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Computational modeling of hydrogel cross-linking based on reaction-diffusion theory

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Alginate-based hydrogel is widely used as bio-ink in 3D bioprinting. For producing the bio-ink and stabilizing the polymer network, the hydrogel shall undergo a gelation process which can be obtained by adding an ionic cross-linker agent, such as Calcium ions for alginate. The diffusion of the crosslinker in the alginate stabilizes the polymeric network thanks to the reaction of Calcium ions with alginate monomers. This work presents a reaction-diffusion computational model of the gelation mechanism in alginate hydrogels. The coupled chemical system is solved using finite element discretizations considering the inhomogeneous evolution of the gelation process in time and space.

1 Introduction

Sodium alginate is an anionic copolymer composed by mannuronic (M) blocks and guluronic acid (G) blocks. Chemical gelation occurs when G-blocks belonging to different monomers are attached to each other by means of reactive ions diffusing within the gel. Calcium chloride ($CaCl_2$) is one of the most used alginate cross-linking agents. The G-blocks of the alginate interact with the cross-linking agents, i.e. divalent cations Ca^{2+}, forming intersections in which calcium ions are placed, referred to as egg-boxes [1]. Therefore, $CaCl_2$ allows for a simple and rapid gelation. At the same time, cross-linking via $CaCl_2$ is not a controlled process due to the high solubility of $CaCl_2$ in aqueous solutions. Therefore, the fidelity and effectiveness of bioprinting strategies depend on coupled effects of cross-linking mechanisms and diffusive processes [2]. The proposed study aims at developing a computational model for the mechanisms occurring during gelation. A solution of $CaCl_2$ in water is considered in contact with the gel. The reactive-diffusive mechanisms governing Calcium diffusion are described, together with the diffusion of water in the hydrogel.

2 Modeling

The reaction-diffusion mechanisms in the hydrogel described on the basis of the Mikkelsen-Elgsaeter model under the assumption of negligible free-alginate diffusion [3]. A one-dimensional problem is considered. Hence, the geometry of the hydrogel is defined by means of the scalar coordinate variable $x \in [0, l]$, where $l = 28$ is the length of the gel. For describing the cross-linking dynamics, the time variable $t > 0$ is also introduced. The chemical system is defined by three internal variables: $\alpha = \alpha(x,t)$ gelation degree, calcium concentration $c_c = c_c(x,t)$, and water concentration $c_w = c_w(x,t)$. The gelation degree α depicts the ratio between the solid gel concentration c_g of the chemically cross-linked polymer chains and the initial concentration of free-alginate c_A, here in the range of 6-10%(w/v). Under the assumption of negligible free-alginate diffusion, it results $c_g \leq c_A$. The evolution of α w.r.t time results:

$$\frac{\partial \alpha}{\partial t} = K \frac{c_c}{c_A}(1-\alpha)\,, \qquad \text{with} \qquad \alpha = \frac{c_g}{c_A} \in [0,1]. \tag{1}$$

where the reaction rate K is $0.03\ \text{s}^{-1}$ from [4]. Calcium c_c, and water c_w concentrations are governed by:

$$\frac{\partial c_c}{\partial t} = \nabla \cdot (D_c(\alpha) \nabla c_c) - N_c c_A \frac{\partial \alpha}{\partial t}\,, \qquad \frac{\partial c_w}{\partial t} = \nabla \cdot (D_w(\alpha) \nabla c_w)\,, \tag{2}$$

where the consumption term in Eq. (2) depends on the stoichiometric coefficient N_c which describes the avarage number of Ca^{2+} ions per alginate-alginate formation ($N_c = 0.1$) [4]. Note that diffusivities D_c, and D_w are functions of the cross-linking degree α and that, in general, the latter depends on the coordinate x. Therefore, $D_c(\alpha)$ and $D_w(\alpha)$ in Eq. (2) are implicit functions of space. The function is defined as

$$D_\beta(\alpha) = D_\beta^0 \left(1 + (\delta - 1)\frac{\exp(-n\alpha/\alpha_{\text{gel}}) - 1}{\exp(-n/\alpha_{\text{gel}}) - 1}\right), \qquad D_\beta = D_c, D_w, \tag{3}$$

where, D_β^0 is the initial diffusion coefficient, and $\delta = 0.5$ is the difference between the initial and the crosslinked diffusion coefficient based on [5]. Moreover, the gel point in Eq. (3) is chosen as $\alpha_{\text{gel}} = 0.2$, and $n = 5$ as a model parameter governing the rate of diffusivity change.

