Asymptotic Phases in a Cell Differentiation Model

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Abstract

T cells of the immune system, upon maturation, differentiate into either Th1 or Th2 cells that have different functions. The decision to which cell type to differentiate depends on the concentrations of transcription factors T-bet (x_1) and GATA-3 (x_2). The population density of the T cells, $\phi(t, x_1, x_2)$, satisfies a conservation law $\partial\phi/\partial t + (\partial/\partial x_1)(f_1\phi) + (\partial/\partial x_2)(f_2\phi) = g\phi$ where f_i depends on (t, x_1, x_2) and, in a nonlinear nonlocal way, on ϕ. It is proved that, as $t \to \infty$, $\phi(t, x_1, x_2)$ converges to a linear combination of 1,2, or 4 Dirac measures. Numerical simulations and their biological implications are discussed.

keywords: Cell differentiation, Th1/Th2 cells, conservation law, multistationary, integro-differential equation, transcription factors

1 Introduction

The development of a multicellular organism from a single fertilized egg cell to specialized cells depends on programs of gene expression. Following the initial stage of cell determination is a maturation process called differentiation by which cells acquire specific recognizable phenotypes and functions. In particular, the T lymphocytes of the immune system, upon maturation, differentiate into either Th1 or

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Th2 cells that have different functions. The decision to which of the cell type to differentiate depends on the concentration of transcription factors T-bet (x_1) and GATA-3 (x_2). If x_1 is high (low) and x_2 is low (high), the T cell will differentiate into Th1 (Th2).

A mathematical model by Yates et. al. [15] describes the differentiation process in terms of two differential equations

$$\frac{dx_i}{dt} = f_i(t, x_1, x_2, \phi) \quad (i = 1, 2) \tag{1.1}$$

where $\phi(t, x_1, x_2)$ is the population density of cells with concentration (x_1, x_2) at time t; ϕ satisfies the conservation of mass law

$$\frac{\partial \phi}{\partial t} + \frac{\partial}{\partial x_1}(f_1\phi) + \frac{\partial}{\partial x_2}(f_2\phi) = g\phi, \tag{1.2}$$

where g is the growth rate. Here $f_i(t, x_1, x_2, \phi)$ is a nonlinear, nonlocal function of $\phi(t, x_1, x_2)$.

In this paper we analyze the asymptotic behaviour of $\phi(t, x_1, x_2)$ as $t \to \infty$. We prove that

$$\phi(t, x_1, x_2) \to \sum \omega_j \delta_{(\overline{a}_1^j, \overline{a}_2^j)} \quad \text{as} \quad t \to \infty \tag{1.3}$$

where the limit is a linear combination of Dirac measures at $(\overline{a}_1^j, \overline{a}_2^j)$, and the number of terms in the linear combination is 1, 2 or 4, depending on the parameters which occur in the definition of the f_i. Conservation laws of the form (1.2), but with very different velocity terms (f_1, f_2), were considered in [6](Chap. 3), [7], [8], [16] and [9](Chap.3), and some asymptotic estimates were derived in [6], [7], [9]. A theoretical study of bistable switches appeared in [3]. An analytic approach in studying multistationary dynamics for neural networks was reported in [2], [12], [14]. We finally note that mathematical models of differentiation of T cell and other cells appeared in [4], [5] and [13], respectively; see also [1](Chap.9).

2 The Mathematical Model

Lymphocytes are white blood cells that play important roles in the immune system. T cells and B cells are two major types of lymphocytes. B cells produce antibodies against pathogens while T cells are involved in autoimmunity. Th lympocytes represent a subtype of T cells that are identified by the presence of surface antigens called

CD4; they are referred to as $CD4^+$ T cells. Other subtypes of T cells include cytotoxic T cells ($CD8^+$) and regulatory T cells. Th cells are the most numerous of the T cells in a healthy person. After an initial antigenic stimulation, Th lymphocytes differentiate into either one of two distinct types of cells called Th1 and Th2. Th1 cells make IFNγ that combat intracellular pathogens, and this immune response, if abnormal, is associated with inflammatory and autoimmune diseases. Th2 cells produce cytokines that activate B cells to produce antibodies against extracellular pathogens; this response, if abnormal, is associated with allergies such as asthma. Whether a precurser Th cell (henceforth to be denoted by Th0) becomes Th1 or Th2 depends on 'polorizing' signals.

The Yates et. al. [15] model of Th differentiation is based on the interaction of two transcription factors, T-bet and GATA-3. High protein level of T-bet or GATA-3 corresponds to the Th1 phenotype or the Th2 phenotype. We shall denote by S_1 and S_2 the Th1 and Th2 polarizing cytokines, and by x_1 and x_2 the concentrations of T-bet and GATA-3, respectively, in a Th0 cell. Then the dynamics of x_1 and x_2 is described by

$$\frac{dx_1}{dt} = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1}{\rho_1 + S_1}) \cdot \frac{1}{1 + x_2/\gamma_2} + \beta_1, \tag{2.1}$$

$$\frac{dx_2}{dt} = -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2}{\rho_2 + S_2}) \cdot \frac{1}{1 + x_1/\gamma_1} + \beta_2. \tag{2.2}$$

The first term on the right-hand side of each equation represents the rate of protein degradation. The last term β_i is the constant basal rate of protein synthesis. The autoactivation rate of protein x_i is represented by the term

$$\alpha_i \frac{x_i^n}{k_i^n + x_i^n}$$

where n is the Hill exponent that tunes the sharpness of the activation switch. The contribution of external signaling to the rate of growth in x_i is given by the term

$$\sigma_i \frac{S_i}{\rho_i + S_i}.$$

The cross-inhibition between x_1 and x_2 occurs at both the autoactivation level and external (membrane) signaling level, and is represented by the cross-inhibition factors

$$\frac{1}{1 + x_i/\gamma_i}.$$

The parameter γ_i represents the value of x_i at which the ratio of production of x_j, $i \neq j$, is halved (due to the combined autoactivation and external signaling).

We denote by $\phi(t, x_1, x_2)$ the population density of CD4$^+$ T cells with concentration (x_1, x_2) at time t. Then the total levels of expression of T-bet and GATA-3, at time t in the cell population are given, respectively, by

$$\int x_i \phi(t, x_1, x_2) dx_1 dx_2, \;\; i = 1, 2.$$

If we denote by $C_i(t)$ the exogenous (non-T cell) signals that stimulate T-bet and GATA-3 expression, then the total signal S_i is given by

$$S_i(t) = \frac{C_i(t) + \int x_i \phi(t, x_1, x_2) dx_1 dx_2}{\int \phi(t, x_1, x_2) dx_1 dx_2}, \;\; i = 1, 2. \tag{2.3}$$

Here, a normalization by total cell numbers is adopted to impose the limitation of access to cytokines due to cell crowding. The evolution of the population density is then derived from the equation of continuity, or mass conservation law:

$$\frac{\partial \phi}{\partial t} + \frac{\partial}{\partial x_1}(f_1 \phi) + \frac{\partial}{\partial x_2}(f_2 \phi) = g\phi, \tag{2.4}$$

where

$$f_1(x_1, x_2, S_1(t)) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1(t)}{\rho_1 + S_1(t)}) \cdot \frac{1}{1 + x_2/\gamma_2} + \beta_1, \tag{2.5}$$

$$f_2(x_1, x_2, S_2(t)) = -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2(t)}{\rho_2 + S_2(t)}) \cdot \frac{1}{1 + x_1/\gamma_1} + \beta_2. \tag{2.6}$$

In [15], the extrinsic and intrinsic cytokine interactions during the differentiation process were described in detail. Several numerical simulations have been made there to illustrate the changes of percentage of population under varying magnitudes of stimulus. Switches of population between Th0 to Th2 (high GATA-3) or from Th1 (high T-bet) to Th0, and then to Th2, under various levels of stimulus by extrinsic cytokines IL4 and IL12 were demonstrated.

The primary aim of the present paper is to analyze the behavior of the dynamical system (2.1)-(2.2) and the associated conservation law (2.4). We prove that when the parameters in (2.1)-(2.2) belong to a well defined regime $P_i, 1 \leq i \leq 6$, the solution $\phi(t, x_1, x_2)$ will tend to 1-peak Dirac measure if $i = 1$, 2-peak Dirac measures if $i = 2, 3, 4, 5$ and 4-peak Dirac measure if $i = 6$. We use numerical simulation to examine the intermediate behavior of $\phi(t, x_1, x_2)$, and to draw biological implications.

Note that (2.4) is associated with the velocity field described by

$$\frac{dx_1(t)}{dt} = f_1(x_1(t), x_2(t), S_1(t)), \tag{2.7}$$

$$\frac{dx_2(t)}{dt} = f_2(x_1(t), x_2(t), S_2(t)). \tag{2.8}$$

We consider (2.4) on a (closed) domain

$$\Omega = [0, A_1] \times [0, A_2]$$

which is an attracting set for (2.7)-(2.8); for convenience, we choose

$$A_i = \frac{\alpha_i + \sigma_i + \beta_i}{\mu}, \;\; i = 1, 2, \tag{2.9}$$

and assume that

$$\phi(0, x_1, x_2)|_{\partial\Omega} = 0.$$

Then

$$\phi(t, x_1, x_2)|_{\partial\Omega} = 0 \quad \text{for all} \quad t > 0.$$

Assuming that $g = g(t)$, and setting $G(t) = \int_0^t g(s)ds$,

$$\psi(t, x_1, x_2) = e^{-G(t)}\phi(t, x_1, x_2),$$

we can replace (2.4) by

$$\frac{\partial\psi}{\partial t} + \frac{\partial}{\partial x_1}(f_1\psi) + \frac{\partial}{\partial x_2}(f_2\psi) = 0, \tag{2.10}$$

with

$$S_i(t) = \frac{C_i(t)e^{-G(t)}}{N_0} + \frac{\int x_i\psi(t, x_1, x_2)dx_1dx_2}{N_0}, \tag{2.11}$$

where N_0 is the initial total population and the integral is taken over Ω.

Let $\Phi(t, x_1, x_2)$ be the solution map (flow map) of (2.7)-(2.8) and let $\Omega(t) = \Phi(t, \Omega)$. Then the transport equation (2.10) yields

$$\frac{d}{dt}\int_{\Omega(t)} \psi(t, x_1, x_2)dx_1dx_2 = 0.$$

Furthermore, if $\Omega(t) \to (\bar{a}_1, \bar{a}_2)$ as $t \to \infty$ then for any continuous function $h(x_1, x_2)$,

$$\int_\Omega h(x_1, x_2)\psi(t, x_1, x_2)dx_1dx_2 \to h(\bar{a}_1, \bar{a}_2)N_0 \text{ as } t \to \infty,$$

i.e.,

$$\psi(t, x_1, x_2) \to N_0 \delta_{(\bar{a}_1, \bar{a}_2)} \text{ in measure as } t \to \infty. \tag{2.12}$$

In the subsequent sections we study the behavior of the solution of (2.7), (2.8) in conjunction with the behavior of $\Omega(t)$.

In section 3 we prove existence and uniqueness for the initial value problem of equation (2.10). In sections 4-8, we establish the assertion (1.3) under some assumptions on the parameters of (2.5)-(2.6). Numerical simulation illustrating the dynamics of the single cell model and the formation of peak-solutions as t increases are given in section 9. In the concluding section 10, we give a biological interpretation of our results.

3 Existence and Uniqueness

We shall prove the existence and uniqueness for equation (2.10) with initial values

$$\psi|_{t=0} = \psi_0(x_1, x_2) \quad \text{in} \quad \Omega \tag{3.1}$$

where

$$\begin{gathered} \psi_0 \text{ vanishes on } \partial\Omega, \int_{\Omega(0)} \psi_0 = N_0, \\ \psi_0, \nabla\psi_0 \text{ are continuous functions in } \Omega, \\ G(t) \text{ and } C_i(t) \text{ are continuous functions for } t \geq 0. \end{gathered} \tag{3.2}$$

Set $f = (f_1, f_2)$ and write

$$f = f(t, \mathbf{x}, \psi) = F(\mathbf{x}) + G(t, \mathbf{x}, \psi(t, \cdot)). \tag{3.3}$$

The characteristic curves of (2.10) are given by

$$\frac{d\xi_{t,\mathbf{x}}}{d\tau} = F(\xi_{t,\mathbf{x}}(\tau)) + G(t, \xi_{t,\mathbf{x}}(\tau), \psi(\tau, \cdot)), \quad 0 < \tau < t, \tag{3.4}$$

$$\xi_{t,\mathbf{x}}(t) = \mathbf{x}. \tag{3.5}$$

Note that if $x \in \Omega$ then $\xi_{t,\mathbf{x}}(\tau) \in \Omega$ for all $0 \leq \tau < t$.

We introduce the space $C^1(\Omega)$ of continuous functions $\psi(\mathbf{x})$ with norm

$$||\psi|| = \max_{\mathbf{x} \in \Omega} (|\psi(\mathbf{x})| + |\nabla\psi(\mathbf{x})|)$$

and the space $C^1_T(\Omega)$ of continuous functions $\psi(t, \mathbf{x})$ in $\Omega_T = \Omega \times [0, T]$ with continuous derivative $\nabla_{\mathbf{x}}\psi(t, \mathbf{x})$ in Ω_T, and with norm

$$||\psi||_T = \max_{\mathbf{x} \in \Omega, 0 \leq t \leq T} (|\psi(t, \mathbf{x})| + |\nabla_{\mathbf{x}}\psi(t, \mathbf{x})|).$$

Theorem 3.1. Under the condition (3.2) there exists a unique solution of (2.10), (3.1), with f_i, S_i defined by (2.5), (2.6), (2.11), for all $t > 0$ such that $\psi \in C^1_{T_0}(\Omega)$ for all $T_0 > 0$.

Proof. Take any constant M, $M > ||\psi_0||$, and introduce the set

$$X_M = \left\{\psi \in C^1_T(\Omega), ||\psi||_T \leq M\right\}$$

for T small to be determined. We define a mapping W from X_M into itself and prove that it has a unique fixed point. Given any $\psi \in X_M$, set $\bar{\psi} = W(\psi)$ where $\bar{\psi}$ is the solution of

$$\frac{\partial \bar{\psi}}{\partial t} + f(t, \mathbf{x}, \psi) \cdot \nabla_{\mathbf{x}} \bar{\psi} = -(\nabla_{\mathbf{x}} \cdot f(t, \mathbf{x}, \psi))\bar{\psi}, \quad \mathbf{x} \in \Omega,\ 0 < t < T, \tag{3.6}$$

$$\bar{\psi}|_{t=0} = \psi_0, \quad \mathbf{x} \in \Omega. \tag{3.7}$$

Using the representation

$$\bar{\psi}(t, \mathbf{x}) = \bar{\psi}(\xi_{t,\mathbf{x}}(0)) - \int_0^t \left[\nabla_{\mathbf{x}} \cdot f(\tau, \xi_{t,\mathbf{x}}(\tau), \psi(\tau, \cdot))\right] \bar{\psi}(\tau, \xi_{t,\mathbf{x}}(\tau)) d\tau, \tag{3.8}$$

we get

$$\max_{\mathbf{x} \in \Omega, 0 \leq t \leq T} |\psi(t, \mathbf{x})| \leq |\psi_0|_{L^\infty(\Omega)} + CT$$

where C is a constant which is actually independent of M.

Differentiating (3.6) with respect to x_i and applying the preceding argument, we obtain a similar bound on $\frac{\partial \bar{\psi}}{\partial x_i}$, so that

$$\left\|\bar{\psi}\right\|_T \leq \|\psi_0\| + CT < M$$

if T is small enough. Hence W maps X_M into X_M. We next claim that W is a contraction. Indeed, given two functions ψ_1, ψ_2 in X_M, denote by $\xi^1_{t,\mathbf{x}}$, $\xi^2_{t,\mathbf{x}}$, the corresponding characteristic curves, and set $\bar{\psi}_i = W(\psi_i)$, $\psi = \psi_1 - \psi_2$, $\bar{\psi} = \bar{\psi}_1 - \bar{\psi}_2$. By ODE theory and (3.3),

$$|\xi^1_{t,\mathbf{x}}(\tau) - \xi^2_{t,\mathbf{x}}(\tau)| \leq CT[\max_{\mathbf{x} \in \Omega, 0 \leq t \leq T} |\psi(t, \mathbf{x})|]. \tag{3.9}$$

Using the representation (3.8) for each $\bar{\psi}_i$, we deduce that

$$\max_{\mathbf{x} \in \Omega, 0 \leq t \leq T} |\bar{\psi}(t, \mathbf{x})| \leq CT \left[\max_{\mathbf{x} \in \Omega, 0 \leq t \leq T} |\psi(t, \mathbf{x})|\right].$$

Similarly we obtain a bound on $\nabla\bar{\psi}(t,\mathbf{x})$ by differentiating (3.6) with respect to x_i, applying the previous argument, and using (3.9). Hence

$$\|\bar{\psi}\|_T \le CT \|\psi\|_T ,$$

so that W is a contraction if T is small enough, and thus existence and uniqueness for (2.10), (3.1) follows for $0 \le t \le T$.

