

Global Existence, Invariant Region, and Enhanced Regularity for an Anisotropic Reaction–Diffusion Model of Myocardial Remodeling in Terms of Dirichlet Concentration Parameters

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Abstract

A multicomponent anisotropic reaction–diffusion model for post-infarction myocardial remodeling is studied in terms of Dirichlet concentration parameters. In this formulation, the state variables encode both tissue composition and uncertainty, which is essential in heterogeneous border-zone regions. The model includes healthy myocardium, inflammatory infiltrate, necrosis, replacement fibrosis, and interstitial fibrosis, and combines fiber-oriented diffusion with a clinically motivated transition structure.

For the original system, weak solutions are proved to exist globally in time. In addition, non-negativity, explicit upper and lower bounds, and invariance of the admissible region are established. The main analytical result is a strengthened gradient-regularity class obtained under additional assumptions on the initial data and the fiber field. This class yields short-time unconditional uniqueness and removes the conditional character of the earlier uniqueness argument. The proof relies on invariant-region techniques, maximal regularity for parabolic equations with spatial VMO coefficients, Morrey-type embedding, and a closed $W^{1,r}$ iteration.

The numerical part illustrates the barrier properties of the model, representative space-time regimes, and the interpretation of the state variables. In a one-dimensional 60-day scenario, the spatially averaged replacement-fibrosis probability increases from 0.091 to 0.811, while the corresponding concentration parameter rises from 11.0 to 15.4. In a two-dimensional test at day 14, the variance reaches 0.038 in the transition zone, compared with 0.009 in the lesion core and 0.004 in healthy tissue. The scheme also shows second-order convergence in space and first-order convergence in time on a smooth manufactured solution.

Keywords: reaction–diffusion system; Dirichlet distribution; invariant region; global existence; $W^{1,r}$ regularity; maximal L^r regularity; VMO coefficients; unconditional uniqueness; anisotropic diffusion; myocardial remodeling.

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1 Introduction

1.1 Motivation

Myocardial fibrosis is one of the key pathological processes that determine the course of ischemic heart disease, dilated cardiomyopathy, and post-infarction remodeling of the left ventricle [1–5]. Of particular clinical interest are transition zones of damage, visualized by late gadolinium enhancement MRI and regarded as a possible substrate for ventricular arrhythmias [6, 7]. For quantitative analysis of such zones, binary or three-phase descriptions are not sufficient; one needs a model that allows for a multicomponent tissue composition together with a probabilistic interpretation of uncertainty.

1.2 Overview of mathematical approaches

Parabolic reaction–diffusion systems are a well-established tool in mathematical biology and physiology; questions of global existence, invariance, and uniqueness are treated in detail in the monographs

by Pao [8] and Smoller [9]. Phase-field and diffuse-interface models [10–12] can describe transitions between phases, but they usually do not provide a probabilistic interpretation of tissue composition. Electrophysiological and bidomain models [13–15] account for fibrosis as a modifier of conductivity, but they do not model the evolution of tissue composition itself. Models of arrhythmogenicity in diffuse fibrosis [16] and biomechanical models of the infarct border zone [17] also do not use a probabilistic description of tissue composition as the main state variable. The anisotropic structure of the myocardium is supported by diffusion tensor MRI data [18, 19]. A description in terms of Dirichlet distribution parameters [20, 21] makes it possible to encode both the expected tissue composition and the degree of confidence in it. To the best of the authors’ knowledge, a formulation in which the local tissue state is described by a vector of Dirichlet parameters and at the same time serves as the state variable of a multicomponent reaction–diffusion system has not previously been considered explicitly for post-infarction myocardial remodeling.

1.3 Regularity of solutions and the uniqueness problem

It is well known that for nonlinear parabolic systems, global existence of a weak solution in the class $L^2(0, T; H^1) \cap C([0, T]; L^2)$ does not automatically imply either uniqueness or higher spatial regularity. In our setting, an additional difficulty comes from the nonlinear dependence of the diffusion tensor on the state vector through the anisotropic term $\beta_k \alpha_{\text{dam}} / (\alpha_0 + \varepsilon)$: different components α_k enter the coefficient in the equation for each α_k .

The standard approach to uniqueness — comparing two solutions $\alpha^{(1)}$ and $\alpha^{(2)}$ through the difference $w_k = \alpha_k^{(1)} - \alpha_k^{(2)}$ — produces the term

$$I_D^{(k)} = \int_{\Omega} (D_k(x, \alpha^{(1)}) - D_k(x, \alpha^{(2)})) \nabla \alpha_k^{(2)} \cdot \nabla w_k \, dx,$$

whose estimate requires $\nabla \alpha_k^{(2)} \in L^\infty(0, S; L^r(\Omega))$ for $r > d$. This is exactly why one has to work in the strengthened class $U_r(S)$.

The key question that is not resolved by the standard uniqueness argument is the following: does there exist at least one solution in the class $U_r(\tau)$ for some finite $\tau > 0$? The paper gives a positive answer to this question.

1.4 Analytical approach and main tools

The answer is based on a sequential use of three standard analytical facts. First, the theorems of Kim–Krylov [22] and Dong–Kim [23] provide maximal L^r regularity for a parabolic equation with a uniformly elliptic coefficient having a small VMO seminorm in the spatial variables. This makes it possible to place the solution in the class $L^r(0, \tau; W^{2,r}) \cap W^{1,r}(0, \tau; L^r)$ and thus move from energy-level H^1 regularity to stronger estimates.

Second, for $r > d$, Morrey’s theorem yields the embedding $W^{1,r}(\Omega) \hookrightarrow C^{0,\mu}(\Omega)$, $\mu = 1 - d/r > 0$. If the iterative function $\bar{\alpha}$ belongs to $L^\infty(0, \tau; W^{1,r})$, then the frozen coefficient $A_k(x, t) = D_k(x, (\bar{\alpha}(x, t))_+)$ is Hölder continuous in x , uniformly in t , and therefore satisfies the VMO condition. Hence the assumption of $W^{1,r}$ regularity for the iterative function returns at the next step as $W^{2,r}$ regularity of the new iterate.

Third, the space $L^r(0, \tau; W^{2,r}) \cap W^{1,r}(0, \tau; L^r)$ embeds into $C([0, \tau]; (W^{2,r}, L^r)_{1/r, r})$ by Amann’s interpolation theorem [24]. For $r > d$ and $d \in \{2, 3\}$, one has the continuous embedding $(W^{2,r}, L^r)_{1/r, r} = W^{2-2/r, r} \hookrightarrow W^{1,r}$, since $2 - 2/r > 1$. As a result, the new iterate belongs to $C([0, \tau]; W^{1,r})$, and the iteration scheme closes in the required class.

1.5 Main results of the paper

1. **A new model formulation.** We propose a reaction–diffusion system whose state variables are Dirichlet distribution parameters. For the specific anisotropic diffusion tensor, in which the intensity of the anisotropic component is controlled by the fraction of damaged tissue, we verify explicitly the structural assumptions of uniform ellipticity and local Lipschitz continuity.
2. **Global existence and invariance.** For the truncated system we first prove local existence of a weak solution and then derive non-negativity, an upper barrier, and a quantitative lower estimate. These results imply invariance of the admissible region and, after continuation, existence of a global weak solution to the original clinical system (Theorem 4.8).
3. **Nonemptiness of the strengthened class and $W^{1,r}$ regularity.** Under the additional hypotheses (29)–(30) ($\alpha_k^0 \in W^{1,r}(\Omega)$, $f \in W^{1,\infty}(\Omega)$, $r > d$), we prove existence of a solution with $\nabla \alpha_k \in L^\infty(0, \tau_r; L^r(\Omega))$ for some explicitly estimated $\tau_r > 0$ (Theorem 5.7).
4. **Unconditional uniqueness in the strengthened class.** Combining items 2 and 3, we obtain that on the interval $[0, \tau_r]$ the class $U_r(\tau_r)$ contains exactly one solution. This removes the conditional character of the uniqueness theorem (Theorem 5.1 and Corollary 5.9).
5. **Entropy balance and stability.** For the reversible auxiliary regime we derive a formal entropy balance. For the clinical irreversible transition matrix we prove a modal spectral stability condition for the linearization through properties of Metzler matrices (Propositions 7.1 and 7.3).
6. **An illustrative numerical section.** For the splitting scheme we derive a positivity condition for the reaction substep relative to an adaptive upper barrier. The one- and two-dimensional computations are used only as illustrations of the analytical results and not as an independent source of model or clinical claims.

1.6 Nature of the novelty

Modeling novelty. The use of a vector of Dirichlet distribution parameters as the state variable of a reaction–diffusion system to describe five tissue states of the myocardium in the context of post-infarction remodeling, to the best of the authors’ knowledge, has not been used before.

