Analysis of a mathematical model of immune response to fungal infection

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Abstract

Fungi are cells found as commensal residents, on the skin, and on mucosal surfaces of the human body, including the digestive track and urogenital track, but some species are pathogenic. Fungal infection may spread into deep-seated organs causing life-threatening infection, especially in immune-compromised individuals. Effective defense against fungal infection requires a coordinated response by the innate and adaptive immune systems. In the present paper we introduce a simple mathematical model of immune response to fungal infection consisting of three partial differential equations, for the populations of fungi (F), neutrophils (N) and cytotoxic T cells (T), taking N and T to represent, respectively, the innate and adaptive immune cells. We denote by λ_F the aggressive proliferation rate of the fungi, by η and ζ the killing rates of fungi by neutrophils and T cells, and by N_0 and T_0 the immune strengths, respectively, of N and T of an infected individual. We take the expression $I = \eta N_0 + \zeta T_0 - \lambda_F$ to represent the coordinated defense of the immune system against fungal infection. We use mathematical analysis to prove the following: If $I > 0$, then the infection is eventually stopped, and $F \to 0$ as $t \to \infty$; and (ii) if $I < 0$ then the infection cannot be stopped and F converges to some positive constant as $t \to \infty$. Treatments of fungal infection include anti-fungal agents and immunotherapy drugs, and both cause the parameter I to increase.

1 Introduction

Fungi are eukaryotic cells, found in soil, water, air, and trees; they also grow in household wallpaper and basement (as mold) and spread in the air. In humans, fungi may cause infection and disease.

There are fungi that live naturally in the human body, and they may be helpful or harmful. They include the family of *Candida albicans*, as well as other *Candida* families. *C. albicans* are found as commensal resident of the skin, digestive tract, urogenital tract, oral cavity, and other mucosal surfaces. *C. albicans* is the most common and most studied fungal pathogen.

Most fungi, including *C. albicans*, are hyphae, cylindrical cells that increase in length by growth in one direction. Life cycle starts with a spore (a slim rod) that grows and branches, with productive branches producing new branches, etc., in a process that forms a radiating system of hyphae, known as mycelium [6]. Fungi feed by absorption of nutrients from the environment around them. Hyphae ligaments grow outward away from each other in order to maximize exploration and invasion opportunities [4, 18]. Hyphae are very motile and can adjust their morphology in response to stimuli and changes in the environment [21].

C. albicans can penetrate the endothelium and disseminate into deep seated organs, causing life threatening infection, especially in immunocompromised individuals [28, 33]. Host defense against *C. albicans* is dependent upon coordination between the innate and adaptive immune response. Innate response to infection is fast rather than specific; it includes macrophages, neutrophils and dendritic cells (DCs).

Neutrophils form an essential part of the innate immune system. Neutrophils circulate in the blood and have the ability to pass through the endothelial lining at the site of infection. Neutrophils and macrophages kill fungal pathogen in different ways. Macrophages ingest pathogens and destroy them in their phagosomes after they mature into phagolysosome; however, pathogen may evade destruction and replicate within macrophages [17]. Neutrophils kill pathogen primarily extracellularly, by secreting oxidative cytotoxic species and inflammatory cytokines, and neutrophil extracellular nets (NETS) [9].

Dendritic cells mediate adaptive T cells immune protection against *C. albicans* [28,33,34]. DCs patrol the peripheral tissue beneath skin and mucosal surfaces. They are recruited to the site of infection by recognizing molecular pattern of fungal cell wall. Fungal cell is phagocytosed by DC, and fungal peptide antigens are then assembled on MHC I or II, and presented to memory T cells. The T cells then become activated as effective *CD4*$^+$ T cells, specifically inflammatory *Th1* cells, under *IL-12* environment [28, 33, 34]. *Th1* cells secrete *IL-2* that activate cytotoxic T cells (CTLs), commonly called *CD8*$^+$ T cells. *CD8*$^+$ T cells kill *C. albicans* [23,30,38]; they do it extracellularly by secreting perforins and granzymes that perforate the fungal cell wall and break down its DNA.

In the present paper we consider a mathematical model of fungal infection, focusing on the interaction between the innate and adaptive immune systems. We denote by N and T the densities of neutrophils and CTLs, respectively. We take N to represent the innate immune response and T to represent the adaptive *CD8*$^+$ T cells response. We consider fungal infection at a colony level, with scale of 0.1 - 1cm. At this scale, we ignore the complex dynamics of hyphae and the network details of mycelium, replacing them by a density F within the territory occupied by the fungi. Mathematical models describing the development of fungal mycelium were developed by G. P. Boswell et al. [3], F. A. Davidson [8], L. Edelstein [14], L. Edelstein and L. A. Segel [15] and collaborators; some models were represented by a system of PDEs with variables that include hyphal tips (p), biochemical chemoattractant (c) and biomass (m).

Neutrohphils are produced in the bone marrow by a tightly regulated process controlled by cytokines. They are released into the blood at a rate of 10^{11} cells per day, and their half-life span is 6-12 hours. The population of neutrophils is highly heterogeneous [31, 36], and some are known not to be passive in homeostasis [31]. Aging predisposes over activation of neutrophils [36]. In homeostasis, aging neutrophils revealed signaling pathways related to changes in inflammatory-associated neutrophils [35]. We accordingly assume that, in homeostasis, there is a subset of neutrophils exhibiting active inflammatory behavior, and denote its concentration by N_0.

We denote by d_N the death rate of N. Then, in homeostasis, the ODE dynamics of N is $\frac{dN}{dt} = -d_N(N - N_0)$, and, under fungal infection,

$$\frac{dN}{dt} = \lambda_N F - d_N(N - N_0), \tag{1.1}$$

where λ_N is the response rate of neutrophils to F. Since there is only a limited study on the effect of fungal infection on neutrophils [20], we take d_N to be constant.

The activation of T through *DC*s can be described by the following sequence of activation/production events:

$$F \longrightarrow DC \longrightarrow \textit{IL-12} \longrightarrow \textit{Th1} \longrightarrow \textit{IL-2} \longrightarrow T.$$

Writing each such event in the form $X_j \to X_{j+1}$ with ODE dynamics

$$\frac{dX_{j+1}}{dt} = \lambda_{j+1} X_j - d_{j+1} X_{j+1}$$

where λ_{j+1} is the actiation/production rate and d_{j+1} is the death/degradation rate of species X_{j+1}, and taking steady state in all intermediate events, we get

$$\frac{dT}{dt} = \lambda_T F - d_T T,$$

where d_T is the death rate of T.

Dendritic cells are the primary antigen presenting cells (*APC*s), but neutrophils are also known to be antigen presenting cells [2, 27]. Neutrophils, after infection, were shown to migrate to the lymph nodes and secrete chemokines that attract $CD4^+$ T cells to the infection site [42]; they are also known to deliver antigens to *DC*s [25]. Hence the complete ODE dynamics for T is

$$\frac{dT}{dt} = \lambda_T F + \lambda_{TN} N - d_T T$$

where λ_{TN} is smaller than λ_T, since *DC*s are the primary *APC*s. We can rewrite this equation in the form

$$\frac{dT}{dt} = \lambda_T F + \lambda_{TN}(N - N_0) - d_T(T - T_0) \tag{1.2}$$

where

$$\lambda_{TN} N_0 - d_T T_0 = 0, \quad \text{or} \quad T_0 = \frac{\lambda_{TN}}{d_T} N_0. \tag{1.3}$$

Our mathematical model consists of a system of PDEs for F, N and T in planar domains $\Omega(t)$ that vary increasingly with time. The area $\Omega(t)$ occupied by the fungal colony may have different shapes. For simplicity we take it to be circular, as seen in the agar petri dish with *C. albicans* isolated from patients [19, Fig. 1]. We assume that immune response to fungal infection is not qualitatively different for other shapes of fungal colonies, such as oval shape or other shapes with smooth boundary. Accordingly, we take F, N

and T to be radially symmetric, that is, functions of (r, t), where $r = |x|$ is the distance from the origin in the 2-d plane, and $\Omega(t) = \{0 \leq r \leq R(t)\}$; we assume that F satisfies a logistic growth at rate λ_F and carrying capacity K, and it is killed by N and T at rates η and ζ, respectively.

The complete model is introduced in Section 2. In the rest of the paper we study the progression of the infection by mathematical analysis. In Sections 3 - 6 we consider the special case where the fungal infection solicits only innate immune response, that is, we take $\zeta = 0$, or equivalently, set $T \equiv 0$.

The parameter $\eta N_0/\lambda_F$ represents the ratio of the neutrophil killing rate, in case $\lambda_N = 0$, to the fungal growth rate, when $K = \infty$. We prove the following results:

(i) Suppose $\eta N_0/\lambda_F > 1$. Then $\lim_{t\to\infty} R(t) < \infty$ and $(F, N) \to (0, N_0)$ as $t \to \infty$.

(ii) Suppose $\eta N_0/\lambda_F < 1$ and $\lim_{t\to\infty} R(t) = \infty$, then $(F, N) \to (F^*, N^*)$ as $t \to \infty$, where (F^*, N^*) is the unique steady state of the space-independent dynamics of the (F, N) system, namely

$$F^* = \left(1 - \frac{\eta N_0}{\lambda_F}\right)\left(\frac{1}{K} + \frac{\eta}{\lambda_F} \cdot \frac{\lambda_N}{d_N}\right)^{-1}, \quad N^* = N_0 + \frac{\lambda_N}{d_N} F^*.$$

A sufficient condition for $\lim_{t\to\infty} R(t) = \infty$ is

$$R(0) > \left[\frac{\delta_F}{\lambda_F - \eta N_0}\right]^{1/2} j_0,$$

whereas a necessary and sufficient condition for $\lim_{t\to\infty} R(t) = \infty$ is

$$R(t_0) > \left[\frac{\delta_F}{\lambda_F - \eta N_0}\right]^{1/2} j_0 \quad \text{for some } t_0 \geq 0;$$

here $j_0 \approx 2.4048$ is the smallest zero of the Bessel function of order zero.

In Section 7 we include the adaptive immune response and prove results similar to (i), (ii); situations analogous to cases (i) and (ii) depend on whether $(\eta N_0 + \zeta T_0)/\lambda_F$ is greater than or smaller than 1.

A mathematical model of fungal spore inhalation was developed in [39]; the model consists of 4 ordinary differential equations for the fungal spore, macrophages, neutrophils, and inflammatory dendritic cells. Another ODE model, in [41], considered fungal infection in immune compromised individuals with fungal strains that are susceptible or resistance to drugs.

