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# Analysis of Coupled Reaction-Diffusion Equations for RNA Interactions

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## Abstract

We consider a system of coupled reaction-diffusion equations that models the interaction between multiple types of chemical species, particularly the interaction between one messenger RNA and different types of non-coding microRNAs in biological cells. We construct various modeling systems with different levels of complexity for the reaction, nonlinear diffusion, and coupled reaction and diffusion of the RNA interactions, respectively, with the most complex one being the full coupled reaction-diffusion equations. The simplest system consists of ordinary differential equations (ODE) modeling the chemical reaction. We present a derivation of this system using the chemical master equation and the mean-field approximation, and prove the existence, uniqueness, and linear stability of equilibrium solution of the ODE system. Next, we consider a single, nonlinear diffusion equation for one species that results from the slow diffusion of the others. Using variational techniques, we prove the existence and uniqueness of solution to a boundary-value problem of this nonlinear diffusion equation. Finally, we consider the full system of reaction-diffusion equations, both steady-state and time-dependent. We use the monotone method to construct iteratively upper and lower solutions and show that their respective limits are solutions to the reaction-diffusion system. For the time-dependent system of reaction-diffusion equations, we obtain the existence and uniqueness of global solutions. We also obtain some asymptotic properties of such solutions.

**Keywords**

RNA; gene expression; reaction-diffusion systems; well-posedness; variational methods; monotone methods; maximum principle

## 1 Introduction

Let $\Omega$ be a bounded domain in $\mathbb{R}^3$ with a smooth boundary $\partial\Omega$. Let $N \geq 1$ be an integer. Let $D_i$ ($i = 1, \dots, N$), $D$, $\beta_i$ ($i = 1, \dots, N$), $\beta$, and $k_i$ ($i = 1, \dots, N$) be positive numbers. Let $\alpha_i$ ($i = 1, \dots, N$) and $\alpha$ be nonnegative functions on $\Omega \times (0, \infty)$. We consider the following system of coupled reaction-diffusion equations:

$$\frac{\partial u_i}{\partial t} = D_i \Delta u_i - \beta_i u_i - k_i u_i \upsilon + \alpha_i \text{ in } \Omega \times (0, \infty), \; i = 1, \dots, N, \quad (1.1)$$

$$\frac{\partial \upsilon}{\partial t} = D \Delta \upsilon - \beta \upsilon - \sum_{i=1}^{N} k_i u_i \upsilon + \alpha \text{ in } \Omega \times (0, \infty), \quad (1.2)$$

together with the boundary and initial conditions

$$\frac{\partial u_i}{\partial \mathrm{n}} = \frac{\partial \upsilon}{\partial \mathrm{n}} = 0 \text{ on } \partial\Omega \times (0, \infty), \; i = 1, \dots, N, \quad (1.3)$$

$$u_i(\cdot, 0) = u_{i0} \text{ and } \upsilon(\cdot, 0) = \upsilon_0 \text{ in } \Omega, \; i = 1, \dots, N, \quad (1.4)$$

where $\partial/\partial n$ denotes the normal derivative along the exterior unit normal $n$ at the boundary $\partial\Omega$, and all $u_{i0}$ ($i = 1, \dots, N$) and $\upsilon_0$ are nonnegative functions on $\Omega$.

The reaction-diffusion system (1.1)–(1.4) is a biophysical model of the interaction between different types of Ribonucleic acid (RNA) molecules, a class of biological molecules that are crucial in the coding and decoding, regulation, and expression of genes [23]. Small, non-coding RNAs (sRNA) regulate developmental events such as cell growth and tissue differentiation through binding and reacting with messenger RNA (mRNA) in a cell. Different sRNA species may competitively bind to different mRNA targets to regulate genes [4, 6, 12, 13, 16, 21]. Recent experiments suggest that the concentration of mRNA and different sRNA in cells and across tissue is linked to the expression of a gene [22]. One of the main and long-term goals of our study of the reaction-diffusion system (1.1)–(1.4) is therefore to possibly provide some insight into how different RNA concentrations can contribute to turning genes "on" or "off" across various length scales, and eventually to the gene expression.

In Eqs. (1.1) and (1.2), the function $u_i = u_i(x, t)$ for each $i$ ($1 \leq i \leq N$) represents the local concentration of the $i$th sRNA species at $x \in \Omega$ and time $t$. We assume a total of $N$ sRNA species. The function $\upsilon = \upsilon(x, t)$ represents the local concentration of the mRNA species at $x \in \Omega$ and time $t$. For each $i$ ($1 \leq i \leq N$), $D_i$ is the diffusion coefficient and $\beta_i$ is the self-degradation rate of the $i$th sRNA species. Similarly, $D$ is the diffusion coefficient and $\beta$ is the self-degradation rate of mRNA. For each $i$ ($1 \le i \le N$), $k_i$ is the rate of reaction between the $i$th sRNA and mRNA. We neglect the interactions among different sRNA species as they can be effectively described through their diffusion and self-degradation coefficients. The reaction terms $u_i \upsilon$ ($i = 1, \ldots, N$) result from the mean-field approximation. The nonnegative functions $\alpha_i = \alpha_i(x, t)$ ($i = 1, \ldots, N$) and $\alpha = \alpha(x, t)$ ($x \in \Omega$, $t > 0$) are the production rates of the corresponding RNA species, and are termed transcription profiles. Notice that we set the linear size of the region $\Omega$ to be of tissue length to account for the RNA interaction across different cells [22].

The reaction-diffusion system model (1.1)–(1.4) was first proposed for the special case $N$ = 1 and one space dimension in [14]; cf. also [12, 15, 19]. The full model with $N(\ge 2)$ sRNA species was proposed in [7].

An interesting feature of the reaction-diffusion system (1.1)–(1.4), first discovered in [14], is that the increase in the diffusivity (within certain range) of an sRNA species sharpens the concentration profile of mRNA. Figure 1 depicts numerically computed steady-state solutions to the system (1.1)–(1.3) in one space dimension with $N = 1$, $\Omega = (0, 1)$, $D = 0$, a few selected values of $D_1$, $\beta_1 = \beta = 0.01$, $k_1 = 1$, and

$$\alpha_1 = 0.1 + 0.1 \tanh(5x - 2.5), \quad (1.5)$$

$$\alpha = 0.1 + 0.1 \tanh(2.5 - 5x). \quad (1.6)$$

One can see that as the diffusion constant $D_1$ of the sRNA increases, the profile of the steady-state concentration $\upsilon = \upsilon(x)$ of the mRNA sharpens.

As one of a series of studies on the reaction-diffusion system modeling, analysis, and computation of the the RNA interactions, the present work focuses on: (1) the construction of various modeling systems with different levels of complexity for the reaction, nonlinear diffusion, and coupled reaction and diffusion, respectively, with the most complex one being the full reaction-diffusion system (1.1)–(1.4); and (2) the mathematical justification for each of the models, proving the well-posedness of the corresponding differential equations. To understand how the reaction terms (i.e., the product terms $u_i \upsilon$ in (1.1) and (1.2)) come from, we shall first, however, present a brief derivation of the corresponding reaction system (i.e., no diffusion) for the case $N$ = 1 using a chemical master equation and the mean-field approximation [19].

We shall consider our different modeling systems in four cases.

Case 1. We consider the following system of ordinary different equations (ODE) for the concentrations $u_i = u_i(t) \ge 0$ ($i = 1, \ldots, N$) and $\upsilon = \upsilon(t) \ge 0$:

$$\frac{du_i}{dt} = -\beta_i u_i - k_i u_i \upsilon + \alpha_i \quad i = 1, \ldots, N, \quad (1.7)$$

$$\frac{d\upsilon}{dt} = -\beta\upsilon - \sum_{i=1}^{N} k_i u_i \upsilon + \alpha, \quad (1.8)$$

where all $\alpha_i$ ($i$ = 1, …, $N$) and $\alpha$ are nonnegative numbers. We shall prove the existence, uniqueness, and linear stability of the steady-state solution to this ODE system; cf. Theorem 3.1.

Case 2. We consider the situation where all the diffusion coefficients $D_i$ ($i$ = 1, …, $N$) are much smaller than the diffusion coefficient $D$. That is, we consider the approximation $D_i = 0$ ($i$ = 1, …, $N$). Assume all $\alpha$ and $\alpha_i$ ($i$ = 1, …, $N$) are independent of time $t$. The steady-state solution of $u_i$ in Eq. (1.1) with $D_i = 0$ leads to $u_i = \alpha_i/(\beta_i+k_i\upsilon)$ ($i$ = 1, …, $N$). These expressions, coupled with the $\upsilon$-equation (1.2), imply that the steady-state solution $\upsilon \geq 0$ should satisfy the following nonlinear diffusion equation and boundary condition:

$$D\Delta\upsilon - \beta\upsilon - \sum_{i=1}^{N} \frac{k_i \alpha_i \upsilon}{\beta_i + k_i \upsilon} + \alpha = 0 \text{ in } \Omega, \quad (1.9)$$

$$\frac{\partial\upsilon}{\partial n} = 0 \text{ on } \partial\Omega. \quad (1.10)$$

The single, nonlinear equation (1.9) is the Euler–Lagrange equation of some energy functional. We shall use the direct method in the calculus of variations to prove the existence and uniqueness of the nonnegative solution to the boundary-value problem (1.9) and (1.10); cf. Theorem 4.1.

Case 3. We consider the following steady-state system corresponding to (1.1)–(1.4) for the concentrations $u_i \geq 0$ ($i$ = 1, …, $N$) and $\upsilon \geq 0$:

$$D_i \Delta u_i - \beta_i u_i - k_i u_i \upsilon + \alpha_i = 0 \text{ in } \Omega, i = 1, \ldots, N, \quad (1.11)$$

$$D\Delta\upsilon - \beta\upsilon - \sum_{i=1}^{N} k_i u_i \upsilon + \alpha = 0 \text{ in } \Omega, \quad (1.12)$$

$$\frac{\partial u_i}{\partial n} = \frac{\partial\upsilon}{\partial n} = 0 \text{ on } \partial\Omega, i = 1, \ldots, N. \quad (1.13)$$

Here again we assume that $\alpha$ and $\alpha_i$ ($i$ = 1, …, $N$) are independent of time $t$. We shall use the monotone method [20] to prove the existence of a solution to this system of reaction-diffusion equations; cf. Theorem 5.1. The monotone method amounts to constructing sequences of upper and lower solutions, extracting convergent subsequences, and proving that the limits are desired solutions.

Case 4. This is the full reaction-diffusion system (1.1)–(1.4). We shall prove the existence and uniqueness of global solution to this system; cf. Theorem 6.1. To do so, we first consider local solutions, i.e., solutions defined on a finite time interval. Again, we use the monotone method to construct iteratively upper and lower solutions and show their limits are the desired solutions. Unlike in the case of steady-state solutions, we are not able to use high solution regularity, as that would require compatibility conditions. Rather, we use an integral representation of solution to our initial-boundary-value problem. We then use the Maximum Principle for systems of linear parabolic equations to obtain the existence and uniqueness of global solution. We also study some additional properties such as the asymptotic behavior of solutions to the full system.

While our underlying reaction-diffusion system has been proposed to model RNA interactions in molecular biology, its basic mathematical properties are similar to some of those reaction-diffusion systems modeling other physical and biological processes. Our preliminary analysis presented here therefore shares some common features in the study of reaction-diffusion systems; cf. e.g., [10, 17] and the references therein. Our continuing mathematical effort in understanding the reaction and diffusion of RNA is to analyze the qualitative properties of solutions to the corresponding equations, in particular, the asymptotic behavior of such solutions as certain parameters become very small or large.

The rest of this paper is organized as follows: In Section 2, we present a brief derivation of the reaction system (1.7) and (1.8) for the case $N = 1$ using a chemical master equation and the mean-field approximation. In Section 3, we consider the system of ODE (1.7) and (1.8) and prove the existence, uniqueness, and linear stability of steady-state solution. In Section 4, we prove the existence and uniqueness of the boundary-value problem of the single nonlinear diffusion equation (1.9) and (1.10) for the concentration $\upsilon$ of mRNA. In Section 5 we prove the existence of a steady-state solution to the system of reaction-diffusion equations (1.11)–(1.13). In Section 6, we prove the existence and uniqueness of global solution to the full system of time-dependent, reaction-diffusion equations (1.1)–(1.4). Finally, in Section 7, we prove some asymptotic properties of solutions to the full system of time-dependent reacation-diffusion equations.

## 2 Derivation of the Reaction System

We give a brief derivation of the reaction system (1.7) and (1.8), and make a remark on how the full reaction-diffusion system (1.1)–(1.4) is formulated.

For simplicity, we shall consider two chemical species: mRNA and one sRNA. Figure 2 describes sRNA-mediated gene silencing within the cell and depicts the different rates in which mRNA and sRNA populations may change at time $t$. In the figure, $\alpha_s$ and $\alpha_m$ describe the sRNA and mRNA production rates, $\beta_s$ and $\beta_m$ describe the sRNA and mRNA independent degradation rates, and $\gamma$ describes the coupled degradation rate at time $t$. Notice in the rate diagram that the mRNA and sRNA binding process is irreversible. The numerical value of each of these rates can be determined via experimental data [15].