Analytical novelty. The main mathematical contribution is Theorem 5.7. Its proof combines maximal L^r regularity with VMO coefficients, Morrey’s theorem, and interpolation in Bochner spaces in a way adapted to the present nonlinear anisotropic system with Markovian reaction dynamics. This yields a closed $W^{1,r}$ iteration argument and removes the conditional character of the uniqueness theorem.

The remaining analytical tools used for results 1–2 and 4–6 are standard in the theory of nonlinear parabolic equations [8, 9, 25–28].

1.7 Structure of the paper

Section 2 introduces the mathematical model and verifies the structural properties of the diffusion tensor. Section 3 studies the extended reaction operator. Section 4 proves existence and invariance. Section 5 establishes nonemptiness of $U_r(\tau_r)$ and derives unconditional uniqueness; this is the main analytical section. Section 6 discusses the probabilistic interpretation of the model. Section 7 deals with entropy balance and stability. Sections 8–9 present the discretization scheme and a limited set of numerical illustrations. Section 10 contains an interpretation of the results and a discussion of the limitations of the model.

2 Mathematical formulation of the model

2.1 Geometry and admissible set of states

Let $\Omega \subset \mathbb{R}^d$, $d \in \{2, 3\}$, be a bounded domain with boundary of class $C^{2+\mu_0}$, $\mu_0 > 0$, and let $T > 0$ be a fixed observation horizon. In this paper we consider a five-component model, that is,

$$K = 5.$$

The components $\alpha_1, \dots, \alpha_5$ are interpreted as the concentration parameters of a Dirichlet distribution for five tissue states: α_1 is healthy myocardium, α_2 is inflammatory infiltrate, α_3 is necrosis, α_4 is replacement fibrosis, and α_5 is interstitial fibrosis.

For $M > 0$ we introduce the admissible region

$$A_0^M := \{a \in \mathbb{R}^K : 0 \leq a_k \leq M, k = 1, \dots, K\}. \quad (1)$$

2.2 Reaction–diffusion system

The system under study has the form

$$\partial_t \alpha_k = \nabla \cdot (D_k(x, \alpha) \nabla \alpha_k) + R_k(\alpha), \quad k = 1, \dots, K, \quad (2)$$

supplemented with homogeneous Neumann boundary conditions and initial data

$$D_k(x, \alpha) \nabla \alpha_k \cdot n = 0 \quad \text{on } \partial\Omega \times (0, T), \quad \alpha_k(x, 0) = \alpha_k^0(x). \quad (3)$$

2.3 Diffusion tensor

We set

$$D_k(x, \alpha) = d_k^{(\text{iso})} I + d_k^{(\text{aniso})}(\alpha) (f(x) \otimes f(x)), \quad (4)$$

where the anisotropic coefficient is defined by

$$d_k^{(\text{aniso})}(\alpha) := \beta_k \frac{\alpha_{\text{dam}}}{\alpha_0 + \varepsilon}, \quad \alpha_{\text{dam}} := \sum_{j=2}^K \alpha_j, \quad \alpha_0 := \sum_{j=1}^K \alpha_j. \quad (5)$$

Biologically, the term $\alpha_{\text{dam}}/(\alpha_0 + \varepsilon)$ represents the fraction of damaged tissue: the higher the local fraction of necrosis and fibrosis at the point x , the stronger the anisotropic diffusion along the fiber direction $f(x)$.

We assume the following conditions:

$$d_k^{(\text{iso})} > 0, \quad \beta_k \geq 0, \quad \varepsilon > 0, \quad f \in L^\infty(\Omega; \mathbb{R}^d), \quad \|f\|_{L^\infty(\Omega)} \leq F_*. \quad (6)$$

2.4 Reaction operator

The reaction term is given by

$$R_k(\alpha) = \sum_{j=1}^K q_{jk} \alpha_j - S_k(\alpha), \quad (7)$$

where the nonlinear sink

$$S_k(\alpha) := \kappa_k \alpha_k \left(\frac{\alpha_k}{M_k} - 1 \right)_+ \quad (8)$$

prevents unbounded growth of the components when $\alpha_k > M_k$. We use the notation

$$q_k^{\text{out}} := -q_{kk}, \quad q_k^{\text{in}} := \sum_{j \neq k} q_{jk}, \quad q_* := \max_{1 \leq k \leq K} q_k^{\text{in}}. \quad (9)$$

We also assume

$$M_k \geq 1, \quad k = 1, \dots, K. \quad (10)$$

Condition (10) will be used in Section 7 when we analyze the entropy functional.

2.5 Clinically motivated transition matrix

We use the transition-rate matrix

$$Q = \begin{pmatrix} -(q_{12} + q_{15}) & q_{12} & 0 & 0 & q_{15} \\ 0 & -(q_{23} + q_{24} + q_{25}) & q_{23} & q_{24} & q_{25} \\ 0 & 0 & -q_{34} & q_{34} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & q_{52} & 0 & q_{54} & -(q_{52} + q_{54}) \end{pmatrix}. \quad (11)$$

The coefficient $q_{jk} \geq 0$ for $j \neq k$ is the rate of transition from state j to state k . The row-balance condition

$$\sum_{k=1}^K q_{jk} = 0, \quad j = 1, \dots, K, \quad (12)$$

is necessary for the stochasticity of the Markov chain. The matrix (11) is irreversible: the replacement fibrosis state ($k = 4$) is absorbing, and detailed balance is impossible for it.

2.6 Biological motivation for the transition topology

Matrix (11) models the dominant directions of post-infarction remodeling according to modern reviews [29–31]: acute inflammatory response, necrosis, scar formation, and reactive interstitial fibrosis.

1. Transition $1 \rightarrow 2$ corresponds to the onset of inflammation in the damage zone.
2. Transitions $2 \rightarrow 3$, $2 \rightarrow 4$, and $2 \rightarrow 5$ describe branching of the inflammatory state into necrosis, replacement fibrosis, and interstitial fibrosis, respectively.
3. Transition $3 \rightarrow 4$ corresponds to replacement of necrotic tissue by scar tissue.
4. Transition $5 \rightarrow 4$ represents local concentration of fibrotic remodeling.
5. Transition $5 \rightarrow 2$ represents reactivation of inflammation in chronically remodeled tissue.

There is no direct transition $1 \rightarrow 4$: replacement scar appears only as the outcome of damage mediated by inflammation, not directly from healthy tissue. The direct transition $1 \rightarrow 5$ is allowed as a simplified description of reactive diffuse fibrosis outside the necrotic zone. The coefficients q_{jk} are understood as effective phenomenological parameters; their quantitative identification requires a separate inverse problem.

2.7 Verification of the structural assumptions for the specific tensor

The theorems in Sections 4–5 are formulated for an abstract class of coefficients satisfying hypotheses (25)–(26) from Section 4.1. For the tensor (4)–(5), these hypotheses are verified explicitly in the following proposition.

Proposition 2.1. *Assume that conditions (6) hold. Then for every $M > 0$ there exist constants $d_{\min} > 0$, $d_{\max}(M) > 0$, and $L_D(M) > 0$ such that for all $a, b \in \mathbb{R}^K$ with $\|a\|_\infty, \|b\|_\infty \leq M$ and all $\xi \in \mathbb{R}^d$,*

$$d_{\min}|\xi|^2 \leq \xi^\top D_k(x, (a)_+) \xi \leq d_{\max}(M)|\xi|^2, \quad (13)$$

$$|D_k(x, (a)_+) - D_k(x, (b)_+)| \leq L_D(M)|a - b|_\infty \quad \text{for a.e. } x \in \Omega. \quad (14)$$

The constants can be chosen explicitly as

$$\begin{aligned} d_{\min} &= \min_k d_k^{(\text{iso})}, \\ d_{\max}(M) &= \max_k \left(d_k^{(\text{iso})} + \beta_k \frac{KM}{\varepsilon} F_*^2 \right), \\ L_D(M) &= \max_k \frac{\beta_k F_*^2}{\varepsilon^2} (K + 1)M. \end{aligned} \quad (15)$$

Proof. By definition,

$$D_k(x, (a)_+) = d_k^{(\text{iso})} I + \beta_k \frac{a_{\text{dam}}^+}{a_0^+ + \varepsilon} (f \otimes f),$$

where $a_{\text{dam}}^+ = \sum_{j=2}^K (a_j)_+$ and $a_0^+ = \sum_{j=1}^K (a_j)_+$.

Lower bound. Since the second term is nonnegative as a tensor product, we have $\xi^\top D_k \xi \geq d_k^{(\text{iso})} |\xi|^2$, which gives $d_{\min} = \min_k d_k^{(\text{iso})} > 0$.

Upper bound. From $0 \leq a_{\text{dam}}^+ / (a_0^+ + \varepsilon) \leq KM / \varepsilon$ and $(f \cdot \xi)^2 \leq F_*^2 |\xi|^2$, we obtain the upper bound in (13) with $d_{\max}(M)$ from (15).

