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Well-posedness and asymptotic behavior a multidimensional model of morphogen transport

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Abstract. Morphogen transport is a biological process, occurring in the tissue of living organisms, which is a determining step in cell differentiation. We present rigorous analysis of a simple model of this process, which is a system coupling parabolic PDE with ODE. We prove existence and uniqueness of solutions for both stationary and evolution problems. Moreover, we show that the solution converges exponentially to the equilibrium in $C^{1,\alpha} \times C^{0,\alpha}$ topology. We prove all results for arbitrary dimension of the domain. Our results improve significantly previously known results for the same model in the case of one-dimensional domain.

1. Introduction

Morphogen transport (MT) is a biological process occurring in the bodies of living organisms. It is known that certain proteins (ligands) act as the morphogen—a conceptually defined substance which is responsible for the development of the shape, size and other properties of the cells. According to the ‘French flag model’ of Wolpert [15] morphogen molecules spread from a localized source through the tissue of newly born individuals and after some time form stable gradients of concentrations. Receptors, located on the surface of the cells, detect those gradients and pass to the kernels the information about levels of morphogen concentration. Then according to these information certain mechanisms begin synthesis of proteins, which finally results in cell differentiation and specialization. Although the role of morphogen gradient in gene expression seems to be widely accepted the exact kinetic mechanism of its formation is still not known. (see [5,10] and [9]).

Recently, various models consisting of PDE–ODE systems were proposed to explain MT. Those models assume that movement of morphogen molecules occurs by different types of diffusion or by chemotaxis in the extracellular medium. Reactions with receptors (reversible binding, transcytosis) and various possibilities of degradation and internalization (of morphogens, receptors, morphogen-receptor complexes) are also being considered (see [2,8,11,13]).

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This article is dedicated to Kate.

For the case of morphogen Decapentaplegic (Dpp) acting in the wing disc of the Drosophila Melanogaster individuals, several models have been proposed in [11]. In this paper we will be concerned with model **[LNW].B** (Model B [11] p. 786). In this model it is assumed that movement of morphogen molecules occurs by passive diffusion while being affected by reactions of reversible binding with receptors and degradation of morphogen-receptor complexes. Morphogen is being delivered to the system by secretion from a source localized on one of the boundaries of the domain $\Omega \subset \mathbb{R}^n$, which represents a fragment of the wing tissue. In mathematical terms the model is a system of two differential equations (PDE+ODE equipped with initial and boundary conditions), governing time evolution of the concentrations of free morphogen and morphogen-receptor complexes.

In case of 1D domains a detailed mathematical analysis of this model was made in [14] and [7].

In [14] the case $\Omega = (0, \infty)$, with a nonlinear dynamic boundary condition at $x = 0$ and vanishing boundary condition at $x \to \infty$, is considered. Well-posedness and $L_p(\Omega)$ convergence of the solution to unique steady state were proved.

In [7] the case $\Omega = (0, 1)$, with nonhomogeneous, constant Neumann condition at $x = 0$ and homogeneous Dirichlet condition at $x = 1$, is analyzed. Finding Lyapunov functional allowed to prove well-posedness and $L_2(\Omega)$ exponential convergence to the unique equilibrium, with rate χ expressed explicitly by the parameters of the model.

The goal of this paper is to examine **[LNW].B** in the [7] setting for bounded domains of arbitrary dimension n. Although $n \in \{1, 2, 3\}$ is, from the biological point of view, the only relevant case, we do not put this restriction on n (methods that we use do not depend on the dimension). Using fixed point theorem and monotonicity of the nonlinearity we prove that our model has a unique nonnegative steady state. Using theory of analytic semigroups and comparison principle arguments we show existence of classical global solutions. We check that Lyapunov functional, obtained in [7], also works for arbitrary n and thanks to appropriate semigroup estimates and bootstrap arguments we improve the topology of the convergence to the equilibrium from $L_2 \times L_2$ to $C^{1,\alpha} \times C^{0,\alpha}$ without losing the exponential rate χ.

2. The model

We consider the system of differential equations governing the space and time evolution of the concentration of free morphogen l and concentration of bounded receptors s in an annular shape domain $\Omega \subset \mathbb{R}^n$. We assume that receptors are distributed uniformly in the tissue so after normalizing the total concentration of receptors (free+bounded) is equal to 1. The model governs the following biological processes

- Passive diffusion of morphogens in the extracellular medium.
- Secretion of morphogens from the source on a subset Γ_N of $\partial\Omega$.
- Binding of morphogens to receptors.
- Unbinding of morphogens from receptors.
- Degradation of bounded morphogens.

