Dynamical Aspects of a Hybrid System Describing Intermittent Androgen Suppression Therapy of Prostate Cancer

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Abstract We consider a mathematical model describing Intermittent Androgen Suppression therapy (IAS therapy) of prostate cancer. The system has a hybrid structure, i.e., the system consists of two different systems by the medium of an unknown binary function denoting the treatment state. In this paper, we shall prove that the hybrid system has a unique solution with the property that the binary function keeps on changing its value. In the clinical point of view, the result asserts that one can plan the IAS therapy for each prostate cancer patient, provided that the tumor satisfies a certain condition.

Keywords Parabolic comparison principle · Indirectly controlled parameter

1 Introduction

Prostate cancer is one of the diseases of male. By the fact that prostate cells proliferate by a male hormone so-called androgen, it is expected that prostate tumors are sensitive to androgen suppression. Huggins and Hodges [10] demonstrated the validity of the androgen deprivation. Since then, the hormonal therapy has been a major therapy of prostate cancer. The therapy aims to induce apoptosis of prostate cancer cells under the androgen suppressed condition. For instance, the androgen suppressed condition can be kept by medicating a patient continuously [22], and the therapy is called Continuous Androgen Suppression therapy (CAS therapy). However, during several years of the CAS therapy, the relapse of prostate tumor often occurs. More precisely, the relapse means that the prostate tumor mutates to androgen independent tumor. Then the CAS therapy is not effective in treating the tumor [5]. The fact was also verified mathematically by [13, 14]. It is known that there exist Androgen-

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Dependent cells (AD cells) and Androgen-Independent cells (AI cells) in prostate tumors. AI cells are considered as one of the causes of the relapse. For, AD cells can not proliferate under the androgen suppressed condition, whereas AI cells are not sensitive to androgen suppression and can still proliferate under the androgen poor condition [2, 18]. Thus the relapse of prostate tumors is caused by progression to androgen independent cancer due to emergence of AI cells.

In order to prevent or delay the relapse of prostate tumors, Intermittent Androgen Suppression therapy (IAS therapy) was proposed and has been studied clinically by many researchers (e.g., see [1, 3, 19], and the references therein). In contrast to the CAS therapy, the IAS therapy does not aim to exterminate prostate cancer. We mention the typical feature of the clinical phenomenon. Since prostate cancer cells produce large amount of Prostate-Specific Antigen, the PSA is regarded as a good biomarker of prostate cancer [21], and the plan of IAS therapy is based on the level:

(F) In the IAS therapy, the medication is stopped when the serum PSA level falls enough, and resumed when the serum PSA level rises enough.

Indeed, if one can *optimally* plan the IAS therapy, then the size of tumor remains in an appropriate range by way of on and off of the medication. In order to comprehend qualitative property of prostate tumors under the IAS therapy, several mathematical models were proposed and have been studied in the mathematical literature, for instance, ODE models ([9, 11, 12, 20], and references therein) and PDE models [8, 15, 23–25]. Due to (F), an unknown binary function, denoting the treatment state, appears in the models. The discontinuity of the binary function is the difficulty in mathematical analysis on the models. To the best of our knowledge, there is no result dealing with switching phenomena of the binary function in the PDE models.

The purpose of this paper is to prove the existence of a solution with the switching property for the PDE model introduced by Tao et al. [23]:

$$\begin{cases} \dfrac{da}{dt}(t) = -\gamma(a(t) - a_*) - \gamma a_* S(t) & \text{in } \mathbb{R}_+, \\ \partial_t u(\rho,t) - \mathscr{L}(v,R)u(\rho,t) = F_u(u(\rho,t), w(\rho,t), a(t)) & \text{in } I_\infty, \\ \partial_t w(\rho,t) - \mathscr{L}(v,R)w(\rho,t) = F_w(u(\rho,t), w(\rho,t), a(t)) & \text{in } I_\infty, \\ v(\rho,t) = \dfrac{1}{\rho^2}\displaystyle\int_0^\rho F_v(u(r,t), w(r,t), a(t)) r^2\, dr & \text{in } I_\infty, \\ \dfrac{dR}{dt}(t) = v(1,t)R(t) & \text{in } \mathbb{R}_+, \\ S(t) = \begin{cases} 0 \to 1 & \text{when } R(t) = r_1 \text{ and } R'(t) > 0, \\ 1 \to 0 & \text{when } R(t) = r_0 \text{ and } R'(t) < 0, \end{cases} & \text{in } \mathbb{R}_+, \\ \partial_\rho u(\rho,t)|_{\rho\in\{0,1\}} = \partial_\rho w(\rho,t)|_{\rho\in\{0,1\}} = 0, \quad v(0,t) = 0, & \text{in } \mathbb{R}_+, \\ (a,u,w,R,S)|_{t=0} = (a_0, u_0(\rho), w_0(\rho), R_0, S_0) & \text{in } I, \end{cases} \tag{IAS}$$

where $I = (0, 1)$, $\mathbb{R}_+ = \{t \in \mathbb{R} \mid t > 0\}$, $I_\infty = I \times \mathbb{R}_+$, and

$$\mathscr{L}(v, R)\varphi = \frac{D}{R(t)^2}\frac{1}{\rho^2}\partial_\rho[\rho^2\partial_\rho\varphi] + \rho v(1, t)\partial_\rho\varphi - \frac{1}{\rho^2}\partial_\rho[\rho^2 v(\rho, t)\varphi], \quad (1)$$

$$F_u = f_1(a)u - c_1uw, \quad F_w = f_2(a)w - c_2uw, \quad F_v = F_u + F_w. \quad (2)$$

The unknowns a, u, w, v, R, and S denote respectively the androgen concentration, the volume fraction of AD cells, the volume fraction of AI cells, the advection velocity of the cancer cells, the radius of the tumor, and the treatment state. Here $S = 0$ and $S = 1$ correspond to the medication state and the non-medication state, respectively. The authors of [23] assumed that the prostate tumor is radially symmetric and densely packed by AD and AI cells. Moreover they regarded the tumor as a three dimensional sphere. Thus the unknowns u, w, and v are radially symmetric functions defined on the unit ball $B_1 = \{x \in \mathbb{R}^3 \mid |x| < 1\}$, i.e., $\rho = |x|$. The unknown $S(t)$ is governed by $R(t)$, for they formulated the serum PSA level as the radius of the tumor. Although the condition on S in (IAS) is a concise form, the precise form is expressed as follows: $S(t) \in \{0, 1\}$ and

$$S(t) = \begin{cases} \{0,1\} \setminus \lim\limits_{\tau\uparrow t} S(\tau) & \text{if } \begin{cases} \lim\limits_{\tau\uparrow t} R'(\tau) > 0, \ \lim\limits_{\tau\uparrow t} R(\tau) = r_1, \ \text{and } \lim\limits_{\tau\uparrow t} S(\tau) = 0, \\ \lim\limits_{\tau\uparrow t} R'(\tau) < 0, \ \lim\limits_{\tau\uparrow t} R(\tau) = r_0, \ \text{and } \lim\limits_{\tau\uparrow t} S(\tau) = 1, \end{cases} \\ \lim\limits_{\tau\uparrow t} S(\tau) & \text{otherwise.} \end{cases}$$

The parameters $a_*, \gamma, c_1, c_2, r_0$, and r_1 denote the normal androgen concentration, the reaction velocity, the effective competition coefficient from AD to AI cells, and from AI to AD cells, the lower and upper thresholds, respectively. The given functions $f_1 : [0, a_*] \to \mathbb{R}$ and $f_2 : [0, a_*] \to \mathbb{R}$ describe the net growth rate of AD and AI cells, respectively. Although the typical form of f_i were given by [23], we deal with general f_i satisfying several conditions, which are stated later.