In Section 2 we present our mathematical model. In Section 3 we establish *a priori* estimates and prove the existence and uniqueness of a solution. We also prove that if $R(t)$ remains bounded as $t \to \infty$, then $(F, N) \to (0, N_0)$ as $t \to \infty$. The proof of (i) is given in Section 5, and the proof that $\lim\limits_{t\to\infty} R(t) = \infty$, in case (ii), is given in Section 5. We prove the remaining part of (ii) in Section 6.

The extension of the results of Sections 3 - 6 to the complete model (2.1)-(2.7) is given in Section 7. In Section 8 we draw biological conclusions from the mathematical results of the paper.

2 Mathematical model

We consider a model of immune response to fungal infection. We denote the fungi density by F, the neutrophils density by N, and the density of *CD8*$^+$ T cells by T. The infected region is a 2-dimensional domain $\Omega(t)$ that varies with time. Hyphae ligaments grow away from each other [21]; hence, the density of F is dispersing, with a diffusion coefficient δ_F. We assume that F has a logistic growth with rate coefficient λ_F and carrying capacity K, and that it is being killed by N at rate η, and by T cells at rate ζ, so that

$$\frac{\partial F}{\partial t} - \delta_F \nabla^2 F = \lambda_F F \left(1 - \frac{F}{K}\right) - \eta N F - \zeta T F. \tag{2.1}$$

Note that λ_F represents the difference between proliferation and death rates of the fungi.

The innate immune response is given by neutrophils whose density N satisfies the following equation:

$$\frac{\partial N}{\partial t} - \delta_N \nabla^2 N = \lambda_N F - d_N (N - N_0) \tag{2.2}$$

where λ_N is the rate of accumulation of neutrophils in response to F, d_N is the death rate of N, and N_0 is the density of active neutrophils in homeostasis [35, 36].

The adaptive immune response is given by T cells. The density T satisfies the following equation:

$$\frac{\partial T}{\partial t} - \delta_T \nabla^2 T = \lambda_T F + \lambda_{TN}(N - N_0) - d_T(T - T_0) \tag{2.3}$$

where λ_T is the rate of accumulation of T cells by activated DCs, λ_{TN} is an additional accumulation by direct antigen presentation by neutrophils [2, 25, 27], and d_T is the death rate of T cells.

The boundary conditions at the free boundary $\partial\Omega(t)$ are taken to be

$$F = 0, \quad N = N_0, \quad T = T_0 = \frac{\lambda_{TN}}{d_T} N_0 \quad \text{on } \partial\Omega(t). \tag{2.4}$$

We denote by $\vec{n}$ the outward normal to $\partial\Omega(t)$. We assume that the fungi territory grows by outward production of new mycelium network from hyphae near the boundary, so that the rate of growth is proportional to the gradient of F. Hence, $\Omega(t)$ grows in response to the flux $-\nabla F \cdot \vec{n}$, and the outward normal velocity V_n of $\partial\Omega(t)$ is given by an equation

$$V_n = h(-\nabla F \cdot \vec{n})$$

where $h(s)$ is a function satisfying the following conditions:

$$\begin{cases} h(0) = 0, \quad h'(0) > 0, \quad \|h'\|_{L^\infty[0,\infty)} < \infty, \\ h'(s) \geq 0 \text{ for all } s > 0. \end{cases} \tag{2.5}$$

It follows that

$$h(s) \leq \mu s \quad \text{for all } s \geq 0$$

where $\mu = \|h'\|_{L^\infty[0,\infty)}$. Particular examples are

$$h(s) = \mu s \quad \text{and} \quad h(s) = \frac{\mu s}{A + s} \quad \text{(for some } A > 0).$$

We consider only the case where F, N, T and $\Omega(t)$ are radially symmetric. Then

$$\begin{cases} \nabla^2 = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}\right), \quad \Omega(t) = \{0 \leq r \leq R(t)\}, \\ F = F(r,t), \quad N = N(r,t), \quad T = T(r,t), \end{cases}$$

and the free boundary $r = R(t)$ satisfies the equation

$$\frac{dR}{dt}(t) = h\left(- \frac{\partial F}{\partial r}(r,t)\bigg|_{r=R(t)} \right). \tag{2.6}$$

We take initial conditions

$$F(r,0) = F^0(r), \quad N(r,0) = N^0(r) \quad T(r,0) = T^0(r) \quad \text{for } 0 \le r \le R(0) \tag{2.7}$$

and F^0, N^0, T^0 are in $C^{2+\alpha}([0,R(0)])$ for some $\alpha \in (0,1)$, such that

$$\begin{cases} 0 < F^0(r) \le K, \quad N^0(r) > 0 \quad T^0(r) > 0 \quad \text{for } 0 \le r < R(0), \\ F^0(R(0)) = 0, \quad N^0(R(0)) = N_0, \quad T^0(R(0)) = T_0. \end{cases}$$

By the maximum principle

$$F(r,t) > 0, \quad N(r,t) > 0, \quad T(r,t) > 0 \quad \text{for all } 0 \le r < R(t),\, t > 0,$$

and

$$\frac{\partial F}{\partial r}(R(t),t) < 0 \quad \text{for all } t > 0.$$

Hence,

$$\frac{dR}{dt}(t) > 0 \quad \text{for all } t > 0.$$

By the maximum principle, we also have

$$F(r,t) \le K \quad \text{for} \quad 0 \le r \le R(t),\, t > 0; \tag{2.8}$$

hence

$$\frac{\partial N}{\partial t} - \delta_N \nabla^2 N \le \lambda_N K + d_N(N_0 - N).$$

By comparison with the function

$$Ae^{-d_N t} + N_0 + \frac{\lambda_N K}{d_N} \quad \text{where } A = \sup_{0 \le r \le R(0)} N^0(r),$$

we then get,

$$N(r,t) \le Ae^{-d_N t} + N_0 + \frac{\lambda_N K}{d_N} \quad \text{for } 0 \le r \le R(t),\, t > 0. \tag{2.9}$$

Similarly, denoting $d_N \wedge d_T = \min\{d_N, d_T\}$, we have

$$T(r,t) \le A_0 e^{-(d_N \wedge d_T)t} + T_0 + \frac{K}{d_T}\left[\lambda_T + \frac{\lambda_N \lambda_{TN}}{d_N}\right] \quad \text{for } r \le R(t),\, t > 0.$$

We refer to the model (2.1)-(2.7) as the *FNT* model, and to the submodel (2.1)-(2.7) with $T \equiv 0$ as the *FN* model. In Sections 3 - 6 we analyze the *FN* model, and in Section 7 we extend the analysis to the *FNT* model.

In Section 3 we prove existence of a unique solution for all $t > 0$, and in the following sections we focus on properties of the solution; in particular on the question whether

$$F \to 0, \quad \text{or} \quad F \to F^* > 0 \ \text{ as } \ t \to \infty.$$

As will be proved, these two different outcomes are associated with the cases

$$\lim_{t\to\infty} R(t) < \infty \quad \text{or} \quad \lim_{t\to\infty} R(t) = \infty.$$

The first case is considered in Section 4 and the second case in Sections 5 - 6.

Part 1. The *FN* Model

In Sections 3 - 6 it is tacitly assumed that $T \equiv 0$, without stating it explicitly each time when we refer to the system (2.1)-(2.7).

3 Existence of solutions

Theorem 3.1. *The system* (2.1)-(2.7) *has a unique solution for all* $t > 0$, *such that*

$$R(t) \in C^{1+\alpha/2}[0,\infty), \quad (F(r,t), N(r,t)) \in [C^{2+\alpha,1+\alpha/2}(\Omega^\infty)]^2,$$

where

$$\Omega^\infty = \{(r,t) : \, 0 \le r \le R(t), \, 0 \le t < \infty\};$$

furthermore,

$$\|\dot{R}\|_{C^{\alpha/2}[0,\infty)} + \|(F(r,t), N(r,t))\|_{C^{2+\alpha,1+\alpha/2}(\Omega^\infty)} < \infty. \tag{3.1}$$

To prove the theorem we first establish *a priori* estimate. The first step is the following lemma, which is adapted from [10, Lemma 4.2].

Lemma 3.2. *There exists a positive number* M *such that*

$$0 \le \dot{R}(t) \le h(2MK) \quad \textit{for all } t > 0. \tag{3.2}$$

Proof. We define a domain

$$\Omega_M := \{(r,t) : t > 0,\, R(t) - 1/M < r < R(t)\}$$

and construct an auxiliary function

$$\overline{F}(r,t) := K[2M(R(t)-r) - M^2(R(t)-r)^2].$$

We will show that M can be chosen large so that $\overline{F}(r,t) \geq F(r,t)$ in Ω_M. Direct calculation shows that, for $(r,t) \in \Omega_M$,

$$\begin{cases} \frac{\partial \overline{F}}{\partial t} = 2KM\dot{R}(t)[1 - M(R(t)-r)] \geq 0, \\ -\frac{\partial \overline{F}}{\partial r} = 2MK[1 - M(R(t)-r)] \geq 0, \\ -\frac{\partial^2 \overline{F}}{\partial r^2} = 2KM^2, \quad \lambda_F \overline{F}\big(1 - \overline{F}/K\big) \leq \lambda_F K. \end{cases} \tag{3.3}$$

It follows that

$$\frac{\partial \overline{F}}{\partial t} - \delta_F \nabla^2 \overline{F} - \lambda_F \overline{F}\big(1 - \overline{F}/K\big) \geq 2\delta_F K M^2 - \lambda_F K \geq 0,$$

provided $M^2 \geq (\lambda_F)/(2\delta_F)$. On the other hand,

$$\overline{F}(R(t) - 1/M, t) = K \geq F(R(t) - 1/M, t), \quad \overline{F}(R(t),t) = 0 = F(R(t),t).$$

Thus, if we can choose M such that $F_0(r) \leq \overline{F}(r,0)$ for $r \in [R(0) - 1/M, R(0)]$, then we can apply the maximum principle to $\overline{F} - F$ over Ω_M to deduce that $F(r,t) \leq \overline{F}(r,t)$ in Ω_M. It follows that

$$0 \geq \frac{\partial F}{\partial r}(R(t),t) \geq \frac{\partial \overline{F}}{\partial r}(R(t),t) = -2MK,$$

and $0 \leq \dot{R}(t) = h\big(-\frac{\partial F}{\partial r}(R(t),t)\big) \leq h(2MK)$, as asserted in (3.2). □