We can extend the solution step-by-step to all $t > 0$ provided we can derive an *a priori* bound, say

$$\|\psi\|_{T_0} \le C + C\exp(\alpha T_0) \quad \text{for all } T_0 > 0 \tag{3.10}$$

where C, α are constants. From (3.8) with $\bar{\psi} = \psi$ and (3.3) we get, by Gronwall's inequality,

$$\sup_{\mathbf{x}\in\Omega} |\psi(t,\mathbf{x})| \le C + Ce^{\alpha t}.$$

Similarly, by differentiating (3.6) with respect to x_i, we derive

$$\sup_{\mathbf{x}\in\Omega} |\nabla\psi(t,\mathbf{x})| \le C + Ce^{\alpha t}.$$

Hence (3.10) holds and the proof of Theorem 3.1 is complete. □

4 Single cell

We consider the single-cell model (2.1)-(2.2) in which S_1, S_2 are regarded as non-negative constants. As we shall see, under some regimes of the parameter space, the system admits monostable, bistable, and quadstable phases. In order to study the dynamics of a single cell, we introduce upper bounds $\hat{f}_i$ for the functions f_i in (2.5), (2.6):

$$\hat{f}_i(x_i) = -\mu x_i + (\alpha_i \frac{x_i^n}{k_i^n + x_i^n} + \sigma_i \frac{S_i}{\rho_i + S_i}) + \beta_i, \quad i = 1, 2. \tag{4.1}$$

Then $\hat{f}_i$ has the following properties:

$$\hat{f}_i(0) > 0,\ \hat{f}_i'(0) < 0, \hat{f}_i(x_i) < 0 \text{ for } A_i \le x_i < \infty. \tag{4.2}$$

Let $B_i \in (0, A_i)$ be greater than the largest zero of $\hat{f}_i, i = 1, 2$. We also introduce lower bounds $\check{f}_i$ for f_i:

$$\check{f}_1(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1}{\rho_1 + S_1}) \cdot \frac{1}{1 + B_2/\gamma_2} + \beta_1, \qquad (4.3)$$

$$\check{f}_2(x_2) = -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2}{\rho_2 + S_2}) \cdot \frac{1}{1 + B_1/\gamma_1} + \beta_2. \qquad (4.4)$$

Indeed,

$$\check{f}_1(x_1) \le f_1(x_1, x_2), \text{ for } (x_1, x_2) \in [0, A_1] \times [0, B_2],$$
$$\check{f}_2(x_2) \le f_2(x_1, x_2), \text{ for } (x_1, x_2) \in [0, B_1] \times [0, A_2].$$

Note that

$$\check{f}_i(0) > 0, \check{f}_i'(0) < 0, \check{f}_i(B_i) < 0 \text{ for } \ i = 1, 2. \qquad (4.5)$$

The functions $\hat{f}_i, \check{f}_i$, extended to $x_i \in (A_i, \infty)$ by the right-hand sides of (4.3), (4.4), have a unique inflection point $\tilde{\xi}_i$, given by

$$\tilde{\xi}_i = k_i (\frac{n-1}{n+1})^{1/n},$$

where the slopes of $\hat{f}_i$ and of $\check{f}_i$ are maximal. Therefore, if $\check{f}_i'(\tilde{\xi}_i) < 0$, then $\check{f}_i'(x_i)$ cannot take positive values. Set

$$\tilde{n} = (n+1)^{1+1/n} (n-1)^{1-1/n} / 4n.$$

We consider the following parameter regimes:
Condition (M1):

$$\mu > \frac{\alpha_1 \tilde{n}}{k_1},$$

Condition (M2):

$$\mu > \frac{\alpha_2 \tilde{n}}{k_2},$$

Condition (B1):

$$\mu < \frac{\alpha_1 \tilde{n}}{k_1} \cdot \frac{1}{1 + B_2/\gamma_2},$$

Condition (B2):

$$\mu < \frac{\alpha_2 \tilde{n}}{k_2} \cdot \frac{1}{1 + B_1/\gamma_1}.$$

Condition (Mi) is equivalent to the inequality $\hat{f}_i'(\tilde{\xi}_i) < 0$, $i = 1, 2$. Under this condition both $\hat{f}_i$ and $\check{f}_i$ are strictly decreasing functions and have a unique zero.

Condition (Bi) is equivalent to $\check{f}_i'(\tilde{\xi}_i) > 0$ and, in that case, if $\tilde{\xi}_i < A_i$ then each $\hat{f}_i$, $\check{f}_i$ has two critical points. Let $\hat{p}_i^{\rm m}, \hat{p}_i^{\rm M}$ (respectively $\check{p}_i^{\rm m}, \check{p}_i^{\rm M}$) be the local minimum and maximum of $\hat{f}_i$ (respectively $\check{f}_i$). Then, $\check{p}_i^{\rm m} < \check{p}_i^{\rm M}$, $\hat{p}_i^{\rm m} < \hat{p}_i^{\rm M}$, and

$$\check{f}_i(\check{p}_i^{\rm m}) < \hat{f}_i(\hat{p}_i^{\rm m}), \check{f}_i(\check{p}_i^{\rm M}) < \hat{f}_i(\hat{p}_i^{\rm M}).$$

We shall consider only the following cases as illustrated in Figure 1:
(Note that if $\tilde{\xi}_i > A_i$ for $i = 1$ or $i = 2$, then only case (Mi) can occur for this i.)
(a) (Mi) holds for $i = 1, 2$;
(b) (Bi) holds and $\hat{f}_i(\hat{p}_i^{\rm M}) < 0$ for $i = 1, 2$;
(c) (Bi) holds and $\check{f}_i(\check{p}_i^{\rm m}) > 0$ for $i = 1, 2$;
(d) (Bi) holds and $\hat{f}_i(\hat{p}_i^{\rm m}) < 0,\ \check{f}_i(\check{p}_i^{\rm M}) > 0$ for $i = 1, 2$.

In cases (a), (b), and (c), $\hat{f}_i$ and $\check{f}_i$ have a unique zero denoted by $\hat{a}_i$ and $\check{a}_i$, respectively. In case (d), $\hat{f}_i$ and $\check{f}_i$ have three zeros, denoted by $(\hat{a}_i, \hat{b}_i, \hat{c}_i)$ and $(\check{a}_i, \check{b}_i, \check{c}_i)$, respectively.

We shall establish the following dynamical phases for (2.1)-(2.2):

Monostable (MS): low x_1-low x_2; low x_1-high x_2; high x_1-low x_2;
high x_1-high x_2 states;

Bistable (BS-ll,lh): low x_1-low x_2 state and low x_1 - high x_2 state;
(BS-ll,hl): low x_1-low x_2 state and high x_1-low x_2 state;
(BS-hl,hh): high x_1-low x_2 state and high x_1 - high x_2 state;
(BS-lh,hh): low x_1-high x_2 state and high x_1-high x_2 state;

Quadstable (QS): low x_1-low x_2 state, high x_1 - low x_2 state,
low x_1 - high x_2 state, and high x_1 - high x_2 state.

These notions of 'low' and 'high' are not directly related to the magnitudes of x_1 and x_2. It will be shown that there exist six parameter regimes so that (2.1)-(2.2), with parameters in each of these regimes admit, respectively, a unique stable equilibrium; two stable equilibria and one unstable equilibrium; and four stable equilibria and five unstable equilibria. Moreover, every solution which is initially not an unstable equilibrium point converges to one of the stable equilibria as time tends to infinity.

In order to guarantee the convergence to equilibrium, we impose the following condition:

$$\frac{(\alpha_1 + \sigma_1)}{\gamma_2} \cdot \frac{(\alpha_2 + \sigma_2)}{\gamma_1} < |\mu - \frac{\alpha_1 \tilde{n}}{k_1}| \cdot |\mu - \frac{\alpha_2 \tilde{n}}{k_2}|. \tag{4.6}$$

Theorem 4.1. Assume that condition (4.6) holds. Then

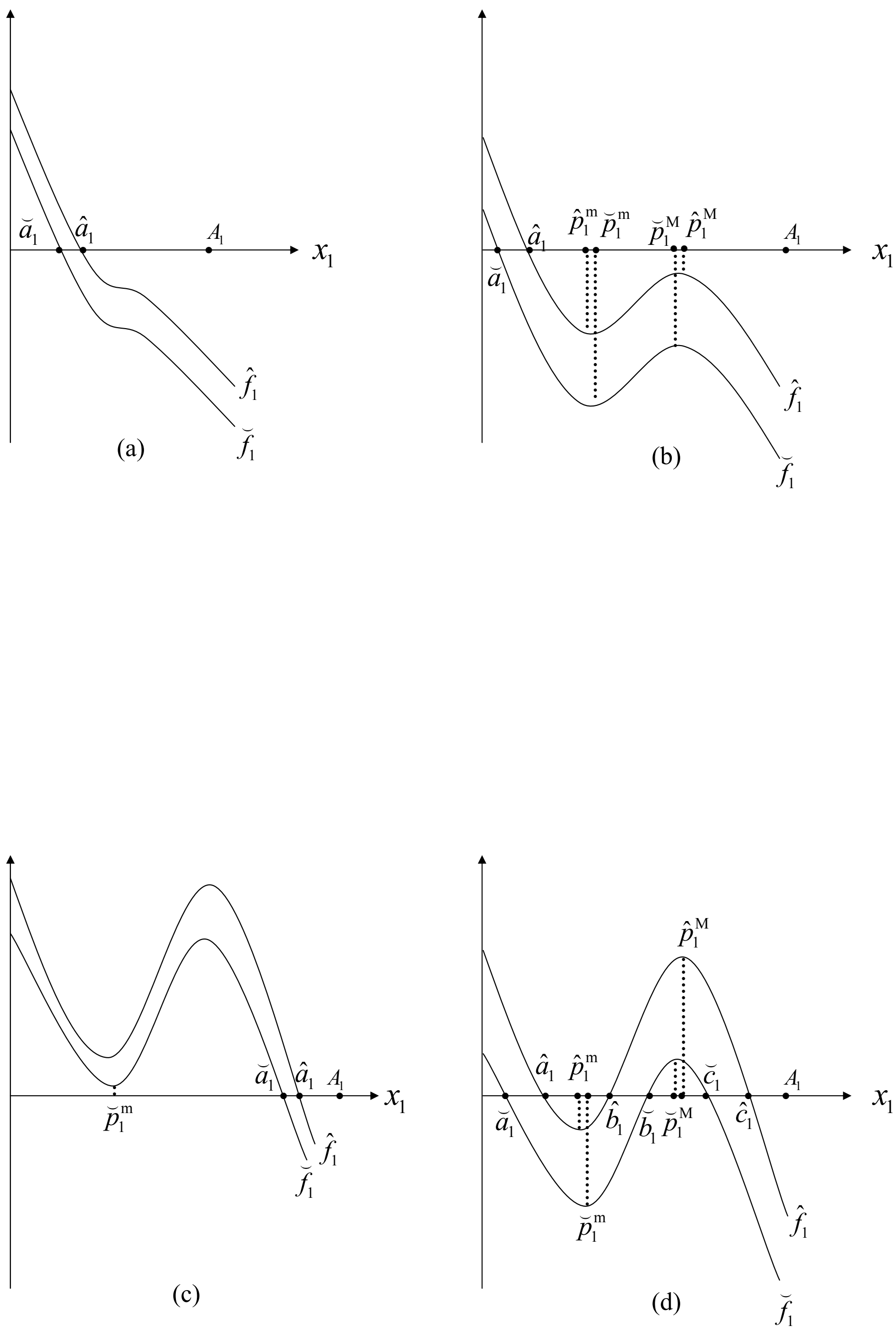


Figure 1: $\hat{f}_1$ and $\check{f}_1$ have one zero in cases (a), (b), (c), and three zeros in case (d).

(i) Phase (MS) takes place under conditions (M1) and (M2), or conditions (B1), (B2) with either $\hat{f}_1(\hat{p}_1^{\mathrm{M}}) < 0$, $\hat{f}_2(\hat{p}_2^{\mathrm{M}}) < 0$ or with $\check{f}_1(\check{p}_1^{\mathrm{m}}) > 0$, $\check{f}_2(\check{p}_2^{\mathrm{m}}) > 0$;
(ii) Phase (BS-ll,lh) takes place under conditions (B2), $\hat{f}_2(\hat{p}_2^{\mathrm{m}}) < 0$, $\check{f}_2(\check{p}_2^{\mathrm{M}}) > 0$, and condition (M1), or (B1) and $\hat{f}_1(\hat{p}_1^{\mathrm{M}}) < 0$;
(iii) Phase (BS-ll,hl) takes place under condition (B1), $\hat{f}_1(\hat{p}_1^{\mathrm{m}}) < 0$, $\check{f}_1(\check{p}_1^{\mathrm{M}}) > 0$, and condition (M2), or (B2), $\hat{f}_2(\hat{p}_2^{\mathrm{M}}) < 0$;
(iv) Phase (BS-hl,hh) takes place under conditions (B2), $\hat{f}_2(\hat{p}_2^{\mathrm{m}}) < 0$, $\check{f}_2(\check{p}_2^{\mathrm{M}}) > 0$, and condition (M1), or (B1) and $\check{f}_1(\check{p}_1^{\mathrm{m}}) > 0$;
(v) Phase (BS-lh,hh) takes place under condition (B1), $\hat{f}_1(\hat{p}_1^{\mathrm{m}}) < 0$, $\check{f}_1(\check{p}_1^{\mathrm{M}}) > 0$, and condition (M2), or (B2), $\check{f}_2(\check{p}_2^{\mathrm{m}}) > 0$;
(vi) Phase (QS) takes place under conditions (B1), (B2), $\hat{f}_i(\hat{p}_i^{\mathrm{m}}) < 0$, $\check{f}_i(\check{p}_i^{\mathrm{M}}) > 0$, for $i = 1, 2$.

The proof of Theorem 4.1 follows from an iteration scheme which is similar to that introduced in sections 5-8; in order to avoid repetition, the proof is omitted.

Remark 1: Note that

$$\text{Condition (B1)}' : \mu < \frac{\alpha_1 \tilde{n}}{k_1} \cdot \frac{1}{1 + A_2/\gamma_2},$$
$$\text{Condition (B2)}' : \mu < \frac{\alpha_2 \tilde{n}}{k_2} \cdot \frac{1}{1 + A_1/\gamma_1},$$

imply respectively, (B1) and (B2). Moreover, with A_i defined in (2.9), if both conditions are satisfied then (4.6) holds. However, these conditions are more restrictive than conditions (B1), (B2), and are not involved with the cytokines rates σ_1, σ_2.

Remark 2: The conditions expressed by the signs of $\hat{f}_i(\hat{p}_i^{\mathrm{m}})$, $\check{f}_i(\check{p}_i^{\mathrm{M}})$ depend on the levels of cytokines S_1, S_2. There exist parameters so that phase (QS) takes place if both S_1 and S_2 are sufficiently large. With the same parameters, the dynamics reduces to phase (BS-ll,lh) (respectively (BS-ll,hl)) if S_2 (respectively S_1) is not large enough and reduces to phase (MS) if both S_1 and S_2 are both not large enough. We shall illustrate this situation numerically in section 9.

5 The Population Model

In the subsequent sections we shall consider the asymptotic behavior of $\psi(t, x_1, x_2)$ and of the corresponding dynamical system (2.7)-(2.8) in case $S_i = S_i(t)$ is defined by (2.11). Typically $g(t) = 2$ day^{-1} for some time $t < t_0$ and $g(t) = 0$ if $t > t_0$, but $C_i(t)$ may not vanish for large t. Throughout this paper we assume that

$$C_i(t) \to C_i(\infty) \geq 0, \quad G(t) \to G(\infty) > 0 \quad \text{as} \quad t \to \infty. \tag{5.1}$$

The derivation of the asymptotic behavior will be based on a sequence of approximations by means of upper bounds $\hat{f}_i^{(k)}$ and lower bounds $\check{f}_i^{(k)}$ of $f_i(x_1, x_2, S_i(t))$. In this section we construct these functions for the case $k = 0$. As in the discussion in section 4, we introduce an upper bound for $f_i(x_1, x_2, S_i(t))$:

$$\hat{f}_i(x_i) = -\mu x_i + (\alpha_i \frac{x_i^n}{k_i^n + x_i^n} + \sigma_i \frac{\hat{C}_i + A_i}{\rho_i + \hat{C}_i + A_i}) + \beta_i,$$

where $\hat{C}_i = \sup\{C_i(t)e^{-G(t)}/N_0 : t \in [0, \infty)\}$; $\hat{f}_i$ clearly satisfies (4.2). Let B_i be the largest zero of $\hat{f}_i$. Thus, $[0, B_1] \times [0, B_2]$ is an attracting set for (2.7)-(2.8).

Next we define a lower bound for f_1 on $\mathbb{R} \times [0, B_2]$ and a lower bound for f_2 on $[0, B_1] \times \mathbb{R}$, respectively:

$$\check{f}_1(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{\check{C}_1}{\rho_1 + \check{C}_1}) \cdot \frac{1}{1 + B_2/\gamma_2} + \beta_1,$$
$$\check{f}_2(x_2) = -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{\check{C}_2}{\rho_2 + \check{C}_2}) \cdot \frac{1}{1 + B_1/\gamma_1} + \beta_2.$$

where $\check{C}_i = \inf\{C_i(t)e^{-G(t)}/N_0 : t \in [0, \infty)\}$, $i = 1, 2$; $\check{f}_i$ clearly satisfies (4.5). The functions $\hat{f}_i, \check{f}_i$ share other properties with those defined in section 4. Indeed, under conditions (Mi), (Bi) with $\hat{f}_i(\hat{p}_i^{\mathrm{M}}) < 0$, or (B$i$) with $\check{f}_i(\check{p}_i^{\mathrm{m}}) > 0$, both $\hat{f}_i$ and $\check{f}_i$ have a unique zero, denoted respectively by $\hat{a}_i, \check{a}_i$; under conditions (Bi), each of $\hat{f}_i$ and $\check{f}_i$ has a local minimum and a local maximum, denoted by $\hat{p}_i^{\mathrm{m}}, \hat{p}_i^{\mathrm{M}}$, and $\check{p}_i^{\mathrm{m}}, \check{p}_i^{\mathrm{M}}$, respectively, and it can be computed that $\check{f}_i(\check{p}_i^{\mathrm{m}}) < \hat{f}_i(\hat{p}_i^{\mathrm{m}})$ and $\check{f}_i(\check{p}_i^{\mathrm{M}}) < \hat{f}_i(\hat{p}_i^{\mathrm{M}})$. Furthermore, under conditions (Bi), and $\hat{f}_i(\hat{p}_i^{\mathrm{m}}) < 0$, $\check{f}_i(\check{p}_i^{\mathrm{M}}) > 0$, both $\hat{f}_i$ and $\check{f}_i$ have three zeros, denoted by $(\hat{a}_i, \hat{b}_i, \hat{c}_i)$, $(\check{a}_i, \check{b}_i, \check{c}_i)$, respectively; cf. Figure 2.