We equip the model with initial conditions l_0, s_0 and boundary conditions on Γ_D, Γ_N - two disjoint parts of $\partial\Omega$. On Γ_N we consider nonhomogeneous, time independent, nonnegative Neumann condition (flow of morphogen into the domain) while on Γ_D we put homogeneous Dirichlet condition (far from the source of morphogen their impact on the whole process is negligible). After normalization we end up with the following model

[LNW].B

$$\begin{aligned} \partial_t l - D\Delta l &= \delta s - l(1-s), && (t,x) \in (0,\infty) \times \Omega \\ \partial_t s &= -(\delta+\epsilon)s + l(1-s), && (t,x) \in (0,\infty) \times \Omega \\ -D\nabla_n l &= -\nu, && (t,x) \in (0,\infty) \times \Gamma_N \\ l &= 0, && (t,x) \in (0,\infty) \times \Gamma_D \\ l(0) &= l_0, && x \in \Omega \\ s(0) &= s_0, && x \in \Omega \end{aligned}$$

where we denote the derivative in the direction of the outer normal vector to Γ_N by ∇_n.

3. Results

In the whole paper we assume that

A1 $n \in \mathbb{N},\ p > n \geq 1$.
A2 $\Omega \subset \mathbb{R}^n$ is a bounded domain (open, connected) with ($\mathcal{C}^{1,1}$) boundary which consists of two disjoint parts: $\partial\Omega = \Gamma_D \sqcup \Gamma_N$.
A3 $0 \leq \nu \in W_p^{1-1/p}(\Gamma_N)$.
A4 $l_0, s_0 \in W_p^1(\Omega);\ 0 \leq l_0(x),\ 0 \leq s_0(x) < 1$, for $x \in \Omega;\ l_0(x) = s_0(x) = 0$, for $x \in \Gamma_D$.

Under the above assumptions we first analyze the stationary problem and prove the following

THEOREM 1. ***[LNW].B*** *has unique nonnegative steady state* (l_∞, s_∞)*, where* $0 \leq l_\infty \in W_p^2(\Omega)$ *is the unique solution to*

$$-D\Delta l_\infty = -\frac{\epsilon l_\infty}{\delta+\epsilon+l_\infty}, \qquad x \in \Omega \tag{1a}$$

$$-D\nabla_n l_\infty = -\nu, \qquad x \in \Gamma_N \tag{1b}$$

$$l_\infty = 0, \qquad x \in \Gamma_D. \tag{1c}$$

and $s_\infty = l_\infty/(\epsilon+\delta+l_\infty)$.

The proof of existence is based on maximal regularity for uniformly elliptic operators in Sobolev spaces, compact embedding, comparison principle and Schauder fixed point theorem. Uniqueness follows from monotonicity of the nonlinear part in (1a).

We next turn to the evolution problem and establish its well-posedness.

THEOREM 2. ***[LNW].B** has unique solution* (l, s) *such that*

$$l - l_\infty \in \mathcal{C}([0,\infty); W_p^1(\Omega)) \cap \mathcal{C}^1((0,\infty); W_p^1(\Omega)) \cap \mathcal{C}((0,\infty); W_p^3(\Omega)) \tag{2a}$$

$$s \in \mathcal{C}^1([0,\infty); W_p^1(\Omega)). \tag{2b}$$

Moreover for $(t, x) \in [0,\infty) \times \Omega$

$$0 \le l(t,x), \quad 0 \le s(t,x) < 1. \tag{2c}$$

Local existence and uniqueness are obtained by putting system **[LNW].B** into the semigroup framework and using general theory for abstract parabolic semilinear problems. Comparison principle allows us to deduce that (2c) is satisfied from which we get that our solution is global.

We finally study the stability of the steady state and show that it attracts all trajectories with the uniform exponential rate.

THEOREM 3. *There exists a positive constant C depending on* $l_0, s_0, \nu, \delta, \epsilon, D, \Omega$, p *such that for every* $t > 0$

$$\|l(t) - l_\infty\|_{1,p} + \|s(t) - s_\infty\|_{1,p} \le C\mathrm{e}^{-(\chi/2)t}, \tag{3a}$$

$$\|l(t) - l_\infty\|_{2,p} \le C \max\{1/\sqrt{t}, 1\}\mathrm{e}^{-(\chi/2)t}, \tag{3b}$$

where

$$\chi = \min\left\{D\lambda_1, \frac{D\lambda_1(\delta+\epsilon)}{2(D\lambda_1+2)} + \frac{\epsilon}{2}\right\} \tag{3c}$$

and λ_1 *is defined in Lemma 1.*

By extending Lyapunov functional (derived in [7] for one dimensional interval) to the case of arbitrary dimension we obtain estimates on the distance between solution and steady state in $L_2 \times L_2$ topology. Using regularizing properties of the heat semigroup we next bootstrap the topology of convergence to $W_p^2 \times W_p^1$.

REMARK. *Using embedding* $W_p^2(\Omega) \times W_p^1(\Omega) \subset C^{1,\alpha}(\Omega) \times C^{0,\alpha}(\Omega)$ *valid for* $p > n$, $0 \le \alpha \le 1 - n/p$ *we obtain topology of convergence as claimed in the introduction.*

4. Notation, semigroup estimates, Gronwall inequality

For $x, y \in \mathbb{R}$ we denote $x \vee y := \max\{x, y\}$, $x \wedge y := \min\{x, y\}$, $x_+ := x \vee 0$, $x_- := (-x) \vee 0$ and extend this notion to real-valued functions. If $(V, \ge)$ is partially ordered vector space we denote its positive cone by $V_+ := \{v \in V : \ v \ge 0\}$.

