Analyzing and Optimizing Bone Scaffolds

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Abstract

We present a three dimensional, homogenized PDE/ODE model for bone fracture healing in the presence of a porous, bio-resorbable scaffold and an associated PDE constrained optimization problem concerning the optimal scaffold density distribution for an ideal healing environment. The model is analyzed mathematically and a well-posedness result is provided. For the optimization problem, we show the existence of an optimal scaffold design and rigorously derive the adjoint equations. Further, we prove a novel $L^p(I, C^\alpha(\Omega))$ regularity result for reaction-diffusion equations with mixed boundary conditions which is crucial for the analysis of the optimal control problem. Numerical simulations for the PDE/ODE system and the PDE constrained optimization problem are presented, illustrating the effect of stress-shielding on optimal scaffold design and providing insight in the sensitivity of the optimal scaffold design with respect to inhibited bone growth and vascularization.

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Chapter 1

Introduction

In this work, we are concerned with the development and well-posedness of a simple and efficient model for bone regeneration in the presence of a bioresorbable porous scaffold and the design of an optimal scaffold using PDE constrained optimization techniques. The essential processes are an interplay between the mechanical and biological environment which we model by a coupled system of PDEs and ODEs. The mechanical environment is represented by a linear elastic equation and the biological environment through reaction-diffusion equations as well as logistic ODEs, modeling signaling molecules and cells/bone respectively. Material properties are incorporated using homogenized quantities not resolving any scaffold microstructure. This makes the model efficient in computations, thus suitable as a forward equation in optimization algorithms and opening up the possibility of patient specific scaffold design in the sense of precision medicine. The main focus of the thesis lies on the mathematical analysis of the PDE-ODE model and the associated PDE constrained optimization system. Additionally, numerical simulations are provided and compared to experimental data. Our numerical findings show that our model resolves clinically relevant stress shielding effects that appear in vivo due to external fixation of the scaffold at the defect site.

The thesis is organized as follows. In Chapter 1, we begin by giving an introduction into tissue engineering for the treatment of severe bone defects and present our computational model. We then proceed by discussing the one-dimensional case in a mathematical rigorous way, proving well-posedness and the existence of an optimal control. This serves as a gentle introduction to the mathematical techniques. In Chapter 2, we prove the existence and uniqueness result for the full model in three dimensions and present numerical simulations. In Chapter 3 we establish the optimal control result in three dimensions, rigorously derive the adjoint system and present numerical simulations of optimized scaffolds. In the Appendix, we discuss technical results required for the proofs of the main results, more precisely, we consider regularity of reaction-diffusion equations, Banach space valued ordinary differential equations and the regularity theory of the Banach space adjoints of time-dependent differential operators.

The main result of this thesis consists of the extension of the PDE-ODE model proposed in Poh et al. (2019) to the three dimensional case and to a more comprehensive biological environment. For this system, a well-posedness result is provided, taking into account realistic boundary conditions. Furthermore, for the corresponding PDE constrained optimization problem, an optimal control result is proven. This requires the extension of known regularity results from the literature for linear reaction-diffusion equations. A rigorous derivation of the adjoint system is carried out. Due to regularity issues this is not completely straight-forward. Finally, numerical simulations for both the forward system and the PDE constrained optimization are presented.

I Modeling Scaffold Mediated Bone Growth

We start by explaining the processes behind bone growth in the presence of a porous scaffold and then introduce our computational model.

1.1 Scaffold Mediated Bone Growth

The regeneration and restoration of skeletal functions of critical-sized bone defects (>25 mm) are very challenging despite a multitude of treatment options, see Nauth et al. (2018). The main problem is the phenomenon of non-union where the bone defect fails to become bridged after >9 months and does not show healing progression for 3 months, cf. Calori et al. (2017). Mills et al. (2017) showed that with 1.9%, the prevalence of non-union per fracture is relatively low, yet the financial burden is high, for example, in the UK, the healthcare cost is estimated to be £320 million annually, see Stewart (2019). Moreover, the risk of non-union increases drastically with comorbidities such as diabetes as in this case the regenerative capability of bone tissue is compromised, we refer to Marin et al. (2018).

Critical-sized defects may not heal and require in-depth planning of their treatment. Currently used therapeutic approaches include bone grafting, distraction osteogenesis, and the so-called "Masquelet" technique, in which a periosteal membrane is formed to induce bone defect healing, cf. Nauth et al. (2018). Despite having a general guideline for treatment of critical-sized bone defects, healing outcomes vary highly, dependent on the site and size of the defect and patient-related aspects, e.g., age, lifestyle and comorbid metabolic/systemic disorders, see Roddy et al. (2018).

Over the years, research demonstrated the potential of using porous, possibly bio-resorbable support structures, so-called scaffolds, as supporting devices to promote bone defect regeneration. Initially, a scaffold is placed in the defect site, acting as a temporary support structure allowing for vascularization while guiding new bone formation. This has recently shown promising results in vivo and in clinical cases, for example Petersen et al. (2018) showed that the architecture of the scaffold can guide the endochondral healing of bone defects in rats. In this study, collagen-based scaffolds with cylindrical pores aligned along the principle stress axis were used. In Cipitria et al. (2012); Paris et al. (2017), 3D-printed scaffolds made from a composite of polycaprolactone (PCL, a slowly degrading, bio-resorbable synthetic thermoplastic) and β-tricalcium phosphate (β-TCP) were used in an ovine experiment. In the studies Petersen et al. (2018); Cipitria et al. (2012); Paris et al. (2017) no relevant bridging of the bone defect was achieved without the addition of exogenous growth factors or cells. However, Pobloth et al. (2018) illustrated that clinically relevant bone formation for scaffold mediated bone regeneration is possible without exogenous growth factors. In this experiment a 3D-printed titanium scaffold with optimized mechanobiological properties was used and displayed clinically relevant functional bridging of a major bone defect in a large animal model. Concluding, the studies Petersen et al. (2018); Cipitria et al. (2012); Paris et al. (2017); Pobloth et al. (2018) indicate the possibility of using a scaffold-mediated bone growth approach for critical-size bone defect healing. Furthermore they indicate that the design and choice of materials are critical questions not yet fully understood.

There are several objectives to be considered when designing a scaffold, such as (a) the porosity, pore size and shape, influencing cell proliferation and differentiation as well as the vascularization process; (b) the overall stability and elastic properties guaranteeing a proper transfer of loads, as mechanical stimulus is indispensable for bone growth; (c) patient specific information such as reduced bone healing capacities, caused for example by diabetes Marin et al. (2018). Therefore, the patient dependent optimal scaffold design is of fundamental importance and with the advent of additive manufacturing technologies the production of personalized scaffolds is – in theory – fully feasible.

However, the design of scaffolds has been dominated by trial-and-error approaches – modifying an existing scaffold architecture based on experimental outcomes, a very costly workflow unsuitable for patient specific design. Over the years, with the help of evolving computer aided design tools, topology optimization techniques have shown potential to address the optimal design question computationally.

This strategy has already been applied to design scaffolds meeting elastic optimality conditions with a given porosity or fluid permeability, we refer for example to Dias et al. (2014); Coelho et al. (2015); Lin et al. (2004); Guest and Prévost (2006); Challis et al. (2012); Kang et al. (2010); Wang et al. (2016); Dondl et al. (2019). Yet, a common limitation to these models is that they do not resolve the time dependence of the bone regeneration process, as scaffold mediated bone regeneration crucially depends on the varying elastic moduli over time.

Highly accurate, fine scale models for bone formation exist (see, e.g., Klika et al. (2014); Sanz-Herrera et al. (2008); Alierta et al. (2014); Checa and Prendergast (2010)). A central issue in most such micro-scale models is that their use in optimization routines for scaffold design is impeded by too high computational cost. Ideally, a bone regeneration scaffold design should be patient specific, i.e., depend on the individual patient's defect site and its biomechanical loading conditions, geometry, and regenerative ability as influenced by, e.g., comorbitities such as type 2 diabetes mellitus. Such an optimization of course relies on the availability of highly efficient models for bone regeneration that nevertheless take into account mechanics and biological signaling.

Based on a previous, one-dimensional study by Poh et al. (2019), we thus propose a model based on homogenized quantities suitable for scaffold optimization in the sense of the first step in the "Shape Optimization by the Homogenization Method" Allaire (2012). This means that our model does not resolve the micro-structure of the scaffold design, but uses coarse-grained values instead. In a scaffold based on a unit cell design, the scaffold volume fraction (or equivalently, the porosity) changes on a larger length-scale than the unit cell design. We use this fact to simplify our model, working with meso-scale averages of the volume fraction instead of the precise micro-structure. Likewise, the other quantities of the model can be viewed as locally averaged values. However, it should be made clear that using such an approach implies that only the averaged quantities can be tracked over the regeneration process and no prediction on how the micro-structure changes over time can be made. Rather, this is required as an input to provide the correct homogenized material properties. Our central assumption is that one can describe the time-evolution of the homogenized quantities in terms of their averages at the initial time-point. Compared to the aforementioned one-dimensional approach, our model can resolve important issues such as bone mass loss due to stress shielding in orthopaedic implants, see Section III for an explicit example.

Another objective of our model is that it allows for a mathematical optimization of the scaffolds volume fraction distribution, similar to the optimization in Poh et al. (2019). This requires the model to be posed in a fully continuous manner, making, e.g., the adjoint method of PDE constrained optimization applicable for which we refer to Hinze et al. (2008). As mentioned before, computational efficiency of the model is necessary for a successful application of PDE constrained optimization methods – these optimization algorithms typically require to evaluate the model for many different scaffold volume fractions. Mathematically, we allow for a wide class of objectives to optimize for. Applications are the amount of regenerated bone after a given healing period or one could maximize the temporal minimum of the elastic modulus of the scaffold-bone composite. We elaborate on these examples in Section 1.4.

As our model is designed for computational efficiency we include only key events in the course of the bone healing process. We keep track of the mechanical environment at every point in time and space, depending on the current state of bone formation and scaffold degradation in terms of its molecular weight. Here we focus on additively manufactured scaffolds made out of PCL, a very promising material for this specific application. Of course, extensions to other materials (e.g., non-degrading titanium) are possible. The biological environment is represented via a concentration of endogenous angiogenic and osteoinductive factors (e.g., intrinsic growth factors/cytokines) which we call bio-active or signaling molecules and a concentration of osteoblasts, a type of bone forming cell. The coupling of the mechanical and biological properties is assumed to be driven through the local strain caused by mechanical loading of the scaffold-bone composite, i.e., mechanical loading leads to stimulus for the biological environment which in turn leads to bone growth and hence changes the mechanical properties.

This results in a coupled system of evolution equations composed of a linear elastic equilibrium equation for every point in time, diffusion equations for the bio-active molecules and ordinary differential equations for the concentration of osteoblasts and the volume fraction of bone. As our main focus lies on the existence and uniqueness results, we do not use concrete homogenized tensors in the equations, but abstract functional relationships. This has the advantage of proving the result for a wide class of imaginable scaffold architectures at once. Explicit micro-structures can then be taken into account when one performs numerical simulations. In the same spirit we keep the rest of the equations abstract, preferring functional relationships over concrete formulas. This constitutes also a perspective for future research: derive concrete homogenized quantities for certain scaffold details, compare the outcome to experimental results, and employ the model in an optimization routine analogous to the one presented in Poh et al. (2019). The 3-dimensionality of the model makes an optimization of the scaffold porosity considerably more challenging from a numerical viewpoint – but due to the efficient, homogenized, model it is within reach to provide patient specific optimal scaffold designs that depend on the individual's defect site and geometry, as well as their regeneration capacity.

1.2 The System of Equations

Let $\Omega \subset \mathbb{R}^3$ be the domain of computation, i.e., the bone defect site, and let $I = [0, T]$ be a finite time interval. On the defect site we keep track of the local scaffold volume fraction called $\rho(x)$, with $x \in \Omega$. Equivalently, the relation to the local scaffold porosity θ is given by $\theta(x) = 1 - \rho(x)$, but we work with ρ exclusively. Note that we do not assume a time dependency for ρ as experimental findings of Pitt et al. (1981) have shown that, in the time-window relevant for us, PCL degrades via bulk erosion. However, the molecular mass decreases and we keep track of this by introducing the exponential decay $\sigma(t) = e^{-k_1 t}$, making the product $\rho(x) \cdot \sigma(t)$ the quantity encoding the mechanical properties of PCL over time and space. Furthermore, we denote the local bone density by $b(t, x)$ and the three quantities b, σ and ρ together determine the mechanical material properties of the bone-scaffold composite. We model this composite in the linear elastic regime using an elastic tensor $\mathbb{C}(\rho, \sigma, b)$ to capture the material properties.

In the spirit of the homogenization approach we assume little on the concrete properties of this tensor, in particular we do not assume isotropy. For a particular choice of micro-structure $\mathbb{C}(\rho, \sigma, b)$ can be made explicit. In order to quantify the elastic stimulus throughout the bone-scaffold composite we introduce a displacement field $u(t, x)$ satisfying the equation of mechanical equilibrium (1.1). The corresponding strain is denoted by $\varepsilon(u)$, with $\varepsilon(u) = \frac{1}{2}(Du + D^T u)$ the symmetrized derivative.

For the biological environment we introduce N bio-active molecules denoted by $a_1(t, x), \ldots, a_N(t, x)$, these are endogenous angiogenic and osteoinductive factors which we assume to diffuse depending on the scaffold density ρ. This is captured by $D_i(\rho)$ in the equation (1.2) and is left as an abstract functional relationship for the same reasoning as the elastic tensor. Furthermore, we assume the bio-active molecules to decay at a certain rate and to be produced in the presence of strain and a local density of specific cells (e.g., osteoblasts) which we denote by $c(t, x)$. The essential quantity for the production of bio-active molecules is $|\varepsilon(u)|_\delta$, where $|\cdot|_\delta$ is a functional relationship which we propose to view as a usual Euclidean norm or a truncated version thereof, see also (2.20). The concentrations of bio-active molecules are normalized to unity in healthy tissue and the choice of decay and production rate should reflect this in a concrete simulation.

Equation (1.3) governing the production of bone forming cells (here: osteoblasts) is modeled by logistic growth and a functional relationship $H(a_1, \ldots, a_N, c, b)$ allowing driving factors for osteoblast production to be the concentrations of bio-active molecules (causing differentiation of stem cells to osteoblasts), the proliferation of osteoblasts and the maturity of the bone present. Note that we do not model diffusion in this equation as we assume that osteoblasts diffuse on a significantly lower level than the bio-active molecules. Of course, more than one cell type is present and responsible for bone growth. For simplicity we only include osteoblasts in this model, but an extension is easily feasible here. Finally, the equation modeling bone growth (1.4) follows the same pattern as the one for osteoblast concentration. In summary, our system of equations reads

$$0 = \operatorname{div}\Big(\mathbb{C}(\rho, \sigma, b)\varepsilon(u)\Big) \qquad \text{(mechanical equilibrium)} \tag{1.1}$$

$$d_t a_i = \operatorname{div}\Big(D_i(\rho)\nabla a_i\Big) + k_{2,i}|\varepsilon(u)|_\delta c - k_{3,i} a_i \qquad \text{(diffusion, generation, and decay of } i = 1 \ldots N \text{ bio-molecules)} \tag{1.2}$$

$$d_t c = H(a_1, \ldots, a_N, c, b)\Big(1 - \frac{c}{1-\rho}\Big) \qquad \text{(osteoblast generation)} \tag{1.3}$$

$$d_t b = K(a_1, \ldots, a_N, c, b)\Big(1 - \frac{b}{1-\rho}\Big) \qquad \text{(bone regeneration driven by } a, b \text{ and } c\text{).} \tag{1.4}$$

In the above system $k_1, k_{2,i}, k_{3,i} \geq 0$, $i = 1, \ldots, N$ are constants that need to be determined from experiments, compare to the Section III where we discuss certain choices. The functional relationships $\mathbb{C}, D_i(\rho), |\cdot|_\delta, H$ and K are all required to satisfy certain technical assumptions that guarantee the well-posedness of the above system. We discuss this in detail in Section I.

Finally, we need to specify boundary conditions. For the elastic equilibrium equation we allow mixed boundary conditions including the limiting cases of a pure displacement boundary condition and a pure stress boundary condition. As for the bio-active molecules we assume that these are in saturation, i.e., $a(t, x) = 1$ adjacent to bone and on the rest of the boundary of Ω we assume no-flux boundary conditions. For the initial time-point we propose $a_i(0, x) = a_{i,0} = 0$ inside of Ω. This choice reflects the scenario of a scaffold that is not preseeded with exogenous growth factors. However, different choices of $a_{i,0}$ are admissible and allow the model to cover, e.g., pre-seeding with osteoinductive factors. Finally, at the initial time we assume that no osteoblasts and no regenerated bone are present inside the domain of computation.

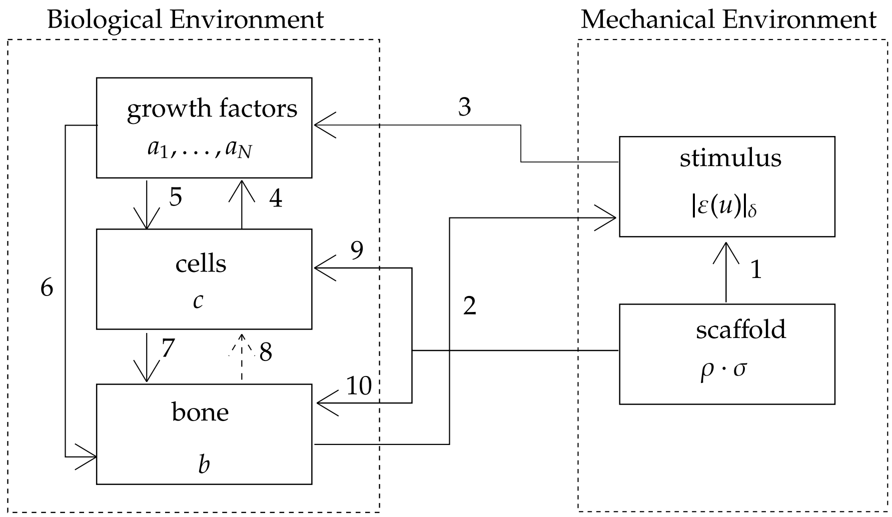


Figure 1.1: Schematic setup of the model's dependencies. 1) & 2) indicate the stimulus' dependence on bone and the scaffold. 3) & 4) represent that the production of growth factors depends on cells and stimulus. 5) encodes the dependence of cell production on growth factors. The cell production is limited through the available space via 9). 6) & 7) indicate that that growth factors and cells drive bone production. The available space in 10) bounds bone production. The dashed arrow in 8) represents a possible dependence of cells on bone, however, we do not include this in our numerical experiments.

In formulas, it holds for all $i = 1, \dots, N$

$$a_i(0,x) = 0 \qquad \text{for all } x \in \Omega \tag{1.5}$$

$$a_i(t,x) = 1 \qquad \text{for all } t \in I,\ x \text{ adjacent to bone} \tag{1.6}$$

$$D_i^\rho \nabla a_i(t,x) \cdot \eta = 0 \qquad \text{for all } t \in I,\ x \text{ not adjacent to bone} \tag{1.7}$$

$$\Big(\mathbb{C}(\rho,\sigma,b)\varepsilon(u(t,x))\Big) \cdot \eta = g_N(x) \qquad \text{on the Neumann boundary of } \Omega \tag{1.8}$$

$$u(t,x) = g_D(x) \qquad \text{on the Dirichlet boundary of } \Omega \tag{1.9}$$

$$c(0,x) = b(0,x) = 0 \qquad \text{for all } x \in \Omega. \tag{1.10}$$

The model allows for a time dependent choice of the mechanical loading g_D and g_N. Due to the long regeneration time horizon of approximately 12 months, however, it is not expedient to resolve very short time-scales of, e.g., the mechanics of physical therapy. Instead, we consider suitably time-averaged loading conditions here.

1.3 The Associated Optimization Problem

In the system (1.1) - (1.4) above, the function ρ, i.e., the scaffold's volume fraction, is a design parameter that we can control in applications. For example, a given scaffold volume fraction distribution could be additively manufactured. Therefore, we call ρ the control variable. Given a certain control variable ρ, we denote the solution of the system (1.1) - (1.4) by

$$y_\rho := (u_\rho, a_\rho^1, \dots, a_\rho^N, c_\rho, b_\rho)$$

to stress the dependency on the control variable. Note however, that we don't always use the subscript ρ throughout the thesis. Depending on the so-called state y_ρ, we can measure the control variable's performance by the value of an objective function J evaluated at ρ and y_ρ. We are interested in minimizing or maximizing the objective function over the set of admissible control variables. In other words, we are interested in the optimization problem of finding

$$\operatorname*{argmin}_\rho J(\rho, y_\rho) \quad \text{subjected to} \quad \rho \in P,$$

where the set P encodes for example that ρ takes values in the unit interval (necessary for a reasonable volume fraction). The fact that corresponding to ρ, we consider the solution y_ρ makes this a PDE-constrained optimization problem and $\rho \in P$ introduces box constraints on the control variable. The concrete form of J is an engineering choice. For instance, the amount of regenerated bone at a certain time-point in the healing process should be maximized. Another alternative we pursue is to maximize the temporal minimum of the elastic modulus. See Section 1.4 for a mathematical formulation of these choices for J.

1.4 Concrete Examples.

We provide a number of possibilities for choosing the functional relationships $\mathbb{C}, D, H$ and K and boundary conditions for the mechanical equilibrium equation 1.1. For an easy example of the elastic tensor that does not need to be derived by a complicated homogenization procedure we simply use the Voigt bound. If we denote by C_b and C_ρ the elastic tensors of matured bone and intact PCL respectively (in their simplest form modeled as isotropic materials) we thus choose

$$\mathbb{C}(\rho, \sigma, b) = bC_b + \rho\sigma C_\rho.$$

This is in accordance with Poh et al. (2019) where the same idea was used in a model with only one spatial variable. Note that this $\mathbb{C}$ naturally is time-dependent as the quantities b and σ vary in time. While this example may serve as a first choice, one could also fix a concrete scaffold micro-structure, such as a gyroid design, and derive the explicit homogenized material properties (see, e.g., Allaire (2012)).

For the diffusivities $D_i(\rho)$ we propose a dependence on the scaffold density ρ, for example

$$D_i(\rho) = k_i(1-\rho)\,\mathrm{Id}$$

where k_i are constants that measure the diffusivity of the bio-active molecule a_i without the presence of the scaffold ρ. The term $(1-\rho)$ accounts for reduced diffusivity for high PCL volume fractions. It is heuristically clear, yet interesting to note, that a too dense scaffold impairs bone regeneration. This is reflected in our model through the diffusivity above, since the amount of bioactive molecules is linked to bone regeneration via the ODE (1.4). One could also imagine to derive the tensor $D_i(\rho)$ through a homogenization process which would then again reflect the choice of a specific micro-structure. For mathematical well-posedness reasons we are unable to allow the diffusivity $D_i(\rho)$ to depend on the bone density b. Furthermore, we also assume that $D_i(\rho)$ does not depend on time.

Finally, we consider the functional relationships H and K inducing the production and proliferation of osteoblasts and bone. We impose a structural condition on K and H that allows us to treat all examples we have in mind. For the explicit assumption see 2.22. Especially, products of any finite number of signaling molecules are allowed. This presents an improvement over our previous results in Dondl et al. (2021). However, note that this is certainly not the most general assumption on H and K that can be made. For simplicity, we provide an example involving two bio-active molecules a_1 and a_2. These can be assumed to have different production rates and half-lives. Then we set

$$H(a_1, a_2, c, b) = H(a_1, a_2, c) = k_6 a_1 a_2 (1 + k_7 c) \tag{1.11}$$

hence bone growth only takes place when the full bio-environment, i.e., both molecules a_1 and a_2 are present. Furthermore the proliferation of osteoblasts is represented by the term $(1 + k_7 c)$. Again k_6 and k_7 are some constants that need to be chosen in accordance with experiments.

For K we propose a similar equation, modeling that bone growth takes place given the presence of osteoblasts and a suitable biological environment, represented in the choice of K through the factor a_1. More precisely we set

$$K(a_1, a_2, c, b) = K(a_1, c) = k_4 a_1 c. \tag{1.12}$$

Another choice for K reflecting that different bio-active molecules are responsible for different stages of bone formation and maturation is possible. This makes the functional relationship dependent of b. We set

$$K(a, b) = f_1(b) a_1 c + f_2(b) a_2 c. \tag{1.13}$$

Now, f_1 can be chosen with support on small values of b, such that in this stage molecule a_1 is driving the growth, and f_2 with support on larger b, thus requiring a_2 in later stages of regeneration. We remark that empirically many different bio-molecules are observed and it is assumed that these are linked to different biological processes, see Kempen et al. (2010).

Examples for the objective function include the maximization of the bone-scaffold's stiffness, i.e., the effective elastic modulus of the structure. In the case of a hard load for the elastic equation, the elastic modulus at a time-point t is proportional to the elastic energy $\mathcal{E}(t)$, i.e.,

$$\mathcal{E}_\rho(t) = \frac{1}{2}\int_\Omega \mathbb{C}(\rho, \sigma(t), b(t))\varepsilon(u(t)) : \varepsilon(u(t))\mathrm{d}x,$$

where u and b solve the system (1.1) - (1.4) corresponding to ρ. The minimum of $\mathcal{E}$ over the whole regeneration process describes the weakest state of the bone-scaffold structure during healing. This gives rise to the objective function

$$\hat{J}(\rho) = \min_{t\in I} \mathcal{E}_\rho(t)$$

and the *maximization* problem of finding

$$\rho^* \in \underset{\rho\in P}{\operatorname{argmax}} \hat{J}(\rho).$$

The set P encodes pointwise constraints on ρ, i.e., the necessity of enforcing $\rho(x) \in [0, 1]$ in order to be a meaningful volume fraction. The notation $\hat{J}$ instead of J is chosen to indicate that the variables u & b appearing in the definition of $\mathcal{E}_\rho$ are solving the system (1.1) - (1.4). Usually, $\hat{J}$ is called the reduced objective function to distinguish it from the objective function J that does not require u and b to solve the PDE system. If we use a soft load instead of a hard load, the elastic modulus is proportional to the inverse of the elastic energy, hence the objective function becomes

$$\hat{J}(\rho) = \max_{t\in I} \mathcal{E}_\rho(t)$$

and the optimization consists of finding

$$\rho^* \in \underset{\rho\in P}{\operatorname{argmin}} \hat{J}(\rho),$$

i.e., is a *minimization* problem.

Remark 1. The proposed objective functions are not smooth as they involve minimizing or maximizing over $t \in I$. For a numerical implementation, one might therefore approximate the minimum or maximum functional by an $L^p(I)$ norm with large value for $-p$ or p respectively.

Another choice of objective function is to consider the amount of regenerated bone after a given time T. This results in the definition

$$\hat{J}(\rho) = \int_\Omega b(T)\mathrm{d}x$$

Remark 2. Care needs to be taken with respect to the functional relationships in the system (1.1) - (1.4) when choosing the amount of regenerated bone as an objective. This requires an adequate choice of $|\cdot|_\delta$. If $|\cdot|_\delta$ is chosen to be the Frobenius norm, the above objective function promotes very weak scaffolds as these lead to high strains and high bone growth. A more sensible choice for $|\cdot|_\delta$ in this case is to use a filter, i.e., only strains with a certain range of magnitude lead to non-vanishing values of $|\cdot|_\delta$.

II Warm-Up Analysis in One Dimension

We begin by providing an existence and uniqueness result together with the existence of an optimal control for a simplified, one-dimensional system similar to (1.1) - (1.4) in the spirit of the system considered in Poh et al. (2019). Here, we keep our proofs short as the Section shall mainly serve to illustrate the plan of attack for the general, i.e., the three-dimensional case. The main difficulties arise from mixed boundary conditions, non-smooth domains and of course worse Sobolev embeddings in the higher spatial dimensions. Therefore, the one-dimensional case is a gentle introduction to the notation and strategy of the analysis. For the existence and uniqueness result, we base our approach on a fixed point argument. We also prove the existence of an optimal control ρ for the associated PDE constrained optimization problem.

2.1 Well-Posedness in One Dimension

Theorem 3. *Let $\Omega = (0, L)$ and $I = [0, T]$ for some $T, L > 0$ be a spatial domain and a time interval, respectively. Fix parameters $\gamma, k_1, \ldots, k_6 > 0$. Set $\sigma : I \to \mathbb{R}$ to $\sigma(t) = e^{-k_1 t}$ and let ρ be a member of $H^1(\Omega)$ that satisfies $c \le \rho(x) \le C$*

for fixed constants $c, C \in (0,1)$. Then there exists a unique weak solution $u^* \in L^2(I, H^1(\Omega))$, $a^* \in H^1(I, H^1(\Omega), H^1_0(\Omega)^*)$ and $b^* \in H^1(I, H^1(\Omega))$ to the system

$$((\rho\sigma + k_6 b)\, u_x)_x = 0 \tag{1.14}$$

$$a_t = (k_5(1-\rho)a_x)_x - k_3 a + k_2 b u_x \tag{1.15}$$

$$b_t = k_4 a\left(1 - \frac{b}{1-\rho}\right) \tag{1.16}$$

with initial and boundary conditions $u(t,0) = 0$, $u(t,L) = \gamma L$ for all $t \in I$, $a(0,x) = 0$ and $a(t,0) = a(t,L) = 1$ for all $(t,x) \in I \times \Omega$ and $b(0,x) = 0$ for all $x \in \Omega$.

Remark 4. As stated above, we prove the existence of a weak solution to the system (1.14)-(1.16). We justify the concept of weak solutions – in particular the fact that we treat the ODEs as Banach space valued and the the solution to the elastic equation as a member of $L^2(I, H^1(\Omega))$ – in Section I. More precisely, it is explained there that in fact, the solution u solves the elastic equation at every time-point and that using Banach space valued ODEs is nothing but a mathematically convenient way of solving parametrized ODEs.

Proof. Associated to the fixed scaffold density $\rho \in H^1(\Omega)$, we consider the convex and closed subset of the space $C^0(I \times \Omega)$

$$W_\rho = \left\{ b \in C^0(I \times \Omega) \mid 0 \le b(t,x) \le 1 - \rho(x) \right\}.$$

Now we define and analyze the following iteration operator

$$\mathcal{I} : W_\rho \to W_\rho, \quad b \mapsto \mathcal{I}(b),$$

where $\mathcal{I}(b)$ is produced by solving equation (1.14) - (1.16) with the start data b, hence decoupling them. More precisely, fix $b \in W_\rho$ and solve (1.14) to obtain $u(b) = u$. With b and $u(b)$ solve (1.15) to obtain $a(b, u(b)) = a$ and finally $\mathcal{I}(b)$ is given as the solution of (1.16) using $a(b, u(b))$. The set of fixed points of $\mathcal{I}$ coincides with the set of solutions of the system (1.14) - (1.16). For the existence and uniqueness we combine Schauder's and Banach celebrated fixed point theorems. We begin by showing that $\mathcal{I}$ is well defined, continuous and compact.

To begin with, note that our assumptions on b and ρ imply that the material tensor

$$\rho\sigma + k_6 b = \mathbb{C}(\rho, \sigma, b) \tag{1.17}$$

is uniformly elliptic for every fixed $t \in I$, hence a solution $u = u(b) \in L^2(I, H^1(\Omega))$ exists as an application of the Lax-Milgram Theorem in the Hilbert Space $L^2(I, H^1_0(\Omega))$, satisfying the correct boundary values. Let us denote by $(\mathcal{T}, \mathrm{tr})$ the following linear homeomorphism

$$(\mathcal{T}_b, \mathrm{tr}) : L^2(I, H^1(\Omega)) \to L^2(I, H^1_0(\Omega))^* \times L^2(I, H^{1/2}(\partial\Omega)) \tag{1.18}$$

given by

$$u \mapsto \left(\int_I \int_\Omega (\rho\sigma + k_6 b) u' \cdot' \,\mathrm{d}x\mathrm{d}t, \mathrm{tr}(u) \right). \tag{1.19}$$

Then, to see that $b \mapsto u(b)$ is continuous and bounded, we factorize using the above homeomorphism

$$b \mapsto ((t,x) \mapsto \rho(x)\sigma(t) + k_6 b(t,x)) \mapsto (\mathcal{T}_b, \mathrm{tr}) \mapsto (\mathcal{T}_b, \mathrm{tr})^{-1} \mapsto (\mathcal{T}_b, \mathrm{tr})^{-1}(0, (0, \gamma L))$$

as a map

$$\begin{aligned} W_\rho \to C^0(I \times \Omega) &\to \mathcal{L}\left(L^2(I, H^1(\Omega)), L^2(I, H^1_0(\Omega))^* \times L^2(I, H^{1/2}(\partial\Omega))\right) \\ &\to \mathcal{L}\left(L^2(I, H^1_0(\Omega))^* \times L^2(I, H^{1/2}(\partial\Omega)), L^2(I, H^1(\Omega))\right) \\ &\to L^2(I, H^1(\Omega)). \end{aligned}$$

Now we look at the diffusion equation. We note first that our assumption on ρ implies that the diffusivity

$$D(\rho) = k_5(1-\rho) \tag{1.20}$$

is uniformly elliptic. Hence the inducing operator

$$D(\rho)a' \cdot' + k_3 a \cdot \in \mathcal{L}(H^1(\Omega), H^1_0(\Omega)^* \times H^{1/2}(\partial\Omega)) \tag{1.21}$$

is coercive and with the right hand side $k_2 b u_x$ in $L^2(I, L^2(\Omega))$ we get a solution $a = a(u,b)$ in $H^1(I, H^1(\Omega), H^1_0(\Omega)^*)$. As u depends continuously in $L^2(I, H^1(\Omega))$ on b in $C^0(I \times \Omega)$, clearly

$$b \mapsto k_2 b u(b)_x \tag{1.22}$$

is continuous and bounded which is thus inherited by $b \mapsto a(u(b), b)$. This can easily be verified using the estimates in Lemma 27 and the linearity of the equation. Finally, to solve the ODE we employ Theorem 71 to produce a solution in $H^1(I, H^1(\Omega))$. The essential requirement is that the map

$$F : I \times H^1(\Omega) \to H^1(\Omega) \quad \text{with} \quad F(t,b) = b\frac{k_4 a}{1-\rho} - k_4 a$$

satisfies a Lipschitz condition of the form

$$\|F(t,b_1) - F(t,b_2)\|_{H^1(\Omega)} \le L(t)\|b_1 - b_2\|_{H^1(\Omega)}$$

with $L \in L^2(I)$. This holds true as in one dimension the space $H^1(\Omega)$ is a Banach algebra. Hence, there is $\overline{b} = \mathcal{I}(b) = \overline{b}(a)$ in $H^1(I, H^1(\Omega))$ solving (1.16) and the abstract Sobolev space embedds compactly into the space of continuous functions on the space-time cylinder

$$H^1(I, H^1(\Omega)) \hookrightarrow C^\alpha(I, C^\alpha(\Omega)) \hookrightarrow\hookrightarrow C^0(I \times \Omega)$$

for a suitable Hölder exponent $\alpha \in (0,1)$. The pointwise property of the set W_ρ is respected by solutions of the ODE (1.16) as the function $a = a(u,b)$ is non-negative, see 60, and the term

$$1 - \frac{b}{1-\rho}$$

prevents the solution from exceeding $1-\rho$. The boundedness and continuity of the map $a \mapsto \overline{b}(a)$ follow from the formula

$$\overline{b}(t) = \int_0^t k_4 a(s) - \overline{b}(s)\frac{k_4 a(s)}{1-\rho}\mathrm{d}s \quad \text{in } H^1(\Omega) \tag{1.23}$$

and an application of Grönwall's Lemma, 73. This brings us in the position to apply Schauder's theorem to produce a fixed point b^* to the map

$$W_\rho \to W_\rho, \quad b \mapsto \mathcal{I}(b).$$

Solving the remaining equations with b^* as in the definition of $\mathcal{I}$ then leads to functions u^*, a^*, b^* solving (1.14) - (1.16).

The uniqueness of this system can be obtained by proving that for a short enough time interval, the map $b \mapsto \mathcal{I}(b)$ is in fact a contraction. Finally an extension argument yields the uniqueness for an arbitrary, finite time interval. □

As mentioned at the end of the proof above, we might prove the existence and uniqueness Theorem using the contraction mapping principle alone and will do so in the three dimensional case. Above, we decided to use Schauder's theorem and only comment briefly on the uniqueness aspect to keep things simple.

2.2 Existence of an Optimal Control in One Dimension

In a next step we prove the existence of an optimal ρ with respect to the objective function J based on the elastic energy as described in Section 1.4. However, the result is also applicable to different choices of J. Note that provided the preceding existence and uniqueness result, we know there is a solution operator ϕ taking ρ to the solution (u,a,b) and consequently we may talk about the reduced objective function $\hat{J}(\rho) = J(\rho, \phi(\rho))$. Also note that in the following Theorem, we artificially enforce a bound in the $H^1(\Omega)$ norm on the admissible functions ρ. It is presently unclear if this bound can be reduced.

Theorem 5 (Optimal Control in 1D)**.** *Let us fix $R > 0$ and $c, C \in (0,1)$ with $c < C$. Consider the set of admissible scaffold densities*

$$P_R := \left\{c \le \rho(x) \le C \mid \|\rho\|_{H^1(\Omega)} \le R\right\} \subset H^1(\Omega).$$

Then there is $\rho^* \in P_R$ maximizing the objective function

$$\hat{J}(\rho) = \min_{t \in I} \int_\Omega \mathbb{C}(b,\sigma,\rho) u_x^2 \mathrm{d}x$$

among all functions in P_R. Here, $\hat{J}$ is the reduced objective, meaning that b and u solve the system (1.14) - (1.16) *corresponding to the datum ρ.*

Proof. The result is proven by the direct method of the calculus of variations. Using the $H^1(\Omega)$ bound that is built in the definition we get for a minimizing sequence (ρ_k) that there is a (not relabeled) subsequence and a function $\rho^* \in P_R$ such that

$$\rho_k \rightharpoonup \rho^* \quad \text{in } H^1(\Omega).$$

One crucial aspect that makes the one-dimensional analysis simpler is the fact that $H^1(\Omega)$ embedds compactly into $C^0(\Omega)$ and therefore we can deduce that $\rho_k \to \rho^*$ converges strongly with respect to the space $C^0(\Omega)$. By the previous proof we know that the associated solutions $(b_k) \subset C^0(I \times \Omega)$ are relatively compact, hence passing to another unlabeled subsequence we get that

$$b_k \to b^* \quad \text{in } C^0(I \times \Omega)$$

for some $b^* \in W_\rho$. Also from the previous proof we know that $b_k(t) \in H^1(\Omega)$ for all timepoints $t \in I$. Together with $\rho \in H^1(\Omega)$ and $\sigma \in C^\infty(I)$ we get, invoking elliptic regularity theory (Dobrowolski, 2010, Chapter 7, Satz 7.6), that $u_k(t) \in H^2(\Omega)$ with a bound on its norm

$$\|u_k(t)\|_{H^2(\Omega)} \le C \cdot \gamma L \quad \text{for all } t \in I.$$

We proceed by showing that the sequence (u_k) is equi-continuous as a subset of $C^0(I, H^1(\Omega))$. To this end we split u_k into $u_k(t,x) = \hat{u}_k(t,x) + \gamma x$, where $\hat{u}_k \in L^2(I, H_0^1(\Omega))$ solves

$$\underbrace{\int_\Omega \mathbb{C}(\rho_k, b_k, \sigma)(t)\hat{u}_k(t)' \cdot' \,\mathrm{d}x}_{=:\mathcal{T}_{b_k(t)}\hat{u}_k(t)} = \underbrace{-\int_\Omega \mathbb{C}(\rho_k, b_k, \sigma)\gamma \cdot' \,\mathrm{d}x}_{=:f_{b_k(t)}} \quad \text{for all } t \in I.$$

For two timepoints $t, s \in I$ we compute

$$\begin{aligned} f_{b_k(t)} - f_{b_k(s)} &= \mathcal{T}_{b_k(t)}\hat{u}_k(t) - \mathcal{T}_{b_k(s)}\hat{u}_k(s) \\ &= \mathcal{T}_{b_k(t)}\left(\hat{u}_k(t) - \hat{u}_k(s)\right) + \mathcal{T}_{b_k(t)-b_k(s)}\left(\hat{u}_k(s)\right). \end{aligned}$$

Hence,

$$\mathcal{T}_{b_k(t)}\left(\hat{u}_k(t) - \hat{u}_k(s)\right) = f_{b_k(t)} - f_{b_k(s)} - \mathcal{T}_{b_k(t)-b_k(s)}\left(\hat{u}_k(s)\right)$$

and by the standard Lax-Milgram energy estimates and straight-forward computations we get

$$\begin{aligned} \|u_k(t) - u_k(s)\|_{H^1(\Omega)} &= \|\hat{u}_k(t) - \hat{u}_k(s)\|_{H^1(\Omega)} \\ &\le \frac{1}{c}\|f_{b_k(t)} - f_{b_k(s)}\|_{H_0^1(\Omega)^*} + \|\mathcal{T}_{b_k(t)-b_k(s)}\left(\hat{u}_k(s)\right)\|_{H_0^1(\Omega)^*} \\ &\le C\|b(t) - b(s)\|_{C^0(\Omega)}. \end{aligned}$$

The last estimate shows that (u_k) inherits its equi-continuity from the equi-continuity of (b_k), which was established via the relative compactness of the sequence (b_k) in $C^0(I, C^0(\Omega))$. Using the Banach space valued version of the Arzelà-Ascoli Theorem 26 yields, inferring the regularity $u_k(t) \in H^2(\Omega)$, that also the sequence $(u_k) \subset C^0(I, H^1(\Omega))$ is relatively compact, hence there is a function $u^* \in C^0(I, H^1(\Omega))$ such that

$$u_k \to u^* \quad \text{in } C^0(I, H^1(\Omega)).$$

Finally, for the solutions a_k of the diffusion equation, we have by the boundedness of the operator $\mathcal{I}$ of the previous proof that, passing to one last subsequence,

$$a_k \rightharpoonup a^* \quad \text{in } H^1(I, H^1(\Omega), H_0^1(\Omega)^*)$$

for a function a^* in $H^1(I, H^1(\Omega), H_0^1(\Omega)^*)$. All these convergences are by far sufficient to pass to the limit in the equations (1.14) and (1.15). For the ODE (1.16), one uses its fixed-point formulation via the fundamental theorem of the space $H^1(I, H^1(\Omega))$, i.e.,

$$b_k(t) = \int_0^t k_4 a_k(s) - b_k(s)\frac{k_4 a_k(s)}{1 - \rho_k}\,\mathrm{d}s \quad \text{in } H^1(\Omega)$$

and pass to the limit yielding a unique solution in $b^* \in W^{1,2}(I, C^0(\Omega))$ as $b^* \in C^0(I \times \Omega)$. Inspecting the resulting ODE, it is clear that also a unique solution b^{**} in $H^1(I, H^1(\Omega))$ must exist as $a^* \in L^2(I, H^1(\Omega))$ and $\rho \in H^1(\Omega)$, hence $b^{**} = b^*$. Consequently (ρ^*, u^*, a^*, b^*) indeed solve (1.14) - (1.16). By the strong convergences we have established it clearly holds

$$\inf_{\rho \in P_R} \hat{J}(\rho) = \lim_{k \to \infty} \hat{J}(\rho_k) = \hat{J}(\rho^*)$$

which implies that ρ^* is an optimal control function. □

Remark 6. Some remarks concerning the above result are in order.

(i) The question of removing the requirement

$$\|\rho\|_{H^1(\Omega)} \leq R$$

remains open. In the one-dimensional case with Dirichlet boundary conditions as assumed in Theorem 5 one might try to exploit the symmetry that one expects from an optimal control ρ^*. However, we do not pursue this idea further as it seems of limited interested in view of the three-dimensional setting. To conclude, we note that adding a Tikhonov penalization to $\hat{J}$, i.e., considering

$$\hat{J}(\rho) + \eta\|\rho\|^2_{H^1(\Omega)}$$

provides $H^1(\Omega)$ bounds for any minimizing sequence (ρ_k) and thus makes Theorem 5 applicable.

(ii) It is not clear whether there exists only one optimal control. The objective function is not convex – it involves a minimum over all timepoints $t \in I$ and a complex solution operator – and thus standard arguments are not applicable.

(iii) We have freedom in the choice of of the objective function. The minimum over all time points that is used in its definition can be replaced by any functional

$$\mathcal{F} : C^0_+(I) \to [0, \infty), \quad v \mapsto \mathcal{F}(v)$$

that is well defined on the cone of continuous and positive functions from I to $\mathbb{R}$, which we denote by $C^0_+(I)$. For instance an $L^p(I)$-type functional with a negative exponent p can be used to smoothly approximate the minimum in the definition of $\hat{J}$. Furthermore, we might incorporate the pointwise constraint $c \leq \rho(x) \leq C$ in form of a suitable penalization

$$\mathcal{K} : C^0(\Omega) \to [0, \infty), \quad v \mapsto \mathcal{K}(v)$$

as long as $\mathcal{K}$ is continuous. One might think of $\mathcal{K}$ as penalizing the deviation of ρ from leaving the interval $[c, C]$. This then allows to define the energy $\hat{J}$ on all of $C^0(\Omega)$ and one still obtains the existence of an optimal control. This is precisely the approach taken in the numerical Section of this work.

(iv) We briefly comment on the core difficulties encountered when transferring the above proof to three dimensions. As we are forced to consider mixed boundary conditions (Dirichlet-Neumann) for the diffusion equation to allow realistic application scenarios, the regularity properties of the solution to the diffusion equation are limited. In order to get compactness for (b_k) we need that (a_k) is bounded in the space $L^2(I, C^\alpha(\Omega))$. It turns out that this holds true in three dimensions but it requires substantial effort. Details can be found in the Appendix II on regularity theory and in Chapter 3 for the main part of the proof in three dimensions. Furthermore, the strong convergence of (u_k) in the space $C^0(I, H^1(\Omega))$ is crucial to allow reasonable choices of the functional relationship $|\cdot|_\delta$ in three dimensions and still being able to pass to the limit in the optimal control result. Only recently, the main result in Haller-Dintelmann et al. (2019) made the desired regularity available. We discuss this in detail in Chapter 3.

Chapter 2

Analyzing Scaffold Mediated Bone Growth

This Chapter is devoted to the mathematical analysis of the system (2.1) – (2.4). We explain the in detail the weak formulation and its appropriateness. Furthermore, exemplary numerical results are provided.

I Mathematical Formulation

In this Section we describe the mathematical setting in which we prove the well-posedness of a solution to the system of equations (2.1) – (2.4). We also state the assumptions the functional relationships $\mathbb{C}$, D_i, $|\cdot|_\delta$ H and K are required to satisfy. For convenience, we recall the system

$$0 = \operatorname{div}\Big(\mathbb{C}(\rho,\sigma,b)\varepsilon(u)\Big) \qquad \text{(mechanical equilibrium)} \tag{2.1}$$

$$d_t a_i = \operatorname{div}\Big(D_i(\rho)\nabla a_i\Big) + k_{2,i}|\varepsilon(u)|_\delta c - k_{3,i}a_i \qquad \text{(diffusion, generation, and decay of } i = 1\dots N \text{ biomolecules)} \tag{2.2}$$

$$d_t c = H(a_1,\dots,a_N,c,b)\Big(1 - \frac{c}{1-\rho}\Big) \qquad \text{(osteoblast generation)} \tag{2.3}$$

$$d_t b = K(a_1,\dots,a_N,c,b)\Big(1 - \frac{b}{1-\rho}\Big) \qquad \text{(bone regeneration driven by } a, b \text{ and } c\text{).} \tag{2.4}$$

with boundary conditions

$$a_i(0,x) = 0 \qquad \text{for all } x \in \Omega \tag{2.5}$$

$$a_i(t,x) = 1 \qquad \text{for all } t \in I,\ x \text{ adjacent to bone} \tag{2.6}$$

$$D_i^\rho \nabla a_i(t,x)\cdot\eta = 0 \qquad \text{for all } t \in I,\ x \text{ not adjacent to bone} \tag{2.7}$$

$$\Big(\mathbb{C}(\rho,\sigma,b)\varepsilon(u(t,x))\Big)\cdot\eta = g_N(x) \qquad \text{on the Neumann boundary of } \Omega \tag{2.8}$$

$$u(t,x) = g_D(x) \qquad \text{on the Dirichlet boundary of } \Omega \tag{2.9}$$

$$c(0,x) = b(0,x) = 0 \qquad \text{for all } x \in \Omega. \tag{2.10}$$

1.1 The Domain

Fix a time interval $I = [0,T]$ with $T > 0$. The spatial domain $\Omega \subset \mathbb{R}^n$, with $n = 1,2,3$ is assumed to be open, bounded and connected and for every equation we split the boundary $\partial\Omega$ into a Dirichlet part and a Neumann part. For the elastic equation we write Γ_D^e and Γ_N^e for Dirichlet and Neumann boundary respectively, here $\Gamma_D^e = \emptyset$ is allowed. For the diffusion equations we write Γ_D^d and Γ_N^d. To simplify notation we do not treat the case of different Dirichlet-Neumann partitions for different diffusion equations, though this does not lead to further mathematical complications. Finally we need to assume some regularity on Ω and the partition $\partial\Omega = \Gamma_D^d \cup \Gamma_N^d$ for the diffusion equations, namely the set $\Omega \cup \Gamma_N^d$ needs to be Gröger regular which is a concept introduced in Gröger (1989), see also Haller-Dintelmann et al. (2009). These regularity assumptions are tailored to provide a certain regularity of the solutions of the diffusion equations, which we discuss in detail in Section II in the Appendix. Our assumptions are very general and cover most cases relevant in practice. Problems may only arise for self-touching domains or domains with cusps.

1.2 Admissible Data

The admissible scaffold volume fractions ρ are given as

$$P := \left\{\rho \in C^0(\Omega) \mid c_P \le \rho(x) \le C_P\right\} \tag{2.11}$$

with some fixed constants $0 < c_P < C_P < 1$, excluding unreasonable scaffold designs. To a scaffold volume fraction $\rho \in P$ we assign the set W_ρ of admissible cell and bone volume fractions, consisting of tuples of continuous functions in time and space

$$W_\rho := \left\{(c, b) \in C^0(I \times \Omega)^2 \mid 0 \le c(t, x),\ b(t, x) \le 1 - \rho(x)\right\}. \tag{2.12}$$

1.3 The Elastic Equation

We begin with the Hookean law $\mathbb{C}$. It depends on the scaffold and bone, i.e., on ρ, σ and b and varies therefore in space and time. We assume that the map

$$W_\rho \to L^\infty(I \times \Omega, \mathcal{L}(\mathcal{M}_s)) \quad \text{with} \quad (c, b) \mapsto ((t, x) \mapsto \mathbb{C}(\rho, \sigma, b)(t, x)) \tag{2.13}$$

is Lipschitz continuous with Lipschitz constant $L_{\mathbb{C}}$ independent of $\rho \in P$. Remember that σ is a fixed exponential decay. Here $\mathcal{M}_s$ denotes the symmetric $n \times n$ matrices and $\mathcal{L}(\mathcal{M}_s)$ is the space of linear maps from $\mathcal{M}_s$ into itself, usually called the space of fourth order tensors. In the following we will often omit the cumbersome notation of dependencies on x and t for $\mathbb{C}$. Spelling out the definitions of the norms in (2.13) this Lipschitz continuity means that for all $M \in \mathcal{M}_s$ it holds

$$|\mathbb{C}(\rho(x), \sigma(t), b_1(t, x))M - \mathbb{C}(\rho(x), \sigma(t), b_2(t, x))M| \le L_{\mathbb{C}}\, \|b_1 - b_2\|_{C^0}\, |M| \tag{2.14}$$

for all (c_1, b_1), $(c_2, b_2) \in W_\rho$ and uniformly in $\rho \in P$ and uniformly on the complement of a set of measure zero in $I \times \Omega$. Furthermore we assume that there are constants $0 < c_{\mathbb{C}} < \infty$ and $0 < C_{\mathbb{C}} < \infty$ such that

$$\sup_{\rho,c,b} \left\|\mathbb{C}(\rho, \sigma, b)\right\|_{L^\infty(I, L^\infty(\Omega, \mathcal{L}(\mathcal{M}_s)))} \le C_{\mathbb{C}} \quad \text{and} \quad \inf_{\rho,c,b} \mathbb{C}(\rho, \sigma, b)M : M \ge c_{\mathbb{C}}|M|^2 \tag{2.15}$$

where the supremum and infimum run over $\rho \in P$ and $b \in W_\rho$ and $A : B = \operatorname{tr} AB^T$ denotes the full contraction of matrices. We now discuss the weak formulation of equation (1.1). Let $\rho \in P$ and $(c, b) \in W_\rho$ be some admissible functions. We first address the case where Γ_D^e has non-vanishing measure and comment on the pure Neumann problem later. The strong form

$$-\operatorname{div}\left(\mathbb{C}(\rho, \sigma, b)\varepsilon(u)\right) = 0 \text{ in } \Omega, \quad u_{|\Gamma_D^e} = g_D^e, \quad \left(\mathbb{C}(\rho, \sigma, b)\varepsilon(u)\right)\eta_{|\Gamma_N^e} = g_N^e$$

encodes that at every point in time mechanical equilibrium is achieved, making the equation time dependent. The function space for the weak formulation is given by: $L^2(I, H^{1,2}(\Omega, \mathbb{R}^n))$ with $H^{1,2}(\Omega, \mathbb{R}^n)$ being the Sobolev space of $\mathbb{R}^n$-valued, square integrable functions with square integrable derivatives, see for example Brezis (2010); Grisvard (2011); Adams and Fournier (2003) for a detailed account of such spaces. If the context is clear, we will usually write $H^1(\Omega)$ instead of $H^{1,2}(\Omega, \mathbb{R}^n)$. Furthermore, the space $L^2(I, H^1(\Omega))$ denotes a Bochner space, i.e., a Banach-space valued Lebesgue space, see, e.g., Diestel and Uhl (1977) or Boyer and Fabrie (2012). The space of test functions is $L^2(I, H^1_{D_e}(\Omega))$, where $H^1_{D_e}(\Omega)$ is the subspace of $H^1(\Omega)$ whose members vanish on Γ_D^e. For the Dirichlet boundary values we require there exists a lift u_D with

$$u_D \in C^0(I, H^1(\Omega)) \quad \text{such that} \quad (u_D)_{|\Gamma_D^e} = g_D^e,$$

in particular $g_D^e(t)$ lies in $H^{1/2}(\Gamma_D^e, \mathbb{R}^n)$, with $H^{1/2}(\Gamma)$, for some $\Gamma \subset \partial\Omega$, being the trace space of $H^1(\Omega)$, see for example Adams and Fournier (2003); Grisvard (2011). The Neumann boundary values can be given as an element of $C^0(I, H^{1/2}(\Gamma_N^e, \mathbb{R}^n)^*)$. Denoting by $\langle \cdot, \cdot \rangle_{H^{1/2}}$ the dual pairing of $H^{1/2}(\Gamma_N^e, \mathbb{R}^n)$ the weak formulation of (1.1) is

$$\begin{aligned} \int_I \int_\Omega \mathbb{C}(\rho, \sigma, b)\varepsilon(u) : \varepsilon(\cdot)\, dxdt &= \int_I \langle g_N^e, \cdot \rangle_{H^{1/2}}\, dt \quad \text{in} \quad L^2(I, H^1_{D_e}(\Omega))^* \\ u &= g_D^e \quad \text{in} \quad L^2(I, H^{1/2}(\Gamma_D^e)). \end{aligned} \tag{2.16}$$

The left hand side of (2.16) equation defines an operator

$$\mathcal{T} : L^2(I, H^1(\Omega)) \to L^2(I, H^1(\Omega))^* \quad \text{with} \quad \mathcal{T} u = \int_I \int_\Omega \mathbb{C}(\rho, \sigma, b)\varepsilon(u) : \varepsilon(\cdot)\, dxdt.$$

Note that the isometry $L^2(I, H^1(\Omega))^* \cong L^2(I, H^1(\Omega)^*)$ implies that the equation (2.16) can be understood to hold almost everywhere in time, which is precisely what we want for our model. A moments' reflection reveals that $\mathbb{C}(\rho, \sigma, b) \in L^\infty(I \times \Omega, \mathcal{L}(\mathcal{M}_s))$ implies that $\mathbb{C}(\rho, \sigma, b)\varepsilon(u) \in L^2(I, L^2(\Omega))$, hence the operator is well defined. Furthermore, Korn's inequality can be used to show that $\mathcal{T}$ is coercive, see Ciarlet (2010). The advantage of the abstract formulation is that it makes the Lax-Milgram Lemma applicable. Now we comment on the pure Neumann boundary value problem, i.e., the case $\Gamma_N^e = \partial\Omega$. We define the spaces $W := \ker(\varepsilon) \subset H^1(\Omega)$ and the quotient $H^1(\Omega)/W$. Note that W consists of the functions of the form $w(x) = Ax + b$, where A is an anti-symmetric matrix and $b \in \mathbb{R}^n$, see for example Ciarlet (1988). For the pure Neumann problem consider the operator

$$\mathcal{T} : L^2(I, H^1(\Omega)/W) \to L^2(I, H^1(\Omega)/W)^*$$

using the induced map $\hat{\varepsilon} : H^1(\Omega)/W \to L^2(\Omega, \mathcal{M}_s)$ in its definition

$$\mathcal{T}(u) = \int_I \int_\Omega \mathbb{C}(\rho, \sigma, b)\hat{\varepsilon}(u) : \hat{\varepsilon}(\cdot)\, dxdt.$$

The codomain of this operator is $L^2(I, H^1(\Omega)/W)^* \cong L^2(I, (H^1(\Omega)/W)^*)$, which encodes a compatibility condition. We assume that our Neumann boundary condition is given as a function $g_N^e \in C^0(I, H^{1/2}(\partial\Omega)^*)$ that satisfies almost everywhere in I

$$\langle g_N^e(t), \cdot\rangle_{H^{1/2}} = 0 \quad \text{for all } w \in W. \tag{2.17}$$

This guarantees that

$$\int_I \langle g_N^e, \cdot\,\rangle_{H^{1/2}}\, dt \in L^2(I, H^1(\Omega)/W)^*$$

is an admissible right hand side. The pure Neumann problem consists then of finding $u \in L^2(I, H^1(\Omega)/W)$ such that

$$\int_I \int_\Omega \mathbb{C}(\rho, \sigma, b)\hat{\varepsilon}(u) : \hat{\varepsilon}(\cdot)\, dxdt = \int_I \langle g_N^e, \cdot\,\rangle_{H^{1/2}}\, dt \in L^2(I, H^1(\Omega)/W)^*,$$

Finally, let us remark that one can treat the Dirichlet, the Neumann and the mixed boundary value problem at once by always passing to the quotient $H^1_{D_e}(\Omega)/W$. In the case of a proper Dirichlet boundary condition we then have $W \cap H^1_{D_e}(\Omega) = \{0\}$, which implies $H^1_{D_e}(\Omega)/W = H^1_{D_e}(\Omega)$, hence recovers the Dirichlet or mixed case, and if $\Gamma_N^e = \partial\Omega$ we retrieve the pure Neumann case.