In [23], it was shown that, for each initial data $u_0 \in W_p^2(I)$, there exists a short time solution $u \in W_p^{2,1}(I \times (0, T))$ of (IAS). However, the result is not sufficient to construct a "*switching solution*". For, if (u, w, v, R, a, S) is a switching solution of (IAS), then (IAS) must be solvable at least locally in time for each "initial data" $(u, w, R, a, S)|_{\{t=t_j\}}$, where t_j is a switching time. Nevertheless, the result in [23] does not ensure the solvability.

The existence of switching solutions of (IAS) is a mathematically outstanding question. We are interested in the following mathematical problem:

Problem 1.1 Does there exist a switching solution of (IAS) with appropriate thresholds $0 < r_0 < r_1 < \infty$? Moreover, what is the dynamical aspect of the solution?

We consider the initial data $(u_0, w_0, R_0, a_0, S_0)$ satisfying the following:

$$\begin{cases} u_0, w_0 \in C^{2+\alpha}(B_1), \ \partial_\rho u_0(\rho)|_{\rho\in\{0,1\}} = \partial_\rho w_0(\rho)|_{\rho\in\{0,1\}} = 0, \\ u_0 \geq 0, \ \ w_0 \geq 0, \ \ u_0 + w_0 \equiv 1, \ \ R_0 > 0, \ \ 0 < a_0 < a_*, \ \ S_0 \in \{0, 1\}, \end{cases} \quad (3)$$

where $\alpha \in (0, 1)$. Let f_1 and f_2 satisfy

$$\begin{cases} f_1(a_*) > 0, \quad f_1(0) < 0, \quad f_1 \in C^1([0, a_*]), \quad f_1' > 0 \quad \text{in} \quad [0, a_*], \\ f_2(0) > 0, \quad f_2 \in C^1([0, a_*]), \quad f_2' \le 0 \quad \text{in} \quad [0, a_*]. \end{cases} \tag{A0}$$

We note that (A0) is a natural assumption in the clinical point of view, and typical f_1 and f_2, which were given in [23], also satisfy (A0). In order to comprehend the role of f_i and c_i, we classify asymptotic behavior of non-switching solutions of (IAS) in terms of f_i and c_i under (A0) (see Theorems 3.2–3.5). Following the results obtained by Theorems 3.2–3.5, we impose (A0) and the following assumptions on f_i and c_i:

$$f_1(a_*) - f_2(a_*) - c_1 > 0; \tag{A1}$$

$$f_1(0) - f_2(0) + c_2 > 0. \tag{A2}$$

From now on, let $Q_T := B_1 \times (0, T)$. We denote by $C^{2\kappa+\alpha,\kappa+\beta}(Q_T)$ the Hölder space on Q_T, where $\kappa \in \mathbb{N} \cup \{0\}$, $0 < \alpha < 1$, and $0 < \beta < 1$ (for the precise definition, see [16]).

Then we give an affirmative answer to Problem 1.1:

Theorem 1.1 *Let f_i and c_i satisfy* (A0)–(A2). *Let $(u_0, w_0, R_0, a_0, S_0)$ satisfy* (3)*, $u_0 > 0$ in $\overline{B_1}$, and $S_0 = 0$. Then, there exists a pair (r_0, r_1) with $0 < r_0 < r_1 < \infty$ such that the system* (IAS) *has a unique solution (u, w, v, R, a, S) in the class*

$$u, w \in C^{2+\alpha,1+\alpha/2}(Q_\infty), \quad v \in C^{1+\alpha,\alpha/2}([0, 1) \times \mathbb{R}_+) \cap C^1([0, 1) \times \mathbb{R}_+),$$
$$R \in C^1(\mathbb{R}_+), \quad a \in C^{0,1}(\mathbb{R}_+).$$

Moreover, the following hold:

(i) *There exists a strictly monotone increasing divergent sequence $\{t_j\}_{j=0}^{\infty}$ with $t_0 = 0$ such that $a \in C^1((t_j, t_{j+1}))$ and*

$$S(t) = \begin{cases} 0 & \text{in} \quad [t_{2j}, t_{2j+1}), \\ 1 & \text{in} \quad [t_{2j+1}, t_{2j+2}), \end{cases} \qquad \text{for any} \quad j \in \mathbb{N} \cup \{0\};$$

(ii) *There exist positive constants $C_1 < C_2$ such that*

$$C_1 \le R(t) \le C_2 \quad \text{for any} \quad t \ge 0.$$

We mention the mathematical contributions of Theorem 1.1 and a feature of the system (IAS). The system is composed of two different systems (S0) and (S1) by the medium of the binary function $S(t)$, where (S0) and (S1) respectively denote (IAS) with $S(t) \equiv 0$ and $S(t) \equiv 1$. Generally the system with such structure is called *hybrid system*. Regarding (S0), the assumption (A1) implies that $R(t)$ diverges to infinity as $t \to \infty$ (see Theorem 3.4). On the other hand, regarding (S1), we can show that the assumption (A2) implies the following: (i) $R(t)$ diverges to infinity as $t \to \infty$ if u_0 is sufficiently small (Theorem 3.2); (ii) $R(t)$ converges to 0 as $t \to \infty$ if u_0 is sufficiently close to 1 (Theorem 3.3). It is natural to ask whether a solution $R(t)$ of (IAS) is bounded or not. One of the contributions of the present paper is to show how to determine thresholds $0 < r_0 < r_1 < \infty$ such that (IAS) with the thresholds has a bounded solution with infinite opportunities of switching. Furthermore, due to the discontinuity of $S(t)$, it is expected that the switching solution is not so smooth. However, Theorem 1.1 indicates that the switching solution gains its regularity with the aid of the "indirectly controlled parameter" $a(t)$. The other contribution of this paper is to mathematically clarify the immanent structure of the hybrid system (IAS).

