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A multiphase model for the cross-linking of ultra-high viscous alginate hydrogels

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In this study, a model for the cross-linking of ultra-high viscous alginate hydrogels is provided. The model consists of four kinetic equations describing the process, including the local accumulation and the depletion of mobile alginate, cross-linked alginate and cross-linking cations. For an efficient simulation, finite difference schemes with predictor-corrector algorithms were implemented.

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1 Introduction

Alginate marine biopolymers are extracted from seaweeds. There are almost ubiquitous additives in food, cosmetics and pharmaceutics. Typically, they are used for adjusting rheological properties of fluids, ion regulation, encapsulation, controlled release of drug compounds, external wound covers and topological impressions in dentistry. In tissue engineering, alginates are used as biomaterial for scaffolds for the generation of innovative cell-based models [1,2]. The widespread use of alginates is due to its unique properties: it is completely non-toxic and biocompatible and it gels in gentle conditions like ambient temperature, physiological pH and with non-toxic gelation compounds. Furthermore, alginate gels are highly transparent and, in consequence, optimal for studies using transmission microscopy. From a chemical perspective, alginate polymers consist of unbranched polysaccharide-chain of the monomers mannuronic (M) and guluronic acid (G). Depending on the habitat of the algae, a variation of the G/M ratio and the distribution of homogeneous M- and G-blocks or heterogeneous GMG/MGM blocks is observed. Adjacent G-blocks are able to interact with multivalent cations and form the so-called egg-box structure. This gelation is achieved by cross-linking the biopolymer via multivalent cations like Ca^{2+}, Ba^{2+}, Fe^{2+}. The mechanical properties or the overall stability of produced alginate hydrogels depend on cross-linking agent, time or concentration and results finally in different mechanical properties of the alginate hydrogel. Ultra-high viscosity (UHV) alginates [3,4] emerged as valuable biomaterial in regenerative medicine and tissue engineering in the past decades [5], sharing the same chemistry and cross-linking mechanisms, but having up to tenfold longer polymer chains. This results in superior mechanical and stability properties like lower minimum concentration for stable hydrogel formation, higher chemical resistance and higher elastic modulus. However, the prediction of mechanical properties or cross-linking kinetics has not been implemented so far. In order to design new cell-based models, e.g. for cardiac diseases or cardiotoxicity testing, the prediction of those properties is of high interest in applied research. In addition, cross-linking of the alginate solution leads to considerable changes in diffusion properties of cross-linkers [6] as well as availability of open alginate crosslinking sites [7]. This may lead to a non-uniform degree of cross-linking within a gelled alginate body, concentration, mobility and mechanical gradients, that vice versa effect local cross-linking rates. The properties of a cross-linked alginate construct hence depend strongly on its gelation history [8]. Since in particular for medical application and medical biotechnology defined and reproducible properties are indispensable, a deep understanding of gelation kinetics and predictive tools for specific alginate engineering are essential.

2 Methods and Results

In this work, the fundamentals of such a predictive tool are established based on highly efficient finite difference schemes based on predictor-corrector algorithms and a set of kinetic differential equations describing local accumulation and depletion of mobile alginate, cross-linked alginate and cross-linking cations. These kinetic differential equations are given as a set of diffusion-reaction equations (1)-(4) with the model parameters C^{Mono}, C^{Ba}, C^{Ba}_{κ} and C^{κ} for the reaction process and the model parameters D^{Mono}_0, D^{Ba}_0 and K^{Mono} for the diffusion process. $\varrho^{\mathrm{Mono}}(t,\mathbf{x})$, $\varrho^{\mathrm{Ba}}(t,\mathbf{x})$, $\varrho^{\mathrm{Poly}}(t,\mathbf{x})$ and $\kappa(t,\mathbf{x})$ represent the conserved quantities in the balance equations describing the overall process. Figure 1 illustrates typical simulation results for the problem in one dimension. Here, the system of kinetic equations is equipped with appropriate boundary and initial conditions. A sequential approach was chosen as solution strategy which updated the solutions in numerical order of the four equations. The initial conditions for the process are: $\varrho^{\mathrm{Mono}}(t,\mathbf{x}) = 1$, $\varrho^{\mathrm{Ba}}(t,\mathbf{x}) = 0$, $\varrho^{\mathrm{Poly}}(t,\mathbf{x}) = 0$ and $\kappa(t,\mathbf{x}) = 0$.