1.4 Diffusion Equations

Before we state the weak formulation of the diffusion equations, for the reader's convenience, we recall the concept of the time derivative we are using – namely a regular Banach space valued distribution with a dense embedding $j \in \mathcal{L}(X, X^*)$ just as in Boyer and Fabrie (2012). Let (i, X, H) be a Gelfand triple, i.e., X is a Banach space, H is a Hilbert space and $i \in \mathcal{L}(X, H)$ has dense range. Then we set j to be $j = i^* \circ R \circ i$ where $R : H \to H^*$ is the Riesz isometry and i^* denotes the Banach space adjoint of i. We say a function $a \in L^2(I, X)$ possesses a time derivative $d_t a \in L^2(I, X^*)$ if it holds

$$\int_I (j \circ a)(t)\partial_t \varphi(t)\, dt = -\int_I d_t a(t)\varphi(t)\, dt \quad \forall \varphi \in \mathcal{D}(I).$$

The integrals are X^* valued Bochner integrals and we set $\mathcal{D}(I) := C_c^\infty(I)$ as usual. This is used to define a generalized Sobolev space built on the triple (i, X, H) as

$$H^{1,2,2}(I, X, X^*) = \{a \in L^2(I, X) \mid d_t a \in L^2(I, X^*)\}.$$

See in (Boyer and Fabrie, 2012, Chapter II, section 5) for more information. We only remark that functions in this Sobolev space have representatives in $C^0(I, H)$, hence initial value problems can be formulated.

To get to our concrete diffusion equations we let $\rho \in P$, $(c, b) \in W_\rho$ and, depending on the boundary conditions for the elastic equation, $u \in L^2(I, H^1(\Omega))$ or $u \in L^2(I, H^1(\Omega)/W)$ be some fixed functions. In order to work with homogeneous Dirichlet boundary conditions in space we write

$$a_i(t) = \tilde{a}_i(t) + 1 \quad \text{with} \quad \tilde{a}_i(t) \in H^1_{D_d}(\Omega) \quad \text{for} \quad i = 1, \ldots, N.$$

Here $H^1_{D_d}(\Omega)$ denotes the subspace of $H^1(\Omega)$ with vanishing trace on Γ^d_D. We can thus seek $\tilde{a}_i$ in the space $H^{1,2,2}(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*)$ built around $(\mathrm{id}_{|H^1_{D_d}}, H^1_{D_d}, L^2)$ satisfying the equation

$$\int \langle d_t \tilde{a}_i, \cdot \rangle_{H^1_{D_d}} + \iint D_i^\rho \nabla \tilde{a}_i \nabla \cdot + k_i^3 \tilde{a}_i \cdot \, dxdt = \iint (k_i^2 |\varepsilon(u)|_\delta c - k_i^3) \, \cdot \, dxdt$$
$$\tilde{a}_i(0) = -1.$$

The first equation is an equality in the space $L^2(I, H^1_{D_d}(\Omega))^*$, i.e., it is required to hold when tested with all members of $L^2(I, H^1_{D_d}(\Omega))$. In the second equation, the initial conditions is an equality in the space $L^2(\Omega)$. For every $i = 1, \ldots, N$ we have different constants k_i^2 and k_i^3 and also different diffusivities D_i^ρ. Note that the quantity $|\varepsilon(u)|_\delta$ is well defined, even though the solution of the elastic equation is only unique up to rigid body motions. We assume furthermore that the D_i^ρ are time-independent, measurable, essentially bounded and coercive, precisely

$$D_i^\rho \in L^\infty(\Omega, \mathcal{M}_s) \tag{2.18}$$

$$\langle D_i^\rho \xi, \xi \rangle \geq c_D |\xi|^2 \quad \forall \xi \in \mathbb{R}^n \tag{2.19}$$

where $\mathcal{M}_s$ again denotes the symmetric $n \times n$ matrices and the inequality in (2.19) is to be understood uniformly in $x \in \Omega$, $\rho \in P$ and $i = 1, \ldots, N$. Finally the function $|\cdot|_\delta : \mathbb{R}^{n \times n} \to [0, \infty)$ is required to to be globally Lipschitz and to satisfy an estimate of the form

$$|A|_\delta \leq C_1 |A| + C_2 \quad \text{for all } A \in \mathbb{R}^{n \times n} \tag{2.20}$$

where $C_1, C_2 > 0$ and $|A|$ denotes the Euclidean norm of a matrix.

1.5 Ordinary Differential Equations

We treat the ODEs in the vector valued sense and focus here on the cell equation (1.3), the bone equation (1.4) being treated analogously. For each $x \in \Omega$, we thus seek a function c_x satisfying the ODE

$$c_x'(t) = H(a_1(t, x), \ldots, a_N(t, x), c_x(t), b(t, x)) \Big(1 + \frac{c_x(t)}{1 - \rho(x)} \Big)$$

with $c_x(0) = 0$. If there is a solution for all $x \in \Omega$ we obtain a function c in time and space, i.e., $c : I \times \Omega \to \mathbb{R}$ with $c(t, x) := c_x(t)$. As $H(a_1, \ldots, a_N, c, b)$ can not generally assumed to be continuous, a reasonable space to work in is

$$W^{1,p}(I, X) = \{ c \in L^p(I, X) \mid d_t c \in L^p(I, X) \},$$

similar to the space for the diffusion equation, but without the identification $j : X \hookrightarrow X^*$. An existence and uniqueness result in this setting can be found in the supplement, see Theorem 74.

In our concrete case we choose $X = C^0(\Omega)$, $p = 2$, so for fixed $\rho \in P$ and $a = (a_1, \ldots, a_N) \in H^{1,2,2}(I, H^1(\Omega), H^1_{D_d}(\Omega)^*)^N$ we seek $c \in W^{1,2}(I, C^0(\Omega))$ satisfying

$$d_t c = H(a_1, \ldots, a_N, c, b) \Big(1 - \frac{c}{1 - \rho} \Big) \quad \text{with} \quad c(0) = 0. \tag{2.21}$$

We assume that H is a Nemytskii operator induced by a function which we again denote by H,

$$H : \mathbb{R}^{N+2} \to \mathbb{R} \quad \text{with} \quad (a_1, \ldots, a_N, b, c) = (a, b, c) \mapsto H(a, b, c) \tag{2.22}$$

such that $H(a, c, b) \geq 0$ whenever $a_1, \ldots, a_N, b, c \geq 0$. For the concrete form of H we require that H factorizes into $H = H^2 \circ H^1$, where $H^1 : \mathbb{R}^{N+2} \to \mathbb{R}^M$ for some $M \in \mathbb{N}$ is globally Lipschitz. The function H^2 is the product of its components, i.e.,

$$H^2(h_1, \ldots, h_M) = \prod_{i=1}^M h_i$$

Note that by some abuse of notation we denote by a, b and c both a function in a Sobolev space and a vector in Euclidean space.

For the bone ODE we work in the same space and seek $b \in W^{1,2}(I, C^0(\Omega))$ satisfying

$$d_t b = K(a_1, \dots, a_N, c, b)\left(1 - \frac{b}{1-\rho}\right) \quad \text{with} \quad b(0) = 0. \tag{2.23}$$

We assume the functional relationship K is induced by

$$K : \mathbb{R}^{N+2} \to \mathbb{R} \quad \text{with} \quad (a, b, c) = (a_1, \dots, a_N, b, c) \mapsto K(a, b, c)$$

that satisfies $K(a_1, \dots, a_N, b, c) \geq 0$ for $a_1, \dots, a_N, b, c \geq 0$ and that $K = K^2 \circ K^1$ where again $K^1 : \mathbb{R}^{N+2} \to \mathbb{R}^M$ is globally Lipschitz continuous and K^2 is the product of its components, just as we assumed above for H.

We continue by explaining the connection between Banach space valued ODEs and the formulation as a family of real valued ODEs in our examples (2.21), (2.23).

Lemma 7 (Compatibility of ODEs)**.** *Let $b \in W^{1,2}(I, C^0(\Omega))$, then for every $x \in \overline{\Omega}$ the function $b(\cdot, x)$ is a member of $H^1(I)$ and it holds*

$$t \mapsto d_t b(t, x) = \frac{d}{dt}\left(t \mapsto b(t, x)\right),$$

where d_t denotes the time derivative operator of the space $W^{1,2}(I, C^0(\Omega))$ and $\frac{d}{dt}$ the one corresponding to $H^1(I)$.

Proof. As $b \in W^{1,2}(I, C^0(\Omega)) \subset C^0(I \times \Omega)$, clearly $b(\cdot, x) \in L^2(I)$. Furthermore, $d_t b \in L^2(I, C^0(\Omega))$ implies that $d_t b(\cdot, x) \in L^2(I)$. This is due to the fact that point evaluation at $x \in \Omega$ is a member of $C^0(\Omega)^*$. In fact, point evaluation can be viewed as a member of $W^{1,2}(I, C^0(\Omega))^*$, compare to Lemma 78. Now to the compatibility of the derivatives. For $d_t b$ it holds by definition

$$\int_I d_t b(t)\varphi(t)\, dt = -\int_I b(t)\partial_t \varphi(t)\, dt \quad \forall \varphi \in \mathcal{D}(I).$$

The integral used above is the $C^0(\Omega)$ valued Bochner integral, thus using that point evaluation is a linear and continuous map on the space of continuous functions we find that for every $x \in \overline{\Omega}$ it holds

$$\int_I d_t b(t)(x)\varphi(t)\, dt = -\int_I b(t)(x)\partial_t \varphi(t)\, dt \quad \forall \varphi \in \mathcal{D}(I),$$

meaning that for every fixed $x \in \overline{\Omega}$ the function $t \mapsto b(t)(x)$ satisfies the defining equation of the weak derivative of $H^1(I)$. □

The implication of the above Lemma is that, given a solution b in $W^{1,2}(I, C^0(\Omega))$ to an ODE of the form

$$d_t b(t) = F(t, b(t)), \quad b(0) = b_0$$

for a suitable $F : I \times C^0(\Omega) \to C^0(\Omega)$ and $b_0 \in C^0(\Omega)$ we always get that $b(\cdot, x)$ for fixed $x \in \overline{\Omega}$ solves

$$\frac{d}{dt}\left(t \mapsto b(t, x)\right) = F(t, b(t, x)), \quad b(0, x) = b_0(x)$$

in the space $H^1(I)$. From a modeling perspective, this is precisely the viewpoint we took initially. Hence, using Banach space valued ODEs is justified.

We summarize our setting.

Assumption 8. We assume domain regularity as discussed in Subsection 1.1, define the admissible scaffold densities P in (2.11) and the set W_ρ in (2.12). The material tensor $\mathbb{C}$ satisfies (2.13) and (2.15) and admissible boundary conditions for the elastic equation are given in (2.16) and (2.17). For the diffusion we assume (2.18) and (2.19) and $|\cdot|_\delta$ must satisfy (2.20). The functional relationships H and K need to factorize as described in (2.22).

II Existence and Uniqueness

In this Section we will prove that there exists a unique solution to the system (1.1)–(1.4) in the weak sense, i.e., there are functions $u^* = \tilde{u}^* + u_{g_D^e}$ with $\tilde{u}^* \in L^2(I, H^1_{D_e}(\Omega)/W)$ and $u_{g_D^e|\Gamma_D^e} = g_D^e$, $a^* = \tilde{a}^* + 1$ with $\tilde{a}^* \in H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*)$, $c^* \in W^{1,p}(I, C^0(\Omega))$ and $b^* \in W^{1,q}(I, C^0(\Omega))$ satisfying

$$\int_I \int_\Omega \mathbb{C}(\rho, \sigma, b^*)\hat{\varepsilon}(\tilde{u}^* + u_{g_D^e}) : \hat{\varepsilon}(\cdot)\, dxdt = \int_I \langle g_N^e, \cdot \rangle_{H^{1/2}(\Gamma_N^e)} dt \tag{2.24}$$

$$\int \langle d_t \tilde{a}_i^*, \cdot \rangle + \iint D_i^\rho \nabla \tilde{a}_i^* \nabla \cdot + k_i^3 \tilde{a}_i^* \cdot\, dxdt = \iint (k_i^2 |\varepsilon(u^*)|_\delta c^* - k_i^3) \cdot\, dxdt \tag{2.25}$$

$$\tilde{a}_i^*(0) = -1, \quad \text{with } i = 1, \dots, N, \tag{2.26}$$

$$d_t c^* = H(a_1^*, \dots, a_N^*, c^*, b^*)\Big(1 - \frac{c^*}{1-\rho}\Big) \quad \text{with} \quad c^*(0) = 0, \tag{2.27}$$

$$d_t b^* = K(a_1^*, \dots, a_N^*, c^*, b^*)\Big(1 - \frac{b^*}{1-\rho}\Big) \quad \text{with} \quad b^*(0) = 0. \tag{2.28}$$

The proof of this result relies essentially on the elementary fixed point theorem of Banach which we will employ for the complete metric space W_ρ. The strategy is to fix $\rho \in P$, then start with some arbitrary admissible functions $(c, b) \in W_\rho$ and to solve the equations successively. More precisely, the elastic equation will yield $u = u(c, b)$, the diffusion equations $a_i = a_i(c, u)$, the cell equation will be solved with data a_i and b yielding an updated cell function $\bar{c} = \bar{c}(a_i, b)$ and finally the bone equation will be solved with data a_i and c to get an updated bone function $\bar{b} = \bar{b}(a_i, c)$. This procedure gives rise to an operator $\mathcal{I}$ which we will refer to as the iteration operator, formally

$$\mathcal{I} : W_\rho \to W_\rho \quad \text{with} \quad (c, b) \mapsto (\bar{c}, \bar{b}).$$

It is easy to see that all possible solutions to (2.24)–(2.28) correspond to all possible fixed-points of $\mathcal{I}$. The crucial part of the proof consists of establishing regularity for the solutions of the diffusion equations, see also Section II in the Appendix for a discussion of relevant results from the literature.

Finally, the whole strategy discussed above does only work on a short time interval $I = [0, T]$, i.e., T small enough. However, by a continuation argument we can afterwards extend this solution to span any finite time interval.

Theorem 9 (Existence & Uniqueness)**.** *Let $\rho \in P$ be fixed and let the Assumptions 8 be fulfilled. Then there exist unique functions $u^* = \tilde{u}^* + u_{g_D^e}$ with $\tilde{u}^* \in L^2(I, H^1_{D_e}(\Omega)/W)$ and $u_{g_D^e|\Gamma_D^e} = g_D^e$, $a^* = \tilde{a}^* + 1$ with $\tilde{a}^* \in H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*)$, $c^* \in W^{1,p}(I, C^0(\Omega))$ and $b^* \in W^{1,q}(I, C^0(\Omega))$ solving the system* (2.24) – (2.28).

Proof. We need to establish the contraction and self-mapping property of $\mathcal{I}$. Let us thus fix two tuples (c_1, b_1) and $(c_2, b_2) \in W_\rho$. We aim to show an estimate of the form

$$\begin{aligned} \|\mathcal{I}(c_1, b_1) - \mathcal{I}(c_2, b_2)\|_{C^0(I\times\Omega)^2} &= \left\|\bar{c}_1 - \bar{c}_2\right\|_{C^0(I\times\Omega)} + \left\|\bar{b}_1 - \bar{b}_2\right\|_{C^0(I\times\Omega)} \\ &\leq C(I)\Big(\|c_1 - c_2\|_{C^0(I\times\Omega)} + \|b_1 - b_2\|_{C^0(I\times\Omega)} \Big), \end{aligned}$$

where $C(I) \to 0$ with $|I| \to 0$, making $\mathcal{I}$ the desired self-mapping for T small enough.

The Elastic Equation. We will treat a pure Neumann and a mixed boundary value problem simultaneously. We endow the space $H^1_{D_e}(\Omega)/W$ with the norm $\|\varepsilon(\cdot)\|_{L^2(\Omega)}$, which by Korn's inequality is equivalent to the natural one on $H^1_{D_e}(\Omega)/W$, see for example Ciarlet (2010). By definition of g_D^e, there is a function $u_{g_D^e} \in L^2(I, H^1(\Omega)/W)$ such that $u_{g_D^e|\Gamma_D^e} = g_D^e$. In the weak formulation of the elastic equation we seek $\tilde{u}_i \in L^2(I, H^1_{D_e}(\Omega)/W)$ satisfying

$$\int_I \int_\Omega \mathbb{C}(\rho, \sigma, b_i)\hat{\varepsilon}(\tilde{u}_i + u_{g_D^e}) : \hat{\varepsilon}(\cdot)\, dxdt = \int_I \langle g_N^e, \cdot \rangle_{H^{1/2}(\Gamma_N^e)} dt \tag{2.29}$$

in the space $L^2(I, H^1_{D_e}(\Omega)/W)^*$. Then $u_i := \tilde{u}_i + u_{g_D^e}$ is the solution we are interested in. Note that if Γ_D^e has vanishing measure, we can choose $u_{g_D^e} = 0$ and $H^1_{D_e}(\Omega)/W = H^1(\Omega)/W$. On the other hand, if Γ_D^e has positive measure, then $W \cap H^1_{D_e}(\Omega) = 0$ and $H^1_{D_e}(\Omega)/W = H^1_{D_e}(\Omega)$. The equation (2.29) leads to the operators

$$\mathcal{T}_{b_i} : L^2(I, H^1_{D_e}(\Omega)/W) \to L^2(I, H^1_{D_e}(\Omega)/W)^*$$

with
$$\mathcal{T}_{b_i} v = \int_I \int_\Omega \mathbb{C}(\rho, \sigma, b_i)\hat{\varepsilon}(v) : \hat{\varepsilon}(\cdot)\, dxdt$$
and right hand sides
$$f_{b_i} = \underbrace{\int_I \langle g_N^e, \cdot \rangle_{H^{1/2}(\Gamma_N^e)} dt}_{=:f^N} - \underbrace{\int_I \int_\Omega \mathbb{C}(\rho, \sigma, b_i)\hat{\varepsilon}(u_{g_D^e}) : \hat{\varepsilon}(\cdot)\, dxdt}_{=:f_{b_i}^D}.$$
By our assumption (2.15) and Korn's inequality the operators $\mathcal{T}_{b_i}$ are coercive with coercivity constant $c_{\mathbb{C}}$. Applying the Lax-Milgram Lemma we find that there are unique solutions $\tilde{u}_1$ and $\tilde{u}_2 \in L^2(I, H^1_{D_e}(\Omega)/W)$ to $\mathcal{T}_{b_i}\tilde{u}_i = f_{b_i}$. By the duality
$$L^2(I, H^1(\Omega)/W)^* = L^2(I, (H^1(\Omega)/W)^*)$$
we know that almost everywhere in I the function $u_i(t) = \tilde{u}_i(t) + u_{g_D^e}(t)$ satisfies
$$\begin{aligned}\int_\Omega \mathbb{C}(\rho, \sigma, b_i)(t)\hat{\varepsilon}(\tilde{u}_i)(t) : \hat{\varepsilon}(\cdot)\, dx &= \langle g_N^e(t)\rangle_{H^{1/2}(\Gamma_N^e)} \\ &\quad - \int_\Omega \mathbb{C}(\rho, \sigma, b_i)\hat{\varepsilon}(u_{g_D^e}(t)) : \hat{\varepsilon}(\cdot)\, dx\end{aligned}$$
in the space $H^1(\Omega)/W$. Using Lax-Milgram again we get using the boundedness and coercivity constants from (2.15)
$$\|u_i(t)\|_{H^1(\Omega)/W} \le c_{\mathbb{C}}^{-1}\Big[\, \left\|g_N^e(t)\right\|_{H^{1/2}(\Gamma_N^e)^*} + C_{\mathbb{C}} \left\|u_{g_D^e}(t)\right\|_{H^1(\Omega)/W} \Big].$$
As the above estimate is independent of ρ, c_i and b_i it holds, inferring the continuity in time of g_N^e and $u_{g_D^e}$ that
$$\sup_{\rho,c,b} \left\|u(\rho, b)\right\|_{L^\infty(I, H^1(\Omega)/W)} \le C(I), \tag{2.30}$$
where $u(\rho, c, b)$ denotes the solution of the elastic problem to the data $\rho \in P$ and $(c, b) \in W_\rho$. To show that $C(I)$ tends to zero with $|I| \to 0$ we employ the dominated convergence theorem of Lebesgue. Finally we come back to estimate the difference $u_1 - u_2$. We claim that
$$\|u_1 - u_2\|_{L^2(I, H^1(\Omega)/W)} \le C(I)\, \|b_1 - b_2\|_{C^0(I\times\Omega)} \tag{2.31}$$
where again $C(I) \to 0$ with $|I| \to 0$. To establish this, note that $\tilde{u}_1 - \tilde{u}_2 = u_1 - u_2$ and compute
$$f_{b_1} - f_{b_2} = f_{b_1}^D - f_{b_2}^D = \mathcal{T}_{b_1}\tilde{u}_2 - \mathcal{T}_{b_2}\tilde{u}_2 = \mathcal{T}_{b_1}(\tilde{u}_1 - \tilde{u}_2) + \mathcal{T}_{b_1}\tilde{u}_2 - \mathcal{T}_{b_1}\tilde{u}_2 - \mathcal{T}_{b_2}\tilde{u}_2.$$
Hence $\mathcal{T}_{b_1}(u_1 - u_2) = (\mathcal{T}_{b_2}\tilde{u}_2 - \mathcal{T}_{b_1}\tilde{u}_2) + (f_{b_1}^D - f_{b_2}^D)$ and using $\left\|\mathcal{T}_{b_1}^{-1}\right\| \le c_{\mathbb{C}}^{-1}$ we find
$$\begin{aligned}\|u_1 - u_2\|_{L^2(I, H^1(\Omega)/W)} &\le c_{\mathbb{C}}^{-1} \left\|\mathcal{T}_{b_2}\tilde{u}_2 - \mathcal{T}_{b_1}\tilde{u}_2\right\|_{L^2(I, H^1(\Omega)/W)^*} \\ &\quad + c_{\mathbb{C}}^{-1} \left\|f_{b_1}^D - f_{b_2}^D\right\|_{L^2(I, H^1(\Omega)/W)^*}.\end{aligned}$$
We estimate the terms of the right hand side using the Lipschitz continuity of $\mathbb{C}$ which we assumed in (2.14), combining it with (2.30) to find
$$\begin{aligned}\left\|\mathcal{T}_{b_2}\tilde{u}_2 - \mathcal{T}_{b_1}\tilde{u}_2\right\|_{L^2(I, H^1(\Omega)/W)^*} &\le L_{\mathbb{C}}\, \|b_1 - b_2\|_{C^0(I\times\Omega)}\, \|\tilde{u}_2\|_{L^2(I, H^1(\Omega)/W)} \\ &\le L_{\mathbb{C}} C(I)\, \|b_1 - b_2\|_{C^0(I\times\Omega)} \\ &= C(I)\, \|b_1 - b_2\|_{C^0(I\times\Omega)}\end{aligned}$$
and
$$\begin{aligned}\left\|f_{b_1}^D - f_{b_2}^D\right\|_{L^2(I, H^1(\Omega)/W)^*} &\le L_{\mathbb{C}} \left\|u_{g_D^e}\right\|_{L^2(I, H^1(\Omega)/W)} \|b_1 - b_2\|_{C^0(I\times\Omega)} \\ &= C(I)\, \|b_1 - b_2\|_{C^0(I\times\Omega)}.\end{aligned}$$

The Diffusion Equations. Given the functions c_i, u_i with $i = 1, 2$ and ρ, we turn to the diffusion equations. We seek functions $a^i = \tilde{a}^i + 1$ where the $\tilde{a}^i$ are members of $H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*)^N$, that means $a^i = (a^i_1, \ldots, a^i_N) =$

$(\tilde{a}_1^i + 1, \dots, \tilde{a}_N^i + 1)$, $i = 1, 2$, denoting the components of a^i with lower indices. For $j = 1, \dots, N$ the $\tilde{a}_j^i$ are sought to satisfy the following equation in $L^2(I, H^1_{D_d}(\Omega))^*$

$$\underbrace{\int_I \langle d_t \tilde{a}_j^i, \cdot \rangle_{H^1_D} \, dt}_{=: d_t \tilde{a}_j^i} + \underbrace{\iint D_j^\rho \nabla \tilde{a}_j^i \nabla \cdot + k_j^3 \tilde{a}_j^i \cdot \, dxdt}_{=: \mathcal{M}_j(\rho) \tilde{a}_j^i} = \underbrace{\iint (k_j^2 |\varepsilon(u_i)| c_i - k_j^3) \cdot \, dxdt}_{=: f^j_{u_i, c_i}}$$

and initial value $\tilde{a}_j(0) = -1$ in $L^2(\Omega)$. The operators

$$(d_t + \mathcal{M}_j(\rho), \mathrm{ev}_0) : H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*) \to L^2(I, H^1_{D_d}(\Omega))^* \times L^2(\Omega)$$

are linear homeomorphisms, see for example Ern and Guermond (2013) for a proof, which essentially relies on the coercivity of $\mathcal{M}_j(\rho)$. This explains why we assumed (2.19) and hence we can guarantee the existence of the $\tilde{a}_j^i$. We now state three important properties of the solutions a_j^i and their differences $a_j^1 - a_j^2$. References or proofs can be found in II in the Appendix. The first is a lower pointwise bound, it holds for $j = 1, \dots, N$ and $i = 1, 2$

$$0 \le 1 + \tilde{a}_j^i(t, x) = a_j^i(t, x) \quad \text{almost everywhere in } I \times \Omega. \tag{2.32}$$

This is due to the positivity of the right hand sides $f^j_{u_i, c_i}$. Secondly, we look at the equations satisfied by the differences $a_j^1 - a_j^2$. These equations possess right hand sides $f^j_{u_1, c_1} - f^j_{u_2, c_2}$ in $L^2(I, L^2(\Omega))$ and with $(a_j^1 - a_j^2)(0) = 0$ smooth initial conditions. Then, using regularity for mixed boundary value problems, see Theorem 61, there is $\alpha > 0$ such that

$$\left\| a_j^1 - a_j^2 \right\|_{L^2(I, C^\alpha(\Omega))} \le C \left\| f^j_{u_1, c_1} - f^j_{u_2, c_2} \right\|_{L^2(I, L^2(\Omega))}. \tag{2.33}$$

The constant C is uniform in the data $\rho \in P$, $(c, b) \in W_\rho$ and $u(\rho)$ and does not blow up when $|I| \to 0$, see Appendix II. The third and last property we need is a maximal L^p regularity result. By the estimate (2.30) the right-hand sides satisfy

$$f_{u_i, c_i} = k_j^2 |\varepsilon(u_i)| c_i - k_j^3 \in L^\infty(I, L^2(\Omega))$$

with a bound on their $L^\infty(I, L^2(\Omega))$ norm which is independent of u_i and c_i. The ellipticity and boundedness of the diffusivity $D_i(\rho)$ assumed in (2.18) and (2.19) allows to apply Lemma 28 to produce a bound for a^i of the form

$$\left\| a^i \right\|_{L^p(I, C^\alpha(\Omega)^N)} \le C\Big(p, \lfloor D(\rho) \rfloor, \left\| D(\rho) \right\|_{L^\infty(\Omega, \mathcal{M}_s)}\Big) \cdot \left\| f_{u_i, c_i} \right\|_{L^p(I, L^2(\Omega))} \le \tilde{C}(p) \left\| f_{u_i, c_i} \right\|_{L^p(I, L^2(\Omega))}, \tag{2.34}$$

where p can be chosen arbitrarily in $(1, \infty)$. We claim now that we get the following estimate for the difference $a^1 - a^2$

$$\left\| a^1 - a^2 \right\|_{L^2(I, C^\alpha(\Omega))^N} \le C\Big(\|c_1 - c_2\|_{C^0(I \times \Omega)} + \|u_1 - u_2\|_{L^2(I, H^1/W)} \Big) \tag{2.35}$$

with C not blowing up as $|I| \to 0$. This estimate is obtained, using (2.33) and estimating the difference $f^j_{u_1, c_1} - f^j_{u_2, c_2}$. It holds

$$f^j_{c_1, u_1} - f^j_{c_2, u_2} = k_2^j |\varepsilon(u_1)|_\delta (c_1 - c_2) + k_2^j (|\varepsilon(u_1)|_\delta - |\varepsilon(u_2)|_\delta) c_2.$$

Using the fact that c_1 takes values in the unit interval and the assumptions on $|\cdot|_\delta$, see 2.20, it follows

$$\begin{aligned} \left\| f^j_{c_1, u_1} - f^j_{c_2, u_2} \right\|_{L^2(I, L^2(\Omega))} &\le C\Big(\|\varepsilon(u_1)\|_{L^2(I, L^2(\Omega))} + 1 \Big) \|c_1 - c_2\|_{C^0(I \times \Omega)} \\ &\quad + C \|\varepsilon(u_1 - u_2)\|_{L^2(I, L^2(\Omega))}. \end{aligned}$$

Invoking (2.30) we know that $\|\varepsilon(u_1)\|_{L^2(I, L^2(\Omega))}$ is bounded uniformly in the data $\rho \in P$ and $(c, b) \in W_\rho$. Combining this with the identity

$$\|\varepsilon(u_1 - u_2)\|_{L^2(I, L^2(\Omega))} = \|u_1 - u_2\|_{L^2(I, H^1/W)}$$

we conclude.

The Cell ODE. We turn now to the Cell ODE and solve this equation twice, once with data $\rho, a_1^1, \dots, a_N^1$ and b_1, producing a function $\bar{c}_1$, and once with $\rho, a_1^2, \dots, a_N^2$ and b_2 yielding $\bar{c}_2$. The solutions $\bar{c}_1$ and $\bar{c}_2$ are members of the space $W^{1,2}(I, C^0(\Omega))$ and consequently of $C^0(I \times \Omega)$ satisfying $0 \le \bar{c}_i(t,x) \le 1 - \rho(x)$ solving the ODE

$$d_t \bar{c}_i = H(a_1^i, \dots, a_N^i, b_i, \bar{c}_i)\Big(1 - \frac{\bar{c}_i}{1-\rho}\Big) \quad \text{with} \quad \bar{c}_i(0) = 0.$$

These facts are proven as Lemma 80 in the Appendix. Our goal is to estimate the difference $\bar{c}_1 - \bar{c}_2$ and we claim that it holds

$$\left\|\bar{c}_1 - \bar{c}_2\right\|_{C^0(I\times\Omega)} \le C(I)\Big(\left\|a^1 - a^2\right\|_{L^2(I,C^\alpha(\Omega)^N)} + \|b_1 - b_2\|_{C^0(I\times\Omega)}\Big) \tag{2.36}$$

where $C(I)$ tends to zero with $|I| \to 0$. To prove the estimate (2.36) we use the fundamental theorem of the space $W^{1,2}(I, C^0(\Omega))$ and write

$$\bar{c}_i(t) = \int_0^t \underbrace{H(a^i(s), b_i(s), \bar{c}_i(s))\Big(1 - \frac{\bar{c}_i(s)}{1-\rho}\Big)}_{=:\gamma_i(s)} ds.$$

We claim that the following estimate holds

$$\begin{aligned}
\left\|\gamma_1(s) - \gamma_2(s)\right\|_{C^0(\Omega)} &\le \left\|H(a^1, b_1, \bar{c}_1)(s) - H(a^2, b_2, \bar{c}_2)(s)\right\|_{C^0(\Omega)} \left\|1 - \frac{\bar{c}_1(s)}{1-\rho}\right\|_{C^0(\Omega)} \\
&\quad + \left\|H(a^2, b_2, \bar{c}_2)(s)\right\|_{C^0(\Omega)} \left\|(1-\rho)^{-1}\right\|_{C^0(\Omega)} \left\|\bar{c}_1(s) - \bar{c}_2(s)\right\|_{C^0(\Omega)} \\
&\le \underbrace{f_1(s)\left\|a^1(s) - a^2(s)\right\|_{C^0(\Omega)^N} + f_2(s)\|b_1(s) - b_2(s)\|_{C^0(\Omega)}}_{=:\alpha(s)} + \beta(s)\left\|\bar{c}_1(s) - \bar{c}_2(s)\right\|_{C^0(\Omega)},
\end{aligned} \tag{2.37}$$

where $f_1 \in L^2(I)$ and $f_1 \in L^1(I)$ and $\beta \in L^1(I)$ can be chosen independent of a^i, b_i and c_i. We then apply Grönwall's Lemma 73 and Hölders inequality to obtain

$$\begin{aligned}
\left\|\bar{c}_1(t) - \bar{c}_2(t)\right\|_{C^0(\Omega)} &\le \Big(1 + \|\beta\|_{L^1(I)} \exp\big(\|\beta\|_{L^1(I)}\big)\Big) \cdot \int_I f_1(s)\left\|a^1(s) - a^2(s)\right\|_{C^0(\Omega)^N} + f_2(s)\|b_1(s) - b_2(s)\|_{C^0(\Omega)} \,\mathrm{d}s \\
&\le C\Big(\|\beta\|_{L^1(I)}\Big)\Big[\|f_1\|_{L^2(I)}\left\|a^1 - a^2\right\|_{L^2(I,C^0(\Omega))} + \|f_2\|_{L^1(I)}\|b_1 - b_2\|_{C^0(I\times\Omega)}\Big] \\
&\le C\Big(\|\beta\|_{L^1(I)}\Big) \cdot C\Big(\|f_1\|_{L^2(I)}, \|f_2\|_{L^1(I)}\Big)\Big[\left\|a^1 - a^2\right\|_{L^2(I,C^\alpha(\Omega)^N)} + \|b_1 - b_2\|_{C^0(I\times\Omega)}\Big]
\end{aligned}$$

Then, employing Lebesgue's dominated convergence theorem, we get that $\|f_1\|_{L^2(I)} \to 0$ and $\|f_2\|_{L^1(I)} \to 0$ with $|I| \to 0$ and consequently

$$C(I) = C\Big(\|\beta\|_{L^1(I)}\Big) \cdot C\Big(\|f_1\|_{L^2(I)}, \|f_2\|_{L^1(I)}\Big) \to 0, \quad \text{with} \quad |I| \to 0.$$

As the right side of the estimate is independent of $t \in I$, this shows that (2.36) holds. However, we still need to prove the claim (2.37). To this end, remember the structural assumption made on H, i.e., $H = H^2 \circ H^1$, see (2.22) and use Lemma 79 to estimate

$$\begin{aligned}
&\left\|H(a^1, b_1, \bar{c})(t) - H(a^2, b_2, \bar{c}_1)(t)\right\|_{C^0(\Omega)} \\
&= \left\|\prod_{i=1}^M H_i^1(a^1, b_1, \bar{c}_1)(s) - \prod_{i=1}^M H_i^1(a^2, b_2, \bar{c}_2)(s)\right\|_{C^0(\Omega)} \\
&= \left\|\sum_{k=1}^M \underbrace{\left(\prod_{i=1}^{M-k} H_i^1(a^1, b_1, \bar{c}_1)(s)\right)\left(\prod_{i=M-k+2}^{M} H_i^1(a^2, b_2, \bar{c}_2)(s)\right)}_{(*)}\Big(H_{M-k+1}^1(a^1, b_1, \bar{c}_1)(s) - H_{M-k+1}^1(a^2, b_2, \bar{c}_2)(s)\Big)\right\|_{C^0(\Omega)}
\end{aligned}$$

We treat $(*)$ first. Estimating for any $k = 1, \dots, M$ yields

$$\prod_{i=1}^{M-k} H_i^1(a^1, b_1, \bar{c}_1)(s) \le \prod_{i=1}^{M} \left(H_i^1(a^1, b_1, \bar{c}_1)(s) + 1 \right).$$

The global Lipschitz continuity of H^1 implies then for any $i = 1, \dots, M$ the estimate

$$\left\| H_i^1(a^1, b_1, \bar{c}_1)(s) \right\|_{C^0(\Omega)} \le L_{H^1} \left(\left\| a^1(s) \right\|_{C^0(\Omega)^N} + \| b_1(s) \|_{C^0(\Omega)} + \left\| \bar{c}_1 \right\|_{C^0(\Omega)} \right) + \left\| H_i^1(0,0,0) \right\|_{C^0(\Omega)}.$$

Combining the two preceding estimates yields

$$\begin{aligned}
\prod_{i=1}^{M-k} \left\| H_i^1(a^1, b_1, \bar{c}_1)(s) \right\|_{C^0(\Omega)} &\le \prod_{i=1}^{M} \left[L_{H^1} \left(\left\| a^1(s) \right\|_{C^0(\Omega)^N} + \| b_1(s) \|_{C^0(\Omega)} + \left\| \bar{c}_1(s) \right\|_{C^0(\Omega)} \right) + \left\| H_i^1(0,0,0) \right\|_{C^0(\Omega)} + 1 \right] \\
&\le \prod_{i=1}^{M} \left[L_{H^1} \left(\left\| a^1(s) \right\|_{C^0(\Omega)^N} + 2 \right) + \left\| H_i^1(0,0,0) \right\|_{C^0(\Omega)} + 1 \right] \\
&\le \tilde{f}_1(s),
\end{aligned}$$

where $\tilde{f}_1(s) \in L^4(I)$ with a bound on $\left\| \tilde{f}_1 \right\|_{L^4(I)}$ only depending on a bound on the $\left\| a^1 \right\|_{L^p(I, C^0(\Omega)^N)}$ norm of a^1 for a suitable, large value of p. By the maximal L^p regularity result, such a bound is available, see (2.34). The second factor in $(*)$ can also be estimated by $\tilde{f}_1(s)$. This yields

$$\begin{aligned}
\left\| H(a^1, b_1, \bar{c}_1)(s) - H(a^2, b_2, \bar{c}_2)(s) \right\|_{C^0(\Omega)} &\le \tilde{f}_1(s)^2 \sum_{i=1}^{M} \left\| H_i^1(a^1, b_1, \bar{c}_1)(s) - H_i^1(a^2, b_2, \bar{c}_2)(s) \right\|_{C^0(\Omega)} \\
&\le \tilde{f}_1^2(s) L_{H_1} \left[\left\| a^1(s) - a^2(s) \right\|_{C^0(\Omega)^N} + \| b_1(s) - b_2(s) \|_{C^0(\Omega)} + \left\| \bar{c}_1(s) - \bar{c}_2(s) \right\|_{C^0(\Omega)} \right]
\end{aligned}$$

Thus, f_1, f_2 and β in (2.37) can be chosen to $f_1^2(s) L_{H_1}$.

The Bone ODE. Finally we treat the Bone ODE. Again we solve it twice, with data $a_1^i, \dots, a_N^i, c_i$ and ρ producing $\bar{b}_i$ with $i = 1, 2$. The functions $\bar{b}_1$ & $\bar{b}_2$ are members of $W^{1,2}(I, C^0(\Omega))$ and consequently of $C^0(I \times \Omega)$ satisfying $0 \le \bar{b}_i(t, x) \le 1 - \rho(x)$ and

$$d_t \bar{b}_i = K(a_1^i, \dots a_N^i, \bar{b}_i, c_i) \Big(1 - \frac{\bar{b}_i}{1 - \rho} \Big)$$

This means that $\bar{b}_i \in W_\rho$, hence making the iteration map $\mathcal{I}$ a self mapping. All these properties are established as in the case of the Cell ODE. Repeating our computations for $\bar{c}_1 - \bar{c}_2$ we find

$$\left\| \bar{b}_1 - \bar{b}_2 \right\|_{C^0(I \times \Omega)} \le C(I) \Big(\left\| a^1 - a^2 \right\|_{L^2(I, C^\alpha(\Omega)^N)} + \| c_1 - c_2 \|_{C^0(I \times \Omega)} \Big). \tag{2.38}$$

and the constant $C(I)$ tends to zero as $|I| \to 0$.

Contraction Property of $\mathcal{I}$. We collect all estimates to see that $\mathcal{I}$ is a contractive self-mapping for $|I|$ small enough. Use (2.38), (2.36), (2.35), and (2.31) to conclude

$$\begin{aligned}
\left\| \bar{b}_1 - \bar{b}_2 \right\|_{C^0(I \times \Omega)} &\le C(I) \Big(\left\| a^1 - a^2 \right\|_{L^2(I, C^\alpha(\Omega)^N)} + \| c_1 - c_2 \|_{C^0(I \times \Omega)} \Big) \\
&\le C(I) \Big(\left\| u^1 - u^2 \right\|_{L^2(I, H^1(\Omega)/W)} + \| c_1 - c_2 \|_{C^0(I \times \Omega)} \Big) \\
&\le C(I) \Big(\| b_1 - b_2 \|_{C^0(I \times \Omega)} + \| c_1 - c_2 \|_{C^0(I \times \Omega)} \Big).
\end{aligned}$$

and the estimate for $\left\| \bar{c}_1 - \bar{c}_2 \right\|_{C^0(I \times \Omega)}$ works identically. Consequently, it holds

$$\| \mathcal{I}(c_1, b_1) - \mathcal{I}(c_2, b_2) \|_{C^0(I \times \Omega)^2} \le C(I) \Big[\| c_1 - c_2 \|_{C^0(I \times \Omega)} + \| b_1 - b_2 \|_{C^0(I \times \Omega)} \Big]$$

As $C(I) \to 0$ with $|I| \to 0$, the contraction map principle implies that $\mathcal{I} : (c, b) \mapsto (\bar{c}, \bar{b})$ possesses a unique fix point for $|I|$ small enough.

Long-Time Existence. We established the existence of a solution (u^*, a^*, c^*, b^*) on an interval $[0, T]$ where $T > 0$ is chosen to make $\mathcal{I}$ a contraction. Now we use the well defined functions $c^*(T, \cdot)$ and $b^*(T, \cdot) \in C^0(\Omega)$ as initial data for the ODEs and as $a^* \in C^0([0, T], L^2(\Omega)^N)$ the function $a^*(T) \in L^2(\Omega)^N$ serves as start value for the diffusion equations. Repeating the computations we find that there exists a unique solution $(u^{**}, a^{**}, c^{**}, b^{**})$ to the system on the interval $[T - \varepsilon, 2T - \varepsilon]$ for some small $\varepsilon > 0$. On the overlap $[T - \varepsilon, T]$ the solutions $(u^{**}, a^{**}, c^{**}, b^{**})$ and (u^*, a^*, c^*, b^*) agree and thus we found the unique solution on the interval $[0, 2T - \varepsilon]$. As T does not depend on the initial values of neither a^*, c^* nor b^* this iterates to span every finite time interval. □

Lemma 10. *Let Assumption 8 hold and assume that for any choice of ρ and $b \in W_\rho$ the function $a \in H^1(I, H^1_{D_a}(\Omega), H^1_{D_a}(\Omega)^*)^N$ produced by the iteration operator $\mathcal{I}$ is a member of $L^\infty(I \times \Omega)^N$ with a bound on the $L^\infty(I \times \Omega)$ norm that is uniform in $\rho \in P$ and $b \in W_\rho$. Then local Lipschitz continuity of H and K is sufficient to ensure the existence and uniqueness asserted in Theorem 9.*

Proof. We discuss this briefly. The essential ingredient in the proofs is that (for bounded sets $B \subset C^0(\Omega)$), we have that for $a \in L^\infty(I \times \Omega)$ and $b \in C^0(I \times \Omega)$ the following subset of $\mathbb{R}^{N+2}$

$$\{(a(t, x), c(x), b(t, x)) \mid c \in B,\ (t, x) \in I \times \Omega\}$$

is relatively compact. This implies that H and K are Lipschitz continuous on sets of this form (and not merely locally Lipschitz). Exploiting this fact, one easily parallels Lemma 80 and the crucial estimates in the proof of Theorem 9. □

Remark 11. We discuss when one can expect $L^\infty(I \times \Omega)$ regularity of the diffusion equations in order to apply Lemma 10.

(i) Assume that $|\cdot|_\delta : \mathbb{R}^{n \times n} \to \mathbb{R}$ is a bounded function. Then the solution to the diffusion equations lie in $L^\infty(I \times \Omega)$ with a bound on the uniform norm not depending on $\rho \in P$ and $b \in W_\rho$. This is a standard result and can be seen by Stampacchia's truncation method, see Section II in the Appendix.

(ii) Assume that we consider a pure Dirichlet problem for the diffusion equations and that the Dirichlet data on the parabolic boundary lies in the space $L^\infty(I, L^\infty(\partial\Omega))$. Theorem 7.1 and Corollary 7.1 in Ladyzhenskaia et al. (1968) show that the solutions of the diffusion equations are members of $L^\infty(I \times \Omega)$ with a uniform bound on their norms. Here one crucially needs the Dirichlet information on the parabolic boundary, thus the assumptions. We currently do not know whether a similar result is available in the case of mixed boundary conditions.

(iii) If we do not assume anything besides the setting of Section I and consequently only have access to $L^p(I, C^0(\Omega))$ regularity for $p < \infty$, some further assumptions on H and K need to be made. In our approach we chose the factorization assumption, see (2.22).

Remark 12 (Diffusivity Depending on Bone)**.** In principle, one can desire to allow the diffusivity tensor D to depend on bone and not just the scaffold. This leads to diffusion equations of the form

$$d_t a = \operatorname{div}\left(D(\rho, b)\, \nabla a\right) - a + f, \quad a(0) = a_0 \tag{2.39}$$

leaving out constants and using a generic right-hand side f. However, this poses challenges to our existence analysis which relies crucially on higher regularity properties of solutions to such equations. More precisely, let b_1, b_2 and f_1, f_2 be admissible data for (2.39) and denote by a_1 and a_2 the corresponding solution, that a priori lie only in the space $H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*)$. Then setting $\overline{b} = b_1 - b_2$, $\overline{f} = f_1 - f_2$ and $\overline{a} = a_1 - a_2$ we get that $\overline{a}$ solves

$$d_t\overline{a} - \operatorname{div}\left(D(\rho, b_2)\nabla\overline{a}\right) + \overline{a} = \overline{f} + \operatorname{div}(D(\rho, \overline{b})\nabla a_1), \quad \overline{a}(0) = 0.$$

The strategy of our proof requires an estimate of the $L^2(I, C^0(\Omega))$ norm of $\overline{a}$. However, the term $\operatorname{div}(D(\overline{b})\nabla a_1)$ is a priori of low regularity, namely only in $L^2(I, H^1_D(\Omega))^*$. It is presently unclear to us if there are suitable regularity results available to show that indeed the $L^2(I, C^0(\Omega))$ norm of $\overline{a}$ can be controlled in a suitable way. In view of the results for elliptic operators such as Haller-Dintelmann et al. (2009), one might investigate higher integrability of ∇a_1 and seek to transfer this to the parabolic, non-autonomous case.

III Numerical Experiments

In Cipitria et al. (2015) porous PCL scaffolds with a periodic honeycomb structure and 87% porosity were used as a treatment strategy for 30mm tibial defects in an ovine model. This experiment was conducted in two groups, one preseeding the scaffold with a special bio-active molecule (BMP) and the second group without such preseeding. Here, we aim to numerically recreate the experiment without preseeding, using a concrete instance of our computational model.

As usual, the experimental setup in Cipitria et al. (2015) includes the use of a so-called fixateur – a titanium or steel plate that is fixed to the bone surrounding the defect site using screws. This fixateur is used to provide additional mechanical stability. We include this device in a simplistic manner in our simulations, neglecting the effect of screws. From a modeling perspective, the fixateur acts as a stress shield on one side of the defect and thus influences bone growth significantly.

As a concrete instance of our model we use two bioactive molecules and consider the following system of equations

$$
\begin{aligned}
0 &= \operatorname{div}\Big(\mathbb{C}(\rho,\sigma,b)\varepsilon(u)\Big)\\
d_t a_1 &= \operatorname{div}\Big(D(\rho)\nabla a_1\Big) + k_{2,1}|\varepsilon(u)|c - k_{3,1}a_1\\
d_t a_2 &= \operatorname{div}\Big(D(\rho)\nabla a_2\Big) + k_{2,2}|\varepsilon(u)|c - k_{3,2}a_2\\
d_t c &= k_6 a_1 a_2 (1 + k_7 c)\Big(1 - \frac{c}{1-\rho}\Big)\\
d_t b &= k_4 a_1 c\Big(1 - \frac{b}{1-\rho}\Big).
\end{aligned}
$$

We use mixed boundary values for the elastic equilibrium equation, with a surface traction stemming from a force of 0.3kN on the top of the cylinder in the model with fixateur. The bottom of the computational domain is assumed to be fixed, i.e., subjected to zero Dirichlet boundary conditions and the remaining part of the boundary is subject to zero stress boundary conditions. These boundary conditions are chosen to represent the maximal stress that repeatedly occurs, having an ovine model in mind, where a specimen can weigh between 45–160kg. For a healthy individual without bone defect, we assume a force of 2.25kN. This difference is important as it will influence the choice of the generation and decay rate of the bio-active molecules that are normalized for healthy bone. For the bio-active molecules we assume that they are present in saturation, i.e. $a_1(t,x) = a_2(t,x) = 1$, adjacent to bone and otherwise we assume a non-flux boundary condition. Osteoblast and bone density is set to zero at the initial time-point. Note that the concrete choice of boundary conditions here should be considered a proof of concept. Further, more detailed numerical studies are forthcoming.

3.1 Model Parameters

We report the choices for the constants and functional relationships in table 2.1. Some comments are in order.

(a) In a healthy individual, given appropriate clinical interventions, bone defects should be completely bridged with low to medium weight-bearing capacity after 6 months, see Zimmermann and Moghaddam (2010). The bone remodeling process to follow can take 3 to 5 years until the full function of the bone is restored. We therefore consider a time span of 12 months for our model, which we identified as the critical phase for scaffold mediated bone healing.

(b) The PCL decay parameter, k_1, is based on the experimental studies in Pitt et al. (1981), which shows that after one year 30% of the molecular mass remains.

(c) The surface traction is set to 0.001gPa corresponding to a force of 0.3kN over a surface of 300 mm^2. We propose to view this time-constant surface traction as an averaged maximal stress. Furthermore we assume that due to the injury this averaged maximal stress is considerably lower than what is to be expected in a healthy individual, where we set it to 0.0075gPa corresponding to the aforementioned 2.25kN.

(d) The constants $k_{2,i}, k_{3,i}, i = 1, 2$ governing the generation and decay of bioactive molecules are difficult to obtain from the literature compare for example to the discussion in Poh et al. (2019). The values for $k_{3,1}$ and $k_{3,2}$ correspond to a half-life of 31 and 62 hours respectively and are chosen to achieve a realistic model outcome. Consequently generation rate constants $k_{2,1}$ and $k_{2,2}$ are chosen such that a surface traction of 0.0075gPa – corresponding to a force of 2.25 kN over a surface of 300mm^2 – results in an equilibrium state for $a_1 = a_2 = 1$ when $c = 1$, that is when the concentration of osteoblast equals that of healthy bone.

(e) The diffusivity $D(\rho) = k_5(1 - \rho)$ is controlled by the porosity $1 - \rho$ and the constant k_5. With $k_5 = 260\text{mm}^2/\text{month}$ we set it to a standard value for the diffusion of bioactive molecules that is measured for soluble proteins, see Badugu et al. (2012) and Yu et al. (2009).

(f) We use Voigt's bound as an approximation of the material properties of the bone-scaffold composite. More precisely, we model bone and PCL as linear isotropic materials with material constants chosen as collected in Table 2.1. The effective properties of the compositum are then obtained by adding the weighted tensors.