Lipschitz continuity. The function $g(z) := z_{\text{dam}}^+ / (z_0^+ + \varepsilon)$ has bounded gradient on $[0, M]^K$: $|\partial_{z_l} g| \leq 1/\varepsilon + KM/\varepsilon^2 \leq (K + 1)M/\varepsilon^2$ (for $M \geq 1$). Since the mapping $a \mapsto (a)_+$ is Lipschitz with constant 1, the chain rule gives

$$|g((a)_+) - g((b)_+)| \leq \frac{(K + 1)M}{\varepsilon^2} |a - b|_\infty.$$

Multiplying by $\beta_k F_*^2$ yields (14) with $L_D(M)$ from (15). \square

Remark 2.2. Therefore all results of Sections 4–5 apply to the specific tensor (4)–(5).

3 Extended reaction operator

3.1 Truncated operator

To work with the system outside the nonnegative cone \mathbb{R}_+^K , we introduce

$$\tilde{R}_k(\alpha) := \sum_{j \neq k} q_{jk} (\alpha_j)_+ - q_k^{\text{out}} (\alpha_k)_+ - \kappa_k (\alpha_k)_+ \left(\frac{(\alpha_k)_+}{M_k} - 1 \right)_+. \quad (16)$$

On \mathbb{R}_+^K this operator coincides with the original one:

$$\tilde{R}_k(\alpha) = R_k(\alpha), \quad \alpha \in \mathbb{R}_+^K. \quad (17)$$

3.2 Quasi-positivity

Lemma 3.1. *If $\alpha_k \leq 0$, then $\widetilde{R}_k(\alpha) = \sum_{j \neq k} q_{jk}(\alpha_j)_+ \geq 0$.*

Proof. If $\alpha_k \leq 0$, then $(\alpha_k)_+ = 0$, so the negative terms in (16) disappear. The remaining terms are nonnegative because $q_{jk} \geq 0$ for $j \neq k$. \square

3.3 One-sided estimates

Lemma 3.2. *Let $\alpha \in \mathbb{R}_+^K$. Then*

$$R_k(\alpha) \geq -q_k^{\text{out}} \alpha_k, \quad 0 \leq \alpha_k \leq M_k, \quad (18)$$

$$R_k(\alpha) \geq -\left[q_k^{\text{out}} + \kappa_k \left(\frac{\alpha_k}{M_k} - 1 \right) \right] \alpha_k, \quad \alpha_k > M_k, \quad (19)$$

$$R_k(\alpha) \leq q_k^{\text{in}} |\alpha|_\infty. \quad (20)$$

If, in addition, $0 \leq \alpha_k \leq M_T$, then

$$R_k(\alpha) \geq -\Lambda_k \alpha_k, \quad \Lambda_k := q_k^{\text{out}} + \kappa_k \left(\frac{M_T}{M_k} - 1 \right)_+. \quad (21)$$

Proof. Estimate (18). If $0 \leq \alpha_k \leq M_k$, then $S_k = 0$, so $R_k = \sum_{j \neq k} q_{jk} \alpha_j - q_k^{\text{out}} \alpha_k \geq -q_k^{\text{out}} \alpha_k$, since all incoming terms are nonnegative.

Estimate (19). If $\alpha_k > M_k$, then $S_k = \kappa_k \alpha_k (\alpha_k / M_k - 1)$, hence $R_k \geq -[q_k^{\text{out}} + \kappa_k (\alpha_k / M_k - 1)] \alpha_k$.

Estimate (20). Dropping the negative terms, we get $R_k \leq \sum_{j \neq k} q_{jk} \alpha_j \leq q_k^{\text{in}} |\alpha|_\infty$.

Estimate (21). If $0 \leq \alpha_k \leq M_T$, then from (18)–(19) we obtain $R_k \geq -[q_k^{\text{out}} + \kappa_k (M_T / M_k - 1)_+] \alpha_k = -\Lambda_k \alpha_k$. \square

3.4 Local Lipschitz continuity with an explicit constant

Lemma 3.3. *For every $M > 0$,*

$$|\widetilde{R}(\alpha) - \widetilde{R}(\beta)|_\infty \leq L_R(M) |\alpha - \beta|_\infty, \quad |\alpha|_\infty, |\beta|_\infty \leq M, \quad (22)$$

where

$$L_R(M) := \max_{1 \leq k \leq K} \left(\sum_{j \neq k} |q_{jk}| + q_k^{\text{out}} + \kappa_k \left(\frac{2M}{M_k} + 1 \right) \right). \quad (23)$$

Proof. For fixed k , define $h_k(z) := z_+(z_+ / M_k - 1)_+$. The function h_k is piecewise quadratic: $h_k(z) = 0$ for $z \leq M_k$ and $h_k(z) = z^2 / M_k - z$ for $z > M_k$, so $|h'_k(z)| \leq 2M / M_k + 1$ on $[-M, M]$. Therefore h_k is Lipschitz on $[-M, M]$ with constant $L_{h,k}(M) := 2M / M_k + 1$. Applying the triangle inequality to (16) and using that $z \mapsto z_+$ is Lipschitz with constant 1, we obtain (22) with $L_R(M)$ from (23). \square

3.5 Reaction balance

Lemma 3.4. *For $\alpha \in \mathbb{R}_+^K$,*

$$\sum_{k=1}^K R_k(\alpha) = - \sum_{k=1}^K S_k(\alpha) \leq 0. \quad (24)$$

Proof. From (7) we have

$$\sum_k R_k = \sum_k \sum_j q_{jk} \alpha_j - \sum_k S_k = \sum_j \alpha_j \sum_k q_{jk} - \sum_k S_k.$$

By the row-balance condition (12), we have $\sum_k q_{jk} = 0$, which implies (24). \square

Remark 3.5. Equality (24) means that the total concentration parameter $\alpha_0 = \sum_k \alpha_k$ decreases in time only because of the sink terms S_k , that is, because of departure from the physiologically admissible range $[0, M_k]$. Inside the admissible region ($\alpha_k \leq M_k$ for all k), the reaction preserves α_0 , which is natural for the probabilistic parametrization introduced here.

4 Global existence and invariance

4.1 Structural hypotheses

(H1) Uniform ellipticity.

$$d_{\min} |\xi|^2 \leq \xi^\top D_k(x, (a)_+) \xi \leq d_{\max} |\xi|^2. \quad (25)$$

For $|a|_\infty, |b|_\infty \leq M$, we also assume local Lipschitz continuity with respect to the state variable:

(H2) Local Lipschitz continuity in the state variable.

$$|D_k(x, (a)_+) - D_k(x, (b)_+)| \leq L_D(M) |a - b|_\infty. \quad (26)$$

The initial data satisfy

(H3) Boundedness and strict positivity of the initial data.

$$\alpha_k^0 \in L^2(\Omega) \cap L^\infty(\Omega), \quad 0 < \delta_0 \leq \alpha_k^0 \leq M_0 \quad \text{a.e.} \quad (27)$$

and the boundary of the domain belongs to the class

(H4) Smoothness of the domain boundary.

$$\partial\Omega \in C^{2+\mu_0}, \quad \mu_0 > 0. \quad (28)$$

For the $W^{1,r}$ theory, we additionally assume

(H5) $W^{1,r}$ regularity of the initial data.

$$\alpha_k^0 \in W^{1,r}(\Omega), \quad \|\nabla \alpha_k^0\|_{L^r} \leq R_0, \quad r > d, \quad (29)$$

and

(H6) Regularity of the fiber field.

$$f \in W^{1,\infty}(\Omega; \mathbb{R}^d), \quad \|\nabla f\|_{L^\infty} \leq F_1. \quad (30)$$

Remark 4.1. Conditions (25)–(28) are sufficient for global existence (Theorem 4.8). Conditions (29)–(30) are additionally needed for $W^{1,r}$ regularity and unconditional uniqueness (Theorem 5.7 and Corollary 5.9).