Proof of Theorem 3.1. For $t_0 \geq 0$, define

$$\check{F}(\check{r},t) = F\left(\frac{R(t)}{R(t_0)}\check{r}, t\right) \quad \text{and} \quad \check{N}(\check{r},t) = N\left(\frac{R(t)}{R(t_0)}\check{r}, t\right)$$

for $0 \leq \check{r} \leq R(t_0)$, $t \geq 0$. The functions $\check{F}(\check{r},t)$ and $\check{N}(\check{r},t)$ satisfy the following equations:

$$\begin{cases} \frac{\partial \check{F}}{\partial t} - \delta_F \frac{R(t_0)^2}{R(t)^2} \nabla^2 \check{F} - \check{r}\dot{R}(t)\frac{R(t_0)}{R(t)}\frac{\partial \check{F}}{\partial \check{r}} = \check{F}\left[\lambda_F\left(1 - \frac{\check{F}}{K}\right) - \eta \check{N}\right], \\ \frac{\partial \check{N}}{\partial t} - \delta_N \frac{R(t_0)^2}{R(t)^2} \nabla^2 \check{N} - \check{r}\dot{R}(t)\frac{R(t_0)}{R(t)}\frac{\partial \check{N}}{\partial \check{r}} = \lambda_N \check{F} - d_N(\check{N} - N_0), \end{cases} \tag{3.4}$$

with $\|\dot{R}\|_{L^\infty[0,\infty)} < \infty$. Since $\check{F}$ and $\check{N}$ are uniformly bounded (by (2.8) and (2.9)), we may use the L^p parabolic estimates to conclude that there is a positive constant C (independent of t_0) such that, for any $t_0 \geq 0$,

$$\int_{t_0}^{t_0+1} dt \int_{R(t_0)-R(0)}^{R(t_0)} \check{r} \left[|\nabla^2 \check{F}|^p + |\nabla^2 \check{N}|^p + \left|\frac{\partial \check{F}}{\partial t}\right|^p + \left|\frac{\partial \check{N}}{\partial t}\right|^p \right] d\check{r} \leq C,$$

Then, by interpolation [24, p. 80, Lemma 3.3]

$$\left\| \frac{\partial \check{F}}{\partial \check{r}}(R(t_0), t) \right\|_{C^{\alpha/2}[t_0, t_0+1]} \leq C,$$

with another constant C. Since

$$\dot{R}(t) = h\left(-\frac{R(t_0)}{R(t)} \frac{\partial \check{F}}{\partial \check{r}}(R(t_0), t) \right) \leq -\mu \frac{R(t_0)}{R(t)} \frac{\partial \check{F}}{\partial \check{r}}(R(t_0), t) \quad \text{for } t \in [t_0, t_0+1],$$

we easily deduce that

$$\|\dot{R}(t)\|_{C^{\alpha/2}[0,\infty)} < \infty. \tag{3.5}$$

Using this fact, we may go back to the system (3.4) and conclude that the Schauder estimate (3.1) holds.

One can now use these *a priori* estimates to prove the existence and uniqueness of the solution asserted in Theorem 3.1; the details are by standard arguments used for Stefan-type free boundary problems, as given, for instance, in [16] or [40, Theorem 2.1]. □

In the following sections we consider cases where the limit

$$R(\infty) = \lim_{t\to\infty} R(t)$$

is either finite or infinite. The following result will be useful.

Theorem 3.3. *If $R(\infty) < \infty$, then*

$$\lim_{t\to\infty} \dot{R}(t) = 0 \tag{3.6}$$

and

$$\lim_{t\to\infty} \sup_{0\leq r\leq R(t)} F(r,t) = 0, \tag{3.7}$$

$$\lim_{t\to\infty} \sup_{0\leq r\leq R(t)} |N(r,t) - N_0| = 0, \tag{3.8}$$

Proof. If the assertion (3.6) is not true, then there is a sequence $t_n \to \infty$ and $\beta > 0$ such that $\dot{R}(t_n) \geq \beta$ for all n. We may assume that $t_{n+1} - t_n \geq 1$. By (3.5), there exists $0 < \delta < 1$ such that $|\dot{R}(t) - \dot{R}(s)| < \beta/2$ if $|t-s| \leq \delta$. Hence $\dot{R}(t) \geq 0$ for $t \geq 0$ and $\dot{R}(t) \geq \beta/2$ for $t \in \cup_{n=1}^{\infty}(t_n - \delta, t_n + \delta)$. Integrating from t_n to t_{n+1}, we have

$$R(t_{n+1}) - R(t_n) = \int_{t_n}^{t_{n+1}} \dot{R}(t)\, dt \geq \frac{\delta\beta}{2} \quad \text{for all } n,$$

But this implies $R(t_n) \to \infty$ as $t \to \infty$, which contradicts the assumption that $R_\infty < \infty$. This proves (3.6).

Next we prove (3.7) by contradiction, assuming that

$$\sup_{0 \leq r \leq R(t)} F(r, t_n) \geq \beta > 0 \quad \text{for a sequence } t_n \to \infty. \tag{3.9}$$

From the uniform Schauder estimate in (3.1), it follows that, for some $\delta > 0$,

$$\sup_{0 \leq r \leq R(t)} F(r,t) \geq \frac{\beta}{2} \quad \text{for } |t - t_n| < \delta,\ n = 1, 2, ... \tag{3.10}$$

From (3.1) it also follows that there is a subsequence n' such that the functions

$$\hat{F}_{n'}(r,t) := F\left(\frac{R(t)}{R(\infty)} r, t + t_{n'}\right), \quad \hat{N}_{n'}(r,t) := N\left(\frac{R(t)}{R(\infty)} r, t + t_{n'}\right)$$

converge uniformly in $0 \leq r \leq R(\infty)$, $|t| \leq \delta$ to functions $\hat{F}_\infty(r,t)$ and $\hat{N}_\infty(r,t)$ which satisfy (2.1)-(2.2) in $[0, R(\infty)] \times [-\delta, \delta]$. Since $\hat{F}_\infty(1,0) = 0$ and, by (3.10), $\hat{F}_\infty(r,t) \not\equiv 0$,

$$\frac{\partial \hat{F}_\infty}{\partial \hat{r}}(R(\infty), 0) < 0$$

by the maximum principle, and hence

$$\begin{aligned} \lim_{t_{n'} \to \infty} \dot{R}(t_{n'}) &= \lim_{t_{n'} \to \infty} h\left(-\frac{R(\infty)}{R(t_{n'})} \frac{\partial \hat{F}_{n'}}{\partial \hat{r}}(R(\infty), 0)\right) \\ &= h\left(-\frac{\partial \hat{F}_\infty(R(\infty), 0)}{\partial \hat{r}}\right) > 0, \end{aligned}$$

which is a contradition to (3.6); this completes the proof of (3.7).

To prove (3.8), set $\tilde{N}(x,t) = \hat{N} - N_0$. From (3.7) we obtain, for any $\epsilon > 0$, the inequality

$$\left| \frac{\partial \tilde{N}}{\partial t} - \frac{\delta_N}{R^2(t)} \nabla^2 \tilde{N} - \frac{\hat{r}\dot{R}(t)}{R(t)} \frac{\partial \tilde{N}}{\partial \hat{r}} + d_N \tilde{N} \right| < \epsilon, \tag{3.11}$$

if $0 \le \hat{r} \le 1$ and $t > T_\epsilon$, provided T_ϵ is chosen large enough. By comparison,

$$|\tilde{N}(\hat{r},t)| \le \frac{\epsilon}{d_N} + Ae^{-d_N(t-T_\epsilon)} \qquad \text{for } 0 \le \hat{r} \le 1,\ t > T_\epsilon, \tag{3.12}$$

where $A = \sup\limits_{0 \le \hat{r} \le 1} |\tilde{N}(\hat{r}, T_\epsilon)|$. Letting $t \to \infty$ and then $\epsilon \to 0$, the assertion (3.8) follows. □

4 The case $R(\infty) < \infty$ and $F \to 0$ as $t \to \infty$

In this section we prove the following theorem.

Theorem 4.1. *If $\eta N_0 > \lambda_F$, then $R(\infty) < \infty$ and hence, by Theorem 3.3,*

$$\sup_{0 \le r \le R(t)} F(r,t) \to 0 \qquad \text{as } t \to \infty \tag{4.1}$$

and

$$\sup_{0 \le r \le R(t)} |N(r,t) - N_0| \to 0 \qquad \text{as} \quad t \to \infty. \tag{4.2}$$

Proof. Define

$$X(t) = \int_0^{R(t)} rF(r,t)\,dr. \tag{4.3}$$

Since $F(R(t),t) = 0$ and $\frac{\partial F}{\partial r}(R(t),t) \le 0$,

$$\begin{aligned} \frac{dX}{dt}(t) &= \int_0^{R(t)} r \frac{\partial F}{\partial t}(r,t)\,dr \\ &\le \int_0^{R(t)} r\left[\lambda_F - \eta N(r,t)\right] F(r,t)\,dr. \end{aligned}$$

By comparison,

$$N(r,t) \ge N_0(1 - e^{-d_N t}),$$

so that

$$\frac{dX}{dt}(t) \le \int_0^{R(t)} r[\lambda_F - \eta N_0 + \eta N_0 e^{-d_N t}] F(r,t)\, dr.$$

Define $\gamma = \frac{1}{2}(\eta N_0 - \lambda_F)$, then $\gamma > 0$ and

$$\frac{dX}{dt}(t) \le -\gamma \int_0^{R(t)} rF(r,t)\, dr = -\gamma X(t)$$

if $t \ge \max\{0, t_\gamma\}$ where $t_\gamma = -\frac{1}{d_N}\log\left(\frac{\gamma}{\eta N_0}\right)$, so that

$$X(t) \le X(t_\gamma) e^{-\gamma(t-t_\gamma)} \qquad \text{for } t \ge \max\{0, t_\gamma\}.$$

Hence, by integration,

$$\int_{t_\gamma}^{\infty} \int_0^{R(t)} rF(r,t)\, drdt \le \frac{1}{\gamma} X(t_\gamma).$$