We denote by $M_t$ and $S_t$ the numbers of mRNA and sRNA, respectively, in a given cell at time $t$, and consider the two continuous-time processes $(M_t)_{t\geq 0}$ and $(S_t)_{t\geq 0}$. We assume that $(M_t, S_t)_{t\geq 0}$ is a stationary continuous-time Markov chain with state space $S$ with the following ordering:

$$S=\{(0,0),\ldots,(m-1,s-1),(m-1,s),(m,s-1),(m,s),(m,s+1),\ldots\}.$$

We assume that the total numbers of mRNA and sRNA are finite, and hence the state space is finite. For any given state $(m, s) \in S$, we denote by $P_{m,s}(t)$ the probability that the system is in this state, i.e., $P_{m,s}(t) = P(M_t = m, S_t = s)$. For convenience, we extend $S$ to include integer pairs $(m, s)$ for $m < 0$ or $s < 0$ and set $P_{m,s}(t) = 0$ if $m < 0$ or $s < 0$. Note that

$$\sum_{(m,s)\in S} P_{m,s}(t)=1 \quad (2.1)$$

for any $t \geq 0$. Note also that the averages $\langle M_t\rangle$, $\langle S_t\rangle$, and $\langle M_tS_t\rangle$ are defined by

$$\langle M_t\rangle=\sum_{(m,s)\in S} mP_{m,s}(t), \langle S_t\rangle=\sum_{(m,s)\in S} sP_{m,s}(t), \text{and} \langle M_tS_t\rangle=\sum_{(m,s)\in S} msP_{m,s}(t). \quad (2.2)$$

The following master equation describes the reactions defined in Figure 2:

$$\begin{aligned}\dot{P}_{m,s}(t)=&\alpha_m P_{m-1,s}(t)\\&+\alpha_s P_{m,s-1}(t)\\&+\beta_s(s+1)P_{m,s+1}(t)\\&+\beta_m(m+1)P_{m+1,s}(t)\\&+\gamma(m+1)(s+1)P_{m+1,s+1}(t)\\&-(\alpha_m+\alpha_s+\beta_m m+\beta_s s+\gamma ms)P_{m,s}(t),\end{aligned}$$

where a dot denotes the time derivative. Using this and (2.2), we obtain by a series of calculations that

$$\frac{d}{dt}\langle M_t\rangle=\sum_{(m,s)\in S} m\dot{P}_{m,s}(t)=\alpha_m A_m+\alpha_s A_s+\beta_m B_m+\beta_s B_s+\gamma C, \quad (2.3)$$

where

$$\begin{aligned} A_m &= \sum_{(m,s)\in S} mP_{m-1,s}(t) - \sum_{(m,s)\in S} mP_{m,s}(t), \\ A_s &= \sum_{(m,s)\in S} mP_{m,s-1}(t) - \sum_{(m,s)\in S} mP_{m,s}(t), \\ B_m &= \sum_{(m,s)\in S} m(m+1)P_{m+1,s}(t) - \sum_{(m,s)\in S} m^2P_{m,s}(t), \\ B_s &= \sum_{(m,s)\in S} m(s+1)P_{m,s+1}(t) - \sum_{(m,s)\in S} msP_{m,s}(t), \\ C &= \sum_{(m,s)\in S} m(m+1)(s+1)P_{m+1,s+1}(t) - \sum_{(m,s)\in S} m^2sP_{m,s}(t). \end{aligned}$$

By our convention that $P_{m,s}(t) = 0$ if $m < 0$ or $s < 0$, we have by the change of index $m - 1 \to m$ and (2.1) that

$$A_m = \sum_{(m+1,s)\in S} (m+1)P_{m,s}(t) - \sum_{(m,s)\in S} mP_{m,s}(t) = \sum_{(m,s)\in S} (m+1)P_{m,s}(t) - \sum_{(m,s)\in S} mP_{m,s}(t) = \sum_{(m,s)\in S} P_{m,s}(t) = 1.$$

Similarly, by changing the index $s - 1 \to s$, we have

$$A_s = \sum_{(m,s+1)\in S} mP_{m,s}(t) - \sum_{(m,s)\in S} mP_{m,s}(t) = \sum_{(m,s)\in S} mP_{m,s}(t) - \sum_{(m,s)\in S} mP_{m,s}(t) = 0.$$

Changing $m + 1 \to m$, we obtain by (2.2) that

$$\begin{aligned} B_m &= \sum_{(m-1,s)\in S} (m-1)mP_{m,s}(t) - \sum_{(m,s)\in S} m^2P_{m,s}(t) \\ &= \sum_{(m,s)\in S} (m-1)mP_{m,s}(t) - \sum_{(m,s)\in S} m^2P_{m,s}(t) \\ &= -\sum_{(m,s)\in S} mP_{m,s}(t) = -\langle M_t\rangle. \end{aligned}$$

Changing $s + 1 \to s$ and noting $ms = 0$ when $s = 0$, we have

$$B_s = \sum_{(m,s-1)\in S} msP_{m,s}(t) - \sum_{(m,s)\in S} msP_{m,s}(t) = \sum_{(m,s)\in S} msP_{m,s}(t) - \sum_{(m,s)\in S} msP_{m,s}(t), = 0.$$

Finally, changing $m + 1 \to m$ and $s + 1 \to s$, we obtain by (2.2) that

$$
\begin{aligned}
C=&\sum_{(m-1,s-1)\in S}(m-1)msP_{m,s}(t)-\sum_{(m,s)\in S}m^2sP_{m,s}(t)\\
=&\sum_{(m,s)\in S}(m-1)msP_{m,s}(t)-\sum_{(m,s)\in S}m^2sP_{m,s}(t)\\
=&-\sum_{(m,s)\in S}msP_{m,s}(t)\\
=&-\langle M_tS_t\rangle.
\end{aligned}
$$

Inserting all $A_m$, $A_s$, $B_m$, $B_s$ and $C$ into (2.3), we obtain

$$\frac{d}{dt}\langle M_t\rangle=\alpha_m-\beta_m\langle M_t\rangle-\gamma\langle M_tS_t\rangle. \quad (2.4)$$

Similarly, we have

$$\frac{d}{dt}\langle S_t\rangle=\alpha_s-\beta_s\langle S_t\rangle-\gamma\langle M_tS_t\rangle. \quad (2.5)$$

We now make the mean-field assumption: $\langle M_tS_t\rangle = \langle M_t\rangle \langle S_t\rangle$. If we denote by $\upsilon(t) = \langle M_t\rangle$ and $u_1(t) = \langle S_t\rangle$, the spatially homogeneous concentrations of mRNA and sRNA, respectively, then we obtain (1.7) ($N$ = 1) from (2.4) and (1.8) from (2.5) ($N$ = 1), respectively, with $\alpha_1 = \alpha_m$, $\beta_1 = \beta_m$, $k_1 = \gamma$, $\alpha = \alpha_s$, and $\beta = \beta_s$.

We remark that based on Fick's law the spatial diffution of the underlying sRNA and mRNA molecules can be described by $D_i\Delta u_i$ ($i$ = 1, …, $N$) and $D\Delta u$ with all $D_i$ and $D$ the diffusion constants, respectively [1, 11, 17]. Here we have neglected any possible and more complicated processes such as cross diffusion and anomalous diffusion. Combining these terms with the reaction system (1.7) and (1.8), we obtain the full reaction-diffusion system (1.1)–(1.4) as our mathematical model for the RNA interaction.

## 3 Reaction System: Steady-State Solution and Its Linear Stability

### Theorem 3.1

*Assume all $\beta_i$, $k_i$, and $\alpha_i$ ($i$ = 1, …, $N$), and $\beta$, $k$, and $\alpha$ are positive numbers. The system of ODE*

$$\frac{du_i}{dt}=-\beta_iu_i-k_iu_i\upsilon+\alpha_i, i=1,\dots,N, \quad (3.1)$$

$$\frac{d\upsilon}{dt} = -\beta\upsilon - \sum_{i=1}^{N} k_i u_i \upsilon + \alpha \quad (3.2)$$

*has a unique equilibrium solution* $(u_{10}, \ldots, u_{N0}, \upsilon_0) \in \mathbb{R}^{N+1}$ *with all* $u_{i0} > 0$ $(i = 1, \ldots, N)$ *and* $\upsilon_0 > 0$. *Moreover, it is linearly stable*.

**Proof—**If $(u_1, \ldots, u_N, \upsilon) \in \mathbb{R}^{N+1}$ is an equilibrium solution to (3.1) and (3.2) with all $u_i > 0$ $(i = 1, \ldots, N)$ and $\upsilon > 0$, then $S := \sum_{i=1}^{N} k_i u_i$ should satisfy

$$S = \sum_{i=1}^{N} \frac{k_i \alpha_i}{\beta_i + k_i \alpha (\beta + S)^{-1}}, \quad (3.3)$$

and the solution should be given by

$$u_i = \frac{\alpha_i}{\beta_i + k_i \alpha (\beta + S)^{-1}} (i = 1, \ldots, N) \text{and} \upsilon = \frac{\alpha}{\beta + S}. \quad (3.4)$$

Thus the key here is to prove that there is a unique solution $S > 0$ to (3.3).

Define $g : [0, \infty) \to \mathbb{R}$ by

$$g(s) = s - \sum_{i=1}^{N} \frac{k_i \alpha_i}{\beta_i + k_i \alpha (\beta + s)^{-1}}. \quad (3.5)$$

Clearly, $g$ is smooth in $[0, \infty)$, $g(0) < 0$, and $g(+\infty) = +\infty$. Thus $F := \{s \ge 0 : g(s) \ge 0\}$ is nonempty, closed, and bounded below. Let $s_0 = \min F$. Then $s_0 > 0$ and $g(s_0) = 0$. Moreover, $g'(s_0) \ge 0$. By direct calculations, we have

$$g''(s) = 2\alpha \sum_{i=1}^{N} \frac{k_i^2 \alpha_i \beta_i}{[\beta_i (\beta + s) + k_i \alpha]^3} > 0 \text{for} \quad \text{all} s > 0.$$

Thus $g'(s) > g'(s_0) = 0$ for $s > s_0$. Hence $g(s) > g(s_0) = 0$ for $s > s_0$. Therefore $s_0$ is the unique solution to $g = 0$ on $[0, \infty)$.

Set now

$$u_{i0} = \frac{\alpha_i}{\beta_i + k_i \alpha (\beta + s_0)^{-1}}, i = 1, \ldots, N, \quad (3.6)$$

$$\upsilon_0 = \frac{\alpha}{\beta + s_0}. \quad (3.7)$$

Clearly, all $u_{i0} > 0$ $(i = 1, \ldots, N)$ and $\upsilon_{i0} > 0$. Note that $S_0 = \sum_{i=1}^{N} k_i u_{i0}$, since $g(s_0) = 0$. Thus (3.7) implies which together with (3.6) further imply $\beta_i u_{i0} + k_i u_{i0} \upsilon_0 = \alpha_i$ $(i = 1, \ldots, N)$. Therefore $(u_{10}, \ldots, u_{N0}, \upsilon_0)$ is an equilibrium solution to (3.1) and (3.2).

Assume both $(u_{10}, \ldots, u_{N0}, \upsilon_0)$ and $(\bar{u}_{10}, \ldots, \bar{u}_{N0}, \bar{\upsilon}_0)$ are equilibrium solutions to (3.1) and (3.2) with all $u_{i0} > 0$ and $\bar{u}_{i0} > 0$ $(i = 1, \ldots, N)$, $\upsilon_0 > 0$ and $\bar{\upsilon}_0 > 0$. Then, by (3.3) and (3.5), $S_0 := \sum_{i=1}^{N} k_i u_{i0} > 0$ and $\bar{S}_0 := \sum_{i=1}^{N} k_i \bar{u}_{i0} > 0$ satisfy $g(S_0) = 0$ and $g(\bar{S}_0) = 0$, respectively. By the uniqueness of solution $s_0$ of $g = 0$, we then have $S_0 = \bar{S}_0 = s_0$. It then follows from (3.6) and (3.7) that $u_{i0} = \bar{u}_{i0}$ $(i = 1, \ldots, N)$ and $\upsilon_0 = \bar{\upsilon}_0$. Therefore the equilibrium solution is unique.

The linearized system for $(U_1, \ldots, U_N, V)$ around the equilibrium solution $(u_{10}, \ldots, u_{N0}, \upsilon_0)$ is given by

$$\frac{dU_i}{dt} = -(\beta_i + k_i \upsilon_0) U_i - k_i u_{i0} V, i=1, \ldots, N, \quad \frac{dV}{dt} = -\sum_{i=1}^{N} k_i \upsilon_0 U_i - \left(\beta + \sum_{i=1}^{N} k_i u_{i0}\right) V.$$

Let $\mathbf{w} = (U_1, \ldots, U_N, V)^T$, where the superscript $T$ denotes the transpose. This system is then $d\mathbf{w}/dt = M\mathbf{w}$, where

$$M = \begin{pmatrix} -(\beta_1 + k_1 \upsilon_0) & 0 & \ldots & 0 & -k_1 u_{10} \\ 0 & -(\beta_2 + k_2 \upsilon_0) & \ldots & 0 & -k_2 u_{20} \\ \vdots & \vdots & \ddots & & \vdots \\ 0 & 0 & & -(\beta_N + k_N \upsilon_0) & -k_N u_{N0} \\ -k_1 \upsilon_0 & -k_2 \upsilon_0 & \ldots & -k_N \upsilon_0 & -(\beta + \sum_{i=1}^{N} k_i u_{i0}) \end{pmatrix}.$$

It is easy to see that $M$ is strictly column diagonally dominant with negative diagonal entries. Gersǧorin's Theorem (with columns replacing rows) [8] then implies that the real part of any eigenvalue of $M$ is negative. This leads to the desired linear stability.

## 4 A Single Nonlinear Diffusion Equation: Existence and Uniqueness of Solution

### Theorem 4.1

*Assume $\Omega$ is a bounded domain in $\mathbb{R}^3$ with a Lipschitz-continuous boundary $\partial\Omega$. Assume $D$, $\beta$, and all $\beta_i$ and $k_i$ $(i = 1, \ldots, N)$ are positive numbers. Assume $\alpha_i \in L^2(\Omega)$ with $\alpha_i \geq 0$ a.e. in $\Omega$ $(i = 1, \ldots, N)$ and $\alpha \in L^2(\Omega)$ with $\alpha \geq 0$ a.e. in $\Omega$. Then there exists a unique weak solution $\upsilon \in H^1(\Omega)$ with $\upsilon \geq 0$ a.e. in $\Omega$ to the boundary-value problem*

$$D\Delta\upsilon - \beta\upsilon - \sum_{i=1}^{N} \frac{k_i \alpha_i \upsilon}{\beta_i + k_i \upsilon} + \alpha = 0 \quad in \quad \Omega, \tag{4.1}$$

$$\frac{\partial \upsilon}{\partial \mathrm{n}} = 0 \quad on \quad \partial\Omega. \tag{4.2}$$

*The same statement is true if the Neumann boundary condition (4.2) is replaced by the Dirichlet boundary condition $\upsilon = \upsilon_0$ on $\partial\Omega$ for some $\upsilon_0 \in H^1(\Omega)$ with $\upsilon_0 \geq 0$ on $\partial\Omega$.*

**Proof—**We prove the case with the Neumann boundary condition (4.2) as the Dirichlet boundary condition can be treated similarly. We define $J : H^1(\Omega) \to \mathbb{R} \cup \{\pm\infty\}$ by

$$J[u]=\int_\Omega \left\{ \frac{D}{2}|\nabla u|^2+\frac{\beta}{2}u^2+\sum_{i=1}^{N}\frac{\alpha_i\beta_i}{k_i}\left[\frac{k_i}{\beta_i}u-\ln\left(1+\frac{k_i}{\beta_i}u\right)\right]-\alpha u\right\}dx,$$

where $\ln s = -\infty$ for $s \le 0$. Define $g(s) = s - \ln(1 + s)$ for $s \in \mathbb{R}$. It is easy to see that $g = +\infty$ on $(-\infty,-1]$, and $g$ is strictly convex and attains its unique minimum at 0 with $g(0) = 0$ on $(-1,\infty)$. Thus, since the term in the summation in $J$ is $(\alpha_i\beta_i/k_i)g(k_iu/\beta_i) \ge 0$, there exist constants $C_1, C_2 \in \mathbb{R}$ with $C_1 > 0$ such that

$$J[u] \ge C_1\|u\|^2_{H^1(\Omega)}+C_2 \forall u \in H^1(\Omega). \quad (4.3)$$

Denote $\theta = \inf_{u\in H^1(\Omega)} J[u]$. Clearly, $\theta$ is finite. Standard arguments [2, 5, 9] with an energy-minimizing sequence, using Fatou's lemma to treat the lower-order terms in $J$, lead to the existence of $u \in H^1(\Omega)$ such that $J[u] = \theta$.