(g) The constant k_4 drives the rate of bone regeneration, k_6 is related to the overall osteoblast production and k_7 influences the effect of osteoblast proliferation. These values are fitted to achieve realistic outcome in the simulations.

Table 2.1: Parameters for the bone regeneration model

Param.	Value	Description
T	12 months	Period of bone regeneration
Ω	$L = 30\text{mm}$, $r = 10\text{mm}$	Cylinder with length L, radius r
ρ	$\rho \equiv 0.13$	Scaffold volume fraction
$\mathbb{C}(\rho, \sigma, b)$	$b\mathcal{C}_b + \rho\sigma\mathcal{C}_\rho$	Voigt bound for composites
$D(\rho)$	$k_5(1 - \rho)$	Diffusivity of bioactive molecules
(λ_b, μ_b)	(2.88GPa, 1.92GPa)	Derived from $(E_b, \nu_b) = (5\,\text{GPa}, 0.3)$
(λ_ρ, μ_ρ)	(1.97GPa, 0.17GPa)	Derived from $(E_\rho, \nu_\rho) = (0.5\,\text{GPa}, 0.46)$
$\mathcal{C}_b$	$\mathcal{C}_b A = \lambda_b \operatorname{tr}(A) \operatorname{Id} + 2\mu_b A$	Material tensor of healthy bone
$\mathcal{C}_\rho$	$\mathcal{C}_\rho A = \lambda_\rho \operatorname{tr}(A) \operatorname{Id} + 2\mu_\rho A$	Material tensor of PCL
k_1	0.1 per month	PCL absorbation rate constant
$k_{2,1}$	10500	Generation rate first molecule
$k_{2,2}$	5250	Generation rate second molecule
$k_{3,1}$	16	Decay rate first molecule
$k_{3,2}$	8	Decay rate second molecule
k_4	0.2	Bone regeneration constant
k_5	260 mm^2 / month	Diffusivity of the a_i w/o scaffold
k_6	0.5	Osteoblast generation constant
k_7	0.07	Proliferation constant for osteoblasts

3.2 Numerical Implementations

We use a simple first-order implicit in time Euler scheme to solve the equations displayed in the order displayed above. The fact that an implicit approach is feasible is due to the simple structure of the ODEs and the linearity of the diffusion equation. It is worth mentioning that this reduces the computational cost of solving the system drastically as only very few time steps are needed to achieve acceptable accuracy in the simulations. The elastic and the diffusion equation are discretized using P1 elements and the meshes were generated using the Computational Geometry Algorithms Library CGAL Boissonnat et al. (2000).

3.3 Discussion of Numerical Simulations

In Figure 2.1 the domain of computation with an added fixateur is shown. Here we assume the material of the fixateur to be titanium with Young's modulus chosen to 100GPa and a Poisson's ratio of 0.31. Bone growth and osteoblast production is disabled in the space occupied by the fixateur. In Figure 2.3 we present the relative bone density averaged over horizontal slices in the fixateur experiment at 3 and 12 months. We observe that both the regenerated bone after 3 and after 12 months agree well with the experimental results shown in (Cipitria et al., 2015, Figure 2, 'Scaffold only'). There, the same shape of regenerated bone, with a

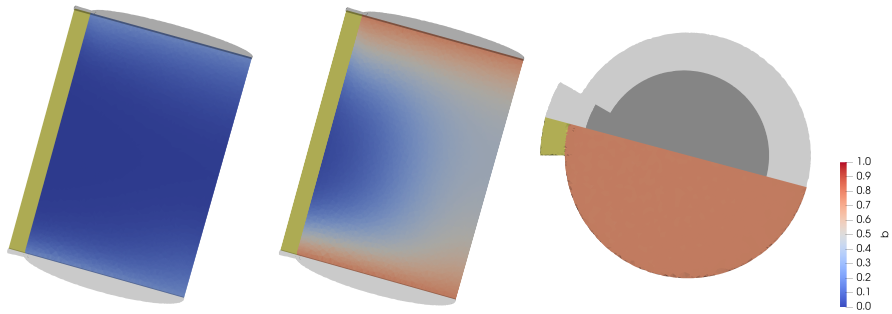


Figure 2.1: Experiment including fixateur. Shown is a vertical section through the cylindrical defect site. Fixateur domain is colored in gold. From left to right: regenerated bone at 3 months, 12 months and a view on top of the defect site. The grey colored areas illustrate the top and bottom cylinder/fixateur caps.

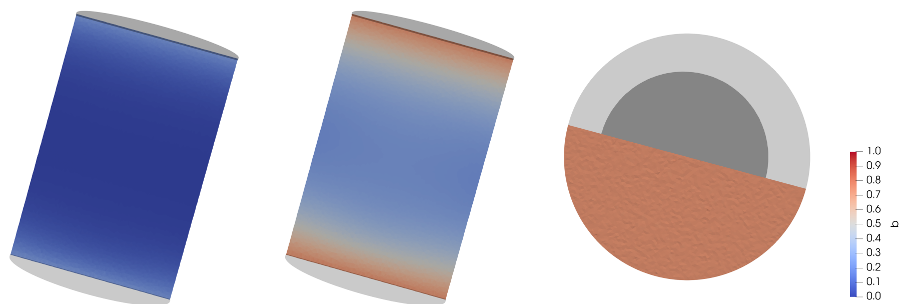


Figure 2.2: Experiment excludig fixateur. Shown is a vertical section through the cylindrical defect site. From left to right: regenerated bone at 3 months, 12 months and a view on top of the defect site. The grey colored areas illustrate the top and bottom cylinder caps.

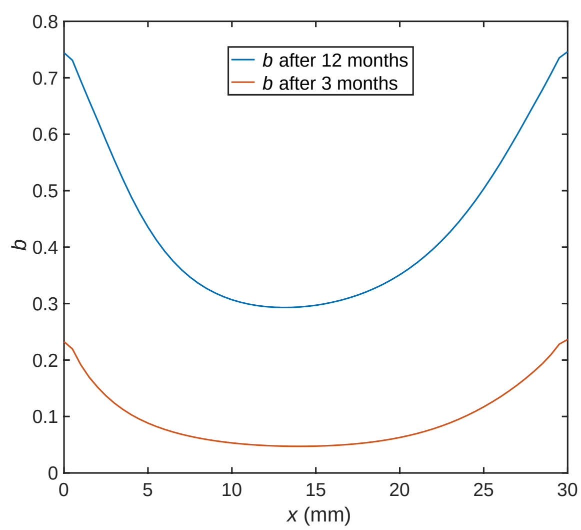


Figure 2.3: Relative bone density averaged over horizontal slices after 3 and 12 months in the experiment including the fixateur.

flat area in the middle of the defect site and a significant gradient towards the proximal and distal interface, is observed.

In Figure 2.1, the result of the stress shielding effect of the fixateur is clearly visible, with little regenerated bone in the central part of the defect site close to the fixateur. Comparing to (Viateau et al., 2007, Figs 4C, 5C) or (Reichert et al., 2011, Figures 3a, 3b) we see that this is also observed in experiments. Bone mass loss due to stress shielding is indeed a long recognized, major issue in orthopaedic surgery Schwyzer et al. (1985); Terjesen et al. (2009).

The computation excluding the fixateur is performed using a reduced surface traction that is set to 70% of the surface traction in the fixateur model to account for the stress shielding of the fixateur. This experiment is the direct analogon of the 1D model in Poh et al. (2019). Naturally, we see that bone regenerates symmetrically and that the result is essentially a one dimensional distribution of bone comparable to the results in Poh et al. (2019). Note that the asymmetries encountered in the more realistic model including the fixateur can not be resolved by a one-dimensional simplification. This has important implications for the porosity optimization of scaffolds where a three dimensional simulation can thus help to achieve a more appropriate optimal design.

Chapter 3

Optimal Scaffold Design

In this Chapter we consider theoretical and numerical aspects of the scaffold density optimization problem. We already discussed the heuristic and modeling aspects of the optimization problem in Chapter 1, Section 1.3 and 1.4. Remember, for a given scaffold design ρ, we find a unique solution $y_\rho = (u_\rho, a_\rho^1, \dots, a_\rho^N, c_\rho, b_\rho)$ solving the equations (1.1) – (1.4) and measure the "quality" of ρ through an objective function J. This leads to a PDE constrained optimization problem.

The structure of this Chapter is as follows: We start with a brief introduction to PDE constrained optimization theory and the adjoint method in Section I. We then prove the existence of an optimal control using the direct method of the calculus of variations in Section II. We continue with deriving the structure of the adjoint system and consequently the derivative of the reduced objective function in Section III and conclude with a presentation of numerical results in Section IV.

I Introduction to the Adjoint Method in PDE Constraint Optimization

We will briefly review the abstract framework of PDE constraint optimization and especially the adjoint approach, for more details we refer the reader to the introductions Hinze et al. (2008) or De los Reyes (2015). Let Y and W be Banach spaces and P either a Banach space or a subset of a Banach space. The space Y is called state space and an element $y \in Y$ a state variable, P is called control space and $\rho \in P$ a control variable. We consider two maps, the objective function $J : Y \times P \to \mathbb{R}$ and the constraint $e : Y \times P \to W$. These names are chosen as we are interested in minimizing J over the set $e^{-1}(\{0\})$, i.e., to find

$$\underset{(y,\rho)\in Y\times P}{\operatorname{argmin}} J(y, \rho) \quad \text{subject to} \quad e(y, \rho) = 0. \tag{3.1}$$

Without further assumptions this problem is ill-posed and difficult to treat in practice. In our application the set $e^{-1}(\{0\})$ can be parametrized by a map $\phi : P \to W$, i.e.,

$$e^{-1}(\{0\}) = \{(\phi(\rho), \rho) \mid \rho \in P\}.$$

In this context ϕ is called the control to state operator. Using ϕ, we can define the reduced objective function $\hat{J}(\rho) := J(\phi(\rho), \rho)$. Then the task 3.1 becomes the unconstrained problem of finding

$$\underset{\rho\in P}{\operatorname{argmin}}\, \hat{J}(\rho). \tag{3.2}$$

In case J, $e : Y \times P \to W$ and $\phi : P \to W$ are C^1 and $e_y(\phi(\rho), \rho)$ is invertible for all $\rho \in P$ we can derive a formula for $D\phi$ and consequently for $D\hat{J}$. Differentiating the equation $e(\phi(\rho), \rho)$ we obtain for fixed $\rho_0 \in P$

$$0 = D\Big(\rho \mapsto e(\phi(\rho), \rho)\Big)(\rho_0) = e_y(\phi(\rho_0), \rho_0) \circ D\phi(\rho_0) + e_\rho(\phi(\rho_0), \rho_0).$$

Combining this with $D\hat{J}(\rho_0) = J_y(\phi(\rho_0), \rho_0) \circ D\phi(\rho_0) + J_\rho(\phi(\rho_0), \rho_0)$ yields for the derivative of the reduced objective function

$$D\hat{J}(\rho_0) = -J_y(\phi(\rho_0), \rho_0) \circ e_y^{-1}(\phi(\rho_0), \rho_0) \circ e_\rho(\phi(\rho_0), \rho_0) + J_\rho(\phi(\rho_0), \rho_0).$$

This formula is not optimal from a numerical viewpoint. On a discretized level, to compute the components of $D\hat{J}(\rho_0)$ we would be required to solve for ξ_i in $e_y(\phi(\rho_0), \rho_0)\xi_i = e_\rho(\phi(\rho_0), \rho_0)c_i$, where c_i iterates through a basis of a finite dimensional subspace of P. This is problematic since solving for ξ_i is usually costly and should be done as seldom as possible, yet the dimension of the finite dimensional subspace is typically large. To address this we can rewrite the equation using the Banach space adjoint maps of $e_\rho(\phi(\rho_0), \rho_0)$ and $e_y(\phi(\rho_0), \rho_0)$, this is known as the adjoint approach:

$$D\hat{J}(\rho_0) = -e_\rho^*(\phi(\rho_0), \rho_0)\Big[e_y^{-*}(\phi(\rho_0), \rho_0)\Big(J_y(\phi(\rho_0), \rho_0)\Big)\Big] + J_\rho(\phi(\rho_0), \rho_0). \tag{3.3}$$

The advantage is that solving the so-called adjoint equation, which consists in finding $\Lambda \in W^*$

$$e_y^*(\phi(\rho_0), \rho_0)\Lambda = J_y(\phi(\rho_0), \rho_0) \tag{3.4}$$

needs only to be done once and the discretized components of $D\hat{J}(\rho_0)$ can be found evaluating $[-e_\rho^*(\phi(\rho_0), \rho_0)\Lambda](c_i)$ with c_i iterating through the basis of the finite dimensional subspace of P. On a discrete level this is less costly as it corresponds to an inner product of two vectors.

II Existence of an Optimal Control

In the first Chapter, we considered quite general functional relationships and allowed for multiple diffusion equations and included and ODE for the behavior of generic type of cells. However, to be able to derive an optimal control result, we need to narrow down these assumptions. The following Section gives the precise framework we use for the optimal control result.

2.1 Setting

We begin by specifying the assumptions on the domain.

The Domain. We consider a finite time interval $I = [0, T]$. The spatial domain $\Omega \subset \mathbb{R}^d$ with $d = 1, 2, 3$ is assumed to be an open, bounded and connected Lipschitz domain. We consider partitions of the boundary $\partial\Omega$, namely

$$\partial\Omega = \Gamma_N^e \cup \partial_D^e, \quad \text{and} \quad \partial\Omega = \Gamma_N^d \cup \Gamma_D^d$$

that will be used for the elastic and the diffusion equation respectively. For the partition of the elastic equation we assume $|\Gamma_D^e| \neq 0$. We require both $\Omega \cup \Gamma_N^e$ and $\Omega \cup \Gamma_N^d$ to be Gröger regular. For the concept of Gröger regularity we refer to Appendix II or the articles Gröger (1989) and Haller-Dintelmann et al. (2009).

Remark 13. Note the following things.

(i) For the elastic equation we exclude a pure Neumann problem, however, we can include this case by passing to a suitable quotient space. We excluded this for convenience and brevity only.

(ii) The assumption of Gröger regularity is very mild and all desirable application settings we have in mind easily satisfy this requirement. Compare to Haller-Dintelmann et al. (2009) for more information.

The Control Space. The set of control variables is defined to be

$$P = \Big\{\rho \in H^2(\Omega) \mid 0 < c_P \leq \rho(x) \leq C_P < 1\Big\}, \tag{3.5}$$

where c_P and C_P are two fixed constants. Note that in the spatial dimensions $d = 1, 2, 3$ the space $H^2(\Omega)$ embeds into $C^0(\Omega)$, hence the pointwise condition imposed in the above definition is well-defined.

The State Space and the Equations. Consider the state space

$$Y = C^0(I, H^1_{D_e}(\Omega)) \times H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*) \cap L^4(I, C^0(\Omega)) \times W_0^{1,2}(I, C^0(\Omega))^2$$

and the space

$$W = L^2(I, H^1_{D_e}(\Omega))^* \times L^2(I, H^1_{D_d}(\Omega))^* \times L^2(\Omega) \times L^2(I, C^0(\Omega))^2.$$

Then the state equations can be written in the form $e(y, \rho) = 0$ with the constraint operator

$$e : Y \times P \to W, \quad (y, \rho) = (\tilde{u}, \tilde{a}_1, \tilde{a}_2, b, c, \rho) \mapsto e(y, \rho)$$

given by

$$e(y,\rho) = \begin{pmatrix} \iint \mathbb{C}(\rho,\sigma,b)\varepsilon(\tilde{u}+u_D) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t - \int_I \int_{\partial\Omega} g_N \cdot \mathrm{d}s\mathrm{d}t \\ \int_I \langle d_t\tilde{a}_1, \cdot\rangle_{H^1_{D_d}(\Omega)}\mathrm{d}t + \iint D(\rho)\nabla\tilde{a}_1\nabla\cdot + k_{3,1}(\tilde{a}_1+1)\cdot\mathrm{d}x\mathrm{d}t - \iint k_{2,1}|\varepsilon(u_0+u_D)|_\delta c\cdot\mathrm{d}x\mathrm{d}t \\ \int_I \langle d_t\tilde{a}_2, \cdot\rangle_{H^1_{D_d}(\Omega)}\mathrm{d}t + \iint D(\rho)\nabla\tilde{a}_2\nabla\cdot + k_{3,2}(\tilde{a}_2+1)\cdot\mathrm{d}x\mathrm{d}t - \iint k_{2,2}|\varepsilon(u_0+u_D)|_\delta c\cdot\mathrm{d}x\mathrm{d}t \\ \tilde{a}_1(0)+1 \\ \tilde{a}_2(0)+1 \\ d_t c - k_6(\tilde{a}_1+1)(\tilde{a}_2+1)(1+k_7c)\left(1-\frac{c}{1-\rho}\right) \\ d_t b - k_4(\tilde{a}_1+1)c\left(1-\frac{b}{1-\rho}\right) \end{pmatrix} \tag{3.6}$$

We frequently use the notation

$$a_i = \tilde{a}_i + 1, \quad \text{and} \quad u = \tilde{u} + u_D.$$

Functional Relationships. To make fully sense of the above definition of e we still need to clarify the assumptions made on the data and functional relationships. We begin with the function σ. We assume that it is smooth, depends only on time and is bounded away from zero, i.e.,

$$\sigma \in C^\infty(I), \quad \text{with } \sigma(t) > 0 \text{ for all } t \in I. \tag{3.7}$$

Usually, we set σ to be an exponential decay. For the material properties $\mathbb{C}$ of the elastic equation we require that it is a map

$$\mathbb{C} : \mathrm{dom}(\mathbb{C}) \subset C^0(I\times\Omega)\times C^0(\Omega) \to C^0(I, L^\infty(\Omega, \mathcal{L}(\mathcal{M}_s))), \quad \text{with} \quad (b,\rho) \mapsto \mathbb{C}(b,\sigma,\rho).$$

The concrete definition of dom($\mathbb{C}$) is not so important, however, as a minimal requirement it should hold

$$\bigcup_{\rho\in P}\{b \in C^0(I\times\Omega) \mid 0 \le b(t,x) \le 1-\rho(x)\} \times \{\rho\} \subset \mathrm{dom}(\mathbb{C}).$$

Furthermore, we need $\mathbb{C}(\cdot,\sigma,\rho)$ to be Lipschitz continuous with Lipschitz constant independent of ρ. Furthermore, $\mathbb{C}$ is assumed to be continuous on all of dom($\mathbb{C}$). Finally, we require

$$\sup_{(b,\rho)\in\mathrm{dom}(\mathbb{C})} \|\mathbb{C}(b,\sigma,\rho)\|_{L^\infty(\Omega,\mathcal{L}(\mathcal{M}_s))} < \infty \tag{3.8}$$

and

$$\inf_{(b,\rho)\in\mathrm{dom}(\mathbb{C})}\left[\inf_{M\in\mathcal{M}_s\setminus\{0\}} \mathbb{C}(b,\sigma,\rho)M : M\right] \ge c_{\mathbb{C}}|M|^2, \tag{3.9}$$

for a constant $c_{\mathbb{C}} > 0$. We need a further regularity property of $\mathbb{C}$. We assume that $b(t) \in C^\alpha(\Omega)$, $\rho \in C^\alpha(\Omega)$ for an $\alpha \in (0,1)$ implies that the coefficient functions

$$C_{ijkl}(t) := [\mathbb{C}(b,\sigma,\rho)(t)]_{ijkl}$$

are members of $C^\alpha(\Omega)$ and that there exists a constant $C > 0$ not depending on b and ρ such that

$$\|C_{ijkl}(t)\|_{C^\alpha(\Omega)} \le C\|b(t)\|_{C^\alpha(\Omega)}\|\rho\|_{C^\alpha(\Omega)}. \tag{3.10}$$

For the boundary data u_D and g_N of the elliptic equation we assume that

$$g_N \in C^0(I, L^2(\partial\Omega)) \tag{3.11}$$

and that the Dirichlet boundary data is given through a function

$$u_D \in C^0(I, H^{1+\theta}(\Omega)), \tag{3.12}$$

meaning that the boundary information can be lifted to all of Ω such that the lift has the above regularity in time and space, where $\theta > 0$ can be arbitrarily small. In practice, this is easy to verify as we mainly work with Dirichlet boundary conditions that do not vary in time. The material properties $D(\rho)$ used in the diffusion equation are a map

$$D : \mathrm{dom}(D) \subset C^0(\Omega) \to L^\infty(\Omega, \mathcal{M}_s), \quad \text{with} \quad \rho \mapsto D(\rho)$$

that we require to be continuous with respect to the uniform norm on $\mathrm{dom}(D)$. The domain of D will usually satisfy

$$\{\rho \in C^0(\Omega) \mid 0 < c_P \leq \rho(x) \leq C_P < 1\} \subset \mathrm{dom}(D),$$

where c_P and C_P are the positive constants appearing in the definition of P. We also require D to be uniformly elliptic independently of $\rho \in \mathrm{dom}(D)$, i.e.,

$$\inf_{\rho \in \mathrm{dom}(D)} \left[\inf_{\xi \in \mathbb{R}^d \setminus \{0\}} D(\rho)\xi \cdot \xi \right] \geq c_D |\xi|^2, \tag{3.13}$$

for a constant $c_D > 0$. Finally, for the function $|\cdot|_\delta$ we assume that it is given through a map on matrices

$$|\cdot|_\delta : \mathbb{R}^{d\times d} \to [0, \infty)$$

that we require to be Lipschitz and to obey an estimate of the form

$$|A|_\delta \leq C_1 |A| + C_2 \quad \text{for all } A \in \mathbb{R}^{d\times d}, \tag{3.14}$$

where $C_1, C_2 > 0$ and $|A|$ denotes the Euclidean (or any) norm of a matrix. Furthermore, we need $|\cdot|_\delta$ to be continuous, more precisely, we assume that if $(v_k) \subset L^2(\Omega, \mathbb{R}^{d\times d})$ is a sequence, then it holds

$$v_k \to v \quad \text{in } L^2(\Omega, \mathbb{R}^{d\times d}) \quad \Rightarrow \quad |v_k|_\delta \to |v|_\delta \quad \text{in } L^2(\Omega). \tag{3.15}$$

We recall the main result of the first Chapter concerning the well-posedness of the PDE-ODE system.

Theorem 14. *Assume that the setting described in this Section holds. Then, for every $\rho \in P$ there exists a unique solution $y = (\tilde{u}, \tilde{a}_1, \tilde{a}_2, b, c) \in Y$ satisfying $e(y, \rho) = 0$, i.e., solving the state equations* (3.6).

Proof. Inspecting the assumptions required for the well-posedness in (8), we see that the requirements on the domain, the control space, the elastic & diffusion equations are (partly) stronger than in (8), hence trivially satisfied. The admissibility of the functional relationships H and K that are implicitly given in (3.6) were already discussed in Section III. □

2.2 Objective Function

Here we formulate the class of objective functions we are able to treat in the setting of the optimal control result. For every time-point $t \in I$ and state control pair $(y, \rho) \in Y \times P$ we consider the elastic energy

$$\mathcal{E} : Y \times P \to C^0(I), \quad \mathcal{E}(y, \rho)(t) = t \mapsto \frac{1}{2} \int_\Omega \mathbb{C}(b(t), \sigma(t), \rho)\varepsilon(u(t)) : \varepsilon(u(t))\mathrm{d}x. \tag{3.16}$$

For most of our objective functions we desire $\mathcal{E}$ to take values in $C^0(I)$, as we want to have access to point evaluations. This is the reason to require the continuity of the solutions to the elastic equation in the definition of Y. Primarily, we are interested in the reduced elastic energy $\hat{\mathcal{E}}$, that is, we are interested in $\mathcal{E}(y, \rho)$ only when (y, ρ) solves the system of equations, i.e., when it holds $e(y, \rho) = 0$. We define

$$\hat{\mathcal{E}} : P \to C^0(I), \quad \hat{\mathcal{E}}(\rho) = \mathcal{E}(y_\rho, \rho) \tag{3.17}$$

and here it holds $e(y_\rho, \rho) = 0$. We provide now the proof that $\mathcal{E}$ takes values in $C^0(I)$.

Lemma 15. *For all $(y, \rho) \in Y \times P$ we have $\mathcal{E}(y, \rho) \in C^0(I)$. If it holds $e(y, \rho) = 0$ and $\tilde{u}(t) + u_D(t) \neq 0$, then $\mathcal{E}(y, \rho)(t) > 0$.*

Proof. As $\tilde{u} + u_D \in C^0(I, H^1(\Omega))$ by the definition of the state space Y and the material tensor $\mathbb{C}$ is a member of the space $C^0(I, L^\infty(\Omega, \mathcal{L}(\mathcal{M}_s)))$ it follows that

$$\mathbb{C}(\sigma, \rho, b)\varepsilon(\tilde{u} + u_D) : \varepsilon(\tilde{u} + u_D) \in C^0(I, L^1(\Omega)).$$

Using the $L^1(I)$ continuity of integration, we get $\mathcal{E}(y,\rho) \in C^0(I)$. Now, let $e(y,\rho) = 0$. We can estimate

$$\mathcal{E}(y,\rho)(t) \geq c\|\tilde{u}(t) + u_D\|^2_{H^1(D)},$$

with the constant $c > 0$ depending on the constant appearing in Korn's inequality and the ellipticity constant $c_{\mathbb{C}}$. As it holds $e(y,\rho) = 0$, for every $t \in I$ the function $\tilde{u}(t) + u_D(t)$ solves an elastic equation, hence can only vanish if the boundary conditions are homogeneous for this time-point which leads to $\tilde{u}(t) + u_D(t) = 0$. This is excluded in the statement of the Lemma and the proof is complete. □

We state now the structural assumption we impose for our admissible objective functions.

Assumption 16. Let $\mathcal{F} : \mathrm{dom}(\mathcal{F}) \subset C^0(I) \to \mathbb{R}$ be a continuous map and assume that the domain of $\mathcal{F}$ satisfies

$$\left\{v \in C^0(I) \mid v(t) > 0 \text{ for all } t \in I\right\} \subset \mathrm{dom}(\mathcal{F}). \tag{3.18}$$

Furthermore, let $\mathcal{G} : C^0(I \times \Omega) \to \mathbb{R}$ be a continuous function. Using the elastic energy $\mathcal{E}$ and functionals $\mathcal{F}$, $\mathcal{G}$ as above, we define the prototypical objective function as

$$J : Y \times P \to \mathbb{R}, \quad J(y,\rho) = \mathcal{F}\left(\mathcal{E}(y,\rho)\right) + \mathcal{G}(b)$$

in case the domain of $\mathcal{F}$ allows $\mathcal{E}(y,\rho)$ as an argument. The function b denotes the bone component of the state variable y. More important, we define the reduced objective

$$\hat{J} : P \to \mathbb{R}, \quad \hat{J}(\rho) = \mathcal{F}\left(\mathcal{E}(\phi(\rho),\rho)\right) + \mathcal{G}(b).$$

Note that the assumption (3.18) together with Lemma 15 guarantees that $\mathcal{E}(\phi(\rho),\rho)$ is an admissible argument of $\mathcal{F}$. Finally, we assume that $\hat{J}$ is bounded from below if we are interested in a minimization problem and we assume $\hat{J}$ to be bounded from above if we are interested in maximization.

Remark 17. We comment on some admissible choices for $\mathcal{F}$ and $\mathcal{G}$.

(i) As main examples for $\mathcal{F}$ we mention the minimum or maximum functional, i.e.,

$$\min : C^0(I) \to \mathbb{R}, \quad v \mapsto \min_{t \in I} v(t)$$

and likewise with the maximum functional.

(ii) Smooth approximations of the minimum and the maximum are given by $L^p(I)$ norms with large values of $|p|$. A positive value for p serves as an approximation of the maximum and a negative value is suitable for the approximation of the minimum. In the latter case, i.e., $p < 0$, one chooses

$$\mathrm{dom}\left(\|\cdot\|_{L^p(I)}\right) := \left\{v \in C^0(I) \mid v(t) > 0 \text{ for all } t \in I\right\}.$$

It is straight forward to show that $\|\cdot\|_{L^p(I)}$ is continuous with respect to the uniform norm, also for negative exponents. In fact, it is even Fréchet differentiable.

(iii) The function $\mathcal{G}$ encodes objectives concerning regenerated bone. One might set

$$\mathcal{G}(b) = \int_\Omega b(T)\mathrm{d}x,$$

i.e., considering the amount of regenerated bone at the final time $T \in I$. Clearly this choice is admissible.

2.3 Main Results

Our main result of this Section establishes the existence of an optimal control in the set $P \subset H^2(\Omega)$ given the objective function $\hat{J}$ is regularized by an $H^2(\Omega)$ norm.

Theorem 18 (Optimal Control)**.** *Assume we are in Setting 2.1 and let $\eta > 0$ be fixed. Then there exists a minimizer $\rho^* = \rho^*(\eta) \in P$ to the regularized objective*

$$\hat{J}(\rho^*) + \eta\|\rho^*\|_{H^2(\Omega)} = \inf_{\rho \in P}\left[\hat{J}(\rho) + \eta\|\rho\|^2_{H^2(\Omega)}\right].$$

Proof. The proof is established in the course of the text. □

In order to incorporate the pointwise constraint encoded in the definition of the control space P, see (3.5), in a numerical simulation one can use a soft penalization. This usually corresponds to a continuous functional $\mathcal{K} : C^0(\Omega) \to [0, \infty)$. Also in this setting we can establish the existence of an optimal control.

Corollary 19. *Assume we are in Setting 2.1 and let $\mathcal{K} : C^0(\Omega) \to [0, \infty)$ be a continuous, non-negative functional. Then there exists an optimal control $\rho^\dagger = \rho^\dagger(\eta, \mathcal{K}) \in H^2(\Omega)$ to the regularized and penalized objective, i.e.,*

$$\hat{J}(\rho^\dagger) + \eta \|\rho^\dagger\|^2_{H^2(\Omega)} + \mathcal{K}(\rho^\dagger) = \inf_{\rho \in H^2(\Omega)} \left[\hat{J}(\rho) + \eta \|\rho\|^2_{H^2(\Omega)} + \mathcal{K}(\rho) \right].$$

Proof. The proof is established in the course of the text. □

Remark 20. A few comments regarding the above results are in order.

(i) For some objectives we might be interested in a maximizer rather than a minimizer. In this case, one subtracts the regularizer $\eta\|\cdot\|_{H^2(\Omega)}$ and the soft penalty $\mathcal{K}$ and the results are still valid. For brevity, we discuss only minimization problems in the remainder.

(ii) As discussed in Section 2.2, we have some freedom in the choice of $\hat{J}$. From a modeling perspective a maximum or minimum over all time-points of the elastic energy seems reasonable. On the other hand, for the numerical treatment a smooth approximation thereof is preferable, e.g., an $L^p(I)$ norm. Note that all these choices are covered by our main result.

(iii) The Tikhonov penalization term $\eta\|\cdot\|^2_{H^2(\Omega)}$ is artificial. It serves to generate compactness of minimizing sequences and an optimal control result without this term seems out of reach.

(iv) The optimal controls $\rho^*(\eta)$ and $\rho^\dagger(\eta, \mathcal{K})$ depend on η and $\mathcal{K}$ and for these hyperparameters there are no canonical choices. We investigate their influence numerically in Section IV.

(v) It is presently unclear to us if the optimal control problem possesses a unique solution.

2.4 Proofs of the Main Results

In this Section we prove Theorem 18 and Corollary 19. It turns out that our approach crucially relies on rather specific regularity properties of the diffusion equations and the elastic equation that imply convenient compact embeddings. To prevent an overly technical section, we begin by assuming the implications of the compact embeddings. We provide full proofs or give appropriate references of the regularity properties at the end of the Section and in the Appendix II. Note that again the mixed boundary conditions, rough coefficients and jump initial conditions are responsible for the technical difficulties.

Proposition 21. *Assume we are in Setting 2.1. Let $(\rho_k) \subset P$ be a minimizing sequence for $\hat{J} + \eta\|\cdot\|^2_{H^2(\Omega)}$ and denote by $(u_k) \subset C^0(I, H^1(\Omega))$, $(a^1_k), (a^2_k) \subset H^1(I, H^1(\Omega), H^1_D(\Omega)^*)$ and $(b_k), (c_k) \subset W^{1,2}(I, C^0(\Omega))$ the corresponding solutions to the system 3.6. Assume that there is a common subsequence (not relabeled) of $(\rho_k), (u_k), (a^1_k), (a^2_k), (b_k), (c_k)$ and elements $\rho^* \in P$, $u^* \in C^0(I, H^1(\Omega))$, $a^*_1, a^*_2 \in H^1(I, H^1(\Omega), H^1_D(\Omega)^*)$ and $b^*, c^* \in W^{1,2}(I, C^0(\Omega))$ such that*

(A1) $\rho_k \to \rho^*$ *in* $C^0(\Omega)$ *and* $\rho_k \rightharpoonup \rho^*$ *in* $H^2(\Omega)$,

(A2) $u_k \to u^*$ *in* $C^0(I, H^1(\Omega))$,

(A3) $a^i_k \rightharpoonup a^*_i$ *in* $H^1(I, H^1(\Omega), H^1_D(\Omega)^*)$, $\quad i = 1, 2$

(A4) $b_k \to b^*$ *in* $C^0(I \times \Omega)$

(A5) $c_k \to c^*$ *in* $C^0(I \times \Omega)$

then $(\rho^*, u^*, a^*_1, a^*_2, b^*)$ solves the system 3.6 and ρ^* is minimizer of $\hat{J} + \eta\|\cdot\|^2_{H^2(\Omega)}$ over the set P, i.e., satisfies

$$\hat{J}(\rho^*) + \eta\|\rho^*\|_{H^2(\Omega)} = \inf_{\rho \in P} \left[\hat{J}(\rho) + \eta\|\rho\|^2_{H^2(\Omega)} \right].$$

Proof. There are two things to show. First, we need to guarantee that the tuple $(\rho^*, u^*, a_1^*, a_2^*, b^*)$ still solves the system of equations 3.6. And secondly, we need to prove that ρ^* is in fact a minimizer. We start with the second point, assuming for the moment that $(\rho^*, u^*, a_1^*, a_2^*, b^*)$ solves the correct equations. We show that it holds

$$\hat{J}(\rho^*) + \eta\|\rho^*\|^2_{H^2(\Omega)} \leq \liminf_{k\to\infty}\left[\hat{J}(\rho_k) + \eta\|\rho_k\|^2_{H^2(\Omega)}\right] = \min_{\rho\in P}\left[\hat{J}(\rho) + \eta\|\rho\|^2_{H^2(\Omega)}\right],$$

that is, the classical lower semi-continuity property required in the application of the direct method of the calculus of variations. Clearly, the map

$$H^2(\Omega) \to \mathbb{R}, \quad \rho \mapsto \eta\|\rho\|^2_{H^2(\Omega)}$$

is convex and norm continuous, hence weakly lower semi-continuous, that is, it holds

$$\eta\|\rho^*\|^2_{H^2(\Omega)} \leq \liminf_{k\to\infty} \eta\|\rho_k\|^2_{H^2(\Omega)}$$

by the assumption $\rho_k \rightharpoonup \rho^*$ in $H^2(\Omega)$ on the minimizing sequence. To proceed, remember our structural assumption on the objective function, i.e.,

$$\hat{J} = \mathcal{F}\left(\hat{\mathcal{E}}(\rho)\right) + \mathcal{G}(b),$$

where $\mathcal{F} : C^0(I) \to \mathbb{R}$ and $\mathcal{G} : C^0(I\times\Omega) \to \mathbb{R}$ are assumed to be continuous. Thus it suffices to show that $\mathcal{E}(\rho_k) \to \mathcal{E}(\rho^*)$ in $C^0(I)$. For convenience, let us now set $\mathbb{C}^* = \mathbb{C}(\rho^*, \sigma, b^*)$ and $\mathbb{C}_k = \mathbb{C}(\rho_k, \sigma, b_k)$. We then compute

$$\begin{aligned}
\|\hat{\mathcal{E}}(\rho_k) - \hat{\mathcal{E}}(\rho^*)\|_{C^0(I)} &= \frac{1}{2}\left\|\int_\Omega \left[\mathbb{C}_k - \mathbb{C}^*\right]\varepsilon(u_k) : \varepsilon(u_k) + \mathbb{C}^*\varepsilon(u_k - u^*) : \varepsilon(u_k) + \mathbb{C}^*\varepsilon(u^*)\varepsilon(u_k - u^*)\mathrm{d}x\right\|_{C^0(I)} \\
&\leq \|\mathbb{C}_k - \mathbb{C}^*\|_{C^0(I,L^\infty(\Omega,\mathcal{L}(\mathcal{M}_s)))}\|\varepsilon(u_k)\|^2_{C^0(I,L^2(\Omega))} \\
&+ \|\mathbb{C}^*\|_{C^0(I,L^\infty(\Omega,\mathcal{L}(\mathcal{M}_s)))}\|\varepsilon(u_k - u^*)\|^2_{C^0(I,L^2(\Omega))}\|\varepsilon(u_k)\|^2_{C^0(I,L^2(\Omega))} \\
&+ \|\mathbb{C}^*\|_{C^0(I,L^\infty(\Omega,\mathcal{L}(\mathcal{M}_s)))}\|\varepsilon(u^*)\|^2_{C^0(I,L^2(\Omega))}\|\varepsilon(u_k - u^*)\|^2_{C^0(I,L^2(\Omega))}.
\end{aligned}$$

Using the continuity assumption for $\mathbb{C}$ and the convergence $b_k \to b^*$ in $C^0(I\times\Omega)$ and $\rho_k \to \rho^*$ in $C^0(\Omega)$ we get that

$$\|\mathbb{C}_k - \mathbb{C}^*\|_{C^0(I,L^\infty(\Omega,\mathcal{L}(\mathcal{M}_s)))} \to 0.$$

Furthermore, the convergence $u_k \to u^*$ in $C^0(I, H^1(\Omega))$ implies both a bound on $\|\varepsilon(u_k)\|$ and the convergence

$$\|\varepsilon(u_k - u^*)\|_{C^0(I,L^2(\Omega))}.$$

Hence, we established $\hat{\mathcal{E}}(\rho_k) \to \hat{\mathcal{E}}(\rho^*)$ and conclude

$$\hat{J}(\rho^*) + \eta\|\rho^*\|^2_{H^2(\Omega)} \leq \lim_{k\to\infty}\hat{J}(\rho_k) + \liminf_{k\to\infty}\eta\|\rho_k\|^2_{H^2(\Omega)} \leq \liminf_{k\to\infty}\left[\hat{J}(\rho_k) + \eta\|\rho_k\|^2_{H^2(\Omega)}\right]$$

which settles the claim.

We still need to show that $(\rho^*, u^*, a_1^*, a_2^*, b^*)$ is in fact a solution to the system 3.6. For the elastic equation we consider for an arbitrary test function $\varphi \in L^2(I, H^1_{D_e}(\Omega))$

$$\iint \mathbb{C}(\rho_k, \sigma, b_k)\varepsilon(u_k) : \varepsilon(\varphi)\mathrm{d}x\mathrm{d}t = \int_I\int_{\partial\Omega} g_N\varphi\mathrm{d}s\mathrm{d}t$$

and the continuity assumption on $\mathbb{C}$ and the convergence assumed for ρ_k, b_k and u_k are by far sufficient to pass to the limit.

In the same spirit, we consider the diffusion equations with a test function $\varphi \in L^2(I, H_{D_d}(\Omega))$

$$\int_I \langle d_t a_k^i, \varphi\rangle_{H^1_{D_d}(\Omega)}\mathrm{d}t + \iint D(\rho_k)\nabla a_k^i\nabla\varphi + k_3(a_k^i)\varphi\mathrm{d}x\mathrm{d}t = \iint k_2|\varepsilon(u_k)|_\delta c_k\varphi\mathrm{d}x\mathrm{d}t, \quad i = 1, 2.$$

For the left-hand side of the diffusion equations we can easily pass to the limit by the weak convergence of a_k^i and the strong convergence of $D(\rho_k)$ that we have available through the continuity assumption on D and $\rho_k \to \rho^*$ in $C^0(\Omega)$. For the right-hand sides we use the implication

$$u_k \to u^* \text{ in } C^0(I, H^1(\Omega)) \quad \Rightarrow \quad |\varepsilon(u_k)|_\delta \to |\varepsilon(u^*)|_\delta \text{ in } L^2(\Omega).$$

Hence, the limit for the diffusion equations can also be correctly identified. To establish the initial condition of the limit, consider the continuous linear map

$$H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*) \to C^0(I, L^2(\Omega)) \to L^2(\Omega), \quad a \mapsto a(0).$$

Using the weak sequential continuity of continuous linear maps shows that $a^*(0)$ vanishes, as desired.

To pass to the limit in the cell ODE, we look at its fixed-point equation

$$c_k(t) = \int_0^t k_6 a_1^k(s) a_2^k(s)(1 + k_7 c_k(s)) \left(1 - \frac{c_k(s)}{1 - \rho_k}\right) \mathrm{d}s,$$

which holds in the space $C^0(\Omega)$, for all $t \in I$. Multiplying the above equation by a smooth test function $\varphi \in C_c^\infty(\Omega)$ and integrating over Ω yields for the left-hand side of the above equation

$$\int_\Omega c_k(t)\varphi \mathrm{d}x \to \int_\Omega c^*(t)\varphi \mathrm{d}x \quad \text{with} \quad k \to \infty.$$

The convergence $c_k \to c^*$ in the space $C^0(I \times \Omega)$ suffices by far for the above limit passage. Before we treat the limit of the right-hand side we note that the compactness result of Aubin-Lions, see for instance Simon (1986), provides the compact embedding

$$H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*) \hookrightarrow\hookrightarrow L^2(I, L^2(\Omega))$$

which is essentially due to the fact that the space triple $(H^1_D(\Omega), L^2(\Omega), H^1_D(\Omega)^*)$ satisfies the requirements of the Ehrling Lemma, being in turn guaranteed by the Rellich-Kochandrov compactness result that provides the compact embedding of $H^1_D(\Omega)$ into $L^2(\Omega)$. Note that the boundary regularity in for Ω is chosen to support the Rellich-Kochandrov theorem. Hence we get the convergence

$$a_1^k a_2^k \to a_1^* a_2^* \quad \text{in} \quad L^1(I, L^1(\Omega)) \cong L^1(I \times \Omega).$$

Using the above convergence and the convergence of $c_k \to c^*$ in $C^0(I \times \Omega)$ and $\rho_k \to \rho^*$ in $C^0(\Omega)$ we compute, employing Fubini's theorem and pass to the limit

$$\begin{aligned}
\int_\Omega \int_0^t k_6 a_1^k a_2^k (1 + k_7 c_k) \left(1 - \frac{c_k}{1 - \rho_k}\right) \mathrm{d}s\varphi \mathrm{d}x &= \int_0^t \int_\Omega k_6 a_1^k a_2^k (1 + k_7 c_k) \left(1 - \frac{c_k}{1 - \rho_k}\right) \varphi \mathrm{d}s \mathrm{d}x \\
&\to \int_0^t \int_\Omega k_6 a_1^* a_2^* (1 + k_7 c^*) \left(1 - \frac{c^*}{1 - \rho^*}\right) \varphi \mathrm{d}x \mathrm{d}s \\
&= \int_\Omega \int_0^t k_6 a_1^* a_2^* (1 + k_7 c^*) \left(1 - \frac{c^*}{1 - \rho^*}\right) \mathrm{d}s\varphi \mathrm{d}x
\end{aligned}$$

Inferring the fundamental lemma of the calculus of variations we obtain

$$c^*(t) = \int_0^t k_6 a_1^* a_2^* (1 + k_7 c^*) \left(1 - \frac{c^*}{1 - \rho^*}\right) \mathrm{d}s$$

for every $t \in I$. This implies that c^* satisfies the correct limit equation. Obviously we can repeat the same argument to guarantee that b^* satisfies an appropriate limit equation. □

Remark 22. Via discussing the requirements $(A1) - (A5)$ above, we give a rough idea of their proof.

(i) The fact that J is bounded from below implies that the regularization term $\eta \|\cdot\|^2_{H^2(\Omega)}$ automatically leads to an $H^2(\Omega)$ bound on any minimizing sequence $(\rho_k) \subset P$. Thus there exists $\rho^* \in P$ and a (not re-labeled) subsequence (ρ_k) with $\rho_k \rightharpoonup \rho^*$ in $H^2(\Omega)$. Employing the compactness

$$H^2(\Omega) \hookrightarrow\hookrightarrow C^0(\Omega)$$

that holds for three spatial dimensions, this implies the desired convergence $\rho_k \to \rho^*$ in $C^0(\Omega)$.

(ii) A uniform bound in $C^0(I, H^1(\Omega))$ norm of the sequence (u_k) is easily established as Lemma 23 shows. However, this does not provide assumption (A2) which can only be achieved through a compactness argument. In fact – given Hölder continuous coefficients functions of $\mathbb{C}(\rho_k, \sigma, b_k)$ – one is able to show that for every $t \in I$ the solution $u_k(t)$ is a member of $H^{1+\theta}(\Omega)$ for a sufficiently small $\theta > 0$ as an application of the main theorem of Haller-Dintelmann et al. (2019). Compare also to Lemma 25 for a discussion of the applicability of this result. Then, given the relative compactness of the sequences (b_k) in $C^0(I \times \Omega)$ and $(\rho_k) \subset C^0(\Omega)$ one can apply a vector-valued version of the Arzelà-Ascoli theorem to derive the relative compactness of (u_k) in $C^0(I, H^1(\Omega))$. As discussed in (iv), the compactness of (b_k) relies on a Hölder regularity result for diffusion equations.

(iii) Similarly, a uniform bound for the sequences (a_k^i) in $H^1(I, H^1(\Omega), H_D^1(\Omega)^*)$ norm can be established by standard computations, thus implying the desired existence of a_i^* and corresponding subsequence. We provide the details in Lemma 27.

(iv) The existence of a subsequence (b_k) and $b^* \in C^0(I \times \Omega)$ with $b_k \to b^*$ in $C^0(I \times \Omega)$ requires the biggest effort. We achieve this by deriving a $W^{1,2}(I, C^\alpha(\Omega))$ bound on (b_k) for an $\alpha \in (0, 1)$. Investigating the structure of the cell and bone ODEs, we see that such a regularity and bound can only be established if we are able to show that the sequences (a_k^i) are bounded in $L^2(I, C^\alpha(\Omega))$. It is this regularity and boundedness result for the diffusion equation on which the whole proof rests, we discuss it in Appendix II.

Coming back to the boundedness of (b_k) in $W^{1,2}(I, C^\alpha(\Omega))$, note that this implies the desired existence of $b^* \in C^0(I \times \Omega)$ together with a subsequence $b_k \to b^*$ in $C^0(I \times \Omega)$ via the embeddings

$$W^{1,2}(I, C^\alpha(\Omega)) \hookrightarrow C^\beta(I, C^\alpha(\Omega)) \hookrightarrow C^{\min(\alpha,\beta)}(I \times \Omega) \hookrightarrow\hookrightarrow C^0(I \times \Omega).$$

(vi) To summarize: $(A1)$ is clear, $(A3)$ is established in Lemma 27, $(A2)$, $(A4)$ and $(A5)$ rely on the regularity result for diffusion equations stated in Lemma 28 and the main result of Haller-Dintelmann et al. (2019). The derivation of the $W^{1,2}(I, C^\alpha(\Omega))$ bound for (b_k) is carried out in Lemma 32, the bound for (c_k) in Lemma 31.

Lemma 23 ($C^0(I, H^1(\Omega))$ bound for u)**.** *Let $\mathbb{C} \in C^0(I, L^\infty(\Omega, \mathcal{L}(\mathcal{M}_s)))$ be uniformly elliptic with ellipticity constant $\lfloor \mathbb{C} \rfloor$ independent of $t \in I$ and $x \in \Omega$, i.e., it holds*

$$\mathbb{C}(t, x)M : M \geq \lfloor \mathbb{C} \rfloor |M|^2, \quad \text{for all } M \in \mathcal{L}(\mathcal{M}_s) \text{ and } (t, x) \in I \times \Omega.$$

Furthermore, let $f \in C^0(I, H_D^1(\Omega)^*)$ be a fixed right-hand side. Then the unique solution $u \in L^2(I, H_D^1(\Omega))$ to

$$\iint \mathbb{C}\varepsilon(u) : \varepsilon(\cdot) \mathrm{d}x\mathrm{d}t = \int_I \langle f, \cdot \rangle_{H_D^1(\Omega)} \mathrm{d}t \quad \text{in } L^2(I, H_D^1(\Omega))^* \tag{3.19}$$

is a member of the space $C^0(I, H_D^1(\Omega))$ and satisfies

$$\|u\|_{C^0(I,H^1(\Omega))} \leq C\left(\lfloor \mathbb{C} \rfloor, C_{Korn}\right) \cdot \|f\|_{C^0(I,H_D^1(\Omega)^*)}.$$

Proof. The equation (3.19) implies that u satisfies almost everywhere in I

$$\underbrace{\int_\Omega \mathbb{C}(t)\varepsilon(u(t)) : \varepsilon(\cdot)\mathrm{d}x}_{=:\mathcal{T}_t u(t)} = f(t) \quad \text{in } H_D^1(\Omega)^*$$

upon applying the isometry $L^2(I, H_D^1(\Omega))^* \to L^2(I, H_D^1(\Omega)^*)$ to both sides of the equation. Clearly, testing with $u(t)$ yields, inferring Korn's inequality,

$$\lfloor \mathbb{C} \rfloor C_{\text{Korn}} \cdot \|u\|_{H_D^1(\Omega)}^2 \leq \lfloor \mathbb{C} \rfloor \cdot \|\varepsilon(u)\|_{L^2(\Omega)}^2 \leq \|f(t)\|_{H_D^1(\Omega)^*} \|u(t)\|_{H_D^1(\Omega)}.$$

Hence,

$$\|u(t)\|_{H_D^1(\Omega)} \leq \left(\lfloor \mathbb{C} \rfloor C_{\text{Korn}}\right)^{-1} \|f(t)\|_{H_D^1(\Omega)^*} \leq \left(\lfloor \mathbb{C} \rfloor C_{\text{Korn}}\right)^{-1} \|f\|_{C^0(I,H_D^1(\Omega)^*)},$$

meaning that the $H^1(\Omega)$ bound on $u(t)$ is independent of $t \in I$. To show that u is continuous in time, we compute for $t, s \in I$

$$f(t) - f(s) = \mathcal{T}_t u(t) - \mathcal{T}_s u(s) = \mathcal{T}_t(u(t) - u(s)) + \mathcal{T}_t(u(s)) - \mathcal{T}_s u(s).$$

Using the coercivity of $\mathcal{T}_t$ we find

$$\|u(t)-u(s)\|_{H^1(\Omega)} \le \frac{1}{\lfloor \mathbb{C} \rfloor C_{\text{Korn}}} \left[\|f(t)-f(s)\|_{H^1(\Omega)^*} + \|\mathcal{T}_t u(s) - \mathcal{T}_s u(s)\|_{H^1_D(\Omega)^*} \right]$$

By the assumption $f \in C^0(I, H^1_D(\Omega)^*)$ it is clear that the first term above tends to zero when $|t-s| \to 0$. It remains to estimate

$$\begin{aligned} \|\mathcal{T}_t u(s) - \mathcal{T}_s u(s)\|_{H^1_D(\Omega)^*} &\le \sup_{\|\varphi\|_{H^1_D(\Omega)} \le 1} \int_\Omega [\mathbb{C}(t) - \mathbb{C}(s)]\, \varepsilon(u(s)) : \varepsilon(\varphi) \mathrm{d}x \\ &\le \|\mathbb{C}(t) - \mathbb{C}(s)\|_{L^\infty(\Omega, \mathcal{M}_s)} \|u(s)\|_{H^1_D(\Omega)}. \end{aligned}$$

The time-independent bound on $\|u(s)\|_{H^1_D(\Omega)}$ and the continuity assumption on $\mathbb{C}$ imply the assertion. □

Lemma 24 (Equi-Continuity)**.** *Assume $(\rho_k) \subset P$ is any sequence, $(b_k) \subset W_{\rho_k}$ is an equi-continuous sequence in $C^0(I, C^0(\Omega))$ and (f_k) is a equi-continuous and bounded sequence in $C^0(I, H^1_D(\Omega)^*)$. Assume that $\mathbb{C}(\rho_k, \sigma, b_k)$ satisfies the assumption 2.1, i.e., in particular, it holds*

$$\|\mathbb{C}(\rho_k, \sigma, b_k)(t) - \mathbb{C}(\rho_k, \sigma, b_k)(s)\|_{L^\infty(\Omega, \mathcal{L}(\mathcal{M}_s))} \le C\|b_k(t) - b_k(s)\|_{C^0(\Omega)} \tag{3.20}$$

for a constant C that does not depend on the data $\rho_k \in P$ and $b_k \in W_{\rho_k}$ and $t \in I$. Denote by u_k the unique solution of

$$\iint \mathbb{C}(\rho_k, \sigma, b_k) \varepsilon(u_k) : \varepsilon(\cdot) \mathrm{d}x \mathrm{d}t = \int_I \langle f_k, \cdot \rangle_{H^1_D(\Omega)} \mathrm{d}t \quad \textit{in } L^2(I, H^1_D(\Omega))^*.$$

Then, (u_k) lies in $C^0(I, H^1_D(\Omega))$ and is equi-continuous in this space.

Proof. We are in situation of Lemma 23, hence we know that u_k is a member of the space $C^0(I, H^1_D(\Omega))$ and we need only to establish the equi-continuity. To this end, repeating the equations in Lemma 23 for u_k instead of u we arrive at

$$\begin{aligned} \|u_k(t) - u_k(s)\|_{H^1(\Omega)} &\le \frac{1}{\lfloor \mathbb{C}_k \rfloor C_{\text{Korn}}} \left[\|f_k(t) - f_k(s)\|_{H^1(\Omega)^*} + \|\mathbb{C}_k(t) - \mathbb{C}_k(s)\|_{L^\infty(\Omega, \mathcal{L}(\mathcal{M}_s))} \|u_k(s)\|_{H^1(\Omega)} \right] \\ &\le \frac{1}{\lfloor \mathbb{C}_k \rfloor C_{\text{Korn}}} \left[\|f_k(t) - f_k(s)\|_{H^1(\Omega)^*} + C\|b_k(t) - b_k(s)\|_{C^0(\Omega)} \right] \end{aligned}$$

as $\|u_k(t)\|_{H^1(\Omega)}$ is bounded uniformly in $k \in \mathbb{N}$ and $s \in I$ by Lemma 23 through the boundedness we assumed for (f_k). Then, we infer the equi-continuity of (f_k) and (b_k) to derive it for (u_k). □

The following Lemma summarizes the main result of Haller-Dintelmann et al. (2019). We restrict ourselves to the generality necessary needed for our application, which however, is not the most general situation. We refer the reader to Haller-Dintelmann et al. (2019) for a relaxation concerning boundary regularity, regularity of coefficients and the differential operator.

