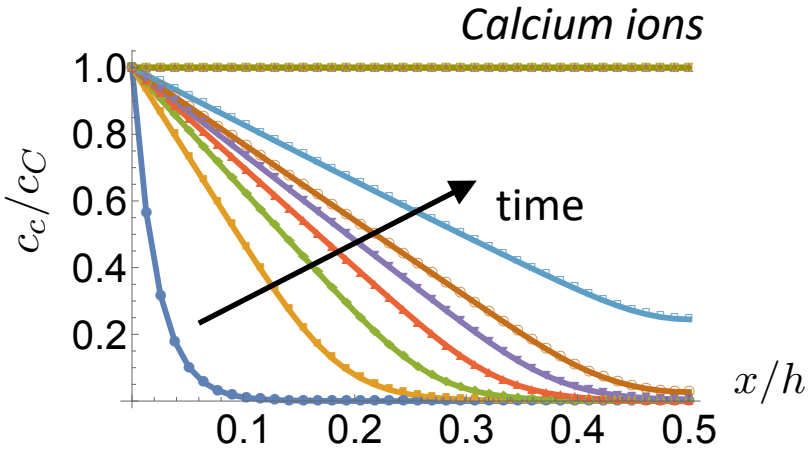
Chemical gelation process: Mikkelsen-Elgsaeter model

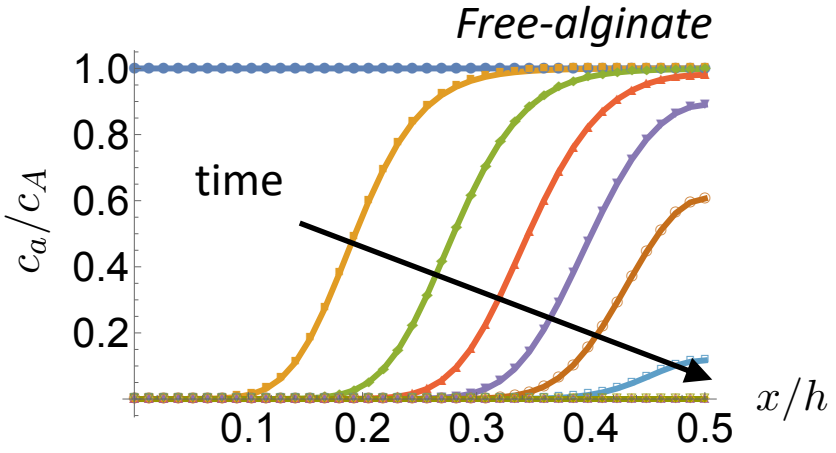
Full ME model:

$$\begin{cases} \dfrac{\partial c_a}{\partial t} = \nabla \cdot (D_a \nabla c_a) - \dfrac{\partial c_g}{\partial t} \\ \dfrac{\partial c_c}{\partial t} = \nabla \cdot (D_c \nabla c_c) - N_c \dfrac{\partial c_g}{\partial t} \\ \dfrac{\partial c_g}{\partial t} = k c_a c_c (c_a + c_g) \end{cases}$$



- **Mild** free-alginate diffusion: $D_a = 0.001 D_c$



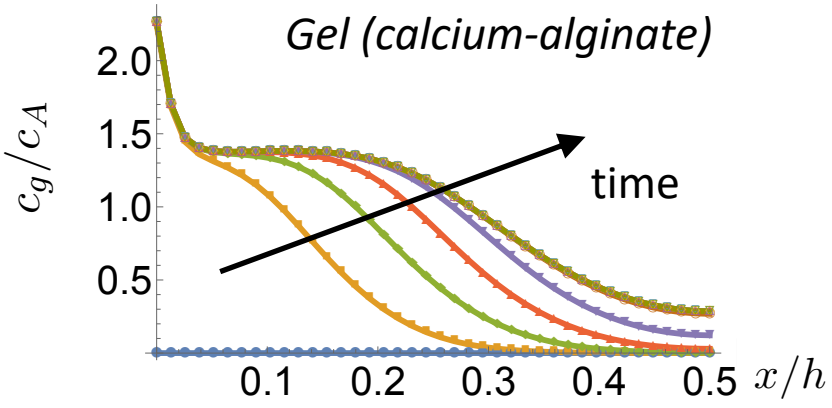


Calcium Alginate

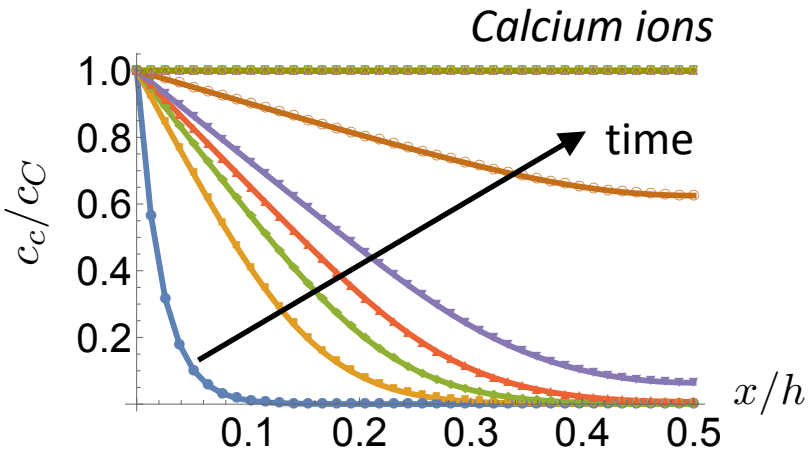
Chemical gelation process: Mikkelsen-Elgsaeter model