We make standard convention that C denotes positive constant which may depend on a subset of $\{l_0, s_0, \nu, \delta, \epsilon, D, \Omega, p\}$ and may change its value from line to line.

For $1 < q < \infty$, $\alpha \in \{1, 2, 3\}$ we introduce the spaces $W^{\alpha}_{q,\mathcal{B}^\alpha}(\Omega)$:

$$W^1_{q,\mathcal{B}^1}(\Omega) = \{u \in W^1_q(\Omega) : u|_{\Gamma_D} = 0\}$$
$$W^2_{q,\mathcal{B}^2}(\Omega) = \{u \in W^2_q(\Omega) : u|_{\Gamma_D} = 0,\ \nabla_n u|_{\Gamma_N} = 0\}$$
$$W^3_{q,\mathcal{B}^3}(\Omega) = \{u \in W^3_q(\Omega) : u|_{\Gamma_D} = 0,\ \nabla_n u|_{\Gamma_N} = 0,\ \Delta u|_{\Gamma_D} = 0\},$$

with standard Sobolev norms $\|.\|_{\alpha,q}$.

We next recall some properties of the heat semigroup generated by laplacian with appropriate boundary conditions.

LEMMA 1. *For $1 < q < \infty$ the Laplace operator $\Delta\colon L_q(\Omega) \supset W^2_{q,\mathcal{B}^2}(\Omega) \to L_q(\Omega)$ generates an analytic, strongly continuous semigroup $\mathrm{e}^{t\Delta}$. For $\alpha, \beta \in \{0, 1, 2, 3\}$, $\alpha \le \beta$, $1 < q_1 \le q_2 < \infty$ and $t > 0$ we have*

$$\|\mathrm{e}^{t\Delta}u\|_{\beta,q} \le C(t \wedge 1)^{(\alpha-\beta)/2}\mathrm{e}^{-\lambda_1 t}\|u\|_{\alpha,q} \le Ct^{(\alpha-\beta)/2}\|u\|_{\alpha,q}, \quad u \in W^{\alpha}_{q,\mathcal{B}^\alpha} \tag{4a}$$

$$\begin{aligned}\|\mathrm{e}^{t\Delta}u\|_{q_2} &\le C(t \wedge 1)^{-n/2(1/q_1-1/q_2)}\mathrm{e}^{-\lambda_1 t}\|u\|_{q_1}, \quad u \in L_{q_1}\\ &\le Ct^{-n/2(1/q_1-1/q_2)}\|u\|_{q_1}\end{aligned} \tag{4b}$$

where $\lambda_1 > 0$ is the first eigenvalue of $-\Delta$ and C depends only on q, q_1, q_2, Ω.

Proof. Noticing that $-\lambda_1 = \sup \mathrm{Re}(\sigma(\Delta))$ we get from [12] following estimates

$$\|\mathrm{e}^{t\Delta}u\|_q \le M_0\mathrm{e}^{-\lambda_1 t}\|u\|_q$$
$$\|t(\Delta + \lambda_1 I)\mathrm{e}^{t\Delta}u\|_q \le M_1\mathrm{e}^{-\lambda_1 t}\|u\|_q$$

We have

$$\begin{aligned}\|\mathrm{e}^{t\Delta}u\|_{2,q} &\le C\|\Delta\mathrm{e}^{t\Delta}u\|_q \le C\|(\Delta + \lambda_1 I)\mathrm{e}^{t\Delta}u\|_q + C\lambda_1\|\mathrm{e}^{t\Delta}u\|_q\\ &\le C(M_1/t + M_0\lambda_1)\mathrm{e}^{-\lambda_1 t}\|u\|_q \le C(t \wedge 1)^{-1}\mathrm{e}^{-\lambda_1 t}\|u\|_q\end{aligned}$$

From [1] we have that

$$[L_q, W^2_{q,B^2}]_{\alpha/2} = W^{\alpha}_{q,B^\alpha}, \quad \alpha \in \{0, 1, 2, 3\},$$
$$[L_{q_1}, W^2_{q_1,B^2}]_\theta \subset L_{q_2}, \quad \theta \ge n/2(1/q_1 - 1/q_2),$$

where for $\theta \in [0, 1]$ $[., .]_\theta$ denotes complex interpolation functor, which is extended for $\theta > 1$ as described in [1]. From this estimates (4a) and (4b) follows. $\square$

We next recall the singular Gronwall inequality

LEMMA 2. *Assume that $f \in \mathcal{C}([0, T); \mathbb{R}^+)$ satisfies for every $t \in [0, T)$ following inequality*

$$f(t) \le a + b\int_0^t (t-s)^{-\alpha} f(s)\mathrm{d}\tau,$$

where a, b are nonnegative constants and $\alpha \in [0, 1)$. Then there exists positive constant $C = C(b, \alpha)$ such that for $t \in [0, T)$

$$u(t) \leq aC\mathrm{e}^{bCt}.$$

Moreover $C(b, 0) = 1$.

