

## 1.5 Hydrogels Models for Soft Biomaterials

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Hydrogels are a material system that is omnipresent in nature. They appear in innumerable biological processes, but also in many smart soft-matter materials as well as medical applications. Hydrogels have an intriguingly complex phase behavior, as they interact with their environment. Their understanding would, on the one hand, help to solve some fundamental problems in soft matter physics and, on the other hand, form the basis for new optimized designs for the use in tissue regeneration, biodegradable implants, articular cartilage repair and replacement, and many other biomaterials. The increased interest in these materials has led to a vast number of theoretical and experimental studies aiming at understanding the principles of their dynamic behavior and pattern formation, reviewed, for example, in Michael S. Dimitriyev et al., *Nano Futures*, **3**:4 (2019).

A major research focus at WIAS is the development of thermodynamically consistent models for complex materials. In this article, we showcase for hydrogels the journey from a novel abstract thermodynamic description, to nonlinear coupled systems that capture the various phase transitions in hydrogels, to agent models for cell motion in these materials. We highlight how the theoretical and numerical framework that we developed for hydrogels answers some of the fundamental problems regarding the interface formation between liquids and hydrogels, how to systematically extend the system to include electrostatic interactions and mechanical properties of biological gel such as elastic strain-stiffening, both properties being fundamental in biomaterials.

In the simplest case, hydrogels are two-phase systems composed of an elastic network of polymer chains immersed in a liquid solvent. The transport of solvent into and out of the network leads to the swelling and drying of the hydrogel, thereby introducing large deformations of the polymer network. Aside from swelling and deswelling with their large volume changes, hydrogels can exhibit a volume phase transition giving rise to coexisting regions with different degrees of swelling and, hence, different levels of elastic stresses. Such volume changes, in turn, may lead to deformation of the boundary in contact with the surrounding bath as well as a host of patterns within the hydrogel. Since the kinetics of swelling and deswelling can change significantly upon the formation of internal interfaces by phase transitions, full time-dependent models that implicitly capture these interfaces were derived in [1], where phase-field theories served as a natural framework for developing kinetic models of hydrogels by accounting for the relevant thermodynamics as well as providing implicit descriptions of the evolving interfaces that form upon phase separation. Based on these ideas, we have developed our numerical approach.

### Variational structure-preserving numerical discretization

Beyond the continuum-mechanical description of fluids and solids, complex material behavior arises from nonlinear material laws, from multiple scales, or from the consideration of additional physics, e.g., material flow, diffusion, phase separation, damage, chemical reactions, charge and heat transport. The complex dynamics in the volume and at the surface of such materials can usually be described by scalar order parameters. For these physical theories, energetic variational principles

are important mathematical structures that ensure the validity of the laws of thermodynamics.

One often considers gradient systems, i.e., triples  $(\mathcal{Q}, \mathcal{F}, K)$ , such that the trajectory in a state space  $q : [0, T] \rightarrow \mathcal{Q}$  with free energy  $\mathcal{F} : \mathcal{Q} \rightarrow \mathbb{R}$  is determined by the evolution law  $\partial_t q = -K(q)D\mathcal{F}(q)$  formulated using a positive geometric operator  $K(q) : \mathcal{Q}^* \rightarrow \mathcal{Q}$ . We propose an extension of this structure by  $(\mathcal{Q}, \mathcal{F}, (M, A, \mathcal{U}, S))$  that generates a saddle-point problem, where we seek chemical potentials  $\eta : [0, T] \rightarrow \mathcal{U}$  and states  $q : [0, T] \rightarrow \mathcal{Q}$  such that

$$\begin{aligned} A(q)\eta + M(q)\partial_t q &= 0 \\ M(q)^*\eta - S(q)\partial_t q &= D\mathcal{F}(q) \end{aligned} \quad \text{in } \mathcal{U}^* \times \mathcal{Q}^*,$$

where dissipative processes are encoded in separate spaces  $\mathcal{Q}, \mathcal{U}$ . Instead of a single  $K$ , one now uses two positive operators  $A(q) : \mathcal{U} \rightarrow \mathcal{U}^*$  and  $S(q) : \mathcal{Q} \rightarrow \mathcal{Q}^*$  that contain irreversible processes; see [3]. The spaces  $\mathcal{Q}$  and  $\mathcal{U}$  are connected by the representation  $M(q) : \mathcal{Q} \rightarrow \mathcal{U}^*$ . This formulation also implies energy decay and therefore thermodynamic consistency by construction

$$\frac{d}{dt}\mathcal{F}(q(t)) = -\langle A(q)\eta, \eta \rangle_{\mathcal{U}} - \langle S(q)\partial_t q, \partial_t q \rangle_{\mathcal{Q}} \leq 0,$$