4.2 Weak solution

Definition 4.2. A vector-valued function α is called a weak solution on $[0, T]$ if $\alpha_k \in L^2(0, T; H^1(\Omega)) \cap C([0, T]; L^2(\Omega))$, $\partial_t \alpha_k \in L^2(0, T; H^{-1}(\Omega))$, and for every $\psi \in L^2(0, T; H^1(\Omega))$ one has

$$\int_0^T \langle \partial_t \alpha_k, \psi \rangle dt + \int_0^T \int_\Omega D_k \nabla \alpha_k \cdot \nabla \psi dx dt = \int_0^T \int_\Omega R_k \psi dx dt. \quad (31)$$

4.3 Comparison principle

Proposition 4.3. *Let u and v be weak solutions such that $\partial_t u - \nabla \cdot (a \nabla u) \leq f$, $\partial_t v - \nabla \cdot (a \nabla v) \geq f$, with the same Neumann boundary conditions and with $u(\cdot, 0) \leq v(\cdot, 0)$ a.e. Then $u \leq v$ a.e. in Ω_T .*

Proof. Testing with $(u - v)_+$ under zero initial data and using ellipticity gives $\frac{1}{2} \frac{d}{dt} \|(u - v)_+\|_{L^2}^2 \leq 0$, hence $(u - v)_+ \equiv 0$. \square

4.4 Local existence

We consider the truncated system

$$\partial_t \alpha_k = \nabla \cdot (D_k(x, (\alpha)_+) \nabla \alpha_k) + \tilde{R}_k(\alpha).$$

Set

$$C_R(M) := \max_k \sup_{|a|_\infty \leq M} |\tilde{R}_k(a)|, \quad \tau_M := \min\{1, M/C_R(2M)\}.$$

Theorem 4.4 (local existence). *Under assumptions (25)–(28) and $\|\alpha_k^{\text{in}}\|_{L^\infty} \leq M$, the truncated system has a weak solution on $[0, \tau_M]$.*

Proof. We define the set

$$K_{\tau_M} := \{\bar{\alpha} : \|\bar{\alpha}_k\|_{L^\infty(\Omega \times (0, \tau_M))} \leq 2M\}$$

and the operator $\Phi : K_{\tau_M} \rightarrow K_{\tau_M}$ that maps $\bar{\alpha}$ to the solution of the frozen linear problem

$$\partial_t \alpha_k - \nabla \cdot (D_k(x, (\bar{\alpha})_+) \nabla \alpha_k) = \tilde{R}_k(\bar{\alpha}), \quad \alpha_k(\cdot, 0) = \alpha_k^{\text{in}}. \quad (32)$$

Step 1 (solvability). By (25), the coefficients are bounded and uniformly elliptic, and the right-hand side belongs to $L^\infty(\Omega_{\tau_M})$. Therefore the standard theory of linear parabolic problems with Neumann boundary conditions gives a unique weak solution; see [8, 25].

Step 2 (self-mapping property). The barriers $B_\pm(t) := \pm M \pm C_R(2M)t$ satisfy

$$\partial_t B_+ - \nabla \cdot (D_k \nabla B_+) \geq \tilde{R}_k, \quad \partial_t B_- - \nabla \cdot (D_k \nabla B_-) \leq \tilde{R}_k,$$

and $B_\pm(0) \geq \alpha_k^{\text{in}}$. By Proposition 4.3,

$$|\alpha_k| \leq M + C_R(2M)\tau_M \leq 2M,$$

so $\Phi(K_{\tau_M}) \subset K_{\tau_M}$.

Step 3 (compactness). Standard energy estimates together with the Aubin–Lions–Simon lemma [26] imply that $\Phi(K_{\tau_M})$ is precompact in $[L^2(\Omega \times (0, \tau_M))]^K$.

Step 4 (continuity and Schauder's theorem). Let $\bar{\alpha}^{(n)} \rightarrow \bar{\alpha}$ in $[L^2]^K$. Then $\tilde{R}_k(\bar{\alpha}^{(n)}) \rightarrow \tilde{R}_k(\bar{\alpha})$ in L^2 by the dominated convergence theorem. For the diffusion term, we split it into two parts, $I_{1,n} + I_{2,n}$: the term $I_{1,n} \rightarrow 0$ because the coefficients $D_k(x, (\bar{\alpha}^{(n)})_+) \rightarrow D_k(x, (\bar{\alpha})_+)$ and by dominated convergence, while $I_{2,n} \rightarrow 0$ follows from weak convergence of the gradients of solutions to the frozen problems. Hence the operator Φ is continuous in the $[L^2]^K$ topology. Schauder's fixed-point theorem then yields a fixed point, which is the desired weak solution. \square

4.5 Non-negativity and barriers

Lemma 4.5. $\alpha_k(x, t) \geq 0$ a.e. in Ω_T .

Proof. Testing with $-(\alpha_k)_-$ and using quasi-positivity of the reaction term (Lemma 3.1) gives $\frac{1}{2} \frac{d}{dt} \|(\alpha_k)_-\|_{L^2}^2 \leq 0$. Since $(\alpha_k^0)_- = 0$, we obtain $(\alpha_k)_- \equiv 0$. \square

Lemma 4.6. Under assumption (27), one has

$$0 \leq \alpha_k(x, t) \leq B(t) := M_0 e^{q_* t} \quad \text{a.e.}$$

for all $k = 1, \dots, K$.

Proof. Introduce $w_k := (\alpha_k - B)_+$ and test the equation for $(\alpha_k - B)$ with w_k . On the set $\{w_k > 0\}$, using non-negativity of α_j and the bound $\alpha_j \leq B + w_j$, we obtain

$$R_k(\alpha) - B'(t) \leq \sum_{j \neq k} q_{jk} w_j,$$

since $q_k^{\text{in}} \leq q_* = B'/B$. Summing over k , using uniform ellipticity and the elementary estimate $w_j w_k \leq (w_j^2 + w_k^2)/2$, we arrive at

$$\frac{1}{2} \frac{d}{dt} \sum_k \|w_k\|_{L^2}^2 + d_{\min} \sum_k \|\nabla w_k\|_{L^2}^2 \leq C_Q \sum_k \|w_k\|_{L^2}^2, \quad C_Q := \frac{1}{2} \max_k (q_k^{\text{in}} + q_k^{\text{out}}).$$

Since $w_k(\cdot, 0) = 0$, Gronwall's lemma gives $\sum_k \|w_k\|_{L^2}^2 \equiv 0$, hence $w_k \equiv 0$ for all k . \square

Lemma 4.7. For all $k = 1, \dots, K$,

$$\alpha_k(x, t) \geq \delta_0 e^{-\Lambda_k t} \quad \text{a.e.},$$

where

$$\Lambda_k := q_k^{\text{out}} + \kappa_k \left(\frac{M_T}{M_k} - 1 \right)_+, \quad M_T := M_0 e^{q_* T}.$$

Proof. By Lemma 4.6 and Lemma 3.2, we have $R_k \geq -\Lambda_k \alpha_k$. The function $v_k := e^{\Lambda_k t} \alpha_k$ satisfies $\partial_t v_k - \nabla \cdot (D_k \nabla v_k) \geq 0$ and $v_k(\cdot, 0) \geq \delta_0$. Proposition 4.3 then yields $v_k \geq \delta_0$. \square

Theorem 4.8 (global existence and invariance). Under assumptions (25)–(28), the original system has a global weak solution $\alpha \in [L^2(0, T; H^1) \cap C([0, T]; L^2)]^K$ satisfying

$$\delta_0 e^{-\Lambda_k t} \leq \alpha_k(x, t) \leq M_0 e^{q_* T} \quad \text{a.e.} \quad (33)$$

for all $k = 1, \dots, K$.

Proof. The local solution on $[0, \tau_{M_0}]$ can be continued step by step with a constant time step that does not depend on the restart point. The assumption $T_{\max} < T$ leads to a contradiction. Non-negativity ensures that the truncated and original systems coincide. \square

5 $W^{1,r}$ regularity and unconditional uniqueness

5.1 Conditional uniqueness

We introduce the strengthened class

$$U_r(S) := \{\alpha \text{ — weak solution} : \nabla \alpha_k \in L^\infty(0, S; L^r(\Omega)), r > d\}.$$

Theorem 5.1. *If $\alpha^{(1)}, \alpha^{(2)} \in U_r(S)$ are two weak solutions, then $\alpha^{(1)} \equiv \alpha^{(2)}$.*

Proof. For the difference $w_k := \alpha_k^{(1)} - \alpha_k^{(2)}$, we estimate the reaction term by Lemma 3.3 and the diffusion term by using the embedding $H^1 \in L^s$ for $r > d$ together with Ehrling's lemma. With a suitable choice of parameters, the coefficient in front of $G = \sum \|\nabla w_k\|_{L^2}^2$ can be absorbed. Gronwall's lemma then yields $\sum_k \|w_k(t)\|_{L^2}^2 \equiv 0$ because the initial difference is zero. \square

Remark 5.2. Theorem 5.1 is conditional, since by itself it does not guarantee that the class $U_r(S)$ is nonempty.

5.2 VMO property of the frozen coefficient

Lemma 5.3. *Assume (26), (30), $r > d$, and $\bar{\alpha} \in [L^\infty(0, \tau; W^{1,r})]^K$ with $\sup_t \|\nabla \bar{\alpha}(t)\|_{L^r} \leq N$. Then for $A_k(x, t) := D_k(x, (\bar{\alpha})_+)$ the following hold:*

- (i) $\sup_t \|\nabla_x A_k(t)\|_{L^r} \leq C_A(1 + N)$;
- (ii) $A_k(t) \in C^{0,\mu}(\Omega)$ with $\mu = 1 - d/r > 0$ uniformly in t , and hence $A_k(t) \in \text{VMO}(\Omega)$ uniformly in t .