Proof. For proof (under more general assumptions) see Lemma 7.1.1 in [6]. □

5. Proof of Theorem 1

For $x \geq 0$ let $f(x) = \frac{\epsilon}{\delta+\epsilon+x}$. Consider the operator $T : L_p(\Omega)_+ \to L_p(\Omega)$, defined by $T(u) = w$ where $w \in W_p^2(\Omega)$ is the unique solution of

$$-D\Delta w + f(u)w = 0, \qquad x \in \Omega \tag{5a}$$

$$-D\nabla_n w = -\nu, \qquad x \in \Gamma_N \tag{5b}$$

$$w = 0, \qquad x \in \Gamma_D \tag{5c}$$

We will show that T has bounded range in $L_p(\Omega)_+$ and is compact and continuous (this via the Schauder theorem will imply existence of a solution of (1) in $W_p^2(\Omega)$). Using the fact that $0 \leq f(x) \leq \frac{\epsilon}{\epsilon+\delta}$ we get from maximal regularity of uniformly elliptic differential operators in Sobolev spaces (see [4] for instance) the following estimate

$$\|w\|_{W_p^2(\Omega)} \leq C\|\nu\|_{W_p^{1-1/p}(\Gamma_N)}$$

which gives boundedness of the range of T in $W_p^2(\Omega)$ and therefore in $L_p(\Omega)$. Compactness of T follows from the compact imbedding $W_p^2(\Omega) \subset\subset L_p(\Omega)$. To show that $w \geq 0$ we multiply (5a) by w_- and integrate by parts (notice that for $p > nw \in W_p^2(\Omega) \subset W_2^1(\Omega)$ hence $w_- \in W_2^1(\Omega)$) to obtain

$$-D\int_\Omega |\nabla w_-|^2 - \int_{\Gamma_N} \nu w_- - \int_\Omega f(u)w_-^2 = 0.$$

Since $w = 0$ on Γ_D therefore $w \geq 0$ in Ω.

Assume that $u_n \to u$ in $L_p(\Omega)$. Let $w = T(u)$, $w_n = T(u_n)$, then

$$\begin{aligned} -D\Delta(w_n - w) + f(u_n)(w_n - w) + w(f(u_n) - f(u)) &= 0, & x \in \Omega \\ -D\nabla_n(w_n - w) &= 0, & x \in \Gamma_N \\ w_n - w &= 0, & x \in \Gamma_D \end{aligned}$$

therefore

$$\begin{aligned} \|w_n - w\|_{L_p(\Omega)} &\leq C\|w(f(u_n) - f(u))\|_{L_p(\Omega)} \\ &\leq C\|w\|_{L_\infty(\Omega)}\|f'\|_{L_\infty(0,\infty)}\|u_n - u\|_{L_p(\Omega)} \end{aligned}$$

which proves that T is continuous. Using Schauder fixed point theorem we obtain existence of $l_\infty \in W_p^2(\Omega)$ which solves (1).

To prove uniqueness, assume that l_∞^1, l_∞^2 are solutions of (1). Subtracting equations (1a) for l_∞^1, l_∞^2, multiplying by $l_\infty^1 - l_\infty^2$, integrating by parts and using the monotonicity of function $\mathbb{R}_+ \ni x \to xf(x)$ we get

$$-D\int_\Omega |\nabla(l_\infty^1 - l_\infty^2)|^2 = \int_\Omega (f(l_\infty^1)l_\infty^1 - f(l_\infty^2)l_\infty^2)(l_\infty^1 - l_\infty^2) \geq 0,$$

which by (1c) implies $l_\infty^1 \equiv l_\infty^2$.

6. Proof of Theorem 2

To deal with nonhomogeneous boundary condition on Γ_N we subtract from (l, s) the stationary state (l_∞, s_∞). Setting $(z_1, z_2) = (l - l_\infty, s - s_\infty)$ we arrive at

$$\partial_t z_1 - D\Delta z_1 = \delta z_2 - z_1(1 - z_2) + s_\infty z_1 + l_\infty z_2, \qquad (t, x) \in (0, \infty) \times \Omega \tag{6a}$$

$$\partial_t z_2 = -(\delta + \epsilon)z_2 + z_1(1 - z_2) - s_\infty z_1 - l_\infty z_2, \quad (t, x) \in (0, \infty) \times \Omega \tag{6b}$$

$$-D\nabla_n z_1 = 0, \qquad (t, x) \in (0, \infty) \times \Gamma_N \tag{6c}$$

$$z_1 = 0, \qquad (t, x) \in (0, \infty) \times \Gamma_D \tag{6d}$$

$$z_1(0) = z_{10} = l_0 - l_\infty, \qquad x \in \Omega \tag{6e}$$

$$z_2(0) = z_{20} = s_0 - s_\infty, \qquad x \in \Omega \tag{6f}$$

We interpret system (6) as a differential equation in a Banach space specified below

$$\dot{z} - \mathcal{A}z = H(z), \qquad t \in (0, \infty) \tag{7a}$$

$$z(0) = z_0 = (z_{10}, z_{20}) \tag{7b}$$

where $z = (z_1, z_2)$, $\mathcal{A}z = (D\Delta z_1, 0)$, $H = (H^1, H^2)$,

$$H^1(z) = \delta z_2 - z_1(1 - z_2) + s_\infty z_1 + l_\infty z_2 \tag{8a}$$

$$H^2(z) = -(\delta + \epsilon)z_2 + z_1(1 - z_2) - s_\infty z_1 - l_\infty z_2. \tag{8b}$$

In the following lemma we prove local existence for (7).