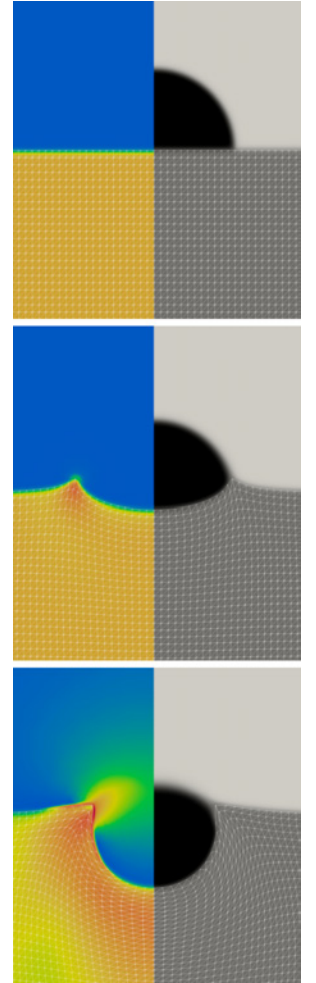
where  $\langle \cdot, \cdot \rangle$  denotes the dual pairing. The thermodynamic consistency is essential for many complex, nonlinear coupled problems that couple mechanics, chemistry, and (inactive) biological materials. While from a formal point of view, this reformulation is equivalent to a formulation of gradient systems using quadratic dissipation potentials  $R(q, \cdot) : \mathcal{Q} \rightarrow \mathbb{R} \cup \{\infty\}$ , we observe several practical advantages. Firstly, the weak form of the saddle-point problem in  $\mathcal{U}^* \times \mathcal{Q}^*$  allows for a direct reformulation using Galerkin methods. The decomposition into  $(M, A, \mathcal{U}, S)$  allows for a finer control of the evolution systems where  $R(q, \cdot)$  is singular so that  $K(q)$  is not invertible, i.e., in the presence of multiple time scales or constraints in the evolution.

Various coupling mechanisms, further constraints and a variety of irreversible, but also reversible effects can be implemented by the appropriate choice of operators, functionals, and function spaces. By defining  $A(q) = K(q) - J(q)$  with the symmetric Onsager operator  $K$  and the skew-symmetric Poisson operator  $J$ , damped Hamiltonian evolution can be incorporated. This connects the saddle-point structure to many recent and classical works on Hamiltonian and Onsager partial differential equation systems, e.g., fluid flows, fluid-structure interaction, nonlinear diffusion, and reactive transport [7], which are highly relevant for biological applications and complex multiphase materials. Now, we apply such a mathematical formulation to a hydrogel.

### Some fundamental problems in soft matter physics

Within the DFG Priority Program SPP 2171 *Dynamic Wetting of Flexible, Adaptive and Switchable Surfaces* and in collaboration with experimental partners (Ralf Seemann, Experimental Physics, U Saarland), we investigated the formation, morphology, and dynamics of interfaces of liquid polymer droplets on hydrogel substrates by varying the softness (elastic modulus) of the hydrogel network.