Since $0 \le F(r,t) \le K$ and $\sup\limits_{t\ge 0} \dot{R}(t) < \infty$, we have

$$\int_0^{\infty} \int_0^{R(t)} rF(r,t)\, drdt \le A(R(0) + \max\{0, t_\gamma\}) \cdot \frac{1}{\gamma} \le A' \frac{R(0) + |\log\gamma|}{\gamma} := A_\gamma \tag{4.4}$$

for some constants A, A', A_γ, where A, A' are independent of γ. Next, since $\frac{dR}{dt}(t) \le -\mu \frac{\partial F}{\partial r}(R(t), t)$,

$$\begin{aligned}
&\frac{d}{dt}\left[\int_0^{R(t)} rF(r,t)\, dr + \frac{\delta_F}{2\mu} R(t)^2\right] \\
&\le \int_0^{R(t)} r\frac{\partial F}{\partial r}(r,t)\, dr - \delta_F R(t) \frac{\partial F}{\partial r}(R(t), t) \\
&= \int_0^{R(t)} r\left[\frac{\partial F}{\partial t}(r,t) - \delta_F \nabla^2 F(r,t)\right] dr \\
&= \lambda_F \int_0^{R(t)} rF(r,t)\left(1 - \frac{F(r,t)}{K}\right) dr - \eta \int_0^{R(t)} rN(r,t)F(r,t)\, dr
\end{aligned}$$

by equation (2.1). Integrating in t and using (4.4), we get

$$\sup_{t\ge 0}\left[\int_0^{R(t)} rF(r,t)\, dr + \frac{\delta_F}{2\mu} R(t)^2\right] \le A_\gamma + \left[\int_0^{R(0)} rF(r,0)\, dr + \frac{\delta_F}{2\mu} R(0)^2\right],$$

hence $\sup_{t\geq 0} R(t) < +\infty$. The remaining assertions (4.1) and (4.2) follow from Theorem 3.3. $\square$

Corollary 4.2. *From the last inequality we deduce that if* $\eta N_0 > \lambda_F$, *then*

$$R(t)^2 \leq C \left[1 + R(0)^2 + \frac{|\log(\eta N_0 - \lambda_F)|}{\eta N_0 - \lambda_F} \right] \tag{4.5}$$

where C *is a constant independent of how small* $\eta N_0 - \lambda_F$ *is. This provides an upper bound on* $R(\infty)$ *as* $\eta N_0 - \lambda_F \searrow 0$.

Remark 4.3. *If we repeat the above proof with the function*

$$X(t) = \int_0^{R(t)} r \left[\epsilon (N - N_0)^2 + F(r,t) \right] dr \tag{4.6}$$

and take $2\epsilon\lambda_N = \eta$, *then we get*

$$\frac{dX}{dt}(t) \leq \int_0^{R(t)} r \left[-2\epsilon (N - N_0)^2 + -(\eta N_0 - \lambda_F) F \right] dr \leq -\gamma X(t)$$

for some $\gamma > 0$ *and* $t \geq 0$. *Hence, in addition to the estimate* (4.2), *we also have the estimate*

$$\int_0^{R(t)} r (N - N_0)^2 \, dr \leq A e^{-\gamma t}. \tag{4.7}$$

5 The case $R(\infty) = \infty$

We denote by j_0 the first root of the Bessel function of order zero; it can be approximated by $j_0 \approx 2.4048$.

Theorem 5.1. *If* $\eta N_0 < \lambda_F$ *and*

$$R(0) > \left[\frac{\lambda_F - \eta N_0}{\delta_F} \right]^{-1/2} j_0, \tag{5.1}$$

then $R(\infty) = \infty$.

Theorem 5.1 implies the following dichotomy.

Theorem 5.2. *If* $\eta N_0 < \lambda_F$ *then either* $R(\infty) = \infty$ *or*

$$R(\infty) \leq \left[\frac{\lambda_F - \eta N_0}{\delta_F}\right]^{-1/2} j_0. \tag{5.2}$$

Proof. Indeed, if the inequality (5.2) is reversed, then

$$R(t_0) > \left[\frac{\lambda_F - \eta N_0}{\delta_F}\right]^{-1/2} j_0$$

for some $t_0 > 0$. Hence $R(\infty) = \infty$, by repeating the proof of Theorem 5.1. $\square$

Proof of Theorem 5.1. Let u_0 denote the minimizer of

$$\inf_u \frac{\int_0^1 r|u'|^2\, dr}{\int_0^1 ru^2\, dr}$$

in the class of functions in $W^{1,2}[0,1]$ which vanish at $r = 1$. Then

$$\begin{cases} -\nabla^2 u_0 = (j_0)^2 u_0 & \text{for } 0 \leq r < 1, \\ u_0(r) > 0 & \text{for } 0 \leq r < 1, \\ u_0(1) = 0. \end{cases}$$

By scaling, we can construct a function $U(r)$ such that

$$\begin{cases} -\delta_F \nabla^2 U = \lambda U & \text{for } 0 \leq r < R^*, \\ U(r) > 0 & \text{for } 0 \leq r < R^*, \\ U(R^*) = 0. \end{cases}$$

for any $\lambda > 0$ and $R^* = [\lambda/\delta_F]^{-1/2} j_0$. We choose

$$\lambda = (1 - \delta)(\lambda_F - \eta N_0)$$

and

$$R^* = \left[(1 - \delta)\frac{\lambda_F - \eta N_0}{\delta_F}\right]^{-1/2} j_0,$$

where $0 < \delta < 1$ is so small that, by (5.1),

$$R(0) > R^*.$$

To prove the theorem, we proceed by contradiction, assuming that $R(\infty) < \infty$. Then, by Theorem 3.3,

$$\sup_{0 \le \hat{r} \le 1} \left[\hat{F}(\hat{r}, t) + |\hat{N}(\hat{r}, t) - N_0| \right] \to 0 \quad \text{as } t \to \infty. \tag{5.3}$$

It follows that for sufficiently large T_δ,

$$\frac{\partial F}{\partial t} - \delta_F \nabla^2 F \ge (1 - \delta)(\lambda_F - \eta N_0) F \quad \text{for } 0 \le r \le R(t),\ t > T_\delta.$$

We note that

$$R(t) \ge R(T_\delta) > R(0) > R^* \quad \text{if } t > T_\delta$$

and take ϵ small such that

$$F(r, T_\delta) > \epsilon U(r) \quad \text{for } 0 \le r \le R^*.$$

Then, by comparison (i.e. applying the maximum principle to $F - \epsilon U$), we conclude that

$$F(r, t) > \epsilon U(r) \quad \text{for } 0 \le r \le R^* \text{ and } t > T_\delta.$$

But this contradicts (5.3) and thus completes the proof of the theorem. □

6 The case $R(\infty) = \infty$: $(F, N) \to (F^*, N^*)$ as $t \to \infty$

In this section we consider the asymptotic behavior of the solution of (2.1)-(2.7) in case $R(\infty) = \infty$. We assume, as in Theorem 5.1, that $\eta N_0 < \lambda_F$, so that if the initial condition (5.1) is satisfied then $R(\infty) = \infty$. When $\eta N_0 < \lambda_F$ there exists a unique non-zero homogeneous steady state (F^*, N^*) of the system (2.1)-(2.2), that is,

$$\lambda_F \left(1 - \frac{F^*}{K}\right) - \eta N^* = 0, \quad \lambda_N F^* - d_N(N^* - N_0) = 0, \tag{6.1}$$

given by

$$F^* = \left(1 - \frac{\eta N_0}{\lambda_F}\right) \left(\frac{1}{K} + \frac{\eta}{\lambda_F} \cdot \frac{\lambda_N}{d_N}\right)^{-1}, \quad N^* = N_0 + \frac{\lambda_N}{d_N} F^*; \tag{6.2}$$

this state is asymptotically stable with respect to spatially independent solutions of the system (2.1)-(2.2). We are interested to know whether it is also asymptotically stable with respect to spatially dependent solutions. In this section we prove the following:

Theorem 6.1. *If $\eta N_0 < \lambda_F$ and $R(\infty) = \infty$, then*

$$(F(r,t), N(r,t)) \to (F^*, N^*) \qquad \text{as } t \to \infty \tag{6.3}$$

locally uniformly in r, for $0 \le r < \infty$.

It will be convenient to set $Q = N - N_0$ and rewrite the system (2.1)-(2.2) in the following form:

$$\frac{\partial F}{\partial t} - \delta_F \nabla^2 F = G(F,Q)F \qquad \text{for } x \in \Omega(t),\ t > 0, \tag{6.4}$$

where $G(p,q) = \lambda_F - \eta N_0 - p\lambda_F/K - \eta q$, and

$$\frac{\partial Q}{\partial t} - \delta_N \nabla^2 Q = d_N \left(\frac{\lambda_N}{d_N} F - Q \right) \qquad \text{for } x \in \Omega(t),\ t > 0, \tag{6.5}$$

with the boundary condition

$$F(x,t) = Q(x,t) = 0 \qquad \text{for } x \in \partial\Omega(t),\ t > 0. \tag{6.6}$$

Here $\Omega(t) \subset \mathbb{R}^2$ is a growing domain such that $\Omega(t) \nearrow \Omega(\infty) = \mathbb{R}^2$ as $t \to \infty$. We will also find it convenient to write $F(r,t)$ as $F(x,t)$, where $x \in \mathbb{R}^2$, $|x| = r$, and similarly the same convention for $Q(r,t)$ and all other functions of (r,t).

The proof of Theorem 6.1 will use a Lyapunov function, but in order to define this function we need to ensure that $\liminf_{t\to\infty} F(r,t) > 0$ uniformly locally in r for $0 \le r < \infty$. This will be proved in Lemmas 6.2 and 6.3. In these lemmas we assume that the initial conditions F^0, N^0 can be arbitrary functions subject to uniform bounds

$$\|(F^0, N^0)\|_{C^{2+\alpha}(\mathbb{R}^2)} \le A < \infty, \qquad \text{and} \qquad F^0(0) > 0. \tag{6.7}$$

Lemma 6.2. *If $\eta N_0 < \lambda_F$ and $\Omega(t) \nearrow \mathbb{R}^2$, then*

$$\liminf_{t\to\infty} F(x,t) \ge \alpha_0 > 0 \qquad \textit{for each } x \in \mathbb{R}^2 \tag{6.8}$$

where α_0 is independent of x, the growing domain $\{(x,t) : t \ge 0, x \in \Omega(t)\}$ and the initial data (F^0, Q^0).

We first prove a weaker result:

Lemma 6.3. *If $\eta N_0 < \lambda_F$ and $\Omega(t) \nearrow \mathbb{R}^2$, then*

$$\limsup_{t\to\infty} F(x,t) \geq \alpha_1 > 0 \quad \text{for each } x \in \mathbb{R}^2 \tag{6.9}$$

where α_1 is independent of x, the growing domain $\{(x,t) : t \geq 0, x \in \Omega(t)\}$ and the initial data (F^0, Q^0).

Such lemmas were proved in [12,13] for the Cauchy problem of predator-prey systems in $\mathbb{R}^2$. Here we adapt their arguments in the context of a free-boundary problem.