Proof. Differentiating the representation of the diffusion tensor gives an estimate for $\nabla_x A_k$ in terms of $\nabla \bar{\alpha}$ and ∇f . We then apply Morrey's theorem, $W^{1,r} \hookrightarrow C^{0,\mu}$, valid for $r > d$. \square

5.3 Maximal L^r regularity

Theorem 5.4 (Regularity statement used below). *For the Neumann problem $\partial_t u - \nabla \cdot (A(x, t) \nabla u) = F$ with uniformly elliptic A having a small VMO seminorm in x , uniformly in t , if $F \in L^p(\Omega_T)$ and $u_0 \in W^{2-2/p, p}(\Omega)$, then the estimate*

$$\|\partial_t u\|_{L^p(\Omega_T)} + \|u\|_{L^p(0, T; W^{2,p})} \leq C_p (\|F\|_{L^p(\Omega_T)} + \|u_0\|_{W^{2-2/p, p}}) \quad (34)$$

holds.

Remark 5.5. Theorem 5.4 is used here as a standard maximal-regularity statement for uniformly elliptic parabolic problems with spatial VMO coefficients. By Lemma 5.3(ii), the coefficient $A_k(t)$ is Holder continuous uniformly in t , and hence has a small VMO seminorm in the sense required below; compare [22, 23].

5.4 $W^{1,r}$ estimate for the iterate

We introduce the strengthened iteration set

$$K_\tau^r(N) := \{\bar{\alpha} \in K_{\tau_M} : \sup_t \|\nabla \bar{\alpha}_k(t)\|_{L^r} \leq N\}.$$

Lemma 5.6. *Assume (25)–(30), let $\bar{\alpha} \in K_\tau^r(N)$, and let α_k solve*

$$\partial_t \alpha_k - \nabla \cdot (D_k(x, (\bar{\alpha})_+) \nabla \alpha_k) = \tilde{R}_k(\bar{\alpha}), \quad \alpha_k(\cdot, 0) = \alpha_k^0 \in W^{1,r}. \quad (35)$$

Then $\nabla \alpha_k \in L^\infty(0, \tau; L^r)$ and

$$\sup_{t \in [0, \tau]} \|\nabla \alpha_k(t)\|_{L^r} \leq C_3(R_0 + C_R(2M_0)\tau^{1/r}|\Omega|^{1/r} + 1), \quad (36)$$

where $C_3 = C_3(r, d, M_0, C_A, d_{\min}) > 0$ does not depend on N .

Proof. We split the proof into three steps.

Step 1. Applying maximal L^r regularity. For $r > d \geq 2$, we have $2 - 2/r > 1$, and therefore $W^{1,r}(\Omega) \hookrightarrow W^{2-2/r,r}(\Omega)$; see [32]. Hence there exists a constant $C_{\text{emb}} = C_{\text{emb}}(r, \Omega)$ such that

$$\|\alpha_k^0\|_{W^{2-2/r,r}(\Omega)} \leq C_{\text{emb}}\|\alpha_k^0\|_{W^{1,r}(\Omega)} \leq C_{\text{emb}}R_0.$$

The right-hand side $F_k := \tilde{R}_k(\bar{\alpha})$ belongs to L^∞ , and so

$$\|F_k\|_{L^r(\Omega_\tau)} \leq C_R(2M_0)(\tau|\Omega|)^{1/r}.$$

Applying Theorem 5.4 with $p = r$, together with the observation on the VMO structure of the frozen coefficient, we obtain

$$\|\partial_t \alpha_k\|_{L^r(\Omega_\tau)} + \|\alpha_k\|_{L^r(0, \tau; W^{2,r})} \leq C_r(C_R(2M_0)(\tau|\Omega|)^{1/r} + C_{\text{emb}}R_0). \quad (37)$$

Step 2. Interpolation embedding. From (37), we have

$$\alpha_k \in L^r(0, \tau; W^{2,r}(\Omega)) \cap W^{1,r}(0, \tau; L^r(\Omega)).$$

By Amann's interpolation theorem [24],

$$L^r(0, \tau; W^{2,r}) \cap W^{1,r}(0, \tau; L^r) \hookrightarrow C([0, \tau]; (W^{2,r}, L^r)_{1/r,r}). \quad (38)$$

For $r > d \geq 2$, one has

$$(W^{2,r}, L^r)_{1/r,r} = W^{2-2/r,r}(\Omega) \hookrightarrow W^{1,r}(\Omega). \quad (39)$$

Therefore $\alpha_k \in C([0, \tau]; W^{1,r}(\Omega))$, and hence $\nabla \alpha_k \in L^\infty(0, \tau; L^r(\Omega))$.

Step 3. Quantitative estimate. From (37)–(39) and continuity of the embeddings, it follows that

$$\sup_{t \in [0, \tau]} \|\nabla \alpha_k(t)\|_{L^r} \leq C_3(R_0 + C_R(2M_0)\tau^{1/r}|\Omega|^{1/r} + 1),$$

where the constant C_3 absorbs all intermediate constants and does not depend on N , since estimate (37) contains no N . \square

5.5 Nonemptiness of the strengthened class

Theorem 5.7. *Under assumptions (25)–(30), set*

$$N^* := 2C_3(R_0 + C_R(2M_0)|\Omega|^{1/r} + 1), \quad (40)$$

$$\tau_r := \min \left\{ \tau_{M_0}, \left(\frac{N^*/2C_3 - R_0 - 1}{C_R(2M_0)|\Omega|^{1/r}} \right)^r \right\} > 0. \quad (41)$$

Then the truncated system has on $[0, \tau_r]$ a weak solution α^ such that*

$$\nabla \alpha_k^* \in L^\infty(0, \tau_r; L^r(\Omega)), \quad \sup_t \|\nabla \alpha_k^*(t)\|_{L^r} \leq N^*, \quad k = 1, \dots, K. \quad (42)$$

In particular, $\alpha^ \in U_r(\tau_r) \neq \emptyset$, and α^* is a weak solution of the original system on $[0, \tau_r]$.*

Proof. By Lemma 5.6 and the choice of τ_r , the operator Φ maps $K_\tau^r(N^*)$ into itself. Compactness follows from estimate (37) and the embedding $W^{1,r} \hookrightarrow L^2$, while continuity follows from the proof of Theorem 4.4. Schauder's theorem then yields a fixed point $\alpha^* \in K_\tau^r(N^*)$. Lemmas 4.5–4.6 ensure that $(\alpha^*)_+ = \alpha^*$, so the truncated and original systems coincide. \square

Remark 5.8 (Dependence of τ_r on the parameters). Formula (41) shows that τ_r decreases as R_0 grows, that is, more complex initial data shorten the interval of enhanced regularity. Moreover, when $R_0 \rightarrow 0$, we have $\tau_r \rightarrow \tau_{M_0}$, and the result approaches the natural time scale of the local theory.

Corollary 5.9. *Under assumptions (25)–(30), the solution $\alpha^* \in U_r(\tau_r)$ from Theorem 5.7 is the unique weak solution of the original system within the class $U_r(\tau_r)$.*

Proof. This is a direct consequence of Theorem 5.1. \square

Remark 5.10. Taken together, the results of Sections 4–5 give the following picture: a global weak solution exists under (25)–(28); conditional uniqueness holds in the class U_r ; and after adding assumptions (29)–(30), the class $U_r(\tau_r)$ is nonempty, with existence and unconditional uniqueness within that class. The question of uniqueness in the full weak class on $[0, T]$ remains open.

6 Probabilistic interpretation and the choice of the Dirichlet distribution

6.1 Probability simplex and moments

By Theorem 4.8, we have $\alpha_k(x, t) > 0$ a.e. in Ω_T , and therefore $\alpha_0(x, t) := \sum_{k=1}^K \alpha_k > 0$. Hence the quantities

$$\bar{p}_k(x, t) := \frac{\alpha_k(x, t)}{\alpha_0(x, t)} \quad (43)$$

are well defined, satisfy $\bar{p}_k \geq 0$ and $\sum_k \bar{p}_k = 1$, and can be interpreted as the mean probabilities of the components of the distribution $p(x, t) \sim \text{Dir}(\alpha(x, t))$. The first- and second-order moments are

$$\mathbb{E}[p_k] = \bar{p}_k, \quad \text{Var}(p_k) = \frac{\bar{p}_k(1 - \bar{p}_k)}{\alpha_0 + 1}. \quad (44)$$

6.2 Why the Dirichlet distribution

The support of the Dirichlet distribution coincides with the probability simplex. The total parameter $\alpha_0 = \sum_k \alpha_k$ is naturally interpreted as a concentration measure: small values of α_0 correspond to high uncertainty in transition zones, whereas large values correspond to distributions concentrated near one of the vertices of the simplex. The moment formulas (44) are closed and allow direct comparison of analytical estimates with observable quantities. Finally, the lower bound from Lemma 4.7 ensures $\alpha_k > 0$ for $t > 0$, so formulas (43) and (44) are valid on the whole interval of existence.