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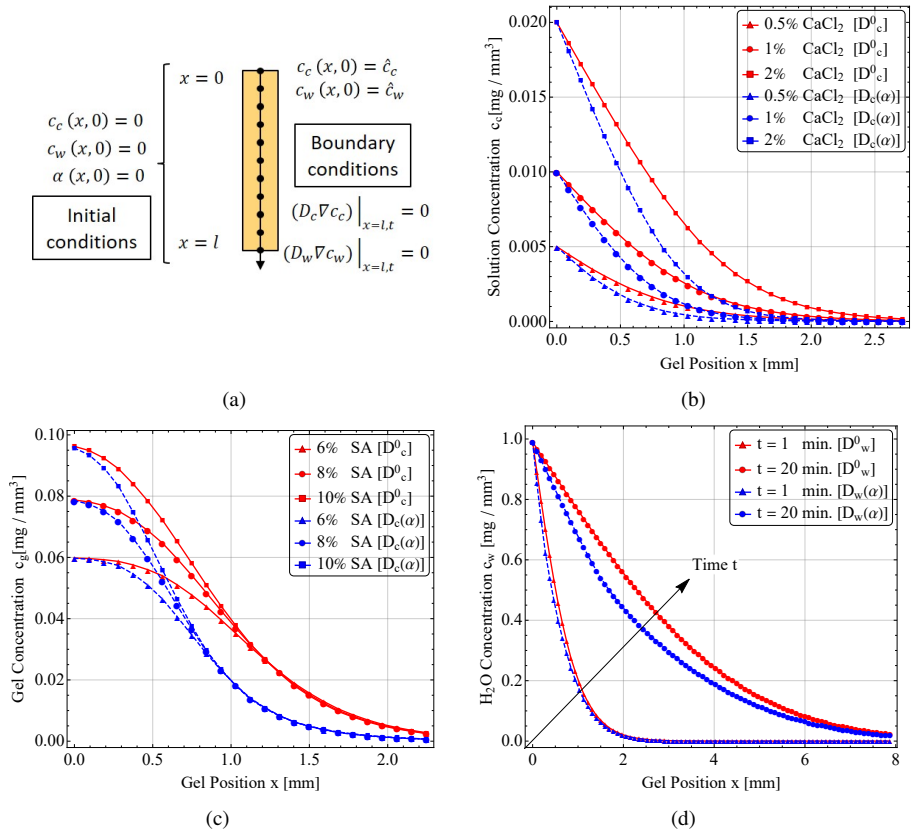

Fig. 1: a) Simulation settings. b) Calcium concentration $c_c(x,t)$ with different applied B.C. $\hat{c}_c = \{0.005, 0.01, 0.02\}$ mg μl^{-1}. c) Gel concentration with different free-Alginate concentrations $c_A = \{0.06, 0.08, 0.1\}$ mg μl^{-1}, and 1%(w/v) $CaCl_2$. d) Water concentration $c_w(x,t)$ with $\hat{c}_w = 0.99$ mg μl^{-1} for $t = \{1, 20\}$ minutes. Results are reported along gel position x mm and for (a) and (b) at time $t = 20$ minutes. The plots are obtained with $D_c^0 = 0.83 \times 10^{-9}$ m^{2}s^{-1}, and $D_w^0 = 0.5 \times 10^{-9}$ m^{2}s^{-1} obtained from [5, 7].

3 Numerical Results

The diffusion equations Eq. (2) are solved by discretizing the unknown functions $c_c(x,t)$, and $c_w(x,t)$ by means of a finite element discretization in space using AceGen and AceFEM [6]. A two-point Gauss quadrature rule is implemented for spatial integration. The gelation evolution in Eq. (1) is solved at each integration point providing the values of $D_c(\alpha)$ and $D_w(\alpha)$. A backward-Euler scheme is employed for the discretization in time. Obtained results allow to predict the evolution of the gel front with respect to time as function of bioink composition and crosslinking protocol (Fig. 1). This estimation might be employed for optimizing the post-bioprinting protocols. Modelling choices (i.e., constant versus cross-linking dependent diffusivity) and the values of model parameters (i.e., diffusive properties and reaction rates) play a major role on estimating the position of the gel front. Variations in the range of $\sim 100\,\mu$m are obtained, being relevant from an applicative viewpoint in the analysis of cell mechanical environment in tissue engineering scaffolds. Ongoing studies are considering the coupling of water movements with swelling mechanisms, as well as shrinking deformations due to egg-blocks formation.

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