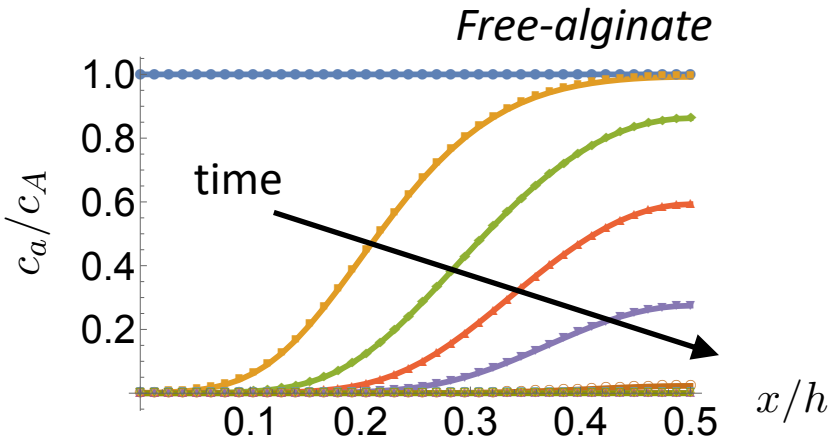
Full ME model:

$$\begin{cases} \dfrac{\partial c_a}{\partial t} = \nabla \cdot (D_a \nabla c_a) - \dfrac{\partial c_g}{\partial t} \\ \dfrac{\partial c_c}{\partial t} = \nabla \cdot (D_c \nabla c_c) - N_c \dfrac{\partial c_g}{\partial t} \\ \dfrac{\partial c_g}{\partial t} = k c_a c_c (c_a + c_g) \end{cases}$$



- **High** free-alginate diffusion: $D_a = 0.01 D_c$

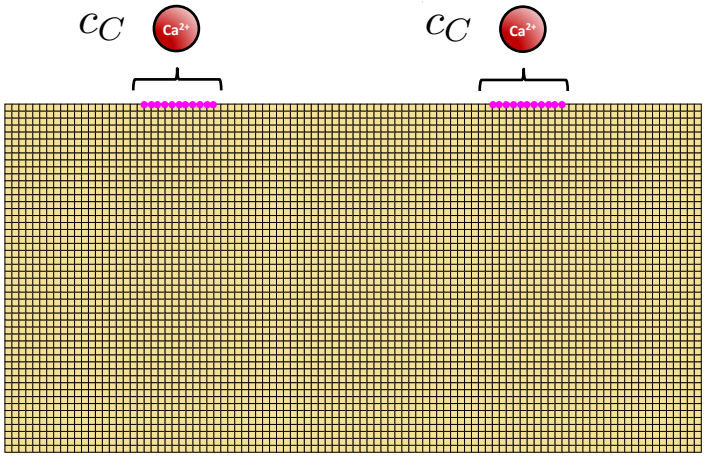




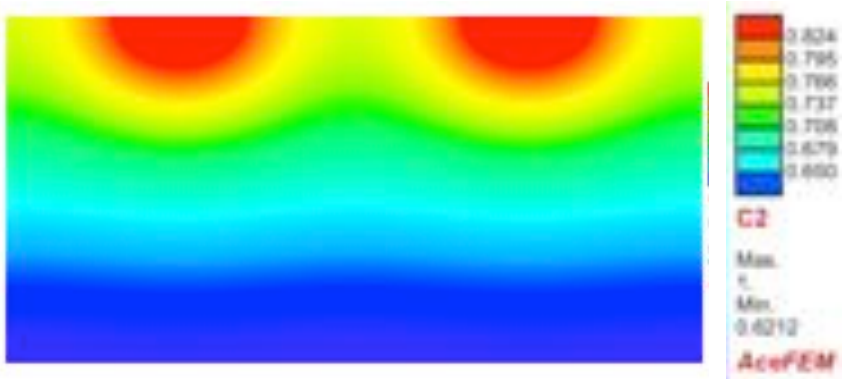
Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

Full ME model: Application



Calcium ions c_c/c_C



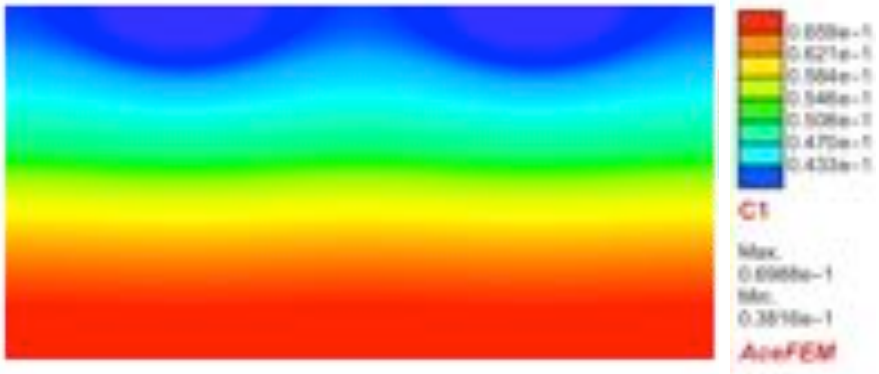
Parameters: $D_a = 0.01 D_c\,,\ L = 0.2\,,\ H = 0.1\,,\ T = 0.5$ (adimensional)

Calcium Alginate

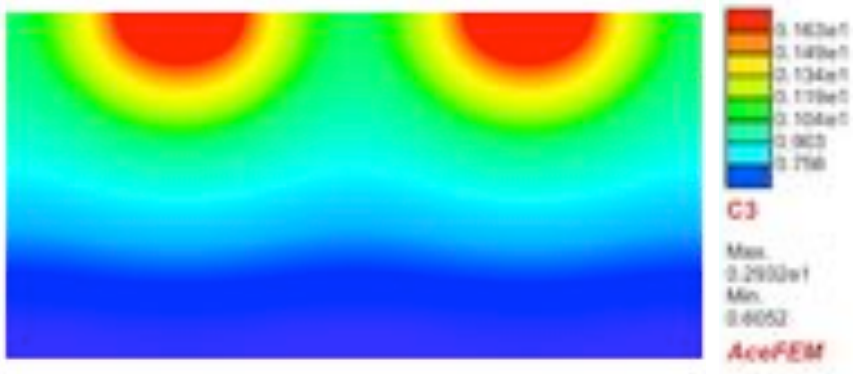
Chemical gelation process: Mikkelsen-Elgsaeter model