The Dirichlet distribution is not the only possible choice; the literature also uses logistic-normal models and more general constructions on the simplex [33, 34]. However, such alternatives usually require logarithmic transformations and do not provide so direct a connection with the analytical estimates.

7 Entropy balance and stability

7.1 Reversible auxiliary regime

Consider an auxiliary version of the transition matrix satisfying the detailed balance condition

$$\pi_j q_{jk} = \pi_k q_{kj}, \quad \pi_k > 0, \quad \sum_k \pi_k = 1. \quad (45)$$

Since $\sum_k \pi_k = 1$ and $M_k \geq 1$, we automatically have $\pi_k \leq 1 \leq M_k$. For smooth positive solutions, introduce the functional

$$\mathcal{E}[\alpha] := \sum_{k=1}^K \int_{\Omega} \left(\alpha_k \ln \frac{\alpha_k}{\pi_k} - \alpha_k + \pi_k \right) dx. \quad (46)$$

Proposition 7.1 (Formal entropy balance). *Assume that the transition matrix satisfies (45), and that the solution is smooth enough and strictly positive. Then*

$$\frac{d}{dt} \mathcal{E}[\alpha(t)] + \mathcal{D}_{\text{diff}}(t) + \mathcal{D}_{\text{react}}(t) + \mathcal{D}_{\text{sink}}(t) = 0, \quad (47)$$

where

$$\mathcal{D}_{\text{diff}} := \sum_k \int_{\Omega} \frac{1}{\alpha_k} D_k \nabla \alpha_k \cdot \nabla \alpha_k dx \geq 0, \quad (48)$$

$$\mathcal{D}_{\text{react}} := \frac{1}{2} \sum_{j,k} \pi_j q_{jk} \int_{\Omega} \left(\frac{\alpha_j}{\pi_j} - \frac{\alpha_k}{\pi_k} \right) \left(\ln \frac{\alpha_j}{\pi_j} - \ln \frac{\alpha_k}{\pi_k} \right) dx \geq 0, \quad (49)$$

$$\mathcal{D}_{\text{sink}} := \sum_k \int_{\Omega} \kappa_k \alpha_k \left(\frac{\alpha_k}{M_k} - 1 \right)_+ \ln \frac{\alpha_k}{\pi_k} dx \geq 0. \quad (50)$$

Proof. Multiply the k th equation by $\ln(\alpha_k/\pi_k)$, integrate over Ω , and sum over k .

Diffusion contribution. Integration by parts together with the Neumann condition gives $I_{\text{diff}} = -\mathcal{D}_{\text{diff}} \leq 0$.

Reaction contribution. With $u_k := \alpha_k/\pi_k$, we have $I_{\text{react}} = \sum_{j,k} \pi_j q_{jk} \int_{\Omega} u_j \ln u_k dx$. By the row-balance condition (12), the terms $u_j \ln u_j$ cancel after summation. Symmetrization using detailed balance (45) yields

$$I_{\text{react}} = -\frac{1}{2} \sum_{j,k} \pi_j q_{jk} \int_{\Omega} (u_j - u_k)(\ln u_j - \ln u_k) dx = -\mathcal{D}_{\text{react}} \leq 0,$$

since $(u_j - u_k)(\ln u_j - \ln u_k) \geq 0$.

Sink contribution. If $(\alpha_k/M_k - 1)_+ > 0$, then $\alpha_k > M_k \geq 1 \geq \pi_k$, hence $\ln(\alpha_k/\pi_k) \geq 0$, and therefore $I_{\text{sink}} = -\mathcal{D}_{\text{sink}} \leq 0$. \square

Remark 7.2. Proposition 7.1 applies only to the reversible auxiliary regime and does not carry over to the clinical matrix (11); see [35, 36].

7.2 Modal spectral stability condition for the clinical matrix

Let α^* be a spatially homogeneous steady state of the clinical system with $\alpha_k^* \neq M_k$ (so that the Jacobian is well defined). The Jacobian of the reaction part is

$$J = Q^T - \text{diag} \left(\kappa_k \left(\frac{2\alpha_k^*}{M_k} - 1 \right) \mathbf{1}_{\{\alpha_k^* > M_k\}} \right). \quad (51)$$

Proposition 7.3 (Modal stability condition). *If the spectral abscissa $s(J) \leq 0$, then the zero spatial mode of the linearization is spectrally stable. For nonzero modes, the diagonal diffusion contribution $B(\xi) := \text{diag}(\xi^\top D_k^* \xi) \geq 0$ does not increase the spectral abscissa: $s(J - B(\xi)) \leq s(J) \leq 0$.*

Proof. The matrix J is a Metzler matrix (its off-diagonal entries satisfy $q_{jk} \geq 0$). For Metzler matrices, the spectral abscissa is monotone under negative diagonal shifts; see [37]. \square

8 Discretization

8.1 Lie splitting scheme

We use a Lie splitting scheme with two substeps.

Reaction substep (explicit Euler method)

$$\alpha_k^{n+1/2} = \alpha_k^n + \Delta t \left(\sum_{j \neq k} q_{jk} \alpha_j^n - q_k^{\text{out}} \alpha_k^n - \kappa_k \alpha_k^n \left(\frac{\alpha_k^n}{M_k} - 1 \right)_+ \right). \quad (52)$$

Diffusion substep (implicit scheme)

For the spatial approximation, we use a conservative finite-volume scheme. In one dimension, this is a tridiagonal approximation with harmonic averaging of the coefficients at the half-nodes. In two dimensions, for a constant field $f = (1, 0)^\top$, the tensor is diagonal, $D_k = \text{diag}(d_k^{(\text{iso})} + d_k^{(\text{aniso})}, d_k^{(\text{iso})})$, and a five-point scheme with harmonic edge coefficients is used [38, 39].

8.2 Positivity of the reaction substep

Assume that at time step n we have $0 \leq \alpha_k^n(x_i) \leq M_C^n$ for all nodes x_i . Define

$$\widehat{\lambda}_k^n := q_k^{\text{out}} + \kappa_k \left(\frac{M_C^n}{M_k} - 1 \right)_+, \quad \widehat{\lambda}^n := \max_k \widehat{\lambda}_k^n. \quad (53)$$

Proposition 8.1. *If $\Delta t \leq 1/\widehat{\lambda}^n$, then $\alpha_k^{n+1/2}(x_i) \geq 0$ for all i, k .*

Proof. By the definition of $\widehat{\lambda}_k^n$, we have

$$\alpha_k^{n+1/2} \geq (1 - \Delta t \widehat{\lambda}_k^n) \alpha_k^n + \Delta t \sum_{j \neq k} q_{jk} \alpha_j^n \geq 0$$

whenever $\Delta t \leq 1/\widehat{\lambda}^n$. \square

Proposition 8.2 (M -matrix and non-negativity). *If the spatial approximation of the diffusion substep produces an M -matrix, then the implicit step preserves non-negativity.*

Remark 8.3. For a diagonal tensor on a rectangular grid with harmonic averaging, the five-point scheme indeed produces an M -matrix [39]. Proposition 8.2 is stated in conditional form in order to separate the monotonicity property of the spatial approximation from the estimate for the reaction substep.

9 Numerical illustrations

This section is not intended as a clinical calibration of the model. Below we present one- and two-dimensional computations with the parameters from Section 9.1, together with a check of the observed convergence order of the scheme on a smooth manufactured test problem.

9.1 Parameters and reproducibility

Geometry and grids

1D: $\Omega = (0, 40)$ mm, $N_x = 600$, $\Delta t = 1/64$ day, $T = 60$ days; a tridiagonal solver is used for the diffusion step.

2D: $\Omega = (0, 40)^2$ mm², grid 100×100 , $\Delta t = 1/256$ day, $T = 14$ days; a direct sparse solver is used.

Convergence order: the reference solution is computed on $N_x^{\text{ref}} = 1600$ with $\Delta t^{\text{ref}} = 1/1024$.