Now, we prove that $|u|$ is also a minimizer of $J$ on $H^1(\Omega)$. In fact, we prove more generally that if $w \in H^1(\Omega)$ then $J[|w|] \le J[w]$. (If $u = \upsilon_0$ on $\partial\Omega$, then $|u| = |\upsilon_0| = \upsilon_0$ on $\partial\Omega$, since $\upsilon_0 \ge 0$ on $\partial\Omega$.) First, $|w|^2 = w^2$ and $|\nabla|w|| = |\nabla w|$ a.e. in $\Omega$. Since $\alpha$ is nonnegative in $\Omega$, we also have $-\alpha|w| \le -\alpha w$ a.e. in $\Omega$. Consider $h(s) = g(|s|) - g(s)$ with again $g(s) = s - \ln(1 + s)$. If $s \le -1$ then $h(s) = -\infty$. For $s \in (-1, 0)$, we have $h(s) = -2s + \ln(1 + s) - \ln(1 - s)$ and $h'(s) = 2s^2/(1 - s^2) > 0$. Thus $h(s) < h(0) = 0$. If $s \ge 0$ then $h(s) = 0$. Hence $h(s) \le 0$ for all $s \in \mathbb{R}$. Consequently, by the definition of $J$ and the fact that all $\alpha \ge 0$ and $\alpha_i \ge 0$ ($i = 1, \ldots, N$) a.e. in $\Omega$, we have $J[|w|] \le J[w]$.

Denote now $\upsilon = |u|$. Then $\upsilon$ is also a minimizer of $J$ on $H^1(\Omega)$ and $\upsilon \ge 0$ in $\Omega$. Let $\eta \in H^1(\Omega) \cap L^\infty(\Omega)$ and fix $i$ ($1 \le i \le N$). It follows from the Mean-Value Theorem and Lebesgue Dominated Convergence Theorem that

$$\left.\frac{d}{dt}\right|_{t=0}\int_\Omega \frac{\alpha_i\beta_i}{k_i}\ln\left(1+\frac{k_i}{\beta_i}(\upsilon+t\eta)\right)dx=\int_\Omega \frac{\alpha_i\beta_i\eta}{\beta_i+k_i\upsilon}dx \forall \eta \in H^1(\Omega)\cap L^\infty(\Omega).$$

Since $\upsilon$ minimizes $J$ over $H^1(\Omega)$, we have $(d/dt)|_{t=0}J[\upsilon+t\eta] = 0$ for all $\eta \in H^1(\Omega)\cap L^\infty(\Omega)$. Standard calculations then imply that

$$\int_\Omega \left[D\nabla\upsilon\cdot\nabla\eta+\eta\left(\beta\upsilon+\sum_{i=1}^{N}\frac{\alpha_i\beta_i}{\beta_i+k_i\upsilon}-\alpha\right)\right]dx=0 \forall \eta \in H^1(\Omega)\cap L^\infty(\Omega).$$

Notice that $0 \le \alpha_i\beta_i/(\beta_i + k_i\upsilon) \le \alpha_i$ a.e. in $\Omega$ for all $i = 1, \ldots, N$. Therefore, since $H^1(\Omega) \cap L^\infty(\Omega)$ is dense in $H^1(\Omega)$, we can replace $\eta \in H^1(\Omega) \cap L^\infty(\Omega)$ by $\eta \in H^1(\Omega)$. Consequently, the minimizer $\upsilon \in H^1(\Omega)$ is a weak solution to (4.1) and (4.2).

If $\hat{\upsilon} \in H^1(\Omega)$ is also a nonnegative weak solution to (4.1) and (4.2), then $w = \upsilon - \hat{\upsilon}$ is a weak solution to $D\Delta w - bw = 0$ in $\Omega$ and $\partial_n w = 0$ on $\partial\Omega$, where

$b = \beta + \sum_{i=1}^{N} \beta_i k_i \alpha_i / [(\beta_i + k_i \upsilon)(\beta_i + k_i \hat{\upsilon})]$ is in $H^1(\Omega)$ and $b \geq \beta > 0$ in $\Omega$. Therefore $w = 0$ a.e. in $\Omega$. Hence the solution is unique.

We remark that the regularity of the solution $\upsilon$ to the boundary-value problem (4.1) and (4.2) depends on the smoothness of the domain $\Omega$ and that of the variable coefficients $\alpha_i$ ($i = 1, \ldots, N$) and the source function $\alpha$. Since the solution $\upsilon$ is nonnegative and the nonlinear term of $\upsilon$ is bounded, the regularity of $\upsilon$ is in fact similar to that of the solution to a linear elliptic problem. For instance, if $\partial\Omega$ is of the class $C^k$ and all $\alpha, \alpha_i \in W^{k,p}(\Omega)$ ($i = 1, \ldots, N$) for some nonnegative integer $k$ and $p \in [2, \infty)$, then $\upsilon \in W^{k+2,p}(\Omega)$. If $\partial\Omega$ is of the class $C^{2,\gamma}$ and all $\alpha, \alpha_i \in C^{0,\gamma}(\overline{\Omega})$ ($i = 1, \ldots, N$) for some $\gamma \in (0, 1)$, then $\upsilon \in C^{2,\gamma}(\overline{\Omega})$.

## 5 Reaction-Diffusion System: Existence of Steady-State Solution

### Theorem 5.1

*Let $\Omega$ be a bounded domain in $\mathbb{R}^3$. Assume all $D_i$, $D$, $\beta_i$, $\beta$, and $k_i$ ($i = 1, \ldots, N$) are positive constants. Assume all $\alpha_i$ and $\alpha$ ($i = 1, \ldots, N$) are nonnegative functions on $\Omega$.*

1. *Assume the boundary $\partial\Omega$ of $\Omega$ is in the class $C^{2,\mu}$ for some $\mu \in (0, 1)$. Assume also $\alpha_i, \alpha \in C^{0,\mu}(\overline{\Omega})$ ($i = 1, \ldots, N$). There exist $u_1, \ldots, u_N, \upsilon \in C^{2,\mu}(\overline{\Omega})$ with $u_i \geq 0$ ($i = 1, \ldots, N$) and $u \geq 0$ in $\Omega$ such that $(u_1, \ldots, u_N, \upsilon)$ is a solution to the boundary-value problem*

$$D_i \Delta u_i - \beta_i u_i - k_i u_i \upsilon + \alpha_i = 0 \text{ in } \Omega, \; i = 1, \ldots, N, \quad (5.1)$$

$$D \Delta \upsilon - \beta \upsilon - \sum_{i=1}^{N} k_i u_i \upsilon + \alpha = 0 \text{ in } \Omega, \quad (5.2)$$

$$\frac{\partial u_i}{\partial n} = \frac{\partial \upsilon}{\partial n} = 0 \text{ on } \partial\Omega, \; i = 1, \ldots, N. \quad (5.3)$$

2. *Assume the boundary $\partial\Omega$ of $\Omega$ is in the class $C^2$ and all $\alpha_i, \alpha \in L^2(\Omega)$ ($i = 1, \ldots, N$). There exist $u_1, \ldots, u_N, \upsilon \in H^2(\Omega)$ with $u_i \geq 0$ ($i = 1, \ldots, N$) and $u \geq 0$ in $\Omega$ such that $(u_1, \ldots, u_N, \upsilon)$ is a solution to the system of boundary-value problems* (5.1)–(5.3).

We remark that we do not know if the solution is unique. Our numerical calculations indicate that the solution may not be unique. If $\alpha_i$ ($i = 1, \ldots, N$) satisfy some additional assumptions, then we may have the solution uniqueness; see [18] (Theorem 6.2, Chapter 8).

**Proof—**(1) We divide our proof in five steps.

Step 1. Construction of upper solutions and lower solutions. We define $\bar{u}_i^{(0)}$, $\bar{\upsilon}^{(0)}$, $\underline{u}_i^{(0)}$, $\underline{\upsilon}^{(0)}$ ($i = 1, \ldots, N$) to be constant functions such that:

$$\bar{u}_i^{(0)} \geq \frac{\|\alpha_i\|_{L^\infty(\Omega)}}{\beta_i}, \text{á£ą}^{(0)} \geq \frac{\|\alpha\|_{L^\infty(\Omega)}}{\beta}, \underline{u}_i^{(0)}=0, \underline{\upsilon}^{(0)}=0 \text{in} \Omega, i=1, \ldots, N. \quad (5.4)$$

It is clear that

$$D_i \Delta \bar{u}_i^{(0)} - \beta_i \bar{u}_i^{(0)} - k_i \bar{u}_i^{(0)} \underline{\upsilon}^{(0)} + \alpha_i \leq 0 \text{in} \Omega, i=1, \ldots, N, \quad (5.5)$$

$$D \Delta \underline{\upsilon}^{(0)} - \beta \underline{\upsilon}^{(0)} - \sum_{i=1}^{N} k_i \bar{u}_i^{(0)} \underline{\upsilon}^{(0)} + \alpha \geq 0 \text{in} \Omega, \quad (5.6)$$

$$\frac{\partial \bar{u}_i^{(0)}}{\partial n} = \frac{\partial \underline{\upsilon}^{(0)}}{\partial n} = 0 \text{on} \partial\Omega, i=1, \ldots, N, \quad (5.7)$$

$$D_i \Delta \underline{u}_i^{(0)} - \beta_i \underline{u}_i^{(0)} - k_i \underline{u}_i^{(0)} \text{á£ą}^{(0)} + \alpha_i \geq 0 \text{in} \Omega, i=1, \ldots, N, \quad (5.8)$$

$$D \Delta \text{á£ą}^{(0)} - \beta \text{á£ą}^{(0)} - \sum_{i=1}^{N} k_i \underline{u}_i^{(0)} \text{á£ą}^{(0)} + \alpha \leq 0 \text{in} \Omega, \quad (5.9)$$

$$\frac{\partial \underline{u}_i^{(0)}}{\partial n} = \frac{\partial \text{á£ą}^{(0)}}{\partial n} = 0 \text{on} \partial\Omega, i=1, \ldots, N. \quad (5.10)$$

Step 2. Iteration. Let

$$c = \max\left\{\beta + \sum_{i=1}^{N} k_i \bar{u}_i^{(0)}, \beta_1 + k_1 \text{á£ą}^{(0)}, \ldots, \beta_N + k_N \text{á£ą}^{(0)}\right\}. \quad (5.11)$$

Define iteratively the functions $\bar{u}_i^{(k)}$, $\underline{\upsilon}^{(k)}$, $\underline{u}_i^{(k)}$, $\bar{\upsilon}^{(k)}$ ($i = 1, \ldots, N$) for $k = 1, 2, \ldots$ by

$$-D_i \Delta \bar{u}_i^{(k)} + c \bar{u}_i^{(k)} = c \bar{u}_i^{(k-1)} - \beta_i \bar{u}_i^{(k-1)} - k_i \bar{u}_i^{(k-1)} \underline{\upsilon}^{(k-1)} + \alpha_i \text{in} \Omega, i=1, \ldots, N, \quad (5.12)$$

$$-D \Delta \underline{\upsilon}^{(k)} + c \underline{\upsilon}^{(k)} = c \underline{\upsilon}^{(k-1)} - \beta \underline{\upsilon}^{(k-1)} - \sum_{i=1}^{N} k_i \bar{u}_i^{(k-1)} \underline{\upsilon}^{(k-1)} + \alpha \text{in} \Omega, \quad (5.13)$$

$$\frac{\partial \bar{u}_i^{(k)}}{\partial n} = \frac{\partial \underline{\upsilon}^{(k)}}{\partial n} = 0 \text{on} \partial\Omega, i=1, \ldots, N, \quad (5.14)$$

$$-D_i \Delta \underline{u}_i^{(k)} + c \underline{u}_i^{(k)} = c \underline{u}_i^{(k-1)} - \beta_i \underline{u}_i^{(k-1)} - k_i \underline{u}_i^{(k-1)} \text{á£ą}^{(k-1)} + \alpha_i \text{in} \Omega, i=1, \ldots, N, \quad (5.15)$$

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$$-D\Delta \text{á£ą}^{(k)}+c\text{á£ą}^{(k)}=c\text{á£ą}^{(k-1)}-\beta \text{á£ą}^{(k-1)}-\sum_{i=1}^{N}k_i\underline{u}_i^{(k-1)}\text{á£ą}^{(k-1)}+\alpha \text{in}\Omega, \quad (5.16)$$

$$\frac{\partial \underline{u}_i^{(k)}}{\partial n}=\frac{\partial \text{á£ą}^{(k)}}{\partial n}=0\text{on}\partial\Omega, i=1,\dots,N. \quad (5.17)$$

We recall that, for any constants $\hat{D} > 0$ and $\hat{c} > 0$, and any $q \in C^{0,\mu}(\bar{\Omega})$, the standard theory of elliptic boundary-value problems guarantees the existence and uniqueness of solution $w \in C^{2,\mu}(\bar{\Omega})$ to the boundary-value problem [5]

$$-\hat{D}\Delta w+\hat{c}w=q\text{in}\Omega,\ \frac{\partial w}{\partial n}=0\text{on}\partial\Omega.$$

Moreover, there exists a constant $C > 0$, independent of $q$, such that

$$\|w\|_{C^{2,\mu}(\bar{\Omega})} \le C\|q\|_{C^{0,\mu}(\bar{\Omega})}. \quad (5.18)$$

It therefore follows from (5.4) and a simple induction argument that there are unique solutions to the above boundary-values problems (5.12)–(5.17), defining our functions $\bar{u}_i^{(k)}$, $\underline{\upsilon}^{(k)}$, $\underline{u}_i^{(k)}$, $\bar{\upsilon}^{(k)}$, $i = 1, \dots, N$ and $k = 1, 2, \dots$, all in $C^{2,\mu}(\bar{\Omega})$.

