J. Differential Equations 252 (2012) 5679–5711

Contents lists available at SciVerse ScienceDirect

Journal of Differential Equations

www.elsevier.com/locate/jde

Asymptotic limit in a cell differentiation model with consideration of transcription

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ARTICLE INFO

Article history:
Received 25 August 2011
Revised 21 January 2012
Available online 20 February 2012

Keywords:
Cell differentiation
Th1/Th2 cells
Conservation law
Multistationary
Integro-differential equation
Transcription factors
mRNA

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). These factors are translated by the mRNA whose levels of expression, y_1 and y_2, depend, respectively, on x_1 and x_2 in a nonlinear nonlocal way. The population density of T cells, $\phi(t, x_1, x_2, y_1, y_2)$, satisfies a hyperbolic conservation law with coefficients depending nonlinearly and nonlocally on (t, x_1, x_2, y_1, y_2), while the x_i, y_i satisfy a system of ordinary differential equations. We study the long time behavior of ϕ and show, under some conditions on the parameters of the system of differential equations, that the gene expressions in the T-cell population aggregate at one, two or four points, which connect to various cell differentiation scenarios.

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. For example, the T lymphocytes of the immune system, upon maturation, differentiate into either Th1 or Th2 cells. These cells are different by the repertoire of chemokines they produce. Th1 cells secrete IFNγ needed to combat intracellular pathogens and, if abnormal, are associated with inflammatory and autoimmune diseases. Th2 cells secrete cytokines that activate B cells to produce

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0022-0396/$ – see front matter
doi:10.1016/j.jde.2012.02.006

antibodies against extracellular pathogens and, if abnormal, are associated with asthma and other allergies.

The variables of primary interest in a quantitative description of gene expression are the number of mRNA copies of a given gene and the number of transcription factors (proteins). The mRNA are translated into proteins, and transcription factors promote the mRNA transcription by genes. Hence in order to determine quantitatively the cellular concentration of mRNA and protein, we need a mathematical model that connects these two concentrations. In terms of the balance equations, these concentrations are governed by

$$\frac{d(\mathrm{mRNA})}{dt} = v_{\text{transcription}} - v_{\text{mRNA degradation}}, \tag{1.1}$$

$$\frac{d(\mathrm{protein})}{dt} = v_{\text{translation}} - v_{\text{protein degradation}}, \tag{1.2}$$

where the v's are the rates of transcription, translation, and degradation as indicated; cf. [9].

In the case of T cell differentiation, the decision to which cell type to differentiate, Th1 or Th2, depends on proteins x_1 and x_2, and their mRNA y_1 and y_2, where x_1 is the concentration of transcription factor T-bet and x_2 is the concentration of transcription factor GATA-3; y_i is the concentration of the mRNA which translates into x_i. By (1.2), we then have

$$\frac{dx_i}{dt} = v_i y_i - \tau_i x_i =: g_i, \tag{1.3}$$

where v_i, τ_i are constants. On the other hand, the rate of change dy_i/dt is far more complex, since $v_{\text{transcription}}$ depends on intrinsic signals from all the T cells and on extrinsic signals by IL4 and IL12. Yates et al. [10] introduced the following model for the rate of the transcription of x_i:

$$v_{\text{transcription}} = \left(\alpha_i \frac{x_i^n}{k_i^n + x_i^n} + \sigma_i \frac{S_i}{\rho_i + S_i}\right) \cdot \frac{1}{1 + x_j/\gamma_j} + \beta_i,$$

where α_i, k_i, σ_i, ρ_i, γ_i, β_i are constants and $j = 2$ if $i = 1$, $j = 1$ if $i = 2$. Here S_i is the combined intrinsic/extrinsic signal, and x_j inhibits x_i $(j \neq i)$; the autocatalytic process, given by $\alpha_i x_i^n/(k_i^n + x_i^n)$, is modeled by Hill's dynamics with exponents $n \geqslant 2$. The first balance equation (1.1) then becomes

$$\frac{dy_i}{dt} = -\mu_i y_i + \left(\alpha_i \frac{x_i^n}{k_i^n + x_i^n} + \sigma_i \frac{S_i}{\rho_i + S_i}\right) \cdot \frac{1}{1 + x_j/\gamma_j} + \beta_i =: f_i, \tag{1.4}$$

for $(i, j) = (1, 2)$ and $(i, j) = (2, 1)$.

Introducing the population density of cells with concentration (x_1, x_2, y_1, y_2) at time t, $\phi(t, x_1, x_2, y_1, y_2)$, the mass conservation law then yields

$$\frac{\partial \phi}{\partial t} + \sum_{i=1}^{2} \frac{\partial}{\partial x_i}(g_i \phi) + \sum_{i=1}^{2} \frac{\partial}{\partial y_i}(f_i \phi) = g^* \phi, \tag{1.5}$$

where g^* is the growth factor.

For a healthy normal individual in homeostasis, the expressions of mRNA/T-bet and mRNA/GATA-3 are at stationary levels, and, at intermediate times, Th0 does not differentiate into Th1 or Th2. However, when a strong signal S_i is generated in response to pathogens, the Th cells differentiate into either Th1 or Th2, but usually not both. In the present model, a single cell with high (low) concentration of T-bet (x_1) and low (high) concentration of GATA-3 (x_2) corresponds to the polarization toward differentiation into Th1 (Th2). For cell population model (1.5), the expressions of mRNA/T-bet and mRNA/GATA-3 may aggregate at one or several points $\bar{y}_1/\bar{x}_1$ and $\bar{y}_2/\bar{x}_2$, respectively. For those cells whose expressions aggregate at the point with low-$\bar{x}_1$ and low-$\bar{x}_2$, cell differentiation does not occur, while the cells whose expressions aggregate at the point with high (low) $\bar{x}_1$ and low (high) $\bar{x}_2$, differentiate into Th1 (Th2). The model parameters (although similar to those in Yates et al. [10]) are not experimentally known; hence our aim is to show that with a specific choice of parameters, the present model illustrates the main biological phenomena on cell differentiation. The fact that we end up with 1, 2, or 4 limit aggregations may not be biologically significant; the model with other parameters may end up with different number of aggregation points. What is important is that although there may be a number of limit points, only points with significant contrast of protein concentrations, i.e., $\bar{x}_2 \gg \bar{x}_1$ or $\bar{x}_1 \gg \bar{x}_2$, indicate cell differentiation. In a recent paper, we studied the asymptotic behavior of the reduced system (with $y_i \equiv x_i$)

$$\frac{dx_i}{dt} = -\mu_i x_i + \left(\alpha_i \frac{x_i^n}{k_i^n + x_i^n} + \sigma_i \frac{S_i}{\rho_i + S_i}\right) \cdot \frac{1}{1 + x_j/\gamma_j} + \beta_i =: \tilde{f}_i, \tag{1.6}$$

for $(i, j) = (1, 2)$ and $(i, j) = (2, 1)$, with the conservation law

$$\frac{\partial \phi}{\partial t} + \sum_{i=1}^{2} \frac{\partial}{\partial x_i}(\tilde{f}_i \phi) = g^* \phi, \tag{1.7}$$

where $\phi = \phi(t, x_1, x_2)$, and proved under some conditions on the parameters of (1.6) that $\phi(t, x_1, x_2)$ converges to a linear combination of one, two, or four Dirac functions, as $t \to \infty$.

In the present paper, we consider the more general model (1.3), (1.4), (1.5) and establish similar asymptotic behaviors for the population density of T cells, $\phi(t, x_1, x_2, y_1, y_2)$. The proof, however, involves a far deeper analysis than the analysis we used in the reduced case of (1.6) and (1.7).

2. The mathematical model

Denote x_1 and x_2 as the concentrations of transcription factors T-bet and GATA-3, respectively, and by y_1 and y_2 their respective mRNA concentrations. By combining the models of Yates et al. [10] and Mariani et al. [9] (see also [1]), we obtain the following system:

$$\begin{cases} \dfrac{dy_1}{dt} = -\mu_1 y_1 + \left(\alpha_1 \dfrac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \dfrac{S_1}{\rho_1 + S_1}\right) \dfrac{1}{1 + x_2/\gamma_2} + \beta_1 =: f_1(x_1, x_2, y_1, S_1), \\ \dfrac{dy_2}{dt} = -\mu_2 y_2 + \left(\alpha_2 \dfrac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \dfrac{S_2}{\rho_2 + S_2}\right) \dfrac{1}{1 + x_1/\gamma_1} + \beta_2 =: f_2(x_1, x_2, y_2, S_2), \\ \dfrac{dx_1}{dt} = \nu_1 y_1 - \tau_1 x_1 =: g_1(x_1, y_1), \\ \dfrac{dx_2}{dt} = \nu_2 y_2 - \tau_2 x_2 =: g_2(x_2, y_2). \end{cases} \tag{2.1}$$

The first term on the right-hand side of the y_i-equation represents the rate of mRNA degradation, and β_i is a constant basal rate of mRNA 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 $n \geqslant 2$ is the Hill exponent that tunes the sharpness of the activation switch. The contribution of combined cytokine signaling to the rate of growth in y_i is given by the term

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

The cross-inhibition between y_1 and y_2 occurs at both the autoactivation level and the cytokine (membrane) signaling level, and is represented by the factors

$$\frac{1}{1 + x_j/\gamma_j}.$$

The parameter γ_j is the value of x_j at which the ratio of production of y_i ($i \neq j$), due to the combined autoactivation and cytokine signaling, is halved.

We denote by $\phi(t, x_1, x_2, y_1, y_2)$ the population density of T cells with protein concentration (x_1, x_2) and mRNA concentration (y_1, y_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 by

$$\int x_i \tilde{\phi}(t, x_1, x_2)\, dx_1\, dx_2,$$

for $i = 1$ and $i = 2$, respectively, where $\tilde{\phi}(t, x_1, x_2) = \int \phi(t, x_1, x_2, y_1, y_2)\, dy_1\, dy_2$. If we denote by $E_i(t)$ the exogenous (non-T cell) signals that stimulate T-bet and GATA-3 expressions, then the total cytokine S_i is given by

$$S_i(t) = \frac{E_i(t) + \int x_i \tilde{\phi}(t, x_1, x_2)\, dx_1\, dx_2}{\int \tilde{\phi}(t, x_1, x_2)\, dx_1\, dx_2}, \quad i = 1, 2. \tag{2.2}$$

Here, a normalization by total cell numbers is adopted in order 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:

$$\frac{\partial \phi}{\partial t} + \frac{\partial}{\partial x_1}(g_1 \phi) + \frac{\partial}{\partial x_2}(g_2 \phi) + \frac{\partial}{\partial y_1}(f_1 \phi) + \frac{\partial}{\partial y_2}(f_2 \phi) = g^* \phi, \tag{2.3}$$

where g^* is a growth factor. Note that (2.3) is associated with the velocity field described by

$$\frac{dx_i(t)}{dt} = g_i\big(x_i(t), y_i(t)\big), \tag{2.4}$$

$$\frac{dy_i(t)}{dt} = f_i\big(t, x_i(t), y_i(t), S_i(t)\big), \tag{2.5}$$

where f_i and g_i are defined in (2.1). We shall consider system (2.4)–(2.5) in the rectangular region

$$\Omega = \{0 \leqslant x_1 \leqslant B_1,\ 0 \leqslant x_2 \leqslant B_2,\ 0 \leqslant y_1 \leqslant A_1,\ 0 \leqslant y_2 \leqslant A_2\}$$

where

$$B_i = \frac{\nu_i}{\tau_i} A_i, \quad i = 1, 2, \tag{2.6}$$

$$A_i = \frac{\alpha_i + \sigma_i + \beta_i}{\mu_i}, \quad i = 1, 2, \tag{2.7}$$

and set

$$\tilde{\Omega} = \{0 \leqslant x_1 \leqslant B_1,\ 0 \leqslant x_2 \leqslant B_2\}.$$

Then Ω is a positively invariant and an attracting set for (2.4)–(2.5). Therefore, in order to solve (2.3) for (x_1, x_2, y_1, y_2) in Ω, we need to assign both initial and boundary conditions to ϕ:

$$\phi(0, x_1, x_2, y_1, y_2) = \phi_0(x_1, x_2, y_1, y_2) \quad \text{in } \Omega, \tag{2.8}$$

$$\phi(t, x_1, x_2, y_1, y_2)|_{\partial\Omega} = 0 \quad \text{for all } t > 0. \tag{2.9}$$

Assuming, for simplicity, that $g^* = g^*(t)$, and setting

$$G(t) = \int_0^t g^*(s)\,ds, \qquad N_0 = \int_\Omega \phi_0(x_1, x_2, y_1, y_2), \tag{2.10}$$

$$\psi(t, x_1, x_2, y_1, y_2) = e^{-G(t)}\phi(t, x_1, x_2, y_1, y_2), \tag{2.11}$$

$$\tilde{\psi}(t, x_1, x_2) = \int \psi(t, x_1, x_2, y_1, y_2)\,dy_1\,dy_2,$$

we can replace (2.3) by the simpler equation

$$\frac{\partial\psi}{\partial t} + \frac{\partial}{\partial x_1}(g_1\psi) + \frac{\partial}{\partial x_2}(g_2\psi) + \frac{\partial}{\partial y_1}(f_1\psi) + \frac{\partial}{\partial y_2}(f_2\psi) = 0, \tag{2.12}$$

and rewrite $S_i(t)$ in the form

$$S_i(t) = \frac{E_i(t)e^{-G(t)}}{N_0} + \frac{\int x_i\tilde{\psi}(t, x_1, x_2)\,dx_1\,dx_2}{N_0}, \tag{2.13}$$

where N_0 is the initial total population, and the integral in (2.13) is taken over $\tilde{\Omega}$.

Let $\Phi(t, x_1, x_2, y_1, y_2)$ denote the solution map (flow map) of (2.4)–(2.5) and set $\Omega(t) = \Phi(t, \Omega)$. Integrating the transport equation (2.12) over $\Omega(t)$, we find that

$$\frac{d}{dt}\int_{\Omega(t)} \psi(t, x_1, x_2, y_1, y_2)\,dx_1\,dx_2\,dy_1\,dy_2 = 0.$$

Furthermore, if $\Omega(t) \to (\bar{a}_1, \bar{a}_2, \bar{a}_3, \bar{a}_4)$ as $t \to \infty$, then for any continuous function $h(x_1, x_2, y_1, y_2)$,

$$\int_\Omega h(x_1, x_2, y_1, y_2)\psi(t, x_1, x_2, y_1, y_2)\,dx_1\,dx_2\,dy_1\,dy_2 \to h(\bar{a}_1, \bar{a}_2, \bar{a}_3, \bar{a}_4)N_0 \quad \text{as } t \to \infty,$$

i.e.,

$$\psi(t, x_1, x_2, y_1, y_2) \to N_0\delta_{(\bar{a}_1, \bar{a}_2, \bar{a}_3, \bar{a}_4)} \quad \text{in measure, as } t \to \infty.$$

In the subsequent sections, we study the asymptotic behavior of the solutions of (2.4)–(2.5) in conjunction with the behavior of $\Omega(t)$. Similarly to [2], one can prove that the system (2.3), (2.8), (2.9) has a unique solution for all $t \geqslant 0$. Hence we shall focus here only on the asymptotic behavior of the solution. We shall prove that $\Omega(t)$ converges to one, two, or four points, as $t \to \infty$, depending on the parameters of the dynamical system (2.4)–(2.5). The asymptotic study of dynamical system (2.4)–(2.5) will require a far deeper analysis than that developed for Eqs. (1.6)–(1.7) in [2].

3. Upper and lower dynamics

The system (2.1) can be written as a system of two second-order equations,

$$\frac{d^2x_1}{dt^2} + (\tau_1 + \mu_1)\frac{dx_1}{dt} = h_1\big(x_1, x_2, S_1(t)\big), \tag{3.1}$$

$$\frac{d^2x_2}{dt^2} + (\tau_2 + \mu_2)\frac{dx_2}{dt} = h_2\big(x_1, x_2, S_2(t)\big), \tag{3.2}$$

where

$$h_1\big(x_1, x_2, S_1(t)\big) = -\mu_1\tau_1x_1 + \nu_1\left(\alpha_1\frac{x_1^n}{k_1^n + x_1^n} + \sigma_1\frac{S_1(t)}{\rho_1 + S_1(t)}\right)\frac{1}{1 + x_2/\gamma_2} + \nu_1\beta_1,$$

$$h_2\big(x_1, x_2, S_2(t)\big) = -\mu_2\tau_2x_2 + \nu_2\left(\alpha_2\frac{x_2^n}{k_2^n + x_2^n} + \sigma_2\frac{S_2(t)}{\rho_2 + S_2(t)}\right)\frac{1}{1 + x_1/\gamma_1} + \nu_2\beta_2.$$

We introduce the upper bounds $\hat{h}_i$ for the functions h_i:

$$\hat{h}_i(x_i) = -\mu_i\tau_ix_i + \nu_i\left(\alpha_i\frac{x_i^n}{k_i^n + x_i^n} + \sigma_i\frac{\hat{S}_i}{\rho_i + \hat{S}_i}\right) + \nu_i\beta_i \quad \text{for } 0 \leqslant x_i < \infty,\ i = 1, 2, \tag{3.3}$$

where $\hat{S}_i = \sup_{t>0} S_i(t)$, and lower bounds $\check{h}_i$ for h_i:

$$\check{h}_1(x_1) = -\mu_1\tau_1x_1 + \nu_1\left(\alpha_1\frac{x_1^n}{k_1^n + x_1^n} + \sigma_1\frac{\check{S}_1}{\rho_1 + \check{S}_1}\right)\cdot\frac{1}{1 + B_2/\gamma_2} + \nu_1\beta_1, \tag{3.4}$$

$$\check{h}_2(x_2) = -\mu_2\tau_2x_2 + \nu_2\left(\alpha_2\frac{x_2^n}{k_2^n + x_2^n} + \sigma_2\frac{\check{S}_2}{\rho_2 + \check{S}_2}\right)\cdot\frac{1}{1 + B_1/\gamma_1} + \nu_2\beta_2, \tag{3.5}$$

where $\check{S}_i = \inf_{t>0} S_i(t)$. Clearly,

$$\hat{h}_i(0) > 0, \qquad \hat{h}_i'(0) < 0, \qquad \hat{h}_i(x_i) < 0,$$
$$\check{h}_i(0) > 0, \qquad \check{h}_i'(0) < 0, \qquad \check{h}_i(x_i) < 0,$$

for $B_i \leqslant x_i < \infty$. Also

$$\hat{h}_i'(x_i) = -\mu_i\tau_i + \nu_i\alpha_i\frac{nk_i^nx_i^{n-1}}{(k_i^n + x_i^n)^2},$$

and, as easily verified, the maximum of the last term is attained at the point

$$\tilde{\xi}_i = k_i\left(\frac{n-1}{n+1}\right)^{1/n}, \quad \text{and} \quad \hat{h}_i'(\tilde{\xi}_i) = -\mu_i\tau_i + \frac{\nu_i\alpha_i\tilde{n}}{k_i} \tag{3.6}$$

where

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

The maximum of $\check{h}_i'$ is also attained at the same point $\tilde{\xi}_i$ with

$$\check{h}_i'(\tilde{\xi}_i) = -\mu_i\tau_i + \frac{\nu_i\alpha_i\tilde{n}}{k_i}\cdot\frac{1}{1+B_j/\gamma_j}$$

for $(i,j)=(1,2)$ and $(i,j)=(2,1)$. Clearly, $\check{h}_i'(\xi) < \hat{h}_i'(\xi)$ for all ξ.