We mention the clinical contribution of Theorem 1.1. Although one can expect that the system (IAS) gives us how to optimally plan the IAS therapy for each prostate cancer patient, it is not trivial matter. To do so, first we have to prove the existence of admissible thresholds for each patient. Moreover, if the admissible threshold is not unique, then we investigate the optimality of the admissible thresholds. Here, we say that the thresholds is admissible for a prostate cancer patient, if for the initial data (IAS) with the thresholds has a switching solution. Although [23] indicated that the problem, even the existence, is difficult to analyze mathematically, they numerically showed that (i) the IAS therapy fails for unsuitable thresholds, more precisely, the radius of tumor diverges to infinity after several times of switching opportunities, and while, (ii) the IAS therapy succeeds for suitable thresholds, i.e., the radius of tumor remains in a bounded range by way of infinitely many times of switching opportunities. One of the clinical contribution of Theorem 1.1 is to prove the existence of admissible thresholds for each patients, provided that (A0)–(A2) are fulfilled. Moreover, Theorem 1.1 also implies that the IAS therapy has an advantage over the CAS therapy for some patients. Indeed, Theorem 3.2 gives an instance showing a failure of the CAS therapy, whereas Theorem 1.1 asserts that the patient can be treated successfully by the IAS therapy. The fact is an example that switching strategy under the IAS therapy is able to be a successful strategy. On the other hand, the pair of admissible thresholds given by Theorem 1.1 is not uniquely determined. Thus, in order to optimally plan the IAS therapy, we have to investigate its optimality. However the optimality of the admissible thresholds is an outstanding problem.

The paper is organized as follows: In Sect. 2, we give a modified system of (IAS) and reduce the system to a simple hybrid system. Making use of the modified system, we prove the short time existence of the solution to (IAS). In Sect. 3, we show the existence of the non-switching solution of (IAS) for any finite time. Moreover, we classify the asymptotic behaviors of the non-switching solutions in terms of f_i and c_i. In Sect. 4, we prove Theorem 1.1, i.e., we show the existence of a switching solution of (IAS) and give its property.

2 Short Time Existence

The main purpose of this section is to show the short time existence of the solution of (IAS). As [23] mentioned, it is difficult to prove that (IAS) has a short time solution in the Hölder space (see Remark 4.1 in [23]). The difficulty rises from the singularity of v/ρ at $\rho = 0$. Indeed, the singularity prevents us from applying the Schauder estimate. To overcome the difficulty, first we consider a modified hybrid system. More precisely, we replace the "boundary condition"

$$v(0,t) = 0 \quad \text{in} \quad \mathbb{R}_+ \tag{4}$$

by

$$\frac{v(\rho,t)}{\rho}\Big|_{\rho=0} = \frac{1}{3} F_v(u(0,t), w(0,t), a(t)) \quad \text{in} \quad \mathbb{R}_+.$$

Then the modified hybrid system is expressed as follows:

$$\begin{cases} \dfrac{da}{dt}(t) = -\gamma(a(t) - a_*) - \gamma a_* S(t) & \text{in} \ \ \mathbb{R}_+, \\ \partial_t u(\rho,t) - \mathscr{L}(v,R)u(\rho,t) = F_u(u(\rho,t), w(\rho,t), a(t)) & \text{in} \ \ I_\infty, \\ \partial_t w(\rho,t) - \mathscr{L}(v,R)w(\rho,t) = F_w(u(\rho,t), w(\rho,t), a(t)) & \text{in} \ \ I_\infty, \\ v(\rho,t) = \dfrac{1}{\rho^2}\displaystyle\int_0^\rho F_v(u(r,t), w(r,t), a(t)) r^2\, dr & \text{in} \ \ I_\infty, \\ \dfrac{dR}{dt}(t) = v(1,t)R(t) & \text{in} \ \ \mathbb{R}_+, \\ S(t) = \begin{cases} 0 \to 1 & \text{when} \ \ R(t) = r_1 \ \ \text{and} \ \ R'(t) > 0, \\ 1 \to 0 & \text{when} \ \ R(t) = r_0 \ \ \text{and} \ \ R'(t) < 0, \end{cases} & \text{in} \ \ \mathbb{R}_+, \\ \partial_\rho u(\rho,t)|_{\rho\in\{0,1\}} = \partial_\rho w(\rho,t)|_{\rho\in\{0,1\}} = 0 & \text{in} \ \ \mathbb{R}_+, \\ \dfrac{v(\rho,t)}{\rho}\Big|_{\rho=0} = \dfrac{1}{3} F_v(u(0,t), w(0,t), a(t)) & \text{in} \ \ \mathbb{R}_+, \\ (a,u,w,R,S)|_{t=0} = (a_0, u_0(\rho), w_0(\rho), R_0, S_0) & \text{in} \ \ I. \end{cases} \tag{mIAS}$$

To begin with, we show that $u + w$ is invariant under (mIAS).

Lemma 2.1 *Let $(u_0, w_0, R_0, a_0, S_0)$ be an initial data satisfying* (3)*. Assume that (u, w, v, R, a, S) is a solution of* (mIAS) *with $u, w \in C^{2+\alpha, 1+\alpha/2}(Q_T)$ and $S(t) \equiv S_0$ in $[0, T)$. Then $u + w \equiv 1$ in $B_1 \times [0, T)$.*

Proof Setting $V := u + w$, we reduce (mIAS) to the following system:

$$\begin{cases} \dfrac{da}{dt}(t) = -\gamma(a(t) - a_*) - \gamma a_* S_0 & \text{in } \mathbb{R}_+, \\ \partial_t V(\rho, t) - \mathscr{L}(v, R)V(\rho, t) = \dfrac{1}{\rho^2}\partial_\rho[\rho^2 v(\rho, t)] & \text{in } I_\infty, \\ v(\rho, t) = \dfrac{1}{\rho^2}\displaystyle\int_0^\rho F_v(u(r, t), w(r, t), a(t))r^2\,dr & \text{in } I_\infty, \\ \dfrac{dR}{dt}(t) = v(1, t)R(t) & \text{in } \mathbb{R}_+, \\ \partial_\rho V(\rho, t)|_{\rho\in\{0,1\}} = 0,\ \dfrac{v(\rho, t)}{\rho}\Big|_{\rho=0} = \dfrac{1}{3}F_v(u(0, t), w(0, t), a(t)), & \text{in } \mathbb{R}_+, \\ V(\rho, 0) = 1, \quad a(0) = a_0, \quad R(0) = R_0, & \text{in } I. \end{cases} \tag{5}$$

In the derivation of the second equation in (5), we used the fact $F_u + F_w = F_v$ and the equation on v. We shall prove that $V \equiv 1$ in $B_1 \times [\,0, T\,)$. The second equation in (5) is written as

$$\partial_t V = \frac{D}{R(t)^2}\Delta_x V - \frac{x}{\rho}\cdot\nabla_x\{v(V-1)\} + v(1, t)x\cdot\nabla_x V - \frac{2}{\rho}v(V-1) \tag{6}$$

in terms of the three-dimensional Cartesian coordinates, where $\rho = |x|$. In what follows, we use ∇ and Δ instead of ∇_x and Δ_x, respectively, if there is no fear of confusion. First, we observe from (6) that

$$\frac{d}{dt}\|V-1\|^2_{L^2(B_1)} = -\frac{2D}{R(t)^2}\|\nabla(V-1)\|^2_{L^2(B_1)} - 2\int_{B_1}(V-1)\frac{x}{\rho}\cdot\nabla\{v(V-1)\}\,dx$$
$$+ 2\int_{B_1}(V-1)v(1, t)x\cdot\nabla V\,dx - 2\int_{B_1}\frac{v}{\rho}(V-1)^2\,dx =: J_1 + J_2 + J_3 + J_4.$$