Full ME model: Application

Free-alginate c_a/c_A



Gel (calcium-alginate) c_g/c_A

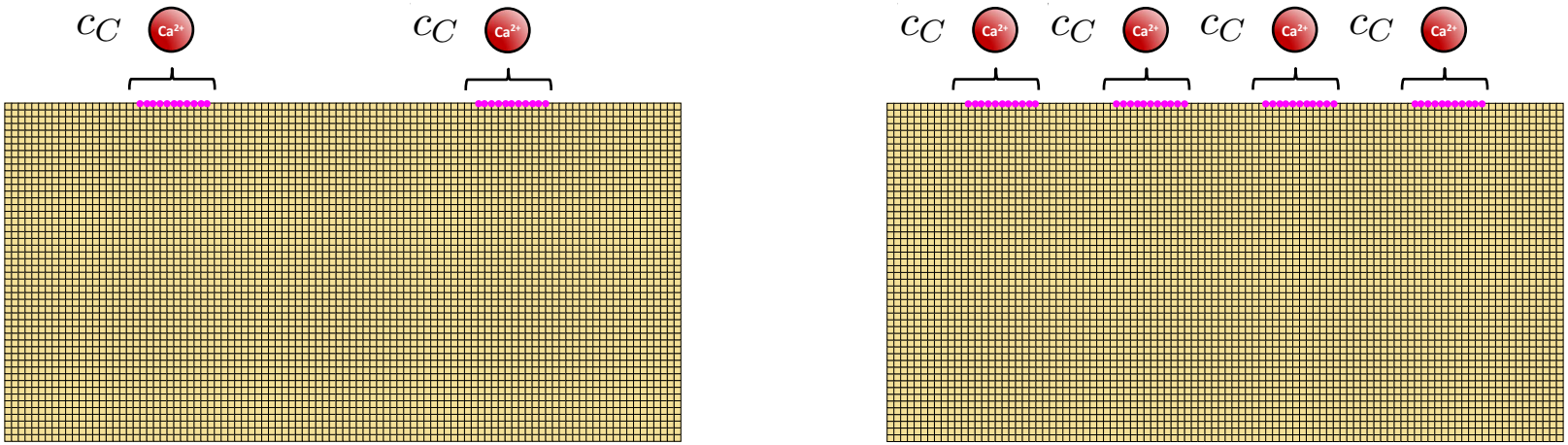


Parameters: $D_a = 0.01 D_c\,,\ L = 0.2\,,\ H = 0.1\,,\ T = 0.5$ (adimensional)

Calcium Alginate

Chemical gelation process: Mikkelsen-Elgsaeter model

Full ME model: Application



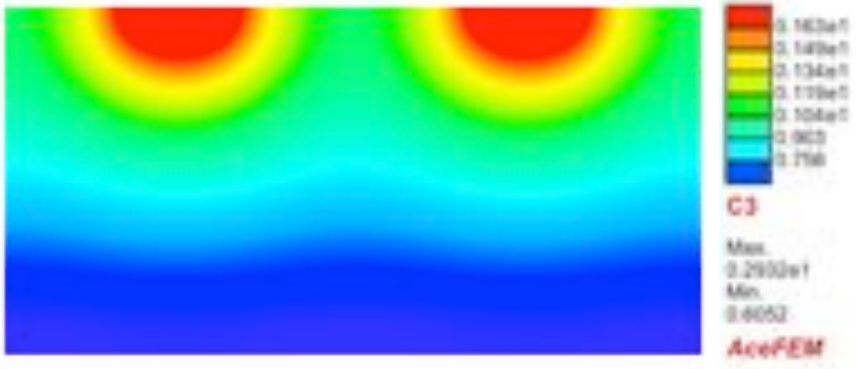
Parameters: $D_a = 0.01 D_c\,,\ L = 0.2\,,\ H = 0.1\,,\ T = 0.5$ (adimensional)

Calcium Alginate

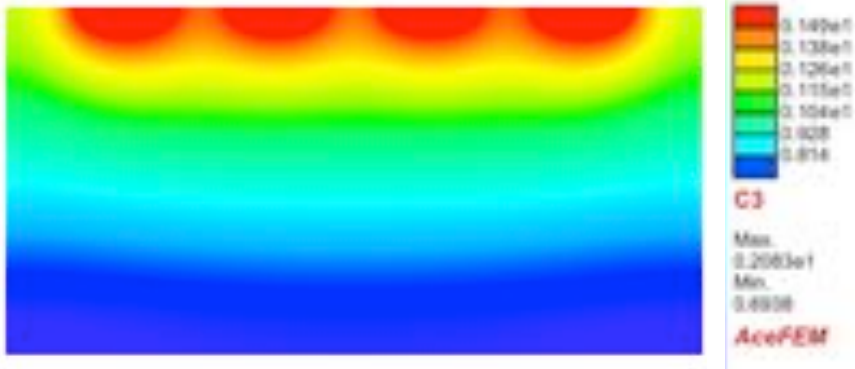
Chemical gelation process: Mikkelsen-Elgsaeter model