The systems

$$\frac{d^2\hat{x}_i}{dt^2} + (\tau_i+\mu_i)\frac{d\hat{x}_i}{dt} = \hat{h}_i(\hat{x}_i) \quad (i=1,2), \tag{3.7}$$

$$\frac{d^2\check{x}_i}{dt^2} + (\tau_i+\mu_i)\frac{d\check{x}_i}{dt} = \check{h}_i(\check{x}_i) \quad (i=1,2), \tag{3.8}$$

will be used to provide the upper and lower bounds for the dynamics of (3.1)–(3.2).

It will be convenient to use a change of variables $(x_1, y_1, x_2, y_2) \leftrightarrow (x_1, v_1, x_2, v_2)$ where

$$v_1 = \nu_1 y_1 - \tau_1 x_1, \qquad v_2 = \nu_2 y_2 - \tau_2 x_2$$

so that the system (2.1) can be rewritten in the form

$$\frac{dx_i}{dt} = v_i, \tag{3.9}$$

$$\frac{dv_i}{dt} = -(\tau_i+\mu_i)v_i + h_i(x_1, x_2, S_i), \tag{3.10}$$

$i=1,2$, in the transformed region

$$\Omega^* = \{0 \leqslant x_1 \leqslant B_1,\ -\tau_1 x_1 \leqslant v_1 \leqslant \nu_1 A_1 - \tau_1 x_1,\ 0 \leqslant x_2 \leqslant B_2,\ -\tau_2 x_2 \leqslant v_2 \leqslant \nu_2 A_2 - \tau_2 x_2\}.$$

Notice that Ω^* remains positively invariant under (3.9)–(3.10).

We need several lemmas to study the asymptotic behavior of (3.9)–(3.10). The first one deals with a system

$$\frac{du}{dt} = v, \tag{3.11}$$

$$\frac{dv}{dt} = -\delta v + q(u), \tag{3.12}$$

where δ is a positive constant and q is a continuously differentiable function on $[0,\infty)$. We shall consider (3.11)–(3.12) on a region $D \subseteq [0,\infty)\times\mathbb{R}$, which is positively invariant under the flow Ψ_t generated from the system. Let $B_\epsilon(u,v)\subset\mathbb{R}^2$ be an open disc with center (u,v) and radius ϵ, and K be a compact set in D.

Lemma 3.1. *Assume that* $\lim_{u\to\infty} q(u) = -\infty$. *Then the following holds.*

(i) *Every solution of* (3.11)–(3.12) *tends to the set* $\{(\bar{u},0) \in D\colon\ q(\bar{u}) = 0\}$, *as* $t \to \infty$; *if, in addition, the set of zeros for q is finite, then each solution of* (3.11)–(3.12) *tends to a single point in set* $\{(\bar{u},0) \in D\colon\ q(\bar{u}) = 0\}$, *as* $t \to \infty$.

(ii) *If q has a unique zero a with* $q'(a) < 0$ *and* $(a,0) \in D$, *then* $\mathcal{A} := \{(a,0)\}$ *is the global attractor*; *thus, for any small* $\epsilon > 0$, *there exists a T such that* $\Psi_t(K) \subset B_\epsilon(a,0)$, *for all* $t \geqslant T$.

(iii) *If q has exactly three zeros* a,b,c *with* $a < b < c$, $q'(a) < 0$, $q'(b) > 0$, $q'(c) < 0$, *and* $(a,0)$, $(b,0)$, $(c,0) \in D$, *then* $\mathcal{A} := W^u(b,0) \cup \{(a,0)\} \cup \{(c,0)\}$ *is the global attractor, where* $W^u(b,0)$ *is the unstable manifold of* $(b,0)$. *Moreover, for any small* $\epsilon > 0$, *there exists a* $T > 0$ *such that* $|\Psi_t(K \setminus W^s_\epsilon(b,0)) - \{(a,0),(c,0)\}| < \epsilon$, *for all* $t \geqslant T$, *where* $W^s_\epsilon(b,0) := \{(u,v)\colon\ |(u,v) - W^s(b,0)| < \epsilon\}$ *is the* ϵ*-neighborhood of* $W^s(b,0)$.

Proof. (i) Consider the Lyapunov function

$$V(u,v) = \frac{1}{2}v^2 - \int_0^u q(s)\,ds.$$

Then

$$\begin{aligned}\dot{V}(u,v) &= v\cdot\left[-\delta v + q(u)\right] - q(u)\cdot v\\ &= -\delta v^2 \leqslant 0,\end{aligned} \tag{3.13}$$

and $\dot{V} = 0$ if and only if $v = 0$. All solutions are bounded in forward time due to $\lim_{u\to\infty} q(u) = -\infty$. By LaSalle's invariance principle [4,5], every solution of (3.11)–(3.12) tends to the maximal invariant set in

$$\{(u,v)\colon\ \dot{V}(u,v) = 0\} = \{(u,0)\}$$

which is the set

$$\{(\bar{u},0)\colon\ q(\bar{u}) = 0\},$$

as $t \to \infty$. Since the ω-limit set of an orbit is connected, if q has a finite number of zeros, then the ω-limit set for an orbit of (3.11)–(3.12) is a single point $(\bar{u},0)$, where $\bar{u}$ is a zero of q.

(ii) If q has a unique zero a with $q'(a) < 0$, then $(a,0)$ is a sink. From (3.13), it follows that $\{(a,0)\}$ is the global attractor for (3.11)–(3.12). The assertion about $\Psi_t(K) \subset B_\epsilon(a,0)$ for $t \geqslant T$ follows from [5,8].

(iii) If q has exactly three zeros a,b,c with $a < b < c$ and $q'(a) < 0$, $q'(b) > 0$, $q'(c) < 0$, then $(a,0)$, $(c,0)$ are both sinks, and $(b,0)$ is a saddle, for system (3.11)–(3.12). By (3.13), the level curve analysis, and Poincare–Bendixson Theorem, the unstable manifold $W^u(b,0)$ for $(b,0)$ consists of heteroclinic orbits connecting $(b,0)$ with $(a,0)$ and with $(c,0)$ respectively; cf. Fig. 1. It follows that $\mathcal{A} := W^u(b,0) \cup \{(a,0)\} \cup \{(c,0)\}$ is the global attractor for (3.11)–(3.12); cf. [6, p. 395]. Therefore, for any $\epsilon > 0$ there exists a $T > 0$, so that $\Psi_t(K)$ falls within a distance $\epsilon > 0$ from $\mathcal{A}$, for all $t \geqslant T$. Moreover, for every point (u,v) in compact set $K \setminus W^s_\epsilon(b,0)$, $\Phi_t(u,v)$ approaches $(a,0)$ or $(c,0)$, as t tends to infinity. By the continuity with respect to initial condition and the compactness of K, there exists a $T > 0$ such that $\Psi_t(u,v) \in B_\varepsilon(a,0)$ or $B_\varepsilon(c,0)$, for all $(u,v) \in K \setminus W^s_\epsilon(b,0)$, for all $t \geqslant T$. $\square$

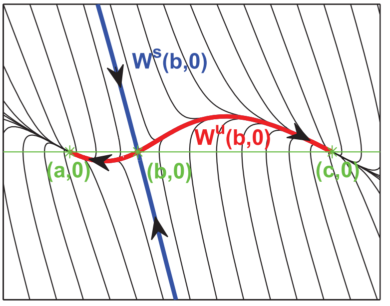

Fig. 1. Stable manifold $W^s(b,0)$ (indicated as blue lines) and unstable manifold $W^u(b,0)$ (indicated as red lines) of the saddle point $(b,0)$ of (3.11)–(3.12). The green dots allocate three equilibria $(a,0)$, $(b,0)$, $(c,0)$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Lemma 3.1 applies to system (3.7)–(3.8) on the domain D_i, $i=1,2$, respectively, where

$$D_i := \{(x_i, v_i)\colon 0 \leqslant x_i \leqslant B_i,\ -\tau_i x_i \leqslant v_i \leqslant \nu_i A_i\} \subset \mathbb{R}^2.$$

In particular, every solution $\hat{x}_i(t)$ (resp., $\check{x}_i(t)$) of (3.7) (resp., (3.8)) tends to the set of zeros of $\hat{h}_i$ (resp., $\check{h}_i$), as $t \to \infty$, $i = 1, 2$.

Lemma 3.2. *Consider the non-autonomous equation*

$$\frac{d^2 z}{dt^2} + (\tau + \mu)\frac{dz}{dt} + a(t)z = f(t), \quad 0 < t < \infty, \tag{3.14}$$

where $a(t) \leqslant \alpha$, $f(t) \geqslant 0$ for $0 \leqslant t < \infty$, and $f(0) > 0$, $0 < 4\alpha < (\tau+\mu)^2$. If $z(0) = (dz/dt)(0) = 0$, then $z(t) \geqslant 0$ for all $t \geqslant 0$.

Proof. We rewrite (3.14) in the form

$$\frac{d^2 z}{dt^2} + (\tau + \mu)\frac{dz}{dt} + \alpha z = f(t) + \big(\alpha - a(t)\big)z(t). \tag{3.15}$$

Eq. (3.15) has two linearly independent homogeneous solutions $e^{\lambda_1 t}$, $e^{\lambda_2 t}$ where

$$\lambda_{1,2} = \frac{-(\tau+\mu) \pm \sqrt{(\tau+\mu)^2 - 4\alpha}}{2}$$

and, by assumption, $\lambda_1 < \lambda_2 < 0$. Since $z(0) = (dz/dt)(0) = 0$, we can represent z, by the variation of constant formula, in the form

$$z(t) = \int_0^t \frac{e^{\lambda_2(t-s)} - e^{\lambda_1(t-s)}}{(\lambda_2 - \lambda_1)}\big[f(s) + \big(\alpha - a(s)\big)z(s)\big]\,ds; \tag{3.16}$$

indeed observe that the right-hand side vanishes at $t = 0$ together with its first derivative.

Since $f(0) - (\alpha - a(0))z(0) = f(0) > 0$, $z(t) > 0$ for small t. We claim that $z(t) > 0$ for all $t > 0$. Indeed, otherwise there exists a smallest time $t = t_0$ such that $z(t) > 0$ if $0 < t < t_0$ and $z(t_0) = 0$. But since $\alpha - a(t) \geqslant 0$, we have $f(t) + (\alpha - a(t))z(t) > 0$ for $0 < t < t_0$ and from (3.16) we obtain $z(t_0) > 0$, a contradiction. $\square$

Remark 3.1. By approximation, the lemma remains true if $f(0)=0$ and $4\alpha \leqslant (\tau+\mu)^2$.

Lemma 3.2 can be used to compare solutions $(x_1(t), x_2(t))$ of (3.1)–(3.2) with solutions $\hat{x}_1(t), \hat{x}_2(t)$ of (3.7), and $\check{x}_1(t), \check{x}_2(t)$ of (3.8), provided they have the same initial conditions.

Lemma 3.3. *Let $(x_1(t), x_2(t))$ be a solution of (3.1), (3.2). Suppose*

$$\min\{\check{h}_i'(\eta)\colon\ \eta \in [0, B_i]\} \geqslant \mu_i\tau_i, \quad i=1 \text{ or } i=2.$$

(i) *If a solution $\hat{x}_i(t)$ of (3.7) satisfies*

$$\hat{x}_i(0) = x_i(0), \qquad (d\hat{x}_i/dt)(0) = (dx_i/dt)(0)$$

then

$$\hat{x}_i(t) \geqslant x_i(t) \quad \text{for all } t > 0.$$

(ii) *If a solution $\check{x}_i(t)$ of (3.8) satisfies*

$$\check{x}_i(0) = x_i(0), \qquad (d\check{x}_i/dt)(0) = (dx_i/dt)(0)$$

then

$$\check{x}_i(t) \leqslant x_i(t) \quad \text{for all } t > 0.$$

(iii) *If solutions $\hat{x}_i(t), \check{x}_i(t)$ of (3.7)–(3.8) satisfy*

$$\hat{x}_i(0) = \check{x}_i(0), \qquad (d\hat{x}_i/dt)(0) = (d\check{x}_i/dt)(0)$$

then

$$\hat{x}_i(t) \geqslant \check{x}_i(t) \quad \text{for all } t > 0.$$

Proof. From (3.3), (3.4), and (3.5), it follows that

$$\hat{h}_i'(\eta) \geqslant -\mu_i\tau_i, \qquad \check{h}_i'(\eta) \geqslant -\mu_i\tau_i. \tag{3.17}$$

Consider case (i). The function $X = \hat{x}_i - x_i$ satisfies

$$\frac{d^2X}{dt^2} + (\tau_i + \mu_i)\frac{dX}{dt} = \hat{h}_i(\hat{x}_i) - h_i(x_1, x_2)$$

and the right-hand side is equal to

$$\hat{h}_i(\hat{x}_i) - \hat{h}_i(x_i) + \hat{h}_i(x_i) - h_i(x_1, x_2) = \hat{h}_i'(\eta_i)X + \hat{h}_i(x_i) - h_i(x_1, x_2)$$

where $\eta_i = \eta_i(t)$ lies between x_i and $\hat{x}_i$, by the mean value theorem. Hence

$$\frac{d^2X}{dt^2} + (\tau_i + \mu_i)\frac{dX}{dt} + a(t)X = \hat{h}_i(x_i) - h_i(x_1, x_2)$$

where

$$a(t) = -\hat{h}_i'(\eta_i) \leqslant \mu_i \tau_i$$

by (3.17) and $\hat{h}_i(x_i) - h_i(x_i, x_j) \geqslant 0$, $(i, j) = (1, 2)$, $(i, j) = (2, 1)$. Applying Lemma 3.2 and Remark 3.1, we conclude that $X(t) \geqslant 0$ for all $t > 0$. Hence

$$\hat{x}_i(t) \geqslant x_i(t) \quad \text{for all } t > 0.$$

The proofs of cases (ii) and (iii) are similar. □

3.1. Single equilibrium

In this section, let us discuss the conditions under which $\hat{h}_i$ (resp., $\check{h}_i$) has a single zero and, consequently, by Lemma 3.1, all solutions to (3.7) (resp., (3.8)) converge to a single point $(\hat{a}_i, 0)$ (resp., $(\check{a}_i, 0)$), as $t \to \infty$.

According to (3.6), if

$$\mu_i \tau_i > \frac{\nu_i \alpha_i \tilde{n}}{k_i} \tag{3.18}$$

then $\hat{h}_i'(\tilde{\xi}_i) < 0$ and, consequently,

$$-\mu_i \tau_i \leqslant \hat{h}_i'(x_i) < 0 \quad \text{for all } 0 \leqslant x_i \leqslant B_i;$$

then also

$$\check{h}_i'(x_i) < 0 \quad \text{and} \quad \frac{\partial h_i(x_1, x_2)}{\partial x_i} < 0 \quad \text{for } 0 \leqslant x_i \leqslant B_i.$$

Note that $\partial h_i(x_1, x_2)/\partial x_i$ (with x_2 fixed if $i = 1$ and x_2 fixed if $i = 2$) attains its maximum at the same point $x_i = \tilde{\xi}_i$ where $\hat{h}_i(x_i)$ attains its maximum.

In addition to condition (3.18), we consider other situations which are more of biological interest. Analogously to [2], we assume that, for a given i ($i = 1$ or $i = 2$),

$$\mu_i \tau_i < \frac{\nu_i \alpha_i \tilde{n}}{k_i} \cdot \frac{1}{1 + B_j/\gamma_j}, \quad j \neq i. \tag{3.19}$$

These conditions are equivalent to $\check{h}_i'(\tilde{\xi}_i) > 0$ and, in that case, if $\tilde{\xi}_i < B_i$ then each of $\hat{h}_i$, $\check{h}_i$ has two critical points. Let $\hat{p}_i^{\mathrm{m}}, \hat{p}_i^{\mathrm{M}}$ (resp., $\check{p}_i^{\mathrm{m}}, \check{p}_i^{\mathrm{M}}$) denote the points where $\hat{h}_i$ (resp., $\check{h}_i$) achieves its local minimum and maximum. Each of functions $\hat{h}_i, \check{h}_i$ may have one or three zeros as illustrated in Fig. 2.

We consider the following cases for $i = 1$ or $i = 2$:

(Ma$_i$) $\hat{h}_i(\hat{p}_i^{\mathrm{M}}) < 0$;
(Mb$_i$) $\check{h}_i(\check{p}_i^{\mathrm{m}}) > 0$;
(B$_i$) $\hat{h}_i(\hat{p}_i^{\mathrm{m}}) < 0$, $\check{h}_i(\check{p}_i^{\mathrm{M}}) > 0$.

From Lemma 3.1 we deduce the following:

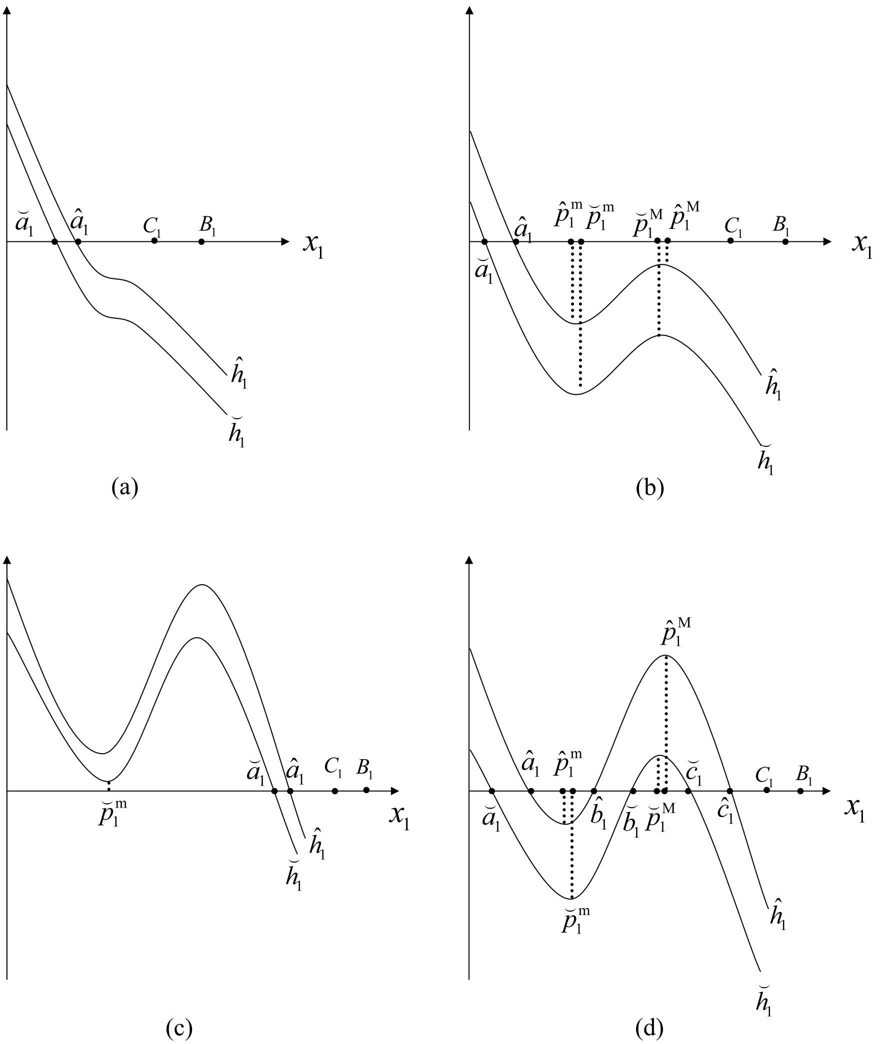

Fig. 2. $\hat{h}_1$ and $\check{h}_1$ have one zero in cases (a), (b), (c), and three zeros in case (d).