Set

$$S_i^{\min}(t) = \inf\{S_i(s) : s \in [t, \infty)\}, \; S_i^{\max}(t) = \sup\{S_i(s) : s \in [t, \infty)\},$$

for $i = 1, 2$ and $t \geq 0$. Then $S_i^{\min}(t) \geq \check{C}_i, S_i^{\max}(t) \leq \hat{C}_i + A_i$, and $S_i^{\min}(t) \leq S_i(t) \leq S_i^{\max}(t)$. Note that $S_i^{\min}(t)$ is nondecreasing, $S_i^{\max}(t)$ is nonincreasing, and

$$\frac{S_i^{\min}(t)}{\rho_i + S_i^{\min}(t)} \leq \frac{S_i(t)}{\rho_i + S_i(t)} \leq \frac{S_i^{\max}(t)}{\rho_i + S_i^{\max}(t)} \text{ for } i = 1, 2, \text{ and } t \geq 0.$$

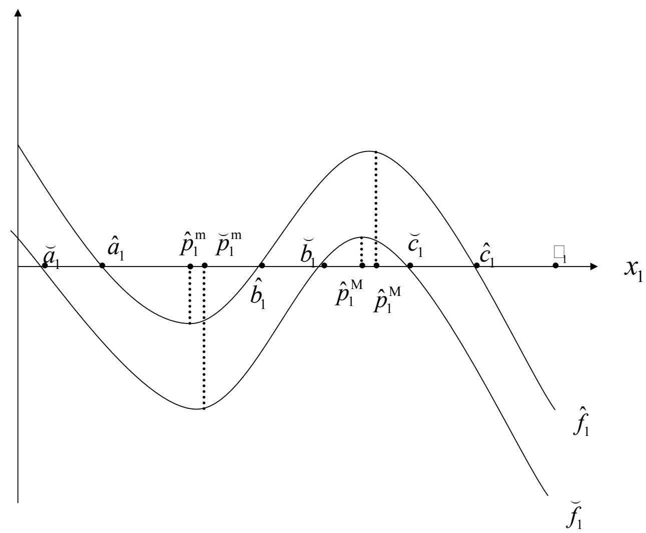


Figure 2: $\hat{f}_1$ and $\check{f}_1$ have two zeros.

We formulate the first step for the iteration scheme via the functions

$$\hat{f}_i^{(0)}(x_i) = -\mu x_i + (\alpha_i \frac{x_i^n}{k_i^n + x_i^n} + \sigma_i \frac{S_i^{\max}(0)}{\rho_i + S_i^{\max}(0)}) + \beta_i \text{ for } i = 1, 2,$$
$$\check{f}_1^{(0)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(0)}{\rho_1 + S_1^{\min}(0)}) \cdot \frac{1}{1 + B_2/\gamma_2} + \beta_1,$$
$$\check{f}_2^{(0)}(x_2) = -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\min}(0)}{\rho_2 + S_2^{\min}(0)}) \cdot \frac{1}{1 + B_1/\gamma_1} + \beta_2.$$

Then $\hat{f}_i^{(0)}, \check{f}_i^{(0)}$ admit the same properties as in (4.2) and (4.5). Moreover,

$$\check{f}_i(x_i) \le \check{f}_i^{(0)}(x_i) < \hat{f}_i^{(0)}(x_i) \le \hat{f}_i(x_i),\ i = 1, 2.$$

Therefore, $\hat{f}_i(\hat{p}_i^{\mathrm{m}}) < 0$ implies $\hat{f}_i^{(0)}(\hat{p}_i^{\mathrm{m}}) < 0$, whereas $\check{f}_i(\check{p}_i^{\mathrm{M}}) > 0$ implies $\check{f}_i^{(0)}(\check{p}_i^{\mathrm{M}}) > 0$. In addition, $\check{f}_i^{(0)\prime}(x_i) < \hat{f}_i^{(0)\prime}(x_i)$ for all $x_i \in [0, \infty)$, and both of $\hat{f}_i^{(0)}$ and $\check{f}_i^{(0)}$ have their inflection points at $\tilde{\xi}_i = k_i(\frac{n-1}{n+1})^{1/n}$ where they attain their largest slopes. Observe that

$$\check{f}_i^{(0)}(x_i) \le f_i(x_1, x_2, S_i(t)) \le \hat{f}_i^{(0)}(x_i), \tag{5.2}$$

for $i = 1, 2$ and $(x_1, x_2) \in [0, B_1] \times [0, B_2]$, $t \ge 0$. In addition, for all $t \ge 0$,

$$f_1(x_1, x_2, S_1(t)) \le \hat{f}_1^{(0)}(x_1) \text{ if } (x_1, x_2) \in [0, A_1] \times [B_2, A_2], \tag{5.3}$$
$$f_2(x_1, x_2, S_2(t)) \le \hat{f}_2^{(0)}(x_2) \text{ if } (x_1, x_2) \in [B_1, A_1] \times [0, A_2]. \tag{5.4}$$

In the sequel, $\mathbf{x}(t, \mathbf{x}_0)$ denotes the solution of (2.7)-(2.8) starting from point $\mathbf{x}_0$ at $t = 0$.

6 Asymptotic one-peak solution

Similarly to the case of Theorem 4.1(i) we assume that one of the following conditions holds:

$$(M1) \text{ and } (M2); \tag{6.1}$$
$$(B1) \text{ and } (B2) \text{ with } \hat{f}_1(\hat{p}_1^{\mathrm{M}}) < 0, \hat{f}_2(\hat{p}_2^{\mathrm{M}}) < 0; \tag{6.2}$$
$$(B1) \text{ and } (B2) \text{ with } \check{f}_1(\check{p}_1^{\mathrm{m}}) > 0, \check{f}_2(\check{p}_2^{\mathrm{m}}) > 0. \tag{6.3}$$

Then each $\hat{f}_i^{(0)}$ and $\check{f}_i^{(0)}$ has a unique zero which is denoted by $\hat{a}_i^{(0)}$ and $\check{a}_i^{(0)}$, respectively. Let $\varepsilon_0 > 0$ be small so that

$$\hat{f}_i^{(0)}(x_i) \le \hat{f}_i^{(0)}(\hat{a}_i^{(0)} + \varepsilon_0) < 0, \text{ for all } x_i \ge \hat{a}_i^{(0)} + \varepsilon_0,$$
$$\check{f}_i^{(0)}(x_i) \ge \check{f}_i^{(0)}(\check{a}_i^{(0)} - \varepsilon_0) > 0, \text{ for all } x_i \le \check{a}_i^{(0)} - \varepsilon_0,$$

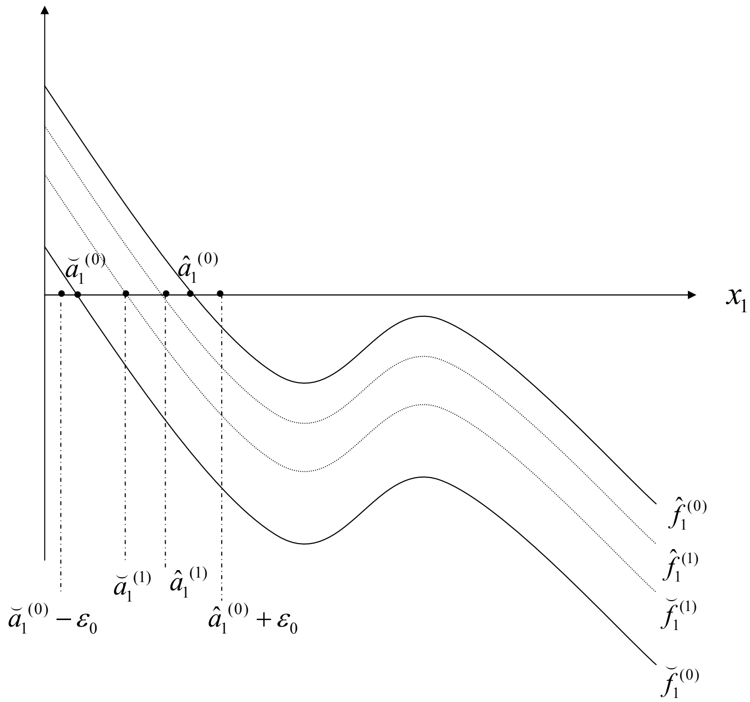


Figure 3: The configuration of $\hat{f}_1^{(0)}, \breve{f}_1^{(0)}, \hat{f}_1^{(1)}, \breve{f}_1^{(1)}$ and their zeros, under conditions (B1) and $\hat{f}_1(\hat{p}_1^{\mathrm{M}}) < 0$.

for $i = 1, 2$; cf. Figure 3. Combining these with inequalities (5.2)-(5.4), we deduce that there exists a $T_0 > 0$ such that any solution $\mathbf{x}(t, \mathbf{x}_0)$ starting from a point $\mathbf{x}_0 \in [0, A_1] \times [0, A_2]$ falls into the rectangle

$$\Omega^{(0)} := [\breve{a}_1^{(0)} - \varepsilon_0, \hat{a}_1^{(0)} + \varepsilon_0] \times [\breve{a}_2^{(0)} - \varepsilon_0, \hat{a}_2^{(0)} + \varepsilon_0] \subset [0, B_1] \times [0, B_2],$$

for $t \geq T_0$. Define

$$\hat{f}_1^{(1)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_0)}{\rho_1 + S_1^{\max}(T_0)}) \cdot \frac{1}{1 + (\check{a}_2^{(0)} - \varepsilon_0)/\gamma_2} + \beta_1,$$
$$\check{f}_1^{(1)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_0)}{\rho_1 + S_1^{\min}(T_0)}) \cdot \frac{1}{1 + (\hat{a}_2^{(0)} + \varepsilon_0)/\gamma_2} + \beta_1,$$
$$\hat{f}_2^{(1)}(x_2) = -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(T_0)}{\rho_2 + S_2^{\max}(T_0)}) \cdot \frac{1}{1 + (\check{a}_1^{(0)} - \varepsilon_0)/\gamma_1} + \beta_2,$$
$$\check{f}_2^{(1)}(x_2) = -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\min}(T_0)}{\rho_2 + S_2^{\min}(T_0)}) \cdot \frac{1}{1 + (\hat{a}_1^{(0)} + \varepsilon_0)/\gamma_1} + \beta_2.$$

Then $\check{f}_i^{(0)}(x_i) < \check{f}_i^{(1)}(x_i) < \hat{f}_i^{(1)}(x_i) < \hat{f}_i^{(0)}(x_i)$ for $x_i \in [0, A_i]$, $i = 1, 2$. Let $\hat{a}_i^{(1)}$ and $\check{a}_i^{(1)}$ denote the unique zeros of $\hat{f}_i^{(1)}$ and $\check{f}_i^{(1)}$ respectively. Then $\hat{a}_i^{(1)} < \hat{a}_i^{(0)}$ and $\check{a}_i^{(1)} > \check{a}_i^{(0)}$. Furthermore,

$$\check{f}_i^{(1)}(x_i) \le f_i(x_1, x_2,\ S_i(t)) \le \hat{f}_i^{(1)}(x_i) \tag{6.4}$$

for all $(x_1, x_2) \in \Omega^{(0)}$, $t \ge T_0$, $i = 1, 2$, and $\check{f}_i^{(1)}(x_i) > 0$ for $x_i < \check{a}_i^{(1)}$, $\hat{f}_i^{(1)}(x_i) < 0$ for $x_i > \hat{a}_i^{(1)}$. Hence for any small $\varepsilon_1 > 0$ there exist a $T_1 > T_0$ such that any solution $\mathbf{x}(t, \mathbf{x}_0)$ starting from a point $\mathbf{x}_0 \in [0, A_1] \times [0, A_2]$ falls into the region

$$\Omega^{(1)} := [\check{a}_1^{(1)} - \varepsilon_1, \hat{a}_1^{(1)} + \varepsilon_1] \times [\check{a}_2^{(1)} - \varepsilon_1, \hat{a}_2^{(1)} + \varepsilon_1] \subset \Omega^{(0)},$$

for $t \ge T_1$; cf. Figure 4. We can proceed in a similar manner to define successively $\hat{f}_i^{(k)}$ and $\check{f}_i^{(k)}$, $k \ge 2$ by

$$\hat{f}_1^{(k)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_{k-1})}{\rho_1 + S_1^{\max}(T_{k-1})}) \cdot \frac{1}{1 + (\check{a}_2^{(k-1)} - \varepsilon_{k-1})/\gamma_2} + \beta_1,$$
$$\check{f}_1^{(k)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_{k-1})}{\rho_1 + S_1^{\min}(T_{k-1})}) \cdot \frac{1}{1 + (\hat{a}_2^{(k-1)} + \varepsilon_{k-1})/\gamma_2} + \beta_1,$$
$$\hat{f}_2^{(k)}(x_2) = -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(T_{k-1})}{\rho_2 + S_2^{\max}(T_{k-1})}) \cdot \frac{1}{1 + (\check{a}_1^{(k-1)} - \varepsilon_{k-1})/\gamma_1} + \beta_2,$$
$$\check{f}_2^{(k)}(x_2) = -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\min}(T_{k-1})}{\rho_2 + S_2^{\min}(T_{k-1})}) \cdot \frac{1}{1 + (\hat{a}_1^{(k-1)} + \varepsilon_{k-1})/\gamma_1} + \beta_2.$$

and their zeros $\hat{a}_i^{(k)}, \check{a}_i^{(k)}$, i.e.,

$$\hat{f}_i^{(k+1)}(\hat{a}_i^{(k)}) = 0,\ \check{f}_i^{(k+1)}(\check{a}_i^{(k)}) = 0. \tag{6.5}$$

We may clearly assume that $\varepsilon_k \to 0$ and $T_k \to \infty$ as $k \to \infty$.

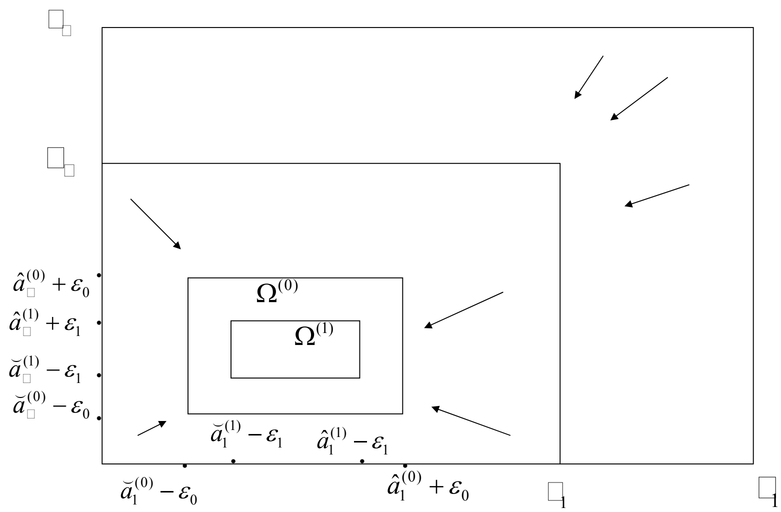


Figure 4: $\Omega^{(0)}$ and $\Omega^{(1)}$, for one-peak case.

We can then prove that for any small $\epsilon_k > 0$ there exists a T_k such that any solution $\mathbf{x}(t, \mathbf{x}_0)$ starting from a point $\mathbf{x}_0 \in [0, A_1] \times [0, A_2]$ falls into the region $\Omega^{(k)} := [\check{a}_1^{(k)} - \varepsilon_k, \hat{a}_1^{(k)} + \varepsilon_k] \times [\check{a}_2^{(k)} - \varepsilon_k, \hat{a}_2^{(k)} + \varepsilon_k] \subset \Omega^{(k-1)}$ for $t \geq T_k$.

We shall need the following condition:

$$\frac{(\alpha_2 + \sigma_2)}{\gamma_1} < |\mu - \frac{\alpha_1 \tilde{n}}{k_1}| - \frac{\sigma_1}{\rho_1}, \ \frac{(\alpha_1 + \sigma_1)}{\gamma_2} < |\mu - \frac{\alpha_2 \tilde{n}}{k_2}| - \frac{\sigma_2}{\rho_2}. \tag{6.6}$$

Lemma 6.1. Under the conditions (6.6) and either (6.1), (6.2) or (6.3), the intersection $\cap_{k=1}^{\infty} \Omega^{(k)}$ consists of a single point $(\bar{a}_1, \bar{a}_2)$.

Proof. Note that for each $i = 1, 2$, $\{\check{a}_i^{(k)} - \varepsilon_k\}$ is an increasing sequence, $\{\hat{a}_i^{(k)} + \varepsilon_k\}$ is a decreasing sequence, $\check{a}_i^{(k)} - \varepsilon_k < \hat{a}_i^{(k)} + \varepsilon_k$ for each k, and $\varepsilon_k \to 0$ as $k \to \infty$. Hence

$$\check{a}_i^* = \lim_{k \to \infty} \check{a}_i^{(k)}, \hat{a}_i^* = \lim_{k \to \infty} \hat{a}_i^{(k)}, \text{ exists, and } \check{a}_i^* \leq \hat{a}_i^* \text{ for } \ i = 1, 2.$$

Assuming that $\cap_{k=1}^{\infty} \Omega^{(k)}$ is not a single point so that $\hat{a}_i^* > \check{a}_i^*$ for either $i = 1$ or $i = 2$ (or both), we shall derive a contradiction.