Lemma 25 (Higher Regularity for Elliptic Systems)**.** *Let $\mathbb{C} \in L^\infty(\Omega, \mathcal{L}(\mathcal{M}_s))$ be uniformly elliptic, i.e., there exists $\lfloor \mathbb{C} \rfloor > 0$ such that*

$$\mathbb{C}M : M \ge \lfloor \mathbb{C} \rfloor |M|^2, \quad \textit{for all } M \in \mathcal{M}_s.$$

Assume that $\mathbb{C}_{ijkl} \in C^\alpha(\Omega)$ for a fixed but arbitrary small $\alpha > 0$. Then, there exists $\theta = \theta(\alpha) > 0$ such that for every $f \in H^{1-\theta}(\Omega)^*$ the solution $u \in H^1_D(\Omega)$ to

$$\int_\Omega \mathbb{C}\varepsilon(u) : \varepsilon(\cdot) \mathrm{d}x = f \quad \textit{in } H^1_D(\Omega)^*$$

is in fact a member of $H^{1+\theta}(\Omega)$ and we can estimate

$$\|u\|_{H^{1+\theta}(\Omega)} \le C\|\mathbb{C}\|_{C^\alpha(\Omega)} \|f\|_{H^{1-\theta}_D(\Omega)^*},$$

where C does not depend on the concrete form of $\mathbb{C}$.

Proof. This follows from Theorem 1 and Lemma 1 in Haller-Dintelmann et al. (2019). □

The last result we need to establish the relative compactness of (u_k) in $C^0(I, H^1_D(\Omega))$ is – little surprisingly – a vector valued version of the Arzelà-Ascoli Theorem which we recall here for convenience.

Theorem 26 (Characterization of Relative Compactness in $C^0(K, X)$ Spaces)**.** *Let X be a Banach space and K a compact metric space. Then a set $\mathcal{F} \subset C^0(K, X)$ is relatively compact if and only if the following two conditions hold:*

(i) The set $\mathcal{F}$ is equi-continuous, that is, for all $t \in K$ and all $\varepsilon > 0$ there exists a neighborhood $U(t) \subset K$ such that

$$\sup_{u\in\mathcal{F}} \|u(t) - u(s)\|_X \leq \varepsilon \quad \textit{for all } s \in U(t).$$

(ii) For all $t \in K$ the set

$$\{u(t) \mid u \in \mathcal{F}\} \subset X$$

is relatively compact.

The focus of the next Lemma lies on the a priori estimates for linear parabolic equations.

Lemma 27 (A Priori Estimate for Parabolic Evolution Equations)**.** *Let (i, X, H) be a Gelfand triple, $M : X \to X^*$ a linear coercive operator with coercivity constant $\lfloor M \rfloor$, i.e., it holds*

$$\langle Ma, a\rangle_X \geq \lfloor M \rfloor \|a\|_X^2, \quad \textit{for all } a \in X.$$

Let $I = [0, T]$ denote a time interval and $f \in L^2(I, X^*)$ a fixed right-hand side. Then there exists a unique solution $a \in H^1(I, X, X^*)$ to

$$\int_I \langle d_t a, \cdot\rangle \mathrm{d}t + \int_I \langle Ma, \cdot\rangle_X \mathrm{d}t = \int_I \langle f, \cdot\rangle_X \mathrm{d}t, \quad \textit{in } L^2(I, X)^*$$

Furthermore, the norm of the solution a can be estimated by

$$\|a\|_{H^1(I,X,X^*)} \leq C\left(\|M\|_{\mathcal{L}(X,X^*)}, \lfloor M \rfloor^{-1}\right) \cdot \left(\|a(0)\|_H + \|f\|_{L^2(I,X^*)}\right), \tag{3.21}$$

with C being monotonously increasing in $\|M\|_{\mathcal{L}(X,X^*)}$ and $\lfloor M \rfloor^{-1}$.

Proof. We establish only the estimate (3.21), the existence of a solution is the well known maximal regularity result of J. L. Lions, see for instance (Ern and Guermond, 2013, Part II, Section 6). To derive the estimate, we note that by the natural isometry $L^2(I, X^*) = L^2(I, X)^*$ the function a satisfies a pointwise almost-everywhere equation in X^*, namely

$$d_t a(s) + M(a(s)) = f(a(s))$$

which, at time $s \in I$, we can test with $a(s) \in X$ and integrate from 0 to t. Then, we apply the partial integration formula for Gelfand triples and estimate using the coercivity of M and Young's inequality

$$\begin{aligned}
\frac{1}{2}\|a(t)\|_H^2 + \lfloor M \rfloor \int_0^t \|a(s)\|_X^2 \mathrm{d}s &\leq \frac{1}{2}\|a(0)\|_H^2 + \|f\|_{L^2(I,X^*)}\|a\|_{L^2(I,X)} \\
&\leq \frac{1}{2}\|a(0)\|_H^2 + \frac{1}{2\lfloor M \rfloor}\|f\|^2_{L^2([0,t],X^*)} + \frac{\lfloor M \rfloor}{2}\|a\|^2_{L^2([0,t],X)},
\end{aligned}$$

which leads to

$$\frac{1}{2}\|a(t)\|_H^2 + \frac{\lfloor M \rfloor}{2} \int_0^t \|a(s)\|_X^2 \mathrm{d}s \leq \frac{1}{2}\|a(0)\|_H^2 + \frac{1}{2\lfloor M \rfloor}\|f\|^2_{L^2([0,t],X^*)}.$$

We get by estimating the terms of the left-hand side separately and taking the supremum over $t \in I$ both

$$\|a\|^2_{C^0(I,L^2(\Omega))} \leq \|a(0)\|_H^2 + \frac{1}{\lfloor M \rfloor}\|f\|^2_{L^2(I,X^*)} \quad \text{and} \quad \|a\|_{L^2(I,X)} \leq \|a(0)\|_H^2 + \frac{1}{\lfloor M \rfloor^2}\|f\|^2_{L^2(I,X^*)}.$$

To estimate the $L^2(I, X)^*$ norm of $d_t a$, we use that a is the solution of the parabolic equation to estimate

$$\begin{aligned}
\|d_t a\|_{L^2(I,X)^*} &= \sup_{\|\varphi\|_{L^2(I,X)\leq 1}} \int_I \langle d_t a, \varphi\rangle_X \mathrm{d}t \\
&\leq \sup_{\|\varphi\|_{L^2(I,X)\leq 1}} \left[\int_I |\langle Ma, \varphi\rangle_X| \mathrm{d}t + \int_I |\langle f, \varphi\rangle_X| \mathrm{d}t\right] \\
&\leq \|M\|_{\mathcal{L}(X,X^*)}\|a\|_{L^2(I,X)} + \|f\|_{L^2(I,X^*)}.
\end{aligned}$$

If we infer the previous estimates for a in $L^2(I, X)$ norm, we can bound $d_t a$ in $L^2(I, X)^*$ norm. Combining the considerations for a and $d_t a$ lets us bound the $H^1(I, X, X^*)$ as desired. □

Lemma 28 ($L^p(I, C^\alpha(\Omega))$ Bound for (a_k))**.** *Assume $\Omega \subset \mathbb{R}^d$ with $d = 1, 2, 3$ and $\partial\Omega = \Gamma_N \cup \Gamma_D$ where $\Omega \cup \Gamma_N$ is Gröger regular. Let $D \in L^\infty(\Omega, \mathcal{M}_s)$ be uniformly elliptic with ellipticity constant $\lfloor D \rfloor > 0$, $k > 0$, $f \in L^p(I, L^2(\Omega))$ for a fixed $p > 2$ and $a_0 \in L^\infty(\Omega)$ some essentially bounded initial condition. Then there exists $\alpha = \alpha(p) \in (0, 1)$ independent of D and f such that the solution $a \in H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*)$ to*

$$\int_I \langle d_t a, \cdot \rangle_{H^1_D(\Omega)} \mathrm{d}t + \iint D\nabla a \nabla \cdot + ka \cdot \mathrm{d}x\mathrm{d}t = \iint f \cdot \mathrm{d}x\mathrm{d}t$$
$$a(0) = a_0$$

is a member of $L^p(I, C^\alpha(\Omega))$ and satisfies the estimate

$$\|a\|_{L^p(I, C^\alpha(\Omega))} \le C\left(p, \lfloor D \rfloor, \|D\|_{L^\infty(\Omega, \mathcal{M}_s)}\right) \|f\|_{L^p(I, L^2(\Omega))}.$$

Proof. The proof requires some work, we refer to Section II. □

Remark 29. We comment on some of the aspects leading to the complexity of the proof of Lemma 28.

(i) The mixed boundary conditions, rough coefficients and the jump initial condition prevents the standard theory from being applicable. If it wasn't for this roughness, an $L^2(I, H^2(\Omega))$ result could be derived by standard theory, see for instance Evans (1998).

(ii) Even invoking the theory of abstract parabolic equations as described in Amann (1995) does only almost suffice. In fact, combining the results in Amann (1995) with Haller-Dintelmann et al. (2009) yields $L^2(I, C^\alpha(\Omega))$ regularity only if a_0 lies in a suitable trace space for initial conditions. The trace space in this case is $H^1_D(\Omega)$ and not $L^\infty(\Omega)$.

(iii) The strategy to prove Lemma 28 is therefore to treat the cases $f = 0$, $a(0) = a_0$ and $f = f$, $a(0) = 0$ separately and then to use the superposition principle available for linear equations.

We treat now the cell ODE. We need to establish that a solution in $W^{1,2}(I, C^\alpha(\Omega))$ exists and is suitably bounded in the data. We have already access to the fact that a long-time solution in $W^{1,2}(I, C^0(\Omega))$ exists, hence the crucial part is to control the Hölder norm of this solution. This can be done by accessing the solution c through its formulation as a fixed-point and then estimating its Hölder norm if suitable regularity for the data is given.

Lemma 30. *Let a_1 and a_2 be functions in $L^4(I, C^\alpha(\Omega))$ with $a_1, a_2 \ge 0$. Assume that $\rho \in C^\alpha(\Omega)$ satisfies $0 < \rho < 1$ and k_6 and k_7 are positive constants. Then there exists a solution $c \in W^{1,2}(I, C^0(\Omega))$ to the equation*

$$d_t c = k_6 a_1 a_2 (1 + k_7 c)\left(1 - \frac{c}{1 - \rho}\right), \quad c(0) = 0$$

with $0 \le c \le 1$. Furthermore, we can control the α-Hölder seminorm of c in the following way

$$\lfloor c(t) \rfloor_\alpha \le C\left(\|a_1\|_{L^2(I, C^\alpha(\Omega))}, \|a_2\|_{L^2(I, C^\alpha(\Omega))}, \|\rho\|_{C^\alpha(\Omega)}\right),$$

with the constant C being monotone in its arguments.

Proof. The existence of a solution in the space $W^{1,2}(I, C^0(\Omega))$ was already established in Theorem 9. We are only concerned with the control over the Hölder seminorm. To simplify notation, we prove the statement for an ODE of the form

$$d_t c = m(1 + c)(1 - \theta c), \quad c(0) = 0 \tag{3.22}$$

with $m \in L^2(I, C^\alpha(\Omega))$ and $\theta \in C^\alpha(\Omega)$ with $0 < \theta^{-1}(x) < 1$, which implies that the solution c to (3.22) takes values in the unit interval, i.e., $c(t, x) \in [0, 1]$, see Lemma 77. The existence of c in $W^{1,2}(I, C^0(\Omega))$ solving (3.22) implies upon applying integrating that $c(t)$ is given by

$$c(t) = \int_0^t m(s)(1 + c(s))(1 - \theta c(s)) \mathrm{d}s,$$

with the integral being a $C^0(\Omega)$ valued Bochner integral. As point evaluation at $x \in \overline{\Omega}$ is continuous and linear from $C^0(\Omega)$ to $\mathbb{R}$, it also holds

$$c(t, x) = \int_0^t m(s, x)(1 + c(s, x))(1 - \theta(x) c(s, x)) \mathrm{d}s.$$

We use the above formula and the triangle inequality to estimate

$$|c(t,x)-c(t,y)| \leq \underbrace{\int_0^t |m(s,x)-m(s,y)|\mathrm{d}s}_{=:A} + \underbrace{\int_0^t |m(s,x)c(s,x)-m(s,y)c(s,y)|\mathrm{d}s}_{=:B}$$
$$+ \underbrace{\int_0^t |m(s,y)\theta(y)c(s,y)-m(s,x)\theta(x)c(s,x)|\mathrm{d}s}_{=:C}$$
$$+ \underbrace{\int_0^t |m(s,y)\theta(y)c(s,y)^2-m(s,x)\theta(x)c(s,x)^2|\mathrm{d}s}_{=:D}.$$

For brevity, we set $\tilde{m}(t,x) = m(t,x)\theta(x)$. Inferring that c takes values in $[0,1]$, we claim that the above estimate leads to

$$|c(t,x)-c(t,y)| \leq \int_0^t \Big(2\lfloor m(s)\rfloor_\alpha + \|m(s)\|_{C^0(\Omega)}\lfloor c(s)\rfloor_\alpha + 3\|\tilde{m}(s)\|_{C^0(\Omega)}\lfloor c(s)\rfloor_\alpha + 2\lfloor\tilde{m}(s)\rfloor_\alpha\Big)|x-y|^\alpha \mathrm{d}s. \tag{3.23}$$

Dividing by $|x-y|^\alpha$ and taking the supremum over pairs $(x,y)\in\overline{\Omega}^2$ with $x\neq y$ we get

$$\lfloor c(t)\rfloor_\alpha \leq \int_0^t \underbrace{2\left(\lfloor m(s)\rfloor_\alpha + \lfloor\tilde{m}(s)\rfloor_\alpha\right)}_{=:\alpha(s)} + \underbrace{\Big(\|m(s)\|_{C^0(\Omega)} + 3\|\tilde{m}(s)\|_{C^0(\Omega)}\Big)}_{=:\beta(s)}\lfloor c(s)\rfloor_\alpha \mathrm{d}s.$$

Hence, by Grönwall's lemma we get

$$\lfloor c(t)\rfloor_\alpha \leq \Big(1+\|\beta\|_{L^1(I)}\exp\Big(\|\beta\|_{L^1(I)}\Big)\Big)\|\alpha\|_{L^1(I)}$$

with

$$\|\alpha\|_{L^1(I)} \leq 2\|m\|_{L^1(I,C^\alpha(\Omega))} + 2\|\tilde{m}\|_{L^1(I,C^\alpha(\Omega))}$$
$$\|\beta\|_{L^1(I)} \leq \|m\|_{L^1(I,C^0(\Omega))} + 3\|\tilde{m}\|_{L^1(I,C^0(\Omega))}.$$

As for a bounded intervals the L^2 norm dominates the L^1 norm, we are done, given we still provide the details of the computations that led to (3.23). To this end, note that we may estimate (A) by

$$\int_0^t |m(s,x)-m(s,y)|\mathrm{d}s \leq \int_0^t \lfloor m(s)\rfloor_\alpha |x-y|^\alpha \mathrm{d}s.$$

Using the triangle inequality and the pointwise properties of c, we estimate (B) by

$$\int_0^t |m(s,x)c(s,x)-m(s,y)c(s,y)|\mathrm{d}s \leq \int_0^t |m(s,x)|\lfloor c(s)\rfloor_\alpha|x-y|^\alpha\mathrm{d}s + \int_0^t |c(s,y)|\lfloor m(s)\rfloor_\alpha|x-y|^\alpha\mathrm{d}s$$
$$\leq \int_0^t \|m(s)\|_{C^0(\Omega)}\lfloor c(s)\rfloor_\alpha|x-y|^\alpha\mathrm{d}s + \int_0^t \lfloor m(s)\rfloor_\alpha|x-y|^\alpha\mathrm{d}s.$$

Using again the abbreviation $\tilde{m}=m\theta$ and noting that $\tilde{m}$ has the same regularity as m, we can estimate the term (C) in analogy to term (B) by

$$\int_0^t |m(s,y)\theta(y)c(s,y)-m(s,x)\theta(x)c(s,x)|\mathrm{d}s \leq \int_0^t \|\tilde{m}(s)\|_{C^0(\Omega)}\lfloor c(s)\rfloor_\alpha|x-y|^\alpha + \int_0^t \lfloor\tilde{m}(s)\rfloor_\alpha|x-y|^\alpha\mathrm{d}s.$$

To estimate (D) we need to split the term

$$(D) = \underbrace{\int_0^t |\tilde{m}(s,y)|\left|c(s,y)^2-c(s,x)^2\right|\mathrm{d}s}_{=:D_1} + \underbrace{\int_0^t |c(s,x)|^2\left|\tilde{m}(s,y)-\tilde{m}(s,x)\right|\mathrm{d}s}_{=:D_2}.$$

Using $c(s,y)^2 - c(s,x)^2 = c(s,y)(c(s,y) - c(s,x)) + c(s,x)(c(s,y) - c(s,x))$ and $c(s,x) \in [0,1]$, we estimate (D_1)

$$\begin{aligned}(D_1) &\leq \int_0^t |\tilde{m}(s,y)|\,|c(s,y)|\,\lfloor c(s)\rfloor_\alpha |x-y|^\alpha + |\tilde{m}(s,y)|\,|c(s,x)|\,\lfloor c(s)\rfloor_\alpha |x-y|^\alpha \mathrm{d}s \\ &\leq \int_0^t 2|\tilde{m}(s,y)|\,\lfloor c(s)\rfloor_\alpha |x-y|^\alpha \mathrm{d}s \\ &\leq \int_0^t 2\|\tilde{m}(s)\|_{C^0(\Omega)}\,\lfloor c(s)\rfloor_\alpha |x-y|^\alpha \mathrm{d}s\end{aligned}$$

and for (D_2)

$$(D_2) \leq \int_0^t |c(s,x)|^2 \lfloor \tilde{m}(s)\rfloor_\alpha |x-y|^\alpha \mathrm{d}s \leq \int_0^t \lfloor \tilde{m}(s)\rfloor_\alpha |x-y|^\alpha \mathrm{d}s.$$

Collecting all estimates yields the claim and the proof is complete. □

Lemma 31. *Let a_1 and a_2 be functions in $L^4(I, C^\alpha(\Omega))$ with $a_1, a_2 \geq 0$. Assume that $\rho \in C^\alpha(\Omega)$ satisfies $0 < \rho < 1$ and k_6 and k_7 are positive constants. Then there exists a unique solution $c \in W^{1,2}(I, C^\alpha(\Omega))$ to the equation*

$$d_t c = k_6 a_1 a_2 (1 + k_7 c)\left(1 - \frac{c}{1-\rho}\right), \quad c(0) = 0$$

with $0 \leq c \leq 1$. Furthermore, we can control the full α-Hölder norm of c in the following way

$$\|c\|_{W^{1,2}(I,C^\alpha(\Omega))} \leq C\left(\|a_1\|_{L^2(I,C^\alpha(\Omega))}, \|a_2\|_{L^2(I,C^\alpha(\Omega))}, \|\rho\|_{C^\alpha(\Omega)}\right),$$

with the constant C being monotone in its arguments.

Proof. We use again the notation

$$d_t c = m(1+c)(1-\theta c), \quad c(0) = 0,$$

where $m \in L^2(I, C^\alpha(\Omega))$ and $m(t,x) \geq 0$ and $\theta \in C^\alpha(\Omega)$. Thus, the inducing function F in the sense of Theorem 74 is given by

$$F : I \times C^\alpha(\Omega) \to C^\alpha(\Omega), \quad F(t,c) = m(t)(1+c)(1-\theta c).$$

To prove the existence of a unique short-time solution in the space $W^{1,2}(I_\delta, C^\alpha(\Omega))$, we need F to be of Carathéodory regularity. Clearly, $F(\cdot, c) : I \to C^\alpha(\Omega)$ is Bochner measurable as m is. Furthermore, $F(t,\cdot) : C^\alpha(\Omega) \to C^\alpha(\Omega)$ is continuous. This is due to the fact that $C^\alpha(\Omega)$ is a Banach algebra.

To proceed, we need a boundedness and a Lipschitz condition on bounded subsets of $C^\alpha(\Omega)$, compare to Theorem 74. To this end, let $B \subset C^\alpha(\Omega)$ be a bounded set. For $c \in B$ we estimate

$$\|F(t,c)\|_{C^\alpha(\Omega)} \leq C\|m(t)\|_{C^\alpha(\Omega)}\|1+c\|_{C^\alpha(\Omega)}\|1-\theta c\|_{C^\alpha(\Omega)}$$

The term $\|1+c\|_{C^\alpha(\Omega)}\|1-\theta c\|_{C^\alpha(\Omega)}$ can be bounded in terms of the measure of Ω, the assumed boundedness of B and the $C^\alpha(\Omega)$ norm of θ. Hence, there exists a constant $C = C(\Omega, \|\theta\|_{C^\alpha(\Omega)}, B)$ such that

$$\|F(t,c)\|_{C^\alpha(\Omega)} \leq C\left(\Omega, \|\theta\|_{C^\alpha(\Omega)}, B\right)\|m(t)\|_{C^\alpha(\Omega)}$$

and by assumption, the map $t \mapsto \|m(t)\|_{C^\alpha(\Omega)}$ is a member of $L^2(I)$. Now, let c and $\bar{c} \in B$ and look at the differences

$$\begin{aligned}\|F(t,c) - F(t,\bar{c})\|_{C^\alpha(\Omega)} &\leq C\|m(t)\|_{C^\alpha(\Omega)}\|(1+c)(1-\theta c) - (1+\bar{c})(1-\theta\bar{c})\|_{C^\alpha(\Omega)} \\ &\leq C\|m(t)\|_{C^\alpha(\Omega)}\left[\|1+\theta\|_{C^\alpha(\Omega)}\|c-\bar{c}\|_{C^\alpha(\Omega)} + \|\theta\|_{C^\alpha(\Omega)}\left\|c^2 - \bar{c}^2\right\|_{C^\alpha(\Omega)}\right].\end{aligned}$$

We look at the quadratic term separately

$$\left\|c^2 - \bar{c}^2\right\|_{C^\alpha(\Omega)} \leq C\|c-\bar{c}\|_{C^\alpha(\Omega)}\|c+\bar{c}\|_{C^\alpha(\Omega)} \leq C(B)\|c-\bar{c}\|_{C^\alpha(\Omega)}.$$

Hence, there exists a function $L_B \in L^2(I)$ such that

$$\|F(t,c) - F(t,\bar{c})\|_{C^\alpha(\Omega)} \leq L_B(t)\|c-\bar{c}\|_{C^\alpha(\Omega)}.$$

Consulting Theorem 74, the estimates above provide the existence of an interval $[0,\delta] = I_\delta$ and a unique function $c \in W^{1,2}(I_\delta, C^\alpha(\Omega))$ solving the ODE.

To show that the solution can be extended to all of $I = [0,T]$, we extend the solution c to the maximal interval $[0,t^*)$ of existence. For any $t_0 \in [0,t^*)$ we set $c_0 = c(t_0)$ and consider the initial value problem

$$d_t c = k_6 a_1 a_2 (1 + k_7 c)\left(1 - \frac{c}{1-\rho}\right), c(t_0) = c_0.$$

Then this has a unique solution in $W^{1,2}([t_0 - \tilde{\delta}, t_0 + \tilde{\delta}] \cap I, C^\alpha(\Omega))$ for some suitable $\tilde{\delta}$. In fact, $\tilde{\delta}$ depends on the $L^2(I, C^\alpha(\Omega))$ norm of $a_1 a_2$, the $C^\alpha(\Omega)$ norm of $(1-\rho)^{-1}$ and the $L^2(I, C^\alpha(\Omega))$ norm of c on $[0,t^*)$. This implies that $\tilde{\delta}$ does not depend on the position of $t_0 \in [0,t^*)$ and thus $t^* = T$ and the interval $[0,t^*)$ can be closed.

Finally, the promised bound on the $W^{1,2}(I, C^\alpha(\Omega))$ norm of c is easily established using $c(t,x) \in [0,1]$ and the estimate on the Hölder seminorm of Lemma 30. □

We show now how to establish the existence of solutions to the bone ODE in the space $W^{1,2}(I, C^\alpha(\Omega))$. Furthermore, we show that the $W^{1,2}(I, C^\alpha(\Omega))$ norm of such solutions can be bounded, given bounded data in the right spaces. This can in principle be done by the same arguments as for the cell equation, however, the bone ODE is linear and thus we can use more elegant approaches.

Lemma 32. *Let X be a Banach algebra and denote by $C_X > 0$ the norm of its multiplication and assume that $p > 1$. By $W^{1,p}_0(I, X)$ we denote the vector-valued Sobolev space with vanishing initial conditions. For a function $m \in L^p(I, X)$ we define the multiplication operator*

$$M : C^0(I, X) \to L^p(I, X), \quad Mv = t \mapsto m(t)v(t).$$

Then the map

$$d_t + M : W^{1,p}_0(I, X) \to L^p(I, X), \quad v \mapsto d_t v + Mv$$

is a linear homeomorphism. Furthermore, given a right-hand side $f \in L^p(I, X)$ we may bound the solution v to $d_t v + Mv = f$ in the following way

$$\|v\|_{W^{1,p}_0(I,X)} \leq C\left(|I|, \|m\|_{L^p(I,X)}, C_X\right) \|f\|_{L^p(I,X)},$$

i.e., the norm of v does only depend on f and m measured in $L^p(I, X)$ norm and the constant C is monotone in these quantities.

Proof. The continuity and linearity of the map $d_t + M$ is clear. Its bijectivity follows as an application of Theorem 71. To this end, note that the inducing function $F : I \times X \to X$ of Theorem 71 is given by

$$F : I \times X \to X, \quad F(t,x) = m(t)x.$$

This is clearly a Carathéodory function and it holds for $x, y \in X$

$$\|F(t,x) - F(t,y)\|_X \leq C\|m(t)\|_X \|x - y\|_X.$$

The function $C\|m(\cdot)\|_X$ is a member of $L^p(I)$ with $p > 1$ and therefore the existence of a unique solution $v \in W^{1,p}_0(I, X)$ is established. To provide the bound, we employ Grönwall's inequality. Note that, by the fundamental theorem, the solution v satisfies the integral identity

$$v(t) = \int_0^t f(s) - m(s)v(s)\mathrm{d}s$$

and consequently the estimate

$$\|v(t)\|_X \leq \int_0^t \|f(s)\|_X + C_X\|m(s)\|_X\|v(s)\|_X \mathrm{d}s.$$

Using Grönwall's inequality yields

$$\|v(t)\|_X \leq \left[1 + C_X\|m\|_{L^1(I,X)} \exp\left(C_X\|m\|_{L^1(I,X)}\right)\right] \cdot \|f\|_{L^1(I,X)}.$$

Clearly, this implies a bound in $C^0(I,X)$ norm for v of the form

$$\|v\|_{C^0(I,X)} \leq C\left(\|m\|_{L^1(I,X)}, C_X\right)\|f\|_{L^1(I,X)}$$

and consequently also in $L^p(I,X)$. To bound $d_t v$, we use the equation satisfied by v and estimate

$$\begin{aligned}\|d_t v\|_{L^p(I,X)} &= \|f - Mv\|_{L^p(I,X)}\\ &\leq \|f\|_{L^p(I,X)} + \|v\|_{C^0(I,X)}\|m\|_{L^p(I,X)}\\ &\leq C\left(|I|, \|m\|_{L^p(I,X)}, C_X\right)\|f\|_{L^p(I,X)}.\end{aligned}$$

□

Lemma 33. *Assume (ρ_k) is a minimizing sequence for $\hat{J} + \eta\|\cdot\|^2_{H^2(\Omega)}$. Then properties $(A1)$-$(A5)$ hold.*

Proof. We begin with $(A1)$. The regularizing term $\eta\|\cdot\|^2_{H^2(\Omega)}$ leads to a $H^2(\Omega)$ bound for any minimizing sequence (ρ_k) of $\hat{J} + \eta\|\cdot\|^2_{H^2(\Omega)}$, as $\hat{J}$ is bounded from below. Then there exists a subsequence (not relabeled) with

$$\rho_k \rightharpoonup \rho^* \quad \text{in } H^2(\Omega).$$

Using the compactness of the embedding $H^2(\Omega) \hookrightarrow\hookrightarrow C^0(\Omega)$, we get

$$\rho_k \to \rho^* \quad \text{in } C^0(\Omega)$$

and inferring the closedness of P in $C^0(\Omega)$ yields $\rho^* \in P$ as desired.

We provide first a weaker statement than $(A2)$. Namely, we prove that (u_k) is bounded uniformly in $C^0(I, H^1(\Omega))$. At the end of the proof, we can show the full validity of $(A2)$. In Setting 2.1 we assumed that the boundary conditions satisfied by u_k are

$$\mathbb{C}(\rho_k, \sigma, b_k)\varepsilon(u_k)\cdot\eta = g_N, \quad u_k = u_D$$

on Γ_N and Γ_D respectively, where $g_N \in C^0(I, L^2(\partial\Omega)) \subset C^0(I, H^{1/2}(\partial\Omega)^*)$ and $u_D \in C^0(I, H^{1+\theta}(\Omega))$ implying that $(u_D)_{|\Gamma_D} \in H^{1/2}(\partial\Omega)$. The unique solutions $\tilde{u}_k \in L^2(I, H^1_D(\Omega))$ to

$$\iint \mathbb{C}(\rho_k, \sigma, b_k)\varepsilon(\tilde{u}_k) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t = \underbrace{\int_I \langle g_N, \cdot\rangle_{H^{1/2}(\partial\Omega)}\mathrm{d}t - \iint \mathbb{C}(\rho_k, \sigma, b_k)\varepsilon(u_D) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t}_{=: f_k \in L^2(I, H^1_D(\Omega))^*} \quad \text{in } L^2(I, H^1_D(\Omega))^* \tag{3.24}$$

have therefore right-hand sides f_k that can be interpreted as members of $C^0(I, H^1_D(\Omega)^*)$. This is due to the assumption $g_N \in C^0(I, H^{1/2}(\partial\Omega)^*)$ and a standard computation that shows that the map

$$t \mapsto \int_\Omega \mathbb{C}(\rho_k, \sigma, b_k)(t)\varepsilon(u_D(t)) : \varepsilon(\cdot)\mathrm{d}x$$

is a member of $C^0(I, H^1_D(\Omega)^*)$. Hence Lemma 23 is applicable and shows that

$$\|\tilde{u}_k\|_{C^0(I, H^1(\Omega))} \leq C\left(\lfloor \mathbb{C}(\rho_k, \sigma, b_k)\rfloor, C_{\text{Korn}}\right)\|f_k\|_{C^0(I, H^1_D(\Omega)^*)}.$$

As $\mathbb{C}$ is coercive and essentially bounded, this estimate can be made independent of $k \in \mathbb{N}$. Clearly, we have not yet proven $(A2)$ but will first continue with the other assumptions.

We are concerned with $(A3)$ now which is an application of Lemma 27. The corresponding Gelfand triple is $(\mathrm{Id}, H^1_D(\Omega), L^2(\Omega))$ and the operators M_k are

$$M_k : H^1_D(\Omega) \to H^1_D(\Omega)^*, \quad M_k a = \int_\Omega D(\rho_k)\nabla a \nabla\cdot + k_3 a \cdot \mathrm{d}x.$$

The coercivity constant of M_k can be estimated from below independently of (ρ_k) by

$$\lfloor M_k \rfloor \geq \min(\lfloor D(\rho_k)\rfloor, k_3).$$

On the other hand, the operator norm of M_k can be estimated to

$$\|M_k\| = \sup_{\|a\|\le 1, \|\varphi\|\le 1} \int_\Omega D(\rho_k)\nabla a \nabla\varphi + k_3 a\varphi \mathrm{d}x \le \|D(\rho_k)\|_{L^\infty(\Omega,\mathcal{M}_s)} + k_3.$$

The right-hand sides of the equation are given by

$$f_k = \iint (k_2|\varepsilon(u_k)|_\delta c_k - k_3)\cdot \mathrm{d}x\mathrm{d}t,$$

consequently their norm can be estimated

$$\begin{aligned}\|f_k\|_{L^2(I,H^1_D(\Omega)^*)} &\le \|f_k\|_{L^2(I,L^2(\Omega)^*)}\\ &\le \left[\iint (k_2|\varepsilon(u_k)|_\delta c_k - k_3)\right]^{1/2}\\ &\le k_2\|c_k\|_{C^0(I\times\Omega)}\|u_k\|_{L^2(I,H^1_D(\Omega))} + |I\times\Omega|^{1/2}k_3.\end{aligned}$$

This is uniformly bound in $k \in \mathbb{N}$ by the bound on (u_k) and the pointwise properties of c_k, i.e., $0 \le c_k \le 1$. Thus we apply Lemma 27 to obtain

$$\begin{aligned}\|a_k\|_{H^1(I,H^1_D(\Omega),H^1_D(\Omega)^*)} &\le C\left(\|M_k\|, \lfloor M_k\rfloor^{-1}\right)\cdot\left(\|a_k(0)\|_{L^2(\Omega)} + \|f_k\|_{L^2(I,H^1_D(\Omega))}\right)\\ &\le C\left(\|D(\rho_k)\|_{L^\infty(\Omega,\mathcal{M}_s)}, \lfloor D(\rho_k)\rfloor^{-1}, k_3\right)\cdot\left(\|a_k(0)\|_{L^2(\Omega)} + \|f_k\|_{L^2(I,H^1_D(\Omega))}\right)\end{aligned}$$

By the ellipticity and boundedness of D, the constant initial conditions $\tilde{a}^i_k(0) \equiv 1$ and the estimate for u_k, we see that (a^i_k) are bounded uniformly in $k \in \mathbb{N}$. Using the reflexivity of the Hilbert space $H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*)$ to produce a weakly convergent subsequence with limit $\tilde{a}^*_i$ we proved $(A3)$.

We proceed with $(A4)$ and aim to apply Lemma 32 to the ODE

$$d_t b_k = k_4 a^1_k\left(1 + \frac{b_k}{1-\rho_k}\right), \quad b_k(0) = 0, \tag{3.25}$$

with $X = C^\alpha(\Omega)$ and $p = 2$. To this end we rearrange (3.25) to

$$d_t b_k - \frac{k_4 a^1_k}{1-\rho_k} b_k = k_4 a^1_k,$$

thus

$$m_k = \frac{k_4 a^1_k}{1-\rho_k} \quad \text{and} \quad f_k = k_4 a^1_k$$

in the notation of Lemma 32. Due to the embedding $H^2(\Omega) \hookrightarrow\hookrightarrow C^\alpha(\Omega)$ in three spatial dimensions, we get $\rho_k \in C^\alpha(\Omega)$ and also $(1-\rho_k)^{-1} \in C^\alpha(\Omega)$ with a uniform bound in Hölder norm. Then, Lemma 32 guarantees that (a^1_k) is bounded uniformly in $L^2(I, C^\alpha(\Omega))$ which implies such a bound for (m_k) and (f_k). We may therefore use Lemma 32 to obtain

$$\|b_k\|_{W^{1,2}(I,C^\alpha(\Omega))} \le C\left(I, C_{C^\alpha(\Omega)}, \|m_k\|_{L^2(I,C^\alpha(\Omega))}\right)\|f_k\|_{L^2(I,C^\alpha(\Omega))}$$

and guarantee that the bound is independent of $k \in \mathbb{N}$. Furthermore, we have the compact embedding

$$W^{1,2}(I, C^\alpha(\Omega)) \hookrightarrow\hookrightarrow C^0(I\times\Omega).$$

This yields the relative compactness of (b_k) in $C^0(I\times\Omega)$ and thus the existence of $b^* \in C^0(I\times\Omega)$ and a (not relabeled) subsequence with

$$b_k \to b^*.$$

To provide the existence of c^* and a subsequence $c_k \to c^*$ in $C^0(I\times\Omega)$, we note that Lemma 31 provides a bound of the $W^{1,2}(I, C^\alpha(\Omega))$ norm of c_k of the form

$$\|c_k\|_{W^{1,2}(I,C^\alpha(\Omega))} \le C\left(\|a^k_1\|_{L^2(I,C^\alpha(\Omega))}, \|a^k_2\|_{L^2(I,C^\alpha(\Omega))}, \|\rho\|_{C^\alpha(\Omega)}\right)$$

with C being increasing in its arguments. As we proved suitable bounds for (a_1^k), (a_2^k) and (ρ_k) this yields a $W^{1,2}(I, C^\alpha(\Omega))$ bound for (c_k) that does not depend on $k \in \mathbb{N}$. Therefore, the sequence (c_k) is relatively compact in $C^0(I \times \Omega)$ and $(A5)$ follows.

We are still left with showing the existence of a subsequence of (u_k) and a function $u^* \in C^0(I, H^1(\Omega))$ such that

$$u_k \to u^* \quad \text{in } C^0(I, H^1(\Omega)).$$

To this end, note that we have established that (b_k) is relatively compact in $C^0(I, C^0(\Omega))$. Hence, applying the Arzelà-Ascoli Theorem, (b_k) is equi-continuous as well. Now, going back to (3.24) we can easily compute that the sequence (f_k) is indeed equi-continuous in $C^0(I, H_D^1(\Omega)^*)$. Again, this is essentially due to the equi-continuity of (b_k) in the space $C^0(I, C^0(\Omega))$. Hence, applying Lemma 24 yields the equi-continuity of (u_k) in $C^0(I, H^1(\Omega))$. In view of the Arzelà-Ascoli Theorem we still need to show that the sets

$$\{u_k(t) \in H^1(\Omega) \mid k \in \mathbb{N}\}$$

are relatively compact in $H^1(\Omega)$. This can be established by looking at the equation satisfied by $u_k(t)$ for every fixed $t \in I$ and applying Lemma 25. Indeed, $u_k(t) = \tilde{u}_k(t) + u_D(t)$ satisfies

$$\int_\Omega \mathbb{C}(\rho_k, \sigma, b_k)(t)\varepsilon(u_0^k(t)) : \varepsilon(\cdot)\mathrm{d}x = \int_{\partial\Omega} g_N(t) \cdot \mathrm{d}s - \int_\Omega \mathbb{C}(\rho_k, \sigma, b_k)(t)\varepsilon(u_D(t)) : \varepsilon(\cdot)\mathrm{d}x.$$

The assumptions on g_N and u_D guarantee that the right-hand side lies in $H^{1-\theta}(\Omega)^*$ and the Hölder regularity established for (b_k), i.e., $(b_k(t)) \subset C^\alpha(\Omega)$ allows to deduce the $H^{1+\theta}(\Omega)$ regularity for $u_k(t)$. Additionally, the uniform $W^{1,2}(I, C^\alpha(\Omega))$ bound for the sequence (b_k) established before yields a bound for the $C^\alpha(\Omega)$ norm of $(b_k(t))$ and also the coefficients of $\mathbb{C}(\rho_k, \sigma, b_k)$ via assumption (3.10). Collecting these bounds in fact implies that

$$\sup_{k\in\mathbb{N}} \|u_k(t)\|_{H^{1+\theta}(\Omega)} \leq C$$

and invoking the compactness result of Rellich which states that

$$H^{1+\theta}(\Omega) \hookrightarrow\hookrightarrow H^1(\Omega)$$

we can conclude the missing piece in order to apply the Arzelà-Ascoli Theorem to (u_k) in the space $C^0(I, H_D^1(\Omega))$. This eventually guarantees the validity of assumption $(A2)$. □

We can now conclude the Section by providing the proofs of Theorem 18 and Corollary 19.

Proof of Theorem 18. Let $(\rho_k) \subset P$ be a minimizing sequence for $\hat{J} + \eta\|\cdot\|^2_{H^2(\Omega)}$. Lemma 33 shows that the assumptions $(A1) - (A5)$ hold and Proposition 21 shows that this leads to the existence of an accumulation point $\rho^* \in P$ of the sequence (ρ_k) which is a minimizer of $\hat{J} + \eta\|\cdot\|^2_{H^2(\Omega)}$. □

Proof of Corollary 19. Let $(\rho_k) \subset H^2(\Omega)$ be a minimizing sequence for $\hat{J} + \eta\|\cdot\|^2_{H^2(\Omega)} + \mathcal{K}$. Revisiting the proof of Proposition 21 shows that the additional term $\mathcal{K}$ does not lead to complications in the lower semicontinuity as it is assumed to be continuous on $C^0(I \times \Omega)$, i.e., a compact perturbation. Furthermore, as we assumed that $\mathcal{K}$ takes non-negative values only, also the coercivity of the objective function is not violated through the addition of $\mathcal{K}$. □

III Rigorous Derivation of Reduced Derivative

In this Section, we want to apply the adjoint approach for the computation of the derivative of the reduced objective function

$$D\hat{J}(\rho_0) = -e_\rho^*(\phi(\rho_0), \rho_0)\Big[e_y^{-*}(\phi(\rho_0), \rho_0)\Big(J_y(\phi(\rho_0), \rho_0)\Big)\Big] + J_\rho(\phi(\rho_0), \rho_0),$$

compare also to Section I for a derivation of this formula. We still essentially work with the system (3.6), for which we already established the existence of an optimal control in the previous Section. However, we need to make some minor adaptions ensuring the differentiabilty of the solution operator ϕ. The precise requirements are collected in Section 3.1.

Our goal with respect to the above formula is to rigorously derive a formulation of the adjoint equations that is useful from an implementations viewpoint. The main difficulty we are facing are the spaces associated to the time dependent equations, compare to the definition of the choice of state space Y in (3.27). For these spaces convenient characterizations of their dual spaces are not known. This forces us to derive regularity properties of the associated adjoint equation by hand.

We illustrate this problem with an example. Let $m \in L^2(I, C^0(\Omega))$ be a fixed function, where $\Omega \subset \mathbb{R}^d$ is some bounded domain. We consider the Banach space valued, linear ODE

$$d_t + m : W_0^{1,2}(I, C^0(\Omega)) \to L^2(I, C^0(\Omega)), \quad v \mapsto d_t v + mv.$$

Here, the zero subscript in the space $W_0^{1,2}(I, C^0(\Omega))$ indicates vanishing initial conditions. Note that by Theorem 71 $d_t + m$ is well posed and a linear homeomorphism. In the adjoint approach, we are – among other types – forced to consider the adjoint of a map of the above form, i.e.,

$$(d_t + m)^* : L^2(I, C^0(\Omega))^* \to W_0^{1,2}(I, C^0(\Omega))^*, h^* \mapsto h^* [d_t \cdot + m \cdot].$$

The problem now is that the space $L^2(I, C^0(\Omega))^*$ lacks a convenient description of its dual. However, given a member of $W_0^{1,2}(I, C^0(\Omega))^*$ of the form

$$\iint f \cdot \mathrm{d}x\mathrm{d}t$$

for a function, say in $L^2(I, L^1(\Omega))$, we are able to show that instead of solving

$$h^* [d_t \cdot + m \cdot] = \iint f \cdot \mathrm{d}x\mathrm{d}t, \quad \text{in } W_0^{1,2}(I, C^0(\Omega))^*$$

we may solve for $h \in W^{1,2}(I, L^1(\Omega))$ satisfying

$$-d_t h + mh = f, \quad \text{with} \quad h(T) = 0$$

for the final time T. For us, the advantage lies in the fact that the latter is easy to solve numerically. Similar problems arise when considering the adjoint diffusion equations, as these are – due to regularity issues – posed on inconvenient function spaces as well. The details can be found in the Appendix IV.

3.1 Setting

We essentially keep the Setting 2.1. However, we work with more concrete assumptions on $\mathbb{C}$, D, $|\cdot|_\delta$ and J. We also need to take into account that we compute derivatives, hence some additional differentiability assumptions are required. The remaining assumptions of Section 2.1 are still valid. In detail we need the following.

(i) For the material tensor we use the Voigt bound

$$\mathbb{C}(\sigma, \rho, b) = \sigma\rho\mathbb{C}_p + b\mathbb{C}_b$$

where $\mathbb{C}_p$ and $\mathbb{C}_b$ are two linear isotropic material, coercive tensors, e.g., corresponding to PCL and bone.

(ii) We also choose a concrete ansatz for the diffusivity, namely the one used earlier in the numerical simulations in Chapter 2

$$D(\rho) = k_5(1 - \rho),$$

where k_5 was some positive parameter.

(iii) In addition to the Lipschitz continuity and grwoth condition for $|\cdot|_\delta$, we require $|\cdot|_\delta : \mathbb{R}^{d\times d} \to \mathbb{R}$ to induce a Fréchet differentiable Nemyckii operator. More precisely, we assume that

$$N_{|\cdot|_\delta} : L^2(\Omega, \mathbb{R}^{d\times d}) \to L^2(\Omega), (x \mapsto f(x)) \mapsto (x \mapsto |f(x)|_\delta)$$

is Fréchet differentiable. This entails differentiability of $|\cdot|_\delta$ and the derivative of $N_{|\cdot|_\delta}$ is given by

$$DN_{|\cdot|_\delta}(f_0)f = x \mapsto D|\cdot|_\delta(f_0(x))f(x)$$

where $f, f_0 \in L^2(\Omega, \mathbb{R}^{d\times d})$.

(iv) Finally, the objective function is chosen to be

$$J(y, \rho) = \left\|\mathcal{E}(y, \rho)\right\|_{L^p(I)} = \frac{1}{2}\left\|\int_\Omega \mathbb{C}(\sigma, \rho, b)\varepsilon(u + u_D) : \varepsilon(u + u_D)\mathrm{d}x\right\|_{L^p(I)}. \tag{3.26}$$

The $L^p(I)$ norm is used as a smooth approximation of a minimum or maximum over all time-points, depending on the signum of the exponent p.

3.2 The Derivative of the Energy

As we are interested in the differentiability and the derivatives of the map $\rho \mapsto J(\phi(\rho), \rho)$ we clearly need to compute

$$J_y(\phi(\rho), \rho), \quad \text{and} \quad J_\rho(\phi(\rho), \rho).$$

A glimse in formula (3.3) reveals that the former enters in the computation of $D\hat{J}(\rho)$ as the right-hand side of the adjoint equation and the latter is an additive term.

The structural assumption on J is

$$J = \|\cdot\|_{L^p(I)} \circ \mathcal{E},$$

where p can be negative and positive and $\mathcal{E}$ is the elastic energy, see (3.26). Fréchet differentiability of $L^p(I)$ norms with respect to the natural norm and $p \in (1, \infty)$ are is well established, see for instance Werner (2006). However, for negative values of p the choice of a "natural" domain is not so clear. In the $L^p(I)$ topology, the subset of positive functions bounded away from zero is not an open set. A convenient way to get around these question is to consider $\|\cdot\|_{L^p(I)}$ only on the set

$$\left\{ f \in C^0(I) \mid f(t) > 0 \text{ for all } t \in I \right\} \subset C^0(I).$$

This integrates well with $\mathcal{E}$, since in Lemma 15 we established that $\mathcal{E}(y, \rho)$ is a member of $C^0(I)$ and if $y = \phi(\rho)$ then it holds $\mathcal{E}(\phi(\rho), \rho)(t) > 0$ for all $t \in I$. Hence we analyze J defined on

$$Y \times P = C^0(I, H^1_{D_e}(\Omega)) \times H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*)^2 \cap L^2(I, C^0(\Omega))^2 \times W^{1,2}_0(I, C^0(\Omega)) \times W^{1,2}_0(I, C^0(\Omega)) \times P.$$

Theorem 34. *Let $(\phi(\rho_0), \rho_0) = (y_0, \rho_0) \in Y \times P$ be a state-control pair, i.e., $e(y_0, \rho_0) = 0$. Then the derivatives of J at (y_0, ρ_0) are given by*

$$\begin{aligned}
J_u(y_0, \rho_0) &= J(y_0, \rho_0)^{1-p} \iint \mathcal{E}(y_0, \rho_0)^{p-1} \mathbb{C}(\rho_0, \sigma, b_0)\varepsilon(u_0 + u_D) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t \in C^0(I, H^1_{D_e}(\Omega))^* \\
J_b(y_0, \rho_0) &= \frac{1}{2} J(y_0, \rho_0)^{1-p} \iint \mathcal{E}(y_0, \rho_0)^{p-1} C_b \varepsilon(u_0 + u_D) : \varepsilon(u_0 + u_D) \cdot \mathrm{d}x\mathrm{d}t \in C^0(I \times \Omega)^* \\
J_\rho(y_0, \rho_0) &= \frac{1}{2} J(y_0, \rho_0)^{1-p} \iint \mathcal{E}(y_0, \rho_0)^{p-1} \sigma C_\rho \varepsilon(u_0 + u_D) : \varepsilon(u_0 + u_D) \cdot \mathrm{d}x\mathrm{d}t \in C^0(\Omega)^* \\
J_{a_1}(y_0, \rho_0) &= J_{a_2}(y_0, \rho_0) = J_c y_0, \rho_0 = 0.
\end{aligned}$$

Furthermore, it will be useful for the computations in the adjoint system to concretize the abstract functionals above. We set

$$\begin{aligned}
f_{J_u(y_0,\rho_0)} &= J(y_0, \rho_0)^{1-p} \int_\Omega \mathcal{E}(y_0, \rho_0)^{p-1} \mathbb{C}(\rho_0, \sigma, b_0)\varepsilon(u_0 + u_D) : \varepsilon(\cdot)\mathrm{d}x \in C^0(I, H^1_{D_e}(\Omega)^*) \\
f_{J_b(y_0,\rho_0)} &= \frac{1}{2} J(y_0, \rho_0)^{1-p} \mathcal{E}(y_0, \rho_0)^{p-1} C_b \varepsilon(u_0 + u_D) : \varepsilon(u_0 + u_D) \in C^0(I, L^1(\Omega)) \\
f_{J_\rho(y_0,\rho_0)} &= \frac{1}{2} J(y_0, \rho_0)^{1-p} \int_I \mathcal{E}(y_0, \rho_0)^{p-1} \sigma C_\rho \varepsilon(u_0 + u_D) : \varepsilon(u_0 + u_D)\mathrm{d}t \in L^1(\Omega).
\end{aligned}$$

Using the above notation it holds

$$\begin{aligned}
J_u(y_0, \rho_0) &= \int_I \langle f_{J_u(y_0,\rho_0)}, \cdot \rangle_{H^1_{D_e}(\Omega)} \mathrm{d}t \in C^0(I, H^1_{D_e}(\Omega))^*, \\
J_b(y_0, \rho_0) &= \int_I \int_\Omega f_{J_b(y_0,\rho_0)} \cdot \mathrm{d}x\mathrm{d}t \in C^0(I \times \Omega)^*, \\
J_\rho(y_0, \rho_0) &= \int_\Omega f_{J_\rho(y_0,\rho_0)} \cdot \mathrm{d}x \in C^0(\Omega)^*.
\end{aligned}$$

Remark 35. The structure of the derivatives of J is crucial in deriving regularity properties of the adjoint equation in Theorem 44.

Proof. We compute, using the chain rule

$$\begin{aligned}
DJ(y_0,\rho_0) &= D\left(\|\cdot\|_{L^p(I)}\circ\mathcal{E}\right)(y_0,\rho_0)\\
&= D\|\cdot\|_{L^p(I)}\left(\mathcal{E}(y_0,\rho_0)\right)\circ D\mathcal{E}(y_0,\rho_0)\\
&= \left[\left\|\mathcal{E}(y_0,\rho_0)\right\|_{L^p(I)}^{1-p}\int_I\left[\mathcal{E}(y_0,\rho_0)\right]^{p-1}\cdot\mathrm{d}t\right]\circ D\mathcal{E}(y_0,\rho_0).
\end{aligned}$$

In the last step above we exploited that $\mathcal{E}(y_0,\rho_0)$ takes values in the set $\{f\in C^0(I)\mid f(t)>0\text{ for all }t\in I\}$ and that $\|\cdot\|_{L^p(I)}$ is Fréchet differentiable on this set for all $p\in\mathbb{R}\setminus\{0\}$ with the respective formula. This is proven in detail in Lemma 37. To get the partial derivatives, we need to replace $D\mathcal{E}$ by the respective partial derivative. These partial derivatives are given by

$$\mathcal{E}_u(y_0,\rho_0)=\int_\Omega\mathbb{C}(\rho,\sigma,b)\varepsilon(u_0+u_D):\varepsilon(\cdot)\mathrm{d}x\in\mathcal{L}(C^0(I,H^1_{D_e}(\Omega)),C^0(I)),$$

where we used that $u\mapsto\mathcal{E}(y,\rho)$ is the composition of a translation $u\mapsto u+u_D$ and a continuous, bilinear map. The partial derivative in direction of b is given by

$$\mathcal{E}_b(y_0,\rho_0)=\frac{1}{2}\int_\Omega C_b\varepsilon(u_0+u_D):\varepsilon(u_0+u_D)\cdot\mathrm{d}x\in\mathcal{L}(C^0(I\times\Omega),C^0(I))$$

and

$$\mathcal{E}_\rho(y_0,\rho_0)=\frac{1}{2}\int_\Omega\sigma C_p\varepsilon(u_0+u_D)$$

□

Lemma 36. *Let $\Omega\subset\mathbb{R}^d$ be bounded, $f\in C^1(\Omega)$ and $U\subset C^0(\Omega)$ an open set. Define the operator*

$$N:C^0(\Omega)\to C^0(\Omega),\quad N(u)=f\circ u.$$

Then, N is continuously Fréchet differentiable with derivative

$$DN:C^0(\Omega)\to\mathcal{L}(C^0(\Omega)),\quad DN(u_0)v=(f'\circ u_0)\cdot v.$$

Proof. We need to show that for $u_0\in U$ it holds

$$\lim_{t\to0}\sup_{\|v\|_{C^0}\le1}\sup_{x\in\overline{\Omega}}\left|\frac{f(u_0(x)+tv(x))-f(u_0(x))}{t}-f'(u_0(x))v(x)\right|=0.$$

The uniformity of v in the unit ball of $C^0(\Omega)$ is the crucial fact that is necessary for the existence of the Fréchet differential. To this end, we define the auxiliary function

$$\phi:[0,\varepsilon]\times[-1,1]\times u_0(\overline{\Omega})\to\mathbb{R},\quad(t,v,u)\mapsto\begin{cases}0, & \text{if }t=0\\ \left|\frac{f(u+tv)-f(u)}{t}-f'(u)v\right|, & \text{if }t\neq0.\end{cases}$$

As f' is continuous, the function ϕ is and as a continuous function defined on a compact set, ϕ is uniformly continuous. □

Lemma 37 (Derivative of $L^p(I)$ Norms)**.** *Let $p\in\mathbb{R}\setminus\{0\}$ and $I=[0,T]$ for some $T>0$. Then the function $\|\cdot\|_{L^p(I)}$ is Fréchet differentiable as a map*

$$\|\cdot\|_{L^p(I)}:\left\{u\in C^0(I)\mid u(t)>0\ \forall t\in I\right\}\subset C^0(I)\to\mathbb{R},\quad u\mapsto\left[\int_I u^p\mathrm{d}t\right]^{\frac{1}{p}}$$

with derivative

$$D\|\cdot\|_{L^p(I)}(u)v=\|u\|_{L^p(I)}^{1-p}\int_I u^{p-1}v\mathrm{d}t.$$

Proof. We factorize $\|\cdot\|_{L^p(I)}$

$$\|\cdot\|_{L^p(I)} = \sqrt[p]{\cdot} \circ \int_I (\cdot)\mathrm{d}t \circ N,$$

where N denotes the Nemyckii operator

$$N : \left\{u \in C^0(I) \mid u(t) > 0 \ \forall t \in I\right\} \to C^0(I), \quad N(u) = x \mapsto u(x)^p.$$

Clearly, the domain of N is open in $C^0(I)$ and the inducing function $x \mapsto x^p$ is smooth, hence N is Fréchet differentiable with derivative

$$DN(u)v = x \mapsto pu(x)^{p-1}v(x),$$

as established in the previous Lemma. Using the chain rule we compute the derivative of $\|\cdot\|_{L^p(I)}$

$$\begin{aligned}
D\|\cdot\|_{L^p(I)}(u)v &= D\left(\sqrt[p]{\cdot} \circ \int_I (\cdot)\mathrm{d}t \circ N\right)(u)v \\
&= D\left(\sqrt[p]{\cdot}\right)\left(\int_I N(u)\mathrm{d}t\right) \cdot \int_I DN(u)v\mathrm{d}t \\
&= \frac{1}{p}\left[\int_I u^p \mathrm{d}t\right]^{\frac{1}{p}-1} \cdot \int_I pu^{p-1}\mathrm{d}t \\
&= \|u\|^{1-p} \int_I u^{p-1}v\mathrm{d}t,
\end{aligned}$$

where we used $\frac{1}{p} - 1 = \frac{1}{p}(1-p)$ in the last step. This establishes the asserted formula. $\square$

3.3 Adjoint Maps between Product Spaces

Before we start, we repeat a simple characterization of the adjoint map between Cartesian product spaces, this will facilitate the later treatment. Our statement treats the case of a linear operator that maps from a product space of two factors into another product space with two factors. The generalization to more factors is straight forward.

