A model of morphogen transport in the presence of glypicans III

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Abstract

We analyze a stationary problem for a two dimensional model of morphogen transport. The model consists of one linear elliptic PDE posed on \((-1, 1) \times (0, h)\) which is coupled via a nonlinear boundary condition with a nonlinear elliptic PDE posed on \((-1, 1) \times \{0\}\). The main result is that the system has a unique steady state for all ranges of parameters present in the system. Moreover we consider the problem of the dimension reduction of the stationary solution. After introducing an appropriate scaling in the model we prove that, as \(h \to 0\), the stationary solution converges to the unique steady state of the dimensional simplification of the model which was analyzed in the first part of the paper. The main difficulty in obtaining appropriate estimates for the solution stems from the presence of a singular source term - a Dirac Delta in the boundary condition.

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1 Introduction

Morphogens are signalling molecules which govern the process of cell differentiation in living organisms. They spread from a source spatially localised in the tissue and after a certain amount of time form stable gradients of concentrations. Then receptors located on the surfaces of the cells detect levels of those concentrations and through intracellular pathways this information is conveyed to the nuclei, where the process of gene expression is initiated (see [15]).

The exact mechanism of morphogen transport is still discussed in the literature (see [7], [8], [9] for modelling and [5], [6], [10], [13], [14] for mathematical analysis). A model proposed in [4] accounts for the transport of morphogen Wingless (Wg) in the imaginal wing disc of the Drosophila Melanogaster. The present paper is the third part of a series of papers where we analyze mathematical properties of this model, which we call [HKCS]. Model [HKCS] has two counterparts - two and one dimensional (denoted respectively [HKCS].2D and [HKCS].1D), depending on the dimension of the domain representing the imaginal wing disc. The main goal of our analysis is a rigourous justification of the so called dimension reduction - [HKCS].1D can be obtained from [HKCS].2D due to shrinking of the rectangular domain in the direction which corresponds to the thickness of the wing disc.

Model [HKCS].2D accounts for the movement of morphogen molecules by (linear) diffusion in the whole domain \(\Omega_h = (-1, 1) \times (0, h)\), where \(h << 1\) denotes thickness of the disc, while being secreted from a point source localised at \(x = 0\) on part of the boundary of the wing disc - \(\partial_1 \Omega_h = (-1, 1) \times \{0\}\). Moreover association-dissociation reactions of morphogen with receptors and glypicans localised on \(\partial_1 \Omega_h\) are

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taken under consideration. After association of morphogen with a receptor (resp. glypican) a morphogen-
receptor (resp. -glypican) complex is being formed. Apart of the association-dissociation mechanism
glypicans also pass among themselves morphogen molecules, which is realised by introducing diffusion of
morphogen-glypicans complexes along $\partial_1 \Omega_h$. Finally morphogen-glypican complexes can further associate
with free receptors creating a triple morphogen-glypican-receptor complexes (which are immotile, similarly
as morphogen-receptor complexes). Model $\text{[HKCS].1D}$ accounts for the same set of reactions between
morphogen, glypican and complexes as $\text{[HKCS].2D}$. However it is assumed that the imaginal wing disc is
completely flat ($h = 0$) so that the whole dynamics takes place only on $\partial_1 \Omega_h$.

In [11] - the first part of our study, we proved that $\text{[HKCS].1D}$ is globally well-posed and has a unique
steady state. Article [12] is devoted to the analysis of the evolutionary problem $\text{[HKCS].2D}$. Apart of
proving global well-posedness we showed that time dependent solutions of $\text{[HKCS].2D}$, when properly
normalised, converge as $h \to 0$ to solutions of $\text{[HKCS].1D}$. In this paper we turn our attention to the sta-
nionary problem associated with $\text{[HKCS].2D}$. We prove that there is a unique steady state which converges
to the equilibrium of $\text{[HKCS].1D}$ as $h \to 0$. We illustrate our result by performing numerical computations
which show that the graph of the stationary solution to $\text{[HKCS].2D}$ becomes homogeneous in $x_2$ direction
as $h \to 0$. It is worth underlying that all our results are proved without imposing any artificial conditions
on the parameters which are present in the system.

1.1 The $\text{[HKCS].2D}$ model.

In this section we recall model $\text{[HKCS].2D}$ in a nondimensional form. The model was described in more
detail and analyzed for the evolutionary case in [12]. For the presentation and analysis of $\text{[HKCS].1D}$ - a
one dimensional simplification we refer to [11]. $\text{[HKCS].2D}$ in a nondimensional form reads:

$$
\begin{align*}
\partial_t u_1^h + div(J_h(u_1^h)) &= -b_1 u_1^h, & (t, x) \in \Omega_T \\
\partial_t u_2^h - d \partial_{x_1}^2 u_2^h &= c_1 u_1^h - (b_2 + c_2 + c_3 u_3^h) u_2^h + c_5 u_5^h, & (t, x) \in (\partial_1 \Omega)_T \\
\partial_t u_3^h &= -(b_3 + u_1^h + c_3 u_3^h) u_3^h + c_4 u_4^h + c_5 u_5^h + p_3, & (t, x) \in (\partial_1 \Omega)_T \\
\partial_t u_4^h &= u_1^h u_3^h - (b_4 + c_4) u_4^h, & (t, x) \in (\partial_1 \Omega)_T \\
\partial_t u_5^h &= c_3 u_2^h u_3^h - (b_5 + c_5) u_5^h, & (t, x) \in (\partial_1 \Omega)_T
\end{align*}
$$

