Author's extended summary (autoreferat) of the dissertation "Mathematical analysis of morphogen transport models"

Marcin Małogrosz

1 The scientific aim of the dissertation

The aim of the dissertation is to analyse mathematically models of morphogen transport - a biological process responsible for cell differentiation and pattern formation in living organisms. We focus on models describing transport of morphogens Wingless (Wg) and Decapentaplegic (Dpp) which act in the imaginal wing discs of the Drosophila Melanogaster embryos. From the mathematical point of view both models are systems of reaction diffusion equations coupled with ordinary differential equations. For the case of morphogen Wg we analyse the model **[HKCS]** proposed by Hufnagel et al. in [13]. An interesting feature of this model is a nonlinear boundary condition including a Dirac Delta which is used to represent a point source of morphogen. Moreover it is assumed that morphogen substance may diffuse not only inside the domain but also on the part of its boundary. In [13] authors present a heuristic analysis of **[HKCS]** which is far from being mathematically rigorous.
For the case of Dpp we analyse the model **[LNW].B** proposed by Lander et al. in [21]. Our results are a generalisation to the domains of arbitrary dimension of the results obtained before by Krzyżanowski et al. in [16] .
One of the biggest problems encountered in modelling processes in life sciences is the selection of the domain to represent the space where the process occurs. It is natural to assume that the space under consideration is three dimensional, but this increases the cost of numerical integration of the system, and may disable the rigorous analytical analysis of qualitative properties of solutions of the model. From this point of view, it makes sense to investigate the behaviour of solutions of models considered for domains with lower dimensions. The main question that we answer in our dissertation is how do properties of solutions to model **[HKCS]** depend on the dimension of the domain which is used to represent a part of the tissue. The most significant result is a mathematically rigorous justification of the fact that the one dimensional version of the **[HKCS]** model can be obtained from the full two dimensional version by an appropriate limiting process in the evolutionary as well as in the stationary case. This process can be interpreted either as dimension reduction (the two dimensional domain of the full model is "ironed" to the interval) or as sending to infinity the flux of morphogen molecules in the direction perpendicular to the wing disc. Above result may be seen as an argument to justify that the one dimensional domain is sufficient to model the process. However the topology of convergence is to weak to exclude one qualitative difference in the behaviour of solutions

at the source point $x = 0$. Namely the concentration of morphogen in the **[HKCS].2D** model blows up at $x \to 0$ while it stays bounded in the case of one dimensional domain. Roughly speaking this phenomenon is a consequence of the fact that the Dirac Delta which is used to represent the point source of morphogen in both models, is a more singular distribution in dimension two than in dimension one.

2 Description of the process of morphogen transport

Morphogen transport 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 [34], 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 [11],[19] and [18]).
Recently various models consisting of PDE-ODE systems were proposed to describe morphogen transport. 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 [21], [17], [4], [30]). In [13] to model the transport of Wg its interaction with gypicans is taken into account. Those proteins located on the surface of the tissue have similar role to the receptors with the distinction that can pass the morphogen molecules from one to another by the 'bucket brigade' mechanism.
Let us point out that understanding the exact mechanism by which morphogen transport takes place is one of the most important goals of evolutionary biology.

3 Presentation of the mathematical models

We present two models **[LNW].B** and **[HKCS]** of the transport of morphogens Dpp and Wg in the imaginary wing disc of the fruit fly. Both models take into account diffusion of morphogen molecules and their reactions with receptors distributed on the cell surface. Model **[HKCS]** additionally accounts for reactions of morphogens with glypicans - special type of receptors which have an active role in the transport. Another feature which distinguish the models is that in **[HKCS]** the transport of morphogens takes place in the extracellular space as well as on the cell surfaces while in **[LNW].B** only the latter mechanism is present. Details are presented in the following sections.

3.1 The [HKCS] model

The model **[HKCS]** introduced by Hufnagel et al. in [13] describes the formation of the gradient of morphogen Wingless (Wg) in the imaginal wing disc of the Drosophila Melanogaster individual. Model **[HKCS]** has two counterparts - one and two dimensional,

depending on the dimensionality of the domain representing the imaginal wing disc. We denote these models **[HKCS].1D** and **[HKCS].2D** respectively. In mathematical terms **[HKCS].1D** is a system of two semilinear parabolic PDEs of reaction diffusion type coupled with three nonlinear ODEs posed on the interval $I^L = (-L, L)$, while **[HKCS].2D** consists of a linear parabolic PDE posed on rectangle $\Omega^{L,H} = (-L, L) \times (0, H)$ which is coupled via nonlinear boundary condition on $\partial_1\Omega^{L,H} = (-L, L) \times \{0\}$ with a semilinear parabolic PDE and three ODEs.