Proposition 3.4. *Suppose one of the conditions* (3.18) *or* (3.19) *with* (Ma$_i$)*, or* (3.19) *with* (Mb$_i$) *holds for* $i = 1$ *or* $i = 2$*. Then every solution of* (3.7) (*resp.,* (3.8)) *converges to a single equilibrium* $(\hat{a}_i, 0)$ (*resp.,* $(\check{a}_i, 0)$)*.*

3.2. Multiple equilibria

In this section we assume that (3.19) and (B$_i$) hold where $i = 1$ or $i = 2$. Then the dynamics (3.7) (resp., (3.8)) has three equilibrium points: $(\hat{a}_i, 0)$, $(\hat{b}_i, 0)$, $(\hat{c}_i, 0)$ (resp., $(\check{a}_i, 0)$, $(\check{b}_i, 0)$, $(\check{c}_i, 0)$) where $\hat{a}_i < \hat{b}_i < \hat{c}_i$ (resp., $\check{a}_i < \check{b}_i < \check{c}_i$) and $\check{a}_i < \hat{a}_i$, $\check{c}_i < \hat{c}_i$, but

$$\check{b}_i > \hat{b}_i. \tag{3.20}$$

From Lemma 3.1, we conclude the following proposition for $i = 1$ or $i = 2$.

Proposition 3.5. *Under the conditions* (3.19) *and* (B_i), *every solution of* (3.7) (*resp.*, (3.8)) *converges to one of the equilibrium points* $(\hat{a}_i, 0)$, $(\hat{b}_i, 0)$, $(\hat{c}_i, 0)$ (*resp.*, $(\check{a}_i, 0)$, $(\check{b}_i, 0)$, $(\check{c}_i, 0)$).

It can easily be computed that the equilibrium points $(\hat{a}_i, 0), (\hat{c}_i, 0)$ (resp., $(\check{a}_i, 0), (\check{c}_i, 0)$) of (3.7) (resp., (3.8)) are both sinks, whereas the equilibrium $(\hat{b}_i, 0)$ (resp., $(\check{b}_i, 0)$) is a saddle. In addition, one branch of the unstable manifold for $(\hat{b}_i, 0)$ (resp., $(\check{b}_i, 0)$) converges to $(\hat{a}_i, 0)$ (resp., $(\check{a}_i, 0)$), and the other branch converges to $(\hat{c}_i, 0)$ (resp., $(\check{c}_i, 0)$), as $t \to \infty$, cf. Fig. 1. We denote by $W^s(\hat{b}_i)$ (resp., $W^s(\check{b}_i)$) the (one-dimensional) stable manifold for $(\hat{b}_i, 0)$ (resp., $(\check{b}_i, 0)$) and set $\hat{y}_i = d\hat{x}_i/dt$, $\check{y}_i = d\check{x}_i/dt$. We partition the phase plane for (3.7) and (3.8) respectively

$$\left\{(\hat{x}_i, \hat{y}_i)\colon\ 0 \leqslant \hat{x}_i \leqslant B_i,\ \hat{y}_i \in \mathbb{R}\right\} = W^s(\hat{b}_i) \cup U(\hat{a}_i) \cup U(\hat{c}_i),$$

$$\left\{(\check{x}_i, \check{y}_i)\colon\ 0 \leqslant \check{x}_i \leqslant B_i,\ \check{y}_i \in \mathbb{R}\right\} = W^s(\check{b}_i) \cup U(\check{a}_i) \cup U(\check{c}_i),$$

where $U(p)$ is the basin of attraction for sink $(p, 0) = (\hat{a}_i, 0)$, $(\hat{c}_i, 0)$, $(\check{a}_i, 0)$, $(\check{c}_i, 0)$. Notice that $W^s(\hat{b}_i)$ and $W^s(\check{b}_i)$ do not intersect. Indeed, if they intersect at one point (u_0, v_0), then we can apply Lemma 3.3(iii) with initial point (u_0, v_0) and deduce that $\hat{b}_i < \check{b}_i$, a contradiction to (3.20). In addition, $W^s(\hat{b}_i)$ lies on the left-hand side of $W^s(\check{b}_i)$, again by Lemma 3.3(iii). Moreover, $W^s(\hat{b}_i)$ (resp., $W^s(\check{b}_i)$) is tangent at $(\hat{b}_i, 0)$ (resp., $(\check{b}_i, 0)$) to the stable subspace E^s which is given, respectively, by

$$E^s(\hat{b}_i, 0) = \operatorname{span}\left\{\left(1, \frac{-(\tau_i + \mu_i) - \sqrt{(\tau_i + \mu_i)^2 + 4\hat{h}_i'(\hat{b}_i)}}{2}\right)\right\},$$

$$E^s(\check{b}_i, 0) = \operatorname{span}\left\{\left(1, \frac{-(\tau_i + \mu_i) - \sqrt{(\tau_i + \mu_i)^2 + 4\check{h}_i'(\check{b}_i)}}{2}\right)\right\}.$$

Let $(\hat{x}_i(t; u_0, v_0), \hat{y}_i(t; u_0, v_0))$ (resp., $(\check{x}_i(t; u_0, v_0), \check{y}_i(t; u_0, v_0))$) be the solution to (3.7) (resp., (3.8)), starting from point (u_0, v_0) at $t = 0$, $i = 1, 2$. Clearly, if $(u_0, v_0) \in U(\hat{a}_i) \cap U(\check{a}_i)$, then as $t \to \infty$,

$$\big(\hat{x}_i(t; u_0, v_0), \hat{y}_i(t; u_0, v_0)\big) \to (\hat{a}_i, 0), \qquad \big(\check{x}_i(t; u_0, v_0), \check{y}_i(t; u_0, v_0)\big) \to (\check{a}_i, 0);$$

if $(u_0, v_0) \in U(\hat{c}_i) \cap U(\check{c}_i)$, then

$$\big(\hat{x}_i(t; u_0, v_0), \hat{y}_i(t; u_0, v_0)\big) \to (\hat{c}_i, 0), \qquad \big(\check{x}_i(t; u_0, v_0), \check{y}_i(t; u_0, v_0)\big) \to (\check{c}_i, 0);$$

if $(u_0, v_0) \in [U(\hat{c}_i) \cap U(\check{a}_i)]$, then

$$\big(\hat{x}_i(t; u_0, v_0), \hat{y}_i(t; u_0, v_0)\big) \to (\hat{c}_i, 0), \qquad \big(\check{x}_i(t; u_0, v_0), \check{y}_i(t; u_0, v_0)\big) \to (\check{a}_i, 0) \quad \text{as } t \to \infty.$$

In addition, $U(\hat{a}_i) \cap U(\check{c}_i) = \emptyset$, according to Lemma 3.3. As seen in Fig. 3, $W^s(\check{b}_i)$ lies to the right of $W^s(\hat{b}_i)$. Orbits of (3.9)–(3.10) cannot enter the region bounded by $W^s(\check{b}_i)$ and $W^s(\hat{b}_i)$, but an orbit initially from this region may exit it.

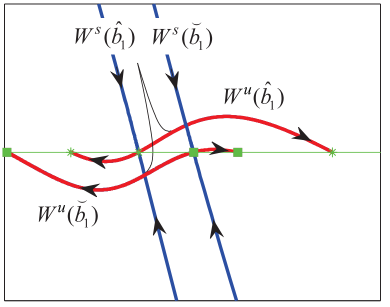

Fig. 3. Stable manifolds $W^s(\hat{b}_1)$, $W^s(\breve{b}_1)$ (indicated as blue lines) and unstable manifolds $W^u(\hat{b}_1)$, $W^u(\breve{b}_1)$ (indicated as red lines) of $(\hat{b}_1, 0)$ and $(\breve{b}_1, 0)$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Asymptotic behavior: single limit point

As in [2], we shall introduce an iterative scheme to prove convergence to a single point; the last step in the convergence proof will require the following condition:

$$\frac{\nu_1(\alpha_1+\sigma_1)}{\gamma_2} < \left|\mu_1\tau_1 - \frac{\nu_1\alpha_1\tilde{n}}{k_1}\right| - \frac{\nu_1\sigma_1}{\rho_1},$$
$$\frac{\nu_2(\alpha_2+\sigma_2)}{\gamma_1} < \left|\mu_2\tau_2 - \frac{\nu_2\alpha_2\tilde{n}}{k_2}\right| - \frac{\nu_2\sigma_2}{\rho_2}. \tag{4.1}$$

We also assume that functions $G(t)$ (in (2.10)) and $E_i(t)$ (in (2.13)) satisfy the following conditions:

$$\lim_{t\to\infty} G(t) \text{ and } \lim_{t\to\infty} E_i(t) \text{ exist.} \tag{4.2}$$

Theorem 4.1. *Assume that* (3.18) *holds for $i = 1$ and $i = 2$, and that* (4.1) *and* (4.2) *hold. Then every solution of* (3.9)–(3.10) *converges to a single point $(\bar{a}_1, 0, \bar{a}_2, 0)$, as $t \to \infty$.*

Corollary 4.2. *The solution ψ of* (2.8)–(2.13) *has the following asymptotic behavior*: $\psi(t, x_1, x_2, y_1, y_2) \to N_0\delta_{(\bar{a}_1, \bar{a}_2, \tau_1\bar{a}_1/\nu_1, \tau_2\bar{a}_2/\nu_2)}$ *in measure, as $t \to \infty$.*

Proof of Theorem 4.1. Set, for $t \geqslant 0$,

$$S_i^{\min}(t) = \inf\{S_i(s)\colon s \in [t,\infty)\}, \qquad S_i^{\max}(t) = \sup\{S_i(s)\colon s \in [t,\infty)\}.$$

Then $S_i^{\min}(t) \leqslant S_i(t) \leqslant S_i^{\max}(t)$. Note that $S_i^{\min}(t)$ is nondecreasing, $S_i^{\max}(t)$ is nonincreasing, and

$$\frac{S_i^{\min}(t)}{\rho_i + S_i^{\min}(t)} \leqslant \frac{S_i(t)}{\rho_i + S_i(t)} \leqslant \frac{S_i^{\max}(t)}{\rho_i + S_i^{\max}(t)} \quad \text{for } t \geqslant 0.$$

Under the condition (3.18), $\hat{h}_i$ (resp., $\breve{h}_i$) is a strictly decreasing function, and has a single zero, denoted by $\hat{a}_i$ (resp., $\breve{a}_i$). Let $(x_1(t), v_1(t), x_2(t), v_2(t))$ be the solution to (3.9)–(3.10), starting from arbitrary initial point $(x_1(0), v_1(0), x_2(0), v_2(0)) \in \Omega^*$. By Lemmas 3.1(ii), 3.3 and Proposition 3.4, for any small $\varepsilon_0 > 0$, there exists a time $T_0 > 0$ such that

$$\begin{aligned}\big(x_1(t), x_2(t)\big) \in \Omega^{(0)} &:= [\check{a}_1 - \varepsilon_0, \hat{a}_1 + \varepsilon_0] \times [\check{a}_2 - \varepsilon_0, \hat{a}_2 + \varepsilon_0] \\ &\subset [0, B_1] \times [0, B_2],\end{aligned}$$

for $t \geqslant T_0$. For the following use of iteration argument, we set $\check{a}_i^{(0)} = \check{a}_i$, $\hat{a}_i^{(0)} = \hat{a}_i$. We define

$$\hat{h}_1^{(1)}(x_1) = -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_0)}{\rho_1 + S_1^{\max}(T_0)}\right) \cdot \frac{1}{1 + (\check{a}_2^{(0)} - \varepsilon_0)/\gamma_2} + \nu_1\beta_1,$$

$$\check{h}_1^{(1)}(x_1) = -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_0)}{\rho_1 + S_1^{\min}(T_0)}\right) \cdot \frac{1}{1 + (\hat{a}_2^{(0)} + \varepsilon_0)/\gamma_2} + \nu_1\beta_1,$$

$$\hat{h}_2^{(1)}(x_2) = -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(T_0)}{\rho_2 + S_2^{\max}(T_0)}\right) \cdot \frac{1}{1 + (\check{a}_1^{(0)} - \varepsilon_0)/\gamma_1} + \nu_2\beta_2,$$

$$\check{h}_2^{(1)}(x_2) = -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\min}(T_0)}{\rho_2 + S_2^{\min}(T_0)}\right) \cdot \frac{1}{1 + (\check{a}_1^{(0)} + \varepsilon_0)/\gamma_1} + \nu_2\beta_2.$$

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

$$\check{h}_i^{(1)}(x_i) \leqslant h_i\big(x_1, x_2, S_i(t)\big) \leqslant \hat{h}_i^{(1)}(x_i)$$

for all $(x_1, x_2) \in \Omega^{(0)}$, $t \geqslant T_0$, $i = 1, 2$, and $\check{h}_i^{(1)}(x_i) > 0$ for $x_i < \check{a}_i^{(1)}$, $\hat{h}_i^{(1)}(x_i) < 0$ for $x_i > \hat{a}_i^{(1)}$. Hence for any small $\varepsilon_1 > 0$, there exists a $T_1 > T_0$ such that

$$\big(x_1(t), x_2(t)\big) \in \Omega^{(1)} := \big[\check{a}_1^{(1)} - \varepsilon_1, \hat{a}_1^{(1)} + \varepsilon_1\big] \times \big[\check{a}_2^{(1)} - \varepsilon_1, \hat{a}_2^{(1)} + \varepsilon_1\big] \subset \Omega^{(0)},$$

for all $t \geqslant T_1$, for the solution $(x_1(t), v_1(t), x_2(t), v_2(t))$ to (3.9)–(3.10), starting from $(x_1(0), x_2(0), v_1(0), v_2(0)) \in \Omega^*$. We can proceed in a similar manner to define successively $\hat{h}_i^{(k)}$ and $\check{h}_i^{(k)}$, $k \geqslant 2$, by

$$\hat{h}_1^{(k)}(x_1) = -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_{k-1})}{\rho_1 + S_1^{\max}(T_{k-1})}\right) \cdot \frac{1}{1 + (\check{a}_2^{(k-1)} - \varepsilon_{k-1})/\gamma_2} + \nu_1\beta_1,$$

$$\check{h}_1^{(k)}(x_1) = -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_{k-1})}{\rho_1 + S_1^{\min}(T_{k-1})}\right) \cdot \frac{1}{1 + (\hat{a}_2^{(k-1)} + \varepsilon_{k-1})/\gamma_2} + \nu_1\beta_1,$$

$$\hat{h}_2^{(k)}(x_2) = -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(T_{k-1})}{\rho_2 + S_2^{\max}(T_{k-1})}\right) \cdot \frac{1}{1 + (\check{a}_1^{(k-1)} - \varepsilon_{k-1})/\gamma_1} + \nu_2\beta_2,$$

$$\check{h}_2^{(k)}(x_2) = -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\min}(T_{k-1})}{\rho_2 + S_2^{\min}(T_{k-1})}\right) \cdot \frac{1}{1 + (\hat{a}_1^{(k-1)} + \varepsilon_{k-1})/\gamma_1} + \nu_2\beta_2,$$

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

$$\hat{h}_i^{(k+1)}\big(\hat{a}_i^{(k)}\big) = 0, \qquad \check{h}_i^{(k+1)}\big(\check{a}_i^{(k)}\big) = 0. \tag{4.3}$$

We can then prove that for any small $\varepsilon_k > 0$, there exists a $T_k > 0$ such that $(x_1(t), x_2(t)) \in \Omega^{(k)} := [\check{a}_1^{(k)} - \varepsilon_k, \hat{a}_1^{(k)} + \varepsilon_k] \times [\check{a}_2^{(k)} - \varepsilon_k, \hat{a}_2^{(k)} + \varepsilon_k] \subset \Omega^{(k-1)}$ for $t \geqslant T_k$, for any solution $(x_1(t), v_1(t), x_2(t), v_2(t))$ starting from $(x_1(0), v_1(0), x_2(0), v_2(0)) \in \Omega^*$. We may clearly assume that $T_k \to \infty$ and $\varepsilon_k \to 0$ as $k \to \infty$.