with boundary and initial conditions

$$
\begin{align*}
-J_h(u_1^h) \nu &= 0, & (t, x) \in (\partial_3 \Omega)_T \\
-J_h(u_1^h) \nu &= -(c_1 + u_3^h) u_1^h + c_2 u_2^h + c_4 u_4^h + p_1 \delta, & (t, x) \in (\partial_1 \Omega)_T \\
\partial_{x_1} u_2^h &= 0, & (t, x) \in (\partial_1 \Omega)_T \\
u^h(0, \cdot) &= u_0,
\end{align*}
$$

where

- $\Omega = (-1, 1) \times (0, 1)$, $\partial \Omega = \partial_3 \Omega \cup \partial_1 \Omega$, $\partial_1 \Omega = (-1, 1) \times \{0\}$, $0 < T \leq \infty$, $\Omega_T = (0, T) \times \Omega$,
- $h > 0$ corresponds to the thickness of the wing disc, $J_h(u) = -\partial_{x_1} u, h^{-2} \partial_{x_2} u$,
- $\nu$ denotes the outer normal unit vector to $\partial \Omega$,
- $\delta$ denotes a one dimensional Dirac Delta i.e $\delta(\phi) = \phi(0)$ for any $\phi \in C([-1, 1])$.

In $\text{[1]}$ $u_1, u_2, u_3, u_4$ and $u_5$ denote concentrations of free morphogen, morphogen-glypican complexes, free
receptors, morphogen-receptor complexes and morphogen-glypican-receptor complexes; $c_i$’s are rates of re-
actions between $u_i$’s; $b_1, b_2$ denote rates of degradations of $u_1, u_2$ while $b_3, b_4, b_5$ are rates of internalisation.
of \(u_3, u_4\) and \(u_5\). Finally \(d\) is the diffusion rate of \(u_2\) along \(\partial_1 \Omega\) while \(p_1, p_3\) denote rates of production of morphogen and free receptors. Notice the dependence of \(J_h(u)\) on parameter \(h\).

From now on we impose the following natural assumptions on the signs of constant parameters

\[
d, b > 0, \quad c, p \geq 0, \tag{2}
\]

where \(b = (b_1, \ldots, b_5)\) and similarly for \(c, p\).

### 1.2 Notation

In the whole article \(\Omega = (-1,1) \times (0,1)\) and \(I = (-1,1)\) are fixed domains. If \(U\) is an open subset of \(\mathbb{R}^n\) and \(1 \leq p \leq \infty, \ s \in \mathbb{R}\), we denote by \(W^s_p(U)\) the fractional Sobolev (also known as Sobolev-Slobodecki) spaces and by \(\mathcal{M}(U)\) the Banach space of finite, signed Radon measures on \(\overline{U}\) equipped with the total variation norm \(-\|\cdot\|_{TV}\).

In various estimates we will use a generic constant \(C\) which may take different values even in the same paragraph. Constant \(C\) may depend on various parameters, but it will never depend on \(h\).

If \(X\) is a normed space we denote by \(X^*\) its topological dual. Furthermore if \(x \in X\) and \(x^* \in X^*\) we denote by \(\langle x^*, x \rangle_{(X^*, X)} = x^*(x)\) a natural pairing between \(X\) and its dual. If \(H\) is a Hilbert space we denote by \((\cdot, \cdot)_H\) its scalar product. In particular \((x|y)_{\mathbb{R}^n} = \sum_{i=1}^n x_i y_i\) and \((f|g)_{L^2(U)} = \int_U fg\). To get more familiar with the notation observe that, due to Riesz theorem, for any \(x^* \in H^*\) there exists a unique \(x \in H\) such that \(\langle x^*, y \rangle_{(H^*, H)} = (x|y)_H\) for all \(y \in H\).

### 2 Results

Let us observe that due to the presence of three ODE’s in the system \([1]\), the stationary problem may be reduced to a system of two elliptic equations:

\[
\begin{align*}
d\text{div}(J_h(u_1)) + b_1 u_1 &= 0, \quad x \in \Omega \quad (3a) \\
d\partial_{x_1}^2 u_2 - c_1 u_1 + (b_2 + c_2 + k_2 H(u_1, u_2)) u_2 &= 0, \quad x \in \partial_1 \Omega \quad (3b)
\end{align*}
\]

with boundary conditions

\[
\begin{align*}
-J_h(u_1) \nu &= 0, \quad x \in \partial_0 \Omega \quad (4a) \\
-J_h(u_1) \nu &= - (c_1 + k_1 H(u_1, u_2)) u_1 + c_2 u_2 + p_1 \delta, \quad x \in \partial_1 \Omega \quad (4b) \\
\partial_{x_1} u_2 &= 0, \quad x \in \partial \partial_1 \Omega, \quad (4c)
\end{align*}
\]

where

\[
k_1 = b_4/(b_4 + c_4), \quad k_2 = c_3 b_5/(b_5 + c_5), \quad H(u_1, u_2) = p_5/(k_1 u_1 + k_2 u_2 + b_3) \tag{5}
\]

and

\[
u_3 = H(u_1, u_2), \quad u_4 = \frac{k_1}{b_4} u_1 H(u_1, u_2), \quad u_5 = \frac{k_2}{b_5} u_2 H(u_1, u_2).
\]