Full ME model: Application

Gel (calcium-alginate) c_g/c_A

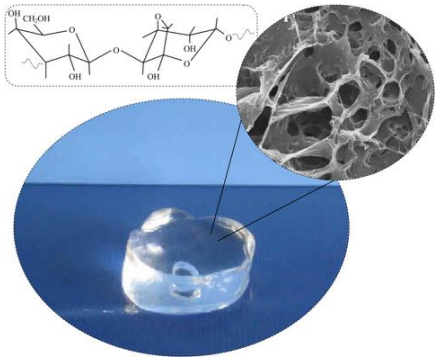


Gel (calcium-alginate) c_g/c_A

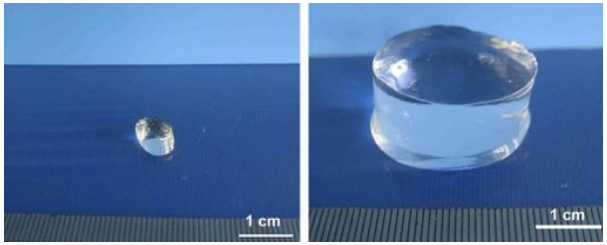


Parameters: $D_a = 0.01 D_c\,,\ L = 0.2\,,\ H = 0.1\,,\ T = 0.5$ (adimensional)

And the fluid content?

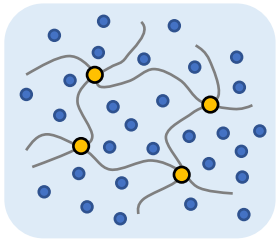


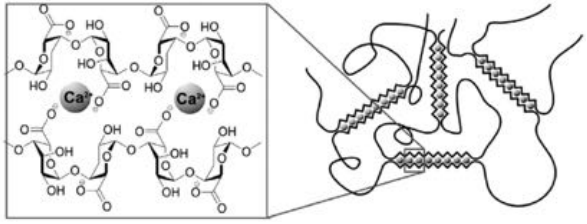
Hydrogels: three-dimensional, hydrophilic, polymeric networks capable of absorbing large amounts of water or biological fluids



Theoretical challenges:

1. Coupled (Multiphysics) mechanisms:
    - Fluid content
    - Chemical reactions (e.g., crosslinking)
2. Large deformations

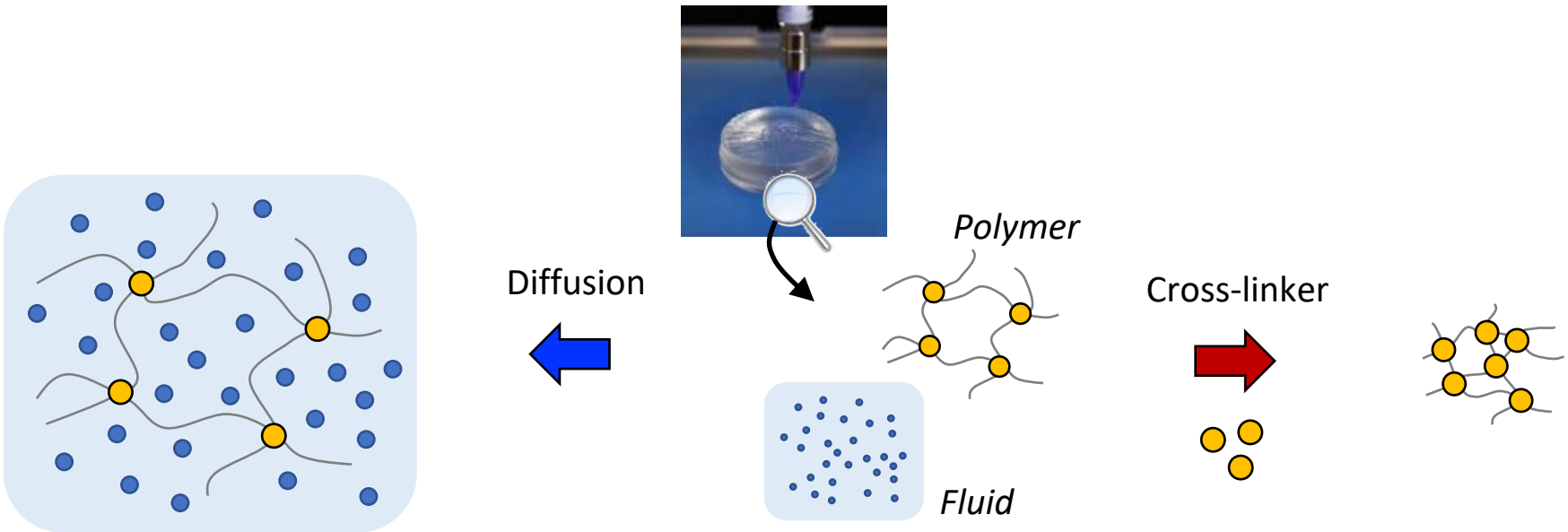




Calcium Alginate Hydrogels

Two concurring mechanisms:

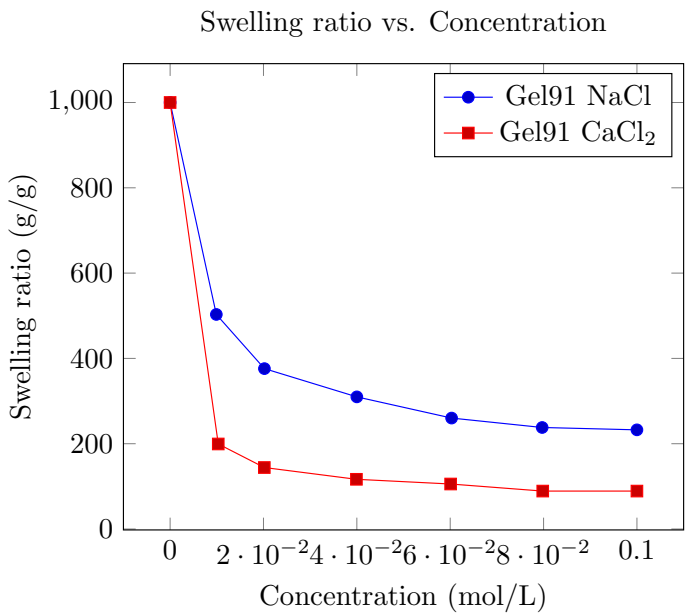
1. Fluid diffusion → **Swelling**
2. Polymer crosslinking → **Shrinking**