LEMMA 3. *For $\alpha \in \{0, 1, 2, 3\}$ denote $Z_{\alpha,p} = W^\alpha_{p,\mathcal{B}^\alpha} \times W^1_{p,\mathcal{B}^1}$. For every $z_0 \in Z_{1,p}$ the Cauchy problem (7) possess a unique maximal local solution*

$$z \in \mathcal{C}([0, T_{\max}); Z_{1,p}) \cap \mathcal{C}^1((0, T_{\max}); Z_{1,p}) \cap \mathcal{C}((0, T_{\max}); Z_{3,p}).$$

which satisfies for $t \in [0, T_{\max})$ the following Duhamel formula:

$$z_1(t) = \mathrm{e}^{tD\Delta} z_{10} + \int_0^t \mathrm{e}^{(t-s)D\Delta} H^1(z(s))\mathrm{d}\tau \tag{9a}$$

$$z_2(t) = z_{20} + \int_0^t H^2(z(s))\mathrm{d}\tau. \tag{9b}$$

Moreover if $T_{\max} < \infty$ *then* $\limsup_{t\to T_{\max}^-} \|z(t)\|_{1,p} = \infty$.

Proof. The operator $\mathcal{A} : Z_p \supset Z_{2,p} \to Z_p$ is a generator of an analytic strongly continuous semigroup $\mathrm{e}^{t\mathcal{A}} = \mathrm{e}^{tD\Delta} \times Id$ (as a product of two generators). Moreover, since $Z_{1,p}$ is a Banach algebra ($p > n$) we observe that $H : Z_{1,p} \to Z_{1,p}$ is locally Lipschitz on bounded sets. The claim follows from Theorem 7.2.1 in [3]. □

We next turn to the proof of (2c).

To prove that for $t \in [0, T_{\max}) l(t), s(t) \geq 0$ we consider the system

$$\begin{aligned}
\partial_t l' - D\Delta l' &= \delta s'_+ - l'_+(1 - s'_+), && (t, x) \in (0, \infty) \times \Omega && \text{(10a)}\\
\partial_t s' &= -(\delta + \epsilon)s'_+ + l'_+(1 - s'_+), && (t, x) \in (0, \infty) \times \Omega && \text{(10b)}\\
-D\nabla_n l' &= -\nu, && (t, x) \in (0, \infty) \times \Gamma_N && \text{(10c)}\\
l' &= 0, && (t, x) \in (0, \infty) \times \Gamma_D && \text{(10d)}\\
l'(0) &= l_0, && x \in \Omega && \text{(10e)}\\
s'(0) &= s_0, && x \in \Omega && \text{(10f)}
\end{aligned}$$

As before one can show that (10) possess unique classical local solution (l', s'). After multiplying (10a) by l_- and integrating by parts we obtain

$$-\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega |l'_-|^2 \mathrm{d}x - D\int_\Omega |\nabla l'_-|^2 \mathrm{d}x - D\int_{\Gamma_N} l'_- \nu \mathrm{d}S = \delta \int_\Omega s'_+ l'_- \mathrm{d}x \geq 0.$$

Similarly multiplying (10b) by s_- yields

$$-\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega |s'_-|^2 \mathrm{d}x = \int_\Omega l'_+ s'_- \mathrm{d}x \geq 0.$$

Therefore for $t \in [0, T_{\max})$

$$\|l'(t)_-\|_2^2 + \|s'(t)_-\|_2^2 \leq \|l'(0)_-\|_2^2 + \|s'(0)_-\|_2^2 = 0$$

and consequently $l'(t) \geq 0, s'(t) \geq 0$. We observe now that (l', s') is a solution of **[LNW].B** and using uniqueness we finally get that $l(t) = l'(t) \geq 0, s(t) = s'(t) \geq 0$ for $t \in [0, T_{\max})$.