We start with an estimate of J_1. Since it follows from the third and fourth equations in (5) that

$$R(t) = R_0\exp\Big[\int_0^t v(1, s)ds\Big] \le R_0 e^{\kappa T},$$

we have

$$J_1 \le -\frac{2D}{R_0^2 e^{2\kappa T}}\|\nabla(V-1)\|^2_{L^2(B_1)},$$

where κ is a positive constant given by

$$3\kappa := \|f_1(a)u + f_2(a)w - (c_1 + c_2)uw\|_{L^\infty(Q_T)}.$$

We turn to J_2. By the relation

$$\partial_\rho v = -2\frac{v}{\rho} + f_1(a(t))u + f_2(a(t))w - (c_1 + c_2)uw,$$

the integral J_2 is reduced to

$$J_2 = 4\int_{B_1} \frac{v}{\rho}|V-1|^2\,dx - 2\int_{B_1}(V-1)\frac{v}{\rho}x\cdot\nabla V\,dx \\ - 2\int_{B_1}\{f_1(a(t))u + f_2(a(t))w - (c_1+c_2)uw\}|V-1|^2\,dx.$$

Observing that

$$\left|\ \frac{v(\rho,t)}{\rho}\ \right| \le \frac{1}{\rho^3}\int_0^\rho |f_1(a(t))u + f_2(a(t))w - (c_1+c_2)uw|r^2\,dr \le \kappa,$$

and using Hölder's inequality and Young's inequality, we find

$$|J_2| \le \varepsilon\|\nabla(V-1)\|^2_{L^2(B_1)} + C(\varepsilon)\|V-1\|^2_{L^2(B_1)}.$$

Regarding J_3 and J_4, the same argument as in the estimate of J_2 asserts that

$$|J_3| \le \varepsilon\|\nabla(V-1)\|^2_{L^2(B_1)} + C(\varepsilon)\|V-1\|^2_{L^2(B_1)}, \quad |J_4| \le 2\kappa\|V-1\|^2_{L^2(B_1)}.$$

Thus, letting $\varepsilon > 0$ small enough, we obtain

$$\frac{d}{dt}\|V-1\|^2_{L^2(B_1)} \le C\|V-1\|^2_{L^2(B_1)}. \tag{7}$$

Since $V(\cdot,0) = 1$, applying Gronwall's inequality to (7), we obtain the conclusion. □

Here we reduce the system (mIAS) to the following hybrid system:

$$\begin{cases} \dfrac{da}{dt}(t) = -\gamma(a(t)-a_*) - \gamma a_* S(t) & \text{in } \mathbb{R}_+, \\ \partial_t u(\rho,t) - \mathcal{L}'(v,R)u(\rho,t) = P(u(\rho,t),a(t)) & \text{in } I_\infty, \\ v(\rho,t) = \dfrac{1}{\rho^2}\displaystyle\int_0^\rho F(u(r,t),a(t))r^2\,dr & \text{in } I_\infty, \\ \dfrac{dR}{dt}(t) = v(1,t)R(t) & \text{in } \mathbb{R}_+, \\ S(t) = \begin{cases} 0 \to 1 & \text{when } R(t) = r_1 \text{ and } R'(t) > 0, \\ 1 \to 0 & \text{when } R(t) = r_0 \text{ and } R'(t) < 0, \end{cases} & \text{in } \mathbb{R}_+, \\ \partial_\rho u(\rho,t)\big|_{\rho\in\{0,1\}} = 0, \quad \dfrac{v(\rho,t)}{\rho}\Big|_{\rho=0} = \dfrac{1}{3}F(u(0,t),a(t)), & \text{in } \mathbb{R}_+, \\ a(0) = a_0,\ u(\rho,0) = u_0(\rho),\ R(0) = R_0,\ S(0) = S_0, & \text{in } I, \end{cases} \tag{P}$$

where

$$\mathscr{L}'(v, R)\varphi = \frac{D}{R(t)^2}\frac{1}{\rho^2}\partial_\rho[\rho^2\partial_\rho\varphi] - [v(\rho,t) - \rho v(1,t)]\,\partial_\rho\varphi, \tag{8}$$
$$P(u,a) = \{f_1(a) - f_2(a) - c_1 + (c_1+c_2)u\}\,u(1-u),$$
$$F(u,a) = f_1(a)u + \{f_2(a) - (c_1+c_2)u\}\,(1-u).$$

The reduction is justified as follows:

Lemma 2.2 *The system* (mIAS) *is equivalent to* (P).

Proof If (u, w, v, R, a, S) satisfies (mIAS), then Lemma 2.1 implies that $u + w \equiv 1$. Using $w = 1 - u$, we can reduce (mIAS) to (P). On the other hand, if (u, v, R, a, S) satisfies (P), then, setting $w := 1 - u$, we obtain (mIAS) from (P). □

In order to prove the short time existence of a solution to (mIAS), we first consider the following system, which is formally derived from (P) provided $S(t) \equiv S_0$.

$$\begin{cases} \dfrac{da}{dt}(t) = -\gamma(a(t) - a_*) - \gamma a_* S_0 & \text{in } \mathbb{R}_+, \\ \partial_t u(\rho,t) - \mathscr{L}'(v,R)u(\rho,t) = P(u(\rho,t), a(t)) & \text{in } I_\infty, \\ v(\rho,t) = \dfrac{1}{\rho^2}\displaystyle\int_0^\rho F(u(r,t),a(t))r^2\,dr & \text{in } I_\infty, \\ \dfrac{dR}{dt}(t) = v(1,t)R(t) & \text{in } \mathbb{R}_+, \\ \partial_\rho u(\rho,t)\big|_{\rho\in\{0,1\}} = 0, \quad \dfrac{v(\rho,t)}{\rho}\Big|_{\rho=0} = \dfrac{1}{3}F(u(0,t),a(t)), & \text{in } \mathbb{R}_+, \\ a(0) = a_0, \ \ u(\rho,0) = u_0(\rho), \ \ R(0) = R_0, & \text{in } I. \end{cases} \tag{PS$_0$}$$

Lemma 2.3 *Let* (u_0, R_0, a_0, S_0) *satisfy* (3). *Then there exists* $T > 0$ *such that the system* (PS$_0$) *has a unique solution* (u, v, R, a) *in the class*

$$C^{2+\alpha,1+\frac{\alpha}{2}}(Q_T)\times(C^{1+\alpha,\frac{\alpha}{2}}([\,0,1\,)\times(\,0,T\,))\cap C^1([\,0,1\,)\times(\,0,T\,)))\times(C^1((\,0,T\,)))^2.$$

Proof We shall prove Lemma 2.3 by the contraction mapping principle. Let us define a metric space $(X_M, \|\cdot\|_X)$ as follows:

$$X_M = \{u \in C^{\alpha,\frac{\alpha}{2}}(Q_T) \mid u(x,t) = u(|x|,t),\, u|_{t=0} = u_0,\, \|u\|_X \le M\},$$

where $\|u\|_X = \|u\|_{C^{\alpha,\alpha/2}(Q_T)}$. We will take the constants $T > 0$ and $M > 0$ appropriately, later.