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, and $\check{a}_i^{(k)} - \varepsilon_k < \hat{a}_i^{(k)} + \varepsilon_k$ for each k. Hence,

$$\check{a}_i^* = \lim_{k\to\infty} \check{a}_i^{(k)}, \ \hat{a}_i^* = \lim_{k\to\infty} \hat{a}_i^{(k)} \text{ exist}, \quad \text{and} \quad \check{a}_i^* \leqslant \hat{a}_i^*.$$

We claim that the intersection $\bigcap_{k=1}^{\infty} \Omega^{(k)}$ consists of just one point. To prove it, we assume that $\bigcap_{k=1}^{\infty} \Omega^{(k)}$ is not a single point, so that $\hat{a}_i^* > \check{a}_i^*$ for either $i = 1$ or $i = 2$ (or both) and proceed to derive a contradiction. By passing to the limit in (4.3), we obtain

$$-\mu_1\tau_1\check{a}_1^* + \nu_1\left[\alpha_1\frac{(\check{a}_1^*)^n}{k_1^n + (\check{a}_1^*)^n} + \sigma_1\frac{\check{S}_1}{\rho_1 + \check{S}_1}\right] \cdot \frac{1}{1 + \hat{a}_2^*/\gamma_2} + \nu_1\beta_1 = 0, \tag{4.4}$$

$$-\mu_2\tau_2\hat{a}_2^* + \nu_2\left[\alpha_2\frac{(\hat{a}_2^*)^n}{k_2^n + (\hat{a}_2^*)^n} + \sigma_2\frac{\hat{S}_2}{\rho_2 + \hat{S}_2}\right] \cdot \frac{1}{1 + \check{a}_1^*/\gamma_1} + \nu_2\beta_2 = 0, \tag{4.5}$$

$$-\mu_1\tau_1\hat{a}_1^* + \nu_1\left[\alpha_1\frac{(\hat{a}_1^*)^n}{k_1^n + (\hat{a}_1^*)^n} + \sigma_1\frac{\hat{S}_1}{\rho_1 + \hat{S}_1}\right] \cdot \frac{1}{1 + \check{a}_2^*/\gamma_2} + \nu_1\beta_1 = 0, \tag{4.6}$$

$$-\mu_2\tau_2\check{a}_2^* + \nu_2\left[\alpha_2\frac{(\check{a}_2^*)^n}{k_2^n + (\check{a}_2^*)^n} + \sigma_2\frac{\check{S}_2}{\rho_2 + \check{S}_2}\right] \cdot \frac{1}{1 + \hat{a}_1^*/\gamma_1} + \nu_2\beta_2 = 0, \tag{4.7}$$

where

$$\hat{S}_i = \lim_{t\to\infty} S_i^{\max}(t), \qquad \check{S}_i = \lim_{t\to\infty} S_i^{\min}(t), \tag{4.8}$$

and

$$\hat{S}_1 \leqslant \hat{a}_1^* + \bar{E}_1, \qquad \check{S}_1 \geqslant \check{a}_1^* + \bar{E}_1, \tag{4.9}$$

$$\hat{S}_2 \leqslant \hat{a}_2^* + \bar{E}_2, \qquad \check{S}_2 \geqslant \check{a}_2^* + \bar{E}_2, \tag{4.10}$$

with

$$\bar{E}_i = \lim_{t\to\infty} E_i(t)e^{-G(t)}/N_0. \tag{4.11}$$

Taking the difference of (4.4), (4.6), we obtain

$$\begin{aligned}
&\mu_1\tau_1\left(\hat{a}_1^* - \check{a}_1^*\right) - \nu_1\alpha_1\left[\frac{(\hat{a}_1^*)^n}{k_1^n + (\hat{a}_1^*)^n} - \frac{(\check{a}_1^*)^n}{k_1^n + (\check{a}_1^*)^n}\right] \cdot \frac{1}{1 + \check{a}_2^*/\gamma_2} \\
&\quad = \nu_1\left[\alpha_1\frac{(\check{a}_1^*)^n}{k_1^n + (\check{a}_1^*)^n} + \sigma_1\frac{\check{S}_1}{\rho_1 + \check{S}_1}\right] \cdot \left[\frac{1}{1 + \check{a}_2^*/\gamma_2} - \frac{1}{1 + \hat{a}_2^*/\gamma_2}\right] \\
&\quad\quad + \nu_1\sigma_1\left[\frac{\hat{S}_1}{\rho_1 + \hat{S}_1} - \frac{\check{S}_1}{\rho_1 + \check{S}_1}\right] \cdot \frac{1}{1 + \check{a}_2^*/\gamma_2}.
\end{aligned}$$

Thus, by the mean value theorem and the estimates (4.9) for $\hat{S}_1$, $\check{S}_1$,

$$\left|\hat{a}_1^* - \check{a}_1^*\right| \cdot \left|\mu_1\tau_1 - \frac{\nu_1\alpha_1\tilde{n}}{k_1}\right| \leqslant \frac{\nu_1(\alpha_1+\sigma_1)}{\gamma_2}\left|\check{a}_2^* - \hat{a}_2^*\right| + \frac{\nu_1\sigma_1}{\rho_1}\left|\hat{a}_1^* - \check{a}_1^*\right|,$$

or

$$\left|\hat{a}_1^* - \check{a}_1^*\right| \cdot \left[\left|\mu_1\tau_1 - \frac{\nu_1\alpha_1\tilde{n}}{k_1}\right| - \frac{\nu_1\sigma_1}{\rho_1}\right] \leqslant \frac{\nu_1(\alpha_1+\sigma_1)}{\gamma_2}\left|\check{a}_2^* - \hat{a}_2^*\right|. \tag{4.12}$$

Similarly, from (4.5), (4.7), (4.10) we obtain

$$\left|\check{a}_2^* - \hat{a}_2^*\right| \cdot \left[\left|\mu_2\tau_2 - \frac{\nu_2\alpha_2\tilde{n}}{k_2}\right| - \frac{\nu_2\sigma_2}{\rho_2}\right] \leqslant \frac{\nu_2(\alpha_2+\sigma_2)}{\gamma_1}\left|\hat{a}_1^* - \check{a}_1^*\right|. \tag{4.13}$$

If the left-hand sides of (4.12) and (4.13) are positive, then these two inequalities yield

$$\begin{aligned}&\left[\left|\mu_1\tau_1 - \frac{\nu_1\alpha_1\tilde{n}}{k_1}\right| - \frac{\nu_1\sigma_1}{\rho_1}\right] \cdot \left[\left|\mu_1\tau_2 - \frac{\nu_2\alpha_2\tilde{n}}{k_2}\right| - \frac{\nu_2\sigma_2}{\rho_2}\right] \\ &\quad < \frac{\nu_2(\alpha_2+\sigma_2)}{\gamma_1} \cdot \frac{\nu_2(\alpha_1+\sigma_1)}{\gamma_2},\end{aligned} \tag{4.14}$$

which is a contradiction to (4.1). We thus conclude that $\check{a}_i^* = \hat{a}_i^*$ for $i = 1, 2$, and the theorem follows. □

Remark 4.1. Theorem 4.1 and Corollary 4.2 remain true with essentially the same proof under the conditions in Proposition 3.4 and conditions (4.1), (4.2).

5. Asymptotic behavior: multiple limit points

5.1. Behavior of solutions of (3.5)–(3.6)

We first investigate the dynamical system (3.9)–(3.10) with $\hat{h}_i$ and $\check{h}_i$ each having three zeros. We assume that the conditions (3.19) and (B_i) hold for either $i = 1$ or $i = 2$. Let us denote by $U(p) \subset \mathbb{R}^2$ the basin of attraction for sinks $(p, 0) = (\hat{a}_i, 0)$, $(\hat{c}_i, 0)$, $(\check{a}_i, 0)$, $(\check{c}_i, 0)$ of (3.7) and (3.8), respectively.

We shall consider the orbits $(x_1(t), v_1(t), x_2(t), v_2(t))$ of (3.9)–(3.10) initiating from any point in Ω^*. However, from Lemma 3.3 and Proposition 3.5, we may take initial conditions to belong to one of the following regions:

(i) $(x_i(0), v_i(0)) \in U(\hat{a}_i) \cap U(\check{a}_i)$,
(ii) $(x_i(0), v_i(0)) \in U(\hat{c}_i) \cap U(\check{c}_i)$,
(iii) $(x_i(0), v_i(0)) \in U(\hat{a}_i) \cap U(\check{c}_i) \cup W^s(\hat{b}_i) \cup W^s(\check{b}_i) =: U(\check{b}_i, \hat{b}_i)$.

For the first two cases, it follows from Lemma 3.3 and Proposition 3.5 that

$$\lim_{t\to\infty} x_i(t) \in [\check{a}_i, \hat{a}_i] \quad \text{if } \big(x_i(0), v_i(0)\big) \in U(\hat{a}_i) \cap U(\check{a}_i),$$

$$\lim_{t\to\infty} x_i(t) \in [\check{c}_i, \hat{c}_i] \quad \text{if } \big(x_i(0), v_i(0)\big) \in U(\hat{c}_i) \cap U(\check{c}_i).$$

In order to analyze the global dynamics in the next sections, we need to establish uniform-in-time properties for all orbits of the system. For a small $\epsilon > 0$, we introduce the ϵ-neighborhood of $U(\check{b}_i, \hat{b}_i)$, namely,

$$U_\epsilon(\check{b}_i, \hat{b}_i) := \big\{(x_i, v_i)\colon \big|(x_i, v_i) - U(\check{b}_i, \hat{b}_i)\big| < \epsilon\big\}$$

and sets

$$U_\epsilon(\check{a}_i, \hat{a}_i) := \big[U(\hat{a}_i) \cap U(\check{a}_i)\big] \setminus \big[U_\epsilon(\check{b}_i, \hat{b}_i) \setminus U(\check{b}_i, \hat{b}_i)\big],$$
$$U_\epsilon(\check{c}_i, \hat{c}_i) := \big[U(\hat{c}_i) \cap U(\check{c}_i)\big] \setminus \big[U_\epsilon(\check{b}_i, \hat{b}_i) \setminus U(\check{b}_i, \hat{b}_i)\big],$$

and consider a decomposition of D_i (in the (x_i, v_i)-plane) as follows

$$D_i = U_\epsilon(\check{b}_i, \hat{b}_i) \cup U_\epsilon(\check{a}_i, \hat{a}_i) \cup U_\epsilon(\check{c}_i, \hat{c}_i).$$

By Lemmas 3.1 and 3.2, we conclude that for a small $\epsilon > 0$, there exists a $\tilde{\tau} > 0$ such that

$$x_i(t) \in (\check{a}_i - \epsilon, \hat{a}_i + \epsilon) \quad \text{for } t \geqslant \tilde{\tau}, \text{ if } \big(x_i(0), v_i(0)\big) \in U_\epsilon(\check{a}_i, \hat{a}_i),$$
$$x_i(t) \in (\check{c}_i - \epsilon, \hat{c}_i + \epsilon) \quad \text{for } t \geqslant \tilde{\tau}, \text{ if } \big(x_i(0), v_i(0)\big) \in U_\epsilon(\check{c}_i, \hat{c}_i).$$

We next track the evolutions of points $(x_1(0), v_1(0), x_2(0), v_2(0))$ in case (iii). These are points $(x_1(0), v_1(0), x_2(0), v_2(0))$ with $(x_i(0), v_i(0))$ lying between and on the stable manifolds $W^s(\hat{b}_i)$ of $(\hat{b}_i, 0)$ and $W^s(\check{b}_i)$ of $(\check{b}_i, 0)$. For these initial points, there are three possibilities:

- $(x_i(t), v_i(t))$ enters into $U(\hat{a}_i) \cap U(\check{a}_i)$ in finite time,
- $(x_i(t), v_i(t))$ enters into $U(\hat{c}_i) \cap U(\check{c}_i)$ in finite time,
- $(x_i(t), v_i(t))$ stays in $U(\check{b}_i, \hat{b}_i)$ for all time.

Note that once $(x_i(t), v_i(t))$ enters $U(\hat{a}_i) \cap U(\check{a}_i)$ (resp., $U(\hat{c}_i) \cap U(\check{c}_i)$), then it will be attracted to segment $\{(x_i, 0)\colon x_i \in [\check{a}_i, \hat{a}_i]\}$ (resp., $\{(x_i, 0)\colon x_i \in [\check{c}_i, \hat{c}_i]\}$).

Next, we claim that a dichotomy can be established for all orbits $(x_1(t), v_1(t), x_2(t), v_2(t))$ evolved from $U_\epsilon(\check{b}_i, \hat{b}_i)$; namely, there exists a $\tau^* > 0$ such that, for all $t > \tau^*$, either

(iii-a) $(x_i(t), v_i(t))$ enters into $U_\epsilon(\hat{a}_i, \check{a}_i)$ or $U_\epsilon(\hat{c}_i, \check{c}_i)$, or
(iii-b) $(x_i(t), v_i(t))$ lies in an arbitrarily small neighborhood of the segment connecting $\hat{b}_i, \check{b}_i$.

The assertion will be justified by considerations that involve local Lyapunov functions and analysis of vector field and level curves of the Lyapunov functions. We first observe that

$$\hat{L}_i(x_1, v_1, x_2, v_2) = \hat{L}_i(x_i, v_i) := \frac{1}{2}v_i^2 - \int_0^{x_i} \hat{h}_i(s)\,ds$$

is a Lyapunov function for (3.9)–(3.10) on the region $v_i \geqslant 0$. Indeed,

$$\begin{aligned}\dot{\hat{L}}_i(x_1, v_1, x_2, v_2) &= v_i \cdot \big[-(\tau_i + \mu_i)v_i + h_i(x_1, x_2, S_i)\big] - \hat{h}_i(x_i) \cdot v_i \\ &= -(\tau_i + \mu_i)v_i^2 - v_i\big[\hat{h}_i(x_i) - h_i(x_1, x_2, S_i)\big] \\ &\leqslant -(\tau_i + \mu_i)v_i^2 \leqslant 0, \end{aligned} \tag{5.1}$$

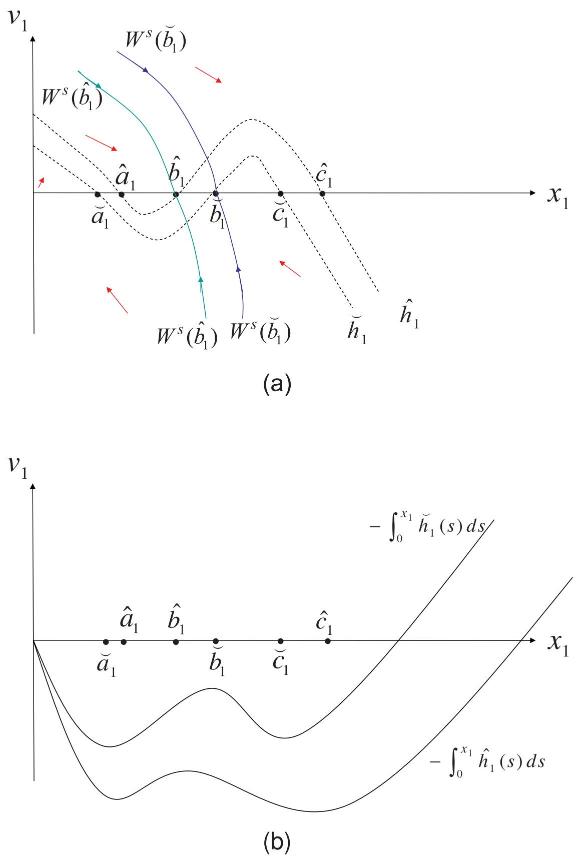

Fig. 4. (a) The vector field for (3.9)–(3.10) projected onto (x_1, v_1)-plane. (b) The graphs for $-\int_0^{x_1} \hat{h}_1(s)\,ds$ and $-\int_0^{x_1} \breve{h}_1(s)\,ds$.

if $v_i \geqslant 0$. Similarly,

$$\breve{L}_i(x_1, v_1, x_2, v_2) = \breve{L}_i(x_i, v_i) := \frac{1}{2}v_i^2 - \int_0^{x_i} \breve{h}_i(s)\,ds,$$

is a Lyapunov functions for (3.9)–(3.10) on the region $v_i \leqslant 0$. Accordingly, the value of $\hat{L}_i$ (resp., $\breve{L}_i$) along an orbit or a portion of an orbit of (3.9)–(3.10) is strictly decreasing when lying in $\{v_i > 0\}$ (resp., $\{v_i < 0\}$). On the other hand, $-\int_0^{x_i} \hat{h}_i(s)\,ds$ (resp., $-\int_0^{x_i} \breve{h}_i(s)\,ds$) has a local maximum at $\hat{b}_i$ (resp., $\breve{b}_i$) and local minimum at $\hat{a}_i$ and $\hat{c}_i$ (resp., $\breve{a}_i$ and $\breve{c}_i$). Moreover, the minimal value of $\hat{L}_i$ (resp., $\breve{L}_i$) is attained at $(x_i, v_i) = (\hat{a}_i, 0)$ or $(\hat{c}_i, 0)$, (resp., $(\breve{a}_i, 0)$ or $(\breve{c}_i, 0)$). Thus, $\hat{L}_i(\breve{b}_i, 0) < \hat{L}_i(\hat{b}_i, 0)$, and $\breve{L}_i(\breve{b}_i, 0) > \breve{L}_i(\hat{b}_i, 0)$. We depict these scenarios in Figs. 4(a), 4(b) (for $i = 1$). Note that as we consider solutions evolved from a compact set in Ω^*, the values of $\hat{L}_i$ and $\breve{L}_i$ on the evolutions of these points are bounded above and below.

Let δ be a sufficiently small positive number. Note that for $(x_i, v_i) \in U_\epsilon(\breve{b}_i, \hat{b}_i) \cap \{|v_i| \leqslant \delta\}$,

$$\hat{L}_i(x_i, v_i) \leqslant \hat{L}_i(\hat{b}_i, \delta) \quad \text{if } v_i > 0, \qquad \breve{L}_i(x_i, v_i) \leqslant \breve{L}_i(\breve{b}_i, \delta) \quad \text{if } v_i < 0; \tag{5.2}$$

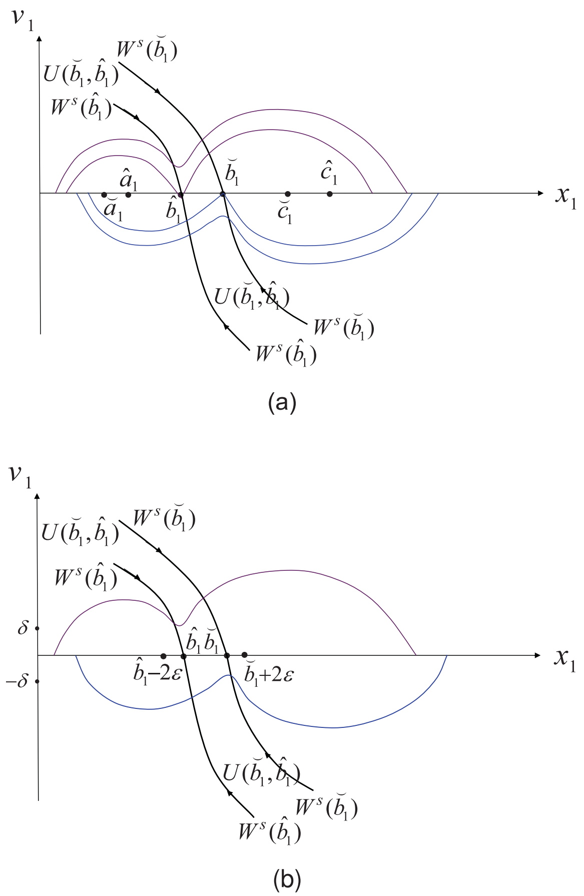

Fig. 5. (a) Level curves for $\hat{L}_1$ in $\{v_1 \geqslant 0\}$, and for $\check{L}_1$ in $\{v_1 \leqslant 0\}$. (b) The bounded region enclosed by $\{(x_1, v_1)\colon \hat{L}_1(x_1, v_1) = \hat{L}_1(\hat{b}_1, \delta),\ v_1 \geqslant 0\}$, $\{(x_1, v_1)\colon \check{L}_1(x_1, v_1) = \check{L}_1(\check{b}_1, -\delta),\ v_1 \leqslant 0\}$, $W^s(\hat{b}_1)$, and $W^s(\check{b}_1)$, lies in $B_{2\epsilon}(\check{b}_1, \hat{b}_1)$.

cf. Fig. 5(a). We divide the orbits of (3.9)–(3.10) evolved from points $(x_1(0), v_1(0), x_2(0), v_2(0))$ with $(x_i(0), v_i(0)) \in U_\epsilon(\check{b}_i, \hat{b}_i)$ into two classes:

Class-I: Orbit starts from $U_\epsilon(\check{b}_i, \hat{b}_i) \cap \{v_i > \delta\}$ and remains in $\{v_i > \delta\}$ before leaving $U_\epsilon(\check{b}_i, \hat{b}_i)$ (i.e., before entering $U_\epsilon(\check{a}_i, \hat{a}_i)$ or $U_\epsilon(\check{c}_i, \hat{c}_i)$), or orbit starts from $U_\epsilon(\check{b}_i, \hat{b}_i) \cap \{v_i < -\delta\}$ and remains in $\{v_i < -\delta\}$ before entering $U_\epsilon(\check{a}_i, \hat{a}_i)$ or $U_\epsilon(\check{c}_i, \hat{c}_i)$;

Class-II: Orbit initiates from, or enters into, $U_\epsilon(\check{b}_i, \hat{b}_i) \cap \{|v_i| \leqslant \delta\}$.