Step 3. Comparison. We now prove for any $k \ge 1$ that

$$0 \le \underline{u}_i^{(0)} \le \underline{u}_i^{(k)} \le \underline{u}_i^{(k+1)} \le \bar{u}_i^{(k+1)} \le \bar{u}_i^{(k)} \le \bar{u}_i^{(0)}\text{in}\bar{\Omega}, i=1,\dots,N, \quad (5.19)$$

$$0 \le \underline{\upsilon}^{(0)} \le \underline{\upsilon}^{(k)} \le \underline{\upsilon}^{(k+1)} \le \text{á£ą}^{(k+1)} \le \text{á£ą}^{(k)} \le \text{á£ą}^{(0)}\text{in}\bar{\Omega}. \quad (5.20)$$

It follows from (5.4), (5.5), (5.12) with $k = 1$, (5.11), (5.7), and (5.14) with $k = 1$ that

$$-D_i\Delta\left(\bar{u}_i^{(0)}-\bar{u}_i^{(1)}\right)+c\left(\bar{u}_i^{(0)}-\bar{u}_i^{(1)}\right) \ge 0\text{in}\Omega, i=1,\dots,N,\ \frac{\partial\left(\bar{u}_i^{(0)}-\bar{u}_i^{(1)}\right)}{\partial n}=0\text{on}\partial\Omega, i=1,\dots,N.$$

The Maximum Principle [5] implies then $\bar{u}_i^{(0)} \ge \bar{u}_i^{(1)}$ in $\bar{\Omega}$ ($i = 1, \dots, N$). Similarly, we have $\underline{u}_i^{(0)} \le \underline{u}_i^{(1)}$, $\bar{\upsilon}^{(0)} \ge \bar{\upsilon}^{(1)}$, and $\underline{\upsilon}^{(0)} \le \underline{\upsilon}^{(1)}$ in $\bar{\Omega}$ for all $i = 1, \dots, N$.

By (5.4), $\underline{u}_i^{(0)} \ge 0$ ($i = 1, \dots, N$) and $\underline{\upsilon}^{(0)} \ge 0$. Next, by (5.12) with $k = 1$, (5.15) with $k = 1$, (5.11), and (5.4), we obtain

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$$
\begin{aligned}
&-D_i\Delta\left(\bar{u}_i^{(1)}\right.\\
&\quad-\underline{u}_i^{(1)}+c\left(\bar{u}_i^{(1)}\right.\\
&\quad-\underline{u}_i^{(1)}=c\left(\bar{u}_i^{(0)}\right.\\
&\quad-\underline{u}_i^{(0)}-\beta_i\left(\bar{u}_i^{(0)}\right.\\
&\quad-\underline{u}_i^{(0)}-k_i\left(\bar{u}_i^{(0)}\underline{\upsilon}^{(0)}\right.\\
&\qquad-\underline{u}_i^{(0)}\text{á£ą}^{(0)}\Big)\\
&\quad=(c-\beta_i-k_i\underline{\upsilon}^{(0)})\left(\bar{u}_i^{(0)}\right.\\
&\quad-\underline{u}_i^{(0)}+k_i\underline{u}_i^{(0)}(\text{á£ą}^{(0)}\\
&\qquad-\underline{\upsilon}^{(0)})\geq 0\text{in}\bar{\Omega},i=1,\ldots,N.
\end{aligned}
$$

We also have by (5.14) and (5.17) with $k$ = 1 that $\partial_n(\bar{u}_i^{(1)}-\underline{u}_i^{(1)})=0$ on $\partial\Omega$ ($i$ = 1, …, $N$). The Maximum Principle then implies $\bar{u}_i^{(1)}\geq\underline{u}_i^{(1)}$ in $\overline{\Omega}$ for all $i$ = 1, …, $N$. Similarly, we have $\bar{\upsilon}^{(1)}\geq\underline{\upsilon}^{(1)}$ in $\overline{\Omega}$. We thus have proved

$$0\leq\underline{u}_i^{(0)}\leq\underline{u}_i^{(1)}\leq\bar{u}_i^{(1)}\leq\bar{u}_i^{(0)}\text{in}\bar{\Omega},i=1,\ldots,N,\ 0\leq\underline{\upsilon}^{(0)}\leq\underline{\upsilon}^{(1)}\leq\text{á£ą}^{(1)}\leq\text{á£ą}^{(0)}\text{in}\bar{\Omega}.$$

Assume now $k\geq 2$ and

$$0\leq\underline{u}_i^{(0)}\leq\cdots\leq\underline{u}_i^{(k-1)}\leq\bar{u}_i^{(k-1)}\leq\cdots\leq\bar{u}_i^{(0)}\text{in}\bar{\Omega},i=1,\ldots,N,\quad(5.21)$$

$$0\leq\underline{\upsilon}^{(0)}\leq\cdots\leq\underline{\upsilon}^{(k-1)}\leq\text{á£ą}^{(k-1)}\leq\cdots\leq\text{á£ą}^{(0)}\text{in}\bar{\Omega}.\quad(5.22)$$

We prove

$$\underline{u}_i^{(k-1)}\leq\underline{u}_i^{(k)}\leq\bar{u}_i^{(k)}\leq\bar{u}_i^{(k-1)}\text{in}\bar{\Omega},i=1,\ldots,N,\quad(5.23)$$

$$\underline{\upsilon}^{(k-1)}\leq\underline{\upsilon}^{(k)}\leq\text{á£ą}^{(k)}\leq\text{á£ą}^{(k-1)}\text{in}\bar{\Omega}.\quad(5.24)$$

By (5.12) with $k-1$ replacing $k$, (5.12), (5.21), (5.22), and (5.11), we obtain

$$-D_i\Delta\left(\bar{u}_i^{(k-1)}-\bar{u}_i^{(k)}\right)+c\left(\bar{u}_i^{(k-1)}-\bar{u}_i^{(k)}\right)=(c-\beta_i-k_i\underline{\upsilon}^{(k-2)})\left(\bar{u}_i^{(k-2)}-\bar{u}_i^{(k-1)}\right)+k_i\bar{u}_i^{(k-1)}(\underline{\upsilon}^{(k-1)}-\underline{\upsilon}^{(k-2)})\ge(c-\beta_i-k_i\text{á£ą}^{(0)})\left(\bar{u}_i^{(k-2)}-\bar{u}_i^{(k-1)}\right)\ge 0 \text{ in } \bar{\Omega}, i=1,\dots,N.$$

We also have by the boundary conditions (5.14) that $\partial_n(\bar{u}_i^{(k-1)}-\bar{u}_i^{(k)})=0$ on $\partial\Omega$ ($i$ = 1, …, $N$). The Maximum Principle now implies $\bar{u}_i^{(k-1)}\ge\bar{u}_i^{(k)}$ in $\bar{\Omega}$ for all $i$ = 1, …, $N$. Similarly, we have $\underline{u}_i^{(k-1)}\le\underline{u}_i^{(k)}$ in $\bar{\Omega}$ ($i$ = 1, …, $N$). By (5.16), (5.21), (5.22), and (5.11), we have

$$-D\Delta(\text{á£ą}^{(k-1)}-\text{á£ą}^{(k)})+c(\text{á£ą}^{(k-1)}-\text{á£ą}^{(k)})=\left(c-\beta-\sum_{i=1}^{N}k_i\underline{u}_i^{(k-2)}\right)(\text{á£ą}^{(k-2)}-\text{á£ą}^{(k-1)})+\sum_{i=1}^{N}k_i\text{á£ą}^{(k-1)}\left(\underline{u}_i^{(k-1)}-\underline{u}_i^{(k-2)}\right)\ge\left(c-\beta-\sum_{i=1}^{N}k_i\bar{u}_i^{(0)}\right)(\text{á£ą}^{(k-2)}-\text{á£ą}^{(k-1)})\ge 0 \text{ in } \bar{\Omega}.$$

Since $\partial_n\bar{\upsilon}^{(k-1)}=\partial_n\bar{\upsilon}^{(k)}$ on $\partial\Omega$, we thus have $\bar{\upsilon}^{(k-1)}\ge\bar{\upsilon}^{(k)}$ in $\bar{\Omega}$. Similarly, $\underline{\upsilon}^{(k-1)}\le\underline{\upsilon}^{(k)}$ in $\bar{\Omega}$.

By (5.12), (5.15), (5.21), (5.22), and (5.11), we have

$$-D_i\Delta\left(\bar{u}_i^{(k)}-\underline{u}_i^{(k)}\right)+c\left(\bar{u}_i^{(k)}-\underline{u}_i^{(k)}\right)=(c-\beta_i-k_i\underline{\upsilon}^{(k-1)})\left(\bar{u}_i^{(k-1)}-\underline{u}_i^{(k-1)}\right)+k_i\underline{u}_i^{(k-1)}(\text{á£ą}^{(k-1)}-\underline{\upsilon}^{(k-1)})\ge(c-\beta_i-\text{á£ą}^{(0)})\left(\bar{u}_i^{(k-1)}-\underline{u}_i^{(k-1)}\right)\ge 0 \text{ in } \bar{\Omega}, i=1,\dots,N.$$

These and the corresponding boundary conditions for $\bar{u}_i^{(k)}$ and $\underline{u}_i^{(k)}$ lead to $\underline{u}_i^{(k)}\le\bar{u}_i^{(k)}$ in $\bar{\Omega}$ for all $i$ = 1, …, $N$. By (5.13), (5.16), (5.21), (5.22), and (5.11), we have

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$$
\begin{aligned}
&- D\Delta(\text{á£ą}^{(k)} \\
&\quad - \underline{\upsilon}^{(k)})+c(\text{á£ą}^{(k)} \\
&\quad -\underline{\upsilon}^{(k)})=\left(c-\beta-\sum_{i=1}^{N}k_i\underline{u}_i^{(k-1)}\right)(\text{á£ą}^{(k-1)}-\underline{\upsilon}^{(k-1)})+\sum_{i=1}^{N}k_i\underline{\upsilon}^{(k-1)}\left(\bar{u}_i^{(k-1)}\right. \\
&\quad \left.-\underline{u}_i^{(k-1)}\right)\geq (c \\
&\quad -\beta-\sum_{i=1}^{N}k_i\bar{u}_i^{(0)}(\text{á£ą}^{(k-1)} \\
&\quad\quad -\underline{\upsilon}^{(k-1)})\geq 0 \text{in} \bar{\Omega}.
\end{aligned}
$$

This together with the fact that $\partial_n\bar{\upsilon}^{(k-1)} = \partial_n\underline{\upsilon}^{(k-1)}$ imply $\underline{\upsilon}^{(k)} \leq \bar{\upsilon}^{(k)}$ in $\bar{\Omega}$. We have proved (5.23) and (5.24). By induction, we have proved (5.19) and (5.20).

Step 4. Regularity and boundedness. From the above iteration (5.5)–(5.10), we obtain by (5.19) and (5.20) uniformly bounded sequences of nonnegative $C^{2,\mu}(\bar{\Omega})$-functions $\{\bar{u}_i^{(k)}\}$, $\{\underline{u}_i^{(k)}\}$, $\{\bar{\upsilon}^{(k)}\}$, and $\{\underline{\upsilon}^{(k)}\}$. By standard Hölder estimates for elliptic problems, we conclude that all the sequences $\{\|\bar{u}_i^{(k)}\|_{C^{2,\mu}(\bar{\Omega})}\}$ $(1 \leq i \leq N)$, $\{\|\underline{u}_i^{(k)}\|_{C^{2,\mu}(\bar{\Omega})}\}$ $(1 \leq i \leq N)$, $\{\|\bar{\upsilon}^{(k)}\|_{C^{2,\mu}(\bar{\Omega})}\}$, and $\{\|\underline{\upsilon}^{(k)}\|_{C^{2,\mu}(\bar{\Omega})}\}$ are bounded.

Step 5. Convergence to solution. From Step 4, the sequences $\{\bar{u}_i^{(k)}\}$ and $\{\underline{u}_i^{(k)}\}$ $(1 \leq i \leq N)$, $\{\bar{\upsilon}^{(k)}\}$, and $\{\underline{\upsilon}^{(k)}\}$ are bounded in $C^2(\bar{\Omega})$ and pointwise monotonic on $\bar{\Omega}$. Therefore, they converge pointwise to some functions $\bar{u}_i$ and $\underline{u}_i$ $(1 \leq i \leq N)$, $\bar{\upsilon}$, and $\underline{\upsilon}$ on $\bar{\Omega}$, respectively. By the Arzela–Ascoli Theorem, there exist $C^2(\bar{\Omega})$-convergent subsequences $\{\bar{u}_i^{(k_j)}\}_{j=1}^{\infty}$ and $\{\underline{u}_i^{(k_j)}\}_{j=1}^{\infty}$ $(1 \leq i \leq N)$, $\{\text{á£ą}^{(k_j)}\}_{j=1}^{\infty}$, and $\{\underline{\upsilon}^{(k_j)}\}_{j=1}^{\infty}$, of $\{\bar{u}_i^{(k)}\}$ and $\{\underline{u}_i^{(k)}\}$ $(1 \leq i \leq N)$, $\{\underline{\upsilon}^{(k)}\}$, and $\{\bar{\upsilon}^{(k)}\}$, respectively. Clearly, these subsequences converge in $C^2(\bar{\Omega})$ to $\bar{u}_i$ $(1 \leq i \leq N)$, $\underline{u}_i$ $(1 \leq i \leq N)$, $\bar{\upsilon}$, and $\underline{\upsilon}$, respectively. Note that each of the subsequences $\{\bar{u}_i^{(k_j-1)}\}$ and $\{\underline{u}_i^{(k_j-1)}\}$ $(1 \leq i \leq N)$, $\{\bar{\upsilon}^{(k_j-1)}\}$, and $\{\underline{\upsilon}^{(k_j-1)}\}$ also converges pointwise to its respective limit. Now replace $k$ in (5.12)–(5.17) by $k_j$ and sending $j \to \infty$, we conclude that $(\bar{u}_1, \cdots, \bar{u}_N, \underline{\upsilon})$ and $(\underline{u}_1, \cdots, \underline{u}_N, \bar{\upsilon})$ are $C^2(\bar{\Omega})$-solutions of the system (5.1)–(5.3).