3.1.1 The [HKCS].2D model.

For $L, H > 0$, and $\infty \geq T > 0$ denote

$$
\begin{aligned}
I^L &= (-L, L),\ x_1 \in I^L,\ I^1 = I,\\
\Omega^{L,H} &= (-L, L) \times (0, H),\ x = (x_1, x_2) \in \Omega^{L,H},\ \Omega = \Omega^{1,1},\\
\partial_0\Omega^{L,H} &= \{-L, L\} \times [0, H] \cup (-L, L) \times \{H\},\ \partial_1\Omega^{L,H} = (-L, L) \times \{0\},\\
\partial\Omega^{L,H} &= \partial_1\Omega^{L,H} \cup \partial_0\Omega^{L,H},\ \Omega_T^{L,H} = (0, T) \times \Omega^{L,H},\ (\partial\Omega^{L,H})_T = (0, T) \times \partial\Omega^{L,H}.
\end{aligned}
$$

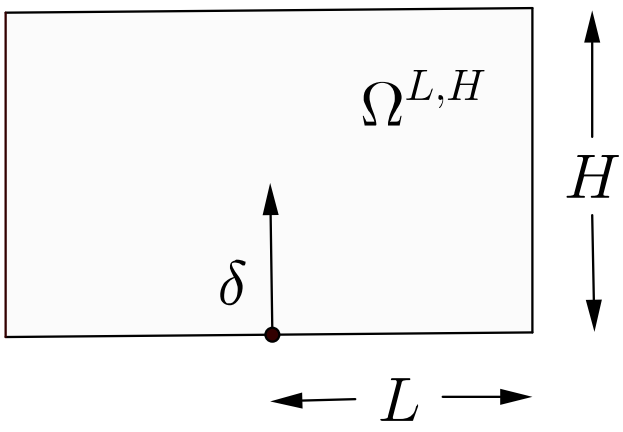

Figure 1: Graph of the domain $\Omega^{L,H}$. The arrow pointing towards the rectangle represents a point source of the morphogen (a Dirac Delta) on the boundary.

The domain $\Omega^{L,H}$ (see Figure 1) represents the imaginal wing disc of the Drosophila Melanogaster individual and the x_2 direction corresponds to the thickness of the disc, so that in practice H is much smaller than L. Let ν denote a unit outer normal vector to $\partial\Omega^{L,H}$ and let δ be a one dimensional Dirac Delta. Moreover denote by $\nabla = (\partial_{x_1}, \partial_{x_2})$ the gradient and by $\Delta = \partial_{x_1}^2 + \partial_{x_2}^2$ the Laplace operator. The model **[HKCS].2D** is a system which consists of one evolutionary PDE posed on $\Omega^{L,H}$, one evolutionary PDE and 3 ODEs posed on $\partial_1\Omega^{L,H}$:

[HKCS].2D

$$\partial_t W - D\Delta W = -\gamma W, \qquad (t,x) \in \Omega_T^{L,H} \tag{1a}$$
$$\partial_t W^* - D^* \partial_{x_1}^2 W^* = -\gamma^* W^* + \Xi_1 - \Xi_2, \qquad (t,x) \in (\partial_1 \Omega^{L,H})_T \tag{1b}$$
$$\partial_t R = -\Xi_2 - \Xi_3 - \alpha R + \Gamma, \qquad (t,x) \in (\partial_1 \Omega^{L,H})_T \tag{1c}$$
$$\partial_t R^* = \Xi_2 - \alpha^* R^*, \qquad (t,x) \in (\partial_1 \Omega^{L,H})_T \tag{1d}$$
$$\partial_t R_g^* = \Xi_3 - \alpha^* R_g^*, \qquad (t,x) \in (\partial_1 \Omega^{L,H})_T \tag{1e}$$

supplemented by the boundary conditions:

$$D\nabla W \nu = 0, \qquad (t,x) \in (\partial_0 \Omega^{L,H})_T \tag{2a}$$
$$D\nabla W \nu = -\Xi_1 - \Xi_2 + s\delta, \qquad (t,x) \in (\partial_1 \Omega^{L,H})_T \tag{2b}$$
$$\partial_{x_1} W^* = 0, \qquad (t,x) \in (\partial \partial_1 \Omega^{L,H})_T \tag{2c}$$

and initial conditions:

$$W(0) = W_0, \qquad x \in \Omega^{L,H} \tag{3a}$$
$$W^*(0) = W_0^*,\ R(0) = R_0,\ R^*(0) = R_0^*,\ R_g^*(0) = R_{g0}^*, \qquad x \in \partial_1 \Omega^{L,H} \tag{3b}$$

where

$$\Xi_1 = \Xi_1(G, W, W^*) = kGW - k'W^*,$$
$$\Xi_2 = \Xi_2(R, W, R^*) = k_R RW - k'_R R^*,$$
$$\Xi_3 = \Xi_3(R, W^*, R_g^*) = k_{Rg} RW^* - k'_{Rg} R_g^*.$$

In (1),(2) and (3) W (resp. G, R, W^*, R^* and R_g^*) denotes concentration of free morphogens Wg (resp. free glypicans Dlp, free receptors, morphogen-glypican complexes, morphogen-receptor complexes and morphogen-glypican-receptor complexes). It is assumed that W is located on $\Omega^{L,H}$ and is thus a function of (t, x_1, x_2), while other substances are present only on $\partial_1 \Omega^{L,H}$ and depend only on (t, x_1). Substances R, R^* and R_g^* may be internalised from the cell surface to its interior. The model takes into account association-dissociation mechanism of

- W and G with rates $k, k' : \Xi_1$,
- W and R with rates $k_R, k'_R : \Xi_2$,
- W^* and R with rates $k_{Rg}, k'_{Rg} : \Xi_3$.

Other terms of the system account for

- diffusion of W in $\Omega^{L,H}$ (resp. W^* on $\partial_1 \Omega^{L,H}$) with rate D (resp D^*): $-D\Delta W$ (resp. $-D^* \partial_{x_1}^2 W^*$),
- degradation of W in $\Omega^{L,H}$ (resp. W^* on $\partial_1 \Omega^{L,H}$) with rate γ (resp. γ^*): $-\gamma W$ (resp. $-\gamma^* W^*$),
- internalisation of R (resp. R^*, R_g^*) with rate α (resp. α^*, α^*) : $-\alpha R$ (resp. $-\alpha^* R^*, -\alpha^* R_g^*$),

- secretion of W with rate s from the source localised at the boundary point $x = 0 \in \partial_1\Omega^{L,H}$: $s\delta$,
- production of R: Γ.

For simplicity we assume that G and Γ are given and constant (in time and space).
In order to analyse the reduction of the dimension of the domain we introduce for $\epsilon > 0$ the **[HKCS].(2D,ϵ)** model, which is obtained from **[HKCS].2D** by changing $\Omega^{L,H}$ into $\Omega^{L,\epsilon H}$ and rescaling the source term for W in the boundary conditions (2):

[HKCS].(2D,ϵ)

$$\begin{aligned}
\partial_t W^\epsilon - D\Delta W^\epsilon &= -\gamma W^\epsilon, && (t,x) \in \Omega_T^{L,\epsilon H} && \text{(4a)}\\
\partial_t W^{*,\epsilon} - D^*\partial_{x_1}^2 W^{*,\epsilon} &= -\gamma^* W^{*,\epsilon} + \Xi_1^\epsilon - \Xi_2^\epsilon, && (t,x) \in (\partial_1\Omega^{L,\epsilon H})_T && \text{(4b)}\\
\partial_t R^\epsilon &= -\Xi_2^\epsilon - \Xi_3^\epsilon - \alpha R^\epsilon + \Gamma, && (t,x) \in (\partial_1\Omega^{L,\epsilon H})_T && \text{(4c)}\\
\partial_t R^{*,\epsilon} &= \Xi_2^\epsilon - \alpha^* R^{*,\epsilon}, && (t,x) \in (\partial_1\Omega^{L,\epsilon H})_T && \text{(4d)}\\
\partial_t R_g^{*,\epsilon} &= \Xi_3^\epsilon - \alpha^* R_g^{*,\epsilon}, && (t,x) \in (\partial_1\Omega^{L,\epsilon H})_T && \text{(4e)}
\end{aligned}$$