We will prove the following two theorems
Theorem 1. For every $h \in (0, 1]$ system (3)-(4) has a unique nonnegative $W^1_1$ solution $(u^h_1, u^h_2)$ i.e. there exists a unique nonnegative $(u^h_1, u^h_2) \in W^1_1(\Omega) \times W^2_2(\partial_1 \Omega)$ such that for every $(v_1, v_2) \in W^1_\infty(\Omega) \times W^4_\infty(\partial_1 \Omega)$

$$- \int_\Omega [J_h(u_1) \nabla v_1 + b_1 u_1 v_1] = p_1 v_1(0) + \int_{\partial_1 \Omega} [- (c_1 + k_1 H(u_1, u_2)) u_1 + c_2 u_2] v_1, \quad (6a)$$

$$\int_{\partial_1 \Omega} d \partial x_1 u_2 \partial x_1 v_2 = \int_{\partial_1 \Omega} [c_1 u_1 - (b_2 + c_2 + k_2 H(u_1, u_2)) u_2] v_2. \quad (6b)$$

Moreover $(u^h_1, u^h_2) \in W^1_p(\Omega) \times W^2_q(\partial_1 \Omega)$ for every $1 \leq p < 2, 1 \leq q < \infty$ and

$$\|u^h_1\|_{W^1_p(\Omega)} + h^{-1} \|\partial_{x_2} u^h_1\|_{L_p(\Omega)} + \|u^h_2\|_{W^2_q(\partial_1 \Omega)} \leq C, \quad (7)$$

where $C$ does not depend on $h$.

Theorem 2. Let $(u^h_1, u^h_2)$ be the unique solution of system (3)-(4). Then for every $1 \leq p < 2, 1 \leq q < \infty$ we have the following weak convergence as $h \to 0^+$

$$u^h_1 \rightharpoonup u^0_1 \quad \text{in} \quad W^1_1(\Omega), \quad (8a)$$

$$u^h_2 \rightharpoonup u^0_2 \quad \text{in} \quad W^2_2(\partial_1 \Omega). \quad (8b)$$

Moreover $\partial_{x_2} u^0_1 = 0$ (so that $u^0_1$ depends only on $x_1$) and $(u^0_1, u^0_2) \in W^1_\infty(I) \times C^2(\bar{I})$ is the unique solution of

$$-u''_1 + (b_1 + c_1 + k_1 H(u_1, u_2)) u_1 - c_2 u_2 = p_1 \delta, \quad x \in I \quad (9a)$$

$$-d u''_2 - c_1 u_1 + (b_2 + c_2 + k_2 H(u_1, u_2)) u_2 = 0, \quad x \in I \quad (9b)$$

$$u'_1 = u'_2 = 0, \quad x \in \partial I. \quad (9c)$$

Remark 1. Notice that (9) is the stationary problem associated with model [HKCS].1D (analyzed previously in [11]). Thus Theorem 2 is the rigorous formulation of the dimension reduction of the model [HKCS].2D in the stationary case.

On Figure (1) we present graphs of $u^h_1$ for several values of $h$. A numerical scheme based on the finite difference method was implemented using the software Octave. Notice that as $h$ becomes smaller the graph of $u^h_1$ becomes homogeneous in the $x_2$ direction.

3 Solvability of certain linear systems with measure valued sources

To prove Theorem 1 we will use two lemmas concerning solvability of linear elliptic boundary value problems with low regularity data.

Lemma 1. Assume that $0 \leq a_0 \in L_\infty(\Omega), \ 0 \leq a_{11} \in L_\infty(\partial_1 \Omega)$. Then for every $h \in (0, 1], \lambda > 0$ and $\mu_\Omega \in \mathcal{M}(\Omega), \mu_I \in \mathcal{M}(I)$ the following boundary value problem

$$\text{div}(J_h(u)) + (\lambda + a_0) u = \mu_\Omega, \quad x \in \Omega \quad (10a)$$

$$-J_h(u) \nu = 0, \quad x \in \partial_0 \Omega \quad (10b)$$

$$-J_h(u) \nu + a_{11} u = \mu_I, \quad x \in \partial_1 \Omega \quad (10c)$$

has a unique $W^1_1$ solution i.e. there exists a unique $u \in W^1_1(\Omega)$ such that for every $v \in W^1_\infty(\Omega)$

$$\int_\Omega [-J_h(u) \nabla v + (\lambda + a_0) uv] + \int_{\partial_1 \Omega} a_{11} uv = \int_\Omega v d \mu_\Omega + \int_{\partial_1 \Omega} v d \mu_I. \quad (11)$$
Moreover $u \in W^1_p(\Omega)$ for every $p < 2$ and
\[ \|u\|_{W^1_p(\Omega)} + h^{-1}\|\partial_{x_2} u\|_{L^p(\Omega)} \leq C(\|\mu_\Omega\|_{TV} + \|\mu_1\|_{TV}), \tag{12} \]
where $C$ depends only on $p, \lambda, \|a_0\|_{L^\infty(\Omega)}, \|a_{11}\|_{L^\infty(\partial\Omega)}$. If $\mu_\Omega, \mu_1 \geq 0$ then $u \geq 0$.

**Proof.** We divide the proof into two parts. In the first part we employ the technique from [1] to prove existence of the solution which additionally satisfies (12). Notice that one has to use a slight modification due to the Robin boundary condition instead of the Dirichlet condition which is treated in [1]. In the second part of the proof, using duality technique from [2], we show that the solution is unique in the $W^1_1$ class.