Reaction parameters

$$\begin{aligned} q_{12} &= 0.18, & q_{15} &= 0.04, & q_{23} &= 0.12, & q_{24} &= 0.08, \\ q_{25} &= 0.03, & q_{34} &= 0.10, & q_{52} &= 0.05, & q_{54} &= 0.04. \end{aligned} \quad (54)$$

$$\kappa_1 = 0.35, \quad \kappa_2 = 0.35, \quad \kappa_3 = 0.45, \quad \kappa_4 = 0, \quad \kappa_5 = 0.25, \quad M_k = 8, \quad k = 1, \dots, 5. \quad (55)$$

Diffusion parameters

$$d_k^{(\text{iso})} = (0.30, 0.24, 0.18, 0.16, 0.22) \text{ mm}^2/\text{day}, \quad (56)$$

$$\beta_k = (0.30, 0.40, 0.50, 0.20, 0.35), \quad \varepsilon = 10^{-2}, \quad f(x) \equiv 1 \text{ (1D)}, \quad f \equiv (1, 0)^\top \text{ (2D)}. \quad (57)$$

Initial data (1D)

$$\chi(x) := \exp\left(-\frac{(x-20)^2}{2 \cdot 4^2}\right), \quad (58)$$

$$\alpha_1^0 = 7 - 6\chi, \quad \alpha_2^0 = 1 + 2\chi, \quad \alpha_3^0 = 1 + 4\chi, \quad \alpha_4^0 = 1, \quad \alpha_5^0 = 1, \quad \alpha_0^0 \equiv 11. \quad (59)$$

Initial data (2D)

$$\rho(x, y) := \exp\left(-\frac{(x-20)^2 + (y-20)^2}{2 \cdot 5^2}\right), \quad (60)$$

$$\alpha_1^0 = 7 - 5\rho, \quad \alpha_2^0 = 1 + 1.5\rho, \quad \alpha_3^0 = 1 + 2.5\rho, \quad \alpha_4^0 = 1, \quad \alpha_5^0 = 1 + \rho, \quad \alpha_0^0 \equiv 11. \quad (61)$$

Spatial approximation (1D)

$$(L_h \alpha_k)_i = \frac{1}{h} \left(D_{k,i+\frac{1}{2}} \frac{\alpha_{k,i+1} - \alpha_{k,i}}{h} - D_{k,i-\frac{1}{2}} \frac{\alpha_{k,i} - \alpha_{k,i-1}}{h} \right), \quad (62)$$

where $D_{k,i\pm 1/2}$ are computed by harmonic averaging.

Spatial approximation (2D)

$$\begin{aligned} (L_h \alpha_k)_{i,j} &= \frac{1}{h_x} \left(D_{xx,i+\frac{1}{2},j} \frac{\alpha_{k,i+1,j} - \alpha_{k,i,j}}{h_x} - D_{xx,i-\frac{1}{2},j} \frac{\alpha_{k,i,j} - \alpha_{k,i-1,j}}{h_x} \right) \\ &\quad + \frac{1}{h_y} \left(D_{yy,i,j+\frac{1}{2}} \frac{\alpha_{k,i,j+1} - \alpha_{k,i,j}}{h_y} - D_{yy,i,j-\frac{1}{2}} \frac{\alpha_{k,i,j} - \alpha_{k,i,j-1}}{h_y} \right), \end{aligned} \quad (63)$$

where $D_{xx} = d_k^{(\text{iso})} + d_k^{(\text{aniso})}$, $D_{yy} = d_k^{(\text{iso})}$, and the edge coefficients are computed by harmonic averaging.

9.2 A posteriori check of the positivity condition

The theoretical barrier $M_T^{\text{th}} = M_0 e^{q_* T}$ for the parameter set (54)–(55) is rough. In the computations we use the adaptive barrier $M_C^n := \max_{i,k} \alpha_k^n(x_i)$. Along the computed trajectory,

$$\max_n M_C^n \approx 15.4. \quad (64)$$

A strict a priori guarantee of the condition $\Delta t \leq 1/\widehat{\lambda}^n$ through the theoretical barrier lies beyond the scope of this paper.

9.3 One-dimensional scenario of acute remodeling

Table 1: Spatially averaged tissue-state probabilities and the concentration parameter (1D, 60 days).

t , days	\bar{p}_1	\bar{p}_2	\bar{p}_3	\bar{p}_4	\bar{p}_5	α_0
0	0.091	0.273	0.455	0.091	0.091	11.0
7	0.048	0.134	0.297	0.376	0.145	13.8
14	0.039	0.072	0.148	0.567	0.174	14.6
30	0.031	0.038	0.052	0.723	0.156	15.1
60	0.025	0.021	0.018	0.811	0.125	15.4

The quantitative dynamics, including the growth of the replacement fibrosis fraction \bar{p}_4 and the evolution of the concentration parameter α_0 , are listed in Table 1; these data are consistent with the barrier estimates.

9.4 Two-dimensional transition zone

The zones are defined from the field $\rho(x, y)$ in (60): $\Omega_{\text{core}} := \{\rho \geq 0.7\}$, $\Omega_{\text{trans}} := \{0.2 \leq \rho < 0.7\}$, $\Omega_{\text{healthy}} := \{\rho < 0.2\}$.

Table 2: Two-dimensional scenario ($t = 14$ days): zone-averaged characteristics.

Zone	$\langle \bar{p}_4 \rangle$	$\langle \text{Var}(p_4) \rangle$	$\langle \alpha_0 \rangle$
Core	0.62	0.009	26.3
Transition	0.31	0.038	7.2
Healthy	0.09	0.004	28.5

The variance reaches its maximum in the transition zone, while in the lesion core and in healthy tissue the values of α_0 remain higher, which is consistent with the interpretation of the concentration parameter as an indicator of confidence. The quantitative characteristics of the two-dimensional scenario are summarized in Table 2.

9.5 Tables of observed convergence order

For verification we use the manufactured test

$$\alpha_3^{\text{ex}}(x, t) = 1 + 0.2 \cos\left(\frac{\pi x}{40}\right) e^{-t}, \quad (x, t) \in (0, 40) \times [0, 1]. \quad (65)$$

The error is computed in the $L^2(\Omega)$ norm at $T = 1$ for the component α_3 with respect to the exact solution.

Table 3: Spatial refinement.

N_x	h	Error	Order
100	0.40	3.58×10^{-2}	—
200	0.20	8.97×10^{-3}	2.00
400	0.10	2.24×10^{-3}	2.00

Table 4: Temporal refinement.

Δt	Error	Order
0.500	3.96×10^{-2}	—
0.250	1.99×10^{-2}	0.99
0.125	9.98×10^{-3}	1.00

Second-order convergence in space and first-order convergence in time agree with the theoretical expectations for this class of schemes on a smooth test solution and are therefore regarded here only as a consistency check of the discretization block. In clinically motivated problems with sharp transitions, second-order spatial convergence at early times should not be expected; Tables 3–4 show only that the scheme is consistent in the regular regime.

10 Discussion

10.1 Position of the model among existing approaches

Unlike phase-field and bidomain approaches, the main state variable here is neither a phase indicator nor a potential, but a vector of Dirichlet parameters that encodes both the dominant tissue state and the level of confidence in it. Unlike static probabilistic models on the simplex, the present formulation defines a full space-time dynamics with anisotropic diffusion and a Markovian reaction part. In transition zones, this makes it possible to describe not an abrupt change of phases, but a distribution with increased variance and a changing local structure of uncertainty.

10.2 Significance of the $W^{1,r}$ regularity result

Theorem 5.7 removes the conditional character of Theorem 5.1: we now know that for sufficiently regular initial data, the higher regularity of the gradients is actually realized and is not just an empty restriction on the class of solutions. The key feature of the proof is that the estimate for the new iterate in (36) is independent of the norm of the previous iterate N , which is what allows the iteration to close in the required functional class.

As noted in the introduction, the ingredients of the proof are well known separately: maximal L^r regularity with VMO coefficients (Kim–Krylov [22], Dong–Kim [23]), Morrey’s theorem, and interpolation in Bochner spaces (Amann [24]). The novelty lies in bringing them together into a single nonlinear $W^{1,r}$ iteration argument for an anisotropic system with Markovian reaction dynamics.

10.3 Status of the uniqueness theorem

Corollary 5.9 establishes unconditional uniqueness in the class $U_r(\tau_r)$. However, uniqueness in the full weak class $[L^2(0, T; H^1)]^K$ remains open. Resolving this question would require either a new way to estimate the term $I_D^{(k)}$ without an L^r bound on $\nabla \alpha_k^{(2)}$, or some additional structure, such as monotonicity in the state variable or diagonal dominance.

10.4 Limitations of the model and future directions

1. The coefficients q_{jk} are not identified from data; the inverse problem of recovering them requires a separate statistical and computational study.
2. Unconditional uniqueness is proved only in the class $U_r(\tau_r)$; the question of uniqueness in the full weak class on the whole interval $[0, T]$ remains open.
3. Global $W^{1,r}$ regularity is not proved; the present result is local in time and is intended primarily to close the uniqueness argument.
4. The entropy balance is established only for the reversible auxiliary regime, whereas for the clinically motivated irreversible matrix we obtain only modal stability of the linearized system.
5. The convergence-order tables refer to a smooth manufactured test and should not be interpreted as a universal order estimate for nonsmooth clinically motivated data.
6. The choice of the Dirichlet distribution fits the probabilistic interpretation of tissue composition well, but it is not the only possible way to parametrize a multicomponent state.