To show that $s(t, x) < 1$ for $(t, x) \in [0, T_{\max}) \times \overline{\Omega}$ we get from Lemma 3, that for every fixed $x \in \overline{\Omega}$ the function $\underline{s} = 1 - s = 1 - z_2 - s_\infty \in \mathcal{C}^1([0; T_{\max}), \mathbb{R})$ satisfies for $t > 0$ the following ODE

$$\dot{\underline{s}} + (\delta + \epsilon + l)\underline{s} = \delta + \epsilon.$$

Therefore

$$\underline{s}(t) = \mathrm{e}^{-(\delta+\epsilon)t-\int_0^t l(\tau)\mathrm{d}\tau}(1-s_0) + (\delta+\epsilon)\int_0^t \mathrm{e}^{-(\delta+\epsilon)(t-t')-\int_0^{t-t'} l(\tau)\mathrm{d}\tau}\mathrm{d}t' > 0.$$

We finally show that $T_{\max} = \infty$. Reasoning by contradiction assume that $T_{\max} < \infty$. Using uniform L_∞ boundedness of s (and therefore of z_2) we obtain for $t \in (0, T_{\max})$:

$$\|H^1(z(t))\|_p \leq C(1 + \|z_1(t)\|_p) \leq C(1 + \|z_1(t)\|_{1,p}). \tag{11}$$

Using (9a), (4a), (11) we obtain

$$\begin{aligned}\|z_1(t)\|_{1,p} &\leq \|\mathrm{e}^{tD\Delta} z_{10}\|_{1,p} + \int_0^t \|\mathrm{e}^{(t-\tau)D\Delta} H^1(z(\tau))\|_{1,p}\mathrm{d}\tau \\ &\leq C\|z_{10}\|_{1,p} + C\int_0^t (t-\tau)^{-1/2}\|H^1(z(t))\|_p \mathrm{d}\tau \\ &\leq C\|z_{10}\|_{1,p} + C\int_0^t (t-\tau)^{-1/2}(1 + \|z_1(\tau)\|_{1,p})\mathrm{d}\tau \\ &\leq C(\|z_{10}\|_{1,p} + 1) + C\int_0^t (t-\tau)^{-1/2}\|z_1(\tau)\|_{1,p}\mathrm{d}\tau\end{aligned}$$

Using Lemma 2 we get that $\|z_1(t)\|_{1,p} \leq C$ and therefore

$$\|H^2(z(t))\|_{1,p} \leq C(1 + \|z_2(t)\|_{1,p}). \tag{12}$$

Using (9b) and (12) we obtain

$$\begin{aligned}\|z_2(t)\|_{1,p} \leq \|z_{20}\|_{1,p} + \int_0^t \|H^2(z(\tau))\|_{1,p}\mathrm{d}\tau &\leq \|z_{20}\|_{1,p} \\ &+C\int_0^t (1 + \|z_2(\tau)\|_{1,p})\mathrm{d}\tau \\ &\leq C(\|z_{20}\|_{1,p} + 1) + C\int_0^t \|z_2(\tau)\|_{1,p}\mathrm{d}\tau.\end{aligned}$$

Another application of Lemma 2 gives desired contradiction from which we deduce that $T_{\max} = \infty$.

7. Proof of theorem 3

The proof of Theorem 3 is based on L_2 estimates obtained for $n = 1$ in [7] and bootstrap method to improve convergence from X_i-topology to X_{i+1}-topology, where $X_{i+1} \subset X_i$ are appropriately chosen Banach spaces. We use (as long as the regularity of our solution permits) the following two step

Bootstrap scheme

1. $\|z_1(t)\|_{X_i} + \|z_2(t)\|_{X_i} \leq C\mathrm{e}^{-(\chi/2)t}$ gives $\|z_1(t)\|_{X_{i+1}} \leq C\mathrm{e}^{-(\chi/2)t}$.
2. $\|z_1(t)\|_{X_{i+1}} \leq C\mathrm{e}^{-(\chi/2)t}$ gives $\|z_2(t)\|_{X_{i+1}} \leq C\mathrm{e}^{-(\chi/2)t}$.

Step 1. is a consequence of Duhamel formula (9a) and semigroup estimates (4). Step 2. follows from the fact that we can solve equation (6b) explicitly for z_2 in terms of z_1.

7.1. L_2 estimate

We first show that, as in the one dimensional case **[LNW].B** has a Lyapunov functional from which exponential convergence to the equlibrium (l_∞, s_∞) follows.

LEMMA 4. *For $x \in [0, 1)$, $u, v \in W^1_{p,\mathcal{B}^1}(\Omega)$, $0 \leq v < 1$, define*

$$\begin{aligned}
\Sigma_I(x) &= -\ln(1-x)\\
\Lambda_0(v) &= \int_\Omega (1-s_\infty)(l_\infty+\delta+2\epsilon)\left[\Sigma_I(v) - \Sigma_I(s_\infty) - \frac{v-s_\infty}{1-s_\infty}\right]\mathrm{d}x\\
\Lambda(u,v) &= \frac{1}{2}\|u-l_\infty\|_2^2 + \Lambda_0(v)\\
\mathcal{D}_\Lambda(u,v) &= D\|\nabla(u-l_\infty)\|_2^2\\
&\quad + \int_\Omega \frac{[u(1-v)-(\delta+\epsilon)v]^2 + \epsilon(l_\infty+\delta+\epsilon)(v-s_\infty)^2}{1-v}\mathrm{d}x.
\end{aligned}$$

Then for $t \geq 0$

$$\begin{aligned}
\Lambda(l(t), s(t)) + \int_0^t \mathcal{D}_\Lambda(l(\tau), s(\tau))\mathrm{d}\tau &= \Lambda(l_0, s_0)\\
\chi\Lambda(l(t), s(t)) &\leq \mathcal{D}_\Lambda(l(t), s(t))\\
(\delta+\epsilon)\|s(t)-s_\infty\|_2^2 &\leq 2\Lambda_0(s(t))
\end{aligned}$$

and

$$\|l(t)-l_\infty\|_2^2 + (\delta+\epsilon)\|s(t)-s_\infty\|_2^2 \leq 2\Lambda(l_0, s_0)\mathrm{e}^{-\chi t}, \tag{13}$$

where χ satisfies (3c).