Remark 6.4. *The proofs of Lemmas 6.2-6.3 work for general expanding domains in n dimensions, with solutions that are functions in (x,t), not necessarily radially symmetric. The proof Theorem 6.1, however, relies on a classification of entire solutions based on a Lyapunov functional argument that holds only for two-dimensional domains (see Subsection 6.3). For higher dimensional domain, we refer to an alternative Lyapunov function argument in [12], which requires the additional assumption that $\delta_F = \delta_N$.*

Remark 6.5. *A completely different approach to proving the assertions of Theorem 6.1, which is not based on the existence of Lyapunov function, is by constructing two nested sequences of positive numbers*

$$F_2 < F_4 < \cdots < F_3 < F_1, \quad \text{and} \quad N_2 < N_4 < \cdots < N_3 < N_1,$$

which converge to F^* and N^* respectively; this approach was used in [40, Theorem 4.3] for a predator-prey model. The construction of the sequences proceed in 4-step cycles, that proves (i) $F(x,t) \leq F_{2i-1}$; (ii) $N(x,t) \leq N_{2i-1}$; (iii) $F(x,t) \geq F_{2i}$; (iv) $N(x,t) \geq N_{2i}$, using standard comparison. The assertion (6.3) can then be proved by an induction argument. This method works for general expanding domains in n dimensions and does not require the condition $\delta_F = \delta_N$. However, the assumption on coefficients needs to be strengthened from $\frac{\lambda_F}{\eta N_0} > 1$ to $\frac{\lambda_F}{\eta N} > \max\left\{1, \frac{\lambda_N K}{d_N N_0}\right\}$.

6.1 Proof of Lemma 6.3

Since

$$\frac{\partial Q}{\partial t} - \delta_N \nabla^2 Q \geq -d_N Q \quad \text{in } \Omega(t), \quad Q \geq 0 \quad \text{on } \partial\Omega(t)$$

for $t > 0$, and $Q \geq -N_0$ at $t = 0$, we get, by comparison

$$Q(x,t) \geq -N_0 e^{-d_N t};$$

hence

$$\liminf_{t\to\infty} \left[\inf_{x\in\Omega(t)} Q(x,t) \right] \geq 0. \tag{6.10}$$

Similarly, since $F(x,t) \leq K$,

$$\frac{\partial Q}{\partial t} - \delta_N \nabla^2 Q \leq d_N \left(\frac{\lambda_N}{d_N} K - Q \right)$$

and, by comparison,

$$Q(x,t) \leq \frac{\lambda_N}{d_N} K + A_0 e^{-d_N t} \tag{6.11}$$

for some constant A_0, which can be chosen to be independent of the initial data in view of (6.7). Hence,

$$Q(x,t) \leq \frac{\lambda_N}{d_N} K + 1 \equiv M_N \quad \text{if } t \geq t_0,$$

where t_0 is independent of the initial data.

To prove the lemma we assume, to the contrary, that for each $n \in \mathbb{N}$ there is a solution (F_n, Q_n) and growing domains $\Omega_n(t)$ satisfying (6.4)-(6.6), $x_n \in \mathbb{R}^2$ and $t_n \to \infty$ such that

$$F_n(x_n, t) < \frac{1}{n} \quad \text{for all } t > t_n, \tag{6.12}$$

and proceed to derive a contradiction.

By further increasing t_n, we may assume that for each $R \gg 1$, there exists n_R such that $\Omega_n(t_n) \supset B_R(x_n)$ for any $n \geq n_R$. Here $B_R(x_n)$ denotes the disc of radius R centered at x_n. In the following, $B_R = B_R(0)$ denotes the ball of radius R centered at the origin.

Step 1. We claim that for any $R > 0$,

$$\lim_{n\to\infty} Q_n(x_n + x, t + t_n) = 0 \quad \text{uniformly in } (x,t) \in B_R \times [0,\infty). \tag{6.13}$$

To prove it we assume, to the contrary, that there exist $R > 0$, $\delta > 0$, (F_n^0, Q_n^0), $s_n \in (t_n, \infty)$ and $x_n' \in B_R$ such that

$$Q_n(x_n + x_n', s_n) \geq \delta \tag{6.14}$$

for the solution (F_n, Q_n) with initial data (F_n^0, Q_n^0). By passing to a subsequence, we may assume that

$$(F_n, Q_n)(x_n + x, s_n + t) \to (F_\infty, Q_\infty)(x, t)$$

locally uniformly in $(x, t) \in \mathbb{R}^2 \times \mathbb{R}$, where (F_∞, Q_∞) satisfy the system (6.4)-(6.5) over the entire space $\mathbb{R}^2 \times \mathbb{R}$. Since $F_\infty(0,0) = 0$, by (6.12), the maximum principle implies that $F_\infty(x,t) \equiv 0$ for $x \in \mathbb{R}^2$, $t \leq 0$. Hence

$$\frac{\partial Q_\infty}{\partial t} - \delta_n \nabla^2 Q_\infty = -d_N Q_\infty \quad \text{for } x \in \mathbb{R}^2,\ t \leq 0,$$

and, by comparison, for any $x \in \mathbb{R}^2$, $t_0 < t \leq 0$,

$$Q_\infty(x,t) \leq M_N e^{-d_N(t-t_0)}.$$

Letting $t_0 \to -\infty$, we have $Q_\infty(x,t) \leq 0$ while, by (6.10), $Q_\infty \geq 0$; hence $Q_\infty \equiv 0$. Since this is a contradiction to (6.14), the proof of (6.13) is completed.

From (6.11) and (6.13) it follows that for each $R \gg 1$ and $0 < \delta \ll 1$,

$$Q_n(x_n + x, t_n + t) \leq M_N \mathbb{1}_{\mathbb{R}^2 \setminus B_R}(x) + \delta \mathbb{1}_{B_R}(x) := \overline{Q}_{R,\delta}(x)$$

for sufficiently large n; here $\mathbb{1}_D = 1$ if $x \in D$ and $\mathbb{1}_D = 0$ if $x \notin D$.

In the sequel we fix R and δ such that

$$\overline{\gamma} := \frac{K}{\lambda_F}(\lambda_F - \eta N_0 - \eta\delta - \delta_F \mu_R) > 0$$

where (ϕ_R, μ_R) is the eigensolution of

$$-\nabla^2 \phi_R = \mu_R \phi_R \quad \text{in } B_R, \quad \phi_R = 0 \quad \text{on } \partial B_R, \quad \|\phi_R\|_{L^\infty} = 1.$$

Note that $\mu_R \to 0$ if $R \to \infty$, hence we can make $\overline{\gamma}$ prositive by taking R sufficiently large and δ sufficiently small.

Step 2. Let $\underline{F}^n$ denote the solution of

$$\begin{cases} \left(\frac{\partial}{\partial t} - \delta_F \nabla^2\right) \underline{F}^n = G(\underline{F}^n, \overline{Q}_{R,\delta}(x))\underline{F}^n & \text{for } x \in \Omega_n(t+t_n) - x_n,\ t \geq 0, \\ \underline{F}^n(x,t) = 0 & \text{for } x \in \partial\Omega_n(t+t_n) - x_n\, t \geq 0, \end{cases} \tag{6.15}$$

with initial data

$$\underline{F}^n(x,0) = F_n(x_n + x, t_n) \quad \text{for } x \in \Omega_n(t_n) - x_n, \tag{6.16}$$

for n large (so that $B_R \subset \Omega_n(t + t_n) - x_n$). By comparison,

$$F_n(x_n + x, t_n + t) \geq \underline{F}^n(x,t) \quad \text{for } x \in \Omega_n(t + t_n) - x_n,\ t \geq 0. \tag{6.17}$$

Step 3. We extend $\phi_R(x)$ by zero to $\mathbb{R}^2 \backslash B_R$ and consider the maximal interval $(0, \gamma_0]$ such that for all $\gamma \in (0, \gamma_0]$,

$$-\delta_F \nabla^2(\gamma\phi_R) \leq G(\gamma\phi_R, \overline{Q}_{R,\delta}(x))(\gamma\phi(R)) \quad \text{for all } x \in B_R.$$

Since $G(p,q) = \lambda_F - \eta N_0 - p\lambda_F/K - \eta q$,

$$\gamma_0 \geq \overline{\gamma} = \frac{K}{\lambda_F}(\lambda_F - \eta N_0 - \eta\delta - \delta_F - \mu_R) > 0.$$

Note that $\gamma\phi_R$ is a (stationary) sub-solution of (6.15) for $\gamma \in (0, \gamma_0]$.

Consider the solution $\psi_\gamma(x,t)$ of (6.15) with initial data $\gamma\phi_R(x)$. If $0 < \gamma \leq \gamma_0$ then

$$\frac{\partial}{\partial t}\psi_\gamma(x,t)\big|_{t=0} > 0,$$

and $\frac{\partial\psi_\gamma}{\partial t} \geq 0$ on $\partial\Omega(t + t_n) - x_n$, for $t \geq 0$. We may then apply the maximum principle to $\frac{\partial\psi_\gamma}{\partial t}$ to conclude that

$$\frac{\partial\psi_\gamma(x,t)}{\partial t} > 0 \quad \text{for } x \in \Omega_n(t + t_n),\ t > 0.$$

It follows that $\psi_\gamma(x,t) \nearrow p_\gamma(x)$ as $t \to \infty$, where $p_\gamma(x)$ is a positive solution of

$$-\delta_F \nabla^2 p_\gamma = G(p_\gamma, \overline{Q}_{R,\delta}(x))p_\gamma \quad \text{in } \Omega(\infty) = \mathbb{R}^2, \tag{6.18}$$

and

$$p_\gamma(x) > \gamma\phi_R(x) \quad \text{for all } x \in \mathbb{R}^2. \tag{6.19}$$

By comparison,

$$\psi_\gamma(x,t) < \psi_{\gamma'}(x,t) \quad \text{if } 0 < \gamma < \gamma' \leq \gamma_0$$

and hence

$$p_\gamma(x) \leq p_{\gamma_0} \quad \text{for } \gamma \in (0, \gamma_0],\ x \in \mathbb{R}^2.$$

Step 4. If γ is small enough such that

$$\gamma\phi_R(x) \le F_n(x_n + x, t_n) \quad \text{for } x \in \Omega_n(t_n) - x_n,$$

then $\underline{F}^n(x,t)$ and $\psi_\gamma(x,t)$ are a pair of solution and subsolution of (6.15)-(6.16). In view of (6.17), we have

$$F_n(x_n + x, t_n + t) \ge \underline{F}^n(x,t) \ge \psi_\gamma(x,t) \quad \text{for } x \in \Omega_n(t+t_n) - x_n,\ t \ge 0,$$

while, as $t \to \infty$, $\psi_\gamma(x,t) \nearrow p_\gamma(x)$. It follows that

$$\liminf_{t\to\infty} F_n(x_n + x, t_n + t) \ge p_\gamma(x) > \gamma\phi_R(x) \quad \text{locally uniformly for } x \in \mathbb{R}^2,$$

where the strict inequality follows from (6.19). We claim that

$$p_\gamma(x) = p_{\gamma_0}(x) \quad \text{for } x \in \mathbb{R}^2 \text{ and } \gamma \in (0, \gamma_0]. \tag{6.20}$$

Once this is proved, then

$$\liminf_{t\to\infty} F_n(x_n + x, t_n + t) \ge \gamma_0\phi_R(x) \quad \text{locally uniformly for } x \in \mathbb{R}^2.$$

Taking $x = 0$ and recalling (6.12), we see that $\frac{1}{n} > \gamma_0\phi_R(0)$, which is impossible if n is sufficiently large. This contradiction completes the proof of Lemma 6.2. Thus, it remains to prove the assertion (6.20).