**Existence**

Observe that due to linearity of the problem (10) one can assume without loss of generality that
\[ \|\mu_\Omega\|_{TV} + \|\mu_1\|_{TV} \leq 1. \]
First let us consider $\mu \in L_\infty(\Omega), \mu \in L_\infty(\partial \Omega)$. Using the Lax-Milgram lemma we obtain that the problem (10) has a unique solution $u \in W_2^1(\Omega)$. We will now prove that this solution satisfies (12). Observe that if $\phi \in W_1^1(\mathbb{R})$ is such that

$$\|\phi\|_{L_\infty(\mathbb{R})} \leq 1, \ y\phi(y) \geq 0, \ \phi'(y) \geq 0,$$

then testing (11) by $v = \phi(u) \in W_2^1(\Omega)$ we obtain

$$\lambda \int_{\Omega} u \phi(u) \leq 1, \quad (14a)$$

$$0 \leq \int_{\Omega} -\phi'(u) J_h(u) \nabla u \leq 1. \quad (14b)$$

For $n \geq 1$ define

$$\varphi_n(y) = \begin{cases} ny & \text{if } |y| < 1/n \\ \text{sgn}(y) & \text{if } |y| \geq 1/n. \end{cases} \quad (15)$$

Choosing in (14a) $\phi = \varphi_n$ and taking $n \to \infty$ we obtain that

$$\|u\|_{L_1(\Omega)} \leq \frac{1}{\lambda} \leq C. \quad (16)$$

For $n \geq 0$ define $B_n = \{x : n \leq |u(x)| \leq n + 1\}$ and

$$\psi_n(y) = \begin{cases} 0 & \text{if } |y| < n \\ y - \text{sgn}(y) \cdot n & \text{if } n \leq |y| \leq n + 1 \\ \text{sgn}(y) & \text{if } |y| > n + 1 \end{cases}. \quad (17)$$

Choosing in (14b) $\phi = \psi_n$ we obtain that

$$\|m_h(u)1_{B_n}\|_{L^2(\Omega)}^2 = \int_{B_n} -J_h(u) \nabla u \leq 1, \quad (18)$$

where $m_h(u) = \sqrt{\partial_{x_1} u^2 + h^{-2}|\partial_{x_2} u|^2}$. Using Hölder’s inequality with $1 = p/2 + p/p^*$ we have

$$\|m_h(u)1_{B_n}\|_{L^p(\Omega)}^{p} \leq \|m_h(u)1_{B_n}\|_{L^2(\Omega)} \|B_n\|_{p/p^*} \leq |B_n|^{p/p^*} \leq C. \quad (19)$$

Using Sobolev’s inequality and (16) we have

$$\|u\|_{L^p(\Omega)} \leq C(\|m_1(u)\|_{L^p(\Omega)} + \|u\|_{L^1(\Omega)}) \leq C(\|m_1(u)\|_{L^p(\Omega)} + 1). \quad (20)$$

From (18), Hölder inequality (for series) and (19) we have

$$\|m_h(u)\|_{L^p(\Omega)}^{p} = \sum_{n=0}^{N} \|m_h(u)1_{B_n}\|_{L^p(\Omega)}^{p} + \sum_{n=N+1}^{\infty} \|m_h(u)1_{B_n}\|_{L^p(\Omega)}^{p} \leq C(N + 1) + \sum_{n=N+1}^{\infty} |B_n|^{p/p^*} \leq C(N + 1) + \sum_{n=N+1}^{\infty} \|u\|_{L^p(\Omega)}^{p} \leq C(N + 1) + \sum_{n=N+1}^{\infty} \|u\|_{L^p(\Omega)}^{p} \leq C(N + 1) + A(N)^p \|u\|_{L^p(\Omega)}^{p} \leq C(N + 1) + A(N)^p \|m_h(u)\|_{L^p(\Omega)}^{p}(\|m_h(u)\|_{L^p(\Omega)} + 1).$$

Taking $N$ sufficiently large we obtain

$$\|m_h(u)\|_{L^p(\Omega)} \leq C.$$
Finally from (19) it follows that \( \|u\|_{L_p(\Omega)} \leq C\|u\|_{L_p^*(\Omega)} \leq C(\|m_h(u)\|_{L_p(\Omega)} + 1) \leq C \) which completes the proof of (12).

The case of arbitrary Radon measures \( \mu_\Omega, \mu_I \) follows by standard approximation, see [1] for instance.

**Uniqueness**

We shall use duality technique. Let \( u \) be a \( W^1_2 \) solution to

\[
\text{div}(J_h(u)) + (\lambda + a_0)u = 0, \quad x \in \Omega \tag{20a}
\]

\[
-J_h(u)\nu = 0, \quad x \in \partial_0 \Omega \tag{20b}
\]

\[
-J_h(u)\nu + a_{11}u = 0, \quad x \in \partial_1 \Omega. \tag{20c}
\]

We intend to prove that \( u \equiv 0 \). First we assume additionally that \( a_{11} \equiv 0 \). Using [3] we get that for every \( f \in L_q(\Omega), q > 2 \), problem

\[
\text{div}(J_h(v)) + (\lambda + a_0)v = f, \quad x \in \Omega \tag{21a}
\]

\[
-J_h(v)\nu = 0, \quad x \in \partial \Omega \tag{21b}
\]

has a unique solution \( v \in W^2_q(\Omega) \). Since \( q > 2 \) we have \( W^2_q(\Omega) \subset W^1_\infty(\Omega) \), so that for every \( w \in W^1_1(\Omega) \) we have

\[
\int_\Omega [-J_h(v)\nabla w + (\lambda + a_0)vw] = \int_\Omega fw.
\]

Taking \( w = u \) we thus get \( \int_\Omega fu = 0 \) and since \( f \) was arbitrary - \( u \equiv 0 \) follows.