Lemma 38 (Adjoint of Product Maps)**.** *Let X_1, X_2, Y_1 and Y_2 be Banach spaces and let $F : X_1 \times X_2 \to Y_1 \times Y_2$ be linear and denote by $F(x_1, x_2) = (T(x_1, x_2), S(x_1, x_2))$ where $T = F_1 : X_1 \times X_2 \to Y_1$ and $S = F_2 : X_1 \times X_2 \to Y_2$. Then F can be computed by the formal matrix-vector product*

$$F(x_1, x_2) = \begin{pmatrix} T(\cdot, 0) & T(0, \cdot) \\ S(\cdot, 0) & S(0, \cdot) \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

where $T(\cdot, 0) : X_1 \to Y_1$, $T(0, \cdot) : X_2 \to Y_1$, $S(\cdot, 0) : X_1 \to Y_2$ and $S(0, \cdot) : X_2 \to Y_2$. We are interested to bring the adjoint map of F into a similar form. To that end consider the linear homeomorphisms

$$\phi : Y_1^* \times Y_2^* \to (Y_1 \times Y_2)^*, \quad (y_1^*, y_2^*) \mapsto \left((y_1, y_2) \mapsto y_1^*(y_1) + y_2^*(y_2)\right)$$

and

$$\psi : (X_1 \times X_2)^* \to X_1^* \times X_2^*, \quad \xi^* \mapsto (x_1 \mapsto \xi^*(x_1, 0), x_2 \mapsto \xi^*(0, x_2)).$$

Using ϕ and ψ we define

$$F^\dagger : Y_1^* \times Y_2^* \to X_1^* \times X_2^*, \quad F^\dagger := \psi \circ F^* \circ \phi.$$

Then $F^\dagger$ is given by

$$F^\dagger(y_1^*, y_2^*) = \begin{pmatrix} T(\cdot, 0)^* & S(\cdot, 0)^* \\ T(0, \cdot)^* & S(0, \cdot)^* \end{pmatrix} \begin{pmatrix} y_1^* \\ y_2^* \end{pmatrix}.$$

Proof. To see that ϕ and ψ are in fact homeomorphisms note that, if $Y_1 = X_1$ and $Y_2 = X_2$ it holds $\mathrm{Id} = \phi \circ \psi = \psi \circ \phi$ and the continuity of ψ and ϕ is plain. If the spaces X_i and Y_i are different for $i = 1, 2$ then one can still construct inverses to ϕ and ψ in an analogue fashion. Hence the maps are invertible and continuous thus linear homeomorphisms. Now to the proposed structure of $F^\dagger$; for $(y_1^*, y_2^*) \in Y_1^* \times Y_2^*$ and $(x_1, x_2) \in X_1 \times X_2$ we compute

$$\begin{aligned}
\left\langle (F^* \circ \phi)(y_1^*, y_2^*), (x_1, x_2) \right\rangle &= \left\langle \phi(y_1^*, y_2^*) \circ F, (x_1, x_2) \right\rangle \\
&= y_1^* \left(T(x_1, x_2)\right) + y_2^* \left(S(x_1, x_2)\right).
\end{aligned}$$

In order to apply the map ψ we need to insert $(x_1, 0)$ and $(0, x_2)$ in the above composition and find

$$\begin{aligned}\left\langle \left(F^* \circ \phi\right)(y_1^*, y_2^*), (x_1, 0)\right\rangle &= y_1^*\left(T(x_1, 0)\right) + y_2^*\left(S(x_1, 0)\right)\\ &= \left\langle T(\cdot, 0)^*(y_1^*) + S(\cdot, 0)^*(y_2^*), x_1\right\rangle\end{aligned}$$

and

$$\left\langle \left(F^* \circ \phi\right)(y_1^*, y_2^*), (0, x_2)\right\rangle = \left\langle T(0, \cdot)^*(y_1^*) + S(0, \cdot)^*(y_2^*), x_2\right\rangle$$

respectively. This proves the claim. □

3.4 The Linearized State Equations

In order to carry out the adjoint approach as outlined in Section I we need access to the linearized state equations. This means we need to formulate the system that we want to solve as a constraint of the form $\{e(y, \rho) = 0 \text{ in } W \mid (y, \rho) \in Y \times P\}$ for suitable Banach spaces Y, W and P, as we have seen earlier in equation (3.6). The choice of these spaces stems from the well posedness result in Theorem 9. Here we briefly repeat the choices that work for our concrete system. As state space Y we may choose

$$Y = L^2(I, H^1_{D_e}(\Omega)) \times H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*)^2 \cap L^2(I, C^0(\Omega))^2 \times W^{1,2}_0(I, C^0(\Omega)) \times W^{1,2}_0(I, C^0(\Omega)) \tag{3.27}$$

where $W^{1,2}_0(I, C^0(\Omega))$ means that the functions in this space have vanishing initial values. A member $y \in Y$ will be denoted by

$$y = (u, a_1, a_2, c, b).$$

We stress the fact that u, a_1 and a_2 are zero on the corresponding Dirichlet parts of the boundary of Ω. We take care of this in the definition of the constraint operator e and the objective function J. As a codomain for e we set

$$W = L^2(I, H^1_{D_e}(\Omega))^* \times \left[L^2(I, H^1_{D_d}(\Omega))^*\right]^2 \times L^2(\Omega)^2 \times L^2(I, C^0(\Omega)) \times L^2(I, C^0(\Omega)).$$

The admissible scaffold densities are collected in

$$P = \left\{\rho \in C^0(\Omega) \mid 0 < c_P \le \rho(x) \le C_P < 1\right\}$$

for two fixed constants c_P and c_P. Then, as defined previously, we set $e : Y \times P \to W$ with

$$e(y, \rho) = \begin{pmatrix} \int_I \int_\Omega \mathbb{C}(\rho, \sigma, b)\varepsilon(u + u_D) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t - \int_I \int_{\partial\Omega} \langle g_N^{\mathrm{ela}}, \cdot\rangle_{H^{1/2}(\partial\Omega)}\mathrm{d}s\mathrm{d}t \\ \int \langle d_t a_1, \cdot\rangle \mathrm{d}t + \int_I \int_\Omega D(\rho)\nabla a_1 \nabla \cdot + k_{3,1}(a_1 + 1) \cdot \mathrm{d}x\mathrm{d}t - \int_I \int_\Omega k_{2,1}|\varepsilon(u + u_D)|_\delta c \cdot \mathrm{d}x\mathrm{d}t \\ \int \langle d_t a_2, \cdot\rangle \mathrm{d}t + \int_I \int_\Omega D(\rho)\nabla a_2 \nabla \cdot + k_{3,2}(a_2 + 1) \cdot \mathrm{d}x\mathrm{d}t - \int_I \int_\Omega k_{2,2}|\varepsilon(u + u_D)|_\delta c \cdot \mathrm{d}x\mathrm{d}t \\ a_1(0) + 1 \\ a_2(0) + 1 \\ d_t c - k_6(a_1 + 1)(a_2 + 1)(1 + k_7 c)\left(1 - \frac{c}{1-\rho}\right) \\ d_t b - k_4(a_1 + 1)c\left(1 - \frac{b}{1-\rho}\right) \end{pmatrix}$$

For the following computations we use the Voigt bound for $\mathbb{C}(\rho, \sigma, b) = bC_b + \rho\sigma C_\rho$ and for the diffusivity we assume $D(\rho) = k_5(1 - \rho)$.

Having repeated the constraint operator e and clarified its domain we can proceed to compute the linearized state equations. These are obtained by taking the Fréchet derivative of e in direction y.

Theorem 39 (Linearized State Equations)**.** *Let us fix a pair $(y_0, \rho_0) \in Y \times P$, the linearized state equation at (y_0, ρ_0) is given by $e_y(y_0, \rho_0) : Y \to W$ through*

$$e_y(y_0,\rho_0)y = \begin{pmatrix} \iint \mathbb{C}(\rho_0,\sigma,b_0)\varepsilon(u) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t + \iint bC_b\varepsilon(u_0+u_D) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t \\ \begin{aligned}\int\langle d_ta_1,\cdot\rangle\mathrm{d}t + \iint D(\rho)\nabla a_1\nabla\cdot + k_{3,1}a_1\cdot\mathrm{d}x\mathrm{d}t - k_{2,1}\iint D|\cdot|_\delta(\varepsilon(u_0+u_D))\varepsilon(u)c_0\cdot\mathrm{d}x\mathrm{d}t \\ - k_{2,1}\iint|\varepsilon(u_0+u_D)|_\delta c\cdot\mathrm{d}x\mathrm{d}t\end{aligned} \\ \begin{aligned}\int\langle d_ta_2,\cdot\rangle\mathrm{d}t + \iint D(\rho)\nabla a_2\nabla\cdot + k_{3,2}a_2\cdot\mathrm{d}x\mathrm{d}t - k_{2,2}\iint D|\cdot|_\delta(\varepsilon(u_0+u_D))\varepsilon(u)c_0\cdot\mathrm{d}x\mathrm{d}t \\ - k_{2,2}\iint|\varepsilon(u_0+u_D)|_\delta c\cdot\mathrm{d}x\mathrm{d}t\end{aligned} \\ a_1(0) \\ a_2(0) \\ d_tc - k_6(a_{0,1}+1)(a_{0,2}+1)\left(k_7 - \frac{1}{1-\rho_0} - \frac{2k_7c_0}{1-\rho_0}\right)c - k_6(1+k_7c_0)\left(1-\frac{c_0}{1-\rho_0}\right)(a_1(a_{0,2}+1)+a_2(a_{0,1}+1)) \\ d_tb + \frac{k_4(a_{0,1}+1)c_0}{1-\rho_0}b - k_4c_0\left(1-\frac{b_0}{1-\rho_0}\right)a_1 - k_4(a_{0,1}+1)\left(1-\frac{b_0}{1-\rho_0}\right)c \end{pmatrix}$$

Proof. The proof consists of the computations. For the first component of e we compute

$$e^1_u(y_0,\rho_0)u = \iint \mathbb{C}(\rho_0,\sigma,b_0)\varepsilon(u) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t.$$

Here, we used that the map $u \mapsto e^1(u, a_{0,1}, a_{0,2}, c_0, b_0)$ is linear and continuous, hence Fréchet differentiable with derivative $e^1_u(y_0,\rho_0) = u \mapsto e^1(u, a_{0,1}, a_{0,2}, c_0, b_0)$ independently of the choice of (y_0, ρ_0). The other derivatives are given by

$$e^1_{a_1}(y_0,\rho_0)a_1 = e^2_{a_2}(y_0,\rho_0)a_2 = e^1_c(y_0,\rho_0)c = 0$$

and

$$e^1_b(y_0,\rho_0)b = \iint bC_b\varepsilon(u_0+u_D) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t$$

which follows again by exploiting linearity. In the second component e^2 the derivative of $|\cdot|_\delta$ enters. We assumed in Section 3.1 that $|\cdot|_\delta$ induces a Fréchet differentiable Nemyckii operator, i.e.,

$$N_{|\cdot|_\delta} : L^2(\Omega,\mathbb{R}^{n\times n}) \to L^2(\Omega), \quad (x\mapsto f(x)) \mapsto (x \mapsto |f(x)|_\delta)\,,$$

Consequently

$$e^2_u(y_0,\rho_0)u = -k_{2,1}\iint D|\cdot|_\delta(\varepsilon(u_0+u_D))\varepsilon(u)c_0\cdot\mathrm{d}x\mathrm{d}t.$$

Inferring linearity we find

$$e^2_{a_1}(y_0,\rho_0)a_1 = \int_I\langle d_ta_1,\cdot\rangle\mathrm{d}t + \iint D(\rho_0)\nabla a_1\nabla\cdot + k_{3,1}a_1\cdot\mathrm{d}x\mathrm{d}t$$

and

$$e^2_c(y_0,\rho_0)c = -k_{2,1}\iint|\varepsilon(u_0+u_D)|_\delta c\cdot\mathrm{d}x\mathrm{d}t.$$

The remaining partial derivatives vanish

$$e^2_{a_2}(y_0,\rho_0)a_2 = e^2_b(y_0,\rho_0)b = 0.$$

The third component works identical to the second one

$$e^3_u(y_0,\rho_0)u = -k_{2,2}\iint D|\cdot|_\delta(\varepsilon(u_0+u_D))\varepsilon(u)c_0\cdot\mathrm{d}x\mathrm{d}t, \quad e^3_{a_1}(y_0,\rho_0)a_1 = 0$$

$$e^3_{a_2}(y_0,\rho_0)a_2 = \int\langle d_ta_2,\cdot\rangle\mathrm{d}t + \iint D(\rho_0)\nabla a_2\nabla\cdot + k_{3,2}a_2\cdot\mathrm{d}x\mathrm{d}t$$

$$e^3_c(y_0,\rho_0)c = -k_{2,2}\iint|\varepsilon(u_0+u_D)|_\delta c\cdot\mathrm{d}x\mathrm{d}t, \quad e^3_b(y_0,\rho_0)b = 0.$$

As evaluation at a time-point $t \in I$ is a continuous and linear map on $H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*)$ since the space embeds into $C^0(I, L^2(\Omega))$ we get for the fourth and fifth component of e

$$e^4_u(y_0,\rho_0)u = 0, \quad e^4_{a_1}(y_0,\rho_0)a_1 = a_1(0), \quad e^4_{a_2}(y_0,\rho_0)a_2 = e^4_c(y_0,\rho_0)c = e^4_b(y_0,\rho_0)b = 0,$$
$$e^5_u(y_0,\rho_0)u = e^5_{a_1}(y_0,\rho_0)a_1 = 0, \quad e^5_{a_2}(y_0,\rho_0)a_2 = a_2(0), \quad e^5_c(y_0,\rho_0)c = e^5_b(y_0,\rho_0)b = 0.$$

For the sixth component we note that the ODE is quadratic and continuous in c as $W^{1,2}(I, C^0(\Omega))$ embeds into $C^0(I \times \Omega)$, hence it is Fréchet differentiable. All other dependencies are again (affine) linear and continuous. This yields

$$\begin{aligned} e^6_u(y_0,\rho_0)u = 0, \quad e^6_{a_1}(y_0,\rho_0)a_1 &= -k_6(a_{0,2}+1)(1+k_7c_0)\left(1 - \frac{c_0}{1-\rho_0}\right)a_1 \\ e^6_{a_2}(y_0,\rho_0)a_2 &= -k_6(a_{0,1}+1)(1+k_7c_0)\left(1 - \frac{c_0}{1-\rho_0}\right)a_2 \\ e^6_c(y_0,\rho_0)c &= d_tc - k_6(a_{0,1}+1)(a_{0,2}+1)\left(k_7 - \frac{1}{1-\rho_0} - \frac{2k_7c_0}{1-\rho_0}\right)c \\ e^6_b(y_0,\rho_0)b &= 0. \end{aligned}$$

The last component again consists of affine linear maps and is thus easy to differentiate

$$\begin{aligned} e^7_u(y_0,\rho_0)u = 0, \quad e^7_{a_1}(y_0,\rho_0)a_1 &= -k_4a_1c_0\left(1 - \frac{b_0}{1-\rho_0}\right), \\ e^7_{a_2}(y_0,\rho_0)a_2 = 0, \quad e^7_c(y_0,\rho_0)c &= -k_4(a_{0,1}+1)\left(1 - \frac{b_0}{1-\rho_0}\right)c, \\ e^7_b(y_0,\rho_0)b &= d_tb + \frac{k_4(a_{0,1}+1)c_0}{1-\rho_0}b. \end{aligned}$$

The derivative can be written in matrix form

$$e_y(y_0,\rho_0)y = \begin{pmatrix} e^1_u(y_0,\rho_0) & \dots & e^1_b(y_0,\rho_0) \\ \vdots & \ddots & \vdots \\ e^7_u(y_0,\rho_0) & \dots & e^7_b(y_0,\rho_0) \end{pmatrix} \begin{pmatrix} u \\ a_1 \\ a_2 \\ c \\ b \end{pmatrix}.$$

This leads to the asserted form in the statement of the Theorem. □

Remark 40. The matrix form for $e_y(y_0,\rho_0)$ in the above proof will be useful to derive the adjoint operator $e_y(y_0,\rho_0)^*$. Lemma 38 states that we find it by taking the adjoint of every component and transposing the matrix.

3.5 The Adjoint Operator

Remember that $e_y(y_0,\rho_0)$ maps Y into W, hence its adjoint acts between the dual spaces in the reversed direction

$$e_y(y_0,\rho_0)^* : W^* \to Y^*, \quad w^* \mapsto w^* \circ e_y(y_0,\rho_0).$$

However, we make the spaces more concrete (that is transforming them by linear homeomorphisms) by using reflexivity, the Riesz isomorphism of $L^2(\Omega)$ and lemma 38. We set

$$\widehat{W} = L^2(I, H^1_{D_e}(\Omega)) \times L^2(I, H^1_{D_d}(\Omega))^2 \times L^2(\Omega)^2 \times L^2(I, C^0(\Omega))^* \times L^2(I, C^0(\Omega))^*$$

and denote a member $\hat{w} \in \widehat{W}$ by

$$\hat{w} = (\xi, q_1, q_2, \mu_1, \mu_2, g^*, h^*). \tag{3.28}$$

Furthermore, we consider

$$\widehat{\widehat{W}} = L^2(I, H^1_{D_e}(\Omega))^{**} \times \left[L^2(I, H^1_{D_d}(\Omega))^{**}\right]^2 \times \left[L^2(\Omega)^*\right]^2 \times L^2(I, C^0(\Omega)) \times L^2(I, C^0(\Omega))^*.$$

Then the spaces $\widehat{\widehat{W}}$ and W^* are isomorphic with a convenient correspondence given by

$$I_1 : \widehat{\widehat{W}} \to W^*$$

with

$$(\xi^{**}, q_1^{**}, q_2^{**}, \mu_1^*, \mu_2^*, g^*, h^*) \mapsto \Big((\xi, q_1, q_2, \mu_1, \mu_2, g, h) \mapsto \xi^{**}(\xi) + q_1^{**}(q_1) + q_2^{**}(q_2) + \mu_1^*(\mu_1) + \mu_2^*(\mu_2) + g^*(g) + h^*(h)\Big).$$

This precisely the linear homeomorphism ϕ of lemma 38. The linear homeomorphism between the spaces $\widehat{W}$ and $\widehat{\widehat{W}}$ works via

$$I_2 : \widehat{W} \to \widehat{\widehat{W}}, \quad (\xi, q_1, q_2, \mu_1, \mu_2, g^*, h^*) \mapsto \left(J_e(\xi), J_d(q_1), J_d(q_2), \int_\Omega \mu_1 \cdot \mathrm{d}x, \int_\Omega \mu_2 \cdot \mathrm{d}x, g^*, h^*\right),$$

where

$$J_e : L^2(I, H^1_{D_e}(\Omega)) \to L^2(I, H^1_{D_e}(\Omega))^{**}, \quad \xi \mapsto (\xi^* \mapsto \xi^*(\xi))$$

is the canonical surjective isometry between a reflexive Banach space and its bi-dual space. The map J_d denotes the analogon for the space $L^2(I, H^1_{D_d}(\Omega))$. The $L^2(\Omega)$ functions are sent into $L^2(\Omega)^*$ via the Riesz isometry. For $L^2(I, C^0(\Omega))^*$ we do not know any helpful characterization, thus we leave this space as it is.

For the space Y^* we merely concretize it by considering it as a product of dual spaces instead of a dual of a product space, i.e., we define $\widehat{Y}$ to be

$$\widehat{Y} = L^2(I, H^1_{D_e}(\Omega))^* \times \left[\left(H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*) \cap L^2(I, C^0(\Omega))\right)^*\right]^2 \times W_0^{1,2}(I, C^0(\Omega))^* \times W_0^{1,2}(I, C^0(\Omega))^*$$

and the map

$$I_3 : Y^* \to \widehat{Y}$$

is the linear homeomorphism ψ adapted to these spaces. We are now in a position to present the concretized adjoint operator between the spaces $\widehat{W}$ and $\widehat{Y}$.

Lemma 41 (Matrix Form Adjoint Operator)**.** *We use the notation and definitions given above for the spaces $\widehat{W}$, $\widehat{\widehat{W}}$, $\widehat{Y}$ and the maps I_1, I_2 and I_3. Then for fixed $(y_0, \rho_0) \in Y \times P$ the map*

$$I_3 \circ e_y(y_0, \rho_0)^* \circ I_1 \circ I_2 = e_y(y_0, \rho_0)^\dagger \circ I_2 : \widehat{W} \to \widehat{\widehat{W}} \to W^* \to Y^* \to \widehat{Y}$$

is given by the formal matrix-vector product

$$\begin{pmatrix} e_u^1(y_0, \rho_0)^* \circ J_e & e_u^2(y_0, \rho_0)^* \circ J_d & \dots & e_u^7(y_0, \rho_0)^* \\ e_{a_1}^1(y_0, \rho_0)^* \circ J_e & e_{a_1}^2(y_0, \rho_0)^* \circ J_d & \dots & e_{a_1}^7(y_0, \rho_0)^* \\ \vdots & & \ddots & \\ e_b^1(y_0, \rho_0)^* \circ J_e & e_b^2(y_0, \rho_0)^* \circ J_d & \dots & e_b^7(y_0, \rho_0)^* \end{pmatrix} \begin{pmatrix} \xi \\ q_1 \\ q_2 \\ \mu_1 \\ \mu_2 \\ g^* \\ h^* \end{pmatrix}. \tag{3.29}$$

Here, as in Lemma 38 the map $e_y(y_0, \rho_0)^\dagger$ is defined as $I_3 \circ e_y(y_0, \rho_0)^* \circ I_1$.

Proof. Writing out the formal matrix-vector product one sees that Lemma 38 is immediately applicable. □

Remark 42. Inspecting the form of the adjoint operator given in Lemma 41 we see that it again takes the form of a system of equations, much like the state equations. However, the evolution equations still need a considerable amount of attention. This is due to the complicated state spaces and the time dependency.

Computing the adjoint maps appearing in the above matrix, we arrive at the following Proposition.

Proposition 43 (The Adjoint Operator)**.** *We use the preceding notation. Let us fix* $(y_0, \rho_0) \in Y \times P$*. Then for* $(\xi, q_1, q_2, \mu_1, \mu_2, g^*, h^*) \in \widehat{W}$ *the expression*

$$\left(e_y(y_0, \rho_0)^\dagger \circ I_2\right)(\xi, q_1, q_2, \mu_1, \mu_2, g^*, h^*) \in \widehat{Y}$$

is given by

$$\begin{pmatrix} \iint \mathbb{C}(\rho_0, b_0)\varepsilon(\xi) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t - \iint (k_{2,1}q_1 + k_{2,2}q_2)\, c_0 D| \cdot |_\delta(\varepsilon(u_0 + u_D))\varepsilon(\cdot)\mathrm{d}x\mathrm{d}t \\ \int \langle dt\cdot, q_1\rangle \mathrm{d}t + \iint D(\rho_0)\nabla q_1 \nabla\cdot + k_{3,1}q_1 \cdot \mathrm{d}x\mathrm{d}t + \int \mu_1 \,\mathrm{ev}_0(\cdot)\mathrm{d}x + g^*\left[-k_6(a_{0,2}+1)(1+k_7c_0)\left(1 - \frac{c_0}{1-\rho_0}\right)\cdot\right] \\ + h^*\left[-k_4 c_0\left(1 - \frac{b_0}{1-\rho_0}\right)\cdot\right] \\ \int \langle dt\cdot, q_2\rangle \mathrm{d}t + \iint D(\rho_0)\nabla q_2 \nabla\cdot + k_{3,2}q_2 \cdot \mathrm{d}x\mathrm{d}t + \int \mu_2 \,\mathrm{ev}_0(\cdot)\mathrm{d}x + g^*\left[-k_6(a_{0,1}+1)(1+k_7c_0)\left(1 - \frac{c_0}{1-\rho_0}\right)\cdot\right] \\ g^*\left[d_t \cdot - k_6(a_{0,1}+1)(a_{0,2}+1)\left(k_7 - \frac{1-2k_7c_0}{1-\rho_0}\right)\cdot\right] - \iint (k_{2,1}q_1 + k_{2,2}q_2)\, |\varepsilon(u_0 + u_D)|_\delta \cdot \mathrm{d}x\mathrm{d}t \\ + h^*\left[-k_4(a_{0,1}+1)\left(1 - \frac{b_0}{1-\rho_0}\right)\cdot\right] \\ h^*\left[d_t \cdot + \frac{k_4(a_{0,1}+1)c_0}{1-\rho_0}\cdot\right] + \iint \cdot\, (C_b(\varepsilon(u_0 + u_D) : \varepsilon(\xi)))\,\mathrm{d}x\mathrm{d}t \end{pmatrix}$$

Proof. The proof collects the computations. In the first row of the matrix in (3.29) we have members of $Y_1^* = L^2(I, H^1_{D_e}(\Omega))$, namely

$$\begin{aligned} e_u^1(y_0, \rho_0)^*\,(J_e(\xi)) &= J_e(\xi) \circ e_u^1(y_0, \rho_0) \\ &= \iint \mathbb{C}(\rho_0, \sigma, b_0)\varepsilon(\cdot) : \varepsilon(\xi)\mathrm{d}x\mathrm{d}t \\ &= \iint \mathbb{C}(\rho_0, \sigma, b_0)\varepsilon(\xi) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t, \end{aligned}$$

and

$$\begin{aligned} e_u^2(y_0, \rho_0)^*\,(J_d(q_1)) &= J_d(q_1) \circ e_u^2(y_0, \rho_0) \\ &= -k_{2,1} \iint D| \cdot |_\delta(\varepsilon(u_0 + u_D))\varepsilon(\cdot)c_0 q_1 \mathrm{d}x\mathrm{d}t \end{aligned}$$

and

$$\begin{aligned} e_u^3(y_0, \rho_0)^*\,(J_d(q_2)) &= J_d(q_2) \circ e_u^3(y_0, \rho_0) \\ &= -k_{2,2} \iint D| \cdot |_\delta(\varepsilon(u_0 + u_D))\varepsilon(\cdot)c_0 q_2 \mathrm{d}x\mathrm{d}t. \end{aligned}$$

The remaining terms vanish, i.e,

$$e_u^4(y_0, \rho_0)^*\,(R(\mu_1)) = e_u^5(y_0, \rho_0)^*\,(R(\mu_2)) = e_u^6(y_0, \rho_0)^* = e_u^7(y_0, \rho_0)^* = 0.$$

This yields the first component of the adjoint map. For the second component we compute, the elements being members of the space $Y_2^* = \left[H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*) \cap L^2(I, C^0(\Omega))\right]^*$

$$e_{a_1}^1(y_0, \rho_0)^*\,(J_e(\xi)) = e_{a_1}^3(y_0, \rho_0)^*\,(J_d(q_2)) = e_{a_1}^5(y_0, \rho_0)^*\,(R(\mu_2)) = 0$$

and

$$\begin{aligned}
e^2_{a_1}(y_0,\rho_0)^*\left(J_d(q_1)\right) &= J_d(q_1)\circ e^2_{a_1}(y_0,\rho_0)\\
&= \int \langle d_t\cdot, q_1\rangle \mathrm{d}t + \iint D(\rho_0)\nabla\cdot\nabla q_1 + k_{3,1}\cdot q_1 \mathrm{d}x\mathrm{d}t\\
&= \int \langle d_t\cdot, q_1\rangle \mathrm{d}t + \iint D(\rho_0)\nabla q_1\nabla\cdot + k_{3,1} q_1\cdot \mathrm{d}x\mathrm{d}t\\
e^4_{a_1}(y_0,\rho_0)^*\left(R(\mu_1)\right) &= R(\mu_1)\circ e^4_{a_1}(y_0,\rho_0) = \int_\Omega \mu_1\, \mathrm{ev}_0(\cdot)\mathrm{d}x\\
e^6_{a_1}(y_0,\rho_0)^*(g^*) &= -g^*\left[k_6(a_{0,2}+1)(1+k_7c_0)\left(1-\frac{c_0}{1-\rho_0}\right)\cdot\right]\\
e^7_{a_1}(y_0,\rho_0)^*(h^*) &= -h^*\left[k_4c_0\left(1-\frac{b_0}{1-\rho_0}\right)\cdot\right]
\end{aligned}$$

The third component of the adjoint map takes again values in $Y_3^* = \left[H^1(I,H^1_{D_d}(\Omega),H^1_{D_d}(\Omega)^*)\cap L^2(I,C^0(\Omega))\right]^*$. We compute

$$e^1_{a_2}(y_0,\rho_0)^*\left(J_e(\xi)\right) = e^2_{a_2}(y_0,\rho_0)^*\left(J_d(q_1)\right) = e^4_{a_2}(y_0,\rho_0)^*\left(R(\mu_1)\right) = e^7_{a_2}(y_0,\rho_0)^*(h*) = 0$$

and

$$\begin{aligned}
e^3_{a_2}(y_0,\rho_0)^*\left(J_d(q_2)\right) &= J_d(q_2)\circ e^3_{a_2}(y_0,\rho_0)\\
&= \int \langle d_t\cdot, q_2\rangle \mathrm{d}t + \iint D(\rho_0)\nabla\cdot\nabla q_2 + k_{3,2}\cdot q_2 \mathrm{d}x\mathrm{d}t\\
&= \int \langle d_t\cdot, q_2\rangle \mathrm{d}t + \iint D(\rho_0)\nabla q_2\nabla\cdot + k_{3,2} q_2\cdot \mathrm{d}x\mathrm{d}t\\
e^5_{a_2}(y_0,\rho_0)^*\left(R(\mu_2)\right) &= R(\mu_2)\circ e^5_{a_2}(y_0,\rho_0) = \int_\Omega \mu_2\, \mathrm{ev}_0(\cdot)\mathrm{d}x\\
e^6_{a_2}(y_0,\rho_0)^*(g^*) &= -g^*\left[k_6(a_{0,1}+1)(1+k_7c_0)\left(1-\frac{c_0}{1-\rho_0}\right)\cdot\right]
\end{aligned}$$

The fourth component takes values in $Y_4^* = W_0^{1,1}(I,C^0(\Omega))^*$ given by

$$e^1_c(y_0,\rho_0)\left(J_e(\xi)\right) = e^4_c(y_0,\rho_0)\left(R(\mu_1)\right) = e^5_c(y_0,\rho_0)\left(R(\mu_2)\right) = 0$$

and

$$\begin{aligned}
e^2_c(y_0,\rho_0)^*\left(J_d(q_1)\right) &= J_d(q_1)\circ e^2_c(y_0,\rho_0)\\
&= -k_{2,1}\iint |\varepsilon(u_0+u_D)|_\delta q_1\cdot \mathrm{d}x\mathrm{d}t\\
e^3_c(y_0,\rho_0)^*\left(J_d(q_2)\right) &= -k_{2,2}\iint |\varepsilon(u_0+u_D)|_\delta q_2\cdot \mathrm{d}x\mathrm{d}t\\
e^6_c(y_0,\rho_0)^*\left(g^*\right) &= g^*\circ e^6_c(y_0,\rho_0)\\
&= g^*\left[d_t\cdot - k_6(a_{0,1}+1)(a_{0,2}+1)\left(k_7-\frac{1+2k_7c_0}{1-\rho_0}\right)\cdot\right]\\
e^7_c(y_0,\rho_0)^*(h^*) &= h^*\circ e^7_c(y_0,\rho_0)\\
&= -h^*\left[k_4(a_{0,1}+1)\left(1-\frac{b_0}{1-\rho_0}\right)\cdot\right].
\end{aligned}$$

The last component of the adjoint takes values in $W_0^{1,2}(I,C^0(\Omega))^*$ and we compute

$$e^2_b(y_0,\rho_0)^* = e^3_b(y_0,\rho_0)^* = e^4_b(y_0,\rho_0)^* = e^5_b(y_0,\rho_0)^* = e^6_b(y_0,\rho_0)^* = 0$$

and

$$\begin{aligned}
e_b^1(y_0,\rho_0)^*\left(J_e(\xi)\right) &= J_e(\xi)\circ e_b^1(y_0,\rho_0)\\
&= \iint C_b\varepsilon(u_0+u_D):\varepsilon(\xi)\cdot \mathrm{d}x\mathrm{d}t\\
e_b^7(y_0,\rho_0)^*(h^*) &= h^*\circ e_b^7(y_0,\rho_0)\\
&= h^*\left[d_t\cdot+\frac{k_4(a_{0,1}+1)c_0}{1-\rho_0}\cdot\right]
\end{aligned}$$

□

We are now in a position to invoke the theory developed in Section IV. This yields a formulation that is well suited for numerical treatment.

Theorem 44 (Adjoint Equation)**.** *Let $(y_0,\rho_0)=(\phi(\rho_0),\rho_0)\in Y\times P$ be a control-state pair. Assume there is $\Lambda\in W^*$ solving*

$$e_y(\phi(\rho_0),\rho_0)^*\Lambda = E_y(\phi(\rho_0),\rho_0)\quad \textit{in } Y.$$

Assume furthermore, that the assumption of Lemma 91, that serves as an identification of the initial/final values of the diffusion equations, hold. Then this Λ can be computed in terms of $(\xi,q_1,q_2,g,h)\in\hat{W}$, that is

$$\Lambda=(I_1\circ I_2)\left((\xi,q_1,q_2,q_1(0),q_2(0),\iint g\cdot\mathrm{d}x\mathrm{d}t,\iint h\cdot\mathrm{d}x\mathrm{d}t\right),$$

where (ξ,q_1,q_2,g,h) results from solving the following system and I_1 and I_2 are the linear homeomorphisms defined in Section 3.5.

$$\begin{aligned}
\iint \mathbb{C}(\rho_0,\sigma,b_0)\varepsilon(\xi):\varepsilon(\cdot)\mathrm{d}x\mathrm{d}t &= \iint\left(k_{2,1}q_1+k_{2,2}q_2\right)c_0D|\cdot|_\delta\left(\varepsilon(u_0+u_D)\right)\varepsilon(\cdot)\mathrm{d}x\mathrm{d}t+f_{E_u(y_0,\rho_0)}\\
-\int_I\langle d_tq_1,\cdot\rangle_{H_D^1(\Omega)\cap C^0(\Omega)}\mathrm{d}t+\iint D(\rho_0)\nabla q_1\nabla\cdot+k_{3,1}q_1\cdot\mathrm{d}x\mathrm{d}t &= \iint gk_6(a_{0,2}+1)(1+k_7c_0)\left(1-\frac{c_0}{1-\rho_0}\right)\cdot\mathrm{d}x\mathrm{d}t\\
&\quad+\iint hk_4c_0\left(1-\frac{b_0}{1-\rho_0}\right)\cdot\mathrm{d}x\mathrm{d}t\\
-\int_I\langle d_tq_2,\cdot\rangle_{H_D^1(\Omega)\cap C^0(\Omega)}\mathrm{d}t+\iint D(\rho_0)\nabla q_2\nabla\cdot+k_{3,2}q_2\cdot\mathrm{d}x\mathrm{d}t &= \iint gk_6(a_{0,1}+1)(1+k_7c_0)\left(1-\frac{c_0}{1-\rho_0}\right)\cdot\mathrm{d}x\mathrm{d}t\\
-d_tg-k_6(a_{0,1}+1)(a_{0,2}+1)\left(k_7-\frac{1+2k_7c_0}{1-\rho_0}\right)g &= \left(k_{2,1}q_1+k_{2,2}q_2\right)|\varepsilon(u_0+u_D)|_\delta\\
&\quad+k_4h(a_{0,1}+1)\left(1-\frac{b_0}{1-\rho_0}\right)\\
-d_th+\frac{k_4(a_{0,1}+1)c_0}{1-\rho_0}h &= f_{E_b(y_0,\rho_0)}-C_b\varepsilon(u_0+u_D):\varepsilon(\xi).
\end{aligned}$$

with the final time conditions

$$q_1(T)=q_2(T)=0\quad \textit{in } \left[H^1_{D_d}(\Omega)\cap C^0(\Omega)\right]^*$$

and

$$g(T)=h(T)=0\quad \textit{in } L^1(\Omega).$$

Proof. We prove this using the results from 4.IV and begin with the last equation in the system of Proposition 43. Remember that $J_b(y_0,\rho)$ is induced by the $C^0(I,L^1(\Omega))$ function $f_{J_b(y_0,\rho)}$, i.e., it holds

$$J_b(y_0,\rho)=\iint f_{J_b(y_0,\rho_0)}\cdot\mathrm{d}x\mathrm{d}t\quad \text{in } W_0^{1,2}(I,C^0(\Omega))^*.$$

Now, look at the last equation in Proposition 43

$$h^*\Bigg[d_t\cdot+\underbrace{\frac{k_4(a_{0,1}+1)c_0}{1-\rho_0}}_{=:m_{\text{bone}}}\cdot\Bigg]=\iint\Big(\underbrace{f_{E_b(y_0,\rho_0)}-C_b\varepsilon(u_0+u_D):\varepsilon(\xi)}_{=:f_{\text{bone}}\in C^0(I,L^1(\Omega))}\Big)\cdot\mathrm{d}x\mathrm{d}t\quad \text{in } W_0^{1,2}(I,C^0(\Omega))^*.$$

Hence, the equation is of the form

$$h^* \left[d_t \cdot + m_{\text{bone}} \cdot\right] = \iint f_{\text{bone}} \cdot \mathrm{d}x\mathrm{d}t \quad \text{in } W_0^{1,2}(I, C^0(\Omega))^*$$

with $m_{\text{bone}} \in L^2(I, C^0(\Omega))$ and $f_{\text{bone}} \in C^0(I, L^1(\Omega))$. Then Theorem 93 yields that

$$h^* = \iint h \cdot \mathrm{d}x\mathrm{d}t$$

with $h \in W^{1,2}(I, L^1(\Omega))$ and that this h satisfies the final value problem

$$-d_t h + m_{\text{bone}} h = f_{\text{bone}} \quad \text{with} \quad h(T) = 0.$$

In a similar way, we can treat the adjoint cell ODE, i.e., the second last equation in Proposition 43. It is

$$g^*\left[d_t \cdot \underbrace{-k_6(a_{0,1}+1)(a_{0,2}+1)\left(k_7 - \frac{1+2k_7c_0}{1-\rho_0}\right)}_{=:m_{\text{cell}}} \cdot\right] = \iint (k_{2,1}q_1 + k_{2,2}q_2)\, |\varepsilon(u_0+u_D)|_\delta \cdot \mathrm{d}x\mathrm{d}t$$
$$+ \iint h \underbrace{\left[k_4(a_{0,1}+1)\left(1 - \frac{b_0}{1-\rho_0}\right)\right]}_{=:f_{\text{cell}}} \cdot \mathrm{d}x\mathrm{d}t$$

and $m_{\text{cell}} \in L^2(I, C^0(\Omega))$ and $f_{\text{cell}} \in C^0(I, L^1(\Omega))$. As before, this yields that g^* is given as integration against a function $g \in W^{1,2}(I, L^1(\Omega))$ which solves

$$-d_t g + m_{\text{cell}} g = f_{\text{cell}} \quad \text{with} \quad g(T) = 0.$$

For the second adjoint diffusion equation, i.e., the third equation in Proposition 43, we note that its right-hand side is given by

$$\iint g k_6(a_{0,1}+1)(1+k_7c_0)\left(1 - \frac{c_0}{1-\rho_0}\right) \cdot \mathrm{d}x\mathrm{d}t \in \left[L^2(I, C^0(\Omega)) \cap H^1(I, H^1_{D_d}(\Omega), H^1_{D_d}(\Omega)^*)\right]^*$$

and the integrand is a member of $L^2(I, L^1(\Omega))$. Then, by Lemma 89 we get

$$q_2 \in H^1(I, H^1_{D_d}(\Omega), [H^1_{D_d}(\Omega) \cap C^0(\Omega)]^*)$$

and know that q_2 satisfies the equation

$$-\int_I \langle d_t q_2, \cdot \rangle_{H^1_D(\Omega)\cap C^0(\Omega)} \mathrm{d}t + \iint D(\rho_0)\nabla q_2 \nabla \cdot + k_{3,2} q_2 \cdot \mathrm{d}x\mathrm{d}t = \iint g k_6(a_{0,1}+1)(1+k_7c_0)\left(1 - \frac{c_0}{1-\rho_0} \cdot\right) \mathrm{d}x\mathrm{d}t.$$

With the assumption of Lemma 91 we can now identify the final value and get

$$q_2(T) = 0 \quad \text{in} \quad \left[H^1_{D_d}(\Omega) \cap C^0(\Omega)\right]^*.$$

We can argue in the same way for q_1. The right-hand side of this equation is also a member of $L^2(I, L^1(\Omega))$. Finally, the first equation is already in a convenient form. This concludes the proof. □

Remark 45. Some comments are in order.

(i) The variables μ_1 and μ_2 seem to have disappeared in the equations of the preceding Theorem. In fact, they are still implicitly present as $q_1(0) = \mu_1$ and $q_2(0) = \mu_2$.

(ii) Note that the above result does not say anything about the existence of a solution to the adjoint system. The only thing we do is derive regularity, given such a solution exists.

3.6 The Remaining Term of the Derivative

Remember that it holds

$$D\hat{J}(\rho) = -e_\rho^*(\phi(\rho),\rho) \circ e_y^{-*}(\phi(\rho),\rho)(J_y(\phi(\rho),\rho)) + J_\rho(\phi(\rho),\rho)$$

and so far, we computed $J_y(\phi(\rho_0),\rho_0)$ and $J_\rho(\phi(\rho_0),\rho_0)$ and we derived a useful characterization of

$$e_y^{-*}(\phi(\rho),\rho)(J_y(\phi(\rho),\rho)).$$

We now treat the operator

$$e_\rho^*(\phi(\rho),\rho) : W* \to P^*.$$

When comparing to the above formula for $D\hat{J}(\rho_0)$, we see that the input to $e_\rho^*(\phi(\rho_0),\rho_0)$ is the solution $\Lambda \in W^*$ of the adjoint equation. However, due to the necessary concretization of the adjoint system, Λ is computed in terms of $\hat{w} = (\xi, q_1, q_2, \mu_1, \mu_2, g^*, h^*) \in \hat{W}$. Before inserting $\hat{w}$ into $e_\rho^*(\phi(\rho_0),\rho_0)$, we need therefore to apply the isomorphism $\hat{W} \to W^*$ given by

$$(\xi, q_1, q_2, \mu_1, \mu_2, g^*, h^*) \mapsto J_e(\xi) \circ \pi_1 + J_d(q_1) \circ \pi_2 + J_d(q_2) \circ \pi_3 + \int_\Omega \mu_1 \pi_4(\cdot) + \mu_2 \pi_5(\cdot) \mathrm{d}x + g^* \circ \pi_6 + h^* \circ \pi_7$$

Here, π_i denotes the projection on the i-th coordinate of the product space W and J_e and J_d are the natural isometries identifying $L^2(I, H^1_{D_e}(\Omega))$ and $L^2(I, H^1_{D_e}(\Omega))$ with their bi-duals, see also Section 3.5 where these maps have been used before.

Lemma 46. *Let $\Lambda \in W^*$, then there is a unique tuple*

$$(\xi, q_1, q_2, \mu_1, \mu_2, g^*, h^*) \in \widehat{W}$$

such that

$$\Lambda = J_e(\xi) \circ \pi_1 + J_d(q_1) \circ \pi_2 + J_d(q_2) \circ \pi_3 + \int_\Omega \mu_1 \pi_4(\cdot) + \mu_2 \pi_5(\cdot) \mathrm{d}x + g^* \circ \pi_6 + h^* \circ \pi_7, \tag{3.30}$$

where we used the notation explained above. Assume that

$$g^* = \iint g \cdot \mathrm{d}x\mathrm{d}t \quad \textit{and} \quad h^* = \iint h \cdot \mathrm{d}x\mathrm{d}t$$

for functions $g \in W^{1,2}(I, L^1(\Omega))$ and $h \in W^{1,2}(I, L^1(\Omega))$. Then for arbitrary

$$(y_0, \rho_0) = (u_0, a_{0,1}, a_{0,2}, c, b) \in Y \times P$$

it holds

$$\begin{aligned} e_\rho(y_0,\rho_0)^*\Lambda = &\iint \cdot\sigma C_p \varepsilon(u_0 + u_D) : \varepsilon(\xi)\mathrm{d}x\mathrm{d}t - k_5 \iint (\nabla a_{0,1} \nabla q_1 + \nabla a_{0,2} \nabla q_2) \cdot \mathrm{d}x\mathrm{d}t \\ &+ k_6 \iint g(a_{0,1}+1)(a_{0,2}+1)(1+k_7 c_0)c_0 \frac{1}{(1-\rho_0)^2} \cdot \mathrm{d}x\mathrm{d}t \\ &+ k_4 \iint h(a_{0,1}+1)c_0 b_0 \frac{1}{(1-\rho_0)^2} \cdot \mathrm{d}x\mathrm{d}t \in C^0(\Omega)^* \end{aligned}$$

Proof. First we need to compute the partial derivatives of e with respect to $\rho \in P$.

$$\begin{aligned} e^1_\rho(y_0,\rho_0)\rho &= \iint \rho\sigma C_p \varepsilon(u_0 + u_D) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t \\ e^2_\rho(y_0,\rho_0)\rho &= -k_5 \iint \rho \nabla a_{0,1} \nabla \cdot \mathrm{d}x\mathrm{d}t \\ e^3_\rho(y_0,\rho_0)\rho &= -k_5 \iint \rho \nabla a_{0,2} \nabla \cdot \mathrm{d}x\mathrm{d}t \\ e^4_\rho(y_0,\rho_0)\rho &= e^5_\rho(y_0,\rho_0)\rho = 0 \\ e^6_\rho(y_0,\rho_0)\rho &= k_6(a_{0,1}+1)(a_{0,2}+1)(1+k_7c_0)c_0 \frac{\rho}{(1-\rho_0)^2} \\ e^7_\rho(y_0,\rho_0)\rho &= k_4(a_{0,1}+1)c_0 b_0 \frac{\rho}{(1-\rho_0)^2}. \end{aligned}$$

The representation of Λ via the equation (3.30) is precisely the linear homeomorphism $\widehat{W} = W^*$ discussed above and in 3.5. Unwinding the definitions for $e^*_\rho(y_0, \rho_0)$ and Λ yields the assertion

$$\begin{aligned}\Lambda \circ e_\rho(y_0, \rho_0) &= J_e(\xi) \circ e^1_\rho(y_0, \rho_0) + J_d(q_1) \circ e^2_\rho(y_0, \rho_0) + J_d(q_2) \circ e^3_\rho(y_0, \rho_0)\\ &+ \int_\Omega \mu_1 e^4(y_0, \rho_0)(\cdot) + \mu_2 e^4(y_0, \rho_0)(\cdot)\mathrm{d}x + g^* \circ e^6_\rho(y_0, \rho_0)\\ &+ h^* \circ e^7_\rho(y_0, \rho_0).\end{aligned}$$

Inserting the derivatives computed above, we arrive at the assertion. □

IV The Influence of Stress Shielding on Optimal Scaffold Design

In this Section we present the simulations using the adjoint approach for the optimization problem discussed earlier. We use the same domains as we did in Section III of Chapter 2, i.e., simplified models for the 30mm tibial defect as considered in Cipitria et al. (2015). More precisely, we again employ the cylindrical domain and the simplified fixateur model. Our goal is to identify optimal scaffold density distributions for both domains, where optimality refers to maximizing the weakest time-point's stability of the scaffold-bone system, i.e., we use the objective defined in 3.1. Our results illustrate the influence of the stress-shielding effect that results from the fixateur's implantation.

4.1 Stress Shielding

Bone adapts according to the mechanical environment it is subjected to. This important property of bone is well known and commonly referred to as Wolff's law, see Wolff (1892). It has far ranging consequences for bone tissue engineering. More precisely, prosthetic implants are often made of less elastic materials than bone and thus change the mechanical environment in their vicinity. This often leads to bone regions that are subjected to less stress and consequently bone resorption when compared to a healthy bone, a phenomenon known as stress shielding which has been extensively studied, e.g., in the context of total hip arthroplasty, see Sumner and Galante (1992); Huiskes et al. (1992); Behrens et al. (2008); Arabnejad et al. (2017). The bone resorption in the vicinity of the prosthetic implant can lead to serious complications such as periprosthetic fracture and aseptic loosening and revision surgeries – if so needed – can be complicated, we refer to Arabnejad et al. (2017).

It is to be expected that stress shielding effects do also play an important role in scaffold mediated bone growth, for example caused through the external fixation of the scaffold by a metal plate. This leads to under-loading in the vicinity of the fixating element. To be able to quantify these effects it is crucial to use a three dimensional computational model, a simplification as for instance discussed by Poh et al. (2019) cannot resolve the asymmetries that induce the effect.

4.2 Concrete System under Consideration

Our concrete model setup is almost identical to the one presented in Chapter 2 as far as the state equations are concerned. For the readers convenience we repeat the state equations

$$0 = \operatorname{div}\Big(\mathbb{C}(\rho, \sigma, b)\varepsilon(u)\Big) \tag{3.31}$$

$$d_t a_1 = \operatorname{div}\Big(D(\rho)\nabla a_1\Big) + k_{2,1}|\varepsilon(u)|c - k_{3,1}a_1 \tag{3.32}$$

$$d_t a_2 = \operatorname{div}\Big(D(\rho)\nabla a_2\Big) + k_{2,2}|\varepsilon(u)|c - k_{3,2}a_2 \tag{3.33}$$

$$d_t c = k_6 a_1 a_2 (1 + k_7 c)\Big(1 - \frac{c}{1-\rho}\Big) \tag{3.34}$$

$$d_t b = k_4 a_1 c\Big(1 - \frac{b}{1-\rho}\Big). \tag{3.35}$$

We use the same boundary conditions as in Section III of Chapter 2 with the exception of the elastic equation that is subjected to pure Neumann boundary conditions with a constant surface traction stemming from a force of 0.3 kN which is applied to the top and bottom of the cylindrical domain. We propose to view this as a maximal force that repeatedly occurs, compare to the discussion in Dondl et al. (2021) for a more detailed reasoning. The bioactive molecules a_1, a_2 are assumed to be in saturation adjacent to the initial, healthy bone matrix at the top and bottom of the domain and a scenario without preseeding throughout the domain (i.e., a zero initial condition) is considered. For the model constants and functional relationships we refer to Dondl et al. (2021).

As an objective function to measure a scaffold performance, we use the maximum over the temporal evolution of the scaffold-bone composite's elastic energy. Due to the softload in the numerical experiments, the reciprocal of the elastic energy is proportional to the elastic modulus of the scaffold-bone system; a reasonable measure of stability. The optimization's goal is to minimize this temporal maximum while respecting the state equations and an additional constraint on ρ to not take values outside the unit interval[1] In formulas, we denote by $\mathcal{E}$ the elastic energy

$$\mathcal{E}(y,\rho)(t) = \frac{1}{2}\int_\Omega \mathbb{C}(\rho(x), \sigma(t), b(t,x))\varepsilon(u(t,x)) : \varepsilon(u(t,x))\mathrm{d}x$$

where $y = (u, a_1, a_2, c, b)$ is the state variable. The minimization problem is the task to find

$$\rho \in \operatorname{argmin}\left[\max_{t\in I} \mathcal{E}(y,\rho)(t)\right], \quad \text{subjected to } e(y,\rho) = 0 \text{ and } \rho \in P, \tag{3.36}$$

where P encodes that ρ is bounded away from zero and one. Numerically, we replace the temporal maximum by an $L^p(I)$ norm (with, e.g., $p = 5$) to smoothly approximate it. The pointwise constraint is incorporated using a soft penalty. In our simulations we choose

$$\mathcal{K}_{\text{soft}}(\rho) = \int_\Omega (\rho(x) + 0.2)^{40} + (\rho(x) - 0.8)^{40}\mathrm{d}x. \tag{3.37}$$

This penalty function lowers the objective functions value when $\rho(x)$ deviates from its minimum value at the constant function $\rho_0 \equiv 0.3$ and is fine-tuned to be compatible with the magnitude of the objectives gradient.

4.3 Reduced Derivative Computation & Implementation

The optimization problem (3.36) is a PDE constrained optimization problems with an additional pointwise constraint on the control variable. Numerical methods to solve problems of that form are either gradient based or trying to solve optimality conditions directly, see Hinze et al. (2008), where the latter are more efficient but considerably more labor intensive to implement.

For our application gradient descent was deemed sufficient. More precisely, we use an $L^2(\Omega)$ gradient flow, that is, we identify the derivative $D\hat{J}(\rho)$ with an element in $L^2(\Omega)$ which is – by abuse of notation – denoted with the same symbol. Furthermore, the pointwise control-constraint is replaced by a soft penalty as described above. This leaves us with the task of computing the derivative of the reduced objective function. To this end we employ the adjoint method as described in detail earlier in Section I. More precisely, let ρ_i be given. For ρ_0 we choose a suitable initial condition, in our simulations we usually use $\rho_0 \equiv 0.13$. The update rule is

$$\rho_{i+1} = \rho_i - \eta\left(D\hat{J}(\rho_i) + D\mathcal{K}(\rho_i)\right),$$

where $\eta > 0$ is the step-size. The derivative $D\hat{J}(\rho_i)$ is computed in the following four steps.

[1] A scaffold volume fraction should always take values between zero and one in order to be reasonably interpreted as a volume fraction. More restrictive, ρ should even be bounded away from zero and one.