Step 1: *We shall construct a mapping* $\Psi : X_M \to X_M$. Let $u \in X_M$. For $u(\rho,t)$, let us define $(v(\rho,t), R(t))$ as the solution of the following system:

$$\begin{cases} v(\rho,t) = \dfrac{1}{\rho^2}\displaystyle\int_0^\rho F(u(r,t),a(t))r^2\,dr & \text{in} \quad I\times[0,T), \\ \dfrac{dR}{dt}(t) = v(1,t)R(t) & \text{in} \quad (0,T), \\ \dfrac{v(\rho,t)}{\rho}\Big|_{\rho=0} = \dfrac{1}{3}F(u(0,t),a(t)) & \text{in} \quad [0,T), \\ R(0) = R_0. \end{cases} \tag{9}$$

For (v, R) defined by (9), let $\tilde{u}(x,t) = \tilde{u}(|x|,t) = \tilde{u}(\rho,t)$ denote the solution of

$$\begin{cases} \partial_t\tilde{u}(\rho,t) - \mathscr{L}'(v,R)\tilde{u}(\rho,t) = P(u(\rho,t),a(t)) & \text{in} \quad I\times(0,T), \\ \partial_\rho\tilde{u}(0,t) = \partial_\rho\tilde{u}(1,t) = 0 & \text{in} \quad (0,T), \\ \tilde{u}(\rho,0) = u_0(\rho) & \text{in} \quad I. \end{cases} \tag{10}$$

If we consider the problem as an initial-boundary value problem for a one dimensional parabolic equation, the parabolic equation has a singularity at $\rho = 0$. In order to eliminate the singularity, we rewrite the problem in terms of the three dimensional Cartesian coordinate as follows:

$$\begin{cases} \partial_t\tilde{u}(|x|,t) + \left[\dfrac{v(|x|,t)}{|x|} - v(1,t)\right] x\cdot\nabla\tilde{u}(|x|,t) \\ \qquad = \dfrac{D}{R(t)^2}\Delta\tilde{u}(|x|,t) + P(u(|x|,t),a(t)) & \text{in} \quad Q_T, \\ \partial_\rho\tilde{u}(0,t) = \partial_\rho\tilde{u}(1,t) = 0 & \text{in} \quad (0,T), \\ \tilde{u}(|x|,0) = u_0(|x|) & \text{in} \quad B_1. \end{cases} \tag{11}$$

We prove that $\tilde{u} \in X_M$ by applying the Schauder estimate to (11). Since $u \in X_M$, it is clear that $F(u,a) \in C^{\alpha,\alpha/2}(Q_T)$, $P(u,a) \in C^{\alpha,\alpha/2}(Q_T)$, and

$$v(1,t) = \int_0^1 F(u(r,t),a(t))r^2\,dr \in C^{\frac{\alpha}{2}}((0,T)). \tag{12}$$

Moreover, since $R(t) > 0$ in $[0,T)$, the fact (12) implies $1/R(t)^2 \in C^{\alpha/2}((0,T))$. In the following, we will show

$$\mathscr{V}(\rho,t) := \frac{v(\rho,t)}{\rho} \in C^{\alpha,\frac{\alpha}{2}}(Q_T). \tag{13}$$

(i) Let us fix $\rho \in (0,1)$ arbitrarily. Since now $\mathscr{V}$ satisfies, for any $0 < t < s < T$,

$$\mathscr{V}(\rho,s) - \mathscr{V}(\rho,t) = \frac{1}{\rho^3}\int_0^\rho \{F(u(r,s),a(s)) - F(u(r,t),a(t))\}r^2\,dr, \tag{14}$$

we estimate the integrand. It follows from $u \in X_M$ that

$$\begin{aligned} &|F(u(r,s),a(s)) - F(u(r,t),a(t))| \\ &\quad \le C(M)\left\{|u(r,s)-u(r,t)| + \sum_{i=1}^{2} |f_i(a(s)) - f_i(a(t))|\right\} \\ &\quad \le C(M)\left\{M|s-t|^{\frac{\alpha}{2}} + \sum_{i=1}^{2} |f_i(a(s)) - f_i(a(t))|\right\}. \end{aligned} \tag{15}$$

Furthermore, the mean value theorem implies

$$|f_i(a(s)) - f_i(a(t))| \le C|s-t| \quad \text{for} \quad i = 1, 2,$$

where $C = C(f_i, a_*, \gamma)$. Combining the estimate with (15), we find

$$|F(u(r,s),a(s)) - F(u(r,t),a(t))| \le C(M)|s-t|^{\frac{\alpha}{2}}.$$

Consequently, we deduce from (14) that

$$|\mathscr{V}(\rho,s) - \mathscr{V}(\rho,t)| \le C(M)|s-t|^{\frac{\alpha}{2}}.$$

(ii) Let $\rho = 0$. Then by the same argument as in (i), we see that

$$|\mathscr{V}(0,s) - \mathscr{V}(0,t)| = \frac{1}{3}|F(u(0,s),a(s)) - F(u(0,t),a(t))| \le C(M)|s-t|^{\frac{\alpha}{2}}$$

for any $0 < t < s < T$.

(iii) Fix $0 < t < T$ arbitrarily. Then, for any $0 < \rho < \sigma < 1$, it holds that

$$\begin{aligned} \mathscr{V}(\sigma,t) - \mathscr{V}(\rho,t) &= \{\mathscr{V}(\sigma,t) - \mathscr{V}(0,t)\} - \{\mathscr{V}(\rho,t) - \mathscr{V}(0,t)\} \\ &= \frac{1}{\sigma^3}\int_\rho^\sigma \{F(u(r,t),a(t)) - F(u(0,t),a(t))\} r^2\, dr \\ &\quad + \left(\frac{1}{\sigma^3} - \frac{1}{\rho^3}\right)\int_0^\rho \{F(u(r,t),a(t)) - F(u(0,t),a(t))\} r^2\, dr. \end{aligned}$$

Since $u \in X_M$, we observe that

$$|F(u(\rho,t),a(t)) - F(u(0,t),a(t))| \le C(M)|u(\rho,t) - u(0,t)| \le C(M)\rho^\alpha.$$