Calcium Alginate Hydrogels

Two concurring mechanisms:

1. Fluid diffusion ➡ **Swelling**
2. Polymer crosslinking ➡ **Shrinking**



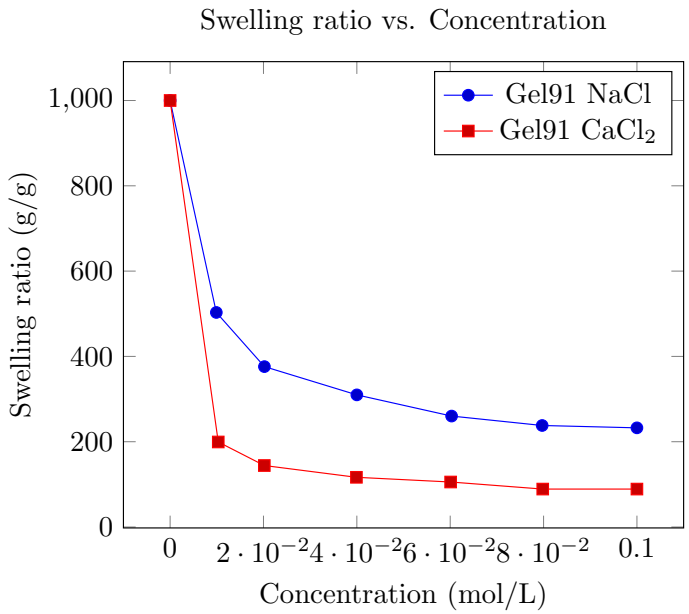
- Swelling ratio of hydrogels decreases with an increase of the ionic strength of the solution
- In $CaCl_2$ solutions, the swelling ratio decreases quicker than in NaCl solutions

Chang et al, European Polymer J 46:92-100 (2010)

Calcium Alginate Hydrogels

Two concurring mechanisms:

1. Fluid diffusion ➡ **Swelling**
2. Polymer crosslinking ➡ **Shrinking**



Why?

- Higher cationic charge of $CaCl_2$ than NaCl

⇨ Difference in the concentration of mobile ions between the hydrogel and the solution is reduced (Donnan equilibrium theory)

- Permanent structural alterations due to Ca-induced crosslinking (egg-boxes)

Chang et al, European Polymer J 46:92-100 (2010)

Calcium Alginate Hydrogels

Two concurring mechanisms:

1. Fluid diffusion ➡ **Swelling**
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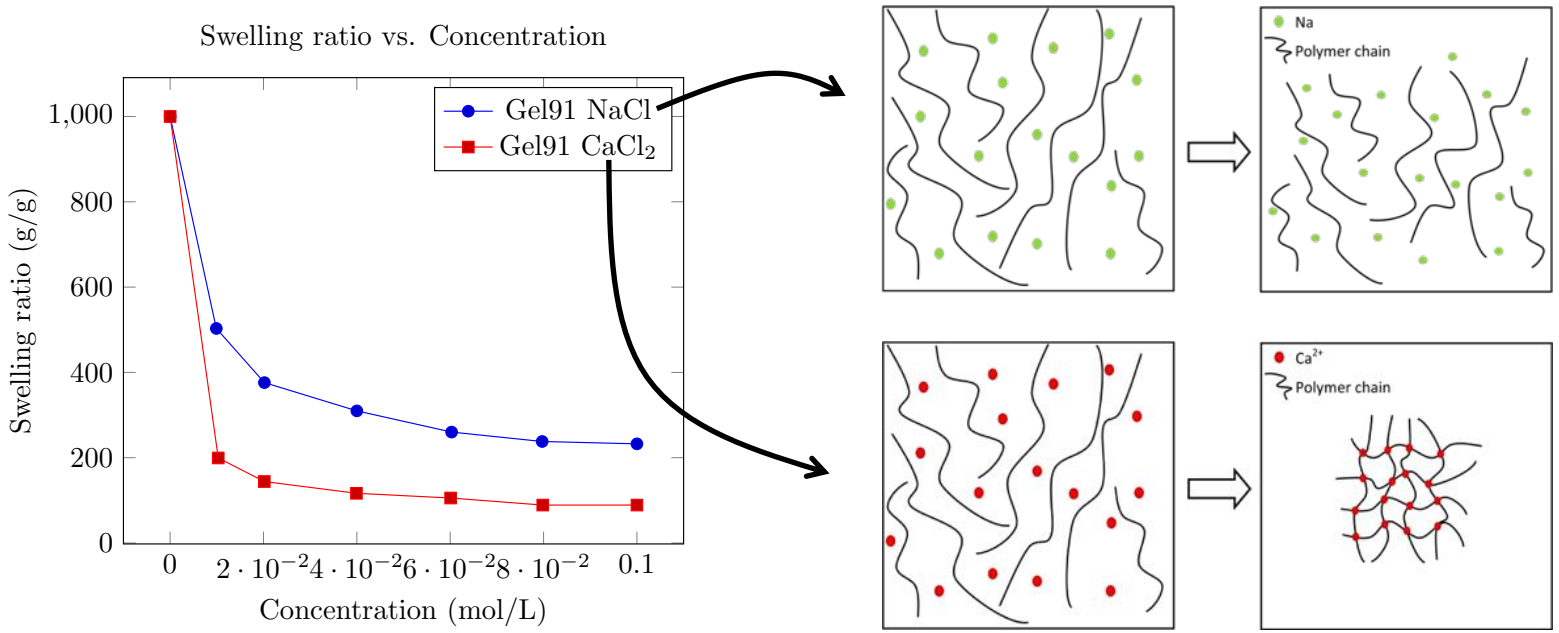

