XX Congreso de Ecuaciones Diferenciales y Aplicaciones
X Congreso de Matemática Aplicada
Sevilla, 24-28 septiembre 2007
(pp. 1–8)

Mathematical analysis of a model of Morphogenesis: steady states

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Keywords: Morphogens, reaction diffusion equations, stability of solutions

Resumen

We consider a simple mathematical model of distribution of morphogens (signaling molecules responsible for the differentiation of cells and the creation of tissue patterns) proposed by Lander, Nie and Wang in 2002. The model consists of a system of two equations: a PDE of parabolic type modeling the distribution of free morphogens and an ODE describing the evolution of bound receptors. Three biological processes are taken into account: diffusion, degradation and reversible binding. We present results concerning the steady states.

1. Introduction

From the beginning of the formation of the embryo, many different phenomena transform its cells. Some of these phenomena are local, as growth, but others, as differentiation or shapes of tissues or organs and its organization respond to global phenomena. That differentiation of the cell depends on its position in the embryo. The cell receives the information of its position by measuring the concentration of signaling molecules, named "morphogens". *Morphogenesis* (the creation "genesis" of shapes "morphe") has been studied from the early 20th century, but only in recent years, growth factors have been identified as morphogens.

Morphogens are synthesized at signaling localized sites and spread into the body creating gradients in the concentration of morphogen as it appears in the experimental data (a constant distribution of morphogens would create an homogeneous differentiation of cells). How the gradients arise is an unclear and controversial question and central issue in Development Biology. Theoretical and experimental scientists consider two main theories

to explain the formation of gradients of morphogens: diffusion theory, where morphogens are spread by diffusion through the extracellular matrix and the positional theory (see Kerszberg and Wolpert [4]) which suggests that morphogen propagation depends on the closeness of cell-to-cell positions, and morphogens are propagated along cell membranes and transferred between cells that are in contact.

Once the morphogens arrive to the cell surface they bind to receptors and other kind of molecules. The diffusion theory considers slow degradation of products and reversible binding (see Lander, Nie, Wang [5]) in contrast the positional theory does not consider degradation (see Kerszberg and Wolpert [4]).

Lander, Nie and Wan [5] studied numerically several mathematical models and focused on the *Drosophila* wing disc. They obtain (by using recent experimental data) that diffusive mechanisms of morphogen transport may produce gradients of morphogens and show that those mechanisms are much more plausible than the non-diffusive ones. They propose several mathematical models, one of them, the diffusion-reversible binding model with degradation, is the model which has been analyzed in the following sections (see also J.I. Tello [16].

Lander, Nie, Vargas and Wang [7] and Lander, Nie and Wang [6] proposed several models of differential equations. The models condsider a PDE of parabolic type to describe the evolution of morphogens and a set of ODE′s to model the receptor and the bound-receptor. They study the steady states and the linear stability of them under the action of a source in a region of the domain.

Merkin and Sleeman [14] have studied the steady states of the system proposed by Lander, Nie and Wan [5] with degradation and without it. They obtain approximated solutions under the assumption of constant concentration at the boundary.

Recently Merkin, Needham and Sleeman [13] have considered a mathematical model with diffusion and have included a chemosensitivity term to describe morphogen concentration. They have presented results on the existence and uniqueness of classical solutions and self-similarity. Their numerical simulations have showed periodic pulse solutions.

Lou, Nie and Wang [10] consider a model with two species of morphogens. The system consists of three PDE′s of parabolic type and one ODE. They study the steady states and numerical simulation for the evolution problem.

In this work we consider the case of diffusive transport of morphogens. In Section 2 we describe the mathematical model proposed by Lander, Nie and Wang [6]. Section 3 we present the mathematical results concerning the steady states. Details on the existence, uniqueness and stability of solutions of the evolution model may be found in J. I. Tello [16].