Therefore we obtain

$$\begin{aligned} |\mathscr{V}(\sigma,t) - \mathscr{V}(\rho,t)| &\le C(M)\frac{1}{\sigma^3}\int_\rho^\sigma r^{2+\alpha}\, dr + C(M)\left|\frac{\rho^3 - \sigma^3}{\sigma^3\rho^3}\right|\int_0^\rho r^{2+\alpha}\, dr \\ &\le C(M)\left|\frac{\sigma^3 - \rho^3}{\sigma^{3-\alpha}}\right| \le C(M)|\sigma - \rho|^\alpha. \end{aligned}$$

(iv) Let us fix $0 < t < T$ arbitrarily. The same argument as in (iii) implies that

$$|\mathscr{V}(\rho, t) - \mathscr{V}(0, t)| \leq C(M)\frac{1}{\rho^3}\int_0^\rho r^{2+\alpha}\,dr \leq C(M)\rho^\alpha \quad \text{for any} \quad \rho \in (0, 1).$$

From (i)–(iv), we conclude (13). Hence, by virtue of (11) we can apply the Schauder estimate (Theorem 5.3, [16]) to (10):

$$\|\tilde{u}\|_{C^{2+\alpha,1+\alpha/2}(Q_T)} \leq C\left(\|P\|_X + \|u_0\|_{C^{2+\alpha}(B_1)}\right) \leq C(M) + C\|u_0\|_{C^{2+\alpha}(B_1)}.$$

On the other hand, it follows from the mean value theorem that

$$\|\tilde{u} - u_0\|_X \leq \max\left\{T, T^{1-\frac{\alpha}{2}}\right\}\|\tilde{u}\|_{C^{2+\alpha,1+\alpha/2}(Q_T)}. \tag{16}$$

Therefore, for $T < 1$, we obtain

$$\begin{aligned}\|\tilde{u}\|_X &\leq T^{1-\frac{\alpha}{2}}\|\tilde{u}\|_{C^{2+\alpha,1+\alpha/2}(Q_T)} + \|u_0\|_{C^{2+\alpha}(B_1)} \\ &\leq T^{1-\frac{\alpha}{2}}\{C(M) + C\|u_0\|_{C^{2+\alpha}(B_1)}\} + \|u_0\|_{C^{2+\alpha}(B_1)}.\end{aligned}$$

Consequently, for $M := 1 + \|u_0\|_{C^{2+\alpha}(B_1)}$, setting $T < 1$ small enough as

$$T^{1-\frac{\alpha}{2}}\{C(M) + C\|u_0\|_{C^{2+\alpha}(B_1)}\} < 1, \tag{17}$$

we deduce that $\tilde{u} \in X_M$. We define a mapping $\Psi : X_M \to X_M$ as $\Psi(u) = \tilde{u}$.

Step 2: *We show that Ψ is a contraction mapping.* Let $u_i \in X_M$. We denote by $(v_i(\rho, t), R_i(t))$ the solution of (9) with $u = u_i$, where $i = 1, 2$. For $\tilde{u}_i := \Psi(u_i)$, set $U := \tilde{u}_1 - \tilde{u}_2$. By a simple calculation, we see that U satisfies

$$\begin{cases}\partial_t U(\rho, t) - \mathscr{L}'(v_2, R_2)U(\rho, t) = G(u_1, u_2) & \text{in} \quad I \times (0, T), \\ \partial_\rho U(0, t) = \partial_\rho U(1, t) = 0 & \text{in} \quad (0, T), \\ U(\rho, 0) = 0 & \text{in} \quad I,\end{cases}$$

where $G(u_1, u_2)$ is given by

$$G(u_1, u_2) = \{\mathscr{L}'(v_1, R_1) - \mathscr{L}'(v_2, R_2)\}\tilde{u}_1 + \{P(u_1) - P(u_2)\}.$$

Adopting a similar argument as in Step 1, we find $G(u_1, u_2) \in C^{\alpha,\alpha/2}(Q_T)$ and

$$\|G(u_1, u_2)\|_X \leq C(T, u_0, R_0)\|u_1 - u_2\|_X.$$

Then the Schauder estimate asserts that

$$\|U\|_{C^{2+\alpha,1+\alpha/2}(Q_T)} \leq C(T, u_0, R_0)\|u_1 - u_2\|_X.$$

By the fact that $U(|x|, 0) = 0$ in B_1 and a similar argument as in (16), it holds that

$$\|\Psi(u_1) - \Psi(u_2)\|_X = \|U\|_X \le T^{1-\frac{\alpha}{2}} \|U\|_{C^{2+\alpha,1+\alpha/2}(Q_T)} \le T^{1-\frac{\alpha}{2}} C\|u_1 - u_2\|_X,$$

where $C = C(T, u_0, R_0)$. Thus, letting T small enough as $T^{1-\alpha/2}C < 1$, we conclude that Ψ is a contraction mapping. Then Banach's fixed point theorem indicates that there exists $u \in X_M$ uniquely such that $\Psi(u) = u$. By the definition of Ψ, u is a unique solution of (PS$_0$) on $[0, T)$. Moreover, we infer from the above argument that $u \in C^{2+\alpha,1+\alpha/2}(Q_T)$.

Finally we prove that $v \in C^{1+\alpha,\alpha/2}([0, 1) \times (0, T)) \cap C^1([0, 1) \times (0, T))$. By a direct calculation, we have $v \in C([0, T); H^1(I))$. Combining the fact with the Sobolev embedding theorem $H^1(I) \hookrightarrow C^{0,1/2}(\bar{I})$, we obtain $v \in C([0, T); C^{0,1/2}(\bar{I}))$, in particular $v \in C(\bar{I} \times [0, T))$. Thus it follows from the continuity that

$$v(0, t) = \lim_{\rho\downarrow 0} v(\rho, t) = 0 \quad \text{for any} \quad t \in [0, T). \tag{18}$$

Then, along the same line as in [23], we see that $v \in C^1([0, 1) \times (0, T))$. Moreover, applying the same argument as in (13) to

$$\partial_\rho v(\rho, t) = \begin{cases} -\dfrac{2}{\rho^3}\displaystyle\int_0^\rho F(u(r, t), a(t))r^2\, dr + F(u(\rho, t), a(t)) & \text{if} \quad \rho > 0, \\ \dfrac{1}{3} F(u(0, t), a(t)) & \text{if} \quad \rho = 0, \end{cases}$$

we find $v \in C^{1+\alpha,\alpha/2}([0, 1) \times (0, T))$. This completes the proof. □

Theorem 2.1 *Let* $(u_0, w_0, R_0, a_0, S_0)$ *satisfy* (3). *Then there exists* $T > 0$ *such that the system* (IAS) *has a unique solution* (u, w, v, R, a, S) *with* $S(t) \equiv S_0$ *in* $[0, T)$ *in the class*

$$\begin{cases} u, w \in C^{2+\alpha,1+\frac{\alpha}{2}}(Q_T), \quad R, a \in C^1((0, T)), \\ v \in C^{1+\alpha,\frac{\alpha}{2}}([0, 1) \times (0, T)) \cap C^1([0, 1) \times (0, T)). \end{cases} \tag{19}$$