Chang et al, European Polymer J 46:92-100 (2010)

Calcium Alginate Hydrogels

Two concurring mechanisms:

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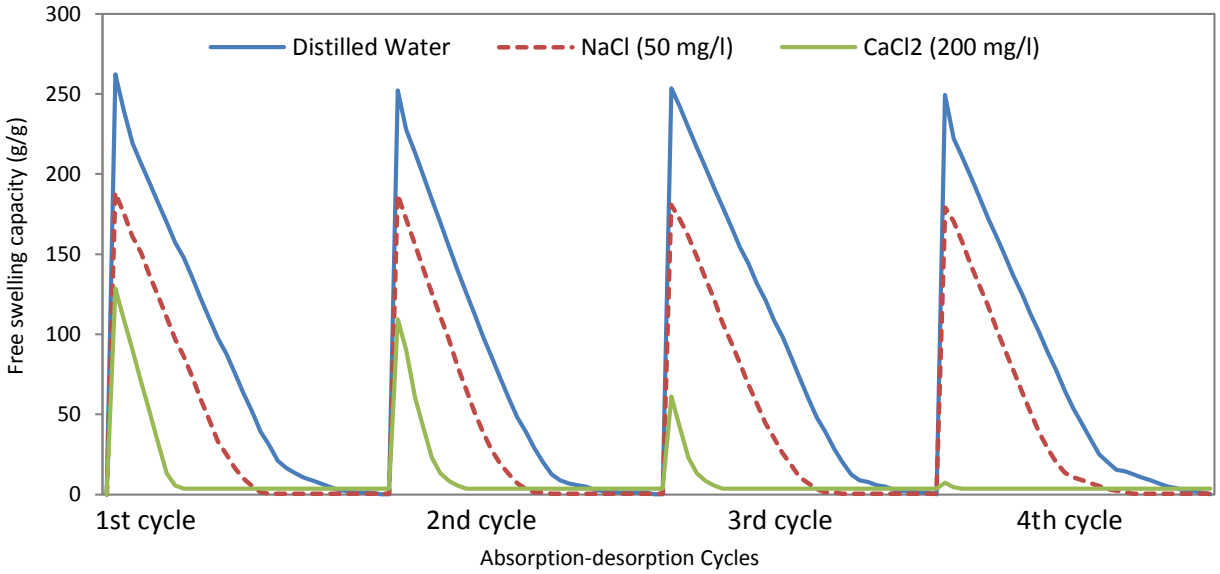
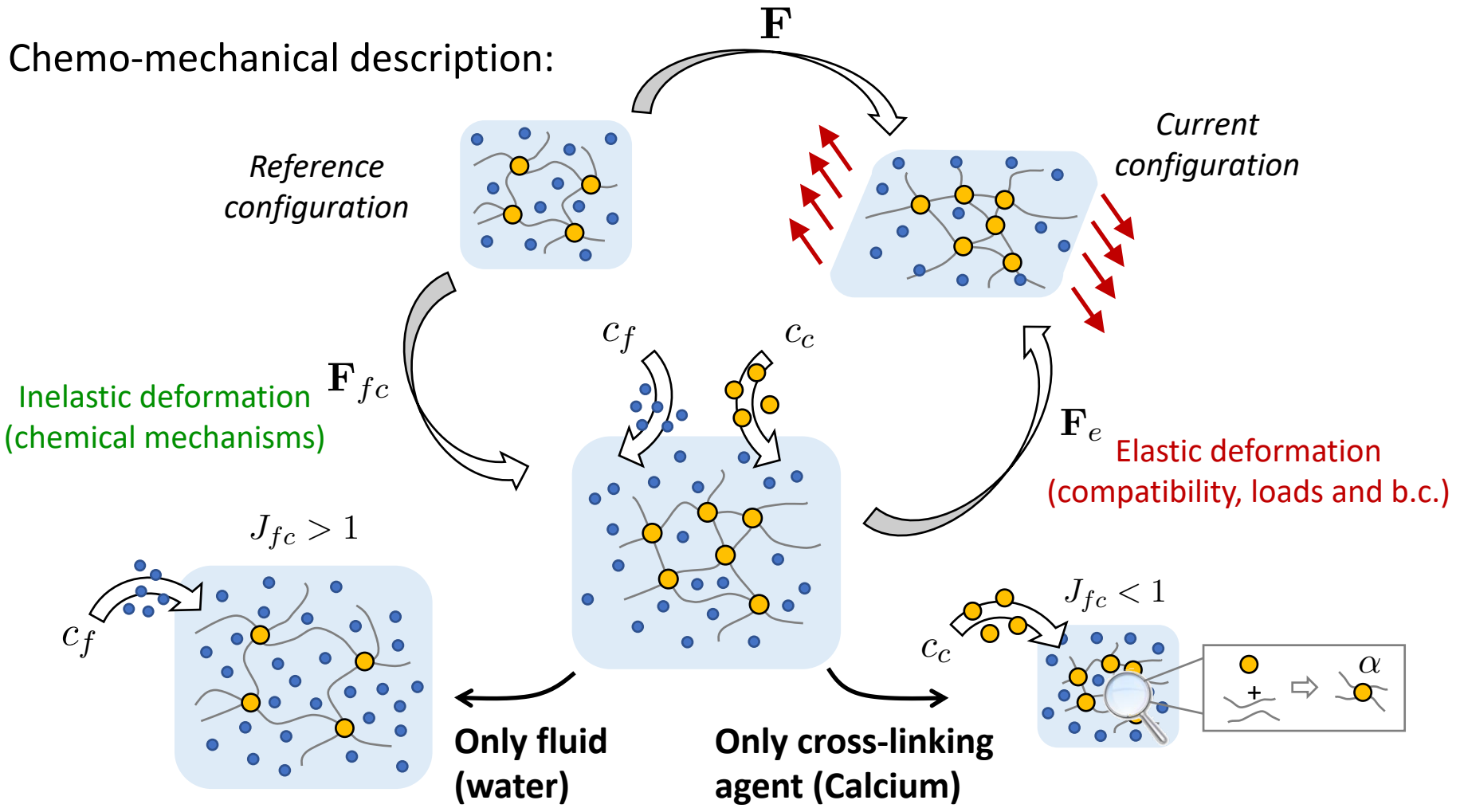