By passing to the limit in (6.5) we get

$$-\mu \check{a}_1^* + [\alpha_1 \frac{(\check{a}_1^*)^n}{k_1^n + (\check{a}_1^*)^n} + \sigma_1 \frac{\check{S}_1}{\rho_1 + \check{S}_1}] \cdot \frac{1}{1 + \hat{a}_2^*/\gamma_2} + \beta_1 = 0, \tag{6.7}$$

$$-\mu \hat{a}_2^* + [\alpha_2 \frac{(\hat{a}_2^*)^n}{k_2^n + (\hat{a}_2^*)^n} + \sigma_2 \frac{\hat{S}_2}{\rho_2 + \hat{S}_2}] \cdot \frac{1}{1 + \check{a}_1^*/\gamma_1} + \beta_2 = 0, \tag{6.8}$$

$$-\mu \hat{a}_1^* + [\alpha_1 \frac{(\hat{a}_1^*)^n}{k_1^n + (\hat{a}_1^*)^n} + \sigma_1 \frac{\hat{S}_1}{\rho_1 + \hat{S}_1}] \cdot \frac{1}{1 + \check{a}_2^*/\gamma_2} + \beta_1 = 0, \tag{6.9}$$

$$-\mu \check{a}_2^* + [\alpha_2 \frac{(\check{a}_2^*)^n}{k_2^n + (\check{a}_2^*)^n} + \sigma_2 \frac{\check{S}_2}{\rho_2 + \check{S}_2}] \cdot \frac{1}{1 + \hat{a}_1^*/\gamma_1} + \beta_2 = 0, \tag{6.10}$$

where

$$\hat{S}_i = \lim_{t \to \infty} S_i^{\max}(t), \check{S}_i = \lim_{t \to \infty} S_i^{\min}(t),$$

and

$$\hat{S}_1 \leq \hat{a}_1^* + \bar{C}_1, \quad , \check{S}_1 \geq \check{a}_1^* + \bar{C}_1 \tag{6.11}$$

$$\hat{S}_2 \leq \hat{a}_2^* + \bar{C}_2, \quad \check{S}_2 \geq \check{a}_2^* + \bar{C}_2, \tag{6.12}$$

with

$$\bar{C}_i = \lim_{t \to \infty} C_i(t) e^{-G(t)}/N_0.$$

Taking the difference of (6.7), (6.9) we obtain

$$\begin{aligned}
&\mu(\hat{a}_1^* - \check{a}_1^*) - \alpha_1[\frac{(\hat{a}_1^*)^n}{k_1^n + (\hat{a}_1^*)^n} - \frac{(\check{a}_1^*)^n}{k_1^n + (\check{a}_1^*)^n}] \cdot \frac{1}{1 + \check{a}_2^*/\gamma_2} \\
= \; & [\alpha_1 \frac{(\check{a}_1^*)^n}{k_1^n + (\check{a}_1^*)^n} + \sigma_1 \frac{\check{S}_1}{\rho_1 + \check{S}_1}] \cdot [\frac{1}{1 + \check{a}_2^*/\gamma_2} - \frac{1}{1 + \hat{a}_2^*/\gamma_2}] \\
& + \sigma_1 [\frac{\hat{S}_1}{\rho_1 + \hat{S}_1} - \frac{\check{S}_1}{\rho_1 + \check{S}_1}] \cdot \frac{1}{1 + \check{a}_2^*/\gamma_2}.
\end{aligned} \tag{6.13}$$

Thus, by the mean value theorem and the estimates (6.11) for $\hat{S}_1$, $\check{S}_1$,

$$\begin{aligned}
& |\hat{a}_1^* - \check{a}_1^*| \cdot |\mu - \frac{\alpha_1 \tilde{n}}{k_1}| \\
\leq \; & \frac{(\alpha_1 + \sigma_1)}{\gamma_2} |\check{a}_2^* - \hat{a}_2^*| + \frac{\sigma_1}{\rho_1} |\hat{a}_1^* - \check{a}_1^*|,
\end{aligned}$$

or

$$|\hat{a}_1^* - \check{a}_1^*| \cdot [|\mu - \frac{\alpha_1 \tilde{n}}{k_1}| - \frac{\sigma_1}{\rho_1}] \leq \frac{(\alpha_1 + \sigma_1)}{\gamma_2} |\check{a}_2^* - \hat{a}_2^*|. \tag{6.14}$$

Similarly, from (6.8), (6.10), (6.12) we obtain

$$|\check{a}_2^* - \hat{a}_2^*| \cdot [|\mu - \frac{\alpha_2 \tilde{n}}{k_2}| - \frac{\sigma_2}{\rho_2}] \leq \frac{(\alpha_2 + \sigma_2)}{\gamma_1} |\hat{a}_1^* - \check{a}_1^*|. \tag{6.15}$$

Assume that the LHS of (6.14) and (6.15) are positive, these two inequalities yield

$$[|\mu - \frac{\alpha_1 \tilde{n}}{k_1}| - \frac{\sigma_1}{\rho_1}] \cdot [|\mu - \frac{\alpha_2 \tilde{n}}{k_2}| - \frac{\sigma_2}{\rho_2}] < \frac{(\alpha_2 + \sigma_2)}{\gamma_1} \cdot \frac{(\alpha_1 + \sigma_1)}{\gamma_2}, \tag{6.16}$$

which is a contradiction to (4.6). We thus conclude that $\check{a}_i^* = \hat{a}_i^*$ for $i = 1, 2$, which proves the lemma. □

From Lemma 6.1 it follows that the limit $(\bar{a}_1, \bar{a}_2)$ of $\Omega^{(k)}$ (as $k \to \infty$), satisfies the equations

$$-\mu \overline{a}_1 + [\alpha_1 \frac{\overline{a}_1^n}{k_1^n + \overline{a}_1^n} + \sigma_1 \frac{\overline{a}_1 + \bar{C}_1}{\rho_1 + \overline{a}_1}] \cdot \frac{1}{1 + \overline{a}_2/\gamma_2} + \beta_1 = 0, \tag{6.17}$$

$$-\mu \overline{a}_2 + [\alpha_2 \frac{\overline{a}_2^n}{k_2^n + \overline{a}_2^n} + \sigma_2 \frac{\overline{a}_2 + \bar{C}_2}{\rho_2 + \overline{a}_2}] \cdot \frac{1}{1 + \overline{a}_1/\gamma_1} + \beta_2 = 0, \tag{6.18}$$

and the solution is unique. We have thus proved:

Theorem 6.2. If (6.6) and one of the conditions (6.1), (6.2), or (6.3) holds, then the solution ψ of (2.10),(3.1), with f_i, S_i defined by (2.5), (2.6), (2.10), satisfies:

$$\lim_{t \to \infty} \psi(t, x_1, x_2) = N_0 \delta_{(\overline{a}_1, \overline{a}_2)}, \tag{6.19}$$

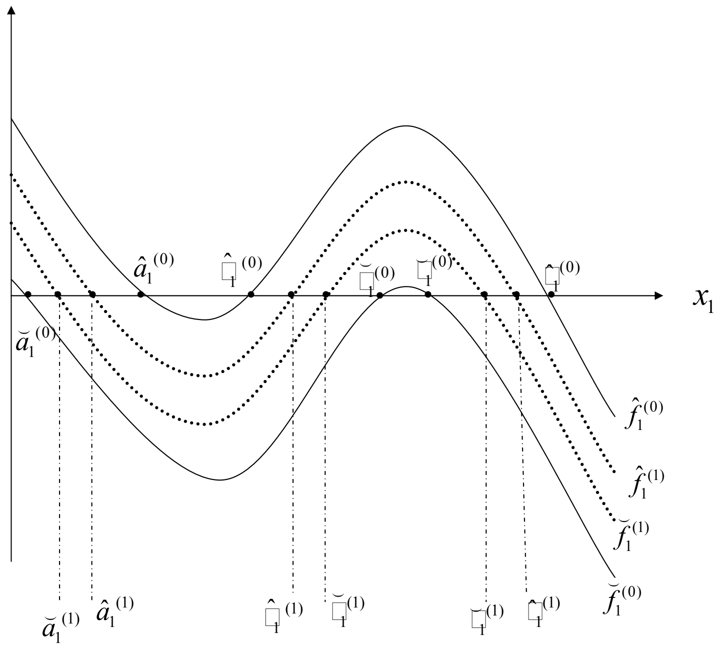


Figure 5: Configurations of functions $\hat{f}_1^{(0)}$, $\check{f}_1^{(0)}$, $\hat{f}_1^{(1)}$, $\check{f}_1^{(1)}$ and their zeros, under condition (B1).

where $\delta_{(\overline{a}_1,\overline{a}_2)}$ is the Dirac measure at point $(\overline{a}_1, \overline{a}_2)$ which is uniquely determined from (6.17)-(6.18), and the convergence in (6.19) is in the sense of convergence in measure as defined in (2.12).

7 Asymptotic two-peak solutions

Analogously to the case of Theorem 4.1(iii) we assume that

$$\text{condition (B1) holds}, \hat{f}_1(\hat{p}_1^{\mathrm{m}}) < 0, \text{and } \check{f}_1(\check{p}_1^{\mathrm{M}}) > 0, \tag{7.1}$$

$$\text{either condition (M2) holds, or (B2) and } \hat{f}_2(\hat{p}_2^{\mathrm{M}}) < 0 \text{ hold.} \tag{7.2}$$

Let $\hat{a}_1^{(0)}, \hat{b}_1^{(0)}, \hat{c}_1^{(0)}$ (respectively $\check{a}_1^{(0)}, \check{b}_1^{(0)}, \check{c}_1^{(0)}$) be the zeros of $\hat{f}_1^{(0)}$ (respectively $\check{f}_1^{(0)}$), and $\hat{a}_2^{(0)}, \check{a}_2^{(0)}$ be the zeros of $\hat{f}_2^{(0)}, \check{f}_2^{(0)}$, respectively; cf. Figure 5.

Then, by (7.1), (7.2) and (5.2)-(5.4), for any small $\varepsilon_0 > 0$ there exists a $T_0 > 0$ such that any solution $\mathbf{x}(t, \mathbf{x}_0)$ starting from a point $\mathbf{x}_0 \in [0, A_1] \times [0, A_2] \setminus K^{(0)}$ falls into the region

$$\Omega^{(0)} = \Omega_{\mathrm{l}}^{(0)} \cup \Omega_{\mathrm{u}}^{(0)}$$

for all $t \geq T_0$, where

$$\begin{aligned} K^{(0)} &= [\hat{b}_1^{(0)}, \check{b}_1^{(0)}] \times [\check{a}_2^{(0)}, \hat{a}_2^{(0)}], \\ \Omega_{\mathrm{l}}^{(0)} &= [\check{a}_1^{(0)} - \varepsilon_0, \hat{a}_1^{(0)} + \varepsilon_0] \times [\check{a}_2^{(0)} - \varepsilon_0, \hat{a}_2^{(0)} + \varepsilon_0], \\ \Omega_{\mathrm{u}}^{(0)} &= [\check{c}_1^{(0)} - \varepsilon_0, \hat{c}_1^{(0)} + \varepsilon_0] \times [\check{a}_2^{(0)} - \varepsilon_0, \hat{a}_2^{(0)} + \varepsilon_0]. \end{aligned}$$

Next, we define

$$\begin{aligned} \hat{f}_1^{(1)}(x_1) &= -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_0)}{\rho_1 + S_1^{\max}(T_0)}) \cdot \frac{1}{1 + (\check{a}_2^{(0)} - \varepsilon_0)/\gamma_2} + \beta_1, \\ \check{f}_1^{(1)}(x_1) &= -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_0)}{\rho_1 + S_1^{\min}(T_0)}) \cdot \frac{1}{1 + (\hat{a}_2^{(0)} + \varepsilon_0)/\gamma_2} + \beta_1, \\ \hat{f}_{2,\mathrm{l}}^{(1)}(x_2) &= -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(T_0)}{\rho_2 + S_2^{\max}(T_0)}) \cdot \frac{1}{1 + (\check{a}_1^{(0)} - \varepsilon_0)/\gamma_1} + \beta_2, \\ \check{f}_{2,\mathrm{l}}^{(1)}(x_2) &= -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\min}(T_0)}{\rho_2 + S_2^{\min}(T_0)}) \cdot \frac{1}{1 + (\hat{a}_1^{(0)} + \varepsilon_0)/\gamma_1} + \beta_2, \\ \hat{f}_{2,\mathrm{m}}^{(1)}(x_2) &= -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(T_0)}{\rho_2 + S_2^{\max}(T_0)}) \cdot \frac{1}{1 + \hat{b}_1^{(0)}/\gamma_1} + \beta_2, \\ \check{f}_{2,\mathrm{m}}^{(1)}(x_2) &= -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\min}(T_0)}{\rho_2 + S_2^{\min}(T_0)}) \cdot \frac{1}{1 + \check{b}_1^{(0)}/\gamma_1} + \beta_2, \\ \hat{f}_{2,\mathrm{u}}^{(1)}(x_2) &= -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(T_0)}{\rho_2 + S_2^{\max}(T_0)}) \cdot \frac{1}{1 + (\check{c}_1^{(0)} - \varepsilon_0)/\gamma_1} + \beta_2, \\ \check{f}_{2,\mathrm{u}}^{(1)}(x_2) &= -\mu x_2 + (\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\min}(T_0)}{\rho_2 + S_2^{\min}(T_0)}) \cdot \frac{1}{1 + (\hat{c}_1^{(0)} + \varepsilon_0)/\gamma_1} + \beta_2. \end{aligned}$$

Let $\hat{a}_2^{(1)}$, $\check{a}_2^{(1)}$ (respectively $\hat{b}_2^{(1)}$, $\check{b}_2^{(1)}$; $\hat{c}_2^{(1)}$, $\check{c}_2^{(1)}$) be the zeros of $\hat{f}_{2,\mathrm{l}}^{(1)}$, $\check{f}_{2,\mathrm{l}}^{(1)}$ (respectively $\hat{f}_{2,\mathrm{m}}^{(1)}$, $\check{f}_{2,\mathrm{m}}^{(1)}$; $\hat{f}_{2,\mathrm{u}}^{(1)}$, $\check{f}_{2,\mathrm{u}}^{(1)}$) respectively, and $\hat{a}_1^{(1)}$, $\check{a}_1^{(1)}$ be the smallest, $\hat{b}_1^{(1)}$, $\check{b}_1^{(1)}$ be the middle, and $\hat{c}_1^{(1)}$, $\check{c}_1^{(1)}$ be the largest zeros of $\hat{f}_1^{(1)}$ and $\check{f}_1^{(1)}$, respectively. (Herein "l", "m" and "u" mean lower, middle, and upper, respectively.) Then for any small $\varepsilon_1 > 0$ there exists a $T_1 > T_0$ such that any solution $\mathbf{x}(t, \mathbf{x}_0)$ starting from a point $\mathbf{x}_0 \in [0, A_1] \times [0, A_2] \setminus K^{(1)}$ falls into the region

$$\Omega^{(1)} = \Omega_{\mathrm{l}}^{(1)} \cup \Omega_{\mathrm{u}}^{(1)} \subset \Omega^{(0)},$$

for $t \geq T_1$, where

$$K^{(1)} = [\hat{b}_1^{(1)}, \check{b}_1^{(1)}] \times [\check{b}_2^{(1)}, \hat{b}_2^{(1)}] \subset K^{(0)},$$
$$\Omega_{\mathrm{l}}^{(1)} = [\check{a}_1^{(1)} - \varepsilon_1, \hat{a}_1^{(1)} + \varepsilon_1] \times [\check{a}_2^{(1)} - \varepsilon_1, \hat{a}_2^{(1)} + \varepsilon_1] \subset \Omega_{\mathrm{l}}^{(0)},$$
$$\Omega_{\mathrm{u}}^{(1)} = [\check{c}_1^{(1)} - \varepsilon_1, \hat{c}_1^{(1)} + \varepsilon_1] \times [\check{c}_2^{(1)} - \varepsilon_1, \hat{c}_2^{(1)} + \varepsilon_1] \subset \Omega_{\mathrm{u}}^{(0)}.$$

In addition, for $t \geq T_1$,

$$S_i(t) \cdot N_0 = C_i(t) e^{-G(t)} + \int\int_{\Omega^{(1)} \cup K^{(1)}} x_i \psi dx_1 dx_2.$$

We proceed to define successively

$$\hat{f}_{1,\mathrm{l}}^{(k)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_{k-1})}{\rho_2 + S_2^{\max}(T_{k-1})}) \cdot \frac{1}{1 + (\check{a}_2^{(k-1)} - \varepsilon_{k-1})/\gamma_2} + \beta_1,$$
$$\check{f}_{1,\mathrm{l}}^{(k)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_{k-1})}{\rho_1 + S_1^{\min}(T_{k-1})}) \cdot \frac{1}{1 + (\hat{a}_2^{(k-1)} + \varepsilon_{k-1})/\gamma_2} + \beta_1,$$
$$\hat{f}_{1,\mathrm{m}}^{(k)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_{k-1})}{\rho_1 + S_1^{\max}(T_{k-1})}) \cdot \frac{1}{1 + \check{b}_2^{(k-1)}/\gamma_2} + \beta_1,$$
$$\check{f}_{1,\mathrm{m}}^{(k)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_{k-1})}{\rho_1 + S_1^{\min}(T_{k-1})}) \cdot \frac{1}{1 + \hat{b}_2^{(k-1)}/\gamma_2} + \beta_1,$$
$$\hat{f}_{1,\mathrm{u}}^{(k)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_{k-1})}{\rho_1 + S_1^{\max}(T_{k-1})}) \cdot \frac{1}{1 + (\check{c}_2^{(k-1)} - \varepsilon_{k-1})/\gamma_2} + \beta_1,$$
$$\check{f}_{1,\mathrm{u}}^{(k)}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1 s^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_{k-1})}{\rho_1 + S_1^{\min}(T_{k-1})}) \cdot \frac{1}{1 + (\hat{c}_2^{(k-1)} + \varepsilon_{k-1})/\gamma_2} + \beta_1,$$

and similarly $\hat{f}_{2,\mathrm{u}}^{(k)}, \check{f}_{2,\mathrm{u}}^{(k)}, \hat{f}_{2,\mathrm{m}}^{(k)}, \check{f}_{2,\mathrm{m}}^{(k)}, \hat{f}_{2,\mathrm{l}}^{(k)}, \check{f}_{2,\mathrm{l}}^{(k)}$, their zeros $\hat{a}_i^{(k)}, \check{a}_i^{(k)}, \hat{b}_i^{(k)}, \check{b}_i^{(k)}, \hat{c}_i^{(k)}, \check{c}_i^{(k)}$, $i = 1, 2$ and domains $\Omega^{(k)}$. Note that the sets $\Omega^{(k)}$ as well as the rectangles $[\hat{b}_1^{(k)}, \check{b}_1^{(k)}] \times [\check{b}_2^{(k)}, \hat{b}_2^{(k)}]$ are shrinking as k increases. Suppose that

$$[\check{a}_1^{(k)}, \hat{a}_1^{(k)}] \to \{\overline{a}_1\}, \ [\hat{b}_1^{(k)}, \check{b}_1^{(k)}] \to \{\overline{b}_1\}, \ [\check{c}_1^{(k)}, \hat{c}_1^{(k)}] \to \{\overline{c}_1\}, \tag{7.3}$$
$$[\check{a}_2^{(k)}, \hat{a}_2^{(k)}] \to \{\overline{a}_2\}, \ [\hat{b}_2^{(k)}, \check{b}_2^{(k)}] \to \{\overline{b}_2\}, \ [\check{c}_2^{(k)}, \hat{c}_2^{(k)}] \to \{\overline{c}_2\}, \tag{7.4}$$

as $k \to \infty$. Then $\Omega^{(k)} \to \{(\overline{a}_1, \overline{a}_2), (\overline{c}_1, \overline{c}_2)\}$ as $k \to \infty$, and

$$S_1(t) \to w_{\mathrm{l}} \cdot \overline{a}_1 + w_{\mathrm{u}} \cdot \overline{c}_1 + \bar{C}_1,$$
$$S_2(t) \to w_{\mathrm{l}} \cdot \overline{a}_2 + w_{\mathrm{u}} \cdot \overline{c}_2 + \bar{C}_2,$$

as $t \to \infty$, for some $w_{\mathrm{l}}, w_{\mathrm{u}} \geq 0$ with $w_{\mathrm{l}} + w_{\mathrm{u}} = 1$. Herein, $w_{\mathrm{l}}, w_{\mathrm{u}}$ represent the percentages of cells whose concentrations tend to levels $(\overline{a}_1, \overline{a}_2)$ and $(\overline{c}_1, \overline{c}_2)$, respectively.