Proof Let (u, v, R, a) be the solution of (PS$_0$). According to Lemma 2.3, we see that the solution (u, v, R, a) belongs to the class

$$C^{2+\alpha,1+\frac{\alpha}{2}}(Q_T) \times (C^{1+\alpha,\frac{\alpha}{2}}([0, 1) \times (0, T)) \cap C^1([0, 1) \times (0, T))) \times (C^1((0, T)))^2$$

for some $T > 0$. To begin with, we prove the existence of a short time solution to (P). If there exists $T_1 \in (0, T]$ such that $R(t) \equiv R_0$ in $[0, T_1)$, then (u, v, R, a, S) with $S(t) \equiv S_0$ is a solution of (P), for the fact that $dR/dt = 0$ in $(0, T_1)$ implies that $S(t)$ does not switch in $(0, T_1)$. On the other hand, if there exists no such T_1, there exists $T_2 \in (0, T]$ such that $R(t) \notin \{r_0, r_1\}$ in $(0, T_2)$, for $R(t)$ is continuous. Then it is clear that (u, v, R, a, S) with $S(t) \equiv S_0$ satisfies (P) in $(0, T_2)$. Thus we see that (u, v, R, a, S) with $S(t) \equiv S_0$ is a solution of (P) in $(0, T^*)$ for some $T^* \in (0, T]$.

We show the uniqueness. Let $(u_1, v_1, R_1, a_1, S_1) \neq (u_2, v_2, R_2, a_2, S_2)$ be solutions of (P) satisfying (19). Along the same line as above, we see that $S_1(t) = S_2(t) = S_0$ in $[0, \widetilde{T})$ for some $\widetilde{T} \in (0, T^*]$. Then the uniqueness of the solution of (PS_0) leads a contradiction.

Thanks to Lemma 2.2, we observe that (mIAS) has a unique solution. Moreover, it follows from (18) that the solution satisfies (IAS). Finally we show the uniqueness of solutions of (IAS). Suppose that $(u_i, w_i, v_i, R_i, a_i, S_0)$ are solutions of (IAS) in the class (19), where $i = 1, 2$. Then, by the proof of Lemma 2.2, we observe that (IAS) is reduced to (P) replaced the condition on v/ρ by (4). It is clear that $a_1(t) = a_2(t)$ in $[0, T)$. Set $U := u_1 - u_2$. Then it follows from Step 2 in the proof of Lemma 2.3 that

$$\|U\|_{C^{2+\alpha,1+\frac{\alpha}{2}}(Q_T)} \leq C\|U\|_{C^{\alpha,\frac{\alpha}{2}}(Q_T)}. \tag{20}$$

Moreover, we find

$$\|U\|_{C^{\alpha,\frac{\alpha}{2}}(Q_T)} \leq T^{1-\frac{\alpha}{2}}\|U\|_{C^{2+\alpha,1+\frac{\alpha}{2}}(Q_T)} \leq CT^{1-\frac{\alpha}{2}}\|U\|_{C^{\alpha,\frac{\alpha}{2}}(Q_T)}. \tag{21}$$

Letting T be small enough such that $CT^{1-\alpha/2} < 1$, we observe from (21) that $\|U\|_{C^{\alpha,\alpha/2}} = 0$. Combining the fact with (20), we obtain the conclusion. □

In order to prove $u, w \in [0, 1]$ in $B_1 \times [0, T)$, we apply a parabolic comparison principle to (IAS). Using (u, v, R, a, S), which is the solution of (P) in Q_T constructed by Theorem 2.1, we define the operator

$$\mathscr{P}_i : C^{2,1}(B_1 \times (0, T)) \cap C(\overline{B_1} \times [0, T)) \to C(B_1 \times (0, T))$$

as follows:

$$\mathscr{P}_1 z := \partial_t z - \mathscr{L}'(v, R)z - P(z, a), \quad \mathscr{P}_2 z := \partial_t z - \mathscr{L}'(v, R)z + P(1 - z, a).$$

Regarding the operator $\mathscr{P}_i$, the following parabolic comparison principle holds:

Lemma 2.4 *Assume that* $z, \zeta \in C^{2,1}(B_1 \times (0, T)) \cap C(\overline{B_1} \times [0, T))$ *satisfy*

$$\begin{cases} \mathscr{P}_i z \geq \mathscr{P}_i \zeta & \text{in} \quad B_1 \times (0, T), \\ \partial_\nu z \geq \partial_\nu \zeta & \text{on} \quad \partial B_1 \times (0, T), \\ z \geq \zeta & \text{in} \quad \overline{B_1} \times \{t = 0\}. \end{cases}$$

Then $z \geq \zeta$ *in* $\overline{B_1} \times [0, T)$.

Proof Since the proof of Lemma 2.3 implies that the coefficients in the operator $\mathscr{L}'(v, R)$ are bounded, we can prove Lemma 2.4 along the standard argument (e.g., see [4, 17]). □

By virtue of Lemma 2.4, one can verify $0 \le u \le 1$ and $0 \le w \le 1$:

Lemma 2.5 *Let* (u, w, v, R, a, S) *be a solution of* (IAS) *obtained by Theorem 2.1. Then,* $0 \le u \le 1$ *and* $0 \le w \le 1$ *in* $\overline{B_1} \times [0, T)$.

We close this section with a property of certain quantities of u and w.

Lemma 2.6 *Let us define*

$$\begin{cases} U(t) := 4\pi R^3(t) \displaystyle\int_0^1 u(\rho, t)\rho^2\, d\rho, \\ W(t) := 4\pi R^3(t) \displaystyle\int_0^1 w(\rho, t)\rho^2\, d\rho, \end{cases} \qquad \begin{cases} V_1(t) := \displaystyle\int_0^1 u(\rho, t)\rho^2\, d\rho, \\ V_2(t) := \displaystyle\int_0^1 w(\rho, t)\rho^2\, d\rho. \end{cases}$$