According to (5.1), all class-I orbits take less than a finite time τ^* to enter $U_\epsilon(\check{a}_i, \hat{a}_i) \cup U_\epsilon(\check{c}_i, \hat{c}_i)$. In addition, it also takes less than a finite time τ^* for all class-II orbits initiating from $U_\epsilon(\check{b}_i, \hat{b}_i) \cap \{|v_i| > \delta\}$ to enter $U_\epsilon(\check{b}_i, \hat{b}_i) \cap \{|v_i| \leqslant \delta\}$, again by (5.1). If an orbit starting from $\{v_i > 0\}$ (resp., $\{v_i < 0\}$) crosses $\{v_i = 0\}$ to enter $\{v_i < 0\}$ (resp., $\{v_i > 0\}$) while it remains in $U_\epsilon(\check{b}_i, \hat{b}_i)$, then the value of $\check{L}_i$ (resp., $\hat{L}_i$) at such orbit cannot exceed $\check{L}_i(\check{b}_i, 0)$ (resp., $\hat{L}_i(\hat{b}_i, 0)$) at all later times while lying in $\{v_i < 0\}$ (resp. $\{v_i > 0\}$). Therefore, the solutions initiating from, or entering into, $U_\epsilon(\check{b}_i, \hat{b}_i) \cap \{|v_i| \leqslant \delta\}$ will be constrained by (5.2) and thus be bounded by the level curves

$$\left\{(x_i, v_i)\colon \hat{L}_i(x_i, v_i) = \hat{L}_i(\hat{b}_i, \delta),\ v_i \geqslant 0\right\},$$

$$\left\{(x_i, v_i)\colon \check{L}_i(x_i, v_i) = \check{L}_i(\check{b}_i, -\delta),\ v_i \leqslant 0\right\}, \tag{5.3}$$

at all future time; cf. Fig. 5(b). For $\xi_1 < \xi_2$ and $\epsilon > 0$, we introduce an ϵ-neighborhood of the segment connecting $(\xi_1, 0)$, $(\xi_2, 0)$ in $\mathbb{R}^2$ by

$$B_\epsilon(\xi_1, \xi_2) := \left\{(x_i, v_i)\colon \left|(x_i, v_i) - \left\{(\eta, 0)\colon \xi_1 \leqslant \eta \leqslant \xi_2\right\}\right| < \epsilon\right\}.$$

Then, the region bounded by (5.3) comprises parts of $U_\epsilon(\check{a}_i, \hat{a}_i)$, $U_\epsilon(\check{c}_i, \hat{c}_i)$, and part of $B_{2\epsilon}(\check{b}_i, \hat{b}_i)$, provided δ is chosen sufficiently small. The dichotomy (iii-a)–(iii-b) is thus justified.

Using the properties of Lyapunov functions $\hat{L}_i$, $\check{L}_i$, and Lemma 3.1, Lemma 3.3, we also conclude that solutions lying in $U_\epsilon(\check{a}_i, \hat{a}_i)$ (resp., $U_\epsilon(\check{c}_i, \hat{c}_i)$) enter $B_\epsilon(\check{a}_i, \hat{a}_i)$ (resp., $B_\epsilon(\check{c}_i, \hat{c}_i)$) in finite time. Summarizing the above discussion, we conclude that for a small $\epsilon > 0$, there exist $\tau_0 > 0$ and $T_0 > 0$ such that for all orbits $(x_1(t), v_1(t), x_2(t), v_2(t))$ of (3.9)–(3.10) initiating from Ω^*, $(x_i(t), v_i(t))$ lie in $B_\epsilon(\check{a}_i, \hat{a}_i)$ or $B_\epsilon(\check{c}_i, \hat{c}_i)$, for all $t > T_0 + \tau_0$ or enter into $B_{2\epsilon}(\check{b}_i, \hat{b}_i)$ at time $t = T_0$. In particular, their x_i-coordinates satisfy either

$$x_i(t) \in [\check{a}_i - \epsilon, \hat{a}_i + \epsilon] \cup [\check{c}_i - \epsilon, \hat{c}_i + \epsilon],$$

for all $t > T_0 + \tau_0$ or $x_i(T_0) \in [\hat{b}_i - 2\epsilon, \check{b}_i + 2\epsilon]$.

5.2. Two limit points

In this section, we prove that system (3.9)–(3.10) admits two limit points provided the conditions (B_1) and (Ma_2) or (Mb_2) hold. The same result can be established under the conditions (B_2) and (Ma_1) or (Mb_1).

Under the conditions (B_1) and (Ma_2) or (Mb_2), $\hat{h}_1$ (resp., $\check{h}_1$) has three zeros $\hat{a}_1, \hat{b}_1, \hat{c}_1$ (resp., $\check{a}_1, \check{b}_1, \check{c}_1$), and $\hat{h}_2$ (resp., $\check{h}_2$) has one zero $\hat{a}_2$ (resp., $\check{a}_2$). According to the discussion in Section 4 and Section 5.1, for a small $\varepsilon_0 > 0$, there exist $\tau_0 > 0$ and $T_0 > 0$ such that all solutions $(x_1(t), v_1(t), x_2(t), v_2(t))$ of (3.9)–(3.10) with initial values from the compact set Ω^* either lie in $[B_{\varepsilon_0}(\check{a}_1, \hat{a}_1) \cup B_{\varepsilon_0}(\check{c}_1, \hat{c}_1)] \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2)$, for all $t > T_0 + \tau_0$ or stay in $B_{2\varepsilon_0}(\check{b}_1, \hat{b}_1) \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2)$ at $t = T_0$. In particular,

$$\begin{gathered}
\big(x_1(t), x_2(t)\big) \in \big([\check{a}_1 - \varepsilon_0, \hat{a}_1 + \varepsilon_0] \cup [\check{c}_1 - \varepsilon_0, \hat{c}_1 + \varepsilon_0]\big) \times [\check{a}_2 - \varepsilon_0, \hat{a}_2 + \varepsilon_0], \quad t > T_0 + \tau_0, \\
\big(x_1(t), x_2(t)\big) \in [\hat{b}_1 - 2\varepsilon_0, \check{b}_1 + 2\varepsilon_0] \times [\check{a}_2 - \varepsilon_0, \hat{a}_2 + \varepsilon_0], \quad t = T_0.
\end{gathered}$$

Therefore, to determine the asymptotic behavior of (3.9)–(3.10) for $t > T_0$, we only need to consider the evolution of points which belong to

$$\left[B_{\varepsilon_0}(\check{a}_1, \hat{a}_1) \cup B_{\varepsilon_0}(\check{c}_1, \hat{c}_1) \cup B_{2\varepsilon_0}(\check{b}_1, \hat{b}_1)\right] \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2) \tag{5.4}$$

at time $t = T_0$.

We first focus on the evolutions of points in $B_{2\varepsilon_0}(\check{b}_1, \hat{b}_1) \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2)$. Let us define sharper upper and lower bounds of h_i, for the evolutions of points from this region:

$$\begin{aligned}
\hat{h}^{(1)}_{1,\mathrm{m}}(x_1) &:= -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_0)}{\rho_1 + S_1^{\max}(T_0)}\right) \cdot \frac{1}{1 + (\check{a}_2 - 2\varepsilon_0)/\gamma_2} + \nu_1\beta_1, \\
\check{h}^{(1)}_{1,\mathrm{m}}(x_1) &:= -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_0)}{\rho_1 + S_1^{\min}(T_0)}\right) \cdot \frac{1}{1 + (\hat{a}_2 + 2\varepsilon_0)/\gamma_2} + \nu_1\beta_1,
\end{aligned}$$

$$\hat{h}_{2,\mathrm{m}}^{(1)}(x_2) := -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2\frac{x_2^n}{k_2^n + x_2^n} + \sigma_2\frac{S_2^{\max}(T_0)}{\rho_2 + S_2^{\max}(T_0)}\right)\cdot\frac{1}{1+(\hat{b}_1 - 3\varepsilon_0)/\gamma_1} + \nu_2\beta_2,$$
$$\check{h}_{2,\mathrm{m}}^{(1)}(x_2) := -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2\frac{x_2^n}{k_2^n + x_2^n} + \sigma_2\frac{S_2^{\min}(T_0)}{\rho_2 + S_2^{\min}(T_0)}\right)\cdot\frac{1}{1+(\check{b}_1 + 3\varepsilon_0)/\gamma_1} + \nu_2\beta_2.$$

Since

$$\check{h}_1 < \check{h}_{1,\mathrm{m}}^{(1)} < \hat{h}_{1,\mathrm{m}}^{(1)} < \hat{h}_1,$$
$$\check{h}_2 < \check{h}_{2,\mathrm{m}}^{(1)} < \hat{h}_{2,\mathrm{m}}^{(1)} < \hat{h}_2,$$

$\check{h}_{1,\mathrm{m}}^{(1)}$ (resp., $\hat{h}_{1,\mathrm{m}}^{(1)}$) has three zeros $\check{a}_{1,\mathrm{m}}^{(1)}, \check{b}_{1,\mathrm{m}}^{(1)}, \check{c}_{1,\mathrm{m}}^{(1)}$ (resp., $\hat{a}_{1,\mathrm{m}}^{(1)}, \hat{b}_{1,\mathrm{m}}^{(1)}, \hat{c}_{1,\mathrm{m}}^{(1)}$), and $\check{h}_{2,\mathrm{m}}^{(1)}$ (resp., $\hat{h}_{2,\mathrm{m}}^{(1)}$) has one zero $\check{a}_{2,\mathrm{m}}^{(1)}$ (resp., $\hat{a}_{2,\mathrm{m}}^{(1)}$). Clearly,

$$\check{a}_{1,\mathrm{m}}^{(1)} > \check{a}_1, \qquad \check{b}_{1,\mathrm{m}}^{(1)} < \check{b}_1, \qquad \check{c}_{1,\mathrm{m}}^{(1)} > \check{c}_1,$$
$$\hat{a}_{1,\mathrm{m}}^{(1)} < \hat{a}_1, \qquad \hat{b}_{1,\mathrm{m}}^{(1)} > \hat{b}_1, \qquad \hat{c}_{1,\mathrm{m}}^{(1)} < \hat{c}_1,$$
$$\hat{a}_{2,\mathrm{m}}^{(1)} < \hat{a}_2, \qquad \check{a}_{2,\mathrm{m}}^{(1)} > \check{a}_2.$$

By continuity, for a short while after T_0, the evolutions of points in $B_{2\varepsilon_0}(\check{b}_1, \hat{b}_1) \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2)$ under (3.9)–(3.10) are constrained by the sharper upper and lower dynamics defined by (3.7)–(3.8) with $\check{h}_i$ and $\hat{h}_i$ replaced by $\check{h}_{i,\mathrm{m}}^{(1)}$ and $\hat{h}_{i,\mathrm{m}}^{(1)}$, respectively. Note that $W^s(\hat{b}_{1,\mathrm{m}}^{(1)})$ and $W^s(\check{b}_{1,\mathrm{m}}^{(1)})$ lie between $W^s(\hat{b}_1)$ and $W^s(\check{b}_1)$, by Lemma 3.3(iii), where $W^s(\hat{b}_{1,\mathrm{m}}^{(1)})$ is the stable manifold of equilibrium point $(\hat{b}_{1,\mathrm{m}}^{(1)}, 0)$ for the new upper system and $W^s(\check{b}_{1,\mathrm{m}}^{(1)})$ is the stable manifold of $(\check{b}_{1,\mathrm{m}}^{(1)}, 0)$ for the new lower system. Accordingly, the region $U(\check{b}_{1,\mathrm{m}}^{(1)}, \hat{b}_{1,\mathrm{m}}^{(1)})$, bounded by $W^s(\hat{b}_{1,\mathrm{m}}^{(1)})$ and $W^s(\check{b}_{1,\mathrm{m}}^{(1)})$, satisfies

$$U\big(\check{b}_{1,\mathrm{m}}^{(1)}, \hat{b}_{1,\mathrm{m}}^{(1)}\big) \subset U(\check{b}_1, \hat{b}_1).$$

In addition, for $t \geqslant T_0$

$$\check{h}_{1,\mathrm{m}}^{(1)}(x_1) < h_1\big(x_1, x_2, S_1(t)\big) < \hat{h}_{1,\mathrm{m}}^{(1)}(x_1) \quad \text{if } x_2 \in [\check{a}_2 - 2\varepsilon_0, \hat{a}_2 + 2\varepsilon_0],$$
$$\check{h}_{2,\mathrm{m}}^{(1)}(x_2) < h_2\big(x_1, x_2, S_2(t)\big) < \hat{h}_{2,\mathrm{m}}^{(1)}(x_2) \quad \text{if } x_1 \in [\hat{b}_1 - 3\varepsilon_0, \check{b}_1 + 3\varepsilon_0].$$

Hence, for any ε_1 with $0 < 3\varepsilon_1 < \varepsilon_0$, one can define $B_{2\varepsilon_1}(\check{b}_{1,\mathrm{m}}^{(1)}, \hat{b}_{1,\mathrm{m}}^{(1)})$ and $B_{\varepsilon_1}(\check{a}_{2,\mathrm{m}}^{(1)}, \hat{a}_{2,\mathrm{m}}^{(1)})$ as before, with

$$B_{2\varepsilon_1}\big(\check{b}_{1,\mathrm{m}}^{(1)}, \hat{b}_{1,\mathrm{m}}^{(1)}\big) \subset B_{2\varepsilon_0}(\check{b}_i, \hat{b}_i), \qquad B_{\varepsilon_1}\big(\check{a}_{2,\mathrm{m}}^{(1)}, \hat{a}_{2,\mathrm{m}}^{(1)}\big) \subset B_{\varepsilon_0}(\check{a}_2, \hat{a}_2),$$

and the following holds:

There exists a $T_1 > T_0$, such that the solutions $(x_1(t), v_1(t), x_2(t), v_2(t))$ of (3.9)–(3.10) with $(x_1(T_0), v_1(T_0), x_2(T_0), v_2(T_0)) \in B_{2\varepsilon_0}(\check{b}_1, \hat{b}_1) \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2)$ for which $(x_1(T_1), v_1(T_1), x_2(T_1), v_2(T_1)) \notin B_{2\varepsilon_1}(\check{b}_{1,\mathrm{m}}^{(1)}, \hat{b}_{1,\mathrm{m}}^{(1)}) \times B_{\varepsilon_1}(\check{a}_{2,\mathrm{m}}^{(1)}, \hat{a}_{2,\mathrm{m}}^{(1)})$ will be attracted to $[B_{\varepsilon_0}(\check{a}_1, \hat{a}_1) \cup B_{\varepsilon_0}(\check{c}_1, \hat{c}_1)] \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2)$, i.e., there exists a $\tau_1 > \tau_0$ such that $(x_1(t), v_1(t), x_2(t), v_2(t)) \in [B_{\varepsilon_0}(\check{a}_1, \hat{a}_1) \cup B_{\varepsilon_0}(\check{c}_1, \hat{c}_1)] \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2)$, for

$t > T_1 + \tau_1$. Hence, after $t = T_1$, we shall focus on the evolution of points lying in $B_{2\varepsilon_1}(\check{b}_{1,\mathrm{m}}^{(1)}, \hat{b}_{1,\mathrm{m}}^{(1)}) \times B_{\varepsilon_1}(\check{a}_{2,\mathrm{m}}^{(1)}, \hat{a}_{2,\mathrm{m}}^{(1)})$. Proceeding by induction we define successively

$$\hat{h}_{1,\mathrm{m}}^{(k)}(x_1) := -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_{k-1})}{\rho_1 + S_1^{\max}(T_{k-1})}\right) \cdot \frac{1}{1 + (\check{a}_{2,\mathrm{m}}^{(k-1)} - 2\varepsilon_{k-1})/\gamma_2} + \nu_1\beta_1,$$

$$\check{h}_{1,\mathrm{m}}^{(k)}(x_1) := -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_{k-1})}{\rho_1 + S_1^{\min}(T_{k-1})}\right) \cdot \frac{1}{1 + (\hat{a}_{2,\mathrm{m}}^{(k-1)} + 2\varepsilon_{k-1})/\gamma_2} + \nu_1\beta_1,$$

$$\hat{h}_{2,\mathrm{m}}^{(k)}(x_2) := -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(T_{k-1})}{\rho_2 + S_2^{\max}(T_{k-1})}\right) \cdot \frac{1}{1 + (\hat{b}_{1,\mathrm{m}}^{(k-1)} - 3\varepsilon_{k-1})/\gamma_1} + \nu_2\beta_2,$$

$$\check{h}_{2,\mathrm{m}}^{(k)}(x_2) := -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\min}(T_{k-1})}{\rho_2 + S_2^{\min}(T_{k-1})}\right) \cdot \frac{1}{1 + (\check{b}_{1,\mathrm{m}}^{(k-1)} + 3\varepsilon_{k-1})/\gamma_1} + \nu_2\beta_2,$$

where $0 < 3\varepsilon_{k-1} < \varepsilon_{k-2}$, $T_{k-1} > T_{k-2}$, $k \geqslant 2$. Let $\check{b}_{1,\mathrm{m}}^{(k)}$ and $\hat{b}_{1,\mathrm{m}}^{(k)}$, be the middle zero of $\check{h}_{1,\mathrm{m}}^{(k)}$ and $\hat{h}_{1,\mathrm{m}}^{(k)}$ respectively, and $\check{a}_{2,\mathrm{m}}^{(k)}$ and $\hat{a}_{2,\mathrm{m}}^{(k)}$ be the unique zero of $\check{h}_{2,\mathrm{m}}^{(k)}$ and $\hat{h}_{2,\mathrm{m}}^{(k)}$ respectively. Then

$$\check{b}_{1,\mathrm{m}}^{(k)} < \check{b}_{1,\mathrm{m}}^{(k-1)}, \qquad \hat{b}_{1,\mathrm{m}}^{(k)} > \hat{b}_{1,\mathrm{m}}^{(k-1)},$$
$$\check{a}_{2,\mathrm{m}}^{(k)} > \check{a}_{2,\mathrm{m}}^{(k-1)}, \qquad \hat{a}_{2,\mathrm{m}}^{(k)} < \hat{a}_{2,\mathrm{m}}^{(k-1)}.$$

For any ε_k with $0 < 3\varepsilon_k < \varepsilon_{k-1}$, there exist $T_k > 0$ and $\tau_k > 0$ such that the solutions $(x_1(t), v_1(t), x_2(t), v_2(t))$ of (3.9)–(3.10) with $(x_1(T_{k-1}), v_1(T_{k-1}),\ x_2(T_{k-1}), v_2(T_{k-1})) \in B_{2\varepsilon_{k-1}}(\check{b}_{1,\mathrm{m}}^{(k-1)}, \hat{b}_{1,\mathrm{m}}^{(k-1)}) \times B_{\varepsilon_{k-1}}(\check{a}_{2,\mathrm{m}}^{(k-1)}, \hat{a}_{2,\mathrm{m}}^{(k-1)})$ but $(x_1(T_k), v_1(T_k), x_2(T_k), v_2(T_k)) \notin B_{2\varepsilon_k}(\check{b}_{1,\mathrm{m}}^{(k)}, \hat{b}_{1,\mathrm{m}}^{(k)}) \times B_{\varepsilon_k}(\check{a}_{2,\mathrm{m}}^{(k)}, \hat{a}_{2,\mathrm{m}}^{(k)})$ will lie in $[B_{\varepsilon_0}(\check{a}_1, \hat{a}_1) \cup B_{\varepsilon_0}(\check{c}_1, \hat{c}_1)] \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2)$, for $t > T_k + \tau_k$.