Notice that points $(\overline{a}_1, \overline{a}_2)$, $(\overline{c}_1, \overline{c}_2)$, and $w_{\text{l}}, w_{\text{u}}$ satisfy the equations

$$-\mu\overline{a}_1 + [\alpha_1 \frac{\overline{a}_1^n}{k_1^n + \overline{a}_1^n} + \sigma_1 \frac{w_{\text{l}} \cdot \overline{a}_1 + w_{\text{u}} \cdot \overline{c}_1 + \bar{C}_1}{\rho_1 + (w_{\text{l}} \cdot \overline{a}_1 + w_{\text{u}} \cdot \overline{c}_1 + \bar{C}_1)}] \cdot \frac{1}{1 + \overline{a}_2/\gamma_2} + \beta_1 = 0, \quad (7.5)$$

$$-\mu\overline{c}_1 + [\alpha_1 \frac{\overline{c}_1^n}{k_1^n + \overline{c}_1^n} + \sigma_1 \frac{w_{\text{l}} \cdot \overline{a}_1 + w_{\text{u}} \cdot \overline{c}_1 + \bar{C}_1}{\rho_1 + (w_{\text{l}} \cdot \overline{a}_1 + w_{\text{u}} \cdot \overline{c}_1 + \bar{C}_1)}] \cdot \frac{1}{1 + \overline{c}_2/\gamma_2} + \beta_1 = 0, \quad (7.6)$$

$$-\mu\overline{a}_2 + [\alpha_2 \frac{\overline{a}_2^n}{k_2^n + \overline{a}_2^n} + \sigma_2 \frac{w_{\text{l}} \cdot \overline{a}_2 + w_{\text{u}} \cdot \overline{c}_2 + \bar{C}_2}{\rho_2 + (w_{\text{l}} \cdot \overline{a}_2 + w_{\text{u}} \cdot \overline{c}_2 + \bar{C}_2)}] \cdot \frac{1}{1 + \overline{a}_1/\gamma_1} + \beta_2 = 0, \quad (7.7)$$

$$-\mu\overline{c}_2 + [\alpha_2 \frac{\overline{c}_2^n}{k_2^n + \overline{c}_2^n} + \sigma_2 \frac{w_{\text{l}} \cdot \overline{a}_2 + w_{\text{u}} \cdot \overline{c}_2 + \bar{C}_2}{\rho_2 + (w_{\text{l}} \cdot \overline{a}_2 + w_{\text{u}} \cdot \overline{c}_2 + \bar{C}_2)}] \cdot \frac{1}{1 + \overline{c}_1/\gamma_1} + \beta_2 = 0. \quad (7.8)$$

We have thus derived an asymptotic two-peak solution $\psi = w_{\text{l}} \cdot \delta_{(\overline{a}_1, \overline{a}_2)} + w_{\text{u}} \cdot \delta_{(\overline{c}_1, \overline{c}_2)}$.

Notice that $\bar{a}_1$, $\bar{a}_2$, $\bar{c}_1$, $\bar{c}_2$, w_{l}, w_{u} are not determined uniquely from the equations (7.5) - (7.8); these quantities depend also on the initial condition (3.1).

In order to complete the proof, it remains to establish (7.3), (7.4). Following the argument in the proof of Lemma 6.1, we argue that if (7.3) and (7.4) are not true then

$$\cap_{k=1}^{\infty} \Omega^{(k)} = \cup_{i=1}^{3} R_i \text{ (disjoint union)}$$

where each R_i is either a rectangle or a single point, and at least one R_i is a rectangle. We denote by $(\check{a}_1^*, \hat{a}_2^*)$ the upper-left vertex of R_1 which is diagonally opposed to $(\check{a}_1^*, \hat{a}_2^*)$; if R_1 is a single point then we take $\check{a}_1^* = \check{a}_1^*$, $\hat{a}_2^* = \hat{a}_2^*$. Similarly we designate the vertices $(\hat{b}_1^*, \check{b}_2^*), (\check{b}_1^*, \hat{b}_2^*)$ for R_2, and $(\hat{c}_1^*, \check{c}_2^*), (\check{c}_1^*, \hat{c}_2^*)$ for R_3. Then analogous to (6.7)-(6.10), the coordinates of these vertices satisfy the following equations:

$$f_1(\check{a}_1^*, \hat{a}_2^*, \check{S}_1) = 0, f_2(\check{a}_1^*, \hat{a}_2^*, \hat{S}_2) = 0, \quad (7.9)$$

$$f_1(\hat{a}_1^*, \check{a}_2^*, \hat{S}_1) = 0, f_2(\hat{a}_1^*, \check{a}_2^*, \check{S}_2) = 0, \quad (7.10)$$

$$f_1(\hat{b}_1^*, \check{b}_2^*, \check{S}_1) = 0, f_2(\hat{b}_1^*, \check{b}_2^*, \hat{S}_2) = 0,$$

$$f_1(\check{b}_1^*, \hat{b}_2^*, \hat{S}_1) = 0, f_2(\check{b}_1^*, \hat{b}_2^*, \check{S}_2) = 0,$$

$$f_1(\check{c}_1^*, \hat{c}_2^*, \check{S}_1) = 0, f_2(\check{c}_1^*, \hat{c}_2^*, \hat{S}_2) = 0, \quad (7.11)$$

$$f_1(\hat{c}_1^*, \check{c}_2^*, \hat{S}_1) = 0, f_2(\hat{c}_1^*, \check{c}_2^*, \check{S}_2) = 0. \quad (7.12)$$

Furthermore,

$$\hat{S}_1 \le [v_1\hat{a}_1^* + v_2\check{b}_1^* + v_3\hat{c}_1^*]/v + \bar{C}_1, \quad (7.13)$$

$$\check{S}_1 \ge [v_1\check{a}_1^* + v_2\hat{b}_1^* + v_3\check{c}_1^*]/v + \bar{C}_1, \quad (7.14)$$

$$\hat{S}_2 \le [v_1\hat{a}_2^* + v_2\check{b}_2^* + v_3\hat{c}_2^*]/v + \bar{C}_2, \quad (7.15)$$

$$\check{S}_2 \ge [v_1\hat{a}_2^* + v_2\check{b}_2^* + v_3\check{c}_2^*]/v + \bar{C}_2, \quad (7.16)$$

where v_1, v_2, v_3 are the areas of the regions R_1, R_2, R_3, and $v_1+v_2+v_3=v$. Among the three quantities

$$(\hat{a}_1^* - \check{a}_1^*), \quad (\check{b}_1^* - \hat{b}_1^*), \quad (\hat{c}_1^* - \check{c}_1^*),$$

we pick the largest one, say $(\hat{a}_1^* - \check{a}_1^*)$, and the corresponding two equations from (7.9), (7.10),

$$f_1(\check{a}_1^*, \hat{a}_2^*, \check{S}_1) = 0, \quad f_1(\hat{a}_1^*, \check{a}_2^*, \hat{S}_1) = 0 \tag{7.17}$$

(analogously to equations (6.7), (6.9)). Similarly, among the quantities

$$(\hat{a}_2^* - \check{a}_2^*), \quad (\check{b}_2^* - \hat{b}_2^*), \quad (\hat{c}_2^* - \check{c}_2^*)$$

we pick the largest one, say $(\hat{c}_2^* - \check{c}_2^*)$, and the corresponding equations (7.11), (7.12),

$$f_2(\check{c}_1^*, \hat{c}_2^*, \hat{S}_2) = 0, \quad f_2(\hat{c}_1^*, \check{c}_2^*, \check{S}_2) = 0 \tag{7.18}$$

(analogously to equations (6.8), (6.10)). From (7.13)-(7.16) we deduce that

$$\begin{aligned} \hat{S}_1 - \check{S}_1 &\leq [v_1(\hat{a}_1^* - \check{a}_1^*) + v_2(\check{b}_1^* - \hat{b}_1^*) + v_3(\hat{c}_1^* - \check{c}_1^*)]/v \qquad (7.19)\\ &\leq \hat{a}_1^* - \check{a}_1^*, \\ \hat{S}_2 - \check{S}_2 &\leq [v_1(\hat{a}_2^* - \check{a}_2^*) + v_2(\check{b}_2^* - \hat{b}_2^*) + v_3(\hat{c}_2^* - \check{c}_2^*)]/v \qquad (7.20)\\ &\leq \hat{c}_2^* - \check{c}_2^*. \end{aligned}$$

We use (7.17) and (7.19) to estimate $|\hat{a}_1^* - \check{a}_1^*|$ in terms of $|\hat{a}_2^* - \check{a}_2^*|$, as in the derivation of (6.12). We next use (7.18) and (7.20) to estimate $|\hat{c}_2^* - \check{c}_2^*|$ in terms of $|\hat{c}_1^* - \check{c}_1^*|$. Finally, from the two estimates on $|\hat{a}_1^* - \check{a}_1^*|$ and $|\hat{c}_2^* - \check{c}_2^*|$ and the inequalities

$$|\hat{a}_2^* - \check{a}_2^*| \leq |\hat{c}_2^* - \check{c}_2^*|, \text{ and } |\hat{c}_1^* - \check{c}_1^*| \leq |\hat{a}_1^* - \check{a}_1^*|, \tag{7.21}$$

we derive the estimates (6.14), (6.15) which yield a contradiction to (6.6). Assertions (7.3) and (7.4) are thus established.

Setting $n_{\mathrm{l}} = N_0 \cdot w_{\mathrm{l}}, n_{\mathrm{u}} = N_0 \cdot w_{\mathrm{u}}$, we summarize:

Theorem 7.1. If conditions (6.6), (7.1) and (7.2) hold then the solution ψ of (2.10), (3.1), with f_i, S_i defined by (2.5), (2.6), (2.11), satisfies:

$$\lim_{t\to\infty} \psi(t, x_2, x_2) = n_{\mathrm{l}}\delta_{(\overline{a}_1,\overline{a}_2)} + n_{\mathrm{u}}\delta_{(\overline{c}_1,\overline{c}_2)} \tag{7.22}$$

where $n_{\mathrm{l}} + n_{\mathrm{u}} = N_0$ and the points $(\overline{a}_1, \overline{a}_2)$ and $(\overline{c}_1, \overline{c}_2)$ together with the weights w_{l}, w_{u} satisfy equation (7.5)-(7.8); the convergence in (7.22) is in the sense of convergence in measure.

Remark 7.1. Theorem 7.1 extends to the case where instead of (7.1), (7.2) we assume that

$$\text{condition (B2) holds}, \hat{f}_2(\hat{p}_2^{\rm m}) < 0, \text{and } \check{f}_2(\check{p}_2^{\rm M}) > 0,$$

$$\text{and either condition (M1) holds, or (B1) and } \hat{f}_1(\hat{p}_1^{\rm M}) < 0 \text{ hold.}$$

8 Asymptotic four-peak solutions

In this section we assume, analogously to the case of Theorem 4.1(vi), that

$$\text{conditions (B1), (B2) hold, and } \hat{f}_i(\hat{p}_i^{\rm m}) < 0, \check{f}_i(\hat{p}_i^{\rm M}) > 0,\ i = 1, 2. \qquad (8.1)$$

As in sections 6,7, in view of (8.1) and (5.3)-(5.4), for any small $\varepsilon_0 > 0$, there exists a $T_0 > 0$ such that any solution $\mathbf{x}(t, \mathbf{x}_0)$ starting from a point $\mathbf{x}_0 \in [0, A_1]\times[0, A_2]\backslash K^{(0)}$, falls into one of the four rectangles

$$\Omega^{(0)} = \Omega_{\rm ll}^{(0)} \cup \Omega_{\rm ul}^{(1)} \cup \Omega_{\rm lu}^{(0)} \cup \Omega_{\rm uu}^{(1)},$$

for $t \geq T_0$, where

$$K^{(0)} = \Omega_{\rm ml}^{(0)} \cup \Omega_{\rm lm}^{(0)} \cup \Omega_{\rm mm}^{(0)} \cup \Omega_{\rm um}^{(0)} \cup \Omega_{\rm mu}^{(0)},$$

$$\begin{aligned}
\Omega_{\rm ll}^{(0)} &= [\check{a}_1^{(0)} - \varepsilon_0, \hat{a}_1^{(0)} + \varepsilon_0] \times [\check{a}_2^{(0)} - \varepsilon_0, \hat{a}_2^{(0)} + \varepsilon_0],\\
\Omega_{\rm ul}^{(0)} &= [\check{c}_1^{(0)} - \varepsilon_0, \hat{c}_1^{(0)} + \varepsilon_0] \times [\check{a}_2^{(0)} - \varepsilon_0, \hat{a}_2^{(0)} + \varepsilon_0],\\
\Omega_{\rm lu}^{(0)} &= [\check{a}_1^{(0)} - \varepsilon_0, \hat{a}_1^{(0)} + \varepsilon_0] \times [\check{c}_2^{(0)} - \varepsilon_0, \hat{c}_2^{(0)} + \varepsilon_0],\\
\Omega_{\rm uu}^{(0)} &= [\check{c}_1^{(0)} - \varepsilon_0, \hat{c}_1^{(0)} + \varepsilon_0] \times [\check{c}_2^{(0)} - \varepsilon_0, \hat{c}_2^{(0)} + \varepsilon_0],\\
\Omega_{\rm ml}^{(0))} &= [\hat{b}_1^{(0)}, \check{b}_1^{(0)}] \times [\check{a}_2^{(0)}, \hat{a}_2^{(0)}], \Omega_{\rm lm}^{(0)} = [\check{a}_1^{(0)}, \hat{a}_1^{(0)}] \times [\hat{b}_2^{(0)}, \check{b}_2^{(0)}],\\
\Omega_{\rm mm}^{(0)} &= [\hat{b}_1^{(0)}, \check{b}_1^{(0)}] \times [\hat{b}_2^{(0)}, \check{b}_2^{(0)}], \Omega_{\rm um}^{(0)} = [\check{c}_1^{(0)}, \hat{c}_1^{(0)}] \times [\hat{b}_2^{(0)}, \check{b}_2^{(0)}],\\
\Omega_{\rm mu}^{(0)} &= [\hat{b}_1^{(0)}, \check{b}_1^{(0)}] \times [\check{c}_2^{(0)}, \hat{c}_2^{(0)}].
\end{aligned}$$

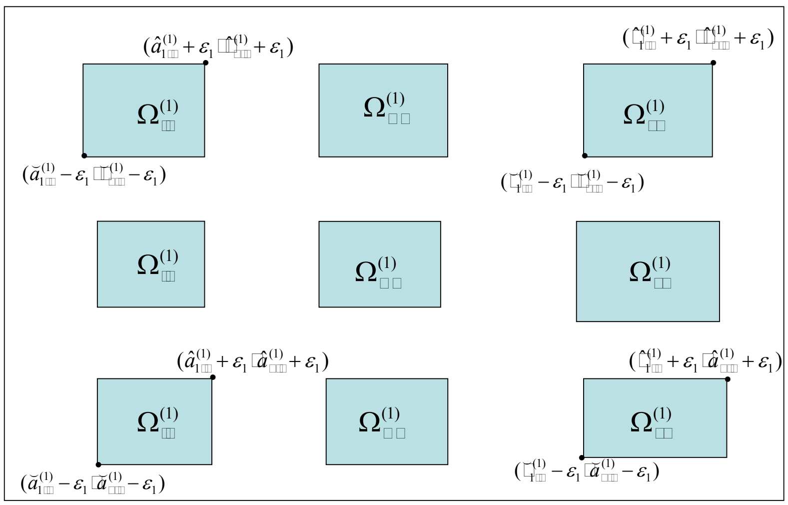


Figure 6: Notations for $\Omega^{(1)}$ and its components, for the four-peak case.

We then need to concentrate only on the dynamics in $\Omega^{(0)}$ and $K^{(0)}$. Define

$$\hat{f}^{(1)}_{1,\mathrm{l}}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_0)}{\rho_1 + S_1^{\max}(T_0)}) \cdot \frac{1}{1 + (\check{a}_2^{(0)} - \varepsilon_0)/\gamma_2} + \beta_1,$$
$$\check{f}^{(1)}_{1,\mathrm{l}}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_0)}{\rho_1 + S_1^{\min}(T_0)}) \cdot \frac{1}{1 + (\hat{a}_2^{(0)} + \varepsilon_0)/\gamma_2} + \beta_1,$$
$$\hat{f}^{(1)}_{1,\mathrm{m}}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_0)}{\rho_1 + S_1^{\max}(T_0)}) \cdot \frac{1}{1 + \hat{b}_2^{(0)}/\gamma_2} + \beta_1,$$
$$\check{f}^{(1)}_{1,\mathrm{m}}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_0)}{\rho_1 + S_1^{\min}(T_0)}) \cdot \frac{1}{1 + \check{b}_2^{(0)}/\gamma_2} + \beta_1,$$
$$\hat{f}^{(1)}_{1,\mathrm{u}}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_0)}{\rho_1 + S_1^{\max}(T_0)}) \cdot \frac{1}{1 + (\check{c}_2^{(0)} - \varepsilon_0)/\gamma_2} + \beta_1,$$
$$\check{f}^{(1)}_{1,\mathrm{u}}(x_1) = -\mu x_1 + (\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_0)}{\rho_1 + S_1^{\min}(T_0)}) \cdot \frac{1}{1 + (\hat{c}_2^{(0)} + \varepsilon_0)/\gamma_2} + \beta_1,$$

and similarly, by interchanging indices $i = 1$ and $i = 2$, define

$$\hat{f}^{(1)}_{2,\mathrm{l}}(x_2), \check{f}^{(1)}_{2,\mathrm{l}}(x_2), \hat{f}^{(1)}_{2,\mathrm{m}}(x_2), \check{f}^{(1)}_{2,\mathrm{m}}(x_2), \hat{f}^{(1)}_{2,\mathrm{u}}(x_2), \check{f}^{(1)}_{2,\mathrm{u}}(x_2).$$