Now let us take \( 0 \leq a_{11} \in L_\infty(\partial_1 \Omega) \). Denote \( g = -a_{11}u \). Observe that \( u \) is a \( W^1_2 \) solution of

\[
\text{div}(J_h(u)) + (\lambda + a_0)u = 0, \quad x \in \Omega \tag{22a}
\]

\[
-J_h(u)\nu = 0, \quad x \in \partial_0 \Omega \tag{22b}
\]

\[
-J_h(u)\nu = g, \quad x \in \partial_1 \Omega. \tag{22c}
\]

As we already showed [22] has a unique \( W^1_2 \) solution and, thus \( u \in W^1_2(\Omega) \) for every \( p < 2 \). In particular \( g \in L_q(\partial_1 \Omega) \) for every \( q < \infty \). We can now use Lax-Milgram theorem to prove that [22] has a unique \( W^1_2 \) solution and thus conclude that \( u \in W^2_2(\Omega) \). It follows that, \( u \) is also a \( W^2_2 \) solution of [20], whence \( u \equiv 0 \).

\[\square\]

**Lemma 2.** Assume that \( d > 0, \ 0 \leq a_0 \in L_\infty(\Omega) \) and

\[
a_{ij} \in L_\infty(\partial_1 \Omega), \ a_{11} \geq |a_{21}|, a_{22} \geq |a_{12}|. \tag{23}\]

Then for every \( h \in (0, 1], \lambda > 0, \mu_\Omega \in M(\Omega), \mu_I \in M(I) \) the following system

\[
\text{div}(J_h(u_1)) + (\lambda + a_0)u_1 = \mu_\Omega, \quad x \in \Omega \tag{24a}
\]

\[
-d\partial_x^2 u_2 - a_{21}u_1 + (\lambda + a_{22})u_2 = 0, \quad x \in \partial_1 \Omega \tag{24b}
\]

with boundary conditions

\[
-J_h(u_1)\nu = 0, \quad x \in \partial_0 \Omega \tag{25a}
\]

\[
-J_h(u_1)\nu + a_{11}u_1 - a_{12}u_2 = \mu_I, \quad x \in \partial_1 \Omega \tag{25b}
\]

\[
\partial_{x_1} u_2 = 0, \quad x \in \partial_\Omega, \tag{25c}
\]

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has a unique $W_1^2$ solution i.e. there exists a unique $(u_1, u_2) \in W_1^1(\Omega) \times W_1^1(\partial_1 \Omega)$ such that for every $(v_1, v_2) \in W_1^1(\Omega) \times W_1^1(\partial_1 \Omega)$:

$$
\int_\Omega [-J_h(u_1) \nabla v_1 + (\lambda + a_0) u_1 v_1] + \int_{\partial_1 \Omega} \left[ d\partial_{x_1} u_2 \partial_{x_1} u_2 + \lambda u_2 v_2 - \left( M(u_1, u_2) \right) (v_1, v_2) \right]_{\mathbb{R}_2} = \int_\Omega v_1 d\mu_\Omega + \int_{\partial_1 \Omega} v_1 d\mu_1,
$$

where $M(u_1, u_2) = (-a_{11} u_1 + a_{21} u_1 + a_{22} u_2)$. Moreover $(u_1, u_2) \in W_1^p(\Omega) \times W_2^q(\partial_1 \Omega)$ for every $1 \leq p < 2, 1 \leq q < \infty$ and

$$
\| u_1 \|_{W_1^p(\Omega)} + h^{-1} \| \partial_{x_2} u_1 \|_{L_p(\Omega)} + \| u_2 \|_{W_2^q(\partial_1 \Omega)} \leq C(\| \mu_\Omega \|_{TV} + \| \mu_1 \|_{TV}),
$$

where $C$ depends only on $p, \lambda, d, \| a_0 \|_{L_\infty(\Omega)}, \| a_{ij} \|_{L_\infty(\partial_1 \Omega)}$. If $\mu_\Omega, \mu_1, a_{12}, a_{21} \geq 0$ then $u_1, u_2 \geq 0$.