Recalling (5.4), we see that it remains to consider the solutions of (3.9)–(3.10) with

$$\bigl(x_1(t), v_1(t), x_2(t), v_2(t)\bigr) \in \bigl[B_{\varepsilon_0}(\check{a}_1, \hat{a}_1) \cup B_{\varepsilon_0}(\check{c}_1, \hat{c}_1)\bigr] \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2) \tag{5.5}$$

for all $t \geqslant T_0 + \tau_0$. These solutions are constrained by sharper upper and lower dynamics defined by (3.7)–(3.8) with $\check{h}_i, \hat{h}_i$ replaced by $\check{h}_{1,\mathrm{l}}^{(1)}, \hat{h}_{1,\mathrm{l}}^{(1)}, \check{h}_{2,\mathrm{l}}^{(1)}, \hat{h}_{2,\mathrm{l}}^{(1)}$ on region $B_{\varepsilon_0}(\check{a}_1, \hat{a}_1) \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2)$, and $\check{h}_{1,\mathrm{u}}^{(1)}, \hat{h}_{1,\mathrm{u}}^{(1)}, \check{h}_{2,\mathrm{u}}^{(1)}, \hat{h}_{2,\mathrm{u}}^{(1)}$ on region $B_{\varepsilon_0}(\check{c}_1, \hat{c}_1) \times B_{\varepsilon_0}(\check{a}_2, \hat{a}_2)$, where

$$\hat{h}_{1,\mathrm{l}}^{(1)}(x_1) := -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(T_0+\tau_0)}{\rho_1 + S_1^{\max}(T_0+\tau_0)}\right) \cdot \frac{1}{1 + (\check{a}_2 - \varepsilon_0)/\gamma_2} + \nu_1\beta_1,$$

$$\check{h}_{1,\mathrm{l}}^{(1)}(x_1) := -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(T_0+\tau_0)}{\rho_1 + S_1^{\min}(T_0+\tau_0)}\right) \cdot \frac{1}{1 + (\hat{a}_2 + \varepsilon_0)/\gamma_2} + \nu_1\beta_1,$$

$$\hat{h}_{2,\mathrm{l}}^{(1)}(x_2) := -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(T_0+\tau_0)}{\rho_2 + S_2^{\max}(T_0+\tau_0)}\right) \cdot \frac{1}{1 + (\check{a}_1 - \varepsilon_0)/\gamma_1} + \nu_2\beta_2,$$

$$\check{h}_{2,\mathrm{l}}^{(1)}(x_2) := -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\min}(T_0+\tau_0)}{\rho_2 + S_2^{\min}(T_0+\tau_0)}\right) \cdot \frac{1}{1 + (\hat{a}_1 + \varepsilon_0)/\gamma_1} + \nu_2\beta_2,$$

and $\hat{h}^{(1)}_{1,\mathrm{u}}, \check{h}^{(1)}_{1,\mathrm{u}}, \hat{h}^{(1)}_{2,\mathrm{u}}, \check{h}^{(1)}_{2,\mathrm{u}}$ are defined similarly. Denote the smallest zeros of $\hat{h}^{(1)}_{1,\mathrm{l}}$ and $\check{h}^{(1)}_{1,\mathrm{l}}$ by $\hat{a}^{(1)}_{1,\mathrm{l}}$ and $\check{a}^{(1)}_{1,\mathrm{l}}$, largest zeros of $\hat{h}^{(1)}_{1,\mathrm{u}}$ and $\check{h}^{(1)}_{1,\mathrm{u}}$ by $\hat{c}^{(1)}_{1,\mathrm{u}}$ and $\check{c}^{(1)}_{1,\mathrm{u}}$, and the unique zeros of $\hat{h}^{(1)}_{2,\mathrm{l}}$, $\check{h}^{(1)}_{2,\mathrm{l}}$, $\hat{h}^{(1)}_{2,\mathrm{u}}$, $\check{h}^{(1)}_{2,\mathrm{u}}$ by $\hat{a}^{(1)}_{2,\mathrm{l}}$, $\check{a}^{(1)}_{2,\mathrm{l}}$, $\hat{a}^{(1)}_{2,\mathrm{u}}$, $\check{a}^{(1)}_{2,\mathrm{u}}$, respectively. Then,

$$\begin{aligned} &\hat{a}^{(1)}_{1,\mathrm{l}} < \hat{a}_1, \qquad \check{a}^{(1)}_{1,\mathrm{l}} > \check{a}_1, \qquad \hat{a}^{(1)}_{2,\mathrm{l}} < \hat{a}_2, \qquad \check{a}^{(1)}_{2,\mathrm{l}} > \check{a}_2, \\ &\hat{c}^{(1)}_{1,\mathrm{u}} < \hat{c}_1, \qquad \check{c}^{(1)}_{1,\mathrm{u}} > \check{c}_1, \qquad \hat{a}^{(1)}_{2,\mathrm{u}} < \hat{a}_2, \qquad \check{a}^{(1)}_{2,\mathrm{u}} > \check{a}_2. \end{aligned}$$

For $0 < \varepsilon_1 < \varepsilon_0$, there exists a $\tilde{T}_1 > 0$ such that

$$\big(x_1(t), v_1(t), x_2(t), v_2(t)\big) \in \big[B_{\varepsilon_1}\big(\check{a}^{(1)}_{1,\mathrm{l}}, \hat{a}^{(1)}_{1,\mathrm{l}}\big) \times B_{\varepsilon_1}\big(\check{a}^{(1)}_{2,\mathrm{l}}, \hat{a}^{(1)}_{2,\mathrm{l}}\big)\big] \cup \big[B_{\varepsilon_1}\big(\check{c}^{(1)}_{1,\mathrm{u}}, \hat{c}^{(1)}_{1,\mathrm{u}}\big) \times B_{\varepsilon_1}\big(\check{a}^{(1)}_{2,\mathrm{u}}, \hat{a}^{(1)}_{2,\mathrm{u}}\big)\big]$$

for all $t \geqslant \tilde{T}_1$, for those solutions in (5.5). Similarly and successively, for $0 < \varepsilon_{k-1} < \varepsilon_{k-2}$, and $\tilde{T}_{k-1} > \tilde{T}_{k-2}$, we can define

$$\hat{h}^{(k)}_{1,\mathrm{l}}(x_1) := -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\max}(\tilde{T}_{k-1})}{\rho_1 + S_1^{\max}(\tilde{T}_{k-1})}\right) \cdot \frac{1}{1 + (\check{a}^{(k-1)}_{2,\mathrm{l}} - \varepsilon_{k-1})/\gamma_2} + \nu_1\beta_1,$$

$$\check{h}^{(k)}_{1,\mathrm{l}}(x_1) := -\mu_1\tau_1 x_1 + \nu_1\left(\alpha_1 \frac{x_1^n}{k_1^n + x_1^n} + \sigma_1 \frac{S_1^{\min}(\tilde{T}_{k-1})}{\rho_1 + S_1^{\min}(\tilde{T}_{k-1})}\right) \cdot \frac{1}{1 + (\hat{a}^{(k-1)}_{2,\mathrm{l}} + \varepsilon_{k-1})/\gamma_2} + \nu_1\beta_1,$$

$$\hat{h}^{(k)}_{2,\mathrm{l}}(x_2) := -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(\tilde{T}_{k-1})}{\rho_2 + S_2^{\max}(\tilde{T}_{k-1})}\right) \cdot \frac{1}{1 + (\check{a}^{(k-1)}_{1,\mathrm{l}} - \varepsilon_{k-1})/\gamma_1} + \nu_2\beta_2,$$

$$\check{h}^{(k)}_{2,\mathrm{l}}(x_2) := -\mu_2\tau_2 x_2 + \nu_2\left(\alpha_2 \frac{x_2^n}{k_2^n + x_2^n} + \sigma_2 \frac{S_2^{\max}(\tilde{T}_{k-1})}{\rho_2 + S_2^{\max}(\tilde{T}_{k-1})}\right) \cdot \frac{1}{1 + (\hat{a}^{(k-1)}_{1,\mathrm{l}} + \varepsilon_{k-1})/\gamma_1} + \nu_2\beta_2,$$

and similarly $\hat{h}^{(k)}_{i,\mathrm{u}}, \check{h}^{(k)}_{i,\mathrm{u}}$, $i = 1, 2$. The corresponding zeros $\hat{a}^{(k)}_{1,\mathrm{l}}, \check{a}^{(k)}_{1,\mathrm{l}}$, $\hat{c}^{(k)}_{1,\mathrm{u}}, \check{c}^{(k)}_{1,\mathrm{u}}$ $\hat{a}^{(k)}_{2,\mathrm{l}}, \check{a}^{(k)}_{2,\mathrm{l}}$ $\hat{a}^{(k)}_{2,\mathrm{u}}, \check{a}^{(k)}_{2,\mathrm{u}}$ respectively satisfy

$$\begin{aligned} &\hat{a}^{(k)}_{1,\mathrm{l}} < \hat{a}^{(k-1)}_{1,\mathrm{l}}, \qquad \check{a}^{(k)}_{1,\mathrm{l}} > \check{a}^{(k-1)}_{1,\mathrm{l}}, \qquad \hat{a}^{(k)}_{2,\mathrm{l}} < \hat{a}^{(k-1)}_{2,\mathrm{l}}, \qquad \check{a}^{(k)}_{2,\mathrm{l}} > \check{a}^{(k-1)}_{2,\mathrm{l}}, \\ &\hat{c}^{(k)}_{1,\mathrm{u}} < \hat{c}^{(k-1)}_{1,\mathrm{u}}, \qquad \check{c}^{(k)}_{1,\mathrm{u}} > \check{c}^{(k-1)}_{1,\mathrm{u}}, \qquad \hat{a}^{(k)}_{2,\mathrm{u}} < \hat{a}^{(k-1)}_{2,\mathrm{u}}, \qquad \check{a}^{(k)}_{2,\mathrm{u}} > \check{a}^{(k-1)}_{2,\mathrm{u}}. \end{aligned}$$

As before for $0 < \varepsilon_k < \varepsilon_{k-1}$, there exists a $\tilde{T}_k > \tilde{T}_{k-1}$, such that

$$\big(x_1(t), v_1(t), x_2(t), v_2(t)\big) \in \big[B_{\varepsilon_k}\big(\check{a}^{(k)}_{1,\mathrm{l}}, \hat{a}^{(k)}_{1,\mathrm{l}}\big) \times B_{\varepsilon_k}\big(\check{a}^{(k)}_{2,\mathrm{l}}, \hat{a}^{(k)}_{2,\mathrm{l}}\big)\big] \cup \big[B_{\varepsilon_k}\big(\check{c}^{(k)}_{1,\mathrm{u}}, \hat{c}^{(k)}_{1,\mathrm{u}}\big) \times B_{\varepsilon_k}\big(\check{a}^{(k)}_{2,\mathrm{u}}, \hat{a}^{(k)}_{2,\mathrm{u}}\big)\big]$$

for all $t \geqslant \tilde{T}_k$, for those solutions in (5.5).

Recall that $S_i^{\min}(t)$ is nondecreasing and $S_i^{\max}(t)$ is nonincreasing in t. A review of the above discussions shows that for $t > T_k + \tilde{T}_k + \tau_k$,

$$\big(x_1(t), v_1(t), x_2(t), v_2(t)\big) \in \big[B_{\varepsilon_k}\big(\check{a}^{(k)}_{1,\mathrm{l}}, \hat{a}^{(k)}_{1,\mathrm{l}}\big) \times B_{\varepsilon_k}\big(\check{a}^{(k)}_{2,\mathrm{l}}, \hat{a}^{(k)}_{2,\mathrm{l}}\big)\big] \cup \big[B_{\varepsilon_k}\big(\check{c}^{(k)}_{1,\mathrm{u}}, \hat{c}^{(k)}_{1,\mathrm{u}}\big) \times B_{\varepsilon_k}\big(\check{a}^{(k)}_{2,\mathrm{u}}, \hat{a}^{(k)}_{2,\mathrm{u}}\big)\big]$$

for all solutions $(x_1(t), v_1(t), x_2(t), v_2(t))$ evolved from Ω^* except possibly those lying in

$$B_{2\varepsilon_k}\big(\check{b}^{(k)}_{1,\mathrm{m}}, \hat{b}^{(k)}_{1,\mathrm{m}}\big) \times B_{\varepsilon_k}\big(\check{a}^{(k)}_{2,\mathrm{m}}, \hat{a}^{(k)}_{2,\mathrm{m}}\big),$$

at $t = T_k$. We may clearly assume that $T_k, \tilde{T}_k \to \infty$ and $\varepsilon_k \to 0$, as $k \to \infty$. Note that, each sequence $\{\check{a}_{1,\mathrm{l}}^{(k)}\}$, $\{\hat{b}_{1,\mathrm{m}}^{(k)}\}$, $\{\check{c}_{1,\mathrm{u}}^{(k)}\}$, $\{\check{a}_{2,\varpi}^{(k)}\}$ is increasing, and each sequence $\{\hat{a}_{1,\mathrm{l}}^{(k)}\}$, $\{\check{b}_{1,\mathrm{m}}^{(k)}\}$, $\{\hat{c}_{1,\mathrm{u}}^{(k)}\}$, $\{\hat{a}_{2,\varpi}^{(k)}\}$ is decreasing, $\varpi = \mathrm{l}, \mathrm{m}, \mathrm{u}$; in addition,

$$\check{a}_{1,\mathrm{l}}^{(k)} < \hat{a}_{1,\mathrm{l}}^{(k)}, \qquad \check{c}_{2,\mathrm{l}}^{(k)} < \hat{c}_{2,\mathrm{l}}^{(k)}, \qquad \hat{b}_{1,\mathrm{m}}^{(k)} < \check{b}_{1,\mathrm{m}}^{(k)},$$
$$\check{a}_{2,\varpi}^{(k)} < \hat{a}_{2,\varpi}^{(k)}, \quad \varpi = \mathrm{l}, \mathrm{m}, \mathrm{u},$$

for each k. Hence,

$$\lim_{k\to\infty} \check{a}_{1,\mathrm{l}}^{(k)} = \check{a}_1^*, \qquad \lim_{k\to\infty} \hat{a}_{1,\mathrm{l}}^{(k)} = \hat{a}_1^*, \qquad \lim_{k\to\infty} \check{c}_{1,\mathrm{r}}^{(k)} = \check{c}_1^*, \qquad \lim_{k\to\infty} \hat{c}_{1,\mathrm{r}}^{(k)} = \hat{c}_1^*,$$
$$\lim_{k\to\infty} \check{b}_{1,\mathrm{m}}^{(k)} = \check{b}_1^*, \qquad \lim_{k\to\infty} \hat{b}_{1,\mathrm{m}}^{(k)} = \hat{b}_1^*, \qquad \lim_{k\to\infty} \check{a}_{2,\varpi}^{(k)} = \check{a}_{2,\varpi}^*, \qquad \lim_{k\to\infty} \hat{a}_{2,\varpi}^{(k)} = \hat{a}_{2,\varpi}^*, \quad \varpi = \mathrm{l}, \mathrm{m}, \mathrm{u}.$$

We shall later prove that

$$\check{a}_1^* = \hat{a}_1^* = \bar{a}_1, \qquad \check{b}_1^* = \hat{b}_1^* = \bar{b}_1, \qquad \check{c}_1^* = \hat{c}_1^* = \bar{c}_1,$$
$$\check{a}_{2,\varpi}^* = \hat{a}_{2,\varpi}^* = \bar{a}_{2,\varpi}, \quad \varpi = \mathrm{l}, \mathrm{m}, \mathrm{u}. \tag{5.6}$$

Assuming the validity of (5.6), it follows that

$$S_1(t) \to w_\mathrm{l} \cdot \bar{a}_1 + w_\mathrm{u} \cdot \bar{c}_1 + \bar{E}_1,$$
$$S_2(t) \to w_\mathrm{l} \cdot \bar{a}_{2,\mathrm{l}} + w_\mathrm{u} \cdot \bar{a}_{2,\mathrm{u}} + \bar{E}_2,$$

as $t \to \infty$, for some nonnegative constants $w_\mathrm{l}, w_\mathrm{u} \geqslant 0$ with $w_\mathrm{l} + w_\mathrm{u} = 1$, where $\bar{E}_i$ is defined in (4.11). We summarize:

Theorem 5.1. *Assume that conditions* (3.19), (4.1), (B_1) *and either* (Ma_2), *or* (Mb_2) *hold. Then almost every solution of* (3.9)–(3.10) *converges to either* $(\bar{a}_1, 0, \bar{a}_{2,\mathrm{l}}, 0)$ *or* $(\bar{c}_1, 0, \bar{a}_{2,\mathrm{u}}, 0)$*, as* $t \to \infty$.