Next, let $\hat{a}^{(1)}_{i,\mathrm{l}}$, $\check{a}^{(1)}_{i,\mathrm{l}}$ (respectively $\hat{a}^{(1)}_{i,\mathrm{m}}$, $\check{a}^{(1)}_{i,\mathrm{m}}$; $\hat{a}^{(1)}_{i,\mathrm{u}}$, $\check{a}^{(1)}_{i,\mathrm{u}}$) be the smallest zeros, $\hat{b}^{(1)}_{i,\mathrm{l}}$, $\check{b}^{(1)}_{i,\mathrm{l}}$ (respectively $\hat{b}^{(1)}_{i,\mathrm{m}}$, $\check{b}^{(1)}_{i,\mathrm{m}}$; $\hat{b}^{(1)}_{i,\mathrm{u}}$, $\check{b}^{(1)}_{i,\mathrm{u}}$) be the middle zeros, and $\hat{c}^{(1)}_{i,\mathrm{l}}$, $\check{c}^{(1)}_{i,\mathrm{l}}$ (respectively $\hat{c}^{(1)}_{i,\mathrm{m}}$, $\check{c}^{(1)}_{i,\mathrm{m}}$; $\hat{c}^{(1)}_{i,\mathrm{u}}$, $\check{c}^{(1)}_{i,\mathrm{u}}$) be the largest zeros of $\hat{f}^{(1)}_{i,\mathrm{l}}$, $\check{f}^{(1)}_{i,\mathrm{l}}$ (respectively $\hat{f}^{(1)}_{i,\mathrm{m}}$, $\check{f}^{(1)}_{i,\mathrm{m}}$; $\hat{f}^{(1)}_{i,\mathrm{u}}$, $\check{f}^{(1)}_{i,\mathrm{u}}$). Then for any small $\varepsilon_1 > 0$ there exists a $T_1 > T_0$ such that any solution $\mathbf{x}(t, \mathbf{x}_0)$ starting from a point $\mathbf{x}_0 \in [0, A_1] \times [0, A_2] \setminus K^{(1)}$ falls into one of the four rectangles

$$\Omega^{(1)} = \Omega^{(1)}_{\mathrm{ll}} \cup \Omega^{(1)}_{\mathrm{ul}} \cup \Omega^{(1)}_{\mathrm{lu}} \cup \Omega^{(1)}_{\mathrm{uu}} \subset \Omega^{(0)},$$

for $t \geq T_1$, where

$$K^{(1)} = \Omega^{(1)}_{\mathrm{ml}} \cup \Omega^{(1)}_{\mathrm{lm}} \cup \Omega^{(1)}_{\mathrm{mm}} \cup \Omega^{(1)}_{\mathrm{um}} \cup \Omega^{(1)}_{\mathrm{mu}} \subset K^{(0)},$$

$$\Omega^{(1)}_{\mathrm{ll}} = [\check{a}^{(1)}_{1,\mathrm{l}} - \varepsilon_1, \hat{a}^{(1)}_{1,\mathrm{l}} + \varepsilon_1] \times [\check{a}^{(1)}_{2,\mathrm{l}} - \varepsilon_1, \hat{a}^{(1)}_{2,\mathrm{l}} + \varepsilon_1] \subset \Omega^{(0)}_{\mathrm{ll}},$$
$$\Omega^{(1)}_{\mathrm{ul}} = [\check{c}^{(1)}_{1,\mathrm{l}} - \varepsilon_1, \hat{c}^{(1)}_{1,\mathrm{l}} + \varepsilon_1] \times [\check{a}^{(1)}_{2,\mathrm{u}} - \varepsilon_1, \hat{a}^{(1)}_{2,\mathrm{u}} + \varepsilon_1] \subset \Omega^{(0)}_{\mathrm{ul}},$$
$$\Omega^{(1)}_{\mathrm{lu}} = [\check{a}^{(1)}_{1,\mathrm{u}} - \varepsilon_1, \hat{a}^{(1)}_{1,\mathrm{u}} + \varepsilon_1] \times [\check{c}^{(1)}_{2,\mathrm{l}} - \varepsilon_1, \hat{c}^{(1)}_{2,\mathrm{l}} + \varepsilon_1] \subset \Omega^{(0)}_{\mathrm{lu}},$$
$$\Omega^{(1)}_{\mathrm{uu}} = [\check{c}^{(1)}_{1,\mathrm{u}} - \varepsilon_1, \hat{c}^{(1)}_{1,\mathrm{u}} + \varepsilon_1] \times [\check{c}^{(1)}_{2,\mathrm{u}} - \varepsilon_1, \hat{c}^{(1)}_{2,\mathrm{u}} + \varepsilon_1] \subset \Omega^{(0)}_{\mathrm{uu}},$$
$$\Omega^{(1)}_{\mathrm{ml}} = [\hat{b}^{(1)}_{1,\mathrm{l}}, \check{b}^{(1)}_{1,\mathrm{l}}] \times [\check{a}^{(1)}_{2,\mathrm{m}}, \hat{a}^{(1)}_{2,\mathrm{m}}] \subset \Omega^{(0)}_{\mathrm{ml}},\ \Omega^{(1)}_{\mathrm{lm}} = [\check{a}^{(1)}_{1,\mathrm{m}}, \hat{a}^{(1)}_{1,\mathrm{m}}] \times [\hat{b}^{(1)}_{2,\mathrm{l}}, \check{b}^{(1)}_{2,\mathrm{l}}] \subset \Omega^{(0)}_{\mathrm{lm}},$$
$$\Omega^{(1)}_{\mathrm{mm}} = [\hat{b}^{(1)}_{1,\mathrm{m}}, \check{b}^{(1)}_{1,\mathrm{m}}] \times [\hat{b}^{(1)}_{2,\mathrm{m}}, \check{b}^{(1)}_{2,\mathrm{m}}] \subset \Omega^{(0)}_{\mathrm{mm}},\ \Omega^{(1)}_{\mathrm{um}} = [\check{c}^{(1)}_{1,\mathrm{m}}, \hat{c}^{(1)}_{1,\mathrm{m}}] \times [\hat{b}^{(1)}_{2,\mathrm{u}}, \check{b}^{(1)}_{2,\mathrm{u}}] \subset \Omega^{(0)}_{\mathrm{um}},$$
$$\Omega^{(1)}_{\mathrm{mu}} = [\hat{b}^{(1)}_{1,\mathrm{u}}, \check{b}^{(1)}_{1,\mathrm{u}}] \times [\check{c}^{(1)}_{2,\mathrm{m}}, \hat{c}^{(1)}_{2,\mathrm{m}}] \subset \Omega^{(0)}_{\mathrm{mu}};$$

Figure 6 describes the four components of $\Omega^{(1)}$ and the five components of $K^{(1)}$.

We then consider the dynamics on $\Omega^{(1)} \cup K^{(1)}$. Successively, we can define $\hat{a}_{i,*}^{(k)}, \check{a}_{i,*}^{(k)}, \hat{b}_{i,*}^{(k)}, \check{b}_{i,*}^{(k)}, \hat{c}_{i,*}^{(k)}, \check{c}_{i,*}^{(k)}$, $i = 1, 2, * = \mathrm{l, m, u}$, and $\Omega^{(k)}$ and $K^{(k)}$, for $k > 2$. Using (6.6) we can extend the argument used in Lemma 6.1 and in section 7 to show that each of the following intervals converges to a single point as $k \to \infty$:

$$[\check{a}_{i,*}^{(k)}, \hat{a}_{i,*}^{(k)}] \to \{\overline{a}_{i,*}\},\ [\hat{b}_{i,*}^{(k)}, \check{b}_{i,*}^{(k)}] \to \{\overline{b}_{i,*}\}, [\check{c}_{i,*}^{(k)}, \hat{c}_{i,*}^{(k)}] \to \{\overline{c}_{i,*}\}, i = 1, 2,\ * = \mathrm{l, m, u},$$

so that

$$\Omega^{(k)} \to \{(\overline{a}_{1,\mathrm{l}}, \overline{a}_{2,\mathrm{l}}), (\overline{c}_{1,\mathrm{l}}, \overline{a}_{2,\mathrm{u}}), (\overline{a}_{1,\mathrm{u}}, \overline{c}_{2,\mathrm{l}}), (\overline{c}_{1,\mathrm{u}}, \overline{c}_{2,\mathrm{u}})\},\ \text{as } k \to \infty.$$

In addition,

$$S_1(t) \to \overline{S}_1 = w_{\mathrm{ll}} \cdot \overline{a}_{1,\mathrm{l}} + w_{\mathrm{ul}} \cdot \overline{c}_{1,\mathrm{l}} + w_{\mathrm{lu}} \cdot \overline{a}_{1,\mathrm{u}} + w_{\mathrm{uu}} \cdot \overline{c}_{1,\mathrm{u}} + \bar{C}_1,$$
$$S_2(t) \to \overline{S}_2 = w_{\mathrm{ll}} \cdot \overline{a}_{2,\mathrm{l}} + w_{\mathrm{ul}} \cdot \overline{a}_{2,\mathrm{u}} + w_{\mathrm{lu}} \cdot \overline{c}_{2,\mathrm{l}} + w_{\mathrm{uu}} \cdot \overline{c}_{2,\mathrm{u}} + \bar{C}_2,$$

as $t \to \infty$, for some $w_{\mathrm{ll}}, w_{\mathrm{ul}}, w_{\mathrm{lu}}, w_{\mathrm{uu}} \geq 0$ with $w_{\mathrm{ll}} + w_{\mathrm{ul}} + w_{\mathrm{lu}} + w_{\mathrm{uu}} = 1$. Here, $w_{\mathrm{ll}}, w_{\mathrm{ul}}, w_{\mathrm{lu}}, w_{\mathrm{uu}}$ represent the percentage of cells whose concentrations tend to levels $(\overline{a}_{1,\mathrm{l}}, \overline{a}_{2,\mathrm{l}}), (\overline{c}_{1,\mathrm{l}}, \overline{a}_{2,\mathrm{u}}), (\overline{a}_{1,\mathrm{u}}, \overline{c}_{2,\mathrm{l}}), (\overline{c}_{1,\mathrm{u}}, \overline{c}_{2,\mathrm{u}})$, respectively. Notice that these points together with the w's weights satisfy

$$f_i(\overline{a}_{1,\mathrm{l}}, \overline{a}_{2,\mathrm{l}}, w_{\mathrm{ll}} \cdot \overline{a}_{1,\mathrm{l}} + w_{\mathrm{ul}} \cdot \overline{c}_{1,\mathrm{l}} + w_{\mathrm{lu}} \cdot \overline{a}_{1,\mathrm{u}} + w_{\mathrm{uu}} \cdot \overline{c}_{1,\mathrm{u}} + \bar{C}_i) = 0, \tag{8.2}$$
$$f_i(\overline{c}_{1,\mathrm{l}}, \overline{a}_{2,\mathrm{u}}, w_{\mathrm{ll}} \cdot \overline{a}_{1,\mathrm{l}} + w_{\mathrm{ul}} \cdot \overline{c}_{1,\mathrm{l}} + w_{\mathrm{lu}} \cdot \overline{a}_{1,\mathrm{u}} + w_{\mathrm{uu}} \cdot \overline{c}_{1,\mathrm{u}} + \bar{C}_i) = 0, \tag{8.3}$$
$$f_i(\overline{a}_{1,\mathrm{u}}, \overline{c}_{2,\mathrm{l}}, w_{\mathrm{ll}} \cdot \overline{a}_{1,\mathrm{l}} + w_{\mathrm{ul}} \cdot \overline{c}_{1,\mathrm{l}} + w_{\mathrm{lu}} \cdot \overline{a}_{1,\mathrm{u}} + w_{\mathrm{uu}} \cdot \overline{c}_{1,\mathrm{u}} + \bar{C}_i) = 0, \tag{8.4}$$
$$f_i(\overline{c}_{1,\mathrm{u}}, \overline{c}_{2,\mathrm{u}}, w_{\mathrm{ll}} \cdot \overline{a}_{1,\mathrm{l}} + w_{\mathrm{ul}} \cdot \overline{c}_{1,\mathrm{l}} + w_{\mathrm{lu}} \cdot \overline{a}_{1,\mathrm{u}} + w_{\mathrm{uu}} \cdot \overline{c}_{1,\mathrm{u}} + \bar{C}_i) = 0, \tag{8.5}$$

for $i = 1, 2$.

Setting $n_{\mathrm{ll}} = N_0 \cdot w_{\mathrm{ll}}, n_{\mathrm{lu}} = N_0 \cdot w_{\mathrm{lu}}, n_{\mathrm{lu}} = N_0 \cdot w_{\mathrm{lu}}, n_{\mathrm{uu}} = N_0 \cdot w_{\mathrm{uu}}$, we summarize:

Theorem 8.1. If the conditions (6.6) and (8.1) hold then the solution ψ of (2.10), (3.1), with f_i, S_i defined by (2.5), (2.6), (2.11), satisfies:

$$\lim_{t\to\infty} \psi(t, x_2, x_2) = n_{\mathrm{ll}} \cdot \delta_{(\overline{a}_{1,\mathrm{l}}, \overline{a}_{2,\mathrm{l}})} + n_{\mathrm{ul}} \cdot \delta_{(\overline{c}_{1,\mathrm{l}}, \overline{a}_{2,\mathrm{u}})} + n_{\mathrm{lu}} \cdot \delta_{(\overline{a}_{1,\mathrm{u}}, \overline{c}_{2,\mathrm{l}})} + n_{\mathrm{uu}} \cdot \delta_{(\overline{c}_{1,\mathrm{u}}, \overline{c}_{2,\mathrm{u}})}. \tag{8.6}$$

where $n_{\mathrm{ll}} + n_{\mathrm{lu}} + n_{\mathrm{lu}} + n_{\mathrm{uu}} = N_0$; the points $(\overline{a}_{1,\mathrm{l}}, \overline{a}_{2,\mathrm{l}})$, $(\overline{c}_{1,\mathrm{l}}, \overline{a}_{2,\mathrm{u}})$, $(\overline{a}_{1,\mathrm{u}}, \overline{c}_{2,\mathrm{l}})$, $(\overline{c}_{1,\mathrm{u}}, \overline{c}_{2,\mathrm{u}})$ and the weights w_{ll}, w_{lu}, w_{lu}, w_{uu} satisfy equations (8.2)-(8.5) and the convergence in (8.6) is in the sense of convergence in measure.

9 Numerical Illustrations

In this section, we provide numerical simulations for the single cell model (2.1) (2.2) and for the population model (2.4).

The single cell model is a system of two ordinary differential equations (ODEs) which can be easily solved by the Runge-Kutta method, using ode45 in MATLAB. The population model (2.4) is essentially an integro-differential equation. The integrations in the $S_i(t)$ need to be carried out through quadrature rule (numerical integration); we shall use Simpson's rule which has third order accuracy. The solution of equation (2.4) is then obtained by using Lax-Friedrichs method [10] [11]. Notice that the asymptotic solution of the population model becomes singular for large time. In order to obtain highly accurate solution, refinement is definitely needed at the places where population density tends to grow, and the corresponding quadrature rule has to be redesigned; this we have done for the one-peak case, but not for the multi-peak cases: we stopped the numerical simulations after the asymptotic singular solutions are observed.

9.1 The single cell model

In Figure 7, we first demonstrate the single cell model results. The parameters for (a)-(e) are chosen as those in [15], namely,

$$\mu = 5 \text{ day}^{-1},\ \alpha_1 = \alpha_2 = 5 \text{ day}^{-1},\ \ \sigma_1 = \sigma_2 = 5 \text{ day}^{-1}, \tag{9.1}$$

$$k_1 = k_2 = 1,\ \rho_1 = \rho_2 = 1,\ \gamma_1 = 1,\ \gamma_2 = 0.5, \tag{9.2}$$

$$\beta_1 = \beta_2 = 0.05 \text{ day}^{-1},\ n = 6. \tag{9.3}$$

For these parameters, we take $A_1 = A_2 = 2.01$. Then

$$\frac{\alpha_1 \tilde{n}}{k_1} \cdot \frac{1}{1 + A_2/\gamma_2} < \mu < \frac{\alpha_1 \tilde{n}}{k_1},$$

$$\frac{\alpha_2 \tilde{n}}{k_2} \cdot \frac{1}{1 + A_1/\gamma_1} < \mu < \frac{\alpha_2 \tilde{n}}{k_2},$$

so that the conditions (M1) and (M2) are not satisfied. Thus, $\hat{f}_i$ defined in (4.1) has a local minimum and a local maximum for $i = 1, 2$.

In addition, conditions (B1), (B2) may hold for the B_i defined in section 4. This gives the flexibility for the system to be either monostable or bistable under different choices of S_1 and S_2. For example, the system is

(a) monostable (MS) for $S_1 = 0.05, S_2 = 0.025$, with the choice of $B_1 = 0.058$ and $B_2 = 0.035$; in this case (B1), (B2) hold and $\hat{f}_i(\hat{p}_i^{\mathrm{M}}) < 0$ $(i = 1, 2)$;
(b) bistable (BS-ll,hl) for $S_1 = 1.2, S_2 = 0.025$ with $B_1 = 1.181$ and $B_2 = 0.035$; in this case (B1), (B2) holds, and $\hat{f}_1(\hat{p}_1^{\mathrm{m}}) < 0,\ \check{f}_1(\check{p}_1^{\mathrm{M}}) > 0,\ \hat{f}_2(\hat{p}_2^{\mathrm{M}}) < 0$ hold;
(c) bistable (BS-ll,lh) for $S_1 = 0.05, S_2 = 1.3$ with $B_1 = 0.058$ and $B_2 = 1.493$; in this case (B1), (B2) hold and $\hat{f}_2(\hat{p}_2^{\mathrm{m}}) < 0,\ \check{f}_2(\check{p}_2^{\mathrm{M}}) > 0,\ \hat{f}_1(\hat{p}_1^{\mathrm{M}}) < 0$ hold.

Each of these cases is shown in Figure 7, where we chose 36 different initial conditions $(x_1(0), x_2(0))$ and depicted their evolution. The blue curve is the nullcline of f_1 while the black curve is the nullcline of f_2. We can clearly see that the solutions converge to a single stable equilibrium in case (a) and to two stable equilibria in case (b) and (c). The bistable-ll,hl (bistable-ll,lh) system with low x_1-low x_2 and high x_1- low x_2 states (low x_1-low x_2 and low x_1- high x_2 states), shown in case (b)((c)) can become monostable with high x_1- low x_2 state (low x_1- high x_2), shown in (d)((e)) by increasing the value of $S_1(S_2)$. Notice that (d)((e)) satisfies conditions (B1), $\check{f}_1(\check{p}_1^{\mathrm{m}}) > 0$ and (B2), $\hat{f}_2(\hat{p}_2^{\mathrm{M}}) < 0$ with $B_1 = 1.626$ and $B_2 = 0.035$ ((B2) $\check{f}_2(\check{p}_2^{\mathrm{m}}) > 0$, (B1), $\hat{f}_1(\hat{p}_1^{\mathrm{M}}) < 0$ with $B_1 = 0.058$ and $B_2 = 1.626$). It is also possible to switch from bistable-ll,hl (bistable-ll,lh) to monostable by decreasing S_2 (S_1).