(2) This part can be proved similarly. The sequences of functions $\{\bar{u}_i^{(k)}\}$ and $\{\underline{u}_i^{(k)}\}$ $(1 \leq i \leq N)$, $\{\bar{\upsilon}^{(k)}\}$, and $\{\underline{\upsilon}^{(k)}\}$ can be defined as weak solutions of the corresponding boundary-value problems. Moreover, By using the estimate $\|w\|_{H^2(\Omega)} \leq C\|q\|_{L^2(\Omega)}$, replacing (5.18), we have that all the sequences are bounded in $H^2(\Omega)$. The monotonicity and pointwise boundedness imply that these sequences converge, respectively, to some functions $\bar{u}_i$ and $\underline{u}_i$ $(1 \leq i \leq N)$, $\bar{\upsilon}$, and $\underline{\upsilon}$ on $\bar{\Omega}$, all being nonnegative. Instead of using the Arzela–Ascoli Theorem, we use the fact that $H^2(\Omega)$ is a Hilbert space and use also Sobolev compact embedding theorem to extract the subsequences $\{\bar{u}_i^{(k_j)}\}_{j=1}^{\infty}$ and $\{\underline{u}_i^{(k_j)}\}_{j=1}^{\infty}$ $(1 \leq i \leq N)$, $\{\text{á£ą}^{(k_j)}\}_{j=1}^{\infty}$, and $\{\underline{\upsilon}^{(k_j)}\}_{j=1}^{\infty}$ that converge weakly in $H^2(\Omega)$ and strongly in $H^1(\Omega)$ to the pointwise limiting functions $\bar{u}_i$

and $\underline{u}_i$ ($1 \le i \le N$), $\bar{\upsilon}$, and $\underline{\upsilon}$, respectively. Finally, we use the weak forms of the equations to pass to the limit. For instance, we have for any $\varphi \in H^1(\Omega)$ and all $j = 1, 2, \ldots$ that

$$\int_\Omega \left[D_i \nabla \bar{u}_i^{(k_j)} \cdot \nabla\phi + c\bar{u}_i^{(k_j)}\phi\right] dx = \int_\Omega \left[c\bar{u}_i^{(k_j-1)} - \beta_i \bar{u}_i^{(k_j-1)} - k_i \bar{u}_i^{(k_j-1)} \underline{\upsilon}^{(k_j-1)} + \alpha_i\right] \phi dx, i=1,\ldots,N.$$

Sending $j \to \infty$, we have by the $H^1(\Omega)$-convergence of $\{\bar{u}_i^{(k_j)}\}_{j=1}^{\infty}$ and the pointwise convergence of $\{\bar{u}_i^{(k)}\}_{k=1}^{\infty}$ and $\{\underline{\upsilon}^{(k)}\}_{k=1}^{\infty}$ that

$$\int_\Omega [D_i \nabla \bar{u}_i \cdot \nabla\phi + c\bar{u}_i \phi] dx = \int_\Omega [c\bar{u}_i - \beta_i \bar{u}_i - k_i \bar{u}_i \underline{\upsilon} + \alpha_i]\phi dx, i=1,\ldots,N.$$

Therefore, $(\bar{u}_1, \ldots, \bar{u}_N, \underline{\upsilon})$ and $(\underline{u}_1, \cdots, \underline{u}_N, \bar{\upsilon})$ are the weak (and nonnegative) solutions in $H^2(\Omega)$ of the system (5.1)–(5.3).

## 6 Reaction-Diffusion System: Existence and Uniqueness of Global Solution to Time-Dependent Problem

Our goal in this section is to prove the existence and uniqueness of global solution for the reaction-diffusion system (1.1)–(1.4). We shall first prove the existence and uniqueness of local solution to this system. Our proof of the existence of a lcoal solution is similar to that of Theorem 5.1 on the existence of steady-state solution but involves the representation formula and regularity of solutions to linear parabolic equations. The uniqueness of a local solution is obtained by the Maximum Principle for systems of linear parabolic equations.

For any set $\Omega \subseteq \mathbb{R}^3$ and any $T > 0$, we denote $\Omega_T = \Omega \times (0, T]$. If $\Omega \subseteq \mathbb{R}^3$ is open, we also denote by $C_1^2(\Omega_T)$ the class of functions $u : \Omega_T \to \mathbb{R}$ of $(x, t)$ that are continuously differentiable in $t$ and twice continuously differentiable in $x = (x_1, x_2, x_3)$ on $\Omega$.

### Theorem 6.1

(Existence and uniqueness of local solution). *Let $\Omega$ be a bounded domain in $\mathbb{R}^3$ with a $C^2$-boundary $\partial\Omega$. Let $D_i$, $\beta_i$, and $k_i$ ($i = 1, \ldots, N$), $D$ and $\beta$, and $T$ be all positive numbers. Let $\alpha_i \in C^1(\overline{\Omega_T})$ ($i = 1, \ldots, N$) and $\alpha \in C^1(\overline{\Omega_T})$ be all nonnegative functions on $\overline{\Omega_T}$. Assume $u_{i0} \in C^1(\overline{\Omega})$ ($i = 1, \ldots, N$) and $\upsilon_0 \in C^1(\overline{\Omega})$ are all nonnegative functions on $\overline{\Omega}$. Then there exist unique $u_i \in C(\overline{\Omega_T}) \cap C_1^2(\Omega_T)$ ($i = 1, \ldots, N$) and $\upsilon \in C(\overline{\Omega_T}) \cap C_1^2(\Omega_T)$ such that all $u_i \ge 0$ ($i = 1, \ldots, N$) and $\upsilon \ge 0$ in $\overline{\Omega_T}$ and*

$$\frac{\partial u_i}{\partial t} = D_i \Delta u_i - \beta_i u_i - k_i u_i \upsilon + \alpha_i \; in \; \Omega_T, \; i=1,\ldots,N, \quad (6.1)$$

$$\frac{\partial \upsilon}{\partial t} = D\Delta\upsilon - \beta\upsilon - \sum_{i=1}^{N} k_i u_i \upsilon + \alpha \; in \; \Omega_T, \quad (6.2)$$

$$\frac{\partial u_i}{\partial n}=\frac{\partial \upsilon}{\partial n}=0 on \partial\Omega \times (0, T], i=1, \dots, N, \quad (6.3)$$

$$u_i(\cdot, 0)=u_{i0} and \upsilon(\cdot, 0)=\upsilon_0 in \bar{\Omega}, i=1, \dots, N. \quad (6.4)$$

**Proof—**We first prove the existence of solution in four steps.

Step 1. Construction of upper solutions and lower solutions. We choose the constant functions $\bar{u}_i^{(0)}$, $\bar{\upsilon}^{(0)}$, $\underline{u}_i^{(0)}$, and $\underline{\upsilon}^{(0)}$ ($i$ = 1, …, $N$) on $\overline{\Omega_T}$ by

$$\bar{u}_i^{(0)} \geq \frac{\|\alpha_i\|_{L^\infty(\Omega_T)}}{\beta_i}+\|u_{i0}\|_{L^\infty(\Omega)}, \text{á£ą}^{(0)} \geq \frac{\|\alpha\|_{L^\infty(\Omega_T)}}{\beta}+\|\upsilon_0\|_{L^\infty(\Omega)}, \underline{u}_i^{(0)}=0, \underline{\upsilon}^{(0)}=0.$$

It is clear that

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$$
\begin{aligned}
&\frac{\partial \bar{u}_i^{(0)}}{\partial t} - D_i \Delta \bar{u}_i^{(0)} \\
&+\beta_i \bar{u}_i^{(0)} + k_i \bar{u}_i^{(0)} \underline{\upsilon}^{(0)} \\
&- \alpha_i \geq 0 \text{in} \Omega_T, i \\
&=1, \dots, N, \frac{\partial \underline{\upsilon}^{(0)}}{\partial t} \\
&- D \Delta \underline{\upsilon}^{(0)} \\
&+\beta \underline{\upsilon}^{(0)} + \sum_{i=1}^{N} k_i \bar{u}_i^{(0)} \underline{\upsilon}^{(0)} \\
&- \alpha \leq 0 \text{in} \Omega_T, \frac{\partial \bar{u}_i^{(0)}}{\partial n} \\
&=0 \text{and} \frac{\partial \underline{\upsilon}^{(0)}}{\partial n} \\
&=0 \text{on} \partial \Omega \\
&\quad \times (0, T], i \\
&=1, \dots, N, \bar{u}_i^{(0)}( \\
&\quad \cdot, 0) \geq u_{i0} \text{and} \underline{\upsilon}^{(0)}(\cdot, 0) \leq \upsilon_0 \text{in} \bar{\Omega}, i \\
&=1, \dots, N, \frac{\partial \underline{u}_i^{(0)}}{\partial t} \\
&- D_i \Delta \underline{u}_i^{(0)} \\
&+\beta_i \underline{u}_i^{(0)} + k_i \underline{u}_i^{(0)} \text{á£ą}^{(0)} \\
&- \alpha_i \leq 0 \text{in} \Omega_T, i \\
&=1, \dots, N, \frac{\partial \text{á£ą}^{(0)}}{\partial t} \\
&- D \Delta \text{á£ą}^{(0)} \\
&+\beta \text{á£ą}^{(0)} + \sum_{i=1}^{N} k_i \underline{u}_i^{(0)} \text{á£ą}^{(0)} \\
&- \alpha \geq 0 \text{in} \Omega_T, \frac{\partial \underline{u}_i^{(0)}}{\partial n} \\
&=0 \text{and} \frac{\partial \text{á£ą}^{(0)}}{\partial n} \\
&=0 \text{on} \partial \Omega \\
&\quad \times (0, T], \underline{u}_i^{(0)}( \\
&\cdot, 0) \leq u_{i0} \text{and} \text{á£ą}^{(0)}( \\
&\quad \cdot, 0) \geq \upsilon_0 \text{in} \bar{\Omega}, i=1, \dots, N.
\end{aligned}
$$

Step 2. Iteration. Let

$$c=\max\left\{\beta+\sum_{i=1}^{N}k_i\bar{u}_i^{(0)},\beta_1+k_1\text{á£ą}^{(0)},\ldots,\beta_{_N}+k_{_N}\text{á£ą}^{(0)}\right\}. \quad (6.5)$$

Define iteratively the functions $\bar{u}_i^{(k)}$, $\underline{\upsilon}^{(k)}$, $\underline{u}_i^{(k)}$, and $\bar{\upsilon}^{(k)}$ ($i$ = 1, …, $N$) on $\Omega_T$ for $k$ = 1, 2, … by

$$\frac{\partial\bar{u}_i^{(k)}}{\partial t}-D_i\Delta\bar{u}_i^{(k)}+c\bar{u}_i^{(k)}=c\bar{u}_i^{(k-1)}-\beta_i\bar{u}_i^{(k-1)}-k_i\bar{u}_i^{(k-1)}\underline{\upsilon}^{(k-1)}+\alpha_i\text{in}\Omega_{_T},i=1,\ldots,N, \quad (6.6)$$

$$\frac{\partial\underline{\upsilon}^{(k)}}{\partial t}-D\Delta\underline{\upsilon}^{(k)}+c\underline{\upsilon}^{(k)}=c\underline{\upsilon}^{(k-1)}-\beta\underline{\upsilon}^{(k-1)}-\sum_{i=1}^{N}k_i\bar{u}_i^{(k-1)}\underline{\upsilon}^{(k-1)}+\alpha\text{in}\Omega_{_T}, \quad (6.7)$$

$$\frac{\partial\bar{u}_i^{(k)}}{\partial n}=\frac{\partial\underline{\upsilon}^{(k)}}{\partial n}=0\text{on}\partial\Omega\times(0,T],i=1,\ldots,N, \quad (6.8)$$

$$\bar{u}_i^{(k)}(\cdot,0)=u_{i,0}\text{and}\underline{\upsilon}^{(k)}(\cdot,0)=\upsilon_0\text{in}\bar{\Omega},i=1,\ldots,N, \quad (6.9)$$

$$\frac{\partial\underline{u}_i^{(k)}}{\partial t}-D_i\Delta\underline{u}_i^{(k)}+c\underline{u}_i^{(k)}=c\underline{u}_i^{(k-1)}-\beta_i\underline{u}_i^{(k-1}-k_i\underline{u}_i^{(k-1)}\text{á£ą}^{(k-1)}+\alpha_i\text{in}\Omega_{_T},i=1,\ldots,N, \quad (6.10)$$

$$\frac{\partial\text{á£ą}^{(k)}}{\partial t}-D\Delta\text{á£ą}^{(k)}+c\text{á£ą}^{(k)}=c\text{á£ą}^{(k-1)}-\beta\text{á£ą}^{(k-1)}-\sum_{i=1}^{N}k_i\underline{u}_i^{(k-1)}\text{á£ą}^{(k-1)}+\alpha\text{in}\Omega_{_T}, \quad (6.11)$$

$$\frac{\partial\underline{u}_i^{(k)}}{\partial n}=\frac{\partial\text{á£ą}^{(k)}}{\partial n}=0\text{on}\partial\Omega\times(0,T],i=1,\ldots,N, \quad (6.12)$$

$$\underline{u}_i^{(k)}(\cdot,0)=u_{i0}\text{andá£ą}^{(k)}(\cdot,0)=\upsilon_0\text{in}\bar{\Omega}. \quad (6.13)$$

The theory for initial-boundary-value problems of linear parabolic equations (cf. Theorem 2 in Chapter 5 of [3], or Theorem 1.2 in Chapter 2 of [18]) guarantees the existence of solutions $\bar{u}_i^{(1)}$, $\underline{\upsilon}^{(1)}$, $\underline{u}_i^{(1)}$, and $\bar{\upsilon}^{(1)}$ ($i$ = 1, …, $N$) for $k$ = 1 that are all in $C(\bar{\Omega})\cap C_1^2(\Omega_{_T})$ and are all Hölder continuous in $x$ uniformly in $\overline{\Omega_{_T}}$. Suppose $\bar{u}_i^{(k)}$, $\underline{\upsilon}^{(k)}$, $\underline{u}_i^{(k)}$, and $\bar{\upsilon}^{(k)}$ ($i$ = 1, …, $N$) for $k \geq 1$ exist, and are all in $C(\bar{\Omega})\cap C_1^2(\Omega_{_T})$ and Hölder continuous in $x$ uniformly in $\overline{\Omega_{_T}}$. Then the theory for initial-boundary-value problems of linear parabolic equations then implies that the solutions $\bar{u}_i^{(k+1)}$, $\underline{\upsilon}^{(k+1)}$, $\underline{u}_i^{(k+1)}$, and $\bar{\upsilon}^{(k+1)}$ ($i$ = 1, …, $N$) all exist, are in $C(\bar{\Omega})\cap C_1^2(\Omega_{_T})$, and are Hölder continuous in $x$ uniformly in $\overline{\Omega_{_T}}$. By induction, we have for all $k = 1, 2, \ldots$ the existence of the solutions $\bar{u}_i^{(k)}$, $\underline{v}^{(k)}$, $\underline{u}_i^{(k)}$, and $\bar{v}^{(k)}$ ($i = 1, \ldots, N$) in $C(\bar{\Omega}) \cap C_1^2(\Omega_T)$ that are Hölder continuous in $x$ uniformly in $\overline{\Omega_T}$.