**Proof. Existence**

Let us define the Hilbert spaces $X_{1/2} = W_2^1(\Omega) \times W_2^1(\partial_1 \Omega)$, $X_{-1/2} = X_{1/2}^*$ and an unbounded operator $A : X_{-1/2} \supset X_{1/2} \rightarrow X_{-1/2}$ by

$$
\langle A(u_1, u_2), (v_1, v_2) \rangle_{(X_{1/2}, X_{-1/2})} = \int_\Omega [-J_h(u_1) \nabla v_1 - a_0 u_1 v_1] + \int_{\partial_1 \Omega} \left[ -d\partial_{x_2} u_2 \partial_{x_2} v_2 + \left( M(u_1, u_2) \right) (v_1, v_2) \right]_{\mathbb{R}_2}.
$$

Due to boundedness of $a_0$ and $a_{ij}$ operator $\lambda - A$ is coercive for $\lambda$ large enough and the Lax-Milgram lemma guarantees that there is $\lambda_0 > 0$ such that $[\lambda_0, \infty) \subset \rho(A)$ ($\rho(A)$ denotes the resolvent set of $A$). Because $X_{1/2}$ is compactly embedded into $X_{-1/2}$ we get that for $\lambda \in \rho(A)$ the resolvent operator $(\lambda - A)^{-1}$ is compact and thus the spectrum $\sigma(A)$ consists entirely of eigenvalues. Choose any $\lambda \in \mathbb{R}, \theta \in X_{-1/2}$ and $u = (u_1, u_2) \in X_{1/2}$ such that $(\lambda - A) u = \theta$. Let $\varphi_n$ be the function defined in (15). Then

$$
\langle \theta, (\varphi_n(u_1), \varphi_n(u_2)) \rangle_{(X_{-1/2}, X_{1/2})} = \langle (\lambda - A)(u_1, u_2), (\varphi_n(u_1), \varphi_n(u_2)) \rangle_{(X_{-1/2}, X_{1/2})}
$$

$$
= \int_\Omega [-\varphi_n'(u_1) J_h(u_1) \nabla u_1 + (\lambda + a_0) u_1 \varphi_n(u_1)]
$$

$$
+ \int_{\partial_1 \Omega} \left[ d\varphi_n(u_2) [d\partial_{x_2} u_2] \right]^2 - \left( M(u_1, u_2) \right) (\varphi_n(u_1), \varphi_n(u_2))_{\mathbb{R}_2} + \lambda u_2 \varphi_n(u_2)
$$

$$
\geq \lambda \left( \int_\Omega u_1 \varphi_n(u_1) + \int_{\partial_1 \Omega} u_2 \varphi_n(u_2) \right) - \int_\Omega \left( M(u_1, u_2) \right) (\varphi_n(u_1), \varphi_n(u_2))_{\mathbb{R}_2}.
$$

Thus taking $n \rightarrow \infty$ and using (23) we get

$$
\liminf_{n \rightarrow \infty} \langle \theta, (\varphi_n(u_1), \varphi_n(u_2)) \rangle_{(X_{-1/2}, X_{1/2})} \geq \lambda(\| u_1 \|_{L_1(\Omega)} + \| u_2 \|_{L_1(\partial_1 \Omega)}).
$$

In particular it follows from (27) that for $\lambda > 0$ equation $(\lambda - A) u = 0$ does not have nontrivial solutions, whence $(0, \infty) \subset \rho(A)$. Observe that when $\mu_\Omega, \mu_1$ are bounded functions then the distribution $\theta$ defined by

$$
\langle \theta, (v_1, v_2) \rangle = \int_\Omega v_1 d\mu_\Omega + \int_\Omega v_1 d\mu_1 = \int_\Omega v_1 \mu_\Omega dx + \int_\Omega v_1 (\cdot, 0) \mu_1 dx
$$

belongs to $X_{1/2}^*$ thus equation $(\lambda - A) u = \theta$ has a unique solution $u = (u_1, u_2) \in X_{1/2}$ which is a solution to problem (24)-(25). We will now prove that $u$ satisfies (26). Due to linearity of (24), (25) we can assume, without loss of generality, that

$$
\| \mu_\Omega \|_{TV} + \| \mu_1 \|_{TV} \leq 1.
$$
Next we prove respectively that

\[
\lambda(\|u_1\|_{L_1(\Omega)} + \|u_2\|_{L_1(\partial_1 \Omega)}) \leq C, \quad (29)
\]
\[
\|u_1\|_{W_1^1(\Omega)} + h^{-1}\|\partial x_1 u_1\|_{L_p(\partial_1 \Omega)} \leq C, \quad (30)
\]
\[
\|u_2\|_{W_2^1(\partial_1 \Omega)} \leq C. \quad (31)
\]

To get (29) observe that from (27) with \( \theta \) given by (28) one has

\[
\lambda(\|u_1\|_{L_1(\Omega)} + \|u_2\|_{L_1(\partial_1 \Omega)}) \leq \liminf_{n \to \infty} \left( \theta_n(u_1), \varphi_n(u_2) \right)_{(X_{1/2}, X_{1/2})} \leq \|\mu_\Omega\|_{L_1(\Omega)} + \|\mu_I\|_{L_1(I)} \leq 1,
\]

since \( |\varphi_n(y)| \leq 1 \) for \( y \in \mathbb{R} \). Then (30) follows from (29) and Lemma 1, while (31) follows from (24b), (30) and the fact that for every \( 1 \leq q < \infty \) there exists \( 1 \leq p < 2 \) such that the trace operator maps \( W_1^1(\Omega) \) into \( L_q(\partial_1 \Omega) \). To prove existence of solutions to (24), (25) for the case when \( \mu_\Omega \) and \( \mu_I \) are finite Radon measures one proceeds by the standard approximation technique with the use of (26).

**Uniqueness**

Let \((u_1, u_2)\) be a \( W_1^1 \) solution of problem (24), (25) with \( \lambda > 0, \mu_\Omega = 0, \mu_I = 0 \).