Step 5. To prove (6.20), we note that if $p_\gamma(x_0) = p_{\gamma_0}(x_0)$ for some x_0, then by the maximum principle applied to $p_{\gamma_0}(x) - p_\gamma(x)$, we conclude that (6.20) holds. Hence, if (6.20) is not true, then, for some $\gamma_1 \in (0, \gamma_0)$,

$$p_{\gamma_1}(x) < p_{\gamma_0}(x) \quad \text{for all } x \in \mathbb{R}^2. \tag{6.21}$$

We proceed to derive a contradiction to (6.21). First we note that there must exist $x_0 \in B_R$ such that

$$\gamma_0\phi_R(x_0) > p_{\gamma_1}(x_0).$$

Since otherwise we can apply the maximum principle to $p_{\gamma_1}(x) - \psi_{\gamma_0}(x,t)$ and conclude that $p_{\gamma_1}(x) - \psi_{\gamma_0}(x,t) > 0$ for all $t > 0$, and hence

$$p_{\gamma_1}(x) \ge \lim_{t\to\infty} \psi_{\gamma_0}(x,t) = p_{\gamma_0}(x),$$

which contradicts (6.21). Hence, setting

$$\gamma^* = \sup\{\gamma \geq 0 : \gamma\phi_R(x) < p_{\gamma_1}(x) \quad \forall x \in \mathbb{R}^2\},$$

we conclude that $\gamma^* < \gamma_0$ (and thus is finite),

$$\gamma^*\phi_R(x) \leq p_{\gamma_1}(x) \text{ in } \mathbb{R}^2 \text{ and } \gamma^*\phi_R(x') = p_{\gamma_1}(x') \text{ for some } x' \in B_R.$$

But since $p_{\gamma_1}(x)$ is a solution of (6.18) while $\gamma^*\phi_R(x)$ is a subsolution, the maximum principle implies that $p_{\gamma_1}(x) = \gamma^*\phi_R(x)$ in $\mathbb{R}^2$, which is impossible since $p_{\gamma_1}(x) > 0$ in $\mathbb{R}^2$ while $\phi_R(x) = 0$ in $\mathbb{R}^2 \setminus B_R$. This completes the proof of (6.20).

6.2 Proof of Lemma 6.2

Following [13] we use a method from persistence theory [37] to derive (6.8) from (6.9). We begin by noting that if (6.8) is not true then for each $n \in \mathbb{N}$, there is a solution (F_n, Q_n) and growing domains $\Omega_n(t)$ satisfying (6.4)-(6.6), and $x_n \in \mathbb{R}^2$ such that

$$\liminf_{t\to\infty} F_n(x_n, t) < \frac{1}{n}.$$

By applying Lemma 6.3, we easily see that there exist sequences $t_n \to \infty$ and $s_n \geq 0$ such that

$$\begin{cases} F_n(x_n, t_n) = \frac{\alpha_1}{2}, \quad F_n(x_n, t) \leq \frac{\alpha_1}{2} \text{ for } t \in [t_n, t_n + s_n], \\ F_n(x_n, t_n + s_n) = \frac{1}{n}. \end{cases} \tag{6.22}$$

By passing to a subsequence we may assume that $(x, t) \mapsto (F_n, Q_n)(x_n + x, t_n + s_n + t)$ converges locally uniformly to (F_∞, Q_∞), an entire solution in $\mathbb{R}^2 \times \mathbb{R}$ of (6.4)-(6.5). Since $F_\infty(0, 0) = 0$, by the maximum principle $F_\infty(x, t) \equiv 0$ for $x \in \mathbb{R}^2$, $t \leq 0$. This implies that $s_n \to \infty$. Indeed, otherwise s_n has a bounded subsequence. We may then pass to a further subsequence so that $s_n \to s^* < \infty$ and then

$$\frac{\alpha_1}{2} = \lim_{n\to\infty} F_n(x_n, t_n) = F_\infty(0, -s^*) = 0.$$

We next consider the function

$$(x, t) \mapsto (F_n, Q_n)(x_n + x, t_n + t)$$

and, by passing to a further subsequence, its limit

$$(\hat{F},\hat{Q})(x,t)=\lim_{n\to\infty}(F_n,Q_n)(x_n+x,t_n+t)\quad\text{ in the local uniform sense.}$$

The pair $(\hat{F},\hat{Q})$ is an entire solution in $\mathbb{R}^2\times\mathbb{R}$ of (6.4)-(6.5), and that $\hat{F}(0,0)=\frac{\alpha_1}{2}$. As a consequence of the maximum principle, $\hat{Q}(x,t)>0$ for all (x,t). The initial data

$$(\hat{F},\hat{Q})(x,0)=\lim_{n\to\infty}(F_n,Q_n)(x_n+x,t_n)$$

belongs to the class (6.7). We can then apply the proof of Lemma 6.3, which works the same in the case where $\Omega(t)\equiv\mathbb{R}^2$ for all $t>0$ (note that the constant $\alpha_1>0$ is independent of $\Omega(t)$ as long as $\Omega(\infty)=\mathbb{R}^2$), to conclude that

$$\limsup_{t\to\infty}\hat{F}(x,t)\geq\alpha_1\quad\text{ for each } x\in\mathbb{R}^2. \tag{6.23}$$

On the other hand, by (6.22),

$$F_n(x_n,t_n+t)\leq\frac{\alpha_1}{2}\quad\text{ for } t\in[0,s_n]$$

and since $s_n\to\infty$ we deduce that $\hat{F}(0,t)\leq\frac{\alpha_1}{2}$, for all t. This contradicts (6.23), and completes the proof of Lemma 6.2.

6.3 Using Lyapunov function

From Lemma 6.2 and (6.10)-(6.11), we have,

$$\begin{cases}0<\alpha_0\leq\liminf\limits_{t\to\infty}\left[\inf\limits_{x\in\Omega(t)}F(x,t)\right]\leq\limsup\limits_{t\to\infty}\left[\sup\limits_{x\in\Omega(t)}F(x,t)\right]\leq K,\\ 0\leq\liminf\limits_{t\to\infty}\left[\inf\limits_{x\in\Omega(t)}Q(x,t)\right]\leq\limsup\limits_{t\to\infty}\left[\sup\limits_{x\in\Omega(t)}Q(x,t)\right]\leq\frac{\lambda_N}{d_N}K.\end{cases}$$

We shall construct a Lyapunov function and use it to prove the assertion (6.3) of Theorem 6.1. Our proof uses the assumption that the dimension of the spatial domain is two. (For higher dimensions, see [12] for a proof which uses the additional assumption $\delta_F=\delta_N$.) Consider also the function $V:(0,\infty)\times\mathbb{R}\to[0,\infty)$ defined by

$$V(F,Q)=V_1(F)+V_2(Q)$$

where

$$V_1(F) = \int_{F^*}^{F} \frac{\xi - F^*}{\xi}\, d\xi, \quad V_2(Q) = \frac{\eta}{2\lambda_N}(Q - N^* + N_0)^2. \tag{6.24}$$

Note that

$$\begin{cases} V_1'(F) = \frac{F-F^*}{F}, & V_1''(F) = \frac{F^*}{F^2}, \\ V_2'(Q) = \frac{\eta}{\lambda_N}(Q - N^* + N_0), & V_2''(Q) = \frac{\eta}{\lambda_N}. \end{cases}$$

The function $V(F,Q)$ was proposed by Ardito and Ricciardi [1], as a suitable Lyapunov function, to prove the global stability of certain predator-prey system.

Note that $V \geq 0$ on the set

$$P := \{(F,Q) \in \mathbb{R}^2 : \alpha_0 \leq F \leq K \text{ and } 0 \leq Q \leq \lambda_N K/d_N\},$$

and that it is strictly convex in P and attains a unique global minimum at $(F^*, N^* - N_0)$. Moreover, there exists $\kappa \in (0,1)$ small enough such that

$$\kappa(|F-F^*|^2 + |Q - N^* + N_0|^2) \leq V(F,Q) \leq \kappa^{-1}(|F-F^*|^2 + |Q - N^* + N_0|^2) \tag{6.25}$$

for all $(F,Q) \in P$. Now define the vector field $\vec{H} : P \to \mathbb{R}^2$ by

$$\vec{H}(F,Q) = (G(F,Q)F, \lambda_N F - d_N Q) = ((\lambda_F - \eta N_0 - \eta Q - \lambda_F F/K)F, \lambda_N F - d_N Q).$$

By computation, using (6.1),

$$\begin{aligned} &\nabla V(F,Q) \cdot \vec{H}(F,Q) \\ &= V_1'(F)(\lambda_F - \eta N_0 - \eta Q - \lambda_F F/K)F + V_2'(Q)(\lambda_N F - d_N Q) \\ &= (F - F^*)[-\eta(Q - N^* + N_0) - (F - F^*)/K] \\ &\quad + \frac{\eta}{\lambda_N}(Q - N^* + N_0)[\lambda_N(F - F^*) - d_N(Q - N^* + N_0)] \\ &= -\frac{1}{K}(F - F^*)^2 - \frac{\eta d_N}{\lambda_N}(Q - N^* + N_0)^2. \end{aligned} \tag{6.26}$$

Recalling (6.25) we see that there exists a positive constant α_2 such that

$$\nabla V(F,Q) \cdot \vec{H}(F,Q) \leq -\alpha_2 V(F,Q) \quad \text{for all } (F,Q) \in P \subset \mathbb{R}^2. \tag{6.27}$$