In fact, there is a representation formula for our solutions. Suppose $q \in C(\overline{\Omega_T})$ is Hölder continuous in $x$ uniformly on $\overline{\Omega_T}$ and suppose $g \in C^1(\bar{\Omega})$. Let $u \in C(\overline{\Omega_T}) \cap C_1^2(\Omega_T)$ satisfy

$$\frac{\partial u}{\partial t} - D\Delta u + cu = q \text{ in } \Omega_T, \quad (6.14)$$

$$u(\cdot, 0) = g(\cdot) \text{ in } \bar{\Omega}, \quad (6.15)$$

$$\frac{\partial u}{\partial n} = 0 \text{ on } \partial\Omega \times (0, T]. \quad (6.16)$$

Then we can extend $g$ to a $C^1$-function on a neighborhood of $\bar{\Omega}$ as the boundary $\partial\Omega$ is of the class $C^2$. Hence we have the following representation of the solution to the initial-boundary-value problem (6.14)–(6.16) (cf. Section 3 of Chapter 5 of [3] and Theorem 8.3.2 of [18]):

$$u(x,t) = \int_\Omega \Gamma(x,t;\xi,0) g(\xi) d\xi + \int_0^t \int_\Omega \Gamma(x,t;\xi,\tau) q(\xi,\tau) d\xi d\tau + \int_0^t \int_{\partial\Omega} \Gamma(x,t;\xi,\tau) \Psi(\xi,\tau) dS_\xi d\tau \quad \forall (x,t) \in \Omega \times (0,T], \quad (6.17)$$

where

$$\Gamma(x,t;\xi,\tau) = [4\pi D(t-\tau)]^{-3/2} e^{-c(t-\tau) - |x-\xi|^2/4D(t-\tau)}, \quad (6.18)$$

$$\Psi(x,t) = 2F(x,t) + 2\sum_{j=1}^{\infty} \int_0^t \int_{\partial\Omega} M_j(x,t;\xi,\tau) F(\xi,\tau) dS_\xi d\tau, \quad (6.19)$$

$$F(x,t) = \int_\Omega \frac{\partial \Gamma(x,t;\xi,0)}{\partial n(x,t)} g(\xi) d\xi + \int_0^t \int_\Omega \frac{\partial \Gamma(x,t;\xi,\tau)}{\partial n(x,t)} q(\xi,\tau) d\xi d\tau,$$

$$M_1(x,t;\xi,\tau) = 2\frac{\partial \Gamma(x,t;\xi,\tau)}{\partial n(x,t)},$$

$$M_{j+1}(x,t;\xi,\tau) = \int_0^t \int_{\partial\Omega} M_1(x,t;y,\sigma) M_j(y,\sigma;\xi,\tau) dS_y d\sigma.$$

Here the infinite series converges and the function $F(x, t)$ is bounded.

Step 3. Comparison. Notice by (6.5) that

$$c-\beta-\sum_{i=1}^{N}k_i\bar{u}_i^{(0)}\geq 0\text{and}c-\beta_i-k_i\text{á£ą}^{(0)}\geq 0\text{in}\Omega_T.$$

By the Maximum Principle for parabolic equations [2, 3, 9, 18] and using arguments similar to those for the steady-state solutions (cf. Step 3 in the proof of Theorem 5.1 in Section 5), we then have from the iteration (6.6)–(6.13) in Step 2 that

$$0=\underline{u}_i^{(0)}\leq\underline{u}_i^{(k)}\leq\underline{u}_i^{(k+1)}\leq\bar{u}_i^{(k+1)}\leq\bar{u}_i^{(k)}\leq\bar{u}_i^{(0)}\text{in}\overline{\Omega_T},\quad(6.20)$$

$$0=\underline{\upsilon}^{(0)}\leq\underline{\upsilon}^{(k)}\leq\underline{\upsilon}^{(k+1)}\leq\text{á£ą}^{(k+1)}\leq\text{á£ą}^{(k)}\leq\text{á£ą}^{(0)}\text{in}\overline{\Omega_T}.\quad(6.21)$$

Step 4. Convergence to solution. By the monotonicity (6.20) and (6.21), we have the pointwise limits

$$\bar{u}_i=\lim_{k\to\infty}\bar{u}_i^{(k)},\text{á£ą}=\lim_{k\to\infty}\text{á£ą}^{(k)},\underline{u}_i=\lim_{k\to\infty}\underline{u}_i^{(k)},\underline{\upsilon}=\lim_{k\to\infty}\underline{\upsilon}^{(k)}\text{in}\overline{\Omega_T},i=1,\ldots,N.$$

These limits are nonnegative bounded measurable functions. In particular,

$$\bar{u}_i(x,0)=\underline{u}_i(x,0)=u_{i0}(x)(i=1,\ldots,N)\text{and}\text{á£ą}(x,0)=\underline{\upsilon}(x,0)=\upsilon_0(x)\forall x\in\bar{\Omega}.$$

Let us now fix *i* ($1 \leq i \leq N$) and set for each integer $k \geq 1$

$$q_i^{(k)}=c\bar{u}_i^{(k-1)}-\beta_i\bar{u}_i^{(k-1)}-k_i\bar{u}_i^{(k-1)}\underline{\upsilon}^{(k-1)}+\alpha_i\text{in}\Omega_T,\ q_i=c\bar{u}_i-\beta_i\bar{u}_i-k_i\bar{u}_i\underline{\upsilon}+\alpha_i\text{in}\Omega_T.\quad(6.22)$$

Note that each $q^{(k)}\in C(\overline{\Omega_T})$ is Hölder continuous in *x* uniformly in $\overline{\Omega_T}$. Moreover,

$$\lim_{k\to\infty}q_i^{(k)}=q_i\text{in}\Omega_T.\quad(6.23)$$

It follows from (6.6), (6.8), and (6.9) that

$$\frac{\partial\bar{u}_i^{(k)}}{\partial t}-D_i\Delta\bar{u}_i^{(k)}+c\bar{u}_i^{(k)}=q_i^{(k)}\text{in}\Omega_T,\quad(6.24)$$

$$\bar{u}_i^{(k)}(\cdot,0)=u_{i0}(\cdot)\text{in}\bar{\Omega},\quad(6.25)$$

$$\frac{\partial\bar{u}_i^{(k)}}{\partial n}=0\text{on}\partial\Omega\times(0,T].\quad(6.26)$$

Therefore, by the representation (6.17) and (6.19) for the solution to (6.14)–(6.16) that are now replaced by (6.24)–(6.26), we have

$$\begin{aligned}&\bar{u}_i^{(k)}(x,t)\\&=\int_\Omega\Gamma(x,t;\xi,0)u_{i0}(\xi)d\xi\\&+\int_0^t\int_\Omega\Gamma(x,t;\xi,\tau)q_i^{(k)}(\xi,\tau)d\xi d\tau\\&+\int_0^t\int_{\partial\Omega}\Gamma(x,t;\xi,\tau)\Psi_i^{(k)}(\xi,\tau)dS_\xi d\tau\forall(x,t)\in\Omega\times(0,T],\end{aligned}$$

$$\Psi_i^{(k)}(x,t)=2F_i^{(k)}(x,t)+2\sum_{j=1}^{\infty}\int_0^t\int_{\partial\Omega}M_j(x,t;\xi,\tau)F_i^{(k)}(\xi,\tau)dS_\xi d\tau,$$

$$F_i^{(k)}(x,t)=\int_\Omega\frac{\partial\Gamma(x,t;\xi,0)}{\partial n(x,t)}u_{i0}(\xi)d\xi+\int_0^t\int_\Omega\frac{\partial\Gamma(x,t;\xi,\tau)}{\partial n(x,t)}q_i^{(k)}(\xi,\tau)d\xi d\tau,$$

where $\Gamma$ is given in (6.18) with $D$ replaced by $D_i$.

Since the sequence $\{q_i^{(k)}\}_{k=1}^{\infty}$ is uniformly bounded in $\overline{\Omega_T}$ and converges (cf. (6.23)), the sequence $\{F_i^{(k)}\}_{k=1}^{\infty}$ is uniformly bounded in $\partial\Omega \times (0, T]$ and converges. Further, the series in the expression of $\Psi_i^{(k)}$ converges absolutely. Therefore, the sequence $\{\Psi_i^{(k)}\}_{k=1}^{\infty}$ is also uniformly bounded on $\partial\Omega \times (0, T]$ and converges. Let the limit be $\Psi_i = \Psi_i(x, t)$. Taking the limit as $k\to\infty$ and using the Lebesgue Dominated Convergence Theorem, we obtain by (6.23) that

$$\begin{aligned}\bar{u}_i(x,t)=&\int_\Omega\Gamma(x,t;\xi,0)u_{i0}(\xi)d\xi\\&+\int_0^t\int_\Omega\Gamma(x,t;\xi,\tau)q_i(\xi,\tau)d\xi d\tau\\&+\int_0^t\int_{\partial\Omega}\Gamma(x,t;\xi,\tau)\Psi_i(\xi,\tau)dS_\xi d\tau,\forall(x,t)\in\Omega\times(0,T],\end{aligned}\tag{6.27}$$

$$\Psi_i(x,t)=2F_i(x,t)+2\sum_{j=1}^{\infty}\int_0^t\int_{\partial\Omega}M_j(x,t;\xi,\tau)F_i(\xi,\tau)dS_\xi d\tau,\tag{6.28}$$

$$F_i(x,t)=\int_\Omega\frac{\partial\Gamma(x,t;\xi,0)}{\partial n(x,t)}u_{i0}(\xi)d\xi+\int_0^t\int_\Omega\frac{\partial\Gamma(x,t;\xi,\tau)}{\partial n(x,t)}q_i(\xi,\tau)d\xi d\tau,$$

where $\Gamma$ is given in (6.18) with $D$ replaced by $D_i$.

Since $u_{i0} \in C^1(\overline{\Omega})$, the first term in (6.27) is a function of $(x. t)$ in $C^2(\Omega_T)$. Since $q_i$ is bounded, the second term in (6.27) is also a continuous function of $(x, t)$ on $\overline{\Omega_T}$. By (6.28), the function $\Psi_i(x, t)$ is continuous on $\partial\Omega \times [0, T]$. Thus the third term in (6.27) and hence $\bar{u}_i = \bar{u}_i(x, t)$ is a continuous function in $\overline{\Omega_T}$. Similarly, $\underline{\upsilon} = \underline{\upsilon}(x, t)$ is a continuous function in $\overline{\Omega_T}$. Therefore, $q_i = q_i(x, t)$ as defined in (6.22) is continuous in $\overline{\Omega_T}$. Repeat the same argument using (6.27) and (6.28), we have that $\bar{u}_i$ is in fact Hölder continuous in $x$ uniformly in $\overline{\Omega_T}$. Similarly, $\underline{\upsilon}$ is Hölder continuous in $x$ uniformly in $\overline{\Omega_T}$. Finally, $q_i$ is Hölder continuous in $x$ uniformly in $\overline{\Omega_T}$. Therefore, we have the interior regularity of all $\bar{u}_i$ ($i = 1, \ldots, N$) and $\underline{\upsilon}$; cf. [3] (Theorem 2 in Section 5.3). Now (6.22), (6.27), and (6.28) imply that $\bar{u}_i$, and $\underline{\upsilon}$, solve (6.1) with $u$ and $\upsilon$ replaced by $\bar{u}_i$ and $\underline{\upsilon}$, respectively. The existence of solutions to other equations can be obtained similarly.

We now prove the uniqueness in three steps.

Step 1. We prove that solutions $(\bar{u}_1, \ldots, \bar{u}_N, \underline{\upsilon})$ and $(\underline{u}_1, \ldots, \underline{u}_N, \bar{\upsilon})$ obtained above satisfy $\underline{u}_i = \bar{u}_i$ ($i = 1, \ldots, N$) and $\underline{\upsilon} = \bar{\upsilon}$ in $\overline{\Omega_T}$.

In fact, setting $w_i = \bar{u}_i - \underline{u}_i$ ($i = 1, \ldots, N$) and $w = \bar{\upsilon} - \underline{\upsilon}$, we have

$$\frac{\partial w_i}{\partial t}=D_i\Delta w_i-\beta_i w_i-k_i\underline{\upsilon}w_i+k_i\underline{u}_i w \text{in} \Omega_T, i=1,\ldots,N,$$

$$\frac{\partial w}{\partial t}=D\Delta w-\beta w-\sum_{i=1}^{N}k_i\underline{u}_i w+\sum_{i=1}^{N}k_i w_i\underline{\upsilon} \text{in} \Omega_T,$$

$$\frac{\partial w_i}{\partial n}=\frac{\partial w}{\partial n}=0 \text{on} \partial\Omega\times(0,T], i=1,\ldots,N,$$

$$w_i(\cdot,0)=0 \text{and} w(\cdot,0)=0 \text{in} \bar{\Omega}, i=1,\ldots,N.$$

The uniqueness of solution to linear systems of parabolic equations then lead to $w_i = 0$ ($i = 1, \ldots, N$) and $w = 0$.

Step 2. We prove the following: If $(u_1^*,\ldots,u_N^*,\upsilon^*)$ is any other solution to (6.1)–(6.4) such that $\underline{u}_i^{(0)} \le u_i^* \le \bar{u}_i^{(0)}$ ($i = 1, \ldots, N$) and $\underline{\upsilon}^{(0)} \le \upsilon^* \le \bar{\upsilon}^{(0)}$ in $\overline{\Omega_T}$, then $\underline{u}_i=u_i^*=\bar{u}_i$ ($i = 1, \ldots, N$) and $\underline{\upsilon} = \upsilon^* = \bar{\upsilon}$ in $\overline{\Omega_T}$.

In fact, let us replace $(\bar{u}_1^{(0)},\ldots,\bar{u}_N^{(0)},\underline{\upsilon}^{(0)})$ by $(u_1^*,\ldots,u_N^*,\upsilon^*)$ and keep $(\underline{u}_1^{(0)},\ldots,\underline{u}_N^{(0)},$ á£ą$^{(0)})$ unchanged in the iteration in Step 2. Then, $(\bar{u}_1^{(k)},\ldots,\bar{u}_N^{(k)},\underline{\upsilon}^{(k)})=(u_1^*,\ldots,u_N^*,\upsilon^*)$ ($k = 0, 1, \ldots$), and the sequence $(\underline{u}_1^{(k)},\ldots,\underline{u}_N^{(k)},$ á£ą$^{(k)})$ ($k = 0, 1, \ldots$) remains unchanged and it converges to the solution $(\underline{u}_1, \ldots, \underline{u}_N, \bar{\upsilon})$. Therefore, by the iteration we get $\underline{u}_i \le u_i^*$ ($i = 1, \ldots, N$) and $\upsilon^* \le \bar{\upsilon}$ in $\overline{\Omega_T}$. A similar argument leads to $u_i^* \le \bar{u}_i$ ($i = 1, \ldots, N$) and $\underline{\upsilon} \le \upsilon^*$ in $\overline{\Omega_T}$. These, together with the result proved in Step 1, imply $\underline{u}_i=u_i^*=\bar{u}_i$ ($i = 1, \ldots, N$) and $\underline{\upsilon} = \upsilon^* = \bar{\upsilon}$ in $\overline{\Omega_T}$.

Step 3. If we have two nonnegative solutions defined on $\overline{\Omega_T}$, then we can choose all $\bar{u}_i^{(0)}$ ($i = 1, \ldots, N$) and $\bar{\upsilon}^{(0)}$ (in the iteration in Step 2 of proving existence) large enough to bound from above these solutions in $\overline{\Omega_T}$. Then, both of these solutions must be the same as those constructed by iterative upper and lower solutions. The uniqueness is therefore proved.