Proof. Proof can be obtained exactly as in [7] (part of Theorem 8 and Proposition 9 pp. 1740–1744). For the case $n = 1$, $p \in (1, 2)$, to justify integration by parts and Poincaré inequality, we observe that for $t > 0 : l(t) \in W^2_p(\Omega) \subset W^1_2(\Omega)$. □

7.2. L_p estimate

In this subsection we will prove that for $t \geq 0$

$$\|z_1(t)\|_p + \|z_2(t)\|_p \leq C\mathrm{e}^{-(\chi/2)t}, \tag{14}$$

the parameter p being defined in **A1**.

Notice that if $p \in (1, 2]$ (which can only happen if $n = 1$), the inequality (14) follows from (13).

Otherwise we have $p > (2 \vee n)$. We choose an increasing sequence $(p_i)_{i=1}^m$ such that

$$p_1 = 2, \quad p_m = p$$
$$n/2(1/p_i - 1/p_{i+1}) < 1$$

(notice that for $n \in \{1, 2, 3, 4\}$ one can take $m = 2$). Inductively we will prove that

$$\|z_1(t)\|_{p_i} + \|z_2(t)\|_{p_i} \le C\mathrm{e}^{-(\chi/2)t}, \quad 1 \le i \le m. \tag{15}$$

For $i = 1$ (15) follows from (13). Assume that (15) is true for some $1 \le i \le m-1$. Then

$$\|H^1(z(t))\|_{p_i} \le \|z_1\|_{p_i}\|1 - z_2 + s_\infty\|_\infty + \|z_2\|_{p_i}\|\delta + \epsilon + l_\infty\|_\infty \le C\mathrm{e}^{-(\chi/2)t}. \tag{16}$$

Using (9a), (4b), (16) and $\chi/2 < D\lambda_1$ we obtain

$$\begin{aligned}
\|z_1(t)\|_{p_{i+1}} &\le \|\mathrm{e}^{tD\Delta}z_{10}\|_{p_{i+1}} + \int_0^t \|\mathrm{e}^{sD\Delta}H^1(z(t-s))\|_{p_{i+1}}\mathrm{d}\tau \\
&\le C\mathrm{e}^{-D\lambda_1 t} + C\int_0^t (Ds \wedge 1)^{-n/2(1/p_i - 1/p_{i+1})}\mathrm{e}^{-D\lambda_1 s}\|H^1(z(t-s))\|_{p_i}\mathrm{d}\tau \\
&\le C\mathrm{e}^{-D\lambda_1 t} + C\int_0^t (Ds \wedge 1)^{-n/2(1/p_i - 1/p_{i+1})}\mathrm{e}^{-D\lambda_1 s}\mathrm{e}^{-(\chi/2)(t-s)}\mathrm{d}\tau \\
&\le C\mathrm{e}^{-D\lambda_1 t} + C\mathrm{e}^{-(\chi/2)t}\int_0^t (Ds \wedge 1)^{-n/2(1/p_i - 1/p_{i+1})}\mathrm{e}^{-(D\lambda_1 - \chi/2)s}\mathrm{d}\tau \\
&\le C\mathrm{e}^{-(\chi/2)t}.
\end{aligned}$$

To show that for $t > 0$ $\|z_2(t)\|_{p_{i+1}} \le C\mathrm{e}^{-(\chi/2)t}$, we obtain from Theorem 2 that for each fixed $x \in \overline{\Omega}$ the function $z_2 \in \mathcal{C}^1([0, \infty); \mathbb{R})$ satisfies the ODE

$$\dot{z}_2 + (\delta + \epsilon + l_\infty + z_1)z_2 = (1 - s_\infty)z_1,$$

hence

$$z_2(t) = A(t)z_{20} + (1 - s_\infty)\int_0^t A(\tau)z_1(t-\tau)\mathrm{d}\tau, \tag{17}$$

where

$$A(t) = \exp\left(-\int_0^t (\delta + \epsilon + l_\infty + z_1(\tau))\mathrm{d}\tau\right). \tag{18}$$

From $l_\infty + z_1 = l \ge 0$ we get $\|A(t)\|_\infty \le \mathrm{e}^{-(\delta+\epsilon)t}$. Using $\chi/2 < \delta + \epsilon$ we obtain

$$\begin{aligned}
\|z_2(t)\|_{p_{i+1}} &\le \|A(t)\|_\infty\|z_{20}\|_{p_{i+1}} + \|1 - s_\infty\|_\infty\int_0^t \|A(\tau)\|_\infty\|z_1(t-\tau)\|_{p_{i+1}}\mathrm{d}\tau \\
&\le C\mathrm{e}^{-(\delta+\epsilon)t} + C\mathrm{e}^{-(\chi/2)t}\int_0^t \mathrm{e}^{-(\delta+\epsilon-\chi/2)\tau}\mathrm{d}\tau \le C\mathrm{e}^{-(\chi/2)t},
\end{aligned}$$

thus finishing the proof of (15), whence that of (14).