with boundary conditions

$$\begin{aligned}
\epsilon^{-1} D\nabla W^\epsilon \nu &= 0, && (t,x) \in (\partial_0\Omega^{L,\epsilon H})_T && \text{(5a)}\\
\epsilon^{-1} D\nabla W^\epsilon \nu &= -\Xi_1^\epsilon - \Xi_2^\epsilon + s\delta, && (t,x) \in (\partial_1\Omega^{L,\epsilon H})_T && \text{(5b)}\\
\partial_{x_1} W^{*,\epsilon} &= 0, && (t,x) \in (\partial\partial_1\Omega^{L,\epsilon H})_T && \text{(5c)}
\end{aligned}$$

and initial conditions

$$\begin{aligned}
W^\epsilon(0) &= W_0^\epsilon, && x \in \Omega^{L,\epsilon H}\\
W^{*,\epsilon}(0) = W_0^*,\ R^\epsilon(0) &= R_0,\ R^{*,\epsilon}(0) = R_0^*,\ R_g^{*,\epsilon}(0) = R_{g0}^*, && x \in \partial_1\Omega^{L,\epsilon H},
\end{aligned}$$

where

$$\begin{aligned}
\Xi_1^\epsilon &= \Xi_1^\epsilon(G, W^\epsilon, W^{*,^\epsilon}) = kGW^\epsilon - k'W^{*,\epsilon},\\
\Xi_2^\epsilon &= \Xi_2^\epsilon(R^\epsilon, W^\epsilon, R^{*,\epsilon}) = k_R R^\epsilon W^\epsilon - k'_R R^{*,\epsilon},\\
\Xi_3^\epsilon &= \Xi_3^\epsilon(R^\epsilon, W^{*,\epsilon}, R_g^{*,\epsilon}) = k_{Rg} R^\epsilon W^{*,\epsilon} - k'_{Rg} R_g^{*,\epsilon},\\
W_0^\epsilon(x_1, x_2) &= W_0(x_1, x_2/\epsilon).
\end{aligned}$$

Observe that **[HKCS].(2D,1)**=**[HKCS].2D**. Roughly speaking besides the well-posedness of **[HKCS]**, our main result is that

$$\lim_{\epsilon\to 0^+} \textbf{[HKCS].(2D,}\epsilon\textbf{)} = \textbf{[HKCS].1D}, \tag{6}$$

where **[HKCS].1D** is a simplified model analysed in Section 2.4. The precise meaning of the limit (6) is given in Theorem 2.3.

3.2 The [LNW].B model

For the case of morphogen Decapentaplegic (Dpp) acting in the wing disc of the Drosophila Melanogaster individuals, several models have been proposed in [21]. In this dissertation we are concerned with model **[LNW].B** (Model B [21] p.786). In mathematical terms the model is a system of two differential equations (PDE+ODE equipped with initial and boundary conditions), posed on an annular shaped domain $\Omega' \subset \mathbb{R}^n$, which represents a fragment of the wing tissue. The boundary of Ω' consists of two disjoint sets Γ'_N and Γ'_D. An example of a two dimensional domain Ω' is provided on Figure 2.
In the model movement of morphogen molecules (A) occurs by passive diffusion while being affected by reactions of reversible binding with receptors (C) and degradation of morphogen-receptor complexes (B). It is assumed that the total concentration of free and bounded receptors $B + C$ is constant and equal to R_{tot}. Morphogen is being delivered to the system by secretion from a source localised on Γ'_N.