2. The mathematical model

Different models of distribution of morphogens have been introduced by several authors in the last decade. We study a simple mathematical model proposed by Lander, Nie and Wang [5] which is described below. They consider the evolution of Decapentaplegic (Dpp) one of the morphogens present in Drogshophilia larvae wing disc. The model simplifies the geometry of the wing disc considering a one-dimensional domain $\Omega := (0, \infty)$. We denote by L the morphogen Dpp (the lingand), by R the receptor per unit of extracellular space,

by LR the complex ligand-receptor and their respective concentrations by $[L]$, $[R]$ and $[LR]$. The processes, when the ligand L binds with a receptor R to form the complex LR and the reversal are expressed in the following formula

$$L + R \underset{\mathrm{k}_{off}}{\overset{\mathrm{k}_{on}}{\rightleftharpoons}} LR,$$

where k_{on} and k_{off} are the binding and dissociation rate constants. Then, the reaction occurs at rates

$$k_{on}[L][R], \quad \text{and} \quad k_{off}[LR].$$

We assume

$$[R] = R_{tot} - [LR], \tag{1}$$

where R_{tot} is the total receptor concentration per unit of extracellular space. Assumption [1] is biologically meaningful only for small intervals of time and reduces the number of equations simplifying the problem. For large intervals of time, degradation of $[R]$ and $[LR]$ has to be considered (see Lander, Nie, Vargas, Wan [7] and J.I. Tello [16]). As we explain in the previous section we consider linear diffusion of $[L]$ with diffusion constant d. Then, $[L]$ satisfies the following equation:

$$\frac{\partial}{\partial t}[L] - d\frac{\partial^2}{\partial x^2}[L] = -k_{on}R_{tot}[L] + k_{on}[L][LR] + k_{off}[LR], \quad x > 0,\ t > 0, \tag{2}$$

where

$$d \sim 10^{-11}M^2s^{-1}; \quad k_{on} \cdot R_{tot} \sim 10^{-2}s^{-1}; \quad k_{on} \sim 10^{6}M^{-1}s^{-1}; \quad k_{off} \sim 10^{-6}s^{-1}$$

(see Lander, Nie and Wang [6] and references there).
The equation governing the bound receptor dynamics does not include diffusion but the degradation of the complex is introduced in the model. Let k_{deg} be the degradation rate constant, then $[LR]$ satisfies the equation:

$$\frac{\partial}{\partial t}[LR] = k_{on}R_{tot}[L] - k_{on}[L][LR] - k_{off}[LR] - k_{deg}[LR], \quad t > 0, \tag{3}$$

where

$$k_{deg} \sim 2 \cdot 10^{-4}s^{-1}.$$

We consider that the morphogen is synthesized at $x = 0$ with rate k_{syn} and that the concentration of $[L]$ goes to 0 as x goes to infinity. Then the boundary conditions for $[L]$ are the following

$$\begin{aligned} &\tfrac{\partial}{\partial t}[L] = k_{syn} - k_{on}R_{tot}[L] + k_{on}[L][LR] + k_{off}[LR], \quad x = 0, \quad t > 0; \\ &\lim_{x\to\infty}[L] = 0, \quad t > 0; \end{aligned} \tag{4}$$

where

$$k_{syn} \sim 5 \cdot 10^{-8}$$

(see Lander, Nie, Wang [5]). The system (2)-(4) is completed with the initial data

$$[L] = [LR] = 0, \quad x > 0, \quad t = 0. \tag{5}$$

We introduce the dimensionless variables:

$$\tilde{t} := k_{on} R_{tot} t; \quad \tilde{x} := \left(\frac{k_{on} R_{tot}}{d}\right)^{1/2} x; \qquad u := \frac{k_{on}}{k_{off}}[L]; \qquad v := \frac{[LR]}{R_{tot}}$$

and the parameters

$$\mu := \frac{k_{deg}}{k_{off} R_{tot}}; \quad \lambda := \frac{k_{off}}{k_{on} R_{tot}}; \quad \nu := \frac{k_{syn}}{k_{off} R_{tot}}.$$