Proof of Theorem 6.1. The proof is adapted from a proof of a similar result for a predator-prey model in $\mathbb{R}^2$ [13], and in bounded domains with Neumann boundary conditions [11]. We proceed by contradiction, assuming that there exists a sequence (x_k, t_k) such that $t_k \to \infty$ and $x_k \to x_\infty$ for some $x_\infty \in \mathbb{R}^2$ and that

$$|F(x_k, t_k) - F^*| + |Q(x_k, t_k) - N^* + N_0| \geq \delta' \quad \text{for some } \delta' > 0. \tag{6.28}$$

Consider the sequence of functions (F_k, Q_k) defined by

$$(F_k, Q_k)(x, t) = (F, Q)(x, t + t_k).$$

By parabolic estimates, we can pass to a sequence and assume that

$$(F_k, Q_k)(x, t) \to (F_\infty, Q_\infty)(x, t) \quad \text{locally uniformly for } (x, t) \in \mathbb{R}^2 \times \mathbb{R},$$

where (F_∞, Q_∞) is a solution of (6.4)-(6.5) in the whole space $(x, t) \in \mathbb{R}^2 \times \mathbb{R}$ and satisfies

$$\alpha_0 \leq F_\infty(x, t) \leq K, \quad 0 \leq Q_\infty(x, t) \leq \frac{\lambda_N}{d_N} K \quad \text{for } x \in \mathbb{R}^2,\ t \in \mathbb{R}. \tag{6.29}$$

i.e. $(F_\infty(x, t), Q_\infty(x, t)) \in P$ for each (x, t).

Let us consider, for each $R > 0$, the function $t \mapsto W_R(t)$ defined by

$$W_R(t) = \int_{\mathbb{R}^2} \rho\left(\frac{x}{R}\right) V(F_\infty(x, t), Q_\infty(x, t))\, dx,$$

where $\rho : \mathbb{R}^2 \to [0, 1]$ is a smooth cut-off function such that

$$\rho(x) = 1 \quad \text{for } |x| \leq 1, \quad \text{and} \quad \rho(x) = 0 \quad \text{for } |x| \geq 2.$$

The time derivative of W_R can be computed as follows:

$$\begin{aligned}
\frac{d}{dt} W_R(t) &= \int_{\mathbb{R}^2} \rho\left(\frac{x}{R}\right) \nabla V(F_\infty, Q_\infty) \cdot \left(\frac{\partial F_\infty}{\partial t}, \frac{\partial Q_\infty}{\partial t}\right) \\
&= \int_{\mathbb{R}^2} \rho\left(\frac{x}{R}\right) \left[V_1'(F_\infty)\delta_F \nabla^2 F_\infty + V_2'(Q_\infty)\delta_N \nabla^2 Q_\infty\right] dx \\
&\quad + \int_{\mathbb{R}^2} \rho\left(\frac{x}{R}\right) \nabla V(F_\infty, Q_\infty) \cdot \vec{H}\,(F_\infty, Q_\infty)\, dx.
\end{aligned}$$

Hence, using (6.27), we obtain

$$\frac{d}{dt}W_R(t) \leq -\alpha_2 W_R(t) + I_R^1(t) + I_R^2(t), \quad \text{for all } t \in \mathbb{R}, \tag{6.30}$$

where

$$\begin{cases} I_R^1(t) & := \delta_F \int_{\mathbb{R}^2} \rho\left(\frac{x}{R}\right) V_1'(F_\infty)\nabla^2 F_\infty dx, \\ I_R^2(t) & := \delta_N \int_{\mathbb{R}^2} \rho\left(\frac{x}{R}\right) V_2'(Q_\infty)\delta_N \nabla^2 Q_\infty \, dx. \end{cases}$$

Next we estimate $I_R^i(t)$ by integration by parts:

$$\begin{aligned} I_R^1(t) &= -\frac{\delta_F}{R}\int_{\mathbb{R}^2} \nabla\rho\left(\frac{x}{R}\right) \cdot \nabla[V_1(F_\infty)]\, dx - \delta_F \int_{\mathbb{R}^2} \rho\left(\frac{x}{R}\right) V_1''(F_\infty)|\nabla F_\infty|^2\, dx \\ &= \frac{\delta_F}{R^2}\int_{\mathbb{R}^2} \nabla^2\rho\left(\frac{x}{R}\right) V_1(F_\infty)\, dx - \delta_F \int_{\mathbb{R}^2} \rho\left(\frac{x}{R}\right) \frac{F^*}{(F_\infty)^2}|\nabla F_\infty|^2\, dx \\ &\leq \frac{\delta_F}{R^2}\int_{\mathbb{R}^2} \nabla^2\rho\left(\frac{x}{R}\right) V_1\left(F_\infty\right)\, dx. \end{aligned}$$

Hence, we deduce that

$$I_R^1(t) \leq \frac{\delta_F}{R^2}\|\nabla^2\rho\|_{L^\infty(\mathbb{R}^2)} \int_{B_{2R}} V_1(F_\infty)\, dx. \tag{6.31}$$

Similarly, we can show that

$$I_R^2(t) \leq \frac{\delta_N}{R^2}\|\nabla^2\rho\|_{L^\infty(\mathbb{R}^2)} \int_{B_{2R}} V_2(Q_\infty)\, dx. \tag{6.32}$$

Recalling (6.29), it follows that

$$\sup_{(x,t)\in\mathbb{R}^2\times\mathbb{R}} V(F_\infty(x,t), Q_\infty(x,t)) = \sup_{(x,t)\in\mathbb{R}^2\times\mathbb{R}} [V_1(F_\infty(x,t)) + V_2(Q_\infty(x,t))] < \infty,$$

so that (6.31)-(6.32) implies the existence of $M > 0$ independent of $R > 0$ such that

$$I_R^1(t) + I_R^2(t) \leq M \quad \text{for all } t \in \mathbb{R};$$

here we used our assumption that the spatial dimension is not larger than two. Thus the inequality (6.30) implies, for each $R > 1$,

$$\frac{d}{dt}W_R(t) \leq -\alpha_2 W_R(t) + M, \quad \text{for all } t \in \mathbb{R}.$$

Solving above differential inequality, we deduce

$$W_R(t) \leq \frac{M}{\alpha_2} \quad \text{for all } t \in \mathbb{R}, \text{ and } R > 1. \tag{6.33}$$

For each $t \in \mathbb{R}$, we can let $R \to \infty$ to obtain

$$W(t) := \int_{\mathbb{R}^2} V(F_\infty(x,t), Q_\infty(x,t))\, dx \leq \frac{M}{\alpha_2} \quad \text{for all } t \in \mathbb{R}.$$

We can then improve the estimates (6.31)-(6.32) to

$$I_R^1(t) + I_R^2(t) \leq \frac{C}{R^2} \int_{B_{2R}} V(F_\infty(x,t), Q_\infty(x,t))\, dx \leq \frac{C}{R^2} W(t) \leq \frac{C}{R^2} \cdot \frac{M}{\alpha_2}.$$

Letting $R \to \infty$, we obtain $\limsup_{R\to\infty} [I_R^1(t) + I_R^2(t)] \leq 0$ uniformly in $t \in \mathbb{R}$. Thus, we can let $R \to \infty$ and then $M \searrow 0$ in (6.33) to deduce that $W(t) \leq 0$ for all $t \in \mathbb{R}$. Since $W(t)$ is nonnegative by construction, it follows that $W(t) \equiv 0$. Hence, it follows that

$$(F_\infty(x,t), Q_\infty(x,t)) \equiv (F^*, N^* - N_0) \quad \text{for all } x \in \mathbb{R}^2,\ t \in \mathbb{R}.$$

This is a contradiction to (6.28). □

7 Part 2. The FNT model

In this section we extend the results of Sections 3-6 to the model (2.1)-(2.7) which includes the variable T. To prove Theorem 3.1 we write the system (2.1)-(2.3) in a form similar to the system (3.4),

$$\begin{cases} \frac{\partial \check{F}}{\partial t} - \delta_F \frac{R(t_0)^2}{R(t)^2} \nabla^2 \check{F} - \check{r}\dot{R}(t) \frac{R(t_0)}{R(t)} \frac{\partial \check{F}}{\partial \check{r}} = \check{F}\left[\lambda_F \left(1 - \frac{\check{F}}{K}\right) - \eta \check{N} - \zeta \check{T}\right], \\ \frac{\partial \check{N}}{\partial t} - \delta_N \frac{R(t_0)^2}{R(t)^2} \nabla^2 \check{N} - \check{r}\dot{R}(t) \frac{R(t_0)}{R(t)} \frac{\partial \check{N}}{\partial \check{r}} = \lambda_N \hat{F} - d_N(\check{N} - N_0), \\ \frac{\partial \check{T}}{\partial t} - \delta_T \frac{R(t_0)^2}{R(t)^2} \nabla^2 \check{T} - \check{r}\dot{R}(t) \frac{R(t_0)}{R(t)} \frac{\partial \check{T}}{\partial \check{r}} = \lambda_T \check{F} + \lambda_{TN}(\check{N} - N_0) - d_T(\check{T} - T_0). \end{cases} \tag{7.1}$$

We can then use Schauder and L^p estimates as in the case of the system (3.4) to establish global existence of a unique solution of (2.1)-(2.7) with

$$(F, N, T) \in [C^{2+\alpha, 1+\alpha/2}(\Omega^\infty)]^3.$$

Theorem 7.1. *If* $R_\infty < \infty$ *then* (3.6)-(3.8) *hold and*

$$\lim_{t\to\infty} \sup_{0\le r\le R(t)} |T(r,t) - T_0| = 0. \tag{7.2}$$

Proof. By Theorem 3.3, (3.6)-(3.8) hold as well as the inequalities (3.11)-(3.12). By repeating the proof of Theorem 3.3, we deduce that for any $\epsilon > 0$, there exists a t_ϵ such that

$$|N(r,t) - N_0| \le \frac{\epsilon}{d_N} + Ae^{-d_N(t-t_\epsilon)} \quad \text{for } 0 \le r \le R(t),\ t > t_\epsilon. \tag{7.3}$$

i.e. $\sup\limits_{0\le r\le R(t)} |N - N_0| \to 0$ as $t \to \infty$. We can then derive, for any $\epsilon > 0$, the following inequality for $\tilde{T}(r,t) = T(r,t) - T_0$:

$$\left| \frac{\partial \tilde{T}}{\partial t} - \delta_T \nabla^2 \tilde{T} + d_T \tilde{T} \right| < \epsilon \quad \text{for } 0 \le r \le R(t),\ t \gg 1.$$

By comparison, we can then establish an inequality similar to (7.3) for $\tilde{T}$. □

Theorem 7.2. *If* $\eta N_0 + \zeta T_0 > \lambda_F$ *then* $\lim\limits_{t\to\infty} R(t) < \infty$*, and hence, by Theorem 7.1, the equations* (4.1), (4.2) *and* (7.2) *hold.*

Proof. As in the proof of Theorem 4.1,

$$N(r,t) \ge N_0(1 - e^{-d_N t}) \quad \text{for } t \ge 0,$$

so that for any small $\epsilon > 0$,

$$\begin{aligned} \frac{\partial T}{\partial t} - \delta_T \nabla^2 T &\ge \lambda_T F - \lambda_{TN} N_0 e^{-d_N t} - d_T(T - T_0) \\ &> - d_T(T - T_0 + \epsilon) \end{aligned}$$

if $t \ge t_\epsilon$ where t_ϵ is sufficiently large. Set

$$\tilde{T}(r,t) = (T_0 - \epsilon)\,(1 - e^{-d_T(t-t_\epsilon)}).$$

Then, by comparison, $T(r,t) \ge \tilde{T}(r,t)$ for $t \ge t_\epsilon$. Hence $T(r,t) \ge T_0 - 2\epsilon$ if $t \ge \bar{t}_\epsilon$ for some large $\bar{t}_\epsilon \in [t_\epsilon, \infty)$.