Denoting \( g_1 = a_{12} u_2 \in L_\infty(I), g_2 = a_{21} u_1 \in L_1(I) \) we see that \( u_1 \) is a \( W_1^1 \) solution of

\[
\text{div}(J_h(u)) + (\lambda + a_0) u = 0, \quad x \in \Omega \quad (32a)
\]
\[
-J_h(u) \nu = 0, \quad x \in \partial_0 \Omega \quad (32b)
\]
\[
-J_h(u) \nu + a_{11} u = g_1, \quad x \in \partial_1 \Omega \quad (32c)
\]

and \( u_2 \) is a \( W_1^1 \) solution of

\[
-d_2 \partial x_1^2 u + (\lambda + a_{22}) u = g_2, \quad x \in I \quad (33a)
\]
\[
\partial x_1 u = 0, \quad x \in \partial I \quad (33b)
\]

Since \( g_1 \in L_\infty(\partial_1 \Omega) \) then by Lax-Milgram lemma problem (32) has a \( W_2^1 \) solution which by Lemma 1 is unique in \( W_2^1 \) class. Thus \( u_1 \) is a \( W_2^1 \) solution of (32) and \( g_2 \in L_2(I) \). From Lax-Milgram lemma we obtain that (33) has a \( W_1^1 \) solution which due to duality technique is unique in \( W_1^1 \) class. Thus \( u_2 \in W_1^1 \). Finally we observe that \((u_1, u_2) \in X_{1/2}\) is in the kernel of the operator \((\lambda - A)\) and thus \((u_1, u_2) \equiv 0\).

4 **Proof of Theorem 1**

**Existence**

Fix \( 1 > s > 1/p, \infty > q > 1 \) and for \( R > 0 \) define

\[
K_R = \{(v_1, v_2) \in W_0^s(\Omega) \times L_q(\partial_1 \Omega) : v_1, v_2 \geq 0, \|v_1\|_{W_0^s(\Omega)} + \|v_2\|_{L_q(\partial_1 \Omega)} \leq R\}.
\]

\( K_R \) is a bounded, convex and closed subset of the Banach space \( B = W_0^s(\Omega) \times L_q(\partial_1 \Omega) \). For \((v_1, v_2) \in K_R\) consider problem (3) with \( H(u_1, u_2) \) replaced by \( H(v_1, v_2) \) (notice that \( v_1(0, \cdot) \) is well defined as \( s > 1/p \)) i.e.

\[
\text{div}(J_h(u_1)) + b_1 u_1 = 0, \quad x \in \Omega \quad (34a)
\]
\[
-d_2 \partial x_1^2 u_2 - c_1 u_1 + (b_2 + c_2 + k_2 H(v_1, v_2)) u_2 = 0, \quad x \in \partial_1 \Omega \quad (34b)
\]

with boundary conditions

\[
-J_h(u_1) \nu = 0, \quad x \in \partial_0 \Omega \quad (35a)
\]
\[
-J_h(u_1) \nu = -(c_1 + k_1 H(v_1, v_2)) u_1 + c_2 u_2 + p_1 \delta, \quad x \in \partial_1 \Omega \quad (35b)
\]
\[
\partial x_1 u_2 = 0, \quad x \in \partial \partial_1 \Omega. \quad (35c)
\]
Using Lemma 2 with
\[
\lambda = \min\{b_1, b_2\}, \quad a_0 = b_1 - \lambda, \quad \mu_\Omega = 0, \quad \mu_I = p_1 \delta, \\
a_{11} = c_1 + k_1 H(v_1, v_2), \quad a_{12} = c_2, \\
a_{21} = c_1, \quad a_{22} = b_2 - \lambda + c_2 + k_2 H(v_1, v_2),
\]
we obtain that problem (34) has the unique solution \((u_1, u_2) = T(v_1, v_2)\) satisfying (26) with \(C\) independent of \(R\) (since \(H\) is bounded on \(\mathbb{R}^2\)). Thus for large \(R\) the nonlinear operator \(T\) maps \(K_R\) into itself. Since \(W^1_0(\Omega) \times W^1_0(\partial \Omega)\) embeds compactly into \(W^2_0(\Omega) \times L_q(\partial \Omega)\) the nonlinear operator \(T\) is compact. Since \(H\) is globally Lipchitz we conclude that \(T\) is continuous in the topology of \(B\). Thus, using Schauder fixed point theorem, \(T\) has a fixed point, which additionally satisfies (7).

**Uniqueness**

Assume that \((u_1, u_2), (v_1, v_2)\) are two \(W^1_0\) solutions of (3)-(4). Denoting \(z_i = u_i - v_i\) for \(i = 1, 2\) we have:

\[
div(J_h(z_i)) + b_1 z_i = 0, \quad x \in \Omega \\
div(J_h(z_i)) + b_1 z_i = 0, \quad x \in \partial \Omega
\]

with boundary conditions
\[
-J_h(z_1) \nu = 0, \quad x \in \partial \Omega \\
-J_h(z_2) \nu = -c_1 z_1 - k_1 H(u_1, u_2) u_1 - H(v_1, v_2) v_1 + c_2 z_2, \quad x \in \partial \Omega \\
\partial z_1 z_2 = 0, \quad x \in \partial \Omega.
\]

Define
\[
D = (k_1 u_1 + k_2 u_2 + b_3)(k_1 v_1 + k_2 v_2 + b_3), \\
w_i = (u_i + v_i)/2, \quad i = 1, 2.
\]