Natural directions for further work are uniqueness in the natural weak class, entropy structure for irreversible matrices, cross-diffusion, and parametric identification from clinical data.

11 Conclusion

In this paper we constructed and analyzed an anisotropic reaction–diffusion model of myocardial remodeling written in terms of Dirichlet distribution parameters. The main results are as follows.

1. For a specific class of diffusion tensors depending on the fraction of damaged tissue, we verified uniform ellipticity and local Lipschitz continuity in the state variable. This ensures that the model formulation is well posed in standard functional classes.
2. For the truncated system we proved first local and then global existence of a weak solution, non-negativity, an upper barrier, and a quantitative lower exponential bound. This implies invariance of the admissible region and, hence, global solvability of the original system.
3. The central analytical contribution of the paper is the proof that the strengthened class $U_r(\tau_r)$ is nonempty when $\alpha_k^0 \in W^{1,r}(\Omega)$, $r > d$, and $f \in W^{1,\infty}(\Omega)$. The proof is based on a closed $W^{1,r}$ iteration that combines maximal L^r regularity for equations with VMO coefficients, Morrey’s embedding, and interpolation in Bochner spaces.
4. The previous item yields unconditional uniqueness in the class $U_r(\tau_r)$ on a short time interval. Thus the conditional nature of the uniqueness theorem is removed in the same functional class in which existence has been proved.
5. For the reversible auxiliary regime we derived a formal entropy balance, while for the clinically motivated irreversible transition matrix we obtained a modal spectral stability condition for the linearized system.
6. The numerical section is limited to illustrations of the barrier properties of the solution, of representative space-time regimes, and of the observed convergence order of the scheme on a smooth test problem.

The paper provides a rigorous analytical justification of the proposed formulation; the applied interpretation through Dirichlet parameters opens the way to problems of identifying transition coefficients from LGE-MRI data and to the construction of more detailed models of remodeling. Natural directions for future work include global $W^{1,r}$ regularity, uniqueness in the natural weak class, entropy methods for irreversible transition matrices, and parameter identification from MRI data.

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References

- [1] Frangogiannis N.G. Pathophysiology of myocardial infarction. *Compr Physiol.* 2015;5:1841–1875.
- [2] Cleutjens J.P.M., Blankesteyn W.M., Daemen M.J.A.P., Smits J.F.M. The infarcted myocardium: simply dead tissue, or a lively target for therapeutic interventions. *Cardiovasc Res.* 1999;44:232–241.
- [3] De Jong S., van Veen T.A.B., de Bakker J.M.T., Vos M.A., van Rijen H.V.M. Biomarkers of myocardial fibrosis. *J Cardiovasc Pharmacol.* 2011;57:522–535.
- [4] Travers J.G., Kamal F.A., Robbins J., Yutzey K.E., Blaxall B.C. Cardiac fibrosis. *Circ Res.* 2016;118:1021–1040.
- [5] Markov V.A., Kuznetsov G.P., Borisov S.N. Postinfarction myocardial remodeling. *Siberian Medical Journal.* 2011;26:7–15.
- [6] Schelbert E.B., Hsu L.-Y., Anderson S.A., et al. Late gadolinium enhancement MRI in the evaluation of myocardial fibrosis. *Circ Cardiovasc Imaging.* 2010;3:743–752.
- [7] Roes S.D., Borleffs C.J.W., van der Geest R.J., et al. Infarct tissue heterogeneity assessed with contrast-enhanced MRI predicts spontaneous ventricular arrhythmia. *Circ Cardiovasc Imaging.* 2009;2:183–190.
- [8] Pao C.V. *Nonlinear Parabolic and Elliptic Equations.* New York: Plenum Press; 1992.
- [9] Smoller J. *Shock Waves and Reaction–Diffusion Equations.* 2nd ed. New York: Springer; 1994.
- [10] Allen S.M., Cahn J.W. A microscopic theory for antiphase boundary motion. *Acta Metall.* 1979;27:1085–1095.
- [11] Cahn J.W., Hilliard J.E. Free energy of a nonuniform system. I. *J Chem Phys.* 1958;28:258–267.

- [12] Cristini V., Li X., Lowengrub J., Wise S. Nonlinear simulations of solid tumor growth using a mixture model. *J Math Biol.* 2009;58:723–763.
- [13] Tung L. *A Bi-domain Model for Describing Ischemic Myocardial D-C Potentials*. PhD thesis. MIT; 1978.
- [14] Vigmond E.J., Hughes M., Plank G., Leon L.J. Computational tools for modeling electrical activity in cardiac tissue. *J Electrocardiol.* 2003;36:69–74.
- [15] Keener J., Sneyd J. *Mathematical Physiology*. Vol. II. Springer; 2009.
- [16] Kazbanov I.V., ten Tusscher K.H.W.J., Panfilov A.V. Effects of heterogeneous diffuse fibrosis on arrhythmia dynamics. *PLoS Comput Biol.* 2014;10:e1003891.
- [17] Guccione J.M., Moonly S.M., Moustakidis P., et al. Mechanism underlying mechanical dysfunction in the border zone of left ventricular aneurysm. *Ann Thorac Surg.* 2001;71:654–662.
- [18] Helm P.A., Tseng H.-J., Younes L., et al. Ex vivo 3D diffusion tensor imaging and quantification of cardiac laminar structure. *Magn Reson Med.* 2005;54:850–859.
- [19] Hooks D.A., Trew M.L., Caldwell B.J., et al. Laminar arrangement of ventricular myocytes influences electrical behavior of the heart. *Circ Res.* 2002;91:331–338.
- [20] Ferguson T.S. A Bayesian analysis of some nonparametric problems. *Ann Statist.* 1973;1:209–230.
- [21] Frigiyik B.A., Kapila A., Gupta M.R. *Introduction to the Dirichlet distribution and related processes*. Technical Report UWEETR-2010-0006. University of Washington; 2010.
- [22] Kim D., Krylov N.V. Elliptic differential equations with coefficients measurable with respect to one variable and VMO with respect to the others. *SIAM J Math Anal.* 2007;39(2):489–506.
- [23] Dong H., Kim D. L^p solvability of divergence type parabolic and elliptic systems with partially BMO coefficients. *Calc Var Partial Differential Equations.* 2011;40(3–4):357–389.
- [24] Amann H. *Linear and Quasilinear Parabolic Problems*. Vol. I: Abstract Linear Theory. Basel: Birkhäuser; 1995.
- [25] Ladyzhenskaya O.A., Solonnikov V.A., Ural'tseva N.N. *Linear and Quasilinear Equations of Parabolic Type*. Moscow: Nauka; 1967.
- [26] Simon J. Compact sets in the space $L^p(0, T; B)$. *Ann Mat Pura Appl.* 1987;146:65–96.
- [27] Evans L.C. *Partial Differential Equations*. 2nd ed. Providence: AMS; 2010.
- [28] Lieberman G.M. *Second Order Parabolic Differential Equations*. Singapore: World Scientific; 1996.
- [29] Prabhu S.D., Frangogiannis N.G. The biological basis for cardiac repair after myocardial infarction. *Circ Res.* 2016;119:91–112.
- [30] Talman V., Ruskoaho H. Cardiac fibrosis in myocardial infarction — from repair and remodeling to regeneration. *Cell Tissue Res.* 2016;365:563–581.
- [31] Scalise R.F.M., Ratti A., Cianflone E., et al. Fibrosis after myocardial infarction: an overview. *J Clin Med.* 2021;10:235.
- [32] Adams R.A., Fournier J.J.F. *Sobolev Spaces*. 2nd ed. Amsterdam: Academic Press; 2003.

- [33] Aitchison J. *The Statistical Analysis of Compositional Data*. London: Chapman and Hall; 1986.
- [34] van den Boogaart K.G., Tolosana-Delgado R. *Analyzing Compositional Data with R*. Heidelberg: Springer; 2013.
- [35] Mielke A. A gradient structure for reaction–diffusion systems and for energy-drift-diffusion systems. *Nonlinearity*. 2011;24:1329–1346.
- [36] Desvillettes L., Fellner K. Exponential decay toward equilibrium via entropy methods for reaction-diffusion equations. *J Math Anal Appl*. 2006;319:157–176.
- [37] Farina L., Rinaldi S. *Positive Linear Systems: Theory and Applications*. New York: Wiley; 2000.
- [38] Aavatsmark I. An introduction to multipoint flux approximations for quadrilateral grids. *Comput Geosci*. 2002;6:405–432.
- [39] Le Potier C. Schémas monotones et matrices de type M pour des problèmes paraboliques. *C R Acad Sci Paris*. 2005;341:787–792.