Sanz Gómez, PhD Thesis Dissertation, Universidad de Sevilla (2015)

Evidence of **permanent structural alterations** due to Ca-induced crosslinking

Calcium Alginate Hydrogels

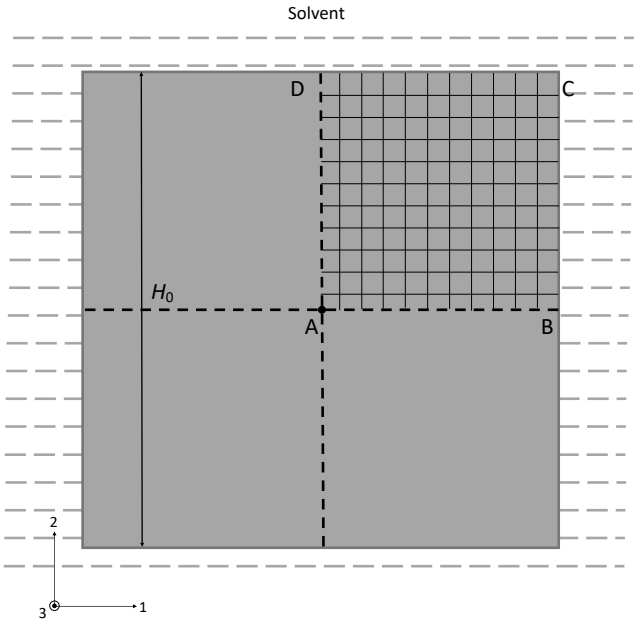
Chemo-mechanical description:

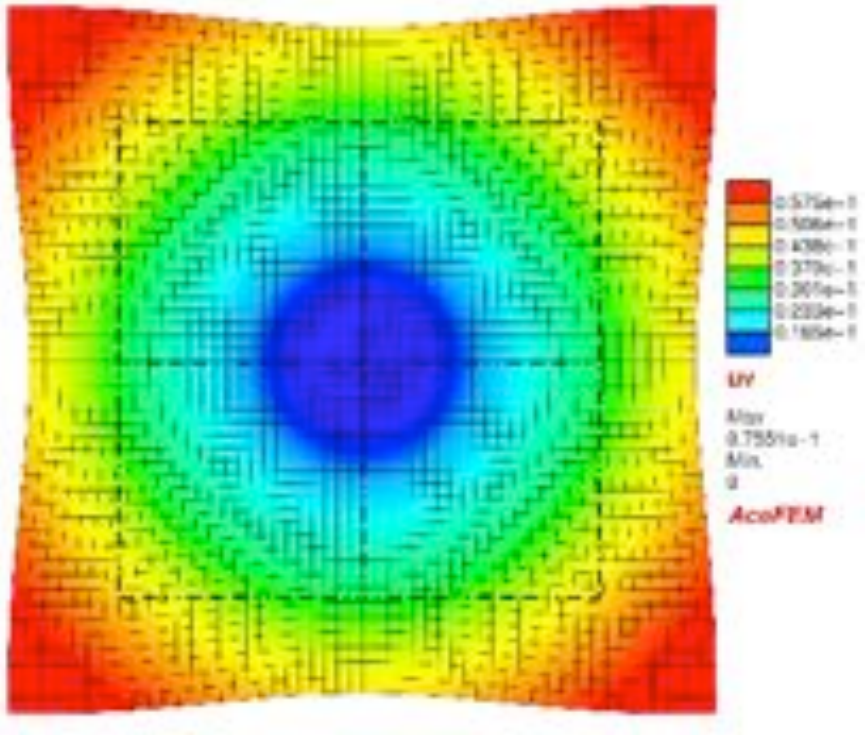


Calcium Alginate Hydrogels

Results: **Free-swelling** (*no Calcium*)

$$\mathbf{F}_{fc} = [J_{fc}(c_f, \alpha)]^{1/3}\mathbf{I} = (1 + \overbrace{\Lambda c_f}^{\text{Swelling}} - \overbrace{\Gamma\alpha}^{\text{Shrinking}})^{1/3}\mathbf{I}$$