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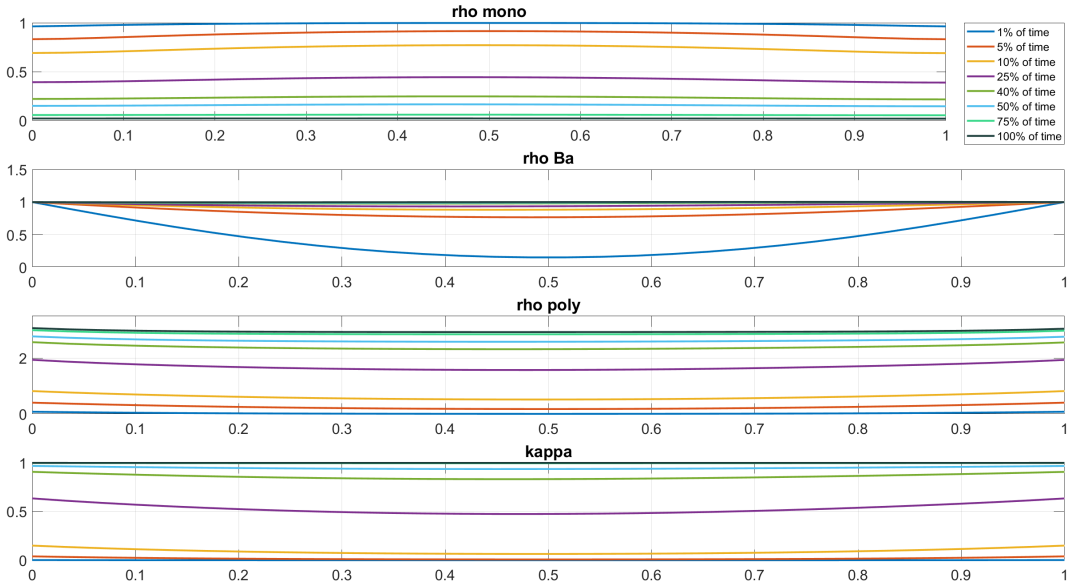

Fig. 1: Typical simulation results for the kinetic differential equations in 1d equipped with appropriate boundary and initial conditions.

The boundary conditions are the no flux condition for $\varrho^{\mathrm{Mono}}(t,\mathbf{x})$ and Dirichlet conditions for the other conserved quantities with $\varrho^{\mathrm{Ba}}(t,\mathbf{x}) = 1$. Together with a thorough physico-chemical characterization of the biopolymers, such a numerical simulation opens up the route towards optimized and well-defined scaffolds, encapsulation shells and immunoisolating matrices for medical products and cell substrates.

$$\frac{\partial}{\partial t}\varrho^{\mathrm{Mono}}(t,\mathbf{x}) = \nabla\cdot\left(D_0^{\mathrm{Mono}} e^{-K^{\mathrm{Mono}}\varrho^{\mathrm{Poly}}(t,\mathbf{x})}\nabla\varrho^{\mathrm{Mono}}(t,\mathbf{x})\right) - C^{\mathrm{Mono}}\varrho^{\mathrm{Mono}}(t,\mathbf{x})\varrho^{\mathrm{Ba}}(t,\mathbf{x}) \tag{1}$$

$$\frac{\partial}{\partial t}\varrho^{\mathrm{Ba}}(t,\mathbf{x}) = \nabla\cdot\left(D_0^{\mathrm{Ba}} e^{-K^{\mathrm{Ba}}\varrho^{\mathrm{Poly}}(t,\mathbf{x})}\nabla\varrho^{\mathrm{Ba}}(t,\mathbf{x})\right) \tag{2}$$

$$-C^{\mathrm{Ba}}\varrho^{\mathrm{Mono}}(t,\mathbf{x})\varrho^{\mathrm{Ba}}(t,\mathbf{x}) - C_\kappa^{\mathrm{Ba}}\varrho^{\mathrm{Ba}}(t,\mathbf{x})\left(1-\kappa(t,\mathbf{x})\right)\varrho^{\mathrm{Poly}}(t,\mathbf{x}) \tag{3}$$

$$\frac{\partial}{\partial t}\varrho^{\mathrm{Poly}}(t,\mathbf{x}) = \left(C^{\mathrm{Mono}} + C^{\mathrm{Ba}}\right)\varrho^{\mathrm{Mono}}(t,\mathbf{x})\varrho^{\mathrm{Ba}}(t,\mathbf{x}) + C_\kappa^{\mathrm{Ba}}\varrho^{\mathrm{Ba}}(t,\mathbf{x})\left(1-\kappa(t,\mathbf{x})\right)\varrho^{\mathrm{Poly}}(t,\mathbf{x})$$

$$\frac{\partial}{\partial t}\kappa(t,\mathbf{x}) = C^{\kappa}\varrho^{\mathrm{Ba}}(t,\mathbf{x})\left(1-\kappa(t,\mathbf{x})\right)\varrho^{\mathrm{Poly}}(t,\mathbf{x}) \tag{4}$$

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