Notice that
\[
H(u_1, u_2) u_1 - H(v_1, v_2) v_1 = p_3 \left( \frac{u_1}{k_1 u_1 + k_2 u_2 + b_3} - \frac{v_1}{k_1 v_1 + k_2 v_2 + b_3} \right) = \frac{p_3}{D} \left( k_2 (u_1 v_2 - u_2 v_1) + b_3 z_1 \right)
\]
\[
= \frac{p_3}{D} \left( (k_2 w_2 + b_3) z_1 - k_2 w_1 z_2 \right),
\]
\[
H(u_1, u_2) u_2 - H(v_1, v_2) v_2 = p_3 \left( \frac{u_2}{k_1 u_1 + k_2 u_2 + b_3} - \frac{v_2}{k_1 v_1 + k_2 v_2 + b_3} \right) = \frac{p_3}{D} \left( -k_1 (u_1 v_2 - u_2 v_1) + b_3 z_2 \right)
\]
\[
= \frac{p_3}{D} \left( -k_1 w_2 z_1 + (k_1 w_1 + b_3) z_2 \right).
\]

Thus
\[
div(J_h(z_i)) + b_1 z_i = 0, \quad x \in \Omega \\
div(J_h(z_i)) + b_1 z_i = 0, \quad x \in \partial \Omega
\]

with boundary conditions
\[
-J_h(z_1) \nu = 0, \quad x \in \partial \Omega \\
-J_h(z_2) \nu + \left( \frac{k_1 p_3 b_3}{D} + c_1 + \frac{k_1 k_2 p_3 w_2}{D} \right) z_1 - \left( c_2 + \frac{k_1 k_2 p_3 w_1}{D} \right) z_2 = 0, \quad x \in \partial \Omega \\
\partial z_1 z_2 = 0, \quad x \in \partial \Omega.
\]
Hence, using the notation introduced in Lemma 2, \((z_1, z_2)\) is a \(W^1_p\) solution of (24), (25) with
\[
\lambda = \min\{b_1, b_2\}, \quad a_0 = b_1 - \lambda, \quad \mu = 0, \quad \mu I = 0
\]
\[
a_{11} = k_1p_3b_3 \frac{D}{c_1} + k_1k_2p_3w_2 \frac{D}{c_1}, \quad a_{12} = c_2 + \frac{k_1k_2p_3w_1}{D},
\]
\[
a_{21} = c_1 + \frac{k_1k_2p_3w_2}{D}, \quad a_{22} = b_2 - \lambda + \frac{k_2p_3b_3}{D} + c_2 + \frac{k_1k_2p_3w_1}{D}.
\]
Since the nonnegativity of \(w_1, w_2\) ensures that assumption (23) is fulfilled we infer that \(z_1 = z_2 = 0\).

5 Proof of Theorem 2

Since the spaces \(W^1_p(\Omega)\) and \(W^2_q(\partial_1\Omega)\) are reflexive for \(1 < p < 2, 1 < q < \infty\) thus, owing to (7), there exists a sequence \((h_k)_{k=1}^{\infty} \subset (0, 1)\) such that \(\lim_{k \to \infty} h_k = 0\) and
\[
u_{1h_k} \to w_1 \quad \text{in} \quad W^1_p(\Omega), \quad (36a)
\]
\[
u_{2h_k} \to w_2 \quad \text{in} \quad W^2_q(\partial_1\Omega). \quad (36b)
\]
Now we claim that
\[
\partial_{x_2} w_1 = 0, \quad (37a)
\]
\[
u_{1h_k}(0, \cdot) \to w_1(0, \cdot) \quad \text{in} \quad L_q(\partial_1\Omega), \quad (37b)
\]
\[
u_{2h_k} \to w_2 \quad \text{in} \quad C(\overline{T}). \quad (37c)
\]
Indeed (37a) comes from (7). To prove (37b) fix any \(1 < q < \infty\), then choose \(s, p\) such that \(1 < p < 2, 1/p < s < 1, s - 2/p \geq -1/q\). Then \(W^1_p(\Omega)\) embeds compactly into \(W^s_p(\Omega)\), the trace operator maps \(W^s_p(\Omega)\) into \(W^{s-1/p}(\partial_1\Omega)\) and the latter space embeds continuously into \(L_q(\partial_1\Omega)\). Finally (37c) follows from compact embedding of \(W^2_q(\partial_1\Omega)\) into \(C(\overline{T})\). Choose \(v_1 \in C^1(\Omega), \ v_2 \in C^1(\overline{T})\), then
\[
\int_{\Omega} [\partial_{x_2} u_{1h_k} \partial_{x_1} v_1 + b_1 u_{1h_k} v_1] + \int_{\partial_1\Omega} [d \partial_{x_1} u_{2h_k} \partial_{x_1} v_2 - c_1 u_{1h_k} v_2] = p_1 v_1(0),
\]
\[
\int_{\partial_1\Omega} [c_1 H(u_{1h_k}, u_{2h_k}) u_{1h_k} v_1 - c_2 u_{2h_k} v_1 + (b_2 + c_2 H(u_{1h_k}, u_{2h_k}) v_2)] = 0.
\]
Using (36) and (37) we can pass to the limit with \(k \to \infty\) and identify that \((w_1, w_2) = (u_1^0, u_2^0)\) is a solution of (3). Finally notice that (3) follows from (36) and the fact that (3) has a unique solution, as was proved in (10).

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