Dropping the tildes and replacing the new variables in equations [2]-[5] we get the dimensionless version of the model:

$$\frac{\partial u}{\partial t} - \frac{\partial^2}{\partial x^2} u = -u(1-v) + v, \quad x > 0, \ t > 0, \tag{6}$$

$$\frac{\partial v}{\partial t} = \lambda \left[u(1-v) - v\right] - \mu v, \quad x > 0, \ t > 0, \tag{7}$$

with boundary conditions

$$\frac{\partial u}{\partial t} = \nu - u(1-v) + v, \quad \text{at} \quad x = 0, \quad t > 0, \tag{8}$$

$$\lim_{x \to \infty} u(x,t) = 0, \quad t > 0, \tag{9}$$

and initial data:

$$u(x,0) = v(x,0) = 0, \qquad x \geq 0. \tag{10}$$

Through the paper, we assume for technical reasons in concordance to experimental data that

$$\frac{\mu}{\lambda} > \nu > 0. \tag{11}$$

3. Steady states

We consider the solutions to

$$0 = \frac{\partial^2}{\partial x^2}\phi - \phi(1-\xi) + \phi; \quad x > 0, \tag{12}$$

$$0 = \lambda \left[\phi(1-\xi) - \xi\right] - \mu\xi, \quad x > 0, \tag{13}$$

satisfying the boundary conditions:

$$0 = \nu - \phi(1-\xi) + \xi, \quad \text{at } x = 0, \qquad \lim_{x \to \infty} \phi(x) = 0. \tag{14}$$

Lemma 1 *For every μ, λ, ν satisfying (11) there exists a unique solution (ϕ, ξ) to (12)-(14). Moreover, ϕ and ξ are monotone decreasing functions.*

Proof: Combining (13) with (14) we get

$$\xi(0) = \frac{\nu\lambda}{\mu} := \beta < 1,$$

which, when combined with (14), yields the boundary condition

$$\phi(0) = \frac{\nu + \beta}{1 - \beta} = \frac{\nu(\mu + \lambda)}{\mu - \nu\lambda} := \alpha > 0. \tag{15}$$

Because of (13), ξ is defined as follows

$$\xi = \frac{\phi}{\phi + 1 + \tilde{\mu}}, \quad \text{for} \quad \tilde{\mu} := \frac{\mu}{\lambda}.$$

Hence, (12) becomes

$$0 = \frac{\partial^2}{\partial x^2}\phi - \tilde{\mu}\frac{\phi}{\phi + 1 + \tilde{\mu}}; \quad x > 0. \tag{16}$$

Multiply equation (16) by $-(-\phi)_+$ (where $(\cdot)_+$ is the positive part function) and integrate by parts over $(0, \infty)$ to obtain, by (15), that $-(-\phi)_+ = 0$, i.e $\phi \geq 0$.
We introduce the system of ODE′s

$$\begin{aligned} \phi' &= \zeta; \\ \zeta' &= \tilde{\mu}\tfrac{\phi}{\phi+1+\tilde{\mu}}, \end{aligned} \tag{17}$$

satisfying the initial datum $\phi(0) = \alpha$ and

$$\lim_{x\to\infty} \phi(x) = \lim_{x\to\infty} \zeta(x) = 0. \tag{18}$$

We examine the phase portrait of (17) in the half plain $\phi \geq 0$. The unique equilibrium is $(0, 0)$ and has eigenvalues $\pm\sqrt{\tilde{\mu}}$, so that $(0, 0)$ is a saddle point.
Notice that:

- $\phi' > 0$, $\zeta' > 0$ for $\phi > 0$, $\zeta > 0$;
- $\phi' < 0$, $\zeta' > 0$ for $\phi > 0$, $\zeta < 0$;
- $\phi' < 0$, $\zeta' < 0$ for $\phi < 0$, $\zeta < 0$;
- $\phi' > 0$, $\zeta' < 0$ for $\phi < 0$, $\zeta > 0$;
- $\phi' > 0$, $\zeta' = 0$ for $\phi = 0$, $\zeta > 0$;
- $\phi' = 0$, $\zeta' > 0$ for $\phi > 0$, $\zeta = 0$;
- $\phi' < 0$, $\zeta' = 0$ for $\phi = 0$, $\zeta < 0$;
- $\phi' = 0$, $\zeta' < 0$ for $\phi < 0$, $\zeta = 0$,

and so there exists a unique orbit which may provide a solution to (17) satisfying

$$\lim_{x\to\infty} \phi(x) = 0.$$

We denote by $\gamma = (\gamma_1, \gamma_2)$ this orbit. To conclude the proof we have to prove that γ intersects with $\phi = \alpha$.
Multiply (17) by (ϕ, ζ) to obtain