### Theorem 6.2

(Existence and uniqueness of global solution). *Let* $\Omega$ *be a bounded domain in* $\mathbb{R}^3$ *with a* $C^2$*-boundary* $\partial\Omega$. *Let* $D_i$ ($i = 1, \ldots, N$), $D$, $\beta_i$ ($i = 1, \ldots, N$), $\beta$, *and* $k_i$ ($i = 1, \ldots, N$) *be all positive numbers*. *Let* $\alpha_i \in C^1(\overline{\Omega} \times [0, \infty))$ ($i = 1, \ldots, N$) *and* $\alpha \in C^1(\overline{\Omega} \times [0, \infty))$ *be all nonnegative functions on* $\overline{\Omega} \times [0, \infty)$. *Assume* $u_{i0} \in C^1(\overline{\Omega})$ ($i = 1, \ldots, N$) *and* $\upsilon_0 \in C^1(\overline{\Omega})$ *are all nonnegative functions on* $\overline{\Omega}$. *Then there exists a unique nonnegative solution* $(u_1, \ldots, u_N, \upsilon)$ *to the system* (1.1)–(1.4) *with all* $u_i$ ($i = 1, \ldots, N$) *and* $\upsilon$ *being continuous on* $\overline{\Omega} \times [0, \infty)$ *and continuously differentiable in* $t \in (0, \infty)$ *and twice continuously differentiable in* $x \in \Omega$.

**Proof—**Let $T_m = m$ ($m = 1, 2, \ldots$). Then for each $T_m$, the system has a unique solution defined on $\overline{\Omega_{T_m}}$. By the uniqueness of local solution, the solution corresponding to $T_m$ and that to $T_n$ are identical on $[0, T_m]$ if $m \le n$. Therefore, on each finite interval of time, all the solutions are the same as long as they are defined on that interval. Hence we have the existence of a global solution. It is unique since the local solution is unique.

## 7 Reaction-Diffusion System: Asymptotic Behavior

We now assume that all $\alpha_i$ ($i = 1, \ldots, N$) and $\alpha$ are independent of time $t$ and consider the initial-boundary-value problem of the full, time-dependent system of reaction-diffusion equations (1.1)–(1.4). Given the initial data $u_{i0}$ ($i = 1, \ldots, N$) and $\upsilon_0$, the system has a unique global solution $u_i = u_i(x, t)$ ($i = 1, \ldots, N$) and $\upsilon = \upsilon(x, t)$ by Theorem 6.2. We ask if the limit of the solution as $t \to \infty$ exists, and if so, if the limit is a steady-state solution.

We first state the following result and omit its proof as it is similar to that for the special case for two equations; cf. Corollary 8.3.1 in [18]:

### Proposition 7.1

*Let* $\Omega$, $T$, *and* $D_i$ ($i = 1, \ldots, N$) *be all the same as in Theorem 6.1*. *Let* $a_{i,j} \in C^1(\overline{\Omega_T})$ ($i, j = 1, \ldots, N$) *be such that* $a_{i,j} \ge 0$ *in* $\Omega_T$ *if* $i \ne j$. *Suppose* $w_i \in C(\overline{\Omega_T}) \cap C_1^2(\Omega_T)$ ($i = 1, \ldots, N$) *satisfy*

$$\frac{\partial w_i}{\partial t} - D_i \Delta w_i \ge \sum_{i,j=1}^{N} a_{i,j}(x,t) w_j \, in \, \Omega_T, \; i=1, \ldots, N, \;\; \frac{\partial w_i}{\partial n} = 0 \, on \, \partial\Omega \times (0, T], \; i=1, \ldots, N, \;\; w_i(\cdot, 0) \ge 0 \, in \, \bar{\Omega}, \; i=1, \ldots, N.$$

*Then* $w_i \ge 0$ *in* $\overline{\Omega_T}$ ($i = 1, \ldots, N$).

The following theorem states indicates particularly that if the initial values are large constant functions then the global solutions to the time-dependent problem are monotonic in time $t$ and the limits as $t \to \infty$ are steady-state solutions.

### Theorem 7.1

*Let* Ω *be a bounded domain in* $\mathbb{R}^3$ *with its boundary* ∂Ω *in the class* $C^{2,\mu}$ *for some* μ ∈ (0, 1). *Let* $D_i$, $\beta_i$, *and* $k_i$ (*i* = 1, …, *N*), *and D and* β *be all the same as in Theorem 6.1. Let* $\alpha_i \in C^1(\overline{\Omega})$ (*i* = 1, …, *N*) *and* $\alpha \in C^1(\overline{\Omega})$ *be all nonnegative on* $\overline{\Omega}$. *Let* $(\bar{U}_1, \ldots, \bar{U}_N, \underline{V})$ *be the nonnegative solution to the system* (1.1)–(1.4) *with the initial values* $\bar{U}_i(\cdot, 0) = \bar{u}_i^{(0)}$ (*i* = 1, …, *N*) *and* $\underline{V}(\cdot, 0) = \underline{v}^{(0)}$ *all being constant functions. Let* $(\underline{U}_1, \ldots, \underline{U}_N, \bar{V})$ *be the nonnegative solution to the system* (1.1)–(1.4) *with the initial values* $\underline{U}_i(\cdot, 0) = \underline{u}_i^{(0)}$ (*i* = 1, …, *N*) *and* $\bar{V}(\cdot, 0) = \bar{v}^{(0)}$ *all being constant functions. Assume* $\bar{u}_i^{(0)} \geq \|\alpha_i\|_{L^\infty(\Omega)}/\beta_i$, $\bar{v}^{(0)} \geq \|\alpha\|_{L^\infty(\Omega)}/\beta$, *and* $\underline{u}_i^{(0)} = \underline{v}^{(0)} = 0$ (*i* = 1, …, *N*). *Then the following hold true:*

1. $\bar{U}_i \geq \underline{U}_i$ (*i* = 1, …, *N*) *and* $\bar{V} \geq \underline{V}$ *in* $\overline{\Omega} \times [0, \infty)$.

2. $\bar{U}_i$ (*i* = 1, …, *N*) *and* $\bar{V}$ *are monotonically nonincreasing in t and* $\underline{U}_i$ (*i* = 1, …, *N*) *and* $\underline{V}$ *are monotonically nondecreasing in t*.

3. *Let*

$$(\bar{U}_{1,s}, \ldots, \bar{U}_{N,s}, \underline{V}_s) = \lim_{t\to\infty}(\bar{U}_1, \ldots, \bar{U}_N, \underline{V}), \ (\underline{U}_{1,s}, \ldots, \underline{U}_{N,s}, \bar{V}_s) = \lim_{t\to\infty}(\underline{U}_1, \ldots, \underline{U}_N, \bar{V}),$$

   *Then* $\bar{U}_{i,s} \geq \underline{U}_{i,s}$ (*i* = 1, …, *N*) *and* $\bar{V}_s \geq \underline{V}_s$ *on* $\overline{\Omega}$. *Moreover, all* $\bar{U}_{i,s}$, $\underline{U}_{i,s}$, $\bar{V}_s$, *and* $\underline{V}_s$ *are in* $C^{2,\mu}(\overline{\Omega})$, *and* $(\bar{U}_{1,s}, \ldots, \bar{U}_{N,s}, \underline{V}_s)$ *and* $(\underline{U}_{1,s}, \ldots, \underline{U}_{N,s}, \bar{V}_s)$ *are solutions of the time-independent system* (5.1)–(5.3).

4. *If* $(u_{1,s}^*, \ldots, u_{N,s}^*, v_s^*)$ *is any solution to* (5.1)–(5.3) *such that* $\underline{u}_i^{(0)} \leq u_{i,s}^* \leq \bar{u}_i^{(0)}$ (*i* = 1, …, *N*) *and* $\underline{v}^{(0)} \leq v_s^* \leq \text{á£ą}^{(0)}$ *on* $\overline{\Omega}$, *then* $\underline{U}_{i,s} \leq u_{i,s}^* \leq \bar{U}_{i,s}$ (*i* = 1, …, *N*) *and* $\underline{V}_s \leq v_s^* \leq \bar{V}_s$ *on* $\overline{\Omega}$.

**Proof—**(1) Let *T* > 0. Let $W_i = \bar{U}_i - \underline{U}_i$ (*i* = 1, …, *N*) and $W = \bar{V} - \underline{V}$. We then have

$$\frac{\partial W_i}{\partial t} = D_i \Delta W_i - \beta_i W_i - k_i \underline{V} W_i + k_i \underline{U}_i W \text{in} \Omega_T, i = 1, \ldots, N,$$

$$\frac{\partial W}{\partial t} = D \Delta W - \beta W - \sum_{i=1}^N k_i \underline{U}_i W + \sum_{i=1}^N k_i W_i \underline{V} \text{in} \Omega_T,$$

$$\frac{\partial W_i}{\partial n} = \frac{\partial W}{\partial n} = 0 \text{on} \partial\Omega \times (0, T], i = 1, \ldots, N,$$

$$W_i(\cdot, 0) = \bar{u}_i^{(0)} - \underline{u}_i^{(0)} \geq 0 \text{and} W(\cdot, 0) = \text{á£ą}^{(0)} - \underline{v}^{(0)} \geq 0 \text{in} \bar{\Omega}, i = 1, \ldots, N.$$

Therefore, we get by Proposition 7.1 that $W_i \geq 0$ (*i* = 1, …, *N*) and *W* ≥ 0 in $\overline{\Omega_T}$. Since *T* > 0 is arbitrary, we obtain the desired inequality on $\overline{\Omega} \times [0, \infty)$.

(2) Let *T* > 0 and δ > 0. Set $W_i(x, t) = \bar{U}_i(x, t) - \bar{U}_i(x, t + \delta)$ (*i* = 1, …, *N*) and $\underline{W}(x, t) = \underline{V}(x, t + \delta) - \underline{V}(x, t)$. Then

$$\frac{\partial \bar{W}_i(x,t)}{\partial t}=D_i\Delta \bar{W}_i(x,t)-\beta_i\bar{W}_i(x,t)-k_i\underline{V}(x,t+\delta)\bar{W}_i(x,t)+k_i\underline{U}_i(x,t)\underline{W}(x,t)\forall(x,t)\in\Omega_T, i=1,\dots,N,$$
$$\frac{\partial \underline{W}(x,t)}{\partial t}=D\Delta\underline{W}(x,t)-\beta\underline{W}(x,t)-\sum_{i=1}^{N}k_i\underline{U}_i(x,t+\delta)\underline{W}(x,t)+\sum_{i=1}^{N}k_i\bar{W}_i(x,t)\underline{V}(x,t)\forall(x,t)\in\Omega_T,$$
$$\frac{\partial \bar{W}_i}{\partial n}=\frac{\partial \underline{W}}{\partial n}=0\text{on}\partial\Omega\times(0,T], i=1,\dots,N,$$
$$\bar{W}_i(\cdot,0)=\bar{u}_i^{(0)}-\bar{U}_i(\delta)\geq 0\text{and}\underline{W}(\cdot,0)=\underline{V}(\delta)-\underline{\upsilon}^{(0)}\geq 0\text{in}\bar{\Omega}, i=1,\dots,N.$$

Again by Proposition 7.1 we get $\bar{W}_i \geq 0$ ($i = 1, \dots, N$) and $\underline{W} \geq 0$. Hence $\bar{U}_i$ ($i = 1, \dots, N$) are monotonically nonincreasing in $t$ and $\underline{V}$ is monotonically nondecreasing in $t$. Similarly, $\underline{U}_i$ ($i = 1, \dots, N$) are monotonically nondecreasing in $t$ and $\bar{V}$ is monotonically nonincreasing in $t$.

(3) By Part (1) we have $\bar{U}_{i,s} \geq \underline{U}_{i,s}$ ($i = 1, \dots, N$) and $\bar{V}_s \geq \underline{V}_s$ on $\bar{\Omega}$. The claim that ($\bar{U}_{1,s}, \dots, \bar{U}_{N,s}, \underline{V}_s$) and ($\underline{U}_{1,s}, \dots, \underline{U}_{N,s}, \bar{V}_s$) are solutions of the time-independent system (5.1)–(5.3) can be proved similarly as the proof of Theorem 10.4.3 in [18] and that of Theorem 3.6 in [20].

(4) This part can proved by the same argument in Step 2 in the proof of uniqueness of solution of Theorem 6.1.

## Theorem 7.2

*Let* $\Omega$, $D_i$, $D$, $\beta_i$, $\beta$, $k_i$, $\alpha_i$, $\alpha$, $\bar{u}_i^{(0)}$, $\underline{u}_i^{(0)}$, $\bar{\upsilon}^{(0)}$, $\underline{\upsilon}^{(0)}$, $\bar{U}_i$, $\underline{U}_i$, $\bar{V}$, *and* $\underline{V}$ ($i = 1, \dots, N$) *be all the same as in Theorem 7.1. Let* $u_{i0} \in C^1(\bar{\Omega})$ ($i = 1, \dots, N$) *and* $\upsilon_0 \in C^1(\bar{\Omega})$ *be such that* $\underline{\upsilon}^{(0)} \leq u_{i0} \leq \bar{u}_i^{(0)}$ *and* $\underline{\upsilon}^{(0)} \leq \upsilon_0 \leq \bar{\upsilon}^{(0)}$ ($i = 1, \dots, N$) *in* $\bar{\Omega}$. *Let* ($u_1, \dots, u_N, \upsilon$) *be the unique nonnegative global solution to the time-dependent problem* (1.1)–(1.4) *with the initial data* ($u_{10}, \dots, u_{N0}, \upsilon_0$). *Then* $\bar{U}_i \geq u_i \geq \underline{U}_i$ ($i = 1, \dots, N$) *and* $\bar{V} \geq \upsilon \geq \underline{V}$ *in* $\bar{\Omega} \times [0, \infty)$.

**Proof—**This is similar to the proof of Part (1) of Theorem 7.1.

The following two corollaries relate the uniqueness of steady-state solution to the asymptotic behavior of solution to the time-dependent problem.