Step I: Forward Equation

Given the current ρ_i, we solve the weak form of the equations (3.31)–(3.35), i.e.,

$$\int_I \int_\Omega \mathbb{C}(\rho_i, \sigma, b)\varepsilon(u + u_D) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t = \int_I \int_{\partial\Omega} \langle g_N^{\mathrm{ela}}, \cdot\rangle_{H^{1/2}(\partial\Omega)}\mathrm{d}s\mathrm{d}t$$
$$\int \langle d_t a_1, \cdot\rangle \mathrm{d}t + \int_I \int_\Omega D(\rho_i)\nabla a_1 \nabla \cdot + k_{3,1}(a_1 + 1) \cdot \mathrm{d}x\mathrm{d}t = \int_I \int_\Omega k_{2,1}|\varepsilon(u + u_D)|_\delta c \cdot \mathrm{d}x\mathrm{d}t$$
$$\int \langle d_t a_2, \cdot\rangle \mathrm{d}t + \int_I \int_\Omega D(\rho_i)\nabla a_2 \nabla \cdot + k_{3,2}(a_2 + 1) \cdot \mathrm{d}x\mathrm{d}t = \int_I \int_\Omega k_{2,2}|\varepsilon(u + u_D)|_\delta c \cdot \mathrm{d}x\mathrm{d}t$$
$$d_t c = k_6(a_1 + 1)(a_2 + 1)(1 + k_7 c)\left(1 - \frac{c}{1 - \rho_i}\right)$$
$$d_t b = k_4(a_1 + 1)c\left(1 - \frac{b}{1 - \rho_i}\right)$$

with

$$a_1(0) = a_2(0) = -1, \quad c(0) = b(0) = 0, \quad u \in L^2(I, H^1_{D_e}(\Omega))$$

and u_D denotes a lift of the Dirichlet boundary conditions and g_N are Neumann boundary conditions. This yields the solutions $u = u(\rho_i), a_1 = a_1(\rho_i), \ldots, b = b(\rho_i)$. For brevity we suppress the dependency on ρ_i in the notation further on. Furthermore, we choose $\mathbb{C}(\rho, \sigma, b)A = bC_b A + \sigma\rho C_p$, where C_b and C_p should use the Lamé formulas for linear isotropic materials. This means we use the Voigt bound for the composite of bone and PCL. We set $D(\rho) = k_5(1 - \rho)$ and

$$|v|_\delta = \sqrt{\sum_{i,j} v_{i,j}^2 + \delta^2}$$

with $\delta > 0$ as a smooth approximation of the Euclidean norm.

Step II: Derivatives of Objective

Using the solutions u, a_1, a_2, c and b of the forward system, we can compute the derivatives of the objective function. This should not be confused with the derivative of the reduced objective function. The following quantities are needed in the subsequent steps. For brevity, we set $y = (u, a_1, a_2, c, b)$.

$$f_{J_u(y,\rho_i)} = J(y, \rho_i)^{1-p} \int_\Omega \mathcal{E}(y, \rho_i)^{p-1}\mathbb{C}(\rho_i, \sigma, b)\varepsilon(u + u_D) : \varepsilon(\cdot)\mathrm{d}x,$$
$$f_{J_b(y,\rho_i)} = \frac{1}{2}J(y, \rho_i)^{1-p}\mathcal{E}(y, \rho_i)^{p-1}C_b\varepsilon(u + u_D) : \varepsilon(u + u_D),$$
$$f_{J_\rho(y,\rho_i)} = \frac{1}{2}J(y, \rho_i)^{1-p} \int_I \mathcal{E}(y, \rho_i)^{p-1}\sigma C_\rho\varepsilon(u + u_D) : \varepsilon(u + u_D)\mathrm{d}t.$$

Again, $\mathcal{E}$ denotes the elastic energy at a time-point $t \in I$, i.e.,

$$\mathcal{E}(y, \rho_i)(t) = \frac{1}{2}\int_\Omega \mathbb{C}(\rho_i, \sigma(t), b(t))\varepsilon(u(t) + u_D(t)) : \varepsilon(u(t) + u_D(t))\mathrm{d}x.$$

Step III: Adjoint Equation

Given the functions $u, a_1, \dots, b$ from the first step, the adjoint equation requires us to find ξ, q_1 and q_2, g and h solving the following system

$$\iint \mathbb{C}(\rho_i, \sigma, b)\varepsilon(\xi) : \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t = \iint (k_{2,1}q_1 + k_{2,2}q_2)\, D|\cdot|_\delta\, (\varepsilon(u + u_D))\, \varepsilon(\cdot)\mathrm{d}x\mathrm{d}t + f_{J_u(y,\rho_i)}$$

$$-\int_I \langle d_t q_1, \cdot\rangle_{H^1_D(\Omega)\cap C^0(\Omega)}\mathrm{d}t + \iint D(\rho_i)\nabla q_1 \nabla \cdot + k_{3,1}q_1 \cdot \mathrm{d}x\mathrm{d}t = \iint g k_6(a_2 + 1)(1 + k_7 c)\left(1 - \frac{c}{1-\rho_i}\right)\cdot \mathrm{d}x\mathrm{d}t$$

$$+ \iint h k_4 c\left(1 - \frac{b}{1-\rho_i}\right)\cdot \mathrm{d}x\mathrm{d}t$$

$$-\int_I \langle d_t q_2, \cdot\rangle_{H^1_D(\Omega)\cap C^0(\Omega)}\mathrm{d}t + \iint D(\rho_i)\nabla q_2 \nabla \cdot + k_{3,2}q_2 \cdot \mathrm{d}x\mathrm{d}t = \iint g k_6(a_1 + 1)(1 + k_7 c)\left(1 - \frac{c}{1-\rho_i}\right)\cdot \mathrm{d}x\mathrm{d}t$$

$$-d_t g - k_6(a_1 + 1)(a_2 + 1)\left(k_7 - \frac{1 + 2k_7 c}{1-\rho_i}\right) g = (k_{2,1}q_1 + k_{2,2}q_2)\,|\varepsilon(u + u_D)|_\delta$$

$$+ k_4 h(a_1 + 1)\left(1 - \frac{b}{1-\rho_i}\right)$$

$$-d_t h + \frac{k_4(a_1 + 1)c}{1-\rho_i} h = f_{J_b(y,\rho_i)} - C_b \varepsilon(u + u_D) : \varepsilon(\xi).$$

with the final time conditions

$$q_1(T) = q_2(T) = 0 \quad \text{and} \quad g(T) = h(T) = 0.$$

In the right hand sides of the adjoint equation the derivatives of the objective enter. These are given by

Step IV: Computing the Reduced Objective

Finally, using all the computations in the preceding steps, we can compute the representative of $D\hat{J}(\rho_i)$ in $L^2(\Omega)$ which we again denote by $D\hat{J}(\rho_i)$. It is given by

$$\begin{aligned} D\hat{J}(\rho_i) = &\int_I k_5 \nabla a_{0,1}\nabla q_1 + \nabla a_{0,2}\nabla q_2 - \sigma C_p \varepsilon(u + u_D) : \varepsilon(\xi)\mathrm{d}t \\ &- \int_I k_6 g(a_1 + 1)(a_2 + 1)\frac{(1 + k_7 c)c}{(1-\rho_i)^2} + \frac{k_4 h(a_1 + 1)cb}{(1-\rho_i)^2}\mathrm{d}t \\ &+ f_{J_\rho(y,\rho_i)}. \end{aligned}$$

The $L^2(\Omega)$ Riesz representative of the soft penalty is given by

$$D\mathcal{K}(\rho_i) = \left[40(\rho(x) + 0.2)^{39} + 40(\rho(x) - 0.8)^{39}\right].$$

4.4 Implementation Details

For the spatial discretization we use tetrahedral meshes with roughly 40k vertices which were generated using the Computational Geometry Algorithms Library CGAL Boissonnat et al. (2000). The forward and adjoint equation are discretized in space using P1 finite elements for the variables $u, a_1, a_2, \xi, q_1, q_2$ and the functions c, b, g and h are approximated by functions that are constant on the finite elements.

For the time stepping an implicit ansatz was chosen where possible, decoupling the equations by using previous function values for the unknown quantities. For instance, in the computation of a_1 at time t_{i+1} the value of $c(t_{i+1})$ is not yet available, hence $c(t_i)$ is used instead. As we do not need a fully explicit scheme, relatively few time-steps suffice to achieve acceptable accuracy. We usually use around 60.

We let the gradient descent/ascent run for 1000 steps, using a rather large step-size of 30 as the energy landscape is extremely flat. After 1000 gradient steps, the derivatives magnitude is at around 10% of its value for the initial guess of ρ. Visually, little happens when letting the gradient descent/ascent running for longer and we content ourselves with this as the computational cost of a single run lies at around a week on a (rather slow) desktop PC.

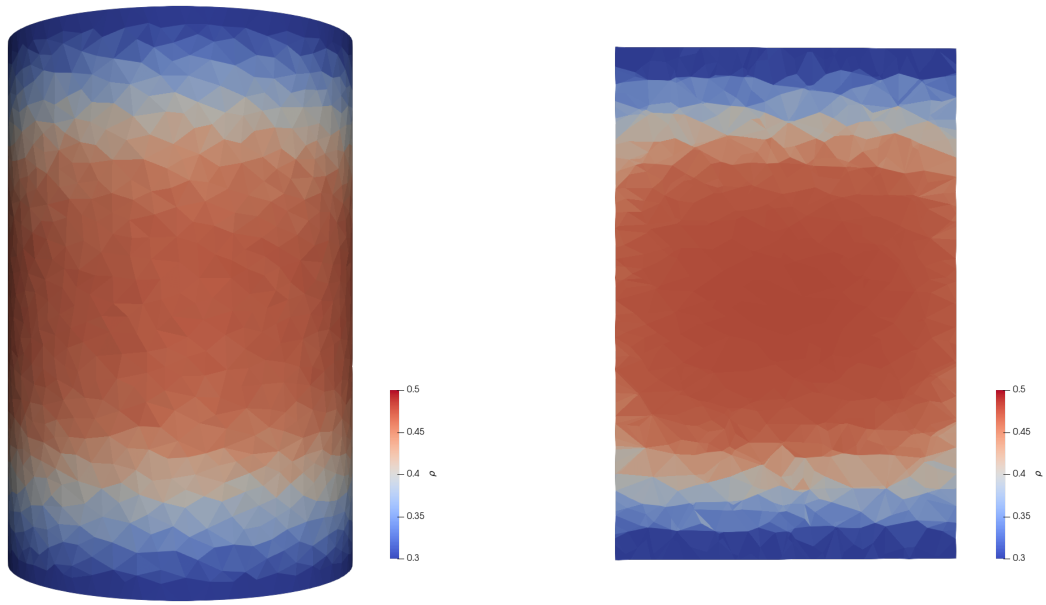


Figure 3.1: Optimal scaffold architecture for the experiment without external fixation. The left picture shows the full specimen, the right picture displays a cut through a vertical plane.

4.5 Discussion of the Simulation's Results

In Figure 3.1 and Figure 3.2 we display two optimized scaffold densities for different mechanical environments. For both experiments we use a cylindric defect site. In the experiment corresponding to Figure 3.2 we additionally include a simplistic external fixation of the scaffold in the model. This is marked in gold in the picture and realized by using the material properties of titanium in the simulations. This corresponds to the practice of fixating a scaffold by a metal plate and this metal plate is commonly called a fixateur. As we apply a compressive softload in both experiments, the mechanical environment is changed drastically by the fixateur. Using external fixation, the mechanical stimulus is almost absent in the vicinity of the fixateur, whereas excluding external fixation it does hardly vary orthogonal to the main axis of the cylinder. Vanishing mechanical stimulus close to external fixation is also observed in vivo and is referred to as stress shielding, compare to the discussion in Section 4.1. Naturally, this influences the scaffold optimization and an important merit of a three dimensional model is the ability to resolve these stress shielding effects and adapt the architecture of an optimal scaffold accordingly.

The optimization in Figure 3.1 depicts a scaffold with a higher density in the middle region. A reasonable outcome, as regenerated bone grows back at the scaffold ends where it is attached to the intact bone tissue. Therefore, the central scaffold region needs to maintain structural integrity for a longer time by itself. The overall shape is very similar to the results obtained by Poh et al. (2019) with a one dimensional model which is not surprising as our experiment is essentially one dimensional.

The optimized scaffold density corresponding to the experiment including the fixateur depicted in Figure 3.2 shows a considerably different distribution. A higher density in the central part is favorable for the same reason as in the experiment excluding the fixateur, however, in vicintiy of the stiff metal plate a comparatively low scaffold density is predicted. High porosity in this region of the scaffold is beneficial as it increases the mechanical stimulus due to reduced stability and enhances vascularization[2]. Both effects lead to a faster bone in-growth in the region close to the fixateur. The small regions of high scaffold density at the top and bottom close to the fixateur are due to stress concentration effects in the simulations. There the material properties change from a bone-scaffold composite to titanium and hence large stress values are to be expected. As the optimization procedure aims to minimize the temporal maximum of the elastic energy and since this maximum tends to be attained close to the initial time-point a high scaffold density is

[2] In our model vascularization is resolved through the diffusion of bio-active molecules.

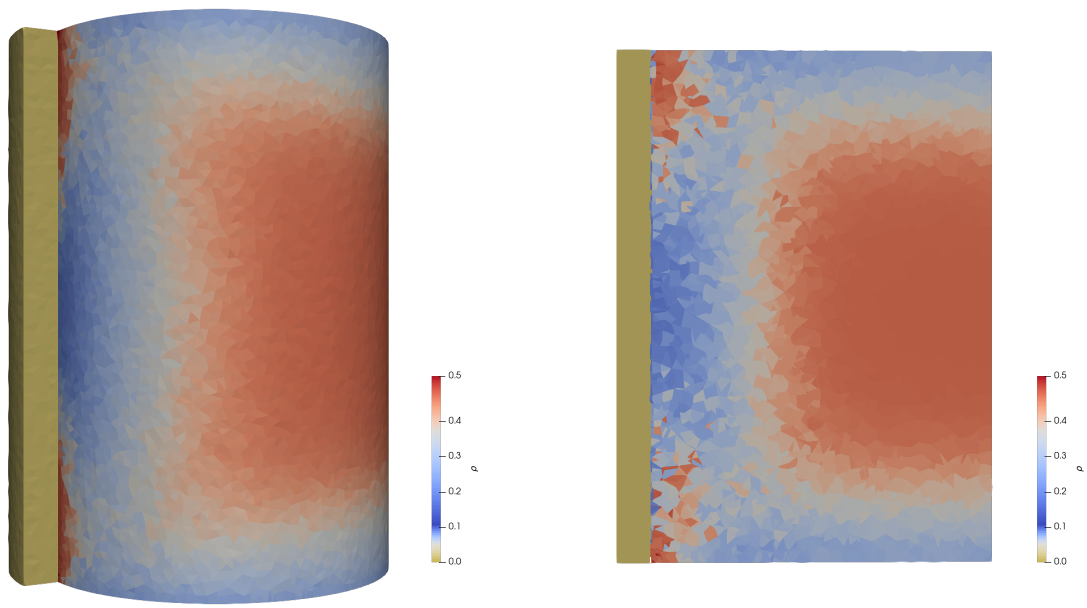


Figure 3.2: Optimal scaffold architecture for the experiment with external fixation, the titanium fixateur is marked in gold. The left picture shows the full specimen, the right picture displays a cut through a vertical plane.

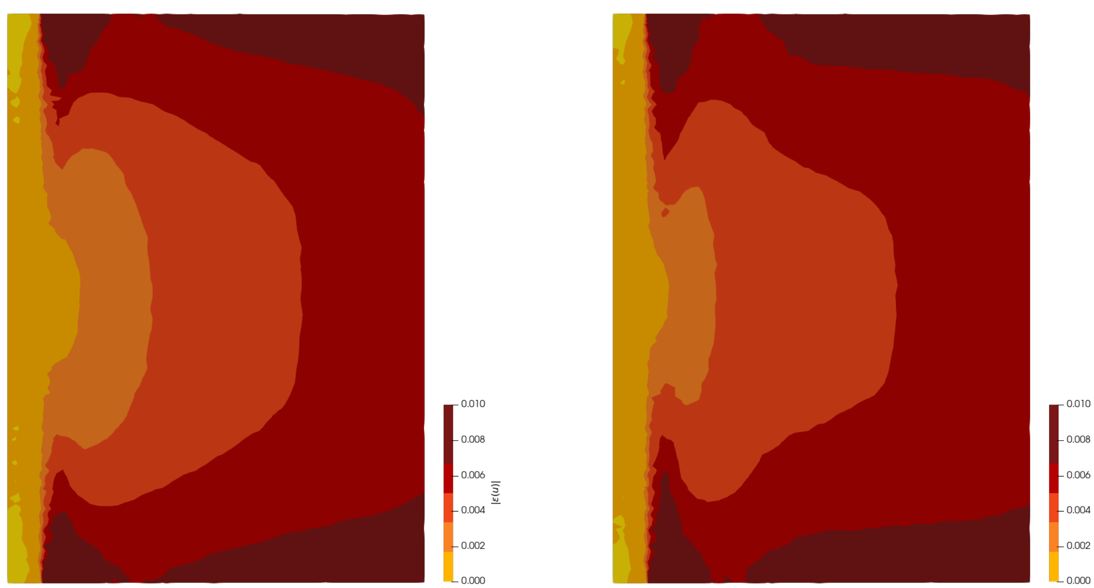


Figure 3.3: The strain magnitude distributions for the scaffold architectures displayed in Figure 3.1 and Figure 3.2 are compared before the healing process, i.e., when no bone has regenerated yet. Note that the cylindric architecture from Figure 3.2 is used in an experiment with external fixation to measure its performance in a more realistic setting.

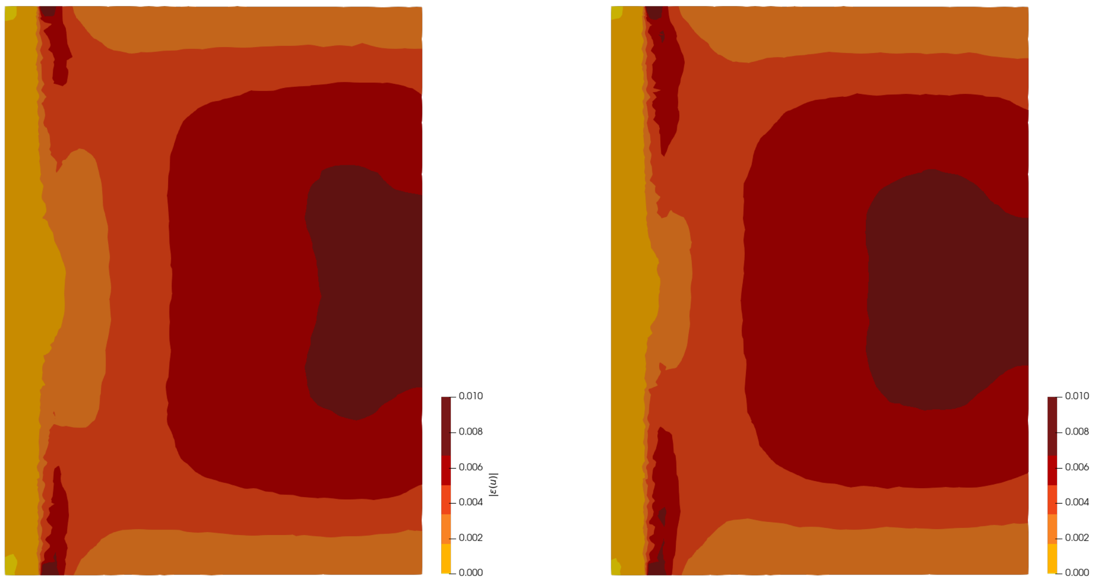


Figure 3.4: The strain magnitude distributions for the scaffold architectures displayed in Figure 3.1 and Figure 3.2 are compared two months in the healing process. Note that the cylindric architecture from Figure 3.2 is used in an experiment with external fixation to measure its performance in a more realistic setting.

favorable in view of this objective function. It is however debatable to what extend this represents a realistic effect or to which extend this should be regarded as a numerical artefact due to the simplistic geometrical set-up.

To illustrate the benefit of the three dimensional model, we compare the magnitude of the strains of the scaffolds from Figure 3.2 and Figure 3.1. Note that we use the scaffold architecture in Figure 3.1 in an experiment *including* external fixation to be able to compare the strain distributions in the same mechanical environment. In Figure 3.3 we compare the strain distributions at the initial time-point, when no bone has regenerated yet and the strain distribution after two months is shown in Figure 3.4. Note that for both time-points a significant stress-shielding effect is visible with a clear low-strain region in the central part of the specimen close to the fixateur. This shows that the scaffold architecture from Figure 3.2 leads to a mitigation of the undesired stress-shielding effects and thus promotes more homogeneous bone growth. We remark that the reduction of stress-shielding is not directly part of the objective function with respect to which the optimization is carried out. Rather, this effect is an implicit favorable consequence of the objective function (3.36) that advocates for its usage in scaffold design optimization.

V Numerical Experiments for Patient Specific Scaffold Optimization

In this Section we present a parameter study focusing on the effect of reduced bone regeneration and/or vascularization on the optimal scaffold architecture. This is of special importance for patients with a co-morbidity such as type 2 diabetes mellitus (T2DM), see Alcaraz et al. (2017; 2014); List et al. (2016). We use a version of the homogenized model (1.1) – (1.4) that does not directly fall into the framework of Chapter 2. We remark that the analysis of Chapter 2 and Chapter 3 can be extended to this model, however, this is not the focus here. This Section is based on Dondl and Zeinhofer (2021).

5.1 An Adapted Model

In this model the relevant quantities are again the scaffold's local volume fraction $\rho(x)$, the molecular weight of the scaffold material $\sigma(t) = \exp(-k_1 t)$ (which diminishes exponentially over time due to bulk erosion) and the local volume fraction of regenerated osteoblast cells c_{ost} that contribute with the mechanical properties of calcified bone, see Perier-Metz et al. (2020). Here we differ slightly in terms of interpretation from the model in Chapter 2, resolving bone via a density of osteoblasts instead of calcified bone. Bone regeneration, i.e., the growth of osteoblasts, depends on the local biological environment modeled through growth factors/cytokines. Clinically, numerous such factors can be observed as discussed in Devescovi et al. (2008), however, having vascularization in focus, we include only vascular endothelial growth factor (VEGF) – responsible for new vessel formation – and bone growth factor (BGF) which drives bone growth. These quantities are represented as $a_{\mathrm{VEGF}}(t,x)$ and $a_{\mathrm{BGF}}(t,x)$. Finally, $c_{\mathrm{vasc}}(t,x)$ is the local fraction of endothelial cells responsible for vascularization.

The spatial domain of computation is the space occupied by the scaffold, which is simplified to a one-dimensional object via considering only the main stress axis in a segmental defect in a long bone. More precisely, the defect is assumed to be 30mm in size, which is resolved by the domain $\Omega = (0,30)$. The time horizon is set to 12 months using the time interval $I = [0,12]$. Concretely, we solve the following system of differential equations

$$0 = \operatorname{div}\left((k_8 c_{\mathrm{ost}} + \rho\sigma)u'\right) \tag{3.38}$$

$$\dot{a}_1 = \operatorname{div}\left(k_5(1-\rho)a_1'\right) + k_{2,1} f(u') c_{\mathrm{ost}} - k_{3,1}a_1 \tag{3.39}$$

$$\dot{a}_2 = \operatorname{div}\left(k_5(1-\rho)a_2'\right) + k_{2,2} c_{\mathrm{ost}} - k_{3,2}a_2 \tag{3.40}$$

$$\dot{v} = k_6 a_2 (1 + k_7 v)\left(1 - \frac{v}{1-\varphi(\rho)}\right) \tag{3.41}$$

$$\dot{c}_{\mathrm{ost}} = k_4 a_1 v \left(1 - \frac{c_{\mathrm{ost}}}{1-\rho}\right) \tag{3.42}$$

In this system, k_i, $i = 1,\ldots,8$ are parameters and f, φ are functional relationships. Equation (3.38) allows to compute the displacement field $u(t,x)$ depending on the scaffold-bone composite. In equation (3.39), the term $k_{2,1} f(u')c_{\mathrm{ost}}$ encodes that BGF gets only produced if osteoblasts sense a suitable mechanical stimulus. Furthermore, the BGF molecules diffuse and decay at certain rates. A similar behavior is modeled for VEGF, however, the production of VEGF does not require the presence of mechanical stimuli. The cell types responsible for vascularization, c_{vasc} and for bone growth c_{ost} are modeled as logistic ODEs pointwise in space. We do not include diffusion as these cells diffuse little if at all, see for instance Perier-Metz et al. (2020). The growth of c_{vasc} is driven through the presence of a_{VEGF} and proliferation and is saturated by the "space-filling" factor $1 - (c_{\mathrm{vasc}})/(1-\varphi(\rho))$. The functional relationship φ represents the special need of blood vessels for space and should be chosen to lie above the identity function. It is now for example the sensitivity of the optimal scaffold design with respect to the parameters k_6 and k_7 that we focus on in this manuscript. Finally, equation (3.42) for osteoblast production is similar to the one previously described. The necessary drivers are here BGF and c_{vasc}.

The initial and boundary conditions are given by

$$u'(t,0) = -u'(t,x) = 0.01 \tag{3.43}$$

$$a_{\mathrm{VEGF}}(0,x) = a_{\mathrm{BGF}}(0,x) = 0 \tag{3.44}$$

$$a_{\mathrm{VEGF}}'(t,0) = a_{\mathrm{VEGF}}'(t,L) = 0 \tag{3.45}$$

$$a_{\mathrm{BGF}}(t,0) = a_{\mathrm{BGF}}(t,L) = 1 \tag{3.46}$$

$$c_{\mathrm{vasc}}(0,x) = 0 \tag{3.47}$$

$$c_{\mathrm{ost}}(0,x) = 0, \tag{3.48}$$

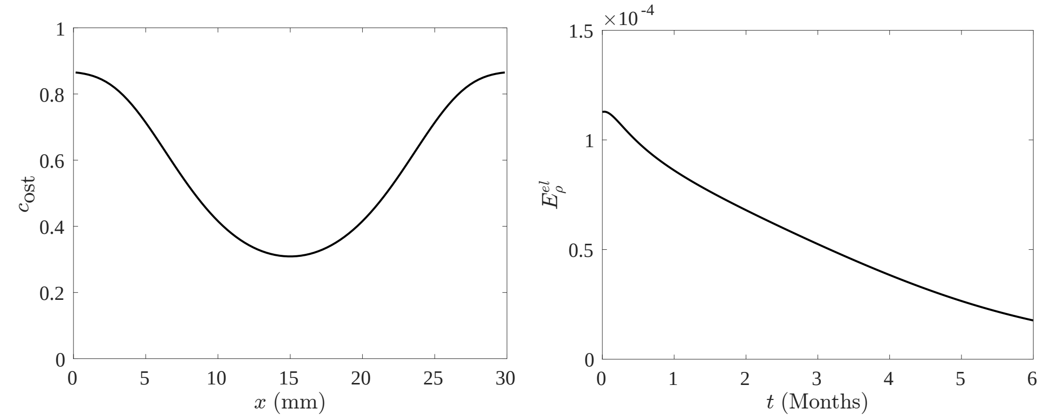
for all $x \in (0,L)$, $t \in [0,T)$, meaning that the elastic equation is subjected to a soft compressive load, BGF diffuses from healthy bone and VEGF is subjected to non-flux boundary conditions. Both molecules are not present at the initial time point. Similarly, neither c_{vasc} nor c_{ost} is present in the beginning after implantation of the scaffold.

The function f is simply a regularization of the usual absolute value, with $f(u') = \sqrt{u'^2 + \delta^2}$, where $\delta = 10^{-4}$. The special cut-off function φ is chosen as $\varphi(\rho) = \sqrt{\rho}$. This ensures that vasculature only occurs to the extent that there is space in the scaffold pores. The default model parameters follow to a large extent the ones in used in Section III and are reported in Table 3.1. They are chosen such that the model with default parameters reproduces the results from the ovine model in Cipitria et al. (2015), see Figure 3.5.

For optimization purposes our approach is identical to Section IV, i.e., we compute the time evolution of the mechanical implant for a given ρ. In our case this is proportional to the inverse of the elastic energy in

k_1	0.1	k_8	9.0	k_5	260	$k_{2,1}$	12 000	$k_{3,1}$	16.0
$k_{2,2}$	8.0	$k_{3,2}$	8.0	k_6	0.8	k_7	1.2	k_4	1.2

Table 3.1: Parameters in the default model.



(a) Regenerated bone density (osteoblasts) c_{ost} at $t = 12$ months.

(b) Time evolution of the elastic energy in the scaffold/bone composite.

Figure 3.5: Outcome of the model for the default set of parameters given in Table 3.1 and a scaffold of constant density $\rho = 0.13$. To be compared with (Cipitria et al., 2015, Figure 2B, Scaffold only).

the system at time $t \in [0, T]$

$$\mathcal{E}^{\mathrm{el}}_{\rho}(t)^{-1} = \left[\frac{1}{2}\int_0^L u'(\rho\sigma + k_8 c_{\mathrm{ost}})u'\,\mathrm{d}x\right]^{-1} \tag{3.49}$$

where ρ, σ, u and c_{ost} solve equations (3.38)–(3.42) with conditions (3.43)–(3.48). Then we use again the (reduced) objective function

$$\hat{J}(\rho) = \left(\int_0^T |\mathcal{E}^{\mathrm{el}}_{\rho}(t)|^5\,\mathrm{d}t\right)^{\frac{1}{5}}, \tag{3.50}$$

which is a good approximation for $\max_{t\in[0,T]} \mathcal{E}^{\mathrm{el}}_{\rho}(t)$, and the optimization problem becomes

$$\min_{\rho} \hat{J}(\rho) \quad \text{subjected to} \quad 0 < c \leq \rho(x) \leq C < 1, \tag{3.51}$$

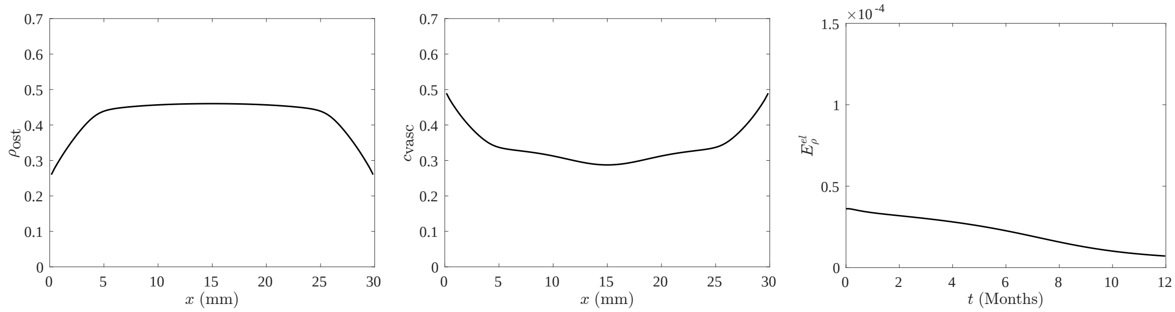
The main question we address in this manuscript is dependence of the optimal scaffold architecture on the parameters k_4, k_6, and k_7 – that means, we solve the optimization problem for different values of these parameters and observe the optimization outcome.

The numerical implementation of the model is based on a simple semi-implicit in time (in the sense that equations (3.38)–(3.42), each of which is a linear equation, are solved individually implicitly one at a time in order) one-dimensional finite element scheme with 100 one-dimensional P1 finite elements and a time discretization using 500 time steps for the interval $[0, T]$. The optimization problem is solved using an $L^2(\Omega)$ gradient flow with the variation of the objective function computed using an adjoint approach.

5.2 Results and Discussion

The outcome of the model for the default set of parameters given in Table 3.1 can be seen in Figure 3.5. One can clearly see that the distinct shape of regenerated bone bone density, with in-growth first from the proximal and distal end of the scaffold, is recovered in this model. The optimal scaffold design for the default set of parameters is displayed in Figure 3.6.

Experiment 1. Varying the rate of regeneration. Figure 3.7 shows the optimal scaffolds for three different rates of bone regeneration k_4. All parameters other than k_4 are as given in Table 3.1.

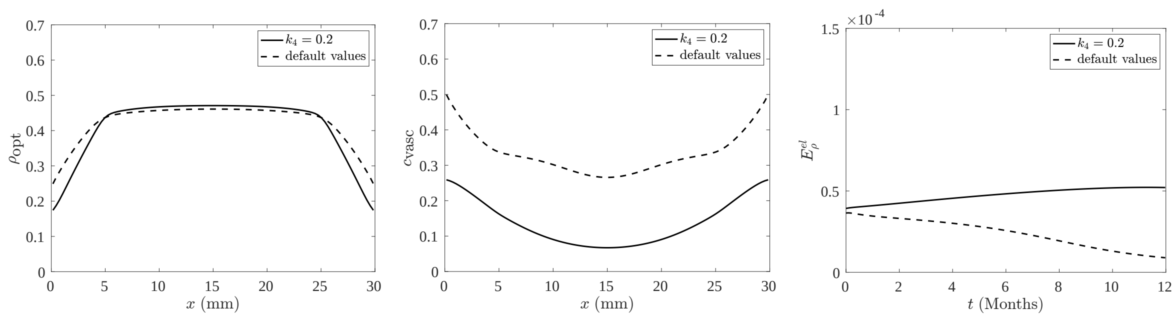


(a) Optimized scaffold density.

(b) Amount of regenerated vasculature at $t = 12$ months.

(c) Time evolution of the elastic energy in the scaffold/bone composite.

Figure 3.6: Optimal scaffold design for the default set of parameters given in Table 3.1.

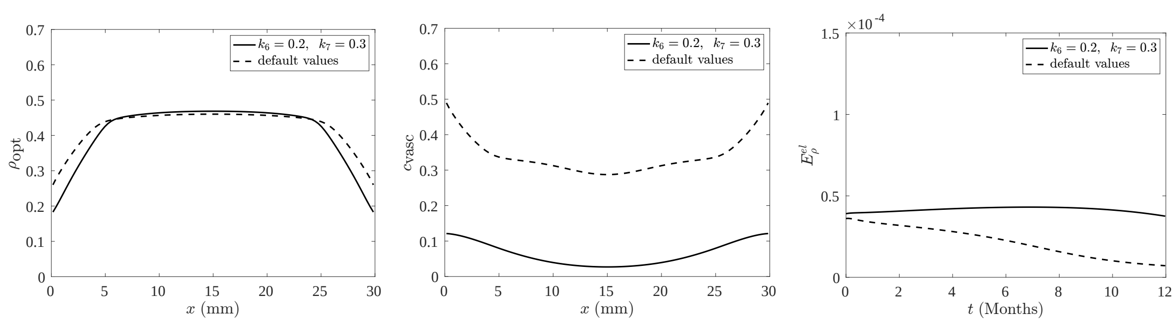


(a) Optimized scaffold density.

(b) Amount of regenerated vasculature at $t = 12$ months.

(c) Time evolution of the elastic energy in the scaffold/bone composite.

Figure 3.7: Optimal scaffold design for different values of k_4.

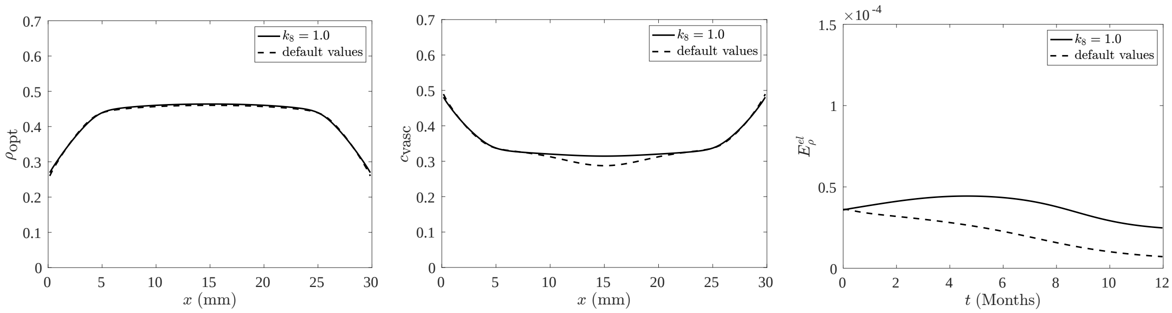


(a) Optimized scaffold density.

(b) Amount of regenerated vasculature at $t = 12$ months.

(c) Time evolution of the elastic energy in the scaffold/bone composite.

Figure 3.8: Optimal scaffold design for different values of k_6 and k_7.



(a) Optimized scaffold density. (b) Amount of regenerated vasculature at $t = 12$ months. (c) Time evolution of the elastic energy in the scaffold/bone composite.

Figure 3.9: Optimal scaffold design for different values of k_8.

Experiment 2. Varying the rate of vasculature formation. Figure 3.8 shows the optimal scaffolds for three different rates for the formation of vasculature k_6, k_7. All parameters other than k_6, k_7 are as given in Table 3.1.

Experiment 3. Varying the relative stiffness of regenerated bone matrix/osteoblasts. Figure 3.9 shows the optimal scaffolds for three different densities of regenerated bone matrix (here indicated by the relative elastic modulus k_8). All parameters other than k_8 are as given in Table 3.1.

Summary. Overall, one can note that impeded regeneration (as in experiments 1 and 2), the optimal scaffold is somewhat less dense at the proximal and distal ends of the defect (where the defect is adjacent to remaining healthy bone. This makes it easier for BGF to diffuse into the defect domain, thus accelerating bone regeneration. If the mechanical properties of regenerated bone are somehow compromised (due to, e.g., osteoporosis), our analysis yields no significant change in optimal scaffold architecture. The cost functional is still increased, however.

Chapter 4

Appendix

I Hölder Regularity of Elliptic Equations with Mixed Boundary Conditions

In this Section we prove a Hölder regularity result for linear elliptic equations with mixed boundary conditions and measurable, bounded coefficients. The Theorem is in the spirit of Stampacchia's result in Stampacchia (1960). However, we extend the results from Stampacchia (1960) to Lipschitz domains with a very weak compatibility condition on the Dirichlet-Neumann partition $\partial\Omega = \Gamma_D \cup \Gamma_N$ of the boundary. More precisely, we require $\Omega \cup \Gamma_N$ to be a regular set in the sense of Gröger, see definition 47. This is exactly the setting in Haller-Dintelmann et al. (2009) and the Hölder regularity result is already proven there. However, in Haller-Dintelmann et al. (2009) no explicit control of the Hölder norm of a solution is provided. Our contribution is to show that the Hölder norm of a solution can be controlled through the norm of the right-hand side multiplied by a constant only depending on the ellipticity constant of the coefficients, the L^∞ bound of the coefficients and the geometry of the domain Ω. To this end, we follow closely the proof in Haller-Dintelmann et al. (2009) and pay attention to all appearing constants.

1.1 Main Result

We say a bounded, open set $\Omega \subset \mathbb{R}^d$ is a Lipschitz domain if $\overline{\Omega}$ is a Lipschitz manifold with boundary, see (Grisvard, 2011, Definition 1.2.1.2). In the following we will denote the cube $[-1,1]^n \subset \mathbb{R}^d$ by Q, its half $\{x \in Q \mid x_d < 0\}$ by Q_-, the hyperplane $\{x \in Q \mid x_d = 0\}$ by Σ and $\{x \in \Sigma \mid x_{d-1} < 0\}$ by Σ_0. The following definition is due to Gröger, see Gröger (1989).

Definition 47 (Gröger Regular Sets)**.** Let $\Omega \subset \mathbb{R}^d$ be bounded and open and $\Gamma \subset \partial\Omega$ a relatively open set. We call $\Omega \cup \Gamma$ Gröger regular, if for every $x \in \partial\Omega$ there are open sets $U, V \subset \mathbb{R}^d$ with $x \in U$, and a bijective, bi-Lipschitz map $\phi : U \to V$, such that $\phi(x) = 0$ and $\phi(U \cap (\Omega \cup \Gamma))$ is either Q_-, $Q_- \cup \Sigma$ or $Q_- \cup \Sigma_0$.

It can easily be seen that a Gröger regular set Ω (no matter the choice $\Gamma \subset \partial\Omega$) is a Lipschitz domain, see (Haller-Dintelmann et al., 2009, Theorem 5.1).

Theorem 48 (Quantitative Hölder Control for Mixed Boundary Value Problems)**.** *Let $\Omega \subset \mathbb{R}^d$ be bounded and open with $d \in \{2,3,4\}$, consider a partition $\partial\Omega = \Gamma_N \cup \Gamma_D$ into Neumann and Dirichlet boundary and assume that $\Omega \cup \Gamma_N$ is Gröger regular. Let $\mathcal{M} \subset L^\infty(\Omega, \mathbb{R}^{d\times d})$ be a set of matrix-valued, measurable functions with a common lower bound $\nu > 0$ on the ellipticity constants and a common upper bound M on the $L^\infty(\Omega, \mathbb{R}^{d\times d})$ norm. For $A \in \mathcal{M}$ define the operator*

$$- \operatorname{div}(A\nabla\cdot) + 1 : H^1_D(\Omega) \to H^1_D(\Omega)^*, \quad u \mapsto \int_\Omega A\nabla u \nabla\cdot + u \cdot \mathrm{d}x. \tag{4.1}$$

Then, for every $q > d$ and $A \in \mathcal{M}$ there exists $\alpha > 0$ such that

$$(-\operatorname{div}(A\nabla\cdot) + 1)^{-1} : W^{-1,q}_D(\Omega) \to C^\alpha(\Omega)$$

is continuous. Stronger, for all $A \in \mathcal{M}$ we may choose the same $\alpha > 0$ and can estimate the operatornorms

$$\sup_{A\in\mathcal{M}} \left\| (-\operatorname{div}(A\nabla\cdot) + 1)^{-1} \right\|_{\mathcal{L}(W^{-1,q}_D(\Omega), C^\alpha(\Omega))} < \infty. \tag{4.2}$$

Proof. The idea of the proof is to localize the equation by a partition of unity, additionally employing the Lipschitz transformations from the definition of a Gröger regular set. Using a suitable reflection technique at the Neumann boundary, this allows to apply Hölder regularity results for pure, homogeneous Dirichlet problems either on a ball or a cuboid. In these cases quantitative regularity results exist. The details of the proof are carried out throughout this Section. As only the quantitative aspects of the transformations are missing, we pay special attention to these and keep the remaining aspects of the proof brief, referring to Haller-Dintelmann et al. (2009) when necessary. □

1.2 Known Regularity Results

We review the known regularity results that we need in the proof of the main Theorem. We begin with a classical Hölder regularity result for elliptic equations without mixed boundary conditions. The following is Theorem C.2 in Kinderlehrer and Stampacchia (2000).

Theorem 49. *Let $\Omega \subset \mathbb{R}^d$ be a ball or a cuboid, $f \in L^q(\Omega, \mathbb{R}^d)$ with $q > d$ and $q > 2$. Assume that $A \in L^\infty(\Omega, \mathbb{R}^{d\times d})$ is uniformly elliptic with ellipticity constant $\nu > 0$ and $L^\infty(\Omega, \mathbb{R}^{d\times d}$ bound $M > 0$. Then, there exist $K = K(\nu, M, \Omega, d) > 0$ and $\alpha = \alpha(\nu, M, \Omega, d) \in (0, 1)$ such that for the solution $u \in H_0^1(\Omega)$ of*

$$\int_\Omega A\nabla u\nabla(\cdot)\mathrm{d}x = \int_\Omega f \cdot \nabla(\cdot)\mathrm{d}x \quad \text{in } H_0^1(\Omega)^*$$

it holds $u \in C^0(\Omega)$ and

$$\max_{\overline{\Omega}\cap B_r(x)} u(x) - \min_{\overline{\Omega}\cap B_r(x)} u(x) = \operatorname*{osc}_{\overline{\Omega}\cap B_r(x)} u \le K\|f\|_{L^q(\Omega,\mathbb{R}^d)} \cdot r^\alpha. \tag{4.3}$$

Proof. This is Theorem C.2 in Kinderlehrer and Stampacchia (2000). The result is proven for domains of class s in this book that however trivially include balls and cuboids. For us the result for balls and cuboids suffices. □

The above result implies a control of the Hölder norm. We collect this fact in a Corollary.

Corollary 50. *Assume we are in the situation of Theorem 49. Then*

$$(-\operatorname{div} A\nabla)^{-1} : W_0^{1,q'}(\Omega)^* \to C^\alpha(\Omega)$$

is well defined and continuous with its operatornorm bounded by

$$\left\|(-\operatorname{div} A\nabla)^{-1}\right\|_{\mathcal{L}(W_0^{1,q'}(\Omega)^*, C^\alpha(\Omega))} \le K,$$

with $K = K(\nu, M, \Omega, d)$, however, possibly different from the constant K in Theorem 49.

Proof. We begin by showing that (4.3) yields a bound on the $C^\alpha(\Omega)$ norm of a solution u to $-\operatorname{div}(A\nabla u) = f$. To this end, take $x, y \in \overline{\Omega}$ and consider the closed ball around x with radius $r = |x - y|$. Then, $y \in B_r(x)$ and (4.3) yields

$$|u(x) - u(y)| \le \operatorname*{osc}_{\overline{\Omega}\cap B_r(x)} u \le K\|f\|_{L^q(\Omega,\mathbb{R}^d)}|x - y|^\alpha,$$

hence

$$|u|_{C^\alpha(\Omega)} \le K\|f\|_{L^q(\Omega,\mathbb{R}^d)}.$$

To bound the $C^0(\Omega)$ norm of u, note that u vanishes on the boundary of Ω. Let $x \in \overline{\Omega}$ and $x_0 \in \partial\Omega$ and use again (4.3) to estimate

$$|u(x)| \le |u(x) - u(x_0)| \le K\|f\|_{L^q(\Omega,\mathbb{R}^d)}|x - x_0|^\alpha \le K\|f\|_{L^q(\Omega,\mathbb{R}^d)} \operatorname{diam}(\Omega)^\alpha.$$

Hence,

$$\|u\|_{C^\alpha(\Omega)} \le K \max(1, \operatorname{diam}(\Omega)^\alpha)\|f\|_{L^q(\Omega,\mathbb{R}^d)}.$$

To conclude the proof, note that any abstract functional $\phi \in W_0^{1,q'}(\Omega)^*$ can be written in the form

$$\phi = \int_\Omega f \cdot \nabla(\cdot)\mathrm{d}x$$

for some $f \in L^q(\Omega, \mathbb{R}^d)$ and clearly it holds for a constant $c = c(\Omega, d)$

$$\left\|\phi\right\|_{W_0^{1,q'}(\Omega)^*} \leq \|f\|_{L^q(\Omega,\mathbb{R}^d)} \leq c \cdot \left\|\phi\right\|_{W_0^{1,q'}(\Omega)^*}.$$

Thus, we can estimate the operatornorm

$$\left\|(-\operatorname{div}(A\nabla))^{-1}\right\|_{\mathcal{L}(W_0^{1,q'}(\Omega)^*),C^\alpha(\Omega)} \leq c \cdot K \max(1, \operatorname{diam}(\Omega)^\alpha)$$

as asserted. □

The next result concerns higher integrability of the gradient of the solution of an elliptic equation subjected to mixed boundary conditions. It is essentially to Gröger, see for example Gröger (1989); Gröger and Rehberg (1989) for the original work and Haller-Dintelmann et al. (2016) for a more recent proof that weakens the assumptions on the domain even further. However, we stay in the realm of Gröger regular sets as this seems general enough for the applications we have in mind. The concrete statement of this fact is Theorem 5.6 in Haller-Dintelmann et al. (2016).

Theorem 51 (Higher Gradient Integrability)**.** *Let $\mathcal{M} \subset L^\infty(\Omega, \mathbb{R}^{d\times d})$ be a set of matrix valued functions with a common lower bound $\nu > 0$ on the ellipticity constants and a common upper bound $M > 0$ on the $L^\infty(\Omega, \mathbb{R}^{d\times d})$ norm. Furthermore, assume that $\Omega \cup \Gamma_N$ is Gröger regular. Then, there is an open interval $I_\mathcal{M}$ around 2 such that for all $A \in \mathcal{M}$ and $p \in I_\mathcal{M}$*

$$-\operatorname{div}(A\nabla) + 1 : W_D^{1,p}(\Omega) \to W_D^{1,p'}(\Omega)^*$$

is a linear homeomorphism and we have

$$\sup_{p\in I_\mathcal{M}} \sup_{A\in\mathcal{M}} \left\|(-\operatorname{div}(A\nabla) + 1)^{-1}\right\|_{\mathcal{L}(W_D^{1,p}(\Omega),W_D^{1,p'}(\Omega)^*)} < \infty.$$

Proof. This is Theorem 5.6 in Haller-Dintelmann et al. (2016). However, we need to guarantee that our assumptions imply the Assumptions 2.3, 3.1 and 5.4 in the notation of that paper (which they a forteriori do). In fact, Gröger regular sets are Lipschitz domains and this ensures Assumption 2.3 in Haller-Dintelmann et al. (2016) and also Assumption 4.11 there. Then, Assumption 4.11 implies Assumption 3.1 as shown in Theorem 4.15 in Haller-Dintelmann et al. (2016). Finally, Assumption 5.4 only requires ellipticity and measurability of the functions $A \in \mathcal{M}$, a fact that we also assumed. □

1.3 Useful Facts concerning Gröger Regular Sets

In the definition of Gröger regular sets, the local model $\{x \in Q \mid x_d < 0\} \cup \{x \in Q \mid x_d = 0,\ x_{d-1} < 0\}$ is redundant. We cite Lemma 4.10 in Haller-Dintelmann et al. (2009).

Lemma 52. *There exists a bi-Lipschitz mapping $\Psi : \mathbb{R}^d \to \mathbb{R}^d$ mapping $Q_- \cup \Sigma_0$ onto $Q_- \cup \Sigma$.*

We state useful characterizations of Gröger regular sets in two and three space definitions. These characterizations allow to check for Gröger regularity almost by the appearance of a domain Ω. We cite the results from Haller-Dintelmann et al. (2009).

Theorem 53 (Gröger Regular Sets in 2D)**.** *Let $\Omega \subset \mathbb{R}^2$ be a Lipschitz domain and $\Gamma \subset \partial\Omega$ be relatively open. Then $\Omega \cup \Gamma$ is Gröger regular if and only if $\overline{\Gamma} \cap (\partial\Omega \setminus \Gamma)$ is finite and no connected component of $\partial\Omega \setminus \Gamma$ consists of a single point.*

Theorem 54 (Gröger Regular Sets in 3D)**.** *Let $\Omega \subset \mathbb{R}^3$ be a Lipschitz domain and $\Gamma \subset \partial\Omega$ be relatively open. Then $\Omega \cup \Gamma$ is Gröger regular if and only if the following two conditions hold*

(i) $\partial\Omega \setminus \Gamma$ is the closure of its interior.

(ii) For any $x \in \overline{\Gamma} \cap (\partial\Omega \setminus \Gamma)$ there is an open neighborhood U_x of x and a bi-Lipschitz map $\phi : U_x \cap \overline{\Gamma} \cap (\partial\Omega \setminus \Gamma) \to (-1, 1)$.

1.4 Technical Lemmas

As the strategy to prove Theorem 48 consists of localization techniques we investigate in the following technical Lemmas how this effects the Hölder control we are interested in. The localization goes through three possible stages: i) a localization by a partition of unity. This involves analyzing how the equation is changed when the solution is multiplied by a smooth cut-off function, ii) in the vicinity of $\partial\Omega$, the Lipschitz transformations to cuboids from the definition of Gröger regular sets need to be employed. This yields a pure Dirichlet problem for the Dirichlet boundary, iii) at the Neumann boundary a reflection technique is used to also produce a pure Dirichlet problem.

This is Lemma 4.6 in Haller-Dintelmann et al. (2009). Our contribution is to control the appearing norms explicitly.

Lemma 55 (Localization by a Cut-Off Function I)**.** *Let $\Omega \subset \mathbb{R}^d$ be open and bounded with a partition $\partial\Omega = \Gamma_D \cup \Gamma_N$ in Dirichlet and Neumann boundary parts. Furthermore, let $\Omega \cup \Gamma_N$ be regular and $\mathcal{U} \subset \mathbb{R}^d$ open, such that $\Omega_\bullet := \Omega \cap \mathcal{U}$ is also a Lipschitz domain. Furthermore, set $\Gamma_\bullet := \Gamma_D \cap \mathcal{U}$ and let $\eta \in C_0^\infty(\mathbb{R}^d)$ with support in $\mathcal{U}$. For arbitrary but fixed $q \in [1,\infty)$ define the maps*

(i) The multiplication-restriction operator

$$R_\eta : W^{1,q}_{\Gamma_D}(\Omega) \to W^{1,q}_{\Gamma_\bullet}(\Omega_\bullet), \quad v \mapsto \eta v_{|\Omega_\bullet}.$$

(ii) The multiplication-extension operator

$$E_\eta : W^{1,q}_{\Gamma_\bullet}(\Omega_\bullet) \to W^{1,q}_{\Gamma_D}(\Omega), \quad v \mapsto \widetilde{\eta v}.$$

Here, the map $v \mapsto \tilde{v}$ denotes the extension by zero outside of $\Omega_\bullet$.