**Multiphase flow with nonlinear diffusion.** Consider a multiphase flow of a liquid droplet on a hydrogel surrounded by an air phase with suitable boundary and interface conditions for a fluid-



**Fig. 1:** The evolution of a deforming liquid droplet on soft gel coupled to diffusion of polymer density  $c$  in the gel phase showing (left) the polymer density  $c$  and (right) a projection of the phase fields  $\psi_i$  with mesh (white)

structure interaction problems with capillary surfaces. Additionally, we consider the diffusion of an concentration  $c$  inside the gel driven by entropic and mechanical forces. For any point in space  $x \in \Omega \subset \mathbb{R}^d$  and time  $t \in (0, T)$ , the system can be modeled using phase fields  $0 \leq \psi_i \leq 1$  and  $\psi_i(t, x) = 1$  in the phase  $i$  and  $\psi_i(t, x) = 0$  otherwise, where  $i \in \{\text{gel}, \text{liquid}, \text{air}\}$  and  $\sum \psi_i = 1$ . To model the additional diffusion, we introduce a polymer concentration  $c$  leading to  $\psi = (\psi_{\text{gel}}, \psi_{\text{liquid}}, \psi_{\text{air}}, c) \in \mathbb{R}^4$ . The mechanical deformation is described by  $\chi(t, x) \in \mathbb{R}^d$  for  $d = 2, 3$ . For  $q = (\psi, \chi)$ , the free energy is composed of an elastic energy and a phase-field potential, i.e.,

$$\mathcal{F}(q) = \int_{\Omega} W_{\text{elast}}(\psi, \mathbf{F}) + W_{\text{phase}}(\psi, \mathbf{F}^{-T} \nabla \psi) dx,$$

with the deformation gradient  $\mathbf{F} = \nabla \chi$ . The concentration  $c$  is characterized by the fact that it lowers the elastic modulus of the gel, and a (non-convex) mixing model must be considered for the mixing with the other phases. This is achieved by an elastic energy of the form  $W_{\text{elast}}(\psi, \mathbf{F}) = \frac{g(\psi)}{2} \text{tr}(\mathbf{F}^T \mathbf{F} - \mathbb{I})$  with elastic modulus  $g(\psi) = \psi_{\text{gel}} g_{\text{gel}}(c)$  that satisfies  $g_{\text{gel}}(c) > 0$  and  $g'_{\text{gel}}(c) \leq 0$ . The phase-field energy of the system is

$$W_{\text{phase}}(\psi, \mathbf{F}^{-T} \nabla \psi) = \sum_{i \in \{\text{gel}, \text{liquid}, \text{air}\}} \gamma_i \left( \frac{\varepsilon}{2} |\mathbf{F}^{-T} \nabla \psi_i|^2 + \frac{1}{4\varepsilon} (4\psi^2 - \psi)^2 \right) + \frac{\delta}{2} |\nabla c|^2 + G(\psi),$$

where standard diffusion in the gel would imply  $G(\psi) = \beta^{-1} c (\log c - 1)$ . However, to contain the polymer in the gel, we introduce a mixing term  $G(\psi) = \beta^{-1} c (\log c - 1) + \chi_{\text{mix}} c \psi_{\text{gel}}$  with the Flory–Huggins mixing parameter  $\chi_{\text{mix}} < 0$ . The remaining part proportional to  $\gamma_i$  describes the energy of the interfaces between liquid, gel, and air phase, and  $\delta > 0$  ensures coercivity.

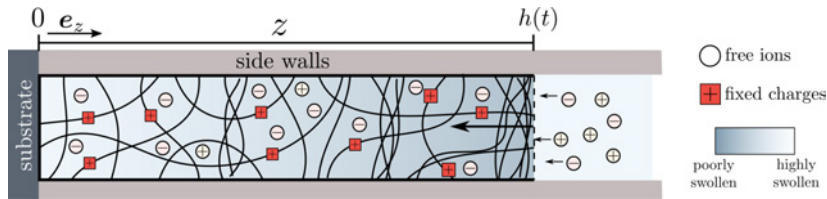
The coupling via  $g$  leads to an increase of the concentration in regions with high stress, i.e., especially at the contact line; see Figure 1. This coupling of mechanics and phase fields is similar to damage models and topology optimization. Resulting phase separation phenomena were observed in soft gels in experiments. However, for theoretical predictions a better understanding of the parameters in the mixing model is required. For models with multiphase flows and diffusion, the identification of sharp interface limits is a fundamental mathematical question; cf. WIAS Preprint no. 2990.