Note that $w_\mathrm{l}, w_\mathrm{u}$ represent the ratios of cells whose concentrations of protein and mRNA tend to levels $(\bar{a}_1, \bar{a}_{2,\mathrm{l}}, \tau_1\bar{a}_1/\nu_1, \tau_2\bar{a}_{2,\mathrm{l}}/\nu_2)$ and $(\bar{c}_1, \bar{a}_{2,\mathrm{u}}, \tau_1\bar{c}_1/\nu_1, \tau_2\bar{a}_{2,\mathrm{u}}/\nu_2)$, respectively. We also observe that the values $\bar{a}_1, \bar{a}_{2,\mathrm{l}}, \bar{c}_1, \bar{a}_{2,\mathrm{u}}$, and $w_\mathrm{l}, w_\mathrm{u}$ satisfy the equations

$$-\frac{\mu_1\tau_1}{\nu_1}\bar{a}_1 + \left[\alpha_1 \frac{\bar{a}_1^n}{k_1^n + \bar{a}_1^n} + \sigma_1 \frac{w_\mathrm{l} \cdot \bar{a}_1 + w_\mathrm{u} \cdot \bar{c}_1 + \bar{E}_1}{\rho_1 + (w_\mathrm{l} \cdot \bar{a}_1 + w_\mathrm{u} \cdot \bar{c}_1 + \bar{E}_1)}\right] \cdot \frac{1}{1 + \bar{a}_{2,\mathrm{l}}/\gamma_2} + \beta_1 = 0, \tag{5.7}$$

$$-\frac{\mu_1\tau_1}{\nu_1}\bar{c}_1 + \left[\alpha_1 \frac{\bar{c}_1^n}{k_1^n + \bar{c}_1^n} + \sigma_1 \frac{w_\mathrm{l} \cdot \bar{a}_1 + w_\mathrm{u} \cdot \bar{c}_1 + \bar{E}_1}{\rho_1 + (w_\mathrm{l} \cdot \bar{a}_1 + w_\mathrm{u} \cdot \bar{c}_1 + \bar{E}_1)}\right] \cdot \frac{1}{1 + \bar{a}_{2,\mathrm{u}}/\gamma_2} + \beta_1 = 0, \tag{5.8}$$

$$-\frac{\mu_2\tau_2}{\nu_2}\bar{a}_{2,\mathrm{l}} + \left[\alpha_2 \frac{\bar{a}_{2,\mathrm{l}}^n}{k_2^n + \bar{a}_{2,\mathrm{l}}^n} + \sigma_2 \frac{w_\mathrm{l} \cdot \bar{a}_{2,\mathrm{l}} + w_\mathrm{u} \cdot \bar{a}_{2,\mathrm{u}} + \bar{E}_2}{\rho_2 + (w_\mathrm{l} \cdot \bar{a}_{2,\mathrm{l}} + w_\mathrm{u} \cdot \bar{a}_{2,\mathrm{u}} + \bar{E}_2)}\right] \cdot \frac{1}{1 + \bar{a}_1/\gamma_1} + \beta_2 = 0, \tag{5.9}$$

$$-\frac{\mu_2\tau_2}{\nu_2}\bar{a}_{2,\mathrm{u}} + \left[\alpha_2 \frac{\bar{a}_{2,\mathrm{u}}^n}{k_2^n + \bar{a}_{2,\mathrm{u}}^n} + \sigma_2 \frac{w_\mathrm{l} \cdot \bar{a}_{2,\mathrm{l}} + w_\mathrm{u} \cdot \bar{a}_{2,\mathrm{u}} + \bar{E}_2}{\rho_2 + (w_\mathrm{l} \cdot \bar{a}_{2,\mathrm{l}} + w_\mathrm{u} \cdot \bar{a}_{2,\mathrm{u}} + \bar{E}_2)}\right] \cdot \frac{1}{1 + \bar{c}_1/\gamma_1} + \beta_2 = 0. \tag{5.10}$$

Notice that $\bar{a}_1$, $\bar{a}_{2,\mathrm{l}}$, $\bar{c}_1$, $\bar{a}_{2,\mathrm{u}}$, w_l, w_u are not determined uniquely from Eqs. (5.7)–(5.10); these quantities depend also on the initial condition.

Corollary 5.2. *Under the conditions of Theorem* 5.1, *the solution* ψ *of* (2.8)–(2.13) *satisfies*

$$\lim_{t\to\infty}\psi(t,x_1,x_2,y_1,y_2)=N_0 w_\mathrm{l}\delta_{(\bar{a}_1,\bar{a}_{2,\mathrm{l}},\tau_1\bar{a}_1/\nu_1,\tau_2\bar{a}_{2,\mathrm{l}}/\nu_2)} + N_0 w_\mathrm{u}\delta_{(\bar{c}_1,\bar{a}_{2,\mathrm{u}},\tau_1\bar{c}_1/\nu_1,\tau_2\bar{a}_{2,\mathrm{u}}/\nu_2)} \tag{5.11}$$

in the sense of convergence in measure, where $\bar{a}_1, \bar{a}_{2,\mathrm{l}}, \bar{c}_1, \bar{a}_{2,\mathrm{u}}$ *and* w_l, w_u *satisfy Eqs.* (5.7)–(5.10).

To prove the theorem, it remains to justify (5.6). Let

$$R_1 := [\check{a}_1^*, \hat{a}_1^*]\times[\check{a}_{2,\mathrm{l}}^*, \hat{a}_{2,\mathrm{l}}^*], \qquad R_2 := [\hat{b}_1^*, \check{b}_1^*]\times[\check{a}_{2,\mathrm{m}}^*, \hat{a}_{2,\mathrm{m}}^*], \qquad R_3 := [\check{c}_1^*, \hat{c}_1^*]\times[\check{a}_{2,\mathrm{u}}^*, \hat{a}_{2,\mathrm{u}}^*].$$

If (5.6) does not hold, then each R_i is either a rectangle or a single point, and at least one R_i is a rectangle. We denote by $(\check{a}_1^*, \hat{a}_{2,\mathrm{l}}^*)$ the upper-left vertex of R_1 which is diagonally opposed to $(\hat{a}_1^*, \check{a}_{2,\mathrm{l}}^*)$; if R_1 is a single point then we take $\check{a}_1^* = \hat{a}_1^*$, $\check{a}_{2,\mathrm{l}}^* = \hat{a}_{2,\mathrm{l}}^*$. Similarly we designate the vertices $(\hat{b}_1^*, \hat{a}_{2,\mathrm{m}}^*)$, $(\check{b}_1^*, \check{a}_{2,\mathrm{m}}^*)$ for R_2, and $(\hat{c}_1^*, \check{a}_{2,\mathrm{u}}^*)$, $(\check{c}_1^*, \hat{a}_{2,\mathrm{u}}^*)$ for R_3. Then the coordinates of these vertices satisfy the following equations:

$$\begin{aligned}
&h_1(\check{a}_1^*, \hat{a}_{2,\mathrm{l}}^*, \check{S}_1)=0, \qquad h_1(\hat{a}_1^*, \check{a}_{2,\mathrm{l}}^*, \hat{S}_1)=0, &(5.12)\\
&h_2(\check{a}_1^*, \hat{a}_{2,\mathrm{l}}^*, \hat{S}_2)=0, \qquad h_2(\hat{a}_1^*, \check{a}_{2,\mathrm{l}}^*, \check{S}_2)=0,\\
&h_1(\hat{b}_1^*, \hat{a}_{2,\mathrm{m}}^*, \check{S}_1)=0, \qquad h_1(\check{b}_1^*, \check{a}_{2,\mathrm{m}}^*, \hat{S}_1)=0,\\
&h_2(\hat{b}_1^*, \hat{a}_{2,\mathrm{m}}^*, \hat{S}_2)=0, \qquad h_2(\check{b}_1^*, \check{a}_{2,\mathrm{m}}^*, \check{S}_2)=0,\\
&h_1(\check{c}_1^*, \hat{a}_{2,\mathrm{u}}^*, \check{S}_1)=0, \qquad h_1(\hat{c}_1^*, \check{a}_{2,\mathrm{u}}^*, \hat{S}_1)=0,\\
&h_2(\check{c}_1^*, \hat{a}_{2,\mathrm{u}}^*, \hat{S}_2)=0, \qquad h_2(\hat{c}_1^*, \check{a}_{2,\mathrm{u}}^*, \check{S}_2)=0, &(5.13)
\end{aligned}$$

where $\check{S}_i = \lim_{t\to\infty} S_i^{\min}(t)$, $\hat{S}_i = \lim_{t\to\infty} S_i^{\max}(t)$, $i = 1, 2$. Furthermore,

$$\hat{S}_1 \leqslant [\zeta_1\hat{a}_1^* + \zeta_2\check{b}_1^* + \zeta_3\hat{c}_1^*]/\zeta + \bar{E}_1, \tag{5.14}$$

$$\check{S}_1 \geqslant [\zeta_1\check{a}_1^* + \zeta_2\hat{b}_1^* + \zeta_3\check{c}_1^*]/\zeta + \bar{E}_1, \tag{5.15}$$

$$\hat{S}_2 \leqslant [\zeta_1\hat{a}_{2,\mathrm{l}}^* + \zeta_2\check{a}_{2,\mathrm{m}}^* + \zeta_3\hat{a}_{2,\mathrm{u}}^*]/\zeta + \bar{E}_2, \tag{5.16}$$

$$\check{S}_2 \geqslant [\zeta_1\check{a}_{2,\mathrm{l}}^* + \zeta_2\hat{a}_{2,\mathrm{m}}^* + \zeta_3\check{a}_{2,\mathrm{u}}^*]/\zeta + \bar{E}_2, \tag{5.17}$$

where $\zeta_1, \zeta_2, \zeta_3$ are the areas of the regions R_1, R_2, R_3, and $\zeta_1 + \zeta_2 + \zeta_3 = \zeta$. 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 (5.12),

$$h_1(\check{a}_1^*, \hat{a}_{2,\mathrm{l}}^*, \check{S}_1)=0, \qquad h_1(\hat{a}_1^*, \check{a}_{2,\mathrm{l}}^*, \hat{S}_1)=0. \tag{5.18}$$

Similarly, among the quantities

$$(\hat{a}^*_{2,\mathrm{l}} - \check{a}^*_{2,\mathrm{l}}), \quad (\hat{a}^*_{2,\mathrm{m}} - \check{a}^*_{2,\mathrm{m}}), \quad (\hat{a}^*_{2,\mathrm{u}} - \check{a}^*_{2,\mathrm{u}}),$$

we pick the largest one, say $(\hat{a}^*_{2,\mathrm{u}} - \check{a}^*_{2,\mathrm{u}})$, and the corresponding equations (5.13),

$$h_2(\check{c}^*_1, \hat{a}^*_{2,\mathrm{u}}, \hat{S}_2) = 0, \qquad h_2(\hat{c}^*_1, \check{a}^*_{2,\mathrm{u}}, \check{S}_2) = 0. \tag{5.19}$$

From (5.14)–(5.17), we deduce that

$$\begin{aligned} \hat{S}_1 - \check{S}_1 &\leqslant \big[\zeta_1(\hat{a}^*_1 - \check{a}^*_1) + \zeta_2(\check{b}^*_1 - \hat{b}^*_1) + \zeta_3(\hat{c}^*_1 - \check{c}^*_1)\big]/\zeta \\ &\leqslant \hat{a}^*_1 - \check{a}^*_1, \end{aligned} \tag{5.20}$$

$$\begin{aligned} \hat{S}_2 - \check{S}_2 &\leqslant \big[\zeta_1(\hat{a}^*_{2,\mathrm{u}} - \check{a}^*_{2,\mathrm{u}}) + \zeta_2(\hat{a}^*_{2,\mathrm{m}} - \check{a}^*_{2,\mathrm{m}}) + \zeta_3(\hat{a}^*_{2,\mathrm{u}} - \check{a}^*_{2,\mathrm{u}})\big]/\zeta \\ &\leqslant \hat{a}^*_{2,\mathrm{u}} - \check{a}^*_{2,\mathrm{u}}. \end{aligned} \tag{5.21}$$

We use (5.18) and (5.20) to estimate $|\hat{a}^*_1 - \check{a}^*_1|$ in terms of $|\hat{a}^*_{2,\mathrm{l}} - \check{a}^*_{2,\mathrm{l}}|$, as in the derivation of (4.12). We next use (5.19) and (5.21) to estimate $|\hat{a}^*_{2,\mathrm{u}} - \check{a}^*_{2,\mathrm{u}}|$ in terms of $|\hat{c}^*_1 - \check{c}^*_1|$. Finally, from the two estimates on $|\hat{a}^*_1 - \check{a}^*_1|$ and $|\hat{a}^*_{2,\mathrm{u}} - \check{a}^*_{2,\mathrm{u}}|$ and the inequalities

$$\big|\hat{a}^*_{2,\mathrm{l}} - \check{a}^*_{2,\mathrm{l}}\big| \leqslant \big|\hat{a}^*_{2,\mathrm{u}} - \check{a}^*_{2,\mathrm{u}}\big|, \quad \text{and} \quad \big|\hat{c}^*_1 - \check{c}^*_1\big| \leqslant \big|\hat{a}^*_1 - \check{a}^*_1\big|, \tag{5.22}$$

we derive the estimate (4.14) which is a contradiction to (4.1). The assertion of Theorem 5.1 is thus established.

5.3. Four limit points

Theorem 5.3. *Assume that* (4.1), (3.19), (B_1) *and* (B_2) *hold. Then almost every solution of* (3.9)–(3.10) *converges to one of the four points*: $(\bar{a}_{1,\mathrm{l}}, 0, \bar{a}_{2,\mathrm{l}}, 0)$, $(\bar{c}_{1,\mathrm{l}}, 0, \bar{a}_{2,\mathrm{u}}, 0)$, $(\bar{a}_{1,\mathrm{u}}, 0, \bar{c}_{2,\mathrm{l}}, 0)$, $(\bar{c}_{1,\mathrm{u}}, 0, \bar{c}_{2,\mathrm{u}}, 0)$, *as* $t \to \infty$.

Corollary 5.4. *Under the conditions of Theorem* 5.3, *the solution* ψ *of* (2.8)–(2.13) *satisfies*

$$\begin{aligned} \lim_{t\to\infty} \psi(t, x_1, x_2, y_1, y_2) = {} & n_{\mathrm{ll}} \cdot \delta_{(\bar{a}_{1,\mathrm{l}}, \bar{a}_{2,\mathrm{l}}, \tau_1\bar{a}_{1,\mathrm{l}}/\nu_1, \tau_2\bar{a}_{2,\mathrm{l}}/\nu_2)} + n_{\mathrm{ul}} \cdot \delta_{(\bar{c}_{1,\mathrm{l}}, \bar{a}_{2,\mathrm{u}}, \tau_1\bar{c}_{1,\mathrm{l}}/\nu_1, \tau_2\bar{a}_{2,\mathrm{u}}/\nu_2)} \\ & + n_{\mathrm{lu}} \cdot \delta_{(\bar{a}_{1,\mathrm{u}}, \bar{c}_{2,\mathrm{l}}, \tau_1\bar{a}_{1,\mathrm{u}}/\nu_1, \tau_2\bar{c}_{2,\mathrm{l}}/\nu_2)} + n_{\mathrm{uu}} \cdot \delta_{(\bar{c}_{1,\mathrm{u}}, \bar{c}_{2,\mathrm{u}}, \tau_1\bar{c}_{1,\mathrm{u}}/\nu_1, \tau_2\bar{c}_{2,\mathrm{u}}/\nu_2)}, \end{aligned}$$

in the sense of convergence in measure, where $n_{\mathrm{ll}} + n_{\mathrm{lu}} + n_{\mathrm{ul}} + n_{\mathrm{uu}} = N_0$. *Furthermore, the coordinates for the limiting points* $\bar{a}_{1,\mathrm{l}}, \bar{a}_{2,\mathrm{l}}, \bar{c}_{1,\mathrm{l}}, \bar{a}_{2,\mathrm{u}}, \bar{a}_{1,\mathrm{u}}, \bar{c}_{2,\mathrm{l}}, \bar{c}_{1,\mathrm{u}}, \bar{c}_{2,\mathrm{u}}$ *and the weights* $w_{\mathrm{ll}} = n_{\mathrm{ll}}/N_0$, $w_{\mathrm{lu}} = n_{\mathrm{lu}}/N_0$, $w_{\mathrm{ul}} = n_{\mathrm{ul}}/N_0$, $w_{\mathrm{uu}} = n_{\mathrm{uu}}/N_0$ *satisfy the following equations for* $i = 1, 2$:

$$h_i(\bar{a}_{1,\mathrm{l}}, \bar{a}_{2,\mathrm{l}}, w_{\mathrm{ll}} \cdot \bar{a}_{1,\mathrm{l}} + w_{\mathrm{ul}} \cdot \bar{c}_{1,\mathrm{l}} + w_{\mathrm{lu}} \cdot \bar{a}_{1,\mathrm{u}} + w_{\mathrm{uu}} \cdot \bar{c}_{1,\mathrm{u}} + \bar{E}_i) = 0,$$

$$h_i(\bar{c}_{1,\mathrm{u}}, \bar{c}_{2,\mathrm{u}}, w_{\mathrm{ll}} \cdot \bar{a}_{1,\mathrm{l}} + w_{\mathrm{ul}} \cdot \bar{c}_{1,\mathrm{l}} + w_{\mathrm{lu}} \cdot \bar{a}_{1,\mathrm{u}} + w_{\mathrm{uu}} \cdot \bar{c}_{1,\mathrm{u}} + \bar{E}_i) = 0,$$

$$h_i(\bar{c}_{1,\mathrm{l}}, \bar{a}_{2,\mathrm{u}}, w_{\mathrm{ll}} \cdot \bar{a}_{1,\mathrm{l}} + w_{\mathrm{ul}} \cdot \bar{c}_{1,\mathrm{l}} + w_{\mathrm{lu}} \cdot \bar{a}_{1,\mathrm{u}} + w_{\mathrm{uu}} \cdot \bar{c}_{1,\mathrm{u}} + \bar{E}_i) = 0,$$

$$h_i(\bar{a}_{1,\mathrm{u}}, \bar{c}_{2,\mathrm{l}}, w_{\mathrm{ll}} \cdot \bar{a}_{1,\mathrm{l}} + w_{\mathrm{ul}} \cdot \bar{c}_{1,\mathrm{l}} + w_{\mathrm{lu}} \cdot \bar{a}_{1,\mathrm{u}} + w_{\mathrm{uu}} \cdot \bar{c}_{1,\mathrm{u}} + \bar{E}_i) = 0.$$

The proof of Theorem 5.3 combines the considerations of Section 5.2 with the convergence scheme which was described in [2]; the details are omitted.

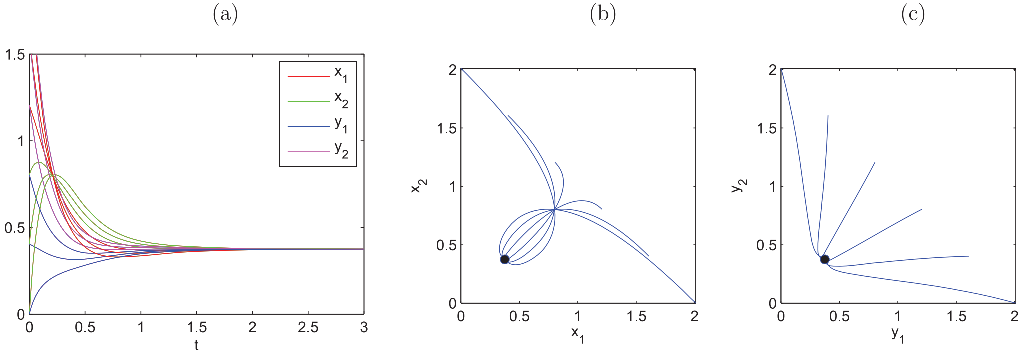

Fig. 6. ODE simulation (a) x_1, x_2, y_1, y_2 versus t, (b) the trajectories in (x_1, x_2)-plane, (c) the trajectories in (y_1, y_2)-plane.

Remark 5.1. Low-x_1 and low-x_2 represent a situation where both T-bet and GATA-3 have low concentrations; hence the T cells do not differentiate. On the other hand, if x_1 is high (low) and x_2 is low (high), then the T cells will differentiate into Th1 (Th2). The case where both x_1, x_2 are high would be biologically rather abnormal.