Then, both maps are well defined, linear and continuous and we may estimate

$$\|\eta v_{|\Omega_\bullet}\|_{W^{1,q}_{\Gamma_\bullet}(\Omega_\bullet)} \leq 2\|\eta\|_{C^1(\Omega_\bullet)} \|v\|_{W^{1,q}_{\Gamma_D}(\Omega)} \quad \& \quad \|\widetilde{\eta v}\|_{W^{1,q}_{\Gamma_D}(\Omega)} \leq 2\|\eta\|_{C^1(\Omega_\bullet)} \|v\|_{W^{1,q}_{\Gamma_\bullet}(\Omega_\bullet)}.$$

Proof. The well definedness of R_η and E_η was established in Lemma 4.6 in Haller-Dintelmann et al. (2009). The estimates can be computed in the following way

$$\begin{aligned}\|\eta v_{|\Omega_\bullet}\|_{W^{1,q}_{\Gamma_\bullet}(\Omega_\bullet)} &= \|\eta v\|_{L^q(\Omega_\bullet)} + \|\nabla(\eta v)\|_{L^q(\Omega_\bullet,\mathbb{R}^d)} \\ &\leq \|\eta v\|_{L^q(\Omega_\bullet)} + \|v\nabla\eta\|_{L^q(\Omega_\bullet,\mathbb{R}^d)} + \|\eta\nabla v\|_{L^q(\Omega_\bullet,\mathbb{R}^d)} \\ &\leq \|\eta\|_{C^0(\Omega_\bullet)}\|v\|_{L^q(\Omega)} + \|\nabla\eta\|_{C^0(\Omega_\bullet)^d}\|v\|_{L^q(\Omega)} + \|\nabla v\|_{L^q(\Omega,\mathbb{R}^d)}\|\eta\|_{C^0(\Omega_\bullet)} \\ &\leq 2\|\eta\|_{C^1(\Omega_\bullet)}\|v\|_{W^{1,q}(\Omega)}.\end{aligned}$$

The expression $\|\widetilde{\eta v}\|_{W^{1,q}(\Omega)}$ can be estimated similarly. □

Lemma 56. *Let $\Omega, \Gamma_N, \Gamma_D, \mathcal{U}, \eta, \Omega_\bullet, \Gamma_\bullet, R_\eta$ and E_η be as in Lemma 55 and denote by $A_\bullet$ the restriction of a function $A \in L^\infty(\Omega, \mathbb{R}^{d\times d})$ to the set $\Omega_\bullet$. For $f \in H^1_D(\Omega)^*$ denote by $v_f \in H^1_D(\Omega)$ the function that satisfies*

$$-\operatorname{div}\left(A\nabla v_f\right) + v_f = f, \quad \text{in } H^1_{\Gamma_D}(\Omega)^*.$$

Define the maps

(i) The adjoint map of E_η for $q \in (1,\infty)$

$$E^*_\eta : W^{1,q'}_{\Gamma_D}(\Omega)^* \to W^{1,q'}_{\Gamma_\bullet}(\Omega_\bullet)^*, \quad f \mapsto f(\widetilde{\eta(\cdot)}) =: f_\bullet$$

(ii) The functional T_{v_f}

$$T_{v_f} : H^1_{\Gamma_\bullet}(\Omega_\bullet) \to \mathbb{R}, \quad w \mapsto \int_{\Omega_\bullet} vA_\bullet\nabla\eta\nabla w \mathrm{d}x.$$

Then, the localization of v_f by η, i.e., $u_f := (\eta v)_{|\Omega_\bullet}$ satisfies the equation

$$-\operatorname{div}\left(A_\bullet\nabla u_f\right) = -(\eta v_f)_{|\Omega_\bullet} - (A_\bullet\nabla v_f)_{|\Omega_\bullet}(\nabla\eta)_{|\Omega_\bullet} + T_{v_f} + f_\bullet =: f^\bullet \quad \text{in } H^1_{\Gamma_\bullet}(\Omega_\bullet)^*. \tag{4.4}$$

Furthermore, if $2 \leq d \leq 4$ and $f \in W^{1,q'}_{\Gamma_D}(\Omega)^*$ with $q > d$, then there exists $p > d$ such that $f^\bullet \in W^{1,p'}_{\Gamma_\bullet}(\Omega_\bullet)^*$ and the map

$$\mathrm{Loc} : W^{1,q'}_{\Gamma_D}(\Omega)^* \to W^{1,p'}_{\Gamma_\bullet}(\Omega_\bullet)^*, \quad f \mapsto f^\bullet$$

possesses an estimate on its operatornorm only depending on ν, M and Ω, i.e.,

$$\|f^\bullet\|_{W^{1,p'}_{\Gamma_\bullet}(\Omega_\bullet)^*} \leq C(\Omega,\nu,M)\|f\|_{W^{1,q'}_{\Gamma_D}(\Omega)^*} \tag{4.5}$$

Proof. This is Lemma 4.7 in Haller-Dintelmann et al. (2009), however, we provide the explicit norm control in (4.5). To this end, we treat the terms in (4.4) separately. First, note that there is $\varepsilon > 0$ such that

$$W^{1,4/3-\varepsilon}_{\Gamma_\bullet}(\Omega_\bullet) \hookrightarrow L^{4/3}(\Omega_\bullet)$$

and we set $p_1' = 4/3 - \varepsilon$ which implies $p_1 > 4$. We then compute for $w \in W^{1,p_1'}_{\Gamma_\bullet}(\Omega_\bullet)$

$$\begin{aligned}\int_{\Omega_\bullet} \eta v_f w \mathrm{d}x &\leq \|\eta\|_{L^\infty(\Omega_\bullet)} \|v_f\|_{L^4(\Omega_\bullet)} \|w\|_{L^{4/3}(\Omega_\bullet)} \\ &\leq C(\Omega)\|\eta\|_{L^\infty(\Omega_\bullet)} \|v_f\|_{H^1_{\Gamma_D}(\Omega)} \|w\|_{W^{1,p_1'}_{\Gamma_\bullet}(\Omega_\bullet)} \\ &\leq C(\Omega,\nu)\|\eta\|_{L^\infty(\Omega_\bullet)} \|f\|_{H^1_{\Gamma_D}(\Omega)^*} \|w\|_{W^{1,p_1'}_{\Gamma_\bullet}(\Omega_\bullet)} \\ &\leq C(\Omega,\nu)\|\eta\|_{L^\infty(\Omega_\bullet)} \|f\|_{W^{1,q'}_{\Gamma_D}(\Omega)^*} \|w\|_{W^{1,p_1'}_{\Gamma_\bullet}(\Omega_\bullet)}\end{aligned}$$

Taking suprema over unit balls in $W^{1,p_1'}_{\Gamma_\bullet}(\Omega_\bullet)$ and $W^{1,q'}_{\Gamma_D}(\Omega)^*$ we get that the map

$$W^{1,q'}_{\Gamma_D}(\Omega)^* \to W^{1,p_1'}_{\Gamma_\bullet}(\Omega_\bullet)^*, \quad f \mapsto -\int_{\Omega_\bullet} \eta v_f(\cdot)\mathrm{d}x$$

has its operatornorm bounded by $C(\Omega,\nu)\|\eta\|_{L^\infty(\Omega_\bullet)}$.

For the second term, note that we may factorize for all small enough $\varepsilon > 0$ using Theorem 51

$$W^{1,q'}_{\Gamma_D}(\Omega)^* \hookrightarrow W^{1,(2+\varepsilon)'}_{\Gamma_D}(\Omega)^* \to W^{1,(2+\varepsilon)}_{\Gamma_D}(\Omega) \to L^{2+\varepsilon}(\Omega_\bullet) \hookrightarrow W^{1,p_2'}_{\Gamma_\bullet}(\Omega_\bullet)^*$$

given by

$$f \mapsto f \mapsto v_f \mapsto A_\bullet \nabla v_f \nabla \eta_{|\Omega_\bullet} \mapsto \int_{\Omega_\bullet} A_\bullet \nabla v_f \nabla \eta(\cdot)\mathrm{d}x,$$

where $q' \leq (2+\varepsilon)'$ and $1/p_2 \geq (d-2-\varepsilon)/(d(2+\varepsilon))$, meaning $p_2 > 4$, the latter being possible due to $2 \leq d \leq 4$. The latter also implies the continuity of the embedding

$$L^{2+\varepsilon}(\Omega_\bullet) \hookrightarrow W^{1,p_2'}_{\Gamma_\bullet}(\Omega_\bullet)^*.$$

The operatornorm of the composition then essentially relies on the operatornorm of

$$W^{1,(2+\varepsilon)'}_{\Gamma_D}(\Omega)^* \to W^{1,2+\varepsilon}_{\Gamma_D}(\Omega), \quad f \mapsto v_f.$$

However, Theorem 51 shows that this is uniform with respect to the ellipticity constant ν of A, its $L^\infty(\Omega, \mathbb{R}^{d\times d})$ bound for A and all small $\varepsilon > 0$.

The third term works similar. Following Haller-Dintelmann et al. (2009) there is $\varepsilon > 0$ such that

$$W^{1,2+\varepsilon}_{\Gamma_D}(\Omega) \hookrightarrow L^{4+\delta}(\Omega)$$

for a $\delta = \delta(d) > 0$. We estimate for $w \in W^{1,(4+\delta)'}_{\Gamma_\bullet}(\Omega_\bullet)$

$$\begin{aligned}\langle T v_f, w\rangle_{W^{1,(4+\delta)'}_{\Gamma_\bullet}(\Omega_\bullet)} &\leq \|v_f\|_{L^{4+\delta}(\Omega_\bullet)} \|A\|_{L^\infty(\Omega,\mathbb{R}^{d\times d})} \|\nabla\eta\|_{L^\infty(\Omega_\bullet)} \|w\|_{W^{1,(4+\delta)'}_{\Gamma_\bullet}(\Omega_\bullet)} \\ &\leq C(\nu, M, \Omega)\|f\|_{W^{1,(2+\varepsilon)'}_{\Gamma_D}(\Omega)^*} \|A\|_{L^\infty(\Omega,\mathbb{R}^{d\times d})} \|\nabla\eta\|_{L^\infty(\Omega_\bullet)} \|w\|_{W^{1,(4+\delta)'}_{\Gamma_\bullet}(\Omega_\bullet)}.\end{aligned}$$

The constant $C(\nu, M, \Omega)$ is again determined through Theorem 51. We set $p_2 = 4 + \delta$.

Finally, the mapping $f \mapsto f_\bullet$ is nothing but E^*_η and thus $\|E^*_\eta\| = \|E_\eta\|$, the latter already being computed in Lemma 55. To conclude the proof we take $p = \min(p_1, p_2, p_3)$. □

The following is Proposition 4.9 in Haller-Dintelmann et al. (2009). We merely cite it as we do not need to explicitly estimate any additional constants in this result.

Proposition 57. *Let $\Omega \subset \mathbb{R}^d$ be a bounded Lipschitz domain, let Γ_N be an open subset of its boundary and denote by Γ_D its complement in $\partial\Omega$. Let ϕ be bi-Lipschitz mapping defined on a neighborhood of Ω into $\mathbb{R}^d$ and denote $\phi(\Omega) = \widehat{\Omega}$ and $\phi(\Gamma_D) = \widehat{\Gamma}_D$. Then the following holds:*

(i) For any $p \in (1,\infty)$, the mapping ϕ induces a linear homeomorphism

$$\Phi_p : W^{1,p}_{\widehat{D}}(\widehat{\Omega}) \to W^{1,p}_D(\Omega), \quad u \mapsto u \circ \phi.$$

(ii) If A is a member of $L^\infty(\Omega, \mathbb{R}^{d\times d})$, then

$$-\Phi^*_{p'} \circ \operatorname{div}(A\nabla\Phi_p(\cdot)) = -\operatorname{div}(\widehat{A}\nabla(\cdot))$$

with

$$\widehat{A}(y) = \frac{D\phi(\phi^{-1}(y))}{\det(D\phi)(\phi^{-1}(y))} A(\phi^{-1}(y))(D\phi)^T(\phi^{-1}(y))$$

for almost all $y \in \widehat{\Omega}$.

(iii) If A is uniformly elliptic and essentially bounded, then so is $\widehat{A}$.

The last result we need is a reflection procedure that allows to transform a mixed Neumann-Dirichlet problem on the model domain $Q_- \cup \Sigma$ to a pure Dirichlet problem on Q and thus makes Corollary 50 applicable.

Lemma 58 (Reflection Principle)**.** *For $x = (x_1, \dots, x_d) \in \mathbb{R}^d$ we set $x_- = (x_1, \dots, x_{d-1}, x_d)$ and for a matrix $A \in \mathbb{R}^{d\times d}$ we define*

$$A^-_{jk} = \begin{cases} A_{jk} & \text{if } j,k < d, \\ -A_{jk} & \text{if } j = d, k \neq d \text{ or } k = d \text{ and } j \neq d, \\ A_{jk} & \text{if } j = k = d. \end{cases}$$

Now let A denote a member of $L^\infty(Q_-, \mathbb{R}^{d\times d})$ and define a member of $L^\infty(Q, \mathbb{R}^{d\times d})$ via

$$\hat{A}(x) = \begin{cases} A(x) & \text{if } x \in Q, \\ (A(x_-))^- & \text{if } x_- \in Q_-. \end{cases}$$

Let us set $\Gamma_D = \partial Q_- \setminus \Sigma$. Then for any fixed $p \in (1,\infty)$ it holds:

(i) If $v \in W^{1,p}_{\Gamma_D}(Q_-)$ satisfies $-\operatorname{div}(A\nabla v) = f \in W^{1,p'}_{\Gamma_D}(Q_-)^*$, then $-\operatorname{div}(\hat{A}\nabla\hat{v}) = \hat{f} \in W^{1,p'}_0(Q)^*$ holds for

$$\hat{v}(x) = \begin{cases} v(x) & \text{if } x \in Q, \\ v(x_-) & \text{if } x_- \in Q_- \end{cases}$$

and $\langle \hat{f}, u\rangle_{W^{1,p}_0(Q)} = \langle f, u|_{Q_-} + u_-|_{Q_-}\rangle_{W^{1,p}_{\Gamma_D(Q_-)}}$, where $u_-(x) = u(x_-)$.

(ii) The map

$$W^{1,p'}_{\Gamma_D}(Q_-)^* \to W^{1,p'}_0(Q)^*, \quad f \mapsto \hat{f}$$

is continuous.

(iii) Furthermore, if $A \in L^\infty(Q_-, \mathbb{R}^{d\times d})$ has ellipticity constant ν and L^∞ bound M, then so does $\hat{A}$.

Proof. The only thing not included in Proposition 4.11 in Haller-Dintelmann et al. (2009) is (iii). However, for all $\xi \in \mathbb{R}^d$ it holds (as we compute later on)

$$A^-\xi \cdot \xi = A\hat{\xi} \cdot \hat{\xi},$$

where $\hat{\xi} = (-\xi_1, \dots, -\xi_{d-1}, \xi_d)$. This implies

$$\inf_{\xi \neq 0} A^-\xi \cdot \xi = \inf_{\xi \neq 0} A\hat{\xi} \cdot \hat{\xi} \geq \nu|\hat{\xi}|^2 = \nu|\xi|^2.$$

Furthermore, it holds $\|A^-\| = \|A\|$ in the Frobenius norm, hence $\hat{A}$ and A share its bound as members of $L^\infty(Q_-, \mathbb{R}^{d\times d})$. Finally, we provide the computations for the above equality

$$\begin{aligned} A^-\xi\cdot\xi &= \sum_{i,j=1}^{d-1} A_{ij}\xi_j\xi_i + \sum_{i=1}^{d-1}(-A_{id})\xi_d\xi_i + \sum_{j=1}^{d-1}(-A_{dj})\xi_j\xi_d + A_{dd}\xi_d^2 \\ &= \sum_{i,j=1}^{d-1} A_{ij}(-\xi_j)(-\xi_i) + \sum_{i=1}^{d-1} A_{id}\xi_d(-\xi_i) + \sum_{j=1}^{d-1} A_{dj}(-\xi_j)\xi_d + A_{dd}\xi_d^2 \\ &= A\hat{\xi}\cdot\hat{\xi}. \end{aligned}$$

□

1.5 Proof of the Main Result

Proof of Theorem 48. We follow the steps in Haller-Dintelmann et al. (2009). For every $x \in \Omega$ choose a ball $B_x \subset \Omega$ centered at x and contained in Ω. For every $x \in \partial\Omega$, by the definition of Gröger regularity, there exists an open neighborhood U_x of x and an open set W_x together with a bi-Lipschitz map $\Psi_x : U_x \to W_x$ such that

$$\Psi_x((\Omega\cup\Gamma_N)\cap U_x) = Q_- \quad \text{or} \quad \Psi_x((\Omega\cup\Gamma_N)\cap U_x) = Q_-\cup\Sigma$$

depending on $x \in \partial\Omega$. The system $\{U_x\}_{x\in\partial\Omega} \cup \{B_x\}_{x\in\Omega}$ forms an open covering of $\overline{\Omega}$. We choose a finite subcovering $U_{x_1}, \dots, U_{x_k}, B_{x_1,\dots,B_{x_l}}$ and a subordinated smooth partition of unity $\eta_1, \dots, \eta_k, \zeta_1, \dots \zeta_l$. Let $A \in \mathcal{M}$, $q > d$ and $f \in W^{1,q'}_{\Gamma_D}(\Omega)^*$ and denote by v the solution of

$$-\operatorname{div}(A\nabla v) + v = f, \quad \text{in } H^1_{\Gamma_D}(\Omega)^*.$$

Then we use the partition of unity to write

$$v = \sum_{i=1}^{k} \eta_i v + \sum_{j=1}^{l} \zeta_j v$$

and we need to estimate $\|\eta_i v\|_{C^\alpha(\Omega)}$ and $\|\zeta_j v\|_{C^\alpha(\Omega)}$. This leads to three cases that need to be treated differently: First, the $\zeta_j v$ on the balls B_{x_j}, then $\eta_i v$ when $(\Omega\cup\Gamma_N)\cap U_x$ equals Q_- and finally the case when $(\Omega\cup\Gamma_N)\cap U_x = Q_-\cup\Sigma$.

First Case. We show that the Hölder norm of the $\zeta_j v$ can be controlled in terms of $C(B_{x_j}, \nu, M)\|f\|_{W^{1,q'}_{\Gamma_D}(\Omega)^*}$. To this end, we employ Lemma 56 with $\mathcal{U} = B_{x_j}$, hence $\Omega_\bullet = B_{x_j}$ and $\Gamma_\bullet = \emptyset$. Then $\zeta_j v_{|B_{x_j}}$ satisfies an equation of the form

$$-\operatorname{div}(A_\bullet\nabla(\zeta_j v_{|B_{x_j}})) = g_j \quad \text{in } W_0^{1,p_j'}(B_{x_j})$$

with $p_j > d$ and it holds

$$\|g_j\|_{W_0^{1,p_j'}(B_{x_j})} \le C(B_{x_j}, \nu, M)\cdot\|f\|_{W^{1,q'}_{\Gamma_D}(\Omega)^*}.$$

Hence, by Corollary 50, there is $\alpha_j \in (0,1)$ such that

$$\|\zeta_j v\|_{C^{\alpha_j}(\Omega)} = \|\zeta_j v_{|B_{x_j}}\|_{C^{\alpha_j}(B_{x_j})} \le C(B_{x_j}, \nu, M)\cdot\|f\|_{W_0^{1,p_j'}(B_{x_j})^*} \le C(B_{x_j}, \nu, M)\cdot\|f\|_{W^{1,q'}_{\Gamma_D}(\Omega)^*}.$$

Second Case. Here we assume that we use η_j subordinated to U_j with

$$\Psi_{x_j}((\Omega\cup\Gamma_N)\cap U_{x_j}) = Q_-. \tag{4.6}$$

Setting $\Omega_j = \Omega\cap U_{x_j}$, Lemma 55 shows that $\eta_j v_{|\Omega_j}$ is a member of $H^1_0(\Omega_j)$ and Lemma 56 implies that $\eta_j v_{|\Omega_j}$ solves

$$-\operatorname{div}(A_\bullet\nabla(\eta_j v_{|\Omega_j})) = f_j, \quad \text{in } H^1_0(\Omega_j)^*$$

with $f_j \in W_0^{1,p_j'}(\Omega_j)^*$ and $p_j > d$ and again

$$\|f_j\|_{W_0^{1,p_j'}(\Omega_j)^*} \le C(\Omega_j, \nu, M)\cdot\|f\|_{W^{1,q'}_{\Gamma_D}(\Omega)^*}.$$

Now, transform the function to Q_- using Proposition 57 with $\phi = \Psi_{x_j}^{-1}$ setting

$$\psi_j := \Phi_{p_j}(\eta_j v_{|\Omega_j}) = (\eta_j v_{|\Omega_j}) \circ \Psi_{x_j}^{-1}.$$

As we assumed (4.6), $\eta_j v_{|\Omega_j}$ is a member of $H_0^1(\Omega_j)$ and ψ_j is a member of $H_0^1(Q_-)$. Furthermore, ψ_j satisfies and equation of the form

$$-\operatorname{div}(\tilde{A}\nabla\psi_j) = h_j := (\Phi_{p_j}^*)^{-1} f_j \quad \text{in } W_0^{1,p_j'}(Q_-)^*$$

and by Corollary 50 there is $\alpha_j \in (0,1)$ such that $\psi_j \in C^{\alpha_j}(Q_-)$ with

$$\|\psi_j\|_{C^{\alpha_j}(Q_-)} \leq C(\nu, M, Q_-) \cdot \|h_j\|_{W^{1,p_j'}(Q_-)^*},$$

where we used that $\tilde{A}$ is still a bounded, measurable, elliptic matrix with possibly different boundedness and ellipticity constants, however controlled through the geometry of Ω_j. As Lipschitz maps preserve Hölder continuity in a controlled way we also have

$$\|\eta_j v_{|\Omega_j}\|_{C^{\alpha_j}(\Omega_j)} \leq C(\Omega_j) \cdot \|\psi_j\|_{C^{\alpha_j}(Q_-)}.$$

Finally, we may estimate

$$\begin{aligned}
\|\eta_j v\|_{C^{\alpha_j}(\Omega)} = \|\eta_j v_{|\Omega_j}\|_{C^{\alpha_j}(\Omega_j)} \leq C(\Omega_j) \cdot \|\psi_j\|_{C^{\alpha_j}(Q_-)} &\leq C(\nu, M, \Omega_j) \cdot \|(\Phi_{p_j'}^*)^{-1} f_j\|_{W_0^{1,p_j'}(Q_-)^*} \\
&\leq C(\nu, M, \Omega_j) \cdot \|f_j\|_{W_0^{1,p_j'}(\Omega_j)^*} \\
&\leq C(\nu, M, \Omega_j) \cdot \|f\|_{W_{\Gamma_D}^{1,q'}(\Omega)^*}.
\end{aligned}$$

Third Case. We use the same notation as in the second case but now it holds

$$\Psi_{x_j}((\Omega \cup \Gamma_N) \cap U_{x_j}) = Q_- \cup \Sigma.$$

Setting $\Gamma_j = \partial\Omega_j \setminus \Gamma_N$, it holds again $-\operatorname{div}(A_\bullet \nabla(\eta_j v_{|\Omega_j})) = f_j$ in $H_{\Gamma_j}^1(\Omega_j)^*$ with $f_j \in W_{\Gamma_j}^{1,p_j'}(\Omega_j)^*$ and $p_j > d$ and an estimate of the form

$$\|f_j\|_{W_{\Gamma_j}^{1,p_j'}(\Omega_j)^*} \leq C(\Omega_j, \nu, M) \cdot \|f\|_{W_{\Gamma_D}^{1,q'}(\Omega)^*}.$$

Now we transform to Q_- as in the second case and then use the reflection principle, see Lemma 58 to transform to Q. This yields ψ_j and $\hat{\psi}_j$, the latter solving a homogeneous problem on Q, the former as above, however with a Neumann condition on Σ. We may estimate for a suitable $\alpha_j \in (0,1)$

$$\begin{aligned}
\|\eta_j v\|_{C^{\alpha_j}(\Omega)} = \|\eta_j v\|_{C^{\alpha_j}(\Omega_j)} \leq C(\Omega_j) \cdot \|\psi_j\|_{C^{\alpha_j}(Q_-)} &\leq C(\Omega_j) \cdot \|\hat{\psi}_j\|_{C^{\alpha_j}(Q)} \\
&\leq C(\nu, M, \Omega_j) \cdot \|\hat{h}_j\|_{W_0^{1,p_j'}(Q)^*} \\
&\leq C(\nu, M\Omega_j) \cdot \|(\Phi_{p_j'}^*)^{-1} f_j\|_{W_{\partial\Omega\setminus\Sigma}^{1,p_j'}(Q_-)^*} \\
&\leq C(\nu, M, \Omega_j) \cdot \|f_j\|_{W_{\Gamma_j}^{1,p_j'}(\Omega_j)^*} \\
&\leq C(\nu, M, \Omega_j) \cdot \|f\|_{W_{\Gamma_D}^{1,q'}(\Omega)^*}.
\end{aligned}$$

Taking the minimal α_j concludes the proof. □

II Parabolic Regularity

In this Section all regularity results concerning the diffusion equations (1.2) are collected. This includes the results necessary for the existence Theorem 9 and the optimal control Theorem 18. We state and prove some known results such as the essential boundedness of diffusion equations given L^∞ data and L^∞ right-hand side and a non-negativity result for non-negative data. These results are collected in Section 2.2.

The main contribution however is a $L^p(I, C^\alpha(\Omega))$, $p \in [2, \infty)$ regularity result in the low regularity regime which is the parabolic counterpart to the results in Section I. That is, we allow mixed boundary conditions, elliptic L^∞ coefficients in the highest order term, $f \in L^p(I, L^2(\Omega))$ right-hand side and a $L^\infty(\Omega)$ initial condition. To the best of our knowledge, the result for the $L^\infty(\Omega)$ initial condition is novel and requires a little more work than a direct application of semi-group theory to the stationary result in Section I. We begin with a short reminder on the terminology of Banach space valued Sobolev spaces.

2.1 Vector Valued Sobolev Spaces

In the following, for a Banach space X, a bounded interval $I = [0, T]$ and $p \in [1, \infty]$ we denote by $L^p(I, X)$ the Bochner space of Bochner measurable, p-integrable functions defined on I and taking values in X, see for example Diestel and Uhl (1977). We also consider Sobolev spaces modeled on $L^p(I, X)$ and we briefly recall some basic definitions and properties of these spaces. These are the natural function spaces that are required for the treatment of time-dependent equations.

We begin with the definition of time derivatives. Due to the structure of parabolic equations, we need to allow a function $u : I \to X$ to possess a derivative in a larger space. More precisely, let X and Y be Banach spaces and

$$j : X \to Y, \quad x \mapsto j(x)$$

and embedding, i.e., a continuous, linear and injective map. Let us fix $p, r \in [1, \infty]$ and let $u \in L^p(I, X)$. We say u possesses a derivative in $L^r(I, X)$ if there exists a function $v \in L^r(I, X)$ such that

$$\int_I (j \circ u)\varphi' \mathrm{d}t = -\int_I v\varphi \mathrm{d}t, \quad \text{for all } \varphi \in C_c^\infty(I)$$

and we set $d_t u \coloneqq v$. We then define

$$W^{1,p,r}(I, X, Y) \coloneqq \{u \in L^p(I, X) \mid d_t u \in L^r(I, Y)\}$$

with the norm

$$\|u\|_{W^{1,p,r}(I,X,Y)} \coloneqq \|u\|_{L^p(I,X)} + \|d_t u\|_{L^r(I,Y)} .$$

Two cases for pairs X and Y with embeddings j are relevant for us. The first is the trivial case

$$X = Y, \quad j = \mathrm{Id}\,.$$

Then usually $p = r$ is the only relevant case and we denote the Sobolev spaces by

$$W^{1,p}(I, X) \coloneqq W^{1,p,p}(I, X, X).$$

These spaces appear naturally in the treatment of (weak) Banach space valued ODEs and parabolic regularity theory and possess nice properties such as an analogue to the fundamental theorem in real analysis. We refer to Boyer and Fabrie (2012) for a treatment.

The natural framework for weak solutions to parabolic equations requires a different setting, however. Here, one is often given a Gelfand triple (i, X, H), that is, X is a reflexive Banach space, H a Hilbert space and

$$i : X \to H, \quad x \mapsto i(x)$$

is an embedding with dense image. Then, we define

$$j : X \overset{i}{\hookrightarrow} H \to H^* \overset{i^*}{\hookrightarrow} X^*, \quad x \mapsto j(x) = (i(x), i(\cdot))_H.$$

The corresponding Sobolev space is modeled with the pair X and X^* and the embedding j and consequently denoted by

$$W^{1,p,r}(I, X, X^*). \tag{4.7}$$

Note that this notation suppresses the choice of the Gelfand triple and one should ensure that it is clear from the context which Gelfand triple is used. In our application X is in fact a Hilbert space and $p = r = 2$ and we write

$$H^1(I, X, X^*) = W^{1,2,2}(I, X, X^*)$$

as $H^1(I, X, X^*)$ is a Hilbert space itself. Finally we want to stress that spaces of the form (4.7) possess certain good properties, such as an embedding into $C^0(I, H)$ and a partial integration formula, we refer again to Boyer and Fabrie (2012). These results allow to prove existence theorems for linear and certain non-linear evolution equations, see for example Ern and Guermond (2013) for the linear case and Růžička (2006) for the non-linear case. We content ourselves with this brief introduction and point the reader towards more specialized results when necessary.

2.2 Pointwise Properties

In this Section we prove an $L^\infty(I \times \Omega)$ regularity result and a non-negativity result for solutions of diffusion equations with suitable data.

Theorem 59 ($L^\infty(I \times \Omega)$ bound)**.** *Let $\Omega \subset \mathbb{R}^d$ be a Lipschitz domain, $I = [0, T]$ and $\partial\Omega = \Gamma_N \cup \Gamma_D$ a partition of the boundary into Dirichlet and Neumann part. Both Γ_D and Γ_N are allowed to have vanishing measure. Further, let $D \in L^\infty(\Omega, \mathbb{R}^{d\times d})$ be uniformly elliptic, $k > 0$, $f \in L^p(I, L^2(\Omega))$ and $a_0 \in L^\infty(\Omega)$. Then the solution $a \in H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*)$ to*

$$\int_I \langle d_t a, \cdot\rangle_{H^1_D(\Omega)} \mathrm{d}t + \int_I\int_\Omega D\nabla a \nabla\cdot + ka(\cdot)\mathrm{d}x\mathrm{d}t = \int_I\int_\Omega f(\cdot)\mathrm{d}x\mathrm{d}t \quad \text{in } L^2(I, H^1_D(\Omega))^*$$
$$a(0) = a_0$$

is a member of $L^\infty(I \times \Omega)$ and it holds

$$\|a\|_{L^\infty(I\times\Omega)} \leq \max(\|f\|_{L^\infty(I\times\Omega)}, \|a_0\|_{L^\infty(\Omega)}).$$

Proof. We use Stampacchias truncation method Stampacchia (1958), that is for a real number $\bar{a}$ we test the PDE with

$$(a_i - \bar{a})^+ := \max(0, a_i - \bar{a}) \quad \text{and} \quad (a_i + \bar{a})^- := -\min(0, a_i + \bar{a}).$$

One can show that $(a_i - \bar{a})^+$ and $(a_i + \bar{a})^-$ are members of $H^1(I, H^1_D(\Omega), H^1_D(\Omega)')$ if a_i is itself in that space and that it holds

$$\int_0^t \langle d_t a_i, (a_i - \bar{a})^+\rangle_{H^1_D(\Omega)}\, dt = \frac{1}{2}\left\|(a_i - \bar{a})^+(t)\right\|^2_{L^2(\Omega)} - \frac{1}{2}\left\|(a_0 - \bar{a})^+\right\|^2_{L^2(\Omega)}$$

and

$$\int_\Omega D\nabla a_i(t)\nabla(a_i - \bar{a})^+(t)\, dx = \int_\Omega D\nabla(a_i - \bar{a})^+(t)\nabla(a_i - \bar{a})^+(t)\, dx$$

such as

$$\int_\Omega a_i(t)(a_i - \bar{a})^+(t)\, dx = \left\|(a_i - \bar{a})^+(t)\right\|^2_{L^2(\Omega)} + \int_\Omega \bar{a}(a_i - \bar{a})^+(t)\, dx$$

Hence it follows for every $t \in I$ and $\bar{a} \geq \max(\left\|f\right\|_{L^\infty(I\times\Omega)}, \|a_0\|_{L^\infty(\Omega)})$

$$\begin{aligned}\frac{1}{2}\left\|(a_i - \bar{a})^+(t)\right\|^2_{L^2(\Omega)} &\leq \int_0^t\int_\Omega (f - \bar{a})(a_i - \bar{a})^+ dxds + \frac{1}{2}\left\|(a_0 - \bar{a})^+\right\|^2_{L^2(\Omega)} \\ &\leq 0.\end{aligned}$$

This implies that $a_i \leq \bar{a}$ almost everywhere in $I \times \Omega$. Similarly one establishes $\bar{a} \leq a_i$ using the test function $(a_i + \bar{a})^-$. □

The following positivity result is formulated with the weak formulation of (1.2) in mind, where for convenience homogeneous Dirichlet boundary conditions are satisfied through the addition of a unity constant. This explains the somewhat specific formulation. The positivity result is general however, see for example Ern and Guermond (2013).

Theorem 60 (Positivity)**.** *Let $\Omega \subset \mathbb{R}^d$ be a Lipschitz domain, $I = [0, T]$ and $\partial\Omega = \Gamma_N \cup \Gamma_D$ a partition of the boundary into Dirichlet and Neumann part. Both Γ_D and Γ_N are allowed to have vanishing measure. Further, let $D \in L^\infty(\Omega, \mathbb{R}^{d\times d})$ be uniformly elliptic, $k > 0$, $f \in L^2(I, L^2(\Omega))$, $f \geq 0$ and assume a function $a \in H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*)$ satisfies the following equality in the space $L^2(I, H^1_D(\Omega))^*$*

$$\int_I \langle d_t a, \cdot\rangle_{H^1_D(\Omega)} \mathrm{d}t + \int_I\int_\Omega D\nabla a\nabla\cdot + k(a+1)(\cdot)\mathrm{d}x\mathrm{d}t = \int_I\int_\Omega f(\cdot)\mathrm{d}x\mathrm{d}t,$$

with $a(0) + 1 = 0$. Then $a + 1 \geq 0$ holds.

Proof. One can check that $(a+1)^- = -\min(0, a+1)$ is a member of $H^1(I, H^1_D(\Omega), H^1_D(\Omega)')$ and that it holds for all $t \in I$

$$\int_0^t \langle d_t a, (a+1)^-\rangle_{H^1_D} ds = \frac{1}{2}\left(\left\|(a+1)^-(0)\right\|^2_{L^2(\Omega)} - \left\|(a+1)^-(t)\right\|^2_{L^2(\Omega)}\right)$$

and

$$\int_0^t \int_\Omega \langle D\nabla a, \nabla(a+1)^-\rangle + k(a+1)(a+1)^- dxds$$
$$= -\int_0^t \int_\Omega \langle D\nabla\big[(a+1)^-\big], \nabla\big[(a+1)^-\big]\rangle + k\big[(a+1)^-\big]^2 dxds \leq 0.$$

Testing the full equation with $(a+1)^-$ and using these computations one finds

$$\frac{1}{2}\left\|(a+1)^-(t)\right\|^2_{L^2(\Omega)} \leq -\int_0^t \int_\Omega f \cdot (a+1)^- \, dxds \leq 0.$$

□

2.3 Parabolic Hölder Regularity

In this Section, we prove a $L^p(I, C^\alpha(\Omega))$ regularity result for certain linear parabolic equations with non-smooth coefficients, mixed boundary conditions and $L^\infty(\Omega)$ initial conditions. We control the $L^p(I, C^\alpha(\Omega))$ norm with respect to the data, showing its dependency on the coefficients. The main result is the following:

Theorem 61. *Let $\Omega \subset \mathbb{R}^d$ with $d = 2, 3$ be a Lipschitz domain, $I = [0, T]$ a time interval, $\partial\Omega = \Gamma_N \cup \Gamma_D$ a partition of the boundary into a Dirichlet and a Neumann part, where both Γ_N and Γ_D are allowed to have vanishing measure. Assume that $\Omega \cup \Gamma_N$ is Gröger regular, let $f \in L^p(I, L^2(\Omega))$ for $p \in [2, \infty)$, $D \in L^\infty(\Omega, \mathcal{M}_s)$ with ellipticity constant $\nu > 0$ and let $k > 0$ be a constant. For $v_0 \in L^\infty(\Omega)$ denote by $v \in H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*)$ the solution to*

$$\underbrace{\int_I \langle d_t v, \cdot\rangle_{H^1_D(\Omega)} \mathrm{d}t}_{=:d_t v} + \underbrace{\int_I \int_\Omega D\nabla v \nabla \cdot + kv(\cdot)\mathrm{d}x\mathrm{d}t}_{=:\mathcal{M}v} = \int_I \int_\Omega f(\cdot)\mathrm{d}x\mathrm{d}t \quad \text{in } L^2(I, H^1_D(\Omega))^*$$
$$v(0) = v_0.$$

Then there is $\beta = \beta(p) \in (0, 1)$ such that $v \in L^p(I, C^\beta(\Omega))$ for all $p \in [2, \infty)$, provided $f \in L^p(I, L^2(\Omega)$, and we may estimate

$$\|v\|_{L^p(I, C^\beta(\Omega))} \leq C\left(\Omega, T, \nu, \|D\|_{L^\infty(\Omega, \mathbb{R}^{d\times d})}, p\right) \cdot \left[\|f\|_{L^p(I, L^2(\Omega))} + \|v_0\|_{L^\infty(\Omega)}\right]. \tag{4.8}$$

In the above estimate, if we fix Ω and p, only a lower bound for ν and upper bounds for $\|D\|$ and T determine the value of the constant C. This provides uniformity for $\nu \in [c_E, C_E]$, $D \in L^\infty(\Omega, \mathcal{M}_s)$ with $\|D\| \leq C_B$ and time intervals $I^* = [0, T^*]$ with $T^* \leq T$.

Proof. Here we discuss only the main ideas and provide the details in the course of the Section. The first ingredient in the proof is the $C^\alpha(\Omega)$ regularity result for the stationary operator, see Theorem 48. This opens the door for maximal parabolic regularity results, however, the initial value as a member of $L^\infty(\Omega)$ does not suffice for a direct application of the theory, which would require v_0 to be a member of $H^1_D(\Omega)$, the trace space in this situation, compare to Arendt et al. (2017). Therefore, we propose to use the superposition principle for linear operators to split the equation into

$$d_t v_1 + \mathcal{M}v_1 = f,$$
$$v_1(0) = 0$$

and

$$d_t v_2 + \mathcal{M}v_2 = 0,$$
$$v_2(0) = v_0.$$

The linearity of the equation implies that $v = v_1 + v_2$. This gives us the advantage to analyze v_1 and v_2 separately. Now, v_1 can be treated by a combination of the maximal regularity results in Amann (1995) and Theorem 48. For v_2 we can quantify the norm blow-up at the initial time-point using standard results from Brezis (2010). More precisely, it holds

$$\|v_2(t)\|_{C^\alpha(\Omega)} \leq C \cdot \left(\frac{1}{t}\|v_0\|_{L^2(\Omega)} + 1\right)$$

and using an interpolation result we are able to mitigate the singularity of $t \mapsto t^{-1}$ by reducing the Hölder exponent. □

Remark 62. Knowing the dependencies of the constants on the data ν and $\|D\|_{L^\infty}$ etc. is crucial in applications as we see in our case of PDE constrained optimization.

Proof of the Main Result

We need some basic facts from semi-group theory for linear, unbounded operators in a Hilbert space H, that is operators of the form $M : \mathrm{dom}(M) \subset H \to H$. However, we started with a linear, bounded and coercive operator defined on a full space X taking values in its dual, i.e., $\mathcal{M} \in \mathcal{L}(X, X^*)$. If we are given a Gelfand triple structure (i, X, H), that is X and H are Hilbert spaces and $i : X \to H$ is an embedding with dense image, i.e., linear, continuous and bounded, we see that the two concepts are closely related.

Definition 63. Let (i, X, H) be a Gelfand triple and $\mathcal{M} \in \mathcal{L}(X, X^*)$ a coercive bounded linear operator. We define its *part in H* as follows

$$\mathrm{dom}(M) := \{v \in X \mid \text{there is } f \in H \text{ with } (f, \cdot)_H = \mathcal{M}v\}$$

and

$$M : \mathrm{dom}(M) \subset H \to H, \quad Mv = R^{-1}(\mathcal{M}v)$$

where R denotes the Riesz isometry of H.

Remark 64. Note that the above definition suppresses the embedding i in various places, treating it like a set-theoretic inclusion. Furthermore, we stress that M is well defined as a map since for every $\mathcal{M}v$ there is at most one $f \in H$ satisfying $(f, \cdot)_H = \mathcal{M}v$ as $i(X)$ is dense in H by assumption.

Lemma 65. *Let (i, X, H) be a Gelfand triple and $\mathcal{M} \in \mathcal{L}(X, X^*)$ a coercive, bounded linear operator. Then, its part M in H is maximal monotone, thus densely defined. If $\mathcal{M}$ is self-adjoint*[1] *as a member of $\mathcal{L}(X, X^*)$, then M is self-adjoint as a densely defined operator in H.*

Proof. Let $u, v \in \mathrm{dom}(M)$ and note that by the definition of $\mathcal{M}$ it holds

$$(Mu, v)_H = (R^{-1}(\mathcal{M}(u)), v)_H = \langle \mathcal{M}u, v\rangle_X. \tag{4.9}$$

This identity makes clear that the coercivity of $\mathcal{M}$ implies the monotonicity of M. Additionally,

$$\mathrm{Id}\,|_H + M : \mathrm{dom}(M) \to H$$

is bijective and hence M is maximal monotone. If $\mathcal{M}$ is self-adjoint, then (4.9) shows that M is symmetric. However, linear symmetric maximal monotone operators are self-adjoint, see Brezis (2010). ◻

The following Proposition is tailored to allow the application of Hille-Yosida's celebrated theorem on solutions to the Cauchy problem.

Proposition 66. *Let $\Omega \subset \mathbb{R}^d$, $d = 1, 2, 3$ be a bounded domain with a partition of the boundary into Dirichlet and Neumann part $\partial\Omega = \Gamma_N \cup \Gamma_D$. Both Γ_D and Γ_N are allowed to have vanishing measure. We assume that $\Omega \cup \Gamma_N$ is Gröger regular. Further, let $D \in L^\infty(\Omega, \mathcal{M}_s)$ be given and assume it is elliptic with ellipticity constant $\nu > 0$. Let $k > 0$, we define the operator*

$$\mathcal{M} : H^1_D(\Omega) \to H^1_D(\Omega)^*, \quad \mathcal{M}v = \int_\Omega D\nabla v \nabla \cdot + kv(\cdot)\mathrm{d}x.$$

Then its part in $L^2(\Omega)$ is maximal monotone and self-adjoint. Further, there exists $\alpha > 0$ such that we have the embedding

$$\left(\mathrm{dom}(M), \|\cdot\|_{L^2(\Omega)} + \|\cdot\|_{L^2(\Omega)}\right) \hookrightarrow C^\alpha(\Omega)$$

together with the estimate

$$\|u\|_{C^\alpha(\Omega)} \le C(\Omega, \nu, \|D\|_{L^\infty(\Omega,\mathcal{M}_s)}) \cdot \|u\|_{\mathrm{dom}(M)}\,.$$

Here, the constant C is precisely $\|\mathcal{M}^{-1}\|_{\mathcal{L}(L^2(\Omega), C^\alpha(\Omega))}$ and depends only on a lower bound for the ellipticity constant and an upper bound on $\|D\|_{L^\infty(\Omega,\mathcal{M}_s)}$.

Proof. Using the Gelfand triple $(\mathrm{Id}_{|L^2(\Omega)}, H^1_D(\Omega), L^2(\Omega))$, we can apply Lemma 65 and deduce the maximal monotonicity of M. Further, the symmetry assumption on D implies that M is self-adjoint, again through Lemma 65. It remains to show the embedding into Hölder spaces – essentially due to Theorem 48 – which yields the existence of $\alpha > 0$ such that

$$M^{-1} : L^2(\Omega) \to C^\alpha(\Omega)$$

[1] We call a map $T \in \mathcal{L}(X, X^*)$ self-adjoint if $T^* \circ J = T$, where $J : X \to X^{**}$ is the natural isometric embedding of a Banach space into its bi-dual and T^* denotes the usual adjoint map.

is well defined and continuous. This requires the assumption $d = 1, 2, 3$. To see that the graph norm on $\mathrm{dom}(M)$ controls the α-Hölder norm, we let $u \in \mathrm{dom}(M) \subset C^\alpha(\Omega)$. Then there exists a unique $f \in L^2(\Omega)$ such that $u = M^{-1} f$ and we compute

$$\|u\|_{C^\alpha(\Omega)} = \|M^{-1} f\|_{C^\alpha(\Omega)} \leq C\|f\|_{L^2(\Omega)} = C\|Mu\|_{L^2(\Omega)} \leq C\|u\|_{\mathrm{dom}(M)}.$$

The only appearing constant is the operator norm of M^{-1} and Theorem 48 guarantees a suitable bound of this norm. □

Theorem 67. *Assume we are in the situation of Proposition 66. Then for every $v_0 \in L^2(\Omega)$ there exists $\alpha > 0$ and*

$$v \in C^1((0, T], L^2(\Omega)) \cap C^0((0, T], C^\alpha(\Omega))$$

solving

$$\begin{aligned} v'(t) + Mv(t) &= 0 \quad \text{on } (0, T] \\ v(0) &= v_0 \end{aligned} \tag{4.10}$$

Furthermore, it holds

$$\|v(t)\|_{C^\alpha(\Omega)} \leq C\left(\Omega, \nu, \|D\|_{L^\infty}\right)\left(1 + \frac{1}{t}\right)\|v_0\|_{L^2(\Omega)}.$$

More precisely, the constant $C\left(\Omega, \lfloor D \rfloor, \|D\|_{L^\infty}\right)$ is the operatornorm of the embedding $\mathrm{dom}(M) \hookrightarrow C^\alpha(\Omega)$.

Proof. From Theorem 7.7 in Brezis (2010) it follows that

$$\|Mv(t)\|_{L^2(\Omega)} \leq \frac{1}{t}\|v_0\|_{L^2(\Omega)} \quad \text{and} \quad \|v(t)\|_{L^2(\Omega)} \leq \|v_0\|_{L^2(\Omega)}.$$

Using this and the embedding $\mathrm{dom}(M) \hookrightarrow C^\alpha(\Omega)$, we get

$$\begin{aligned} \|v(t)\|_{C^\alpha(\Omega)} \leq C\|v(t)\|_{\mathrm{dom}(M)} &= C\|v(t)\|_{L^2(\Omega)} + C\|Mv(t)\|_{L^2(\Omega)} \\ &\leq C\|v_0\|_{L^2(\Omega)} + \frac{C}{t}\|v_0\|_{L^2(\Omega)}. \end{aligned}$$

□

Theorem 68. *Assume we are in the situation of Proposition 66 and assume that $v_0 \in L^\infty(\Omega)$ and denote by $v \in C^1((0, T], L^2(\Omega))$ the solution to* (4.10)*. Then for every $q \in (1, \infty)$ there exists $\beta = \beta(q)$ such that v is a member of $L^q(I, C^\beta(\Omega)) \cap L^\infty(I, C^0(\Omega))$. Furthermore, we can bound the $L^q(I, C^\beta(\Omega))$ norm depending on the data of the problem in the following way*

$$\|v\|_{L^q(I, C^\beta(\Omega))} \leq C\left(\Omega, \nu, \|D\|_{L^\infty}, \|v_0\|_{L^\infty}, I, \alpha, q\right). \tag{4.11}$$

Proof. Let $p > q$ be fixed. Choose $\beta > 0$ such that $\alpha/p > \beta$. Then we can estimate for every $u \in C^\alpha(\Omega)$

$$\|u\|_{C^\beta(\Omega)} \leq C \cdot \|u\|_{C^0(\Omega)}\|u\|^{1/p}_{C^\alpha(\Omega)} + \|u\|_{C^0(\Omega)}.$$

To see this compute

$$\begin{aligned} [u]_\beta &= \sup_{x \neq y} \frac{|u(x) - u(y)|^{1-1/p}|u(x) - u(y)|^{1/p}}{|x - y|^{\alpha/p + (\beta - \alpha/p)}} \\ &= \sup_{x \neq y} |u(x) - u(y)|^{1-1/p}|x - y|^{\alpha/p - \beta} \cdot \left[\frac{|u(x) - u(y)|}{|x - y|^\alpha}\right]^{1/p} \\ &\leq \left(2\|u\|_{C^0(\Omega)}\right)^{1-1/p} \mathrm{diam}(\Omega)^{\alpha/p - \beta}[u]_\alpha^{1/p}. \end{aligned}$$

Using the following estimate

$$\|v(t)\|_{C^0(\Omega)} \leq \|v_0\|_{L^\infty(\Omega)}$$

and the above estimates of the C^β norm and Theorem 67 we obtain

$$\begin{aligned}
\|v(t)\|_{C^\beta(\Omega)} &\le \left(2\|v(t)\|_{C^0(\Omega)}\right)^{1-1/p} \operatorname{diam}(\Omega)^{\alpha/p-\beta}[v(t)]_\alpha^{1/p} + \|v(t)\|_{C^0(\Omega)} \\
&\le \max\left(1, 2\|v_0\|_{L^\infty(\Omega)}\right) \cdot \max\left(1, \operatorname{diam}(\Omega)\right) \cdot [v(t)]_\alpha^{1/p} + \|v_0\|_{L^\infty(\Omega)} \\
&\le C\left(\|v_0\|_{L^\infty(\Omega)}, \Omega\right) \cdot [v(t)]_\alpha^{1/p} + \|v_0\|_{L^\infty(\Omega)} \\
&\le C\left(\|v_0\|_{L^\infty(\Omega)}, \nu, \|D\|_{L^\infty}, \Omega\right) \cdot \left(1 + \frac{1}{t}\right)^{\frac{1}{p}}
\end{aligned}$$

Inferring $q/p < 1$ then shows the integrability of $\|v(t)\|^q_{C^\beta(\Omega)}$ and the asserted bound. □

Remark 69. The constant in (4.11) only depends on the length of the interval I, a lower bound for ν and an upper bound for $\|D\|_{L^\infty(\Omega)}$, hence is uniform for suitable families of operators and time intervals.

Finally we cite a known result from Amann (1995) to treat the case with the vanishing initial condition.

Theorem 70. *Assume we are in the situation of Proposition 66. Let $f \in L^p(I, L^2(\Omega))$ with $p \in [2, \infty)$ and denote by u the solution to*

$$\begin{aligned} u'(t) + Mu(t) &= f \quad \text{on } (0,T] \\ u(0) &= 0. \end{aligned}$$

Then it holds $u \in W^{1,p}(I, L^2(\Omega)) \cap L^p(I, \operatorname{dom}(M))$ with the estimate

$$\|u\|_{W^{1,p}(I,L^2(\Omega))\cap L^p(I,\operatorname{dom}(M))} \le C(\nu, \|D\|_{L^\infty(\Omega)}, p, I) \cdot \left\|f\right\|_{L^p(I,L^2(\Omega))}$$

where $C(\nu, \|D\|_{L^\infty(\Omega)}, p, I)$ does depend on a lower bound for ν, on an upper bound for $\|D\|_{L^\infty}$ and the upper bound T of the time interval $I = [0,T]$.

Proof. We apply Theorem 4.10.8 in Amann (1995), using $E_0 = L^2(\Omega)$, $E_1 = \operatorname{dom}(M)$. The requirement of E_0 being an UMD space holds as it is a Hilbertspace, the other requirements can be shown using the fact that M is self-adjoint and coercive, i.e., a member of $\mathcal{BIP}(L^2(\Omega); 1, 0)$ in the terminology of Amann (1995). As we consider a problem with homogeneous initial conditions we don't need to concern ourselves with the trace space for the initial conditions. □

III Banach Space Valued ODEs

3.1 Banach Space Valued Ordinary Differential Equations

In the main text the need for a Banach space valued ODE theorem arises. We formulate and prove a possible existence theorem here. It is an extension of the one given in Brezis' book Brezis (2010). The difference is that we treat weak ordinary differential equations and that we allow the inducing vector field F to be time dependent.

Theorem 71 (Global Existence)**.** *Let X be a Banach space, $I = [0,T]$ a bounded interval and $F : [0,T] \times X \to X$ a Caratheodory function that satisfies a Lipschitz condition of the following form*

$$\left\|F(t,x) - F(t,y)\right\| \le L(t) \left\|x - y\right\| \tag{4.12}$$

for all $x, y \in X$ and $t \in I$ with a function $L \in L^p(I)$ for some $p > 1$. Assume furthermore that for some $q \in [1, \infty]$ the operator

$$\mathcal{F} : W^{1,q}(I, X) \to L^q(I, X) \quad \text{with} \quad \mathcal{F}u(t) = F(t, u(t)) \tag{4.13}$$

is well defined. Then the following differential operator

$$\mathcal{O} : W^{1,q}(I, X) \to L^q(I, X) \times X \quad \text{with} \quad u \mapsto (d_t u + \mathcal{F}u, u(0))$$

is bijective. Note that this is nothing but an abstract way to say that for every right hand side $f \in L^q(I, X)$ and intial value $u_0 \in X$ the equation $d_t u + \mathcal{F}(u) = f$ with $u(0) = u_0$ has a unique solution.

Addendum. *If we can choose $p \ge q$, i.e., the integrability of the Lipschitz function L is not worse than the q we had for $\mathcal{F}$ then the map $\mathcal{O}$ is Bilipschitzian.*

Remark 72. Note that the Lipschitz assumption (4.12) implies that $x \mapsto F(t,x)$ is continuous up to a set of vanishing measure in I. Also, to establish (4.13) it is enough to check that $t \mapsto \|F(t,u(t))\|^q$ is integrable as the Bochner measurability follows from the Caratheodory regularity of F.

Proof. Given $f \in L^q(I,X)$ and $u_0 \in X$ we need to find $u \in W^{1,q}(I,X)$ with $d_t u + \mathcal{F}(u) = f$ and $u(0) = u_0$. By the fundamental theorem for the space $W^{1,q}(I,X)$ this is equivalent to finding a function $u \in C^0(I,X)$ satisfying

$$u(t) = u_0 + \int_0^t f(s) - F(s,u(s))\,ds.$$

We renorm $C^0(I,X)$ equivalently by $|||u||| := \sup_{t\in I} e^{-kt}\|u(t)\|$ where $k > 0$ is to be fixed later. Setting $\Phi : (C^0(I,X), |||\cdot|||) \to (C^0(I,X), |||\cdot|||)$ with

$$\Phi(u)(t) = u_0 + \int_0^t f(s) - F(s,u(s))\,ds,$$

we seek to apply Banach's fixed point theorem to Φ for a k large enough. The self-mapping property is due to the fundamental theorem (Boyer and Fabrie, 2012, Proposition II.5.11) and the contraction property is established in the following computation

$$\begin{aligned} |||\Phi(u) - \Phi(v)||| &= \sup_{t\in I}\left[e^{-kt}\left\|\int_0^t F(s,v(s)) - F(s,u(s))\,ds\right\|\right] \\ &\le \sup_{t\in I}\left[e^{-kt}\int_0^t e^{ks}e^{-ks}L(s)\,\|v(s)-u(s)\|\,ds\right] \\ &\le |||v-u|||\,\|L\|_{L^p(I)} \underbrace{\sup_{t\in I}\left[e^{-kt}\left\|e^{k\cdot}\right\|_{L^{p'}(0,t)}\right]}_{=(*)} \end{aligned}$$

We will now compute that $(*)$ tends to zero with $k \to \infty$ hence an appropriate choice of k yields the assertion.

$$\begin{aligned} \left\|e^{k\cdot}\right\|_{L^{p'}(0,t)} = \left(\int_0^t e^{kp's}\,ds\right)^{\frac{1}{p'}} = \left(\frac{1}{kp'}e^{kp't} - \frac{1}{kp'}\right)^{\frac{1}{p'}} &\le \left(\frac{1}{kp'}e^{kp't}\right)^{\frac{1}{p'}} \\ &= \left(\frac{1}{kp'}\right)^{\frac{1}{p'}} e^{kt}. \end{aligned}$$

Addendum. Now we prove the bilipschitzian property. Let us first have a look at $\mathcal{O}$. Given $u,v \in W^{1,q}(I,X)$ we know that point evaluation and taking the time derivative is a Lipschitz continuous map. We turn to $\mathcal{F}$ and compute

$$\begin{aligned} \|\mathcal{F}(u) - \mathcal{F}(v)\|^q_{L^q(I,X)} &= \int_I \|F(t,u(t) - F(t,v(t))\|^q\,dt \\ &\le \int_I |L(t)|^q\,\|u(t)-v(t)\|^q\,dt \\ &\le \|L\|^q_{L^q(I)}\,\|u-v\|^q_{C^0(I,X)} \\ &\le C\,\|L\|^q_{L^p(I)}\,\|u-v\|^q_{W^{1,q}(I,X)}, \end{aligned}$$

where we needed $p > q$. The asserted Lipschitz continuity of $\mathcal{O}$ follows easily. Now to $\mathcal{O}^{-1}$. Given $(f,u_0),(g,v_0) \in L^q(I,X)\times X$ we know that the $\mathcal{O}$ preimages satisfy

$$u(t) = u_0 + \int_0^t f(s) - F(s,u(s))\,ds \quad \text{and} \quad v(t) = v_0 + \int_0^t g(s) - F(s,v(s))\,ds.$$

Let the variables γ_1 and γ_2 denote the integrands of the two preceeding integral curves. We estimate their difference

$$\left\|\gamma_1(s) - \gamma_2(s)\right\| \le \left\|f(s) - g(s)\right\| + L(s)\,\|v(s) - u(s)\|.$$

Using Grönwall's inequality we find that

$$\|u - v\|_{C^0(I,X)} \leq C\Big(\|u_0 - v_0\| + \big\|f - g\big\|_{L^1(I,X)} \Big).$$

It remains to have a look at the derivatives. We compute

$$\begin{aligned}\|d_t u(t) - d_t v(t)\|_{L^q(I,X)} &\leq \big\|f - g\big\|_{L^q(I,X)} + \|\mathcal{F}(u) - \mathcal{F}(v)\|_{L^q(I,X)} \\ &\leq \big\|f - g\big\|_{L^q(I,X)} + \|L\|_{L^q(I)} \|u - v\|_{C^0(I,X)}\end{aligned}$$

which yields the desired continuity. □

Lemma 73 (Grönwall Variant)**.** *Let X be a Banach space and $I = [0, T]$ an interval. Let $x_0, y_0 \in X$ and assume that γ_1, γ_2 are members of $L^1(I, X)$. Define x and y to be the integral curves*

$$x(t) = x_0 + \int_0^t \gamma_1(s)\, ds \quad \textit{and} \quad y(t) = y_0 + \int_0^t \gamma_2(s)\, ds.$$

Now assume that we can estimate the integrants γ_1, γ_2 in the following form

$$\big\|\gamma_1(t) - \gamma_2(t)\big\| \leq \alpha(t) + \beta(t) \big\|x(t) - y(t)\big\| \quad \textit{for all } t \in I,$$

where $\alpha, \beta \in L^1(I)$ are non-negative functions. Then it holds that

$$\big\|x(t) - y(t)\big\| \leq C\Big(\big\|x_0 - y_0\big\| + \|\alpha\|_{L^1(I)} \Big) \quad \textit{for all } t \in I$$

and the constant C can be chosen to be $C = 1 + \big\|\beta\big\|_{L^1(I)} \exp(\big\|\beta\big\|_{L^1(I)})$.