[LNW].B

$$\partial_t A - D'\Delta A = k_{off}B - k_{on}A(R_{tot} - B), \qquad (t,x) \in (0,T) \times \Omega' \qquad (7a)$$
$$\partial_t B = k_{on}A(R_{tot} - B) - (k_{off} + k_{deg})B, \qquad (t,x) \in (0,T) \times \Omega' \qquad (7b)$$
$$D'\nabla A\nu = g', \qquad (t,x) \in (0,T) \times \Gamma'_N \qquad (7c)$$
$$A = 0, \qquad (t,x) \in (0,T) \times \Gamma'_D \qquad (7d)$$
$$A(0) = A_0,\ B(0) = B_0, \qquad x \in \Omega' \qquad (7e)$$

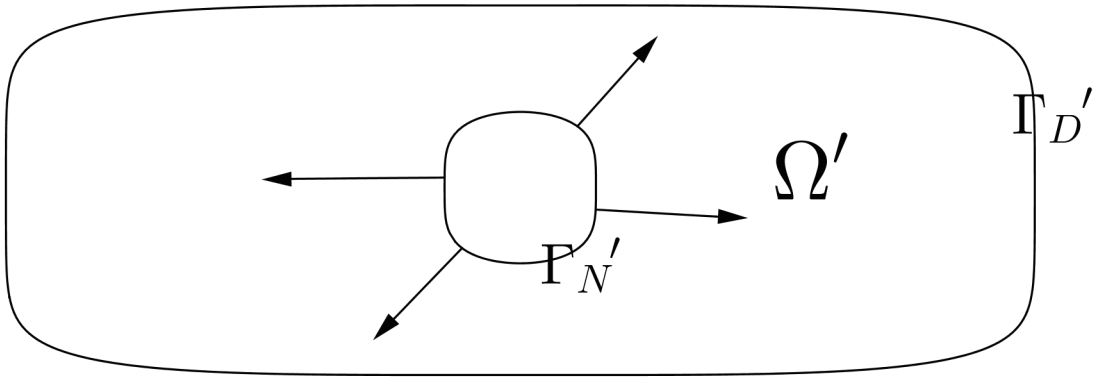

Figure 2: Graph of a two dimensional domain Ω'. The arrows pointing towards Ω' represent the secretion of morphogen from Γ'_N.

In case of a one dimensional domains a detailed mathematical analysis of this model was performed in [16] and [31]. In [16] the case $\Omega' = (0, L)$ is analysed. 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. In [31] 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 the unique steady state were proved.

4 The main results of the dissertation

4.1 The [HKCS] model

In Section 2.2 we analyse the evolution part of the **[HKCS].2D** model. Using analytic semigroup theory we prove its global well-posedness (Theorem 2.2) in appropriately chosen function setting and justify rigorously that the model **[HKCS].1D** can be obtained from **[HKCS].2D** through "ironing of the wing disc" - i.e. dimension reduction of the domain in the direction perpendicular to the surface of the wing disc (Theorem 2.3). However this does not exclude one qualitative difference in the behaviour of solutions at the source point $x = 0$. Namely the concentration of morphogen in the **[HKCS].2D** model blows up at $x \to 0$ while it stays bounded in the case of one dimensional domain. Roughly speaking this phenomenon is a consequence of the fact that the Dirac Delta is a more singular distribution in the dimension two than in dimension one. The main analytic problem stems from two factors: the lack of smoothing effect in the ODEs and the presence of the Dirac Delta in the boundary condition for the equation posed on $(-L, L) \times (0, H)$. We overcome this problem by introducing is Section 2.2.4 a new notion of solution - the M-mild solution which relates the system (4) to a system with regular source and lower regularity initial condition. Stationary problem for the **[HKCS].2D** is analysed in Section 2.3. We prove that there is a unique steady state (Theorem 2.4) which converges to the equilibrium of **[HKCS].1D** as $\epsilon \to 0$ (Theorem 2.5). We illustrate our result by performing numerical computations which show that the graph of the stationary solution to **[HKCS].2D** becomes homogeneous in the x_2 direction as $\epsilon \to 0$ (Figure 2.1). It is worth underlining that all our results are proved without imposing any artifficial conditions on the parameters which are present in the system.
Well-posedness (Theorem 2.7) and the existence of the unique stationary solution (Theorem 2.6) to model **[HKCS].1D** are established in Section 2.4.

4.2 The [LNW].B model

In Chapter 3 we examine model **[LNW].B** in the [16] 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 impose 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 (Theorem 3.1). Using theory of analytic semigroups and comparison principle arguments we show existence of classical global solutions (Theorem 3.2). We check that the Lyapunov functional, obtained in [16], 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 (Theorem 3.3).

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