## Biological gels

Cells as well as any biological tissue are in fact not neutral hydrogels but belong to the class of polyelectrolyte gels, which consist of a network of electrostatically charged macromolecules that is swollen with an ionic fluid. These polyelectrolyte chains interact with dissolved ions in the imbibing fluid. If placed in a salt solution, chemical, electrical, and mechanical interactions occur within the gel that drive it towards an equilibrium state. Applying a stimulus, such as an electric field or a temperature change, enables the equilibrium state of the gel to be finely controlled. In [2, 5], we use non-equilibrium thermodynamics to derive a novel phase-field model for a polyelectrolyte gel that displays spontaneous formation of internal interfaces due to the onset of phase separation. In addition, we develop a thermodynamically consistent model of the surrounding ionic bath. Coupling the gel and bath models via appropriate interfacial conditions provides a means of resolving the

electric double layer, the so-called *Debye layer*, and elucidating the role it plays in the gel dynamics. In addition, our model captures multi-component diffusive transport using the Stefan–Maxwell formulation to avoid anomalous diffusivities, which can arise when the diffusive flux of a species is solely driven by the gradient of its own chemical potential.

Our analysis reveals that the structure of the gel is crucially dependent on the ratio of two length scales inherent in this system: the Debye length, which is the thickness of the electric double layer, and the Kuhn length, which is proportional to the length of a segment of a single macromolecule. When the Debye length is much smaller than the Kuhn length, then the equilibrium states correspond to a gel that has a homogeneous and electrically neutral bulk with a thin electric double layer at its free surface. In our study, we show that the volume phase transition in this regime can occur via two distinct routes, either solely via the propagation of a swelling/deswelling front from the gel–bath interface or in combination with spinodal decomposition ahead of the main transition front. When the Debye and Kuhn lengths are commensurate, our model predicts a novel mode of pattern formation, resulting in stable, spatially localized structures that emanate from the electric double layer and invade the gel. In this case, the equilibrium states of the gel can be non-homogeneous and electrically charged. We show that this novel model of pattern formation arises due to the interplay between phase separation and the formation of electric double layers and can be detected through measurements of the gel size.



**Fig. 2:** Schematic of a laterally confined polyelectrolyte gel that collapses along the  $z$ -axis only. The free interface with the bath is located at  $z = h(t)$ . As solvent is expelled by the gel, the free interface moves towards the left, and salt ions are absorbed/desorbed by the gel so as to maintain electro-neutrality of the gel.

To show this in the simplest case, we consider the case of a constrained gel with monovalent fixed charges, i.e., charges of chemical valence one ( $z_f = +1$ ), which undergoes uni-axial deformation (in the  $z$ -direction) due to the uptake or release of a monovalent ( $z_{\pm} = \pm 1$ ) salt solution; see Figure 2. The gel is assumed to be attached to a substrate at  $z = 0$ , while the interface at  $z = h(t)$  is free to move along frictionless side walls that do not influence the bulk behavior. We can reduce the corresponding governing equations to

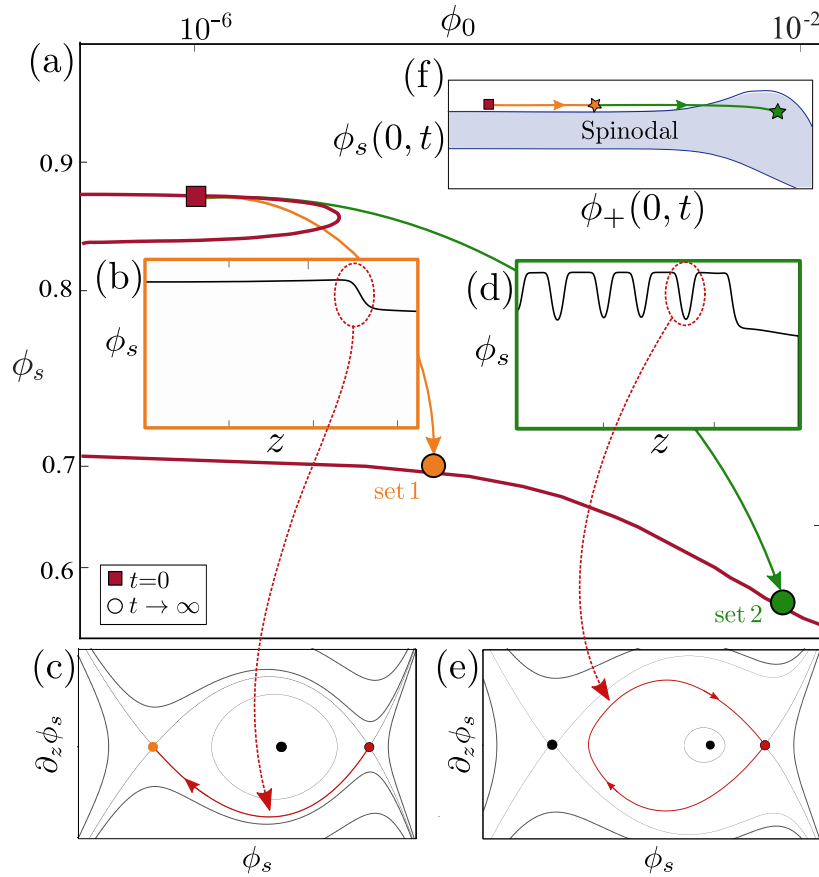
$$\partial_t \phi_s + \partial_z (\phi_s v_n) = -\partial_z j_s, \quad \partial_t \phi_+ + \partial_z (\phi_+ v_n) = -\partial_z j_+,$$