Proof. Just write out the estimate that the difference $\big\|x(t) - y(t)\big\|$ satisfies due to the assumptions and then use the usual integral formulation of Grönwall's inequality, see for example (Qin, 2017, Theorem 1.2.8). □

Theorem 74 (Local Existence)**.** *Let X be a Banach space, $I = [a, b]$ a bounded interval and $F : I \times X \to X$ a Carathéodory function, i.e., $F(\cdot, x)$ is Bochner measurable for all $x \in X$ and $F(t, \cdot)$ is continuous almost everywhere in I. Assume that for every bounded set $B \subset X$ there are functions $m_B \in L^p(I)$, $p \in [1, \infty]$ and $L_B \in L^1(I)$, possibly depending on B, such that*

$$\|F(t, x)\|_X \leq m_B(t) \quad \textit{a.e. in } I,\ \forall x \in B, \tag{4.14}$$

$$\big\|F(t, x) - F(t, y)\big\|_X \leq L_B(t) \big\|x - y\big\| \quad \textit{a.e. in } I,\ \forall x, y \in B. \tag{4.15}$$

Let furthermore $t_0 \in I$, $x_0 \in X$ and $R > 0$ be arbitrary, then there exists a time interval $I_\delta := [t_0 - \delta, t_0 + \delta] \cap I$ such that for any initial value $y_0 \in \overline{B_R(x_0)} \subset X$ there is a unique short time solution $x \in W^{1,p}(I_\delta, X)$ of the ODE

$$d_t x(t) = F(t, x(t)) \quad \textit{and } x(t_0) = y_0.$$

Moreover the map $y_0 \mapsto x(y_0)$ taking the initial value to its solution seen as a map $\overline{B_R(x_0)} \subset X \to C^0(I_\delta, X)$ is continuous.

Remark 75. Note that the Lipschitz assumption (4.15) implies that $x \mapsto F(t, x)$ is continuous. Therefore, to establish the Carathéodory regularity of F it is enough to provide the Bochner measurability of the maps $F(\cdot, x) : I \to X$ for all $x \in X$.

Proof. First we clarify the dependence of δ; we choose it to satisfy

$$\int_{I_\delta} m_{B_{2R}(x_0)}(s)\, ds \leq R \quad \text{and} \quad \int_{I_\delta} L_{B_{2R}(x_0)}(s)\, ds < 1. \tag{4.16}$$

Then we consider the complete metric space $E \subset C^0(I_\delta, X)$ given by

$$E := \{x \in C^0(I_\delta, X) \mid \sup_{t \in I_\delta} \|x(t) - x_0\| \leq 2R\}$$

and define the map

$$\Phi : E \to E \quad \text{with} \quad \Phi(x)(t) = y_0 + \int_{t_0}^t F(s, x(s))\, ds.$$

We now proceed by showing the following facts

(i) For all $x \in E$ the map $t \mapsto F(t, x(t))$ is Bochner integrable as a map $I_\delta \to X$. In fact it is a member of $L^p(I_\delta, X)$.

(ii) The function Φ is a self-mapping and a contraction.

(iii) The fix-point of Φ is a member of $W^{1,p}(I_\delta, X)$ and corresponds to the solution of the ODE.

(iv) The solution depends continuously on the initial data.

To establish (i) note that the assumption of Carathéodory regularity of F implies that $t \mapsto F(t, x(t))$ is Bochner measurable as a map $I_\delta \to X$ for all maps $x : I_\delta \to X$ that are itself Bochner measurable, which clearly holds for members of E. We are left to show the integrability, so we estimate for $x \in E$

$$\int_{I_\delta} \|F(t, x(t))\|_X^p \, dt \leq \int_{I_\delta} |m_{B_{2R}(x_0)}(t)|^p \, dt < \infty,$$

which shows the assertion. Now to (ii). Let again $x \in E$ and estimate

$$\begin{aligned}\sup_{t \in I_\delta} \|\Phi(x)(t) - x_0\|_X &\leq \left\|x_0 - y_0\right\| + \int_{I_\delta} \|F(t, x(t))\|_X \, dt \\ &\leq R + \int_{I_\delta} m_{B_{2R}(x_0)}(t) \, dt \\ &\leq 2R.\end{aligned}$$

To see that Φ is a contraction compute for $x, y \in E$

$$\begin{aligned}\sup_{t \in I_\delta} \left\|\Phi(x)(t) - \Phi(y)(t)\right\|_X &\leq \sup_{t \in I_\delta} \int_{I_\delta} \left\|F(t, x(t)) - F(t, y(t))\right\|_X \, dt \\ &\leq \underbrace{\left\|L_{B_{2R}(x_0)}\right\|_{L^1(I_\delta)}}_{<1} \left\|x - y\right\|_E\end{aligned}$$

The claim (iii) follows as the unique fix-point x of Φ is, by the fundamental theorem, a solution to the ODE. As $d_t x(t) = F(t, x(t))$ the L^p integrability of the derivative of this fix-point follows from the one of $F(\cdot, x(\cdot))$ which was established in (i).

Finally to (iv), where we will employ Grönwall's Lemma. Let y_0 and $\overline{y}_0$ be in $\overline{B_R(x_0)}$, then the according solutions are given by

$$y(t) = y_0 + \int_{t_0}^{t} F(s, y(s)) \, ds \quad \text{and} \quad \overline{y}(t) = \overline{y}_0 + \int_{t_0}^{t} F(s, \overline{y}(s)) \, ds.$$

The difference in the integrands can be estimated by

$$\left\|F(t, y(t)) - F(t, \overline{y}(t))\right\|_X \leq C L_{B_{2R}(x_0)}(t) \left\|y(t) - \overline{y}(t)\right\|_X.$$

So applying Lemma 73 with $\alpha = 0$ and $\beta = L_{B_{2R}(x_0)}$ yields

$$\left\|y(t) - \overline{y}(t)\right\|_X \leq C \left\|y_0 - \overline{y}_0\right\|_X.$$

□

Remark 76. It is often of interest to show the existence of long-time solutions. A particularly simple case in the setting of the above theorem is encountered if it holds that for any initial value $y_0 \in \overline{B_R(x_0)} \subset X$ the solution takes values only in $\overline{B_R(x_0)}$. Then one glues together multiple short-time solutions with the guarantee of δ not deteriorating.

Lemma 77 (Pointwise Properties of Solutions)**.** *Let $I = [a, b]$ be an interval and $K : I \times \mathbb{R} \to \mathbb{R}$ a Carathéodory function such that $x \geq 0$ implies $K(t, x) \geq 0$ for all $t \in I$. For fixed $t_0 \in I$ consider the ODE*

$$x'(t) = K(t, x(t))\left(1 - \frac{x(t)}{\theta}\right) \quad \textit{and} \quad x(t_0) = x_0,$$

where $\theta > 0$ and $\lambda \geq 0$ are fixed numbers and $x_0 \in [0, \theta]$. Assume that there is an interval $I_\delta = [t_0 - \delta, t_0 + \delta] \cap I$ such that for any choice of $x_0 \in [0, \theta]$ we have a solution $x \in W^{1,1}(I_\delta)$ of the ODE which we assume to continuously depend on the initial data x_0, i.e., we assume that for every $x_0 \in [0, \theta]$ there is a neighborhood N_{x_0} around x_0 such that $x_0 \mapsto x$ is continuous as a map $N_{x_0} \to C^0(I_\delta)$, where x is the solution to the ODE with initial value x_0. Then it holds

$$0 \leq x(t) \leq \theta \quad \textit{for all } t \in I_\delta.$$

Proof. We know that x satisfies the identity

$$x(t) = x_0 + \int_{t_0}^{t} K(s, x(s))\Big(1 - \frac{x(s)}{\theta}\Big) ds \quad \text{for all } t \in I_\delta$$

Upper Barrier. We prove this by contradiction. Suppose there was $s_0 \in I_\delta$ with $x(s_0) > \theta$, then on a neighborhood of s_0 solution must be non-increasing which can be seen as follows: Due to the continuity of x there is $\varepsilon > 0$ such that

$$x(t) \geq \theta \quad \text{for all } t \in (s_0 - \varepsilon, s_0 + \varepsilon).$$

If x was not non-increasing on $(s_0 - \varepsilon, s_0 + \varepsilon)$ then there exist $t_1 < t_2$ in that interval such that $x(t_2) > x(t_1)$ and therefore

$$0 < x(t_2) - x(t_1) = \int_{t_1}^{t_2} \underbrace{K(s, x(s))}_{\geq 0} \underbrace{\Big(1 - \frac{x(s)}{\theta}\Big)}_{\leq 0} ds \leq 0,$$

which settles the claim. Now, by judicious Zornification we produce a maximal interval Z around s_0 on which x is non-increasing. Then $t^* := \inf Z = t_0$ (if it was not t_0, repeat the above reasoning and find that Z was not maximal) and hence $\theta < x(t^*) = x(t_0) \leq \theta$ clearly is a contradiction.

Lower Barrier. With an analogue reasoning as in the proof for the upper barrier we can establish the following: If $x(s_0) \in (0, \theta]$ for some $s_0 \in I_\delta$ then $x(t) \in [x(s_0), \theta]$ for all $t \geq s_0$. This yields the claim for all initial values strictly larger than zero. We need $x(s_0)$ to exceed zero to guarantee the existence of a small interval $(s_0 - \delta, s_0 + \delta)$ where $x \geq 0$ still holds, to be able to use $K(s, x(s)) \geq 0$ on this interval. For $x(t_0) = 0$ we approximate the solution by considering initial values $x_n(t_0) = 1/n$, i.e., we find solutions x_n to

$$x_n'(t) = K(s, x_n(s))\Big(1 - \frac{x_n(s)}{\theta}\Big) \quad \text{with} \quad x_n(t_0) = n^{-1}.$$

As shown before we then know that $x_n(t) \in [1/n, \theta]$ for all $t \in I_\delta$. By the continuity we assumed we can pass to the limit in n and obtain $0 \leq x(t) \leq \theta$ for all $t \in I_\delta$. □

Lemma 78 (A snippet)**.** *On the compatibility of abstract and pointwise ODEs.*

Proof. Note that for any function $b \in W^{1,2}(I, C^0(\Omega))$ and arbitrary $x \in \Omega$ we have that $b(\cdot, x)$ is a member of $H^1(I)$ and that it holds

$$\partial_t (b(\cdot, x)) = (d_t b)(\cdot, x),$$

where on the left side of the above equation ∂_t denotes the weak derivative of the space $H^1(I)$ and d_t denotes the abstract derivative of the space $W^{1,2}(I, C^0(\Omega))$. Furthermore we can bound the $H^1(I)$ norm of $b(, \cdot, x)$ in terms of the $W^{1,2}(I, C^0(\Omega))$ norm of b. To this end compute

$$\|b(\cdot, x)\|_{L^2(I)} = \|b\|^2_{C^0(I \times \Omega)} |I|.$$

and

$$\begin{aligned}
\|\partial_t b(\cdot, x)\|_{L^2(I)} = \text{L-}\int_I d_t b(t, x)^2 \mathrm{d}t &= \mathrm{ev}_x \Big(\text{B-}\int_I (d_t b)^2 \mathrm{d}t \Big) \\
&\leq \|\mathrm{ev}_x\|_{C^0(\Omega)^*} \Big\| \text{B-}\int_I (d_t b)^2 \mathrm{d}t \Big\|_{C^0(\Omega)} \\
&\leq \Big(\sup_{\|\varphi\|_{C^0(\Omega)} \leq 1} \varphi(x) \Big) \cdot \text{L-}\int_I \|d_t b\|^2_{C^0(\Omega)} \mathrm{d}t \\
&\leq \|d_t b\|^2_{L^2(I, C^0(\Omega))},
\end{aligned}$$

where we have indicated Bochner integrals by B-$\int$ and Lebesgue integrals by L-$\int$ for clarity. Consequently, $b_k(\cdot, x)$ is bounded uniformly in $k \in \mathbb{N}$ and $x \in \Omega$. For every fixed $x \in \Omega$ we can extract a $C^0(I)$ convergent subsequence (by the compact embedding $H^1(I) \hookrightarrow\hookrightarrow C^0(I)$) and identify its limit as $b^*(\cdot, x) \in H^1(I)$, via the convergence $b_k \to b^*$ in $C^0(I \times \Omega)$. Then $b^*(\cdot, x)$ satisfies the limit ODE and thus b^* does so in $W^{1,2}(I, C^0(\Omega))$. □

Before we apply the existence theorems to the ODEs in the main text, we need an elementary equality that allows us to quantify the violation of the global Lipschitz continuity of the product of real numbers.

Lemma 79. *Let $N \in \mathbb{N}$ and $a_1, \ldots, a_N$ and $\overline{a}_1, \ldots, \overline{a}_N$ be real numbers. Then it holds*

$$\prod_{i=1}^{N} a_i - \prod_{i=1}^{N} \overline{a}_i = \sum_{k=1}^{N} \left[\Big(\prod_{i=1}^{N-k} a_i \Big) \Big(\prod_{i=N-k+2}^{N} \overline{a}_i \Big) (a_{N-k+1} - \overline{a}_{N-k+1}) \right]$$

where of course the empty product is set to the value 1.

Proof. By induction, the formula can easily be guessed by writing out values for small N. It clearly holds for $N = 1$, now suppose we know it to hold for N. We compute

$$\begin{aligned}
\prod_{i=1}^{N+1} a_i - \prod_{i=1}^{N+1} \overline{a}_i &= \Big(\prod_{i=1}^{N} a_i \Big) a_{N+1} - \Big(\prod_{i=1}^{N} \overline{a}_i \Big) \overline{a}_{N+1} \\
&= \Big(\prod_{i=1}^{N} a_i \Big) (a_{N+1} - \overline{a}_{N+1}) + \overline{a}_{N+1} \Big(\prod_{i=1}^{N} a_i - \prod_{i=1}^{N} \overline{a}_i \Big) \\
&= \Big(\prod_{i=1}^{N} a_i \Big) (a_{N+1} - \overline{a}_{N+1}) \\
&\quad + \overline{a}_{N+1} \sum_{k=1}^{N} \left[\Big(\prod_{i=1}^{N-k} a_i \Big) \Big(\prod_{i=N-k+2}^{N} \overline{a}_i \Big) (a_{N-k+1} - \overline{a}_{N-k+1}) \right. \\
&= \Big(\prod_{i=1}^{N} a_i \Big) (a_{N+1} - \overline{a}_{N+1}) \\
&\quad + \sum_{k=2}^{N+1} \left[\Big(\prod_{i=1}^{N+1-k} a_i \Big) \Big(\prod_{i=N+1-k+2}^{N+1} \overline{a}_i \Big) (a_{N+1-k+1} - \overline{a}_{N+1-k+1}) \right] \\
&= \sum_{k=1}^{N+1} \left[\Big(\prod_{i=1}^{N+1-k} a_i \Big) \Big(\prod_{i=N+1-k+2}^{N+1} \overline{a}_i \Big) (a_{N+1-k+1} - \overline{a}_{N+1-k+1}) \right].
\end{aligned}$$

□

We discuss now the existence of a unique solution of the cell ODE.

Lemma 80 (Solveability of the Cell ODE)**.** *Assume $H : \mathbb{R}^{N+2} \to \mathbb{R}$ is locally Lipschitz continuous and that H is non-negative if all its arguments are non-negative. Further, assume that $H = H^2 \circ H^1$ with a Lipschitz continuous map $H^1 : \mathbb{R}^{N+2} \to \mathbb{R}^M$ and the product $H^2(h_1, \ldots, h_M) = \prod_{i=1}^{M} h_i$. Let $a = (a_1, \ldots, a_N)$ be a function in $L^p(I, C^0(\Omega)^N)$ for every $p \in [1, \infty)$ with $a_i(t, x) \geq 0$ for all $(t, x) \in I \times \Omega$ and let $b \in C^0(I \times \Omega)$ with $0 \leq b(t, x) \leq 1$. Furthermore, $\rho \in C^0(\Omega)$ is such that it holds $0 < c_P \leq \rho(x) \leq C_P$ for two positive constants c_P, C_P. Then there is a unique solution $c \in W^{1,2}(I, C^0(\Omega))$ of the equation*

$$d_t c = H(a_1, \ldots, a_N, b, c) \Big(1 - \frac{c}{1 - \rho} \Big) \quad \text{with} \quad c(0) = 0.$$

Furthermore the solution satisfies $0 \leq c(t, x) \leq 1 - \rho(x)$ for all $t \in I$ and $x \in \overline{\Omega}$.

Proof. To begin with, define the auxiliary function

$$\tilde{H} : \mathbb{R}^{N+2} \times [c_P, C_P] \to \mathbb{R} \quad \text{with} \quad \tilde{H}(a, b, c, \rho) = H(a, b, c) \Big(1 - \frac{c}{1 - \rho} \Big).$$

By the Lipschitz continuity of H^1 and the product form of H^2, the function $\tilde{H}$ is locally Lipschitz continuous. Now note that the ODE is induced by

$$F : I \times C^0(\Omega) \to C^0(\Omega) \quad \text{with} \quad F(t,c) = x \mapsto \tilde{H}(a(t,x), b(t,x), c(x), \rho(x)).$$

We aim to apply Theorem 74 to produce a short-time solution, hence we need to guarantee

(i) $F(t,c) \in C^0(\Omega)$ for all $t \in I$ and $c \in C^0(\Omega)$,

(ii) $F(\,\cdot\,, c) : I \to C^0(\Omega)$ is Bochner measurable for all $c \in C^0(\overline{\Omega})$,

(iii) F satisfies (4.14) and (4.15).

The statement (i) is clear as $F(t,c)$ is a composition of continuous functions. To prove (ii) we write a as a pointwise almost everywhere limit of finitely valued, measurable functions $(s_k) \subset \mathcal{S}(I, C^0(\Omega)^N)$ and likewise with b, i.e., b is the pointwise almost everywhere limit of functions $(q_k) \subset \mathcal{S}(I, C^0(\Omega))$. Then $t \mapsto \tilde{H}(s_k(t), q_k(t), c, \rho)$ is a member of $\mathcal{S}(I, C^0(\Omega))$. As $s_k(t) \to a(t)$ in $C^0(\Omega)^N$ almost everywhere in I and the same holds true for $q_k(t) \to b(t)$, for fixed $t \in I$ the set

$$\bigcup_{k\in\mathbb{N}} \{(s_k(t,x), q_k(x), c(x), \rho(x)), (a(t,x), b(x), c(x), \rho(x)) \mid x \in \overline{\Omega}\} \subset \mathbb{R}^{N+3}$$

is relatively compact in $\mathbb{R}^{N+3}$. Hence, on this set, H is Lipschitz continuous and we may estimate

$$\left\|\tilde{H}(s_k(t), b, c, \rho) - \tilde{H}(a(t), b, c, \rho)\right\|_{C^0(\overline{\Omega})} \le C\left(\|s_k(t) - a(t)\|_{C^0(\Omega)} + \|q_k(t) - b(t)\|_{C^0(\Omega)}\right).$$

This establishes the Bochner measurability in (*ii*). To show (iii), let $B \subset C^0(\Omega)$ be a bounded set. By the assumption on the boundedness of ρ, it suffices to consider the following estimate in order to establish (4.14). We let $c \in B$ and estimate

$$\begin{aligned}
\|H(a(t), b(t), c)\|_{C^0(\Omega)} &\le \prod_{i=1}^{M} \left\|H_i^1(a(t), b(t), c)\right\|_{C^0(\Omega)} \\
&\le \prod_{i=1}^{M} \left[\left\|H_i^1(a(t), b(t), c) - H_i^1(0,0,0)\right\|_{C^0(\Omega)} + \left\|H_i^1(0,0,0)\right\|_{C^0(\Omega)}\right] \\
&\le \prod_{i=1}^{M} \left[L_{H^1}\left(\|a(t)\|_{C^0(\Omega)^N} + \|b(t)\|_{C^0(\Omega)} + \|c\|_{C^0(\Omega)}\right) + \left\|H^1(0,0,0)\right\|_{C^0(\Omega)^M}\right] \\
&\le m_B(t)
\end{aligned}$$

As a is a member of $L^p(I, C^0(\Omega)^N)$ for any $p \in [1, p)$, b and ρ are bounded by assumption and $c \in B$, we may choose $m_B \in L^p(I)$ for any $p \in [1, p)$ and in particular for $p = 2$. For $c, \bar{c} \in B$ we use Lemma 79

$$\begin{aligned}
&\left\|H(a(t), b(t), c) - H(a(t), b(t), \bar{c})\right\|_{C^0(\Omega)} \\
=& \left\|\prod_{i=1}^{M} H_i^1(a(t), b(t), c) - \prod_{i=1}^{M} H_i^1(a(t), b(t), \bar{c})\right\|_{C^0(\Omega)} \\
=& \left\|\sum_{k=1}^{M} \underbrace{\left(\prod_{i=1}^{M-k} H_i^1(a(t), b(t), c)\right)\left(\prod_{i=M-k+2}^{M} H_i^1(a(t), b(t), \bar{c})\right)}_{(*)}\left(H^1_{M-k+1}(a(t), b(t), c) - H^1_{M-k+1}(a(t), b(t), \bar{c})\right)\right\|_{C^0(\Omega)}
\end{aligned}$$

We treat $(*)$ first. Estimating for any $k = 1, \dots, M$ yields

$$\prod_{i=1}^{M-k} H_i^1(a(t), b(t), c) \le \prod_{i=1}^{M} \left(H_i^1(a(t), b(t), c) + 1\right).$$

The global Lipschitz continuity of H^1 implies then for any $i = 1, \dots, M$ the estimate

$$\left\|H_i^1(a(t), b(t), c)\right\|_{C^0(\Omega)} \leq L_{H^1}\left(\|a(t)\|_{C^0(\Omega)^N} + \|b(t)\|_{C^0(\Omega)} + \|c\|_{C^0(\Omega)}\right) + \left\|H_i^1(0,0,0)\right\|_{C^0(\Omega)}.$$

Combining the two preceding estimates yields

$$\begin{aligned}\left\|\prod_{i=1}^M H_i^1(a(t), b(t), c)\right\|_{C^0(\Omega)} &\leq \prod_{i=1}^M \left[L_{H^1}\left(\|a(t)\|_{C^0(\Omega)^N} + \|b(t)\|_{C^0(\Omega)} + \|c\|_{C^0(\Omega)}\right) + \left\|H_i^1(0,0,0)\right\|_{C^0(\Omega)} + 1\right] \\ &\leq \tilde{L}_B(t), \quad \text{for } c \in B,\end{aligned}$$

with $\tilde{L}_B \in L^p(I)$ for any $p \in [1, \infty)$, in particular for $p = 4$. Estimating the second factor of $(*)$ identical, we get

$$\begin{aligned}\left\|H(a(t), b(t), c) - H(a(t), b(t), \bar{c})\right\|_{C^0(\Omega)} &\leq \sum_{k=1}^M \tilde{L}_B(t)^2 \left\|H_i^1(a(t), b(t), c) - H_i^1(a(t), b(t), \bar{c})\right\|_{C^0(\Omega)} \\ &\leq M L_{H_1} \tilde{L}_B(t)^2 \left\|c - \bar{c}\right\|_{C^0(\Omega)} \\ &\leq L_B(t) \left\|c - \bar{c}\right\|_{C^0(\Omega)},\end{aligned}$$

with $L_B \in L^2(I)$. To establish a long-time solution note that by our pointwise Lemma 77 we have

$$0 \leq c(t, x) \leq 1 - \rho(x) \leq 1.$$

Using the remark following Theorem 74 we conclude. □

IV Time Adjoint Problems

In this Section of the Appendix we discuss how to treat the adjoint operator of a linear, time dependent equation. A time derivative introduces asymmetry in the choice of the domain and codomain of the whole operator, with the domain being a smaller space. This leads to a large and abstract dual space as the codomain of the adjoint operator. Therefore, it is usually necessary to require regularity properties of the right hand side of the adjoint equation in order to be able to derive a formulation that is suitable for numerical treatment.

As an example, let $I = [0, T]$ be a time interval, $m \in L^\infty(I)$ and consider the linear ODE operator

$$d_t + m : H_0^1(I) \to L^2(I), \quad v \mapsto d_t v + m \cdot v$$

where $H_0^1(I)$ now denotes the functions with vanishing initial value. By Theorem 71, $d_t + m$ is a linear homeomorphism. Its Banach space adjoint is given by

$$(d_t + m)^* : L^2(I)^* \to H_0^1(I)^*, \quad \phi \mapsto \phi\,(d_t \cdot + m \cdot)$$

and can be defined on $L^2(I)$ through the Riesz isometry of $L^2(I)$

$$u \mapsto \int_I u d_t \cdot + u m \cdot \mathrm{d}t \in H_0^1(I)^*.$$

Now, let $\psi \in H^1(I)^*$. Only if ψ is given through $\psi = \int_I f_\psi \cdot \mathrm{d}t$ for $f_\psi \in L^2(I)$ the solution to

$$\int_I u d_t \cdot + u m \cdot \mathrm{d}t = \int_I f_\psi \cdot \mathrm{d}t \quad \text{in } H_0^1(I)^*$$

is actually a member of $H^1(I)$ and satisfies the final value problem

$$-d_t u + u m = f_\psi, \quad u(T) = 0.$$

If $\psi \in H_0^1(I)^* \setminus L^2(I)$, no such regularity can be expected. For the rest of the Section we are concerned with deriving equations of the above final value form in various settings, including parabolic PDEs and Banach space valued ODEs. The reader being content with an equation of this final value form might skip these abstract discussions.

4.1 Time Adjoint Problems on Reflexive Spaces

We begin by deriving the adjoint maps to linear parabolic equations defined on Banach space valued Sobolev spaces. We assume that the underlying space X is reflexive, which is reasonable in the weak formulation for a wide class of parabolic equations. Later, for Banach space valued ODEs and certain regularity related formulations, we drop this reflexivity assumption.

Lemma 81 (Existence of Time Derivatives)**.** *Given a reflexive Banach space X and assume there is a symmetric embedding $j : X \to X^*$, i.e., $\langle j(x), y\rangle = \langle j(y), x\rangle$. We consider the space $W^{1,2,2}(I, X, X^*)$. A function $u \in L^2(I, X)$ has a time derivative in this space if*

$$f : C_c^\infty(I, X) \to \mathbb{R}, \quad \varphi \mapsto \int_I \langle d_t\varphi(t), u(t)\rangle \mathrm{d}t$$

is continuous when $C_c^\infty(I, X)$ is endowed with the $L^2(I, X)$ topology, i.e., if it holds for a constant C

$$|f(\varphi)| \leq C\|\varphi\|_{L^2(I,X)} \quad \text{for all } \varphi \in C_c^\infty(I, X).$$

Proof. As the map f is linear and continuous it is uniformly continuous between the spaces

$$f : \left(C_c^\infty(I, X), \|\cdot\|_{L^2(I,X)}\right) \to \mathbb{R}$$

and can thus be (uniquely) extended to all of $L^2(I, X)$, i.e., is a member of $L^2(I, X)^*$. The duality theory of the space $L^2(I, X)$ implies – by the virtue of the Radon-Nikodým property of X – the existence of $v \in L^2(I, X^*)$ representing f, that is

$$\int_I \langle d_t\varphi(t), u(t)\rangle \mathrm{d}t = \int_I \langle v(t), \varphi(t)\rangle \mathrm{d}t, \quad \text{for all } \varphi \in C_c^\infty(I, X).$$

Now choose $\varphi = x\psi$ for $x \in X$ and $\psi \in \mathcal{D}(I)$. This yields

$$\langle d_t(x\psi)(t), u(t)\rangle_X = \langle j(x\partial_t\psi(t)), u(t)\rangle_X = \langle j(u(t))\partial_t\psi(t), x\rangle_X$$

by the symmetry of j. Hence we have

$$\left\langle \int_I j(u)\partial_t\psi \mathrm{d}t, x\right\rangle_X = \int_I \langle j(u)\partial_t\psi, x\rangle \mathrm{d}t = \int_I \langle v, \psi x\rangle \mathrm{d}t = -\left\langle \int_I -v\psi \mathrm{d}t, x\right\rangle \quad \text{for all } t \in I, x \in X,$$

thus $d_t u = -v$. □

Remark 82. The statement of the above Lemma holds true under the weaker assumption that X possesses the Radon-Nikodým property instead of reflexivity. The Radon-Nikodým property implies the duality $L^2(I, X)^* = L^2(I, X^*)$ and reflexive spaces possess this property. We refer to Diestel and Uhl (1977).

Remark 83. The Lemma above is applicable in the context of Gelfand triples, which is the typical setting encountered in evolution equations. Remember that we call the triple (i, X, H) a Gelfand triple if X is a reflexive Banach space, H is a Hilbert space with Riesz isometry R and $i : X \to H$ is a dense embedding, i.e., linear, continuous and injective with dense range. In this context the map $j : X \to X^*$ is given by

$$j : X \to X^* \quad , u \mapsto (i^* \circ R \circ i)(u) = (i(u), i(\cdot))_H .$$

Then by the symmetry of the inner product, the map j is symmetric.

Now we are in a position to discuss the adjoint equation corresponding to a linear, time-dependent problem modeled on the Sobolev space corresponding to $L^2(I, X)$ where again X is reflexive. Given a Gelfand triple (i, X, H) and an operator $\mathcal{A} \in \mathcal{L}(L^2(I, X), L^2(I, X)^*)$, where $\mathcal{A}$ is assumed to be nothing more but linear and continuous for the moment, we consider the time-dependent problem

$$T : (d_t + \mathcal{A}, \mathrm{ev}_0) : W^{1,2,2}(I, X, X^*) \to L^2(I, X)^* \times H, \quad u \mapsto \left(\int_I \langle d_t u, \cdot\rangle \mathrm{d}t + \mathcal{A}u, u(0)\right).$$

Then we look at the adjoint map T^* modulo some isomorphisms

$$L^2(I, X) \times H \xrightarrow{J\times R} L^2(I, X)^{**} \times H^* \xrightarrow{I} \left(L^2(I, X)^* \times H\right)^* \xrightarrow{T^*} W^{1,2,2}(I, X, X^*)^*.$$

Here, J denotes the natural isometry of a reflexive Banach space and its bi-dual, R denotes the Riesz isometry of the Hilbert space H and I is the isomorphism corresponding to Cartesian products and dualization, compare to ϕ in Lemma 38. Unwinding the definitions of the above composition we get for $(u, u_0) \in L^2(I, X) \times H$ and $v \in W^{1,2,2}(I, X, X^*)$ that

$$\begin{aligned}
\langle (T^* \circ I \circ J \times R)(u, u_0), v \rangle &= \langle I(Ju, Ru_0), Tv \rangle \\
&= \langle Ju, T_1 v \rangle + \langle Ru_0, T_2 v \rangle \\
&= \langle T_1 v, u \rangle + (u_0, T_2 v)_H \\
&= \int_I \langle d_t v, u \rangle_X \mathrm{d}t + \langle \mathcal{A} v, u \rangle_{L^2(I,X)} + (u_0, v(0))_H \\
&= \int_I \langle d_t v, u \rangle_X \mathrm{d}t + \langle (\mathcal{A}^* \circ J) u, v \rangle_{L^2(I,X)} + (u_0, v(0))_H
\end{aligned}$$

Hence setting $T^\dagger = T^* \circ I \circ J \times R$ we computed that

$$T^\dagger : L^2(I, X) \times H \to W^{1,2,2}(I, X, X^*)^*, \quad \text{is given by } T^\dagger(u, u_0) = \int_I \langle d_t \cdot, u \rangle_X \mathrm{d}t + \langle (\mathcal{A}^* \circ J) u, \cdot \rangle_{L^2(I,X)} + (u_0, \mathrm{ev}_0(\cdot))_H .$$

Proposition 84 (Well Posedness in Coercive Setting)**.** *Let X be a Hilbert space and (i, X, H) a Gelfand triple. Assume that $\mathcal{A}$ is induced by a bounded, possibly time-dependent, measurable form $a : I \times X \times X \to \mathbb{R}$ that is coercive with coercivity constant independent of I, then T and consequently $T^\dagger$ defined above are linear homeomorphisms.*

Proof. The celebrated maximal X^*-regularity result of Lions implies that T is a linear homeomorphism in this setting. See for instance Fackler (2017) or for the original work (Dautray and Lions, 2012, p. 513, Theorem 2). Consequently, its adjoint T^* is and as $T^\dagger$ consists of the composition of T^* with linear homeomorphisms, the assertion follows. □

Remark 85. In light of Proposition 84 we see that for every right-hand side f in $H^1(I, X, X^*)^*$, the equation $T^\dagger(u, u_0) = f$ possesses a unique solution $(u, u_0) \in L^2(I, X) \times H$. However, it is not so clear how to numerically approximate this solution. It turns out that assuming the regularity $f \in L^2(I, X)^*$ leads to a more convenient formulation that can be handled numerically.

Theorem 86 (Time Adjoint Problems)**.** *Assume (i, X, H) is a Gelfand triple and $\mathcal{A}$ is a member of $\mathcal{L}(L^2(I, X), L^2(I, X)^*)$. We use the notation of the above paragraph and assume that $f \in L^2(I, X)^*$ and $(u, u_0) \in L^2(I, X) \times H$. Then the following are equivalent*

(i) $T^\dagger(u, u_0) = f$

(ii) The function u is a member of $H^1(I, X, X^*)$ and it satisfies the final-value problem

$$\begin{gathered}
-\int_I \langle d_t u, \cdot \rangle_X \mathrm{d}t + \langle (\mathcal{A}^* \circ J) u, \cdot \rangle_{L^2(I,X)} = f \\
u(T) = 0, \quad u(0) = u_0.
\end{gathered}$$

Proof. We start with the implication $(ii) \Rightarrow (i)$. We test the equation in (ii) by $v \in H^1(I, X, X^*)$

$$-\int_I \langle d_t u, v \rangle_X \mathrm{d}t + \langle (\mathcal{A}^* \circ J) u, v \rangle_{L^2(I,X)} = f(v).$$

Now, we use the partial integration formula for Gelfand triples and unwind $\mathcal{A}^* \circ J$

$$\int_I \langle d_t v, u \rangle_X \mathrm{d}t - (u(T), v(T))_H + (u(0), v(0))_H + \langle \mathcal{A} v, u \rangle_{L^2(I,X)} = f(v)$$

and with the assumptions $u(T) = 0$ and $u(0) = u_0$ this is nothing but

$$\int_I \langle d_t \cdot, u \rangle_X \mathrm{d}t + \langle \mathcal{A} \cdot, u \rangle_{L^2(I,X)} + (u_0, \mathrm{ev}_0(\cdot))_H = f \quad \text{in } H^1(I, X, X^*)^*.$$

Now to (*i*) ⇒ (*ii*). First we show that $T^\dagger(u, u_0) = f$ implies $u \in H^1(I, X, X^*)$. The map

$$\varphi \mapsto \int_I \langle d_t\varphi, u\rangle_X \mathrm{d}t = f(\varphi) - \langle \mathcal{A}\varphi, u\rangle_{L^2(I,X)}$$

is linear and continuous with respect to the $L^2(I, X)$ topology on $C_c^\infty(I, X)$ by the assumption made on f. So we use Lemma 81 to deduce $u \in H^1(I, X, X^*)$. Now we test with $\varphi \in C_c^\infty(I, X)$ and by the deduced regularity of u are in the position to apply the partial integration formula for Gelfand triples. This yields

$$-\int_I \langle d_t u, \varphi\rangle_X \mathrm{d}t + \langle \mathcal{A}\varphi, u\rangle_{L^2(I,X)} = f(\varphi), \tag{4.17}$$

which, by density, holds true not only for $C_c^\infty(I, X)$ but for all of $L^2(I, X)$. We now only need to identify the final and initial values of u. To this end test $T(u, u_0) = f$ with an arbitrary function $v \in H^1(I, X, X^*)$ and use partial integration

$$-\int_I \langle d_t u, v\rangle_X \mathrm{d}t + (u(T), v(T))_H - (u(0), v(0))_H + \langle \mathcal{A}v, u\rangle_{L^2(I,X)} + (u_0, v(0)) = f(v).$$

Using the equation established in (4.17) this becomes

$$(u(T), v(T))_H + (u_0, v(0))_H = (u(0), v(0))_H, \quad \text{for all } v \in H^1(I, X, X^*).$$

Testing with functions v that vanish at the initial time-point yields - upon inferring the density of the embedding $X \hookrightarrow H$ – that $u(T) = 0$. Analogously, testing with functions vanishing at the final time-point, we obtain $u(0) = u_0$. □

Remark 87. We want to draw the readers attention to two points.

(i) Note that in the above proof, no properties besides the linearity and boundedness of $\mathcal{A}$ played a role. However, the duality theory of $L^2(I, X)$ is still important to be able to identify $\mathcal{A}^*$.

(ii) The above theorem applies to linear ODEs, both real valued and Hilbert space valued. This corresponds to the choice of the trivial Gelfand triple, i.e., $X = H = \mathbb{R}$ for the real case and $X = H$ for the Hilbert space valued case. However, it does not apply to ODEs posed on general Banach spaces.

4.2 Time Adjoint Problems on Non-Reflexive Spaces

From the previous discussion in the previous Section we know that a time adjoint problem takes the form

$$\int_I \langle d_t\cdot, u\rangle_X \mathrm{d}t + \langle \mathcal{A}\cdot, u\rangle_{L^2(I,X)} + (u_0, \mathrm{ev}_0(\cdot))_H = f,$$

where f is allowed to be a member of $H^1(I, X, X^*)^*$. Under the assumption of $f \in L^2(I, X)^*$ this equation can be turned into a final value problem which is well-suited for numerical treatment. However, in our application we need to consider a more regular space than merely $H^1(I, X, X^*)$ for the forward problem. We need a space of the form

$$H^1(I, X, X^*) \cap L^2(I, V),$$

where V is a non-reflexive Banach space (also lacking the Radon-Nikodým property) and X and V embed into a joint larger space. If we then define our forward problem on this space

$$(d_t + \mathcal{A}, \mathrm{ev}_0) : H^1(I, X, X^*) \cap L^2(I, V) \to L^2(I, X)^* \times H \tag{4.18}$$

the adjoint operator stays the same in the way it maps, but allows for more general right-hand sides. It is in general unknown to us how to determine the range space of (4.18) in a fruitful way. Therefore, we will only work under the assumption that we are given an element of the range space of the adjoint of (4.18) of a certain regularity and then deduce smoothness properties of its solution. Furthermore, we will not stay in the abstract setting but rather work with the concrete spaces.

Setting 88. Let $\Omega \subset \mathbb{R}^d$ be open and bounded with a partition of the boundary $\partial\Omega = \Gamma_N \cup \Gamma_D$ in a Dirichlet and a Neumann part. The sets Γ_D and Γ_N may have vanishing measure (but must still split all of the boundary between them). Let $A : H^1_D(\Omega) \to H^1_D(\Omega)^*$ be a linear, continuous, coercive and self-adjoint[2] and denote by $\mathcal{A} \in \mathcal{L}(L^2(I, H^1_D(\Omega)), L^2(I, H^1_D(\Omega))^*)$ its induced operator between Bochner spaces. Then we consider the map

$$(d_t + \mathcal{A}, \mathrm{ev}_0) : H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*) \cap L^2(I, C^0(\Omega)) \to L^2(I, H^1_D(\Omega))^* \times L^2(\Omega).$$

The space $H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*)$ is built around the Gelfand triple $(\mathrm{Id}, H^1_D(\Omega), L^2(\Omega))$. As we assume A to be self-adjoint, this property is inherited by $\mathcal{A}$ and the time adjoint problem takes the form

$$(d_t + \mathcal{A}, \mathrm{ev}_0)^\dagger : L^2(I, H^1_D(\Omega)) \times L^2(\Omega) \to \left[H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*) \cap L^2(I, C^0(\Omega))\right]^* =: \mathcal{X}^*$$

with

$$(q, \mu) \mapsto \int_I \langle d_t \cdot, q\rangle_{H^1_D(\Omega)} \mathrm{d}t + \langle \mathcal{A}q, \cdot\rangle_{L^2(I, H^1_D(\Omega))} + \int_\Omega \mu \, \mathrm{ev}_0(\cdot) \mathrm{d}x.$$

This follows exactly as in the previous Section, since we did not change anything in the codomain of the forward problem. We assume for our investigations from now on that we are given $f \in L^2(I, L^1(\Omega))$ together with a solution $(q, \mu) \in L^2(I, H^1_D(\Omega)) \times L^2(\Omega)$ of

$$(d_t + \mathcal{A}, \mathrm{ev}_0)^\dagger (q, \mu) = \iint f \cdot \mathrm{d}x\mathrm{d}t, \quad \text{in } \mathcal{X}^*. \tag{4.19}$$

Lemma 89. *Let $f \in L^2(I, L^1(\Omega))$ be fixed and assume $(q, \mu) \in L^2(I, H^1_D(\Omega)) \times L^2(\Omega)$ solves*

$$\int_I \langle d_t \cdot, q\rangle_{H^1_D(\Omega)} + \langle \mathcal{A}q, \cdot\rangle_{L^2(I, H^1_D(\Omega))} + \int_\Omega \mu \, \mathrm{ev}_0(\cdot) \mathrm{d}x = \iint f \cdot \mathrm{d}x\mathrm{d}t. \tag{4.20}$$

Then q is of the regularity $W^{1,2,2}(I, H^1_D(\Omega), [H^1_D(\Omega) \cap C^0(\Omega)]^*)$ and it satisfies

$$-\int_I \langle d_t q, \cdot\rangle_{H^1(\Omega)\cap C^0(\Omega)} \mathrm{d}t + \langle \mathcal{A}q, \cdot\rangle = \iint f \cdot \mathrm{d}x\mathrm{d}t, \quad \text{in } L^2(I, H^1_D(\Omega) \cap C^0(\Omega))^*.$$

Proof. In order to show that $d_t q \in L^2(I, [H^1_D(\Omega) \cap C^0(\Omega)]^*)$ we need to prove that there is $g \in L^2(I, [H^1_D(\Omega) \cap C^0(\Omega)]^*)$ such that for all $\varphi \in \mathcal{D}(I)$ and $\psi \in H^1_D(\Omega) \cap C^0(\Omega)$ it holds

$$\iint q\psi\partial_t\varphi \mathrm{d}x\mathrm{d}t = -\int_I \langle g, \psi\rangle_{H^1_D(\Omega)\cap C^0(\Omega)} \varphi \mathrm{d}t.$$

This clarifies that the identification underlying the space $W^{1,2,2}(I, H^1_D(\Omega), [H^1_D(\Omega) \cap C^0(\Omega)]^*)$ is meant to be

$$\iota : H^1_D(\Omega) \hookrightarrow (H^1_D(\Omega) \cap C^0(\Omega))^*, \quad \iota(\psi) = \int_\Omega \psi \cdot \mathrm{d}x, \quad \text{in } [H^1_D(\Omega) \cap C^0(\Omega)]^*.$$

Now we test (4.20) with $\varphi\psi$ and use

$$d_t(\varphi\psi) = \iota(\partial_t\varphi\psi) = \partial_t\varphi \int_\Omega \psi \cdot \mathrm{d}x$$

to obtain

$$\begin{aligned}\iint q\psi\partial_t\varphi \mathrm{d}x\mathrm{d}t &= \int_I \langle d_t(\varphi\psi), q\rangle_{H^1_D(\Omega)} \mathrm{d}t \\ &= \underbrace{\int_I \left[\int_\Omega f\psi - \langle Aq, \psi\rangle_{H^1_D(\Omega)}\right] \varphi \mathrm{d}t}_{=\int_I \langle g, \psi\rangle \varphi \mathrm{d}t} - \underbrace{\int_\Omega \mu \, \mathrm{ev}_0(\varphi\psi) \mathrm{d}x.}_{=0}\end{aligned}$$

[2] We call an operator $T\mathcal{L}(X, X^*)$ from a reflexive Banach space to its dual self-adjoint, if it holds $\langle Tx, y\rangle = \langle Ty, x\rangle$ for all $x, y \in X$.

Hence, it follows that $d_t q \in L^2(I, [H^1_D(\Omega) \cap C^0(\Omega)]^*)$ and by the definition of the time derivative

$$\int_I \langle d_t q, \cdot\rangle_{H^1_D(\Omega)\cap C^0(\Omega)} \mathrm{d}t = \int_I \langle Aq, \cdot\rangle_{H^1_D(\Omega)} \mathrm{d}t - \iint f \cdot \mathrm{d}x\mathrm{d}t$$
$$= \langle \mathcal{A}q, \cdot\rangle_{L^2(I,H^1_D(\Omega))} - \iint f \cdot \mathrm{d}x\mathrm{d}t$$

which yields the assertion upon rearranging. □

Remark 90. It remains open how to treat the question of intial/final values in general. We will however give a condition under which $q(T) = 0$ can be obtained.

Lemma 91. *Let $(f_k) \subset L^2(I, L^2(\Omega))$ approximate $f \in L^2(I, L^1(\Omega))$ in the topology of $L^2(I, L^1(\Omega))$ and assume there are solutions $(q_k) \subset W^{1,2,2}(I, H^1_D(\Omega), [H^1_D(\Omega) \cap C^0(\Omega)]^*)$ to the equation*

$$\int_I \langle d_t \cdot, q_k\rangle \mathrm{d}t + \langle \mathcal{A}q_k, \cdot\rangle_{L^2(I,H^1_D(\Omega))} + \int_\Omega \mu\, \mathrm{ev}_0(\cdot)\mathrm{d}x = \iint f_k \cdot \mathrm{d}x\mathrm{d}t, \quad in \mathcal{X}^*$$

that, up to a subsequence, converge to a limit $q \in W^{1,2,2}(I, H^1_D(\Omega), [H^1_D(\Omega) \cap C^0(\Omega)]^*)$ in the topology of $W^{1,2,2}(I, H^1_D(\Omega), [H^1_D(\Omega) \cap C^0(\Omega)]^*)$. Then q solves the final value problem

$$-\int_I \langle d_t q, \cdot\rangle_{H^1(\Omega)\cap C^0(\Omega)} \mathrm{d}t + \langle \mathcal{A}q, \cdot\rangle_{L^2(I,H^1_D(\Omega))} = \iint f \cdot \mathrm{d}x\mathrm{d}t, \quad in\ L^2(I, H^1_D(\Omega) \cap C^0(\Omega))^*$$
$$q(T) = 0, \quad in\ [H^1_D(\Omega) \cap C^0(\Omega)]^*.$$

Proof. As f_k is a member of $L^2(I, L^2(\Omega))$, we can extend the equation for u_k to hold in $H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*)^*$ instead of only $\mathcal{X}^*$. Then Theorem 86 applies and we get $q_k(T) = 0$ in $L^2(\Omega)$. To pass to the limit, note that we have the embedding

$$H^1(I, H^1_D(\Omega), H^1_D(\Omega)^*) \hookrightarrow C^0(I, [H^1_D(\Omega) \cap C^0(\Omega)]^*)$$

which implies that $q_k(T) \to q(T)$ in $[H^1_D(\Omega) \cap C^0(\Omega)]^*$ and hence yields the assertion. □

4.3 ODE Adjoint Maps

We need a result similar to the adjoint characterization for parabolic equations in the case of Banach space valued, linear ODEs. We restrict us to the case of a Banach algebra X (we use $C^0(\Omega)$ or $C^\alpha(\Omega)$) and the Sobolev space $W^{1,p}_0(I, X)$, where the subscript zero means that initial values vanish. The power p lies in $(1, \infty]$. We consider the following ODEs.

Setting 92. Let $m \in L^p(I, X)$ be a fixed function. Consider the multiplication operator M induced by m

$$M : C^0(I, X) \to L^p(I, X), \quad Mv = t \mapsto m(t)v(t).$$

Remember that Theorem 71 showed that the map

$$d_t + M : W^{1,p}_0(I, X) \to L^p(I, X), \quad v \mapsto d_t v + Mv$$

is a linear homeomorphism. Furthermore, we consider the Banach space adjoint of the map $(d_t + M)$. This is given by

$$(d_t + M)^* : L^p(I, X)^* \to W^{1,p}_0(I, X)^*, \quad (d_t + M)^*(h^*) = h^*[d_t \cdot + M\cdot].$$

The following Theorem is a regularity result for the dual operator of $d_t + M$ and is particularly useful for numerical implementation.

Theorem 93 (Regularity for Adjoint ODEs)**.** *Let Ω be an open and bounded subset of $\mathbb{R}^d$ and $m \in L^2(I, C^0(\Omega))$. Denote by M the corresponding multiplication operator. Fix a function $f \in L^2(I, L^1(\Omega))$. Then there exists a unique $h^* \in W^{1,2}_0(I, C^0(\Omega))^*$ satisfying*

$$h^*[d_t \cdot + M\cdot] = \iint f \cdot \mathrm{d}x\mathrm{d}t, \quad in\ W^{1,2}_0(I, C^0(\Omega))^*.$$

Furthermore, there is a unique function $h \in W^{1,2}(I, L^1(\Omega))$ satisfying

$$h^* = \iint h \cdot \mathrm{d}x\mathrm{d}t$$

and h is the unique solution of the final value problem

$$-d_t h + Mh = f, \quad h(T) = 0 \tag{4.21}$$

in the space $W^{1,2}(I, L^1(\Omega))$.

Proof. We show first that (4.21) can be solved uniquely in $W^{1,2}(I, L^1(\Omega))$. To this end we set

$$\tilde{h}(t) = h(T-t), \quad \tilde{m}(t) = m(T-t), \quad \tilde{f}(t) = f(T-t),$$

then the equation (4.21) becomes

$$d_t\tilde{h} + \tilde{M}\tilde{h} = \tilde{f}, \quad \tilde{h}(0) = 0,$$

where $\tilde{m} \in L^2(I, C^0(\Omega)) \subset L^2(I, L^1(\Omega))$ and $\tilde{f} \in L^2(I, L^1(\Omega))$. Using Theorem 71 we find that there exists a unique solution $\tilde{h}$ in $W_0^{1,2}(I, L^1(\Omega))$ and consequently $h(t) = \tilde{h}(T-t)$ solves (4.21).

Let us now remark on the partial integration formula we need in the following argument. Consider the continuous bilinear form

$$B : C^0(\Omega) \times L^1(\Omega) \to \mathbb{R}, \quad B(u, v) = \int_\Omega uv\mathrm{d}x.$$

Then it holds for $u \in W^{1,p}(I, C^0(\Omega))$ and $v \in W^{1,q}(I, L^1(\Omega))$, $p, q \in [1, \infty)$ for time-points $s \leq t$ in I that

$$\begin{aligned}\int_s^t \int_\Omega d_t u \cdot v\mathrm{d}x\mathrm{d}t &= B(u(t), v(t)) - B(u(s), v(s)) - \int_s^t \int_\Omega u d_t v\mathrm{d}x\mathrm{d}t \\ &= \int_\Omega u(t)v(t)\mathrm{d}x - \int_\Omega u(s)v(s)\mathrm{d}x - \int_s^t \int_\Omega d_t v\mathrm{d}x\mathrm{d}t.\end{aligned}$$

This can be proven by an approximation argument using the density of $C^\infty(I, C^0(\Omega))$ in $W^{1,p}(I, C^0(\Omega))$ and $C^\infty(I, L^1(\Omega))$ in $W^{1,q}(I, L^1(\Omega))$ respectively. Now we use this formula applied to the equation (4.21) which we multiply by a function $\varphi \in W_0^{1,2}(I, C^0(\Omega))$ and integrate over all of $I \times \Omega$ to obtain

$$\begin{aligned}\iint f\varphi\mathrm{d}x\mathrm{d}t &= -\iint d_t h\varphi\mathrm{d}x\mathrm{d}t + \iint mh\varphi\mathrm{d}x\mathrm{d}t \\ &= \iint d_t\varphi h\mathrm{d}x\mathrm{d}t + \underbrace{\int_\Omega h(T)\varphi(T)\mathrm{d}x - \int_\Omega h(0)\varphi(0)\mathrm{d}x}_{=0} + \iint mh\varphi\mathrm{d}x\mathrm{d}t \\ &= \iint d_t\varphi h\mathrm{d}x\mathrm{d}t + \iint mh\varphi\mathrm{d}x\mathrm{d}t.\end{aligned}$$

This is nothing but

$$\left[\iint h \cdot \mathrm{d}x\mathrm{d}t\right][d_t \cdot + M\cdot] = \iint f \cdot \mathrm{d}x\mathrm{d}t, \quad \text{in } W_0^{1,2}(C^0(\Omega)),$$

which means that

$$h^* = \iint h \cdot \mathrm{d}x\mathrm{d}t$$

as h^* is unique. The uniqueness of h^* is due to the fact that $(d_t + M)^*$ is a linear homeomorphism as $d_t + M$ is. □

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