6. Numerical illustrations

In this section, we provide numerical simulations for the single cell model (2.1) and the population model (2.3). The parameters used in some of the simulations do not satisfy the assumptions made in the previous theorems.

The single cell model is a system of four ODEs which can be easily solved by the Runge–Kutta method, using ode45 in MATLAB. The population model (2.3) 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 midpoint rule which has second-order accuracy. The solution of Eq. (2.3) is then obtained by using standard Lax–Friedrichs method [3,7]. Notice that the asymptotic solution of the population model becomes singular for large time.

6.1. The single cell model

In Fig. 6, we first show the dynamics of ODE system which exhibit single limit point, with parameters

$$\begin{gathered} n=6, \quad \alpha_1=\alpha_2=5, \quad k_1=k_2=5, \quad \rho_1=\rho_2=1, \quad \beta_1=\beta_2=0.05, \\ \sigma_1=\sigma_2=5, \quad \mu_1=\mu_2=5, \quad \gamma_1=\gamma_2=1, \quad \nu_1=\nu_2=10, \quad \tau_1=\tau_2=5. \end{gathered} \tag{6.1}$$

All the parameters are as in [10] except for k_i (the level of T-bet or GATA-3 at which the rate of auto-stimulation is half-maximum) which is altered from 1 to 5 to make sure that the conditions in (3.18) are satisfied. We choose six different initial points

$$\bigl(x_1(0), x_2(0), y_1(0), y_2(0)\bigr) = \left(\frac{i}{5}B_1, \frac{(5-i)}{5}B_2, \frac{i}{5}A_1, \frac{(5-i)}{5}A_2\right),$$

for integer i from 0 to 5. This means that there are six cells with different initial levels of transcription factors and mRNA. The polarizing cytokines are $S_1 = B_1/2$ and $S_2 = B_2/2$. (The same choice is used in the ODEs' simulations unless otherwise mentioned.) It is clear that all the points from different initial locations converge to a single limit point which has low concentration of T-bet (x_1) and low concentration of GATA-3 (x_2). Thus all six cells do not differentiate. The plot of (x_1, x_2, y_1, y_2) versus

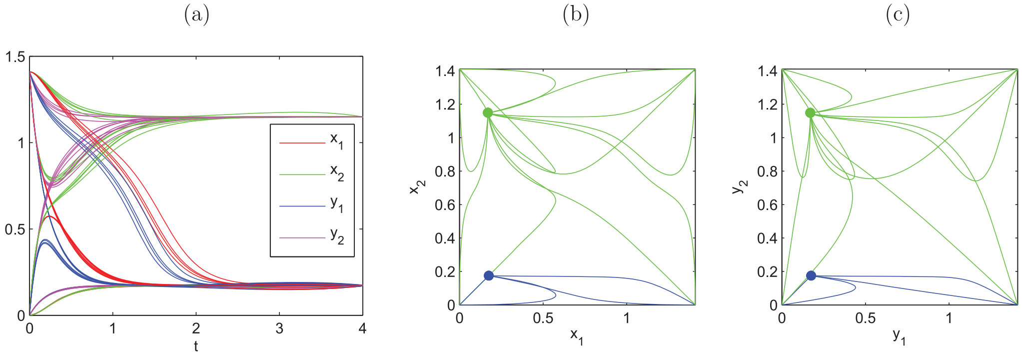

Fig. 7. ODE simulation (a) x_1, x_2, y_1, y_2 versus t, (b) the trajectories in (x_1, x_2)-plane, (c) the trajectories in (y_1, y_2)-plane. (For interpretation of the references to color, the reader is referred to the web version of this article.)

time is shown in Fig. 6(a). The trajectories in (x_1, x_2)-plane and (y_1, y_2)-plane are shown in Figs. 6(b) and 6(c) respectively. The trajectories may cross each other on these projection planes. However, they do not cross each other in the four-dimensional space.

In Fig. 7, we illustrate the case of two limit points with parameters

$$n = 6, \quad \alpha_1 = \alpha_2 = 5, \quad k_1 = 0.9, \quad k_2 = 0.6, \quad \rho_1 = \rho_2 = 1, \quad \beta_1 = \beta_2 = 0.05,$$
$$\sigma_1 = \sigma_2 = 2, \quad \mu_1 = \mu_2 = 5, \quad \gamma_1 = \gamma_2 = 30, \quad \nu_1 = \nu_2 = 5, \quad \tau_1 = \tau_2 = 5.$$

The corresponding time evolution and projection on (x_1, x_2)-plane and (y_1, y_2)-plane are given in Figs. 7(a), 7(b), and 7(c) for 16 different initial conditions. This case demonstrates that there are two stable limit points (blue dot and green dot). The trajectories which converge to blue (green) limit point are colored as blue (green). In this parameter setting, the green point has larger attracting basin. Thus there are more cells with low concentrations of T-bet (x_1) and high concentrations of GATA-3 (x_2) and they differentiate into Th2 cells.

In order to generate quadstable phase, we choose the parameters as

$$n = 6, \quad \alpha_1 = \alpha_2 = 5, \quad k_1 = k_2 = 0.6, \quad \rho_1 = \rho_2 = 1, \quad \beta_1 = \beta_2 = 0.05,$$
$$\sigma_1 = \sigma_2 = 2, \quad \mu_1 = \mu_2 = 5, \quad \gamma_1 = \gamma_2 = 30, \quad \nu_1 = \nu_2 = 5, \quad \tau_1 = \tau_2 = 5.$$

We can see that the system is quadstable, as illustrated in Fig. 8. The corresponding time evolution and projection on (x_1, x_2)-plane and (y_1, y_2)-plane are given in Figs. 8(a), 8(b), and 8(c). We start with 81 different initial conditions; the trajectories converge to one of the four stable limit points. For example, there are nine different trajectories emitting from the center point $(0.705, 0.705)$ on (x_1, x_2)-plane because their initial locations on (y_1, y_2)-plane are different. One, two, two, and four trajectories tend to blue, red, green, and cyan limit points, respectively, which indicate no differentiation (low-x_1, low-x_2), Th1 (high-x_1, low-x_2) differentiation, Th2 (low-x_1, high-x_2) differentiation and undetermined (abnormal). It is hard to distinguish two of the trajectories (colored as mixed cyan and blue) because they overlap each other.

In Fig. 9, we use the same parameters as in [10]:

$$n = 6, \quad \alpha_1 = \alpha_2 = 5, \quad k_1 = k_2 = 1, \quad \rho_1 = \rho_2 = 1, \quad \beta_1 = \beta_2 = 0.05,$$
$$\sigma_1 = \sigma_2 = 5, \quad \mu_1 = \mu_2 = 5, \quad \gamma_1 = 1, \quad \gamma_2 = 0.5, \quad \nu_1 = \nu_2 = 10, \quad \tau_1 = \tau_2 = 5.$$

The parameters do not satisfy the conditions (Ma_1), (Ma_2), (B_1) and (B_2). The number of limit points vary with respect to the polarizing cytokines S_1 and S_2. When $S_1 = 0.05$, $S_2 = 0.025$, the trajectories

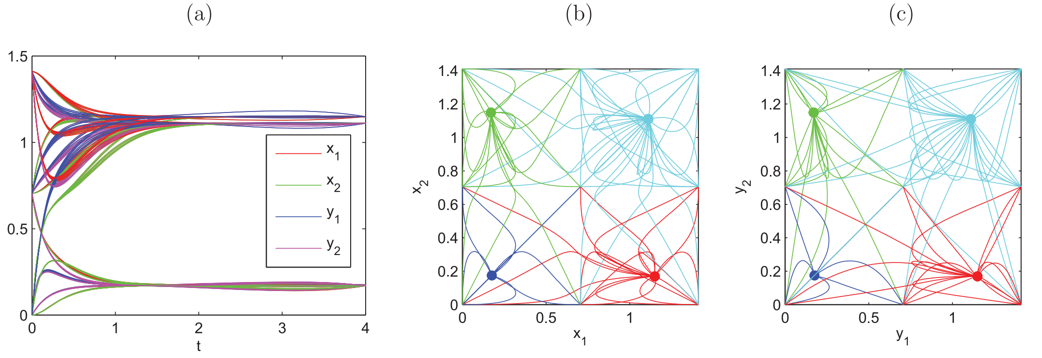

Fig. 8. ODE simulation (a) x_1, x_2, y_1, y_2 versus t, (b) the trajectories in (x_1, x_2)-plane, (c) the trajectories in (y_1, y_2)-plane. (For interpretation of the references to color, the reader is referred to the web version of this article.)

approach to a low–low single limit point (no differentiation). When $S_1 = 0.15$, $S_2 = 1.0$, the trajectories approach two limit points. If we further increase S_2 to 1.7, it becomes one single limit point again. However, the limit point is at a low–high level which indicates the differentiation toward Th2.

6.2. *The population model*

The main difference between single cell model and population model is the coupling dynamics generated from the total signals S_1 and S_2 defined in (2.2) for population model. Since S_1 and S_2 are not constants, their evolutions depend on both the initial population of cells and the external signals $E_1(t)$, $E_2(t)$. In [2], we have demonstrated, for the model (1.6), an interesting behavior, namely, the system may switch from one-peak to two-peak profile at intermediate times. Here we will focus on the singular behaviors which demonstrate one-, two- and four-peak solutions by choosing specific parameters.

In the subsequent numerical simulations we assume that $g = 0$, $\psi_0 = \phi_0 = 0$ on $\partial\Omega$, and $E_i(t) = 0$. We take A_1, A_2, B_1, B_2 as in (2.6), (2.7) and choose the initial condition

$$\psi_0(x_1, x_2, y_1, y_2) = \text{constant} = \frac{1}{A_1 A_2 B_1 B_2} \tag{6.2}$$

so that $N_0 = 1$. Even though the discretization method is the same as the one used in [2], the computations for the present four-dimensional model are much more intensive.

6.2.1. *Asymptotic one-peak solution*

In Fig. 10, we show numerical results under conditions (Ma_1) and (Ma_2) which guarantee a single attracting point. The choice of parameters is as (6.1). In Figs. 10(a), 10(b), and 10(c), we plot $\int \psi \, dy_1 \, dy_2$, at times $t = 0.5, 1, 5$ respectively, because it is hard to visualize the original four-dimensional density function. Since (Ma_1) and (Ma_2) are satisfied no matter what S_1 and S_2 are, there is only one stable equilibrium point. The normalized population density gets more and more concentrated at an attracting point with low-x_1 and low-x_2 so there is no polarization toward differentiation into Th1 or Th2.

6.2.2. *Asymptotic two-peak solution*

Fig. 11 displays the bistable case (two-peak solution). We choose parameters

$$n = 6, \quad \alpha_1 = \alpha_2 = 5, \quad k_1 = 0.9, \quad k_2 = 0.6, \quad \rho_1 = \rho_2 = 1, \quad \beta_1 = \beta_2 = 0.05,$$
$$\sigma_1 = \sigma_2 = 2, \quad \mu_1 = \mu_2 = 5, \quad \gamma_1 = \gamma_2 = 30, \quad \nu_1 = \nu_2 = 5, \quad \tau_1 = \tau_2 = 5.$$

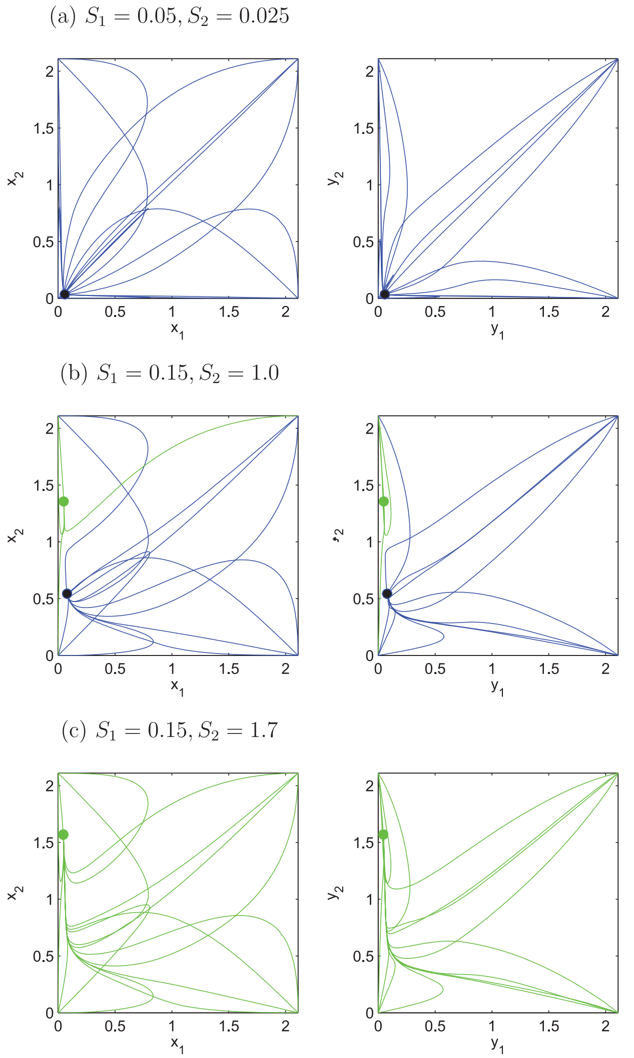

Fig. 9. The trajectories in (x_1, x_2)-plane and (y_1, y_2)-plane for (a) $S_1 = 0.05$, $S_2 = 0.025$, (b) $S_1 = 0.15$, $S_2 = 1.0$, and (c) $S_1 = 0.15$, $S_2 = 1.7$.

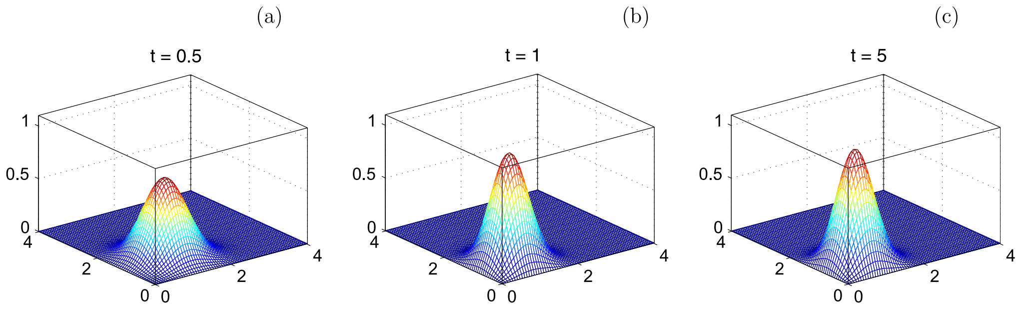

Fig. 10. Monostable: $\int \psi \, dy_1 \, dy_2$ at (a) $t = 0.5$, (b) $t = 1$, (c) $t = 5$.

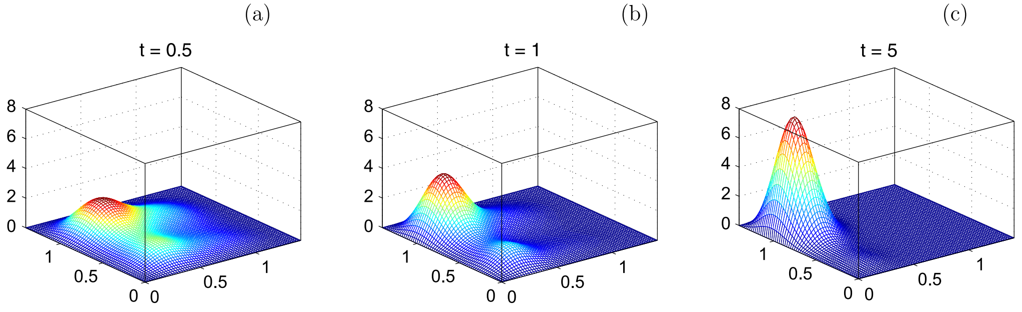

Fig. 11. Bistable (BS-ll,lh): $\int \psi \, dy_1 \, dy_2$ at (a) $t = 0.5$, (b) $t = 1$, (c) $t = 5$.

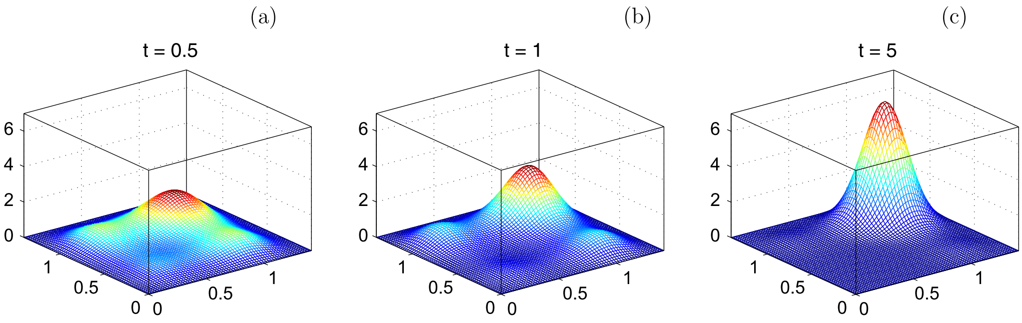

Fig. 12. Quadstable: $\int \psi \, dy_1 \, dy_2$ at (a) $t = 0.5$, (b) $t = 1$, (c) $t = 5$.

We see that integration of the population density with respect to y_1 and y_2 starts to accumulate at two attracting points and the population density is higher in low-x_1 high-x_2 state as time evolves. Thus a large portion of cells differentiates into Th2 while others do not differentiate. The weights w_1 and w_2 in the asymptotic solution depend on the initial population density and the parameters. If most of the initial population is distributed 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).

6.2.3. Asymptotic four-peak solution

In Fig. 12, the population density becomes highly concentrated at four attracting points as expected from Theorem 5.3. In this example, the parameters are chosen as

$$n = 6, \quad \alpha_1 = \alpha_2 = 5, \quad k_1 = k_2 = 0.6, \quad \rho_1 = \rho_2 = 1, \quad \beta_1 = \beta_2 = 0.05,$$
$$\sigma_1 = \sigma_2 = 2, \quad \mu_1 = \mu_2 = 5, \quad \gamma_1 = \gamma_2 = 30, \quad \nu_1 = \nu_2 = 5, \quad \tau_1 = \tau_2 = 5.$$

The weights $w_{\mathrm{ll}}, w_{\mathrm{ul}}, w_{\mathrm{lu}}$ and w_{uu} depend on the parameters of the system as well as on the initial population density. In this case, the population density is higher in high-x_1 high-x_2 state as time evolves. Even though the population densities at the other three points are small and hardly noticeable, there is indeed some population. The parameters chosen satisfy conditions (B_1) and (B_2). Note that the mutual inhibition is small (i.e., γ_1 and γ_2 are large), in this case.

Acknowledgments

A. Friedman was partially supported by the National Science Foundation under Agreement No. 0112050. C.-Y. Kao was partially supported by the National Science Foundation grant DMS-0811003 and Alfred P. Sloan Fellowship. C.-W. Shih was partially supported by the NSC and NCTS of Taiwan; he is grateful to the MBI at OSU for the hospitality and support during his visit in 2007–2008 and 2011.

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