$\phi_s$  and  $\phi_+$  being the volume fractions of the solvent and positive mobile ions, respectively, and  $v_n$  the velocity of the network, having eliminated the volume fractions for the network and the negative mobile ions [5]. This is coupled to the constitutive laws

$$\begin{aligned} j_s &= -\frac{\phi_s^2}{1-\phi_n} \partial_z \mu_s + \frac{2\phi_s}{(1-\phi_n)\mathcal{D}} j_+, \quad j_+ = -\frac{\mathcal{D}\phi_+\phi_-}{\phi_+ + \phi_-} \partial_z \bar{\mu} + \frac{2\phi_+\phi_-}{\phi_s(\phi_+ + \phi_-)} j_s, \\ v_n &= -j_s - 2j_+, \quad \phi_n = \frac{1-\phi_s-2\phi_+}{1+\alpha_f}, \quad \phi_- = \frac{\phi_+ + (1-\phi_s-\phi_+)\alpha_f}{1+\alpha_f}, \\ \bar{\mu} &= A(\phi_s, \phi_+) + 2\omega^2 \phi_s \partial_{zz} \phi_s - \omega^2 (\partial_z \phi_s)^2, \quad \mu_s = B(\phi_s, \phi_+) - (1-\phi_s)\omega^2 \partial_{zz} \phi_s - \frac{\omega^2}{2} (\partial_z \phi_s)^2, \end{aligned}$$

**Fig. 3:** Two routes to collapse: (a) A volume phase transition is triggered by increasing the salt fraction in the bath  $\phi_0$  from  $10^{-6}$  (red square) to  $10^{-4}$  (set 1; orange circle) or  $10^{-2}$  (set 2; green circle). (b) Set 1 leads to the first route to collapse, where a deswelling front invades the gel from the free surface. (c) A heteroclinic orbit, which provides an approximation to the propagating front. (d) The second route to collapse involves front propagation and spinodal decomposition in the bulk of the gel. (e) A two-dimensional projection of a homoclinic orbit; these orbits provide approximations of the phases that form within the bulk of the gel during the second route to collapse. (f) Evolution of the solvent and cation fraction at the substrate ( $z = 0$ ) for parameter set 1 (orange) and set 2 (green). Stars denote the composition after the front has formed. The linearly unstable spinodal regime is shaded.

where in this simple case,  $A(\phi_s, \phi_+)$  and  $B(\phi_s, \phi_+)$  are found as algebraic relation between  $\phi_s, \phi_+$ , the number of fixed charges  $\alpha_f$  and  $\omega$  being a measure for the interface thickness. Together with suitable boundary conditions, the solutions of the model show two routes to gel collapse; cf. Figure 3.