## Corollary 7.1

*With the assumption of Theorem 7.2, the following hold true:*

1. *That* $\bar{U}_{i,s} = \underline{U}_{i,s}$ ($i = 1, \dots, N$) *and* $\bar{V}_s = \underline{V}_s$ *in* $\bar{\Omega}$ *if and only if the steady-state solution* ($u_{1,s}, \dots, u_{N,s}$) $\in (C^2(\bar{\Omega}))^{N+1}$ *satisfying* $\underline{u}_i^{(0)} \leq u_{i,s} \leq \bar{u}_i^{(0)}$ ($i = 1, \dots, N$) *and* $\underline{\upsilon}^{(0)} \leq \upsilon_s \leq \bar{\upsilon}^{(0)}$ *in* $\Omega$ *is unique.*
2. *If the steady-state solution* ($u_{1,s}, \dots, u_{N,s}$) $\in (C^2(\bar{\Omega}))^{N+1}$ *that satisfies* $\underline{u}_i^{(0)} \leq u_{i,s} \leq \bar{u}_i^{(0)}$ ($i = 1, \dots, N$) *and* $\underline{\upsilon}^{(0)} \leq \upsilon_s \leq \bar{\upsilon}^{(0)}$ *in* $\bar{\Omega}$ *is unique, then for any initial data* ($u_{10}, \dots, u_{N0}, \upsilon_0$) $\in (C^1(\bar{\Omega}))^{N+1}$ *with* $\underline{\upsilon}^{(0)} \leq u_{i0} \leq \bar{u}_i^{(0)}$ ($i = 1, \dots, N$) *and*

$\underline{\upsilon}^{(0)} \le \upsilon_0 \le \bar{\upsilon}^{(0)}$ *in* $\overline{\Omega}$, *the corresponding nonnegative solution* $(u_1, \dots, u_N, \upsilon)$ *of the time-dependent problem* (1.1)–(1.4) *converges to* $(u_{1,s}, \dots, u_{N,s}, \upsilon_s)$ *as* $t \to \infty$.

3. *If the nonnegative steady-state solution in* $(C^2(\overline{\Omega}))^{N+1}$ *is unique, then the nonnegative global solution to the time-dependent problem with any nonnegative initial data in* $(C^1(\overline{\Omega}))^{N+1}$ *converges to this steady-state solution as* $t \to \infty$.

**Proof—**(1) This follows immediately from Theorem 7.2.

(2) This follows from Theorem 7.1 and Theorem 7.2.

(3) Choose $\bar{u}_i^{(0)}$ $(i = 1, \dots, N)$ and $\bar{\upsilon}^{(0)}$ all large enough and apply Part (2).

### Corollary 7.2

*With the same assumption as in Corollary 7.1, if* $\bar{U}_{i,s} \ne \underline{U}_{i,s}$ *for some i with* $1 \le i \le N$ *or* $\overline{V_s} \ne \underline{V}_s$, *then: (1) For any initial data* $(u_{10}, \dots, u_{N0}, \upsilon_0) \in (C^1(\overline{\Omega}))^{N+1}$ *with* $\underline{u}_i^{(0)} \le u_{i0} \le \underline{U}_{i,s}$ $(i = 1, \dots, N)$ *and* $\overline{V_s} \le \upsilon_0 \le \bar{\upsilon}^{(0)}$ *in* $\overline{\Omega}$, *the corresponding nonnegative global solution* $(u_1, \dots, u_N, \upsilon)$ *of the time-dependent problem* (1.1)–(1.4) *converges to* $(\underline{U}_{1,s}, \dots, \underline{U}_{N,s}, \overline{V_s})$ *as* $t \to \infty$; *and (2) For any initial data* $(u_{10}, \dots, u_{N0}, \upsilon_0) \in (C^1(\overline{\Omega}))^{N+1}$ *with* $\bar{U}_{i,s} \le u_{i0} \le \bar{u}_i^{(0)}$ $(i = 1, \dots, N)$ *and* $\underline{\upsilon}^{(0)} \le \upsilon_0 \le \underline{V}_s$ *in* $\overline{\Omega}$, *the corresponding nonnegative global solution* $(u_1, \dots, u_N, \upsilon)$ *of the time-dependent problem* (1.1)–(1.4) *converges to* $(\bar{U}_{1,s}, \dots, \bar{U}_{N,s}, \underline{V}_s)$ *as* $t \to \infty$.

**Proof—**This is similar to the proof of Theorem 7.1.

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## References

1. Berg, HC. Random Walks in Biology. Princeton University Press; 1993.
2. Evans, LC. Partial Differential Equations, volume 19 of Graduate Studies in Mathematics. 2nd edition. Amer. Math. Soc.; 2010.
3. Friedman, A. Partial Differential Equations of Parabolic Type. Prentice-Hall, Inc.; 1964.
4. Fröhlich FS. Activation of gene expression by small RNA. Current Opin. Microbiology. 2009; 12:674–682.
5. Gilbarg, D.; Trudinger, NS. Elliptic Partial Differential Equations of Second Order. 2nd edition. Springer–Verlag; 1998.
6. He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nature Rev. Genetics. 2004; 5(7):522–531. [PubMed: 15211354]
7. Hohn, ME. PhD thesis. San Diego: University of California; 2013. Diffusion Equations Models and Numerical Simulations of Gene Expression.
8. Horn, RA.; Johnson, CR. Matrix Analysis. Cambridge University Press; 1990.
9. Jost, J. Partial Differential Equations. Springer; 2002.

10. Lam K-Y, Ni W-M. Uniqueness and complete dynamics in heterogeneous competition-diffusion systems. SIAM J. Applied Math. 2012; 72:1695–1712.
11. Lapham J, Rife JP, Moore PB, Crothers DM. Measurement of diffusion constants for nucleic acids by NMR. J. Biomol. NMR. 1997; 10:255–262. [PubMed: 9390403]
12. Levine E, Hwa T. Small RNAs establish gene expression thresholds. Current Opin. Microbiology. 2008; 11(6):574–579.
13. Levine E, Ben Jacob E, Levine H. Target-specific and global effectors in gene regulation by microRNA. Biophys. J. 2007; 93(11):L52–L54. [PubMed: 17872959]
14. Levine E, McHale P, Levine H. Small regulatory RNAs may sharpen spatial expression patterns. PLoS Comput. Biology. 2007; 3:e233.
15. Levine E, Zhang Z, Kuhlman T, Hwa T. Quantitative characteristics of gene regulation by small RNA. PLoS Biology. 2007; 5(9):1998–2010.
16. Loinger A, Hemla Y, Simon I, Margalit H, Biham O. Competition between small RNAs: A quantitative view. Biophys. J. 2012; 102(8):1712–1721. [PubMed: 22768926]
17. Ni, W-M. The Mathematics of Diffusion. Vol. 82. SIAM; 2011.
18. Pao, CV. Nonlinear Parabolic and Elliptic Equations. New York and London: Plenum Press; 1992.
19. Platini T, Jia T, Kulkarni RV. Regulation by small RNAs via coupled degradation: Mean-field and variational approaches. Phys. Rev. E. 2011; 84:021928.
20. Sattinger DH. Monotone methods in nonlinear elliptic and parabolic boundary value problems. Indiana Univ. Math. J. 1972; 21(11):979–1000.
21. Stefani G, Slack FJ. Small non-coding RNAs in animal development. Nature Rev. Molecular Cell Biology. 2008; 9(3):219–230.
22. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nature Cell Biology. 2007; 9(6):654–659.
23. Watson, JD.; Baker, TA.; Bell, SP.; Gann, A.; Levine, M.; Losick, R. Molecular Biology of the Gene. 7th edition. Benjamin Cummings; 2013.

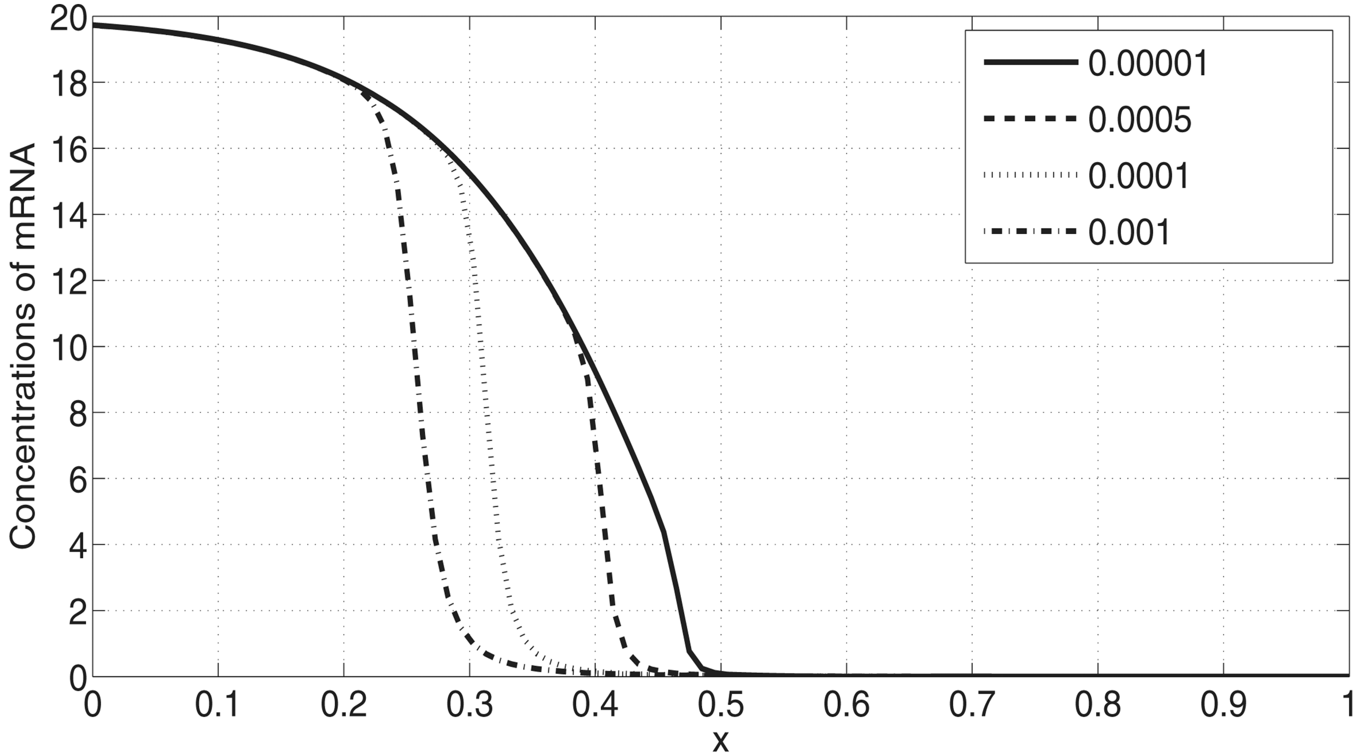


**Figure 1.**

Numerical solutions to the steady-state equations with the boundary conditions (1.1)–(1.3) in one space dimension with $N = 1$, $\Omega = (0, 1)$, $D = 0$, $\beta_1 = \beta = 0.01$, $k_1 = 1$, and $\alpha_1$ and $\alpha$ given in (1.5) and (1.6), respectively. The numerically computed, steady-state concentration of mRNA $\upsilon = \upsilon(x)$ $(0 < x < 1)$ sharpens as the the diffusion constant $D_1$ of the sRNA increases from 0.00001 to 0.0005, 0.0001, and 0.001.

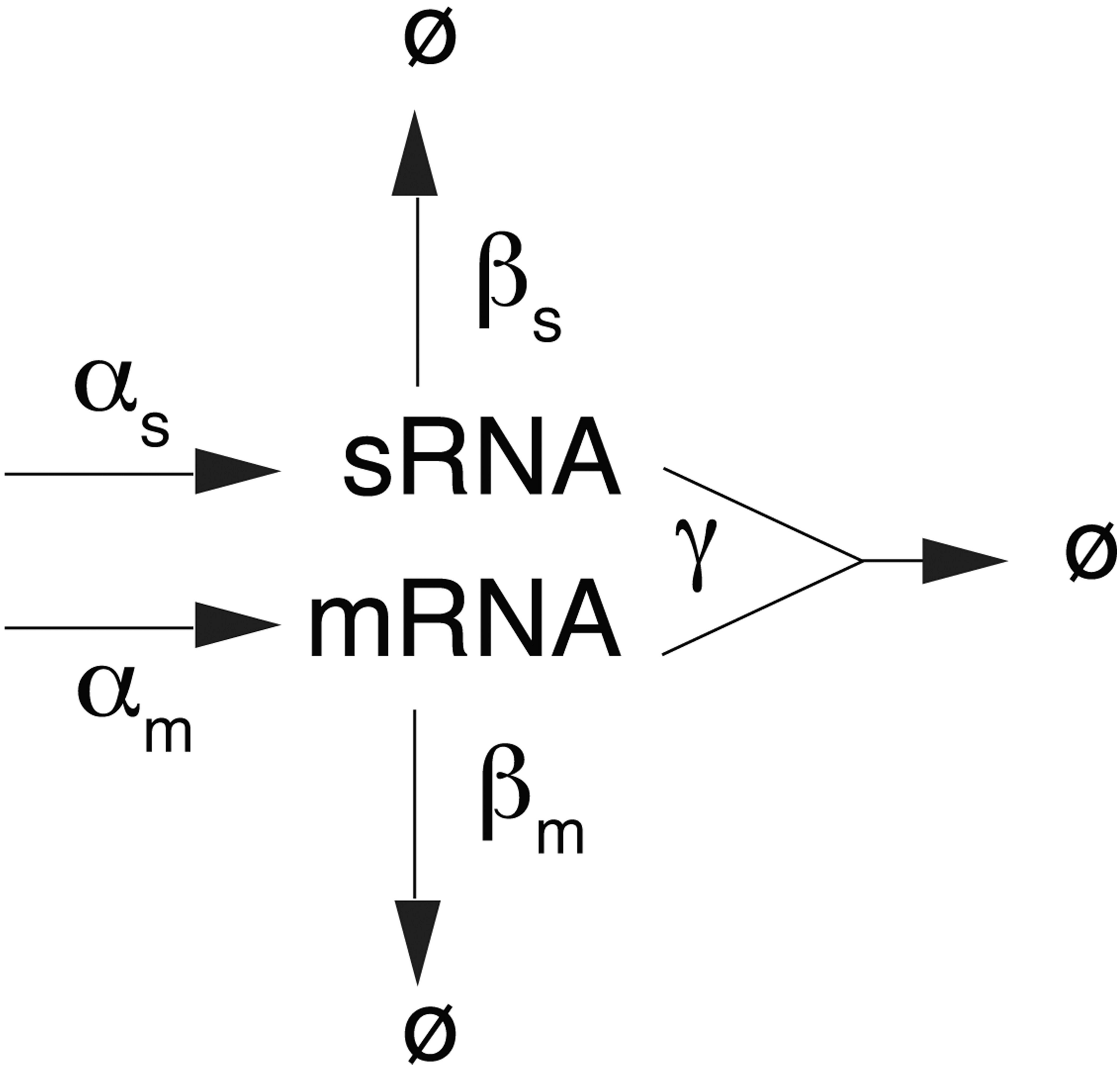


**Figure 2.**

Kinetic scheme of the interaction of sRNA and mRNA in a cell. Here, $\alpha_s$ and $\alpha_m$ represent the production rates of sRNA and mRNA, respectively; $\beta_s$ and $\beta_m$ represent the independent degradation rates of sRNA and mRNA, respectively; and $\gamma$ represents the coupled degradation rate of sRNA and mRNA.