$$\phi\phi' = \zeta\phi,$$

$$\frac{1}{2}(\zeta^2)' = \tilde{\mu}\frac{\zeta\phi}{\phi + 1 + \tilde{\mu}},$$

which implies

$$\frac{1}{2}(\zeta^2)' = \tilde{\mu}\frac{\phi\phi'}{\phi + 1 + \tilde{\mu}},$$

and so

$$\frac{d}{dx}\left(\frac{1}{2}\zeta^2 - \tilde{\mu}\phi - \tilde{\mu}\ln(\phi + 1 + \tilde{\mu})\right) = 0,$$

i.e.

$$\frac{1}{2}\zeta^2(x) - \tilde{\mu}\phi(x) - \tilde{\mu}\ln(\phi(x) + 1 + \tilde{\mu}) = const. \tag{19}$$

Since γ belongs to the region $\phi > 0$, $\zeta < 0$; there are no periodic orbits and the unique equilibrium is $(0, 0)$ we have that

$$\lim_{x\to-\infty} |\gamma| = \infty. \tag{20}$$

(19) and (20) imply that

$$\lim_{x\to-\infty} \gamma_1 = \infty, \qquad \lim_{x\to-\infty} \gamma_2 = -\infty,$$

then, for every $\alpha > 0$, γ intersect the line $\phi = \alpha$ and so there exists a unique solution to (12), (13).

Lemma 2 *There exists a unique solution ϕ to (16) satisfying the boundary condition $\phi(0) = a$, for $a \in (0, \alpha]$. Moreover, for every $a \in (0, \alpha]$, ϕ_a is a monotone decreasing function of x.*

The proof is similar to that of Lemma 1, therefore we omit the details.
We denote by ϕ_a the solution to (16) satisfying $\phi(0) = a > 0$, then

Lemma 3 *$\phi_a \in C^{2,\alpha}(\Omega) \cap H^1(\Omega) \cap L^p(\Omega)$ for $1 \le p \le \infty$ and*

$$\lim_{a\to\alpha} \int_0^\infty |\phi - \phi_a| dx = 0.$$

Proof: By (19) we deduce that

$$|\phi_a'(0)|^2 = 2(\tilde{\mu}(a + ln(a + 1 + \tilde{\mu}))) + const < \infty,$$

which combined with the fact $\phi > 0$ (see Lemma 1) we have $\phi_a' \leq const$. Multiply (16) by ϕ_a^p and integrate over $(0, \infty)$ to obtain

$$\phi_a \in L^p(\Omega) \cap H^1(\Omega), \quad \text{for } 1 \leq p < \infty.$$

$\phi_a \in L^\infty(\Omega)$ is a consequence of the monotonicity of Φ_a, then

$$0 < \phi_a \leq a.$$

Since $\phi_a \in W^{1,\infty}(\Omega) \cap H^1(\Omega)$ we have that $\phi_a \in C^{0,\delta}(\overline{\Omega})$ and then $\frac{d^2}{dx}\phi_a \in C^{0,\alpha}(\Omega)$ which implies $\phi_a \in C^{2,\alpha}(\overline{\Omega})$.
Let x_a be defined as the unique point in $(0, \infty)$ such that $\phi(x_a) = a$ (i.e. $x_a := \phi^{-1}(a)$). Notice that

$$\lim_{a \to \alpha} x_a = 0, \tag{21}$$

and (by uniqueness of solutions) we have that

$$\phi_a(x) = \phi(x + x_a).$$

Then,

$$\int_0^\infty |\phi - \phi_a| \, dx = \int_0^\infty \phi \, dx - \int_0^\infty \phi_a \, dx = \int_0^\infty \phi \, dx - \int_{x_a}^\infty \phi \, dx =$$
$$\int_0^{x_a} \phi \, dx \leq x_a \alpha.$$

Taking limits when $a \to \alpha$ in the above equation, and by using (21) we obtain

$$\lim_{a \to \alpha} \int_0^\infty |\phi - \phi_a| \, dx = 0,$$

which ends the proof.

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