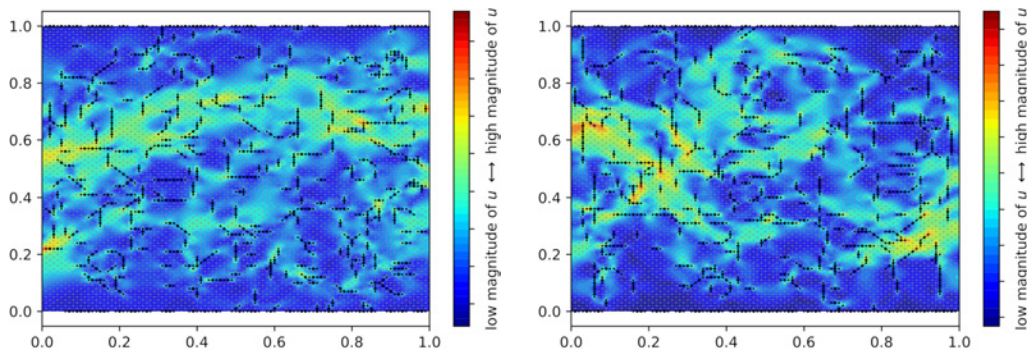


### Designing materials for biological tissue

Apart from the highly complex relation of the mechanical and elastic properties as demonstrated above even in the simplest cases, another important property of biological gels, such as fibrin or collagen gels, is their elastic tendency to strain stiffen, when forces are applied. This has to be taken into account as well when modeling the typical traction forces applied to these gels in the course of tissue remodeling. Together, with collaborators Sara Checa and Ansgar Petersen (Julius Wolff Institute, Charité) within the MATH+ Project AA1-12\*, we derived a new model for a strain-stiffening hydrogel, where the elastic part of the hydrogel is described by the strain energy density function of the incompressible Gent model

$$W_{\text{elast}}(\psi, \mathbf{F}) = -\frac{\mu}{2} J_m \log \left( 1 - \frac{\text{tr}(\mathbf{F}^T \mathbf{F} - \mathbb{I})}{J_m} \right) - \mu \log(\det(\mathbf{F})) + p (\det(\mathbf{F}) - (1 + \psi)),$$

where  $p$  represents the Lagrange multiplier and  $J_m = I_m - 2$ , and  $I_m \in \mathbb{R}$  is the limit value of the first invariant of the right Cauchy–Green deformation tensor  $I_1 = \text{tr}(\mathbf{F}^T \mathbf{F})$ . This is coupled to an agent-based model describing the collective mechanical interactions with a strain-stiffening hydrogel.



**Fig. 4:** Final cell configuration and displacement field. Left: elastic material described by Neo-Hooke model. Right: elastic material described by Gent model with a limit value  $I_m$  of 4.

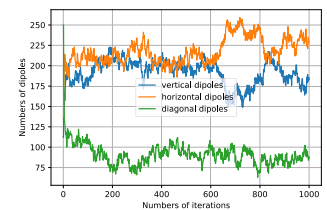
The agent-based model (ABM) describes the collective migration of large distributions of biological cells, such as fibroblasts, on a strain-stiffening hydrogel. After initial *seeding* the cells, modeled here as dipoles, cells probe their hydrogel environment by applying a traction force, and then migrate to an empty location of the hydrogel with highest stiffness, i.e., minimal deformation. Our coupled model predicts how the cells form a pattern with a tendency to long-range alignment and quickly develop a vertical but also horizontal orientation of the dipoles; cf. Figure 4. The diagonal orientation plays only a minor role; cf. Figures 5 and 6.

## Outlook

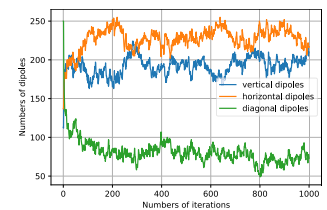
The selection of applied projects shows the potential of the modeling framework and the numerical approach and is currently being extended to include further species; apart from electrostatic interaction, also chemical reaction and damage will need to be coupled as well as further interacting networks in order to develop more realistic models of biomaterials. On the other hand, as exciting and complex as these systems are, the rigorous mathematical theory for even the simplest models for hydrogels is still in its infancy. At WIAS, we have begun with some of the first existence results.

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**Fig. 5:** Time course of cell alignment: Neo-Hooke



**Fig. 6:** Time course of cell alignment: Gent



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