Taking ϵ sufficiently small and introducing the same function $X(t) = \int_0^{R(t)} rF(r,t)\,dr$, we can now follow closely the proof of Theorem 4.1 to establish the estimate (4.4), with ηN_0 replaced by $\eta N_0 + \zeta T_0$, and complete the proof of $\lim\limits_{t\to\infty} R(t) < \infty$. □

Corollary 7.3. *Suppose* $\eta N_0 + \zeta T_0 > \lambda_F$*. From the above proof we deduce, analogously to Corollary 4.2, that for any* $\epsilon > 0$*,*

$$R(t)^2 \le C\left[1 + R(0)^2 + \frac{|\log(\eta N_0 + \zeta T_0 - \lambda_F)|}{\eta N_0 + \zeta T_0 - \lambda_F}\right]$$

Theorem 7.4. *If* $\eta N_0 + \zeta T_0 < \lambda_F$ *and*

$$R(0) > \left[\frac{\lambda_F - \eta N_0 - \zeta T_0}{\delta_F}\right]^{-1/2} j_0,$$

then $\lim\limits_{t\to\infty} R(t) = \infty$*.*

Proof. The proof is the same as in the case of Theorem 5.1, by just replacing ηN_0 by $\eta N_0 + \zeta T_0$. We omit the details. □

We next consider an extension of Theorem 6.1, with the steady point (F^*, N^*, T^*) given by

$$\begin{cases} N^* = N_0 + \frac{\lambda_N}{d_N}F^*, \qquad T^* = T_0 + \left(\lambda_T + \lambda_{TN}\frac{\lambda_N}{d_N}\right)\frac{F^*}{d_N}, \\ F^* = (\lambda_F - \eta N_0 - \zeta T_0)\left[\frac{\lambda_F}{K} + \eta\frac{\lambda_N}{d_N} + \zeta\left(\lambda_T + \lambda_{TN}\frac{\lambda_N}{d_N}\right)\frac{1}{dT}\right]^{-1}. \end{cases}$$

Theorem 7.5. *Assume that*

$$\eta N_0 + \zeta T_0 < \lambda_F \quad \text{and} \quad \zeta\lambda_{TN}^2 < 4\eta d_T d_N \frac{\lambda_T}{\lambda_N}. \tag{7.4}$$

If $R(\infty) = \infty$*, then*

$$(F(r,t), N(r,t), T(r,t)) \to (F^*, N^*, T^*) \quad \text{as } t \to \infty$$

locally uniformly in r*, for* $0 \le r < \infty$*.*

Proof. The proof of Lemma 6.3 extends with small changes. Assuming for contradiction that (6.12) holds, and setting $S = T - T_0$, we can first establish that (6.13) holds and then, in a similar way, that S_n satisfies the same estimate in $B_R \times [0, \infty)$. In addition, S is uniformly bounded, like Q. We can then introduce lower solutions $\underline{F}^n$, similarly to (6.15)-(6.16), with

$$G(\underline{F}^n, \overline{Q}_{R,\delta}(x), \overline{S}_{R,\delta}(x))\underline{F}^n$$

for an appropriate function G, and proceed as in Steps 2-5 to derive a contradicton.

The proof of Lemma 6.2 follows from Subsection 6.2 with just minor changes, replacing Q_n by (Q_n, S_n) everywhere.

We next introduce a Lyapunov function $\hat{V}(F,Q,S) = V_1(F) + V_2(Q) + V_3(S)$, where V_1, V_2 are given in (6.24), and

$$V_3(S) = \frac{\zeta}{2\lambda_T}(S - T^* + T_0)^2.$$

The vector field $\hat{H}(F,Q,S)$ of the full system is

$$\hat{H}(F,Q,S) = \begin{pmatrix} (\lambda_F - \eta N_0 - \eta Q - \zeta T_0 - \zeta S - \lambda_F F/K)F \\ \lambda_N F - d_N Q \\ \lambda_T F + \lambda_{TN} Q - d_T S \end{pmatrix}$$

Then, writing $\tilde{F} = F - F^*$, $\tilde{Q} = Q - (N^* - N_0)$, $\tilde{S} = S - (T^* - T_0)$,

$$\begin{aligned}
&\nabla\hat{V}(F,Q,S)\cdot\hat{H}(F,Q,S)\\
&= \tilde{F}\left[-\eta\tilde{Q} - \zeta\tilde{S} - \frac{\lambda_F}{K}\tilde{F}\right] + \frac{\eta\tilde{Q}}{\lambda_N}\left[\lambda_N\tilde{F} - d_N\tilde{Q}\right] + \frac{\zeta\tilde{S}}{\lambda_T}\left[\lambda_T\tilde{F} + \lambda_{TN}\tilde{Q} - d_T\tilde{S}\right]\\
&= -\frac{\lambda_F}{K}\tilde{F}^2 - \frac{\eta d_N}{\lambda_N}\tilde{Q}^2 - \frac{\zeta d_T}{\lambda_T}\tilde{S}^2 + \frac{\zeta\lambda_{TN}}{\lambda_T}\tilde{S}\tilde{Q}\\
&\le -\alpha_3(\tilde{F}^2 + \tilde{Q}^2 + \tilde{S}^2)\\
&= -\alpha_3[(F - F^*)^2 + (Q - N + N_0)^2 + (S - T + T_0)^2]
\end{aligned}$$

for some $\alpha_3 > 0$, where we used the second condition of (7.4) for the inequality. Hence, we may repeat the arguments in Subsection 6.3 to complete the proof. □

Remark 7.6. *The second inequality in* (7.4) *was needed in the construction of the Lyapunov function; without it we still have, from the proof of Lemma 6.2, that*

$$\liminf_{t\to\infty} \inf_{0\le r\le R(t)} F(r,t) \ge F_* > 0,$$

for some constant $F_* > 0$. We also note, as explained in the introduction of the dynamics (1.2)*, that λ_{TN} is small compared to λ_T, since the activation of T cells is due primarily to dendritic cells, and we can also, if necessary, decrease ζ so that the second inequality in* (7.4) *is satisfied and then conclude that $F_* = F^*$ as asserted in Theorem 7.5.*

8 Conclusion

In this paper we considered a mathematical model of fungal infection, focusing on the interaction between the innate and adaptive immune responses. Candidiasis is a class of fungal infection caused by Candida, a type of yeast. The infection most commonly presents in the mouth and vagina, but if left untreated it may spread to the esophagus, bronchi, trachea, or lung. Such invasive fungal infection (IFI) is a cause of significant morbidity and mortality in immuno-compromised individuals [7, 29, 32]. The mathematical model is presented by a system of PDEs in order to account for the spread of fungal infection.

The model consists of three equations, for the densities of fungi (F), neutrophils (N), and *CTL* or *CD8*$^+$ T cells (T) in the infected domains $\Omega(t)$, as t increases. The critical parameters in the model are the growth rate λ_F of F, the killing rates of fungi by neutrophils (η) and by T cells (ζ), and the "natural defense" in homeostasis N_0 (for N) and T_0 (for T). We assume that all variables are radially symmetric, that $\Omega(t) = \{r \leq R(t)\}$, and that $R(t)$ increases in proportion to the flux of F across the boundary $r = R(t)$. Our main results are:

- If $\eta N_0 + \zeta T_0 > \lambda_F$, then $\lim\limits_{t\to\infty} R(t) < \infty$ and $\lim\limits_{t\to\infty} \limsup\limits_{0\leq r\leq R(t)} F(r,t) = 0$.
- If $\eta N_0 + \zeta T_0 < \lambda_F$ and $R(0)$ is large enough, then $\lim\limits_{t\to\infty} R(t) = \infty$; moreover, $\lim\limits_{t\to\infty} F(r,t) = F^* > 0$ locally uniformly in r if one assumes in addition that $\zeta \lambda_{TN}^2 < 4\eta d_T d_N \frac{\lambda_T}{\lambda_N}$.

Common drugs for the treatment of IFI include antifungal agents that either directly kill fungi or prevent their proliferation [29]. In our model these treatments have the effect of reducing λ_F. Other more recent drugs (mostly experimental or in early clinical trials) aim to strengthen the immune response by (i) augmentation and activation of neutrophils (increasing N_0); (ii) making neutrophils more effective (increasing η); (iii) increasing T cells immunity (increasing T_0); and (iv) increasing antibody immunity (increasing ζ) [29, 32]. Each of the above drugs increases the quantity $\eta N_0 + \zeta T_0 - \lambda_F$, and once it becomes positive, the infection may be considered resolved.

In the present paper we used a simple model whereby the immune response is represented explicitly only by neutrophils and CD8$^+$ T cells. We did not include macrophages and endocytosed fungi that proliferate within macrophages, dendritic cells (except tacitly), and other cells and cytokines involved in the immune response. Including these additional species will lead to a far more complicated model, for which mathematical analysis alone will undoubtedly be insufficient to draw meaningful conclusions on the efficacy of drugs.

We finally note that although we used *C. albicans* as a template for fungal populations, both the mathematical model and the mathematical results are actually applicable to general fungal species.

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