Calcium Alginate Hydrogels

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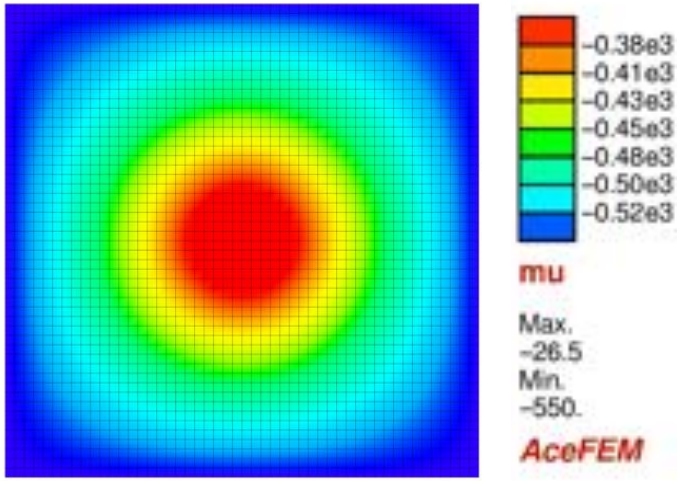
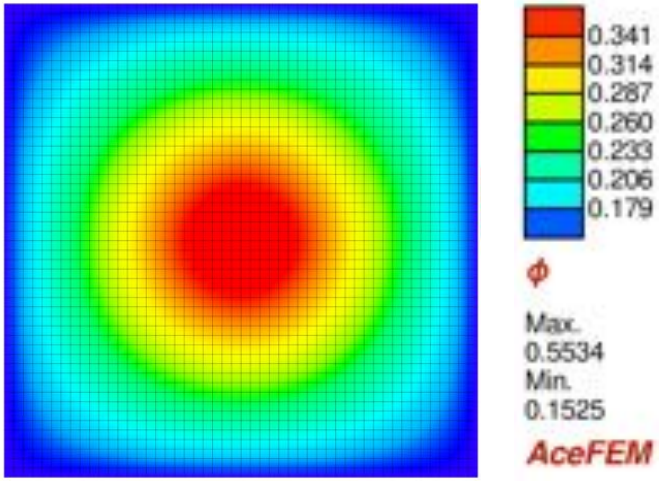
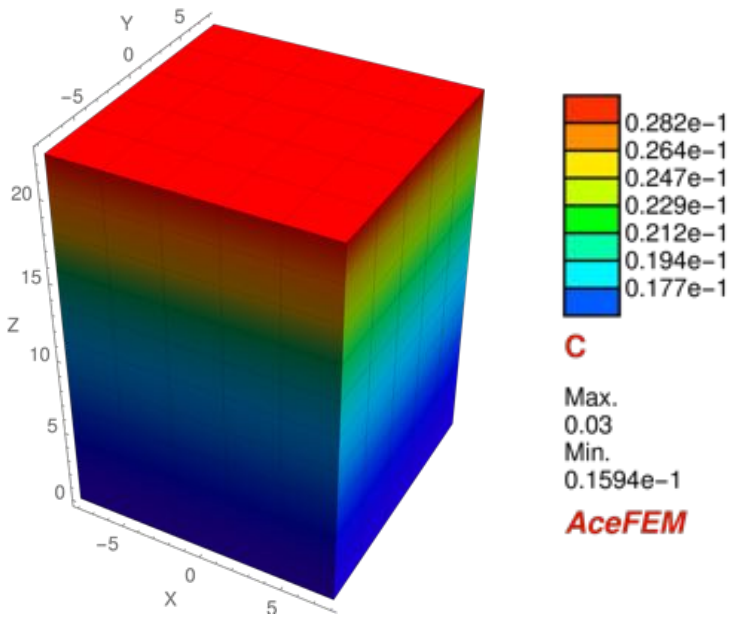


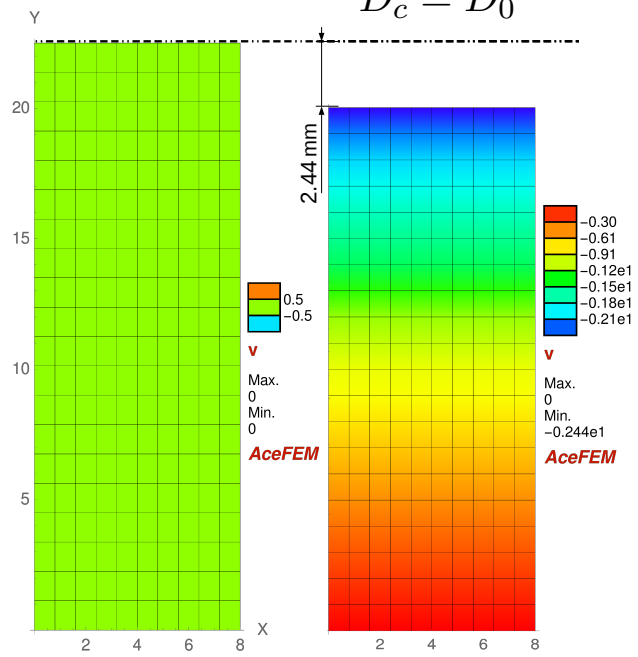


Calcium Alginate Hydrogels

Results: **Drained-Shrinking** (*no swelling*) $\mathbf{F}_{fc} = [J_{fc}(c_f, \alpha)]^{1/3}\mathbf{I} = (1 + \overbrace{\Lambda c_f}^{\text{Swelling}} - \overbrace{\Gamma\alpha}^{\text{Shrinking}})^{1/3}\mathbf{I}$

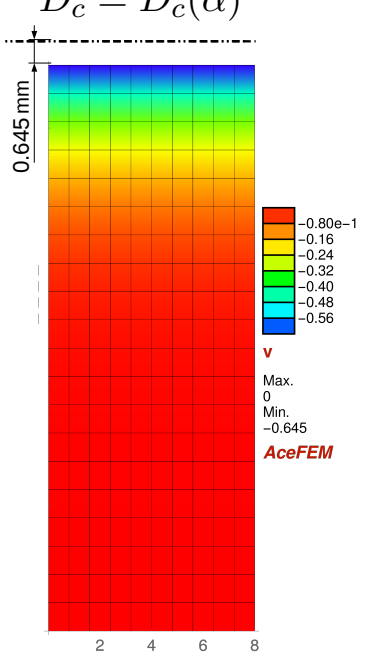


$D_c = D_0$



- 10%

$D_c = D_c(\alpha)$



- 2.5%

Funding: Masterplan SMARTBIOTECS

Thank You
Dankeschön

Group @IKM

Predictive Simulations in Biomechanics

Meike Gierig

Project: *Computational Modelling of In-stent Restenosis*

Aidin Hajikhani

Project: *Chemo-mechanical modelling of hydrogels for bioprinting applications*

Michele MARINO

Group Leader "Predictive Simulations in Biomechanics"

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