In the next two sections we use the smoothing properties of $e^{t\Delta}$ to extend convergence to the first and second derivatives.

7.3. W^1_p estimate

Using (9a), (4a), (14) and $\chi/2 < D\lambda_1$ we obtain

$$\begin{aligned}
\|z_1(t)\|_{1,p} &\le \|\mathrm{e}^{tD\Delta}z_{10}\|_{1,p} + \int_0^t \|\mathrm{e}^{sD\Delta}H^1(z(t-s))\|_{1,p}\mathrm{d}\tau\\
&\le C\mathrm{e}^{-D\lambda_1 t} + C\int_0^t (Ds\wedge 1)^{-1/2}\mathrm{e}^{-\lambda_1 Ds}\|H^1(z(t-s))\|_p\mathrm{d}\tau\\
&\le C\mathrm{e}^{-D\lambda_1 t} + C\int_0^t (Ds\wedge 1)^{-1/2}\mathrm{e}^{-\lambda_1 Ds}\mathrm{e}^{-(\chi/2)(t-s)}\mathrm{d}\tau\\
&\le C\mathrm{e}^{-D\lambda_1 t} + C\mathrm{e}^{-(\chi/2)t}\int_0^t (Ds\wedge 1)^{-1/2}\mathrm{e}^{-(D\lambda_1-\chi/2)s}\mathrm{d}\tau\\
&\le C\mathrm{e}^{-(\chi/2)t}.
\end{aligned}$$

Using the above estimate for z_1 we obtain that $A(t)$ given by (18) satisfies

$$\begin{aligned}
\|A(t)\|_p &\le C\|A(t)\|_\infty \le C\mathrm{e}^{-(\delta+\epsilon)t}\\
\|\nabla A(t)\|_p &= \|-A(t)\int_0^t (\nabla l_\infty + \nabla z_1(\tau))d\tau\|_p\\
&\le \|A(t)\|_\infty \int_0^t (\|\nabla l_\infty\|_p + \|\nabla z_1(\tau)\|_p)\mathrm{d}\tau\\
&\le C\mathrm{e}^{-(\delta+\epsilon)t}\int_0^t (1+\mathrm{e}^{-(\chi/2)\tau})\mathrm{d}\tau \le Ct\mathrm{e}^{-(\delta+\epsilon)t}.
\end{aligned}$$

Thus using (17) we have

$$\begin{aligned}
\|z_2(t)\|_{1,p} &\le \|A(t)\|_{1,p}\|z_{20}\|_{1,p} + C\|1-s_\infty\|_{1,p}\int_0^t \|A(\tau)\|_{1,p}\|z_1(t-\tau)\|_{1,p}\mathrm{d}\tau\\
&\le C(t+1)\mathrm{e}^{-(\delta+\epsilon)t} + C\int_0^t (\tau+1)\mathrm{e}^{-(\delta+\epsilon)\tau}\mathrm{e}^{-(\chi/2)(t-\tau)}\mathrm{d}\tau\\
&\le C(t+1)\mathrm{e}^{-(\delta+\epsilon)t} + C\mathrm{e}^{-(\chi/2)t}\int_0^t (\tau+1)\mathrm{e}^{-(\delta+\epsilon-\chi/2)\tau}\mathrm{d}\tau\\
&\le C\mathrm{e}^{-(\chi/2)t}
\end{aligned}$$

which finishes the proof of (3a).

7.4. W^2_p estimate for z_1

Using (9a), (4a), (3a) and $\chi/2 < D\lambda_1$ we obtain

$$\|z_1(t)\|_{2,p} \le \|\mathrm{e}^{tD\Delta}z_{10}\|_{2,p} + \int_0^t \|\mathrm{e}^{\tau D\Delta}H^1(z(t-\tau))\|_{2,p}\mathrm{d}\tau$$

$$
\begin{aligned}
&\le C(Dt \wedge 1)^{-1/2} \mathrm{e}^{-D\lambda_1 t} + C\int_0^t (D\tau \wedge 1)^{-1/2} \mathrm{e}^{-\lambda_1 D\tau} \mathrm{e}^{-(\chi/2)(t-\tau)} \mathrm{d}\tau \\
&\le C(t \wedge 1)^{-1/2} \mathrm{e}^{-D\lambda_1 t} + C\mathrm{e}^{-(\chi/2)t} \int_0^t (\tau \wedge 1)^{-1/2} \mathrm{e}^{-(D\lambda_1 - \chi/2)\tau} \mathrm{d}\tau \\
&\le C \max\{1/\sqrt{t}, 1\} \mathrm{e}^{-(\chi/2)t},
\end{aligned}
$$

which finishes the proof of (3b).

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