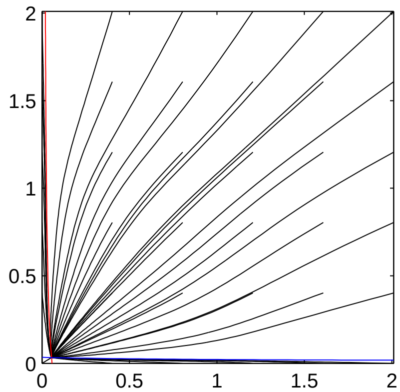
However, the system with parameters (9.1)-(9.3) cannot be quadstable due to the strong mutual inhibition (i.e., small γ_1, γ_2). If we decrease the mutual inhibition by taking parameters $\gamma_1 = \gamma_2 = 30$, $\sigma_1 = \sigma_2 = 2$, $k_1 = k_2 = 0.6$, but keep all the other parameters the same, then conditions (B1), (B2), $\hat{f}_i(\hat{p}_i^{\mathrm{m}}) < 0,\ \check{f}_i(\check{p}_i^{\mathrm{M}}) > 0$, $i = 1, 2$, are satisfied, and by Theorem 4.1 (iv), the system is quadstable, as illustrated in Figure 8.

9.2 The population model

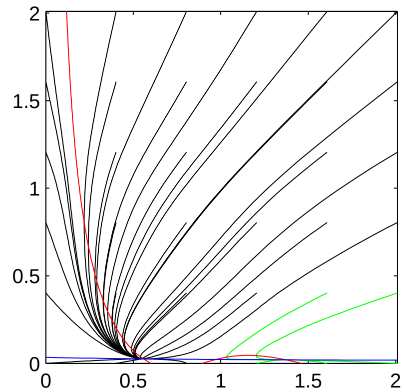
Since in the population model (2.4) S_1 and S_2 are not constant and their evolution depends on both the initial population of cells and the external signals $C_1(t)$, $C_2(t)$, one may expect interesting behavior; for example, the system may switch from one-peak to two-peak profile at intermediate times. In the subsequent numerical simulations we adapt the normalized population density $\psi(t, x_1, x_2)$, take A_1, A_2 as in section 9.1, and choose the initial condition

$$\psi_0(x_1, x_2) = \text{const} = \frac{1}{A_1 A_2} \tag{9.4}$$

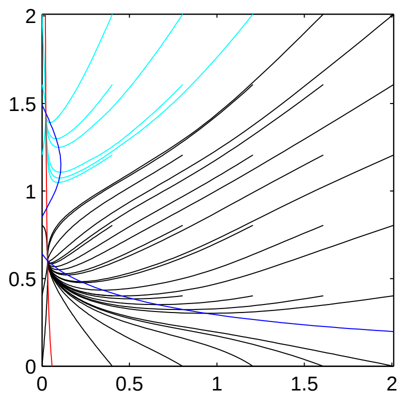
so that $N_0 = 1$. Although in (3.1) we assumed that $\psi_0 = 0$ on $\partial\Omega$, the results of sections 6-8 do not actually use this assumption. Furthermore, the simulations



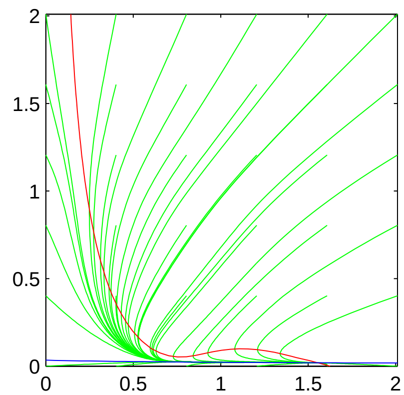
(a) $S_1 = 0.05, S_2 = 0.025$



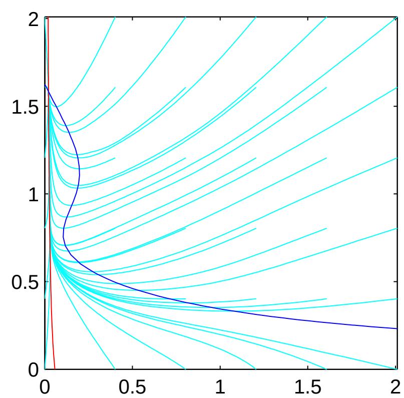
(b) $S_1 = 1.2, S_2 = 0.025$



(c) $S_1 = 0.05, S_2 = 1.3$



(d) $S_1 = 2, S_2 = 0.025$



(e) $S_1 = 0.05, S_2 = 2.0$

Figure 7: Single cell model: (a) Monostable: the stable equilibrium is $(x_1, x_2) \approx (0.055, 0.033)$. (b) Bistable-ll,hl: the stable equilibria are $(x_1, x_2) \approx (0.556, 0.026)$ and $(1.368, 0.020)$; the unstable equlibrium is $(x_1, x_2) \approx (0.976, 0.022)$. (c) Bistable-ll,lh: the stable equilibria are $(0.032, 0.602)$ and $(0.022, 1.444)$; the unstable equlibrium is $(0.027, 0.904)$(d) Monostable: the stable equilibrium is $(1.549, 0.020)$. (e) Monostable: the stable equilibrium is $(0.042, 1.544)$.

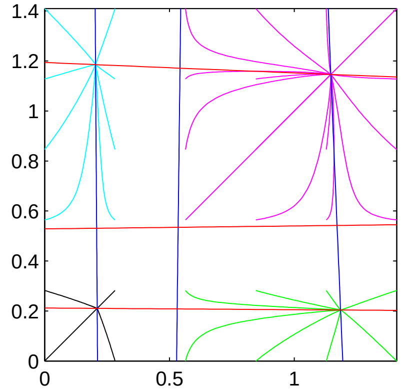


Figure 8: Single cell model: Quadstable: $S_1 = 0.04$, $S_2 = 1.6$, the stable equilibria are $(x_1, x_2) \approx (0.211, 0.211)$, $(0.204, 1.186)$, $(1.186, 0.204)$, $(1.146, 1.146)$ and the unstable equilibria $(x_1, x_2) \approx (0.208, 0.531)$, $(0.531, 0.208)$, $(0.535, 0.535)$, $(0.543, 1.171)$, $(1.171, 0.543)$.

given below do not significantly change if we modify (9.4) near the boundary $\partial\Omega$ so as to make ψ_0 vanish there.

In subsections 9.2.1-9.2.3 we have taken $C_i(t) = 0$, i.e., there is no external stimulus. In section 9.2.4 we examine the effect of the stimulus.

We first demonstrate one-, two-, and four-peak solutions by choosing specific parameters in the regimes we discussed in Theorem 4.1.

9.2.1 Asymptotic one-peak solution

In Figure 9 we show numerical results under conditions (M1) and (M2) which guarantee a single attracting point. Notice that we choose $k_1 = k_2 = 2$ instead of $k_1 = k_2 = 1$ in [15] in order to satisfy conditions (M1) and (M2). In Figure 9(a), 9(b), 9(c) we have plotted ψ and the corresponding vector field (f_1, f_2) at times $t = 0.05, 0.2, 5$. Since (M1) and (M2) are satisfied no matter what S_1 and S_2 are, there is only one stable equilibrium point (although the sufficient condition (6.6) in Theorem 6.2 is not satisfied). The vectors (f_1, f_2) all point toward the attracting point. The normalized population density gets more and more concentrated at an attracting point, and $(S_1(t), S_2(t))$ converges to $(\bar{a}_1, \bar{a}_2) \approx (0.054, 0.081)$.

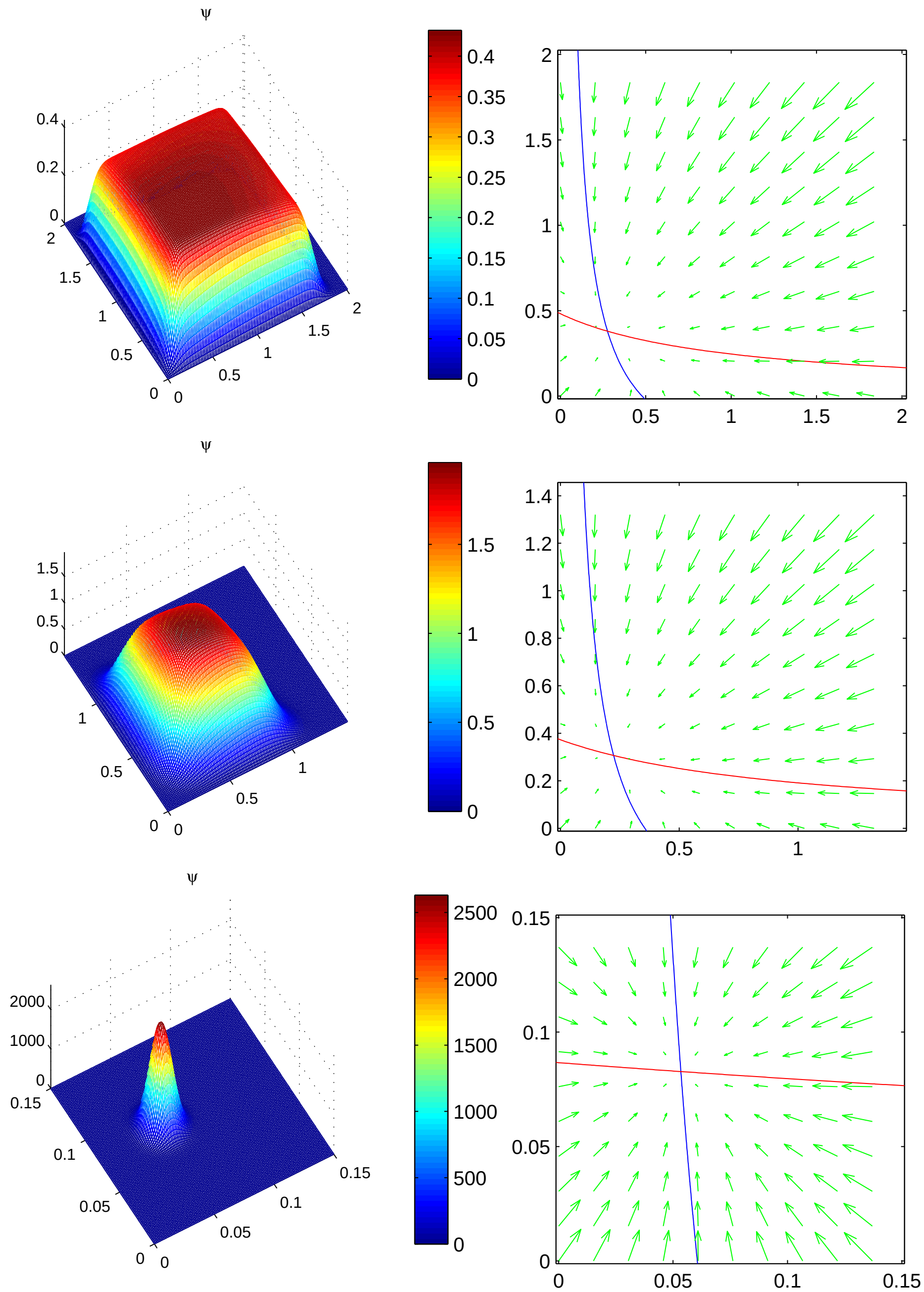


Figure 9: Monostable: $k_1 = k_2 = 2$ but all other parameters are as in (9.1)-(9.3) (a)$t = 0.05$, (b) $t = 0.2$ (c) $t = 5$

9.2.2 Asymptotic two-peak solution

Figure 10 displays bistable case (Bistable-ll,lh) with two-peak solution. We choose parameters $\sigma_1 = \sigma_2 = 2$, $\gamma_1 = 30, \gamma_2 = 1$, $k_1 = 5$, $k_2 = 0.6$. We see that the population density starts to accumulate at two attracting points and the population density is higher in low x_1- high x_2 state as proved in section 7. The weights w_1 and w_2 in the asymptotic solution depend on the initial population density. If most of the population density is initially in the attraction basin of low x_1- low x_2 state, then the weight for the Dirac function with center at low x_1- low x_2 state would be higher (not shown here).

9.2.3 Asymptotic four-peak solution

In Figure 11, the population density becomes highly concentrated at four attracting points as we expect from Theorem 8.1. The weights w_{11}, w_{u1}, w_{1u} and w_{uu} depend on the parameters of the system as well as on initial population density. The parameters chosen satisfy the condition (B1)' and (B2)', (and (6.6) is also satisfied). Note that the mutual inhibition is small (i.e., γ_1 and γ_2 are large).

9.2.4 Effect of the stimulus

In the previous subsections we have assumed that $C_i(t) \equiv 0$ (no external stimulus). We now want to examine the effect of these stimuli. We take the parameters as in (9.1)-(9.3): Figure 12 shows how with no stimuli (i.e with $C_1(t) \equiv C_2(t) \equiv 0$) the uniform populations begins to evolve and move into low-x_1-lowx_2 peak; this is interpreted biologically as no cell differentiation. In Figure 13 we choose $C_1(t) \exp^{-G(t)} = 0.5$ and $C_2(t) \exp^{-G(t)} = 1.5$ for all $t > 0$. We see that the solution develops a two-peak solution. Due to the larger stimulus of x_2 (i.e. $C_2(t) > C_1(t)$), as well as the stronger inhibition of x_1 by x_2, the low x_1 - high x_2 peak has much larger population than the low x_1-low x_2 peak.

In Figure 14 we use the same stimuli as in Figure 13, but have taken ψ_0 to be constant for $x_1 < A_1/5$ and zero elsewhere. Thus we give GATA-3 initial density advantage as well as stimulus advantage. We see that the population density moves again toward two-peak solution, low x_1- low x_2 and low x_1- high x_2, but the

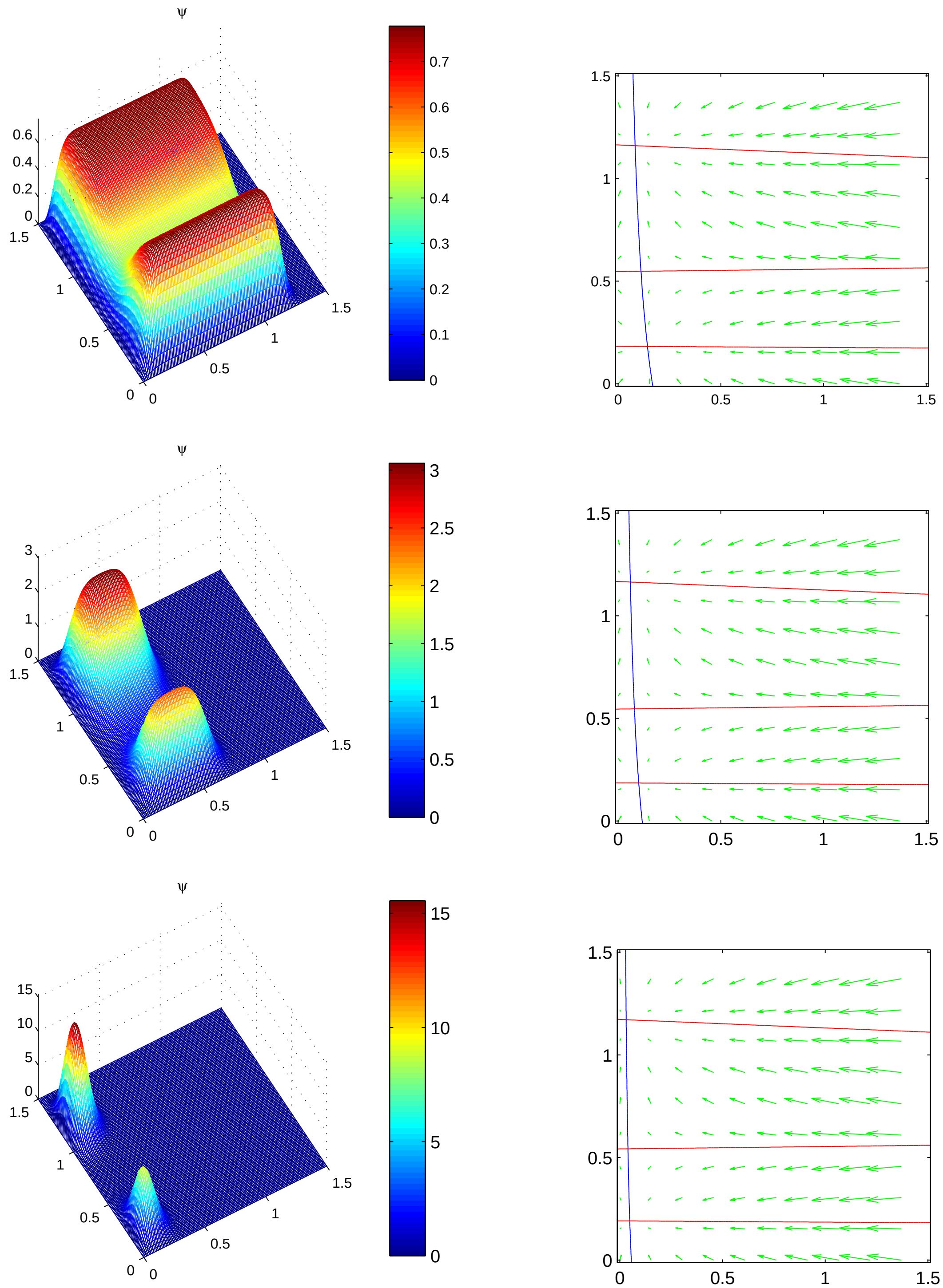


Figure 10: Bistable (BS-ll,lh): $\sigma_1 = \sigma_2 = 2$, $\gamma_1 = 30$,$\gamma_2 = 1$, $k_1 = 5$, $k_2 = 0.6$ and all other parameters are as in (9.1)-(9.3) (a)$t = 0.05$, (b) $t = 0.2$ (c) $t = 1$

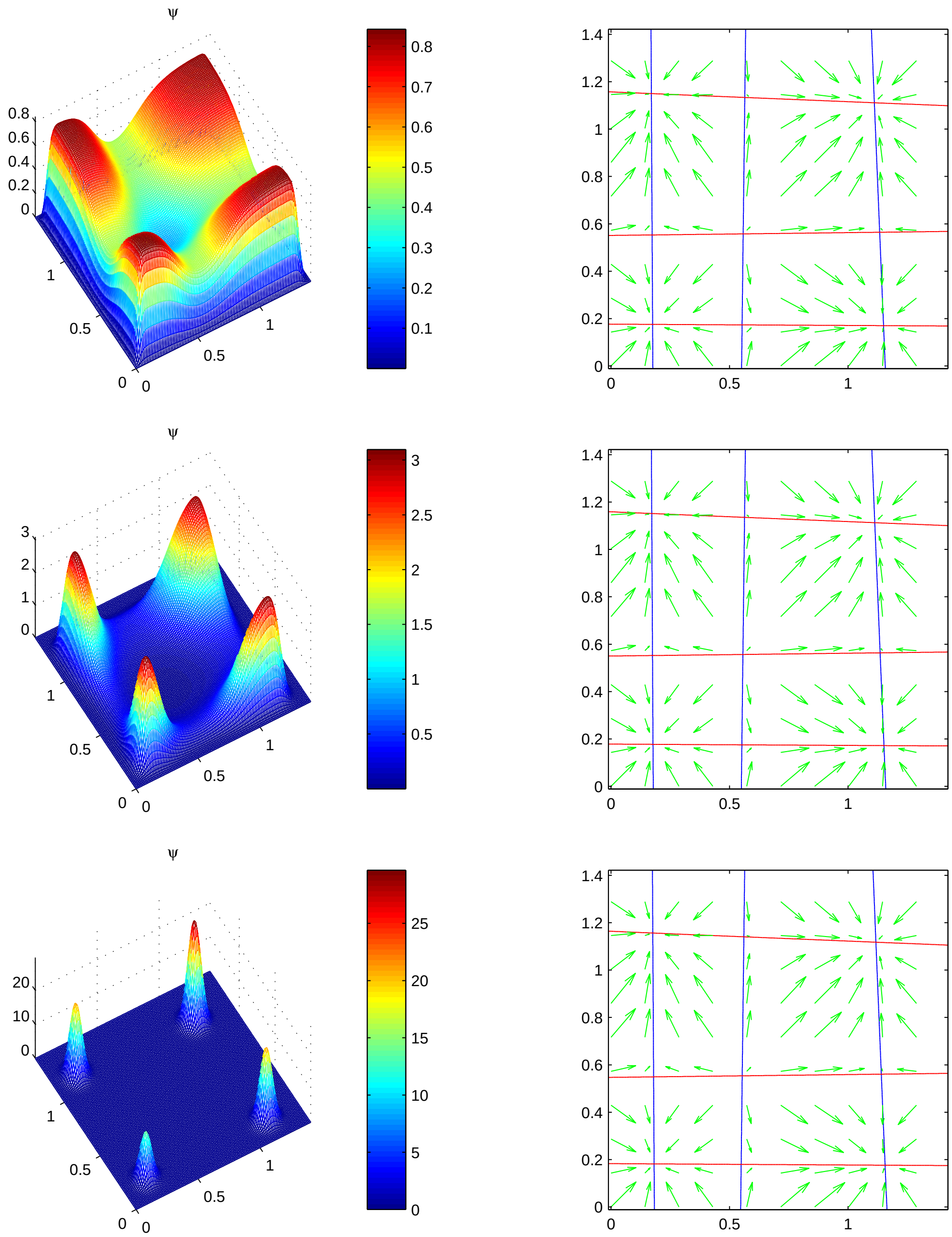


Figure 11: Quadstable: $\sigma_1 = \sigma_2 = 2$, $\gamma_1 = \gamma_2 = 30$, $k_1 = k_2 = 0.6$ and all other parameters are as in (9.1)-(9.3), (a)$t = 0.05$, (b) $t = 0.2$ (c) $t = 1$.

population density at the low x_1-high x_2 is larger than in Figure 13. In both Figure 13 and 14, the low x_1 - high x_2 can be interpreted biologically as a population of differentiated Th2 cells.

10 Conclusions

In this paper, we considered a conservative law of the form

$$\frac{\partial \phi}{\partial t} + \frac{\partial}{\partial x_1}(f_1 \phi) + \frac{\partial}{\partial x_2}(f_2 \phi) = g\phi, \quad \phi = \phi(t, x_1, x_2) \tag{10.1}$$

where the velocity vector $f = (f_1, f_2)$ is a nonlinear nonlocal function of ϕ. This equation arises as a model of T cell differentiation where $x = (x_1, x_2)$, and x_1, x_2 are the concentrations of transcription factors T-bet and GATA-3, respectively. A precursor T cell growing at rate g with x_1 large (small) and x_2 small (large) will differentiate into Th1 (Th2) T cell. Th1 and Th2 have different functions: Th1 T cells combat intracellular pathogens while Th2 T cells induce the activation of B cells to combat extracellular pathogens. A 'good' balance between these two populations of cells is maintained in homeostasis. The function $\phi(t, x_1, x_2)$ represents the population density of T cells with concentrations (x_1, x_2) at time t. Within an individual cell the concentrations of x_1 and x_2 vary according to the equations

$$\frac{dx_i}{dt} = f_i(t, x_1, x_2, \phi(t, \cdot)) \quad (i = 1, 2) \tag{10.2}$$

and the dependence on t and $\phi(t, \cdot)$ arises from stimuli $S_i(t)$ consisting of a stimulus which arises from within the entire population of the T cells and of an external stimulus C_i.

It is natural to ask what is the behavior of ϕ at intermediate and large times and how this depends on $C_i(t)$ and on the initial condition. In this paper, we have depicted six regions from the space of parameters that are introduced in the definition of the f_i. We proved that for the first regime the function $\phi(t, x_1, x_2)$ converges to a 1-peak solution as $t \to \infty$; for regimes 2,3,4, and 5, ϕ converges to a 2-peak solutions, and for regime 6, ϕ convergences to a 4-peak solution; this was illustrated in Figures 9-11 when $C_i(t) \equiv 0$

Numerical simulations given in Figure 12-14, show how the location of these peaks depend on the external signals $C_i(t)$ and the initial conditions. We interpret

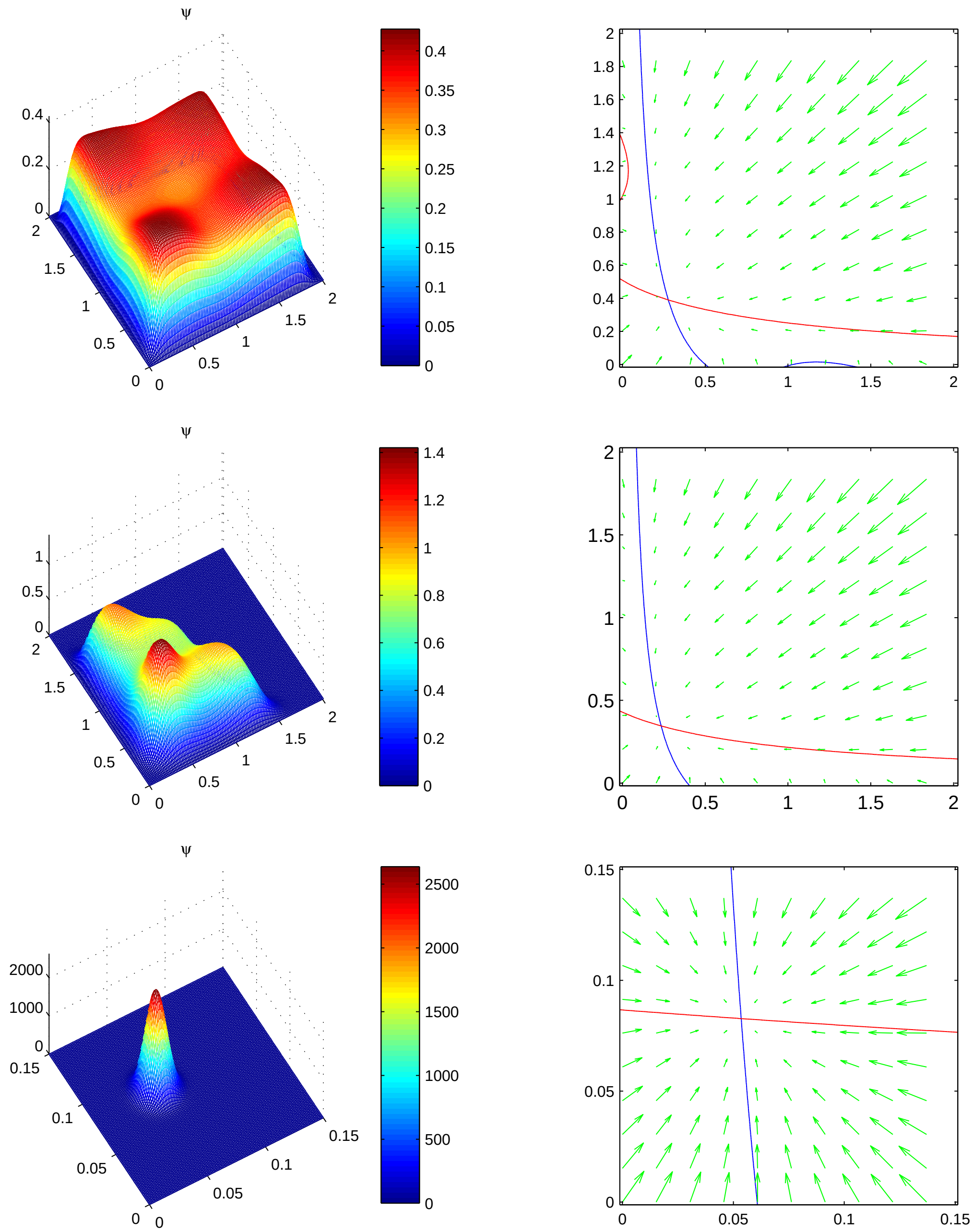


Figure 12: Monostable result: The parameters are as in (9.1)-(9.3). The population density moves toward low x_1- low x_2 state at (a)$t = 0.05$, (b)$t = 1.0$ and (c) $t = 5$.

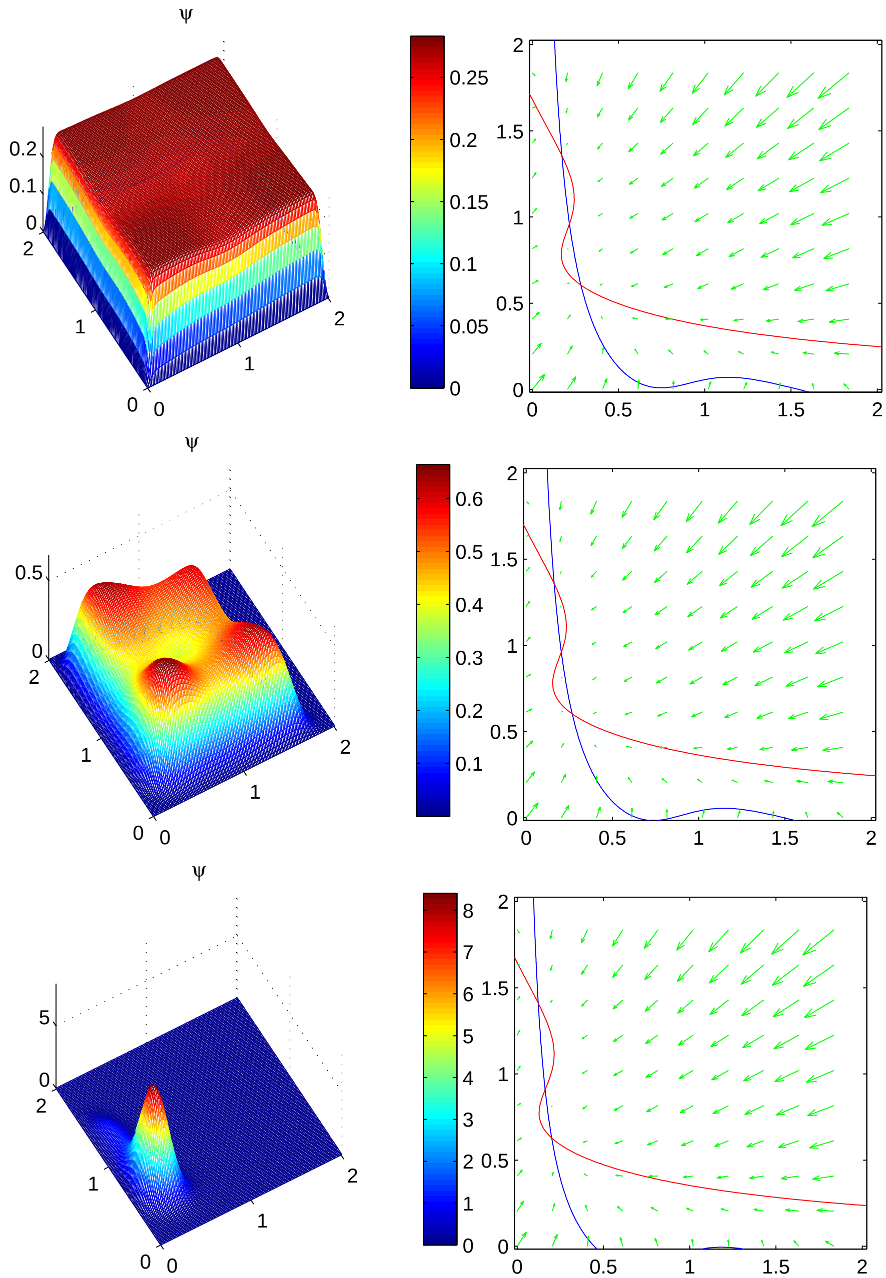


Figure 13: The parameters are as in (9.1)-(9.3). A uniform density evolves toward two stable points under external stimulus $C_1(t)e^{-G(t)} = 0.5$, $C_1(t)e^{-G(t)} = 1.5$. (a)$t = 0.01$ (b) $t = 0.1$ and (c) at $t = 1$

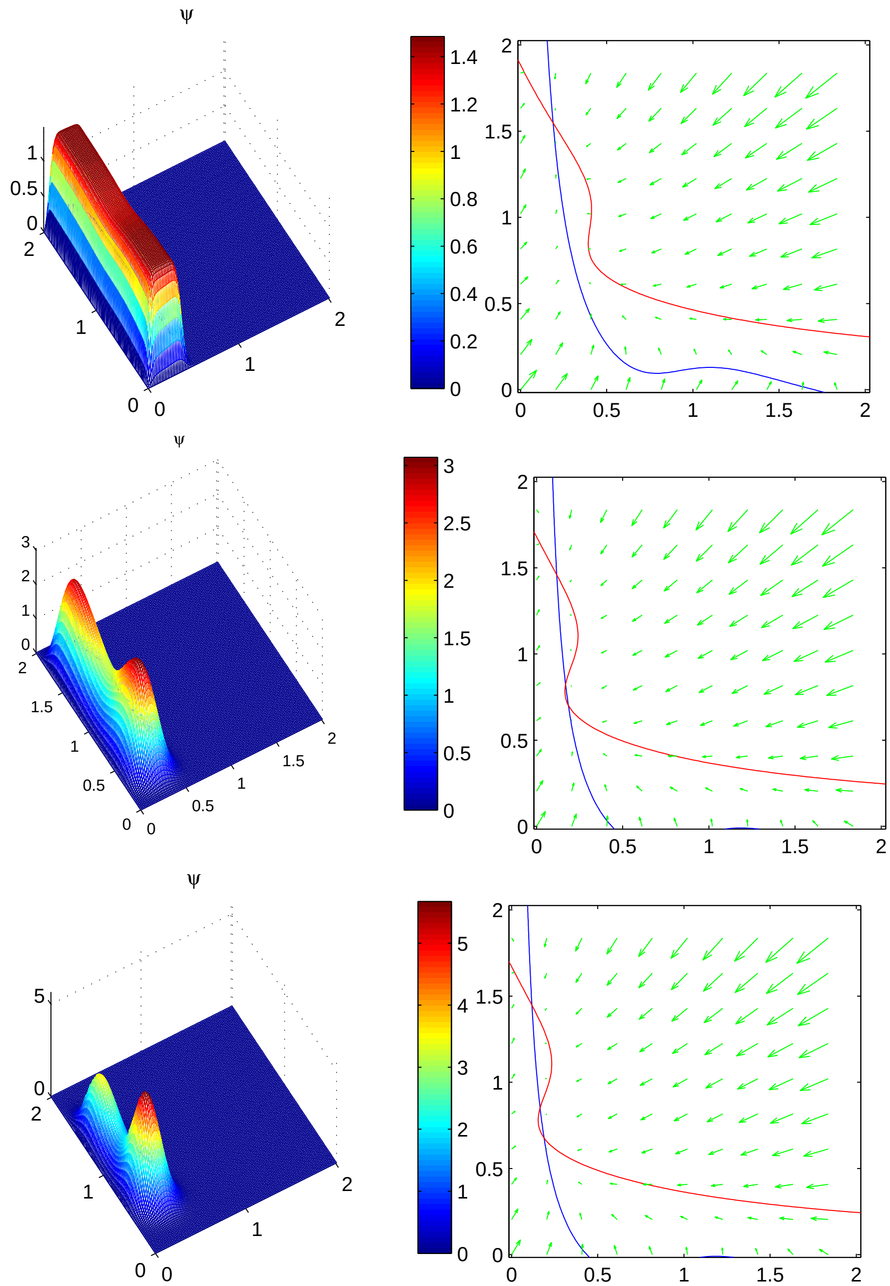


Figure 14: The parameters are as in (9.1)-(9.3). A uniform density at $x_1 < A_1/5$ evolves toward two stable points under external stimulus $C_1(t)e^{-G(t)} = 0.5$, $C_1(t)e^{-G(t)} = 1.5$. (a)$t = 0.01$ (b) $t = 0.1$ and (c) at $t = 1$

a peak centered at (x_1^0, x_2^0) with x_1^0, x_2^0 small as a population of T cell that do not differentiate. A peak with x_1^0 small, x_2^0 large represents a population of T cells that differentiate into Th2. In a similar way, we interpret the case of x_1^0 large, x_2^0 small. Finally, a situation where both x_1^0 and x_2^0 are large in viewed as abnormal: Since the concentrations of both T-bet and GATA-3 are large, the cell receive conflicting instructions to differentiate simultaneously to Th1 and Th2. This situation arises in Figure 11 where the mutual inhibition is weak (namely, $\gamma_1 = \gamma_2 = 30$). Hence one of the conclusions of our simulations is that, in homeostasis, the mutual inhibition cannot be too weak.

The results of the paper are obtained by approximating the full dynamical system

$$\frac{dx_i}{dt} = f_i(t, x_1, x_2, \phi(t, \cdot)) \quad (i = 1, 2) \tag{10.3}$$

from above and below by a sequence of dynamical systems where in each step of approximation the total signaling is constant but is 'sharper' than in the previous step. This method is quite general and could be applied to more general functions $f(t, x, \phi(\cdot))$ and in any number of dimensions for the x variable.

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