Then U, W, V_1, *and* V_2 *satisfy*

$$\frac{dU}{dt}(t) = 4\pi R^3(t) \int_0^1 c_1 u(\rho, t)^2 \rho^2 d\rho + \{f_1(a(t)) - c_1\} U(t), \tag{22}$$

$$\frac{dW}{dt}(t) = 4\pi R^3(t) \int_0^1 c_2 w(\rho, t)^2 \rho^2 d\rho + \{f_2(a(t)) - c_2\} W(t), \tag{23}$$

$$\frac{dV_1}{dt}(t) \begin{cases} \le g(a(t))V_1(t) + 3\{-g(a(t)) + c_1 + c_2\} V_1(t)^2, \\ \ge \{g(a(t)) - c_1\} V_1(t) - 3\{g(a(t)) - c_1\} V_1(t)^2, \end{cases} \tag{24}$$

$$\frac{dV_2}{dt}(t) \begin{cases} \le -g(a(t))V_2(t) + 3\{g(a(t)) + c_1 + c_2\} V_2(t)^2, \\ \ge -\{g(a(t)) + c_2\} V_2(t) + 3\{g(a(t)) + c_2\} V_2(t)^2, \end{cases} \tag{25}$$

respectively, where g *is a function defined by*

$$g(z) := f_1(z) - f_2(z). \tag{26}$$

Proof The Eqs. (22) and (23) were obtained by [23]. We shall show (24) and (25). It follows from Jensen's inequality and Lemma 2.5 that

$$3V_1(t)^2 \le \int_0^1 u(\rho, t)^2 \rho^2\, d\rho \le V_1(t), \quad 3V_2(t)^2 \le \int_0^1 w(\rho, t)^2 \rho^2\, d\rho \le V_2(t). \tag{27}$$

Combining (27) with the same argument as in [23], we obtain the conclusion. □

Remark 2.1 The function g denotes the difference of net *growth* rate of AD cells and AI cells. We employ the notation frequently in the rest of the paper.

3 Asymptotic Behavior of Non-switching Solutions

We devote this section to investigating the asymptotic behavior of "non-switching" solutions of (IAS). To begin with, we shall show the long time existence of the non-switching solutions of (IAS).

Theorem 3.1 *Let* $(u_0, w_0, R_0, a_0, S_0)$ *satisfy* (3) *and* $S_0 = 1$. *Then the system* (IAS) *with* $r_0 = 0$ *has a unique solution* (u, w, v, R, a, S) *with* $S(t) \equiv 1$ *in* $[0, \infty)$ *in the class*

$$\begin{cases} u, w \in C^{2+\alpha, 1+\frac{\alpha}{2}}(Q_\infty), \quad R, a \in C^1(\mathbb{R}_+), \\ v \in C^{1+\alpha, \frac{\alpha}{2}}([0, 1) \times \mathbb{R}_+)) \cap C^1([0, 1) \times \mathbb{R}_+). \end{cases}$$

Proof It follows from Theorem 2.1 that (IAS) with $r_0 = 0$ has a unique solution with $S(t) \equiv 1$ in Q_T for some $T > 0$. Since

$$R(t) = R_0 \exp\Big[\int_0^t v(1, s)\, ds \Big],$$

we observe from the continuity of the solution that $R(t)$ is positive, i.e. $S(t) \equiv 1$, while the solution exists. Thus, by a standard argument (e.g., see [6]), we prove that the solution can be extended beyond for any $T > 0$. Indeed, if there exists $\widetilde{T} > 0$ such that the solution can not be extended beyond $\widetilde{T}$, then the proof of Theorem 2.1 implies that

$$\|u(\cdot, t)\|_{C^{2+\alpha}(B_1)} \to \infty \quad \text{as} \quad t \uparrow \widetilde{T}. \tag{28}$$

On the other hand, since u is a solution of (PS_0) on $[0, \widetilde{T})$, it holds that

$$\|u(\cdot, t)\|_{C^{2+\alpha}(B_1)} \le \|u\|_{C^{2+\alpha, 1+\alpha/2}_{x,t}(Q_{\widetilde{T}})} \le C(C(\widetilde{T}) + \|u_0\|_{C^{2+\alpha}(B_1)}). \tag{29}$$

Since (29) contradicts (28), we obtain the conclusion. □

Remark 3.1 The system (IAS) with $r_0 = 0$ and $S_0 = 1$ describes a tumor growth under the CAS therapy.

Corollary 3.1 *Let* $(u_0, w_0, R_0, a_0, S_0)$ *satisfy* (3) *and* $S_0 = 0$. *Then the system* (IAS) *with* $r_1 = \infty$ *has a unique solution* (u, w, v, R, a, S) *with* $S(t) \equiv 0$ *in* $[0, \infty)$ *in the class*

$$\begin{cases} u, w \in C^{2+\alpha, 1+\frac{\alpha}{2}}(Q_\infty), \quad R, a \in C^1(\mathbb{R}_+), \\ v \in C^{1+\alpha, \frac{\alpha}{2}}([0, 1) \times \mathbb{R}_+)) \cap C^1([0, 1) \times \mathbb{R}_+). \end{cases}$$

In the following, we classify the asymptotic behavior of non-switching solutions obtained by Theorem 3.1 and Corollary 3.1. Recalling Lemma 2.2 and Theorem 2.1, we may consider (P) instead of (IAS).

If u_0 is trivial, i.e., $u_0 \equiv 0$ or $u_0 \equiv 1$, then Lemma 2.4 asserts that u is also trivial in Q_T. Thus it is sufficient to consider the initial data (u_0, R_0, a_0, S_0) satisfying

$$\begin{cases} u_0 \in C^{2+\alpha}(B_1), \quad \partial_\rho u_0(0) = \partial_\rho u_0(1) = 0, \quad 0 \le u_0 \le 1, \\ u_0(\rho) \not\equiv 0, \quad u_0(\rho) \not\equiv 1, \quad 0 < a_0 < a_*, \quad R_0 > 0, \quad S_0 \in \{0, 1\}, \end{cases} \tag{IC}$$

where $0 < \alpha < 1$. Regarding f_i and c_i, we assume (A0) throughout this section.

From now on, for a function $h : [\,0, a_*\,] \to \mathbb{R}$, we define $\|h\|_\infty$ by

$$\|h\|_\infty := \sup_{z \in [\,0, a_*\,]} |h(z)|. \tag{30}$$

First we consider the asymptotic behavior of solutions to (P) with $S \equiv 1$.

Theorem 3.2 *Let $r_0 = 0$. Let (u_0, R_0, a_0, S_0) satisfy* (IC) *and $S_0 = 1$. Assume that either of two assumptions holds*:

(i) $g(0) + c_2 < 0$;

(ii) $g(0) + c_2 > 0$ *and*

$$\int_0^1 u_0(\rho)\rho^2\, d\rho < \frac{1}{3} \frac{-g(0)}{-g(0) + c_1 + c_2} \exp\Big[-\frac{a_0}{\gamma} \|g'\|_\infty \Big]. \tag{31}$$

Then the solution (u, v, R, a, S) of (P) *satisfies $R(t) \to \infty$ as $t \to \infty$.*

Proof To begin with, we note that $S(t) \equiv 1$ under (P) with $r_0 = 0$ and $S_0 = 1$.

We prove the case (i). Since $S \equiv 1$ yields the monotonicity of $a(t)$, especially that of $f_i(a(t))$, from the assumptions (A0) and (i), we find $s_1 > 0$ such that

$$f_1(a(t)) < 0, \quad f_2(a(t)) > 0, \quad -g(a(t)) - c_2 > 0 \quad \text{for any} \quad t \ge s_1.$$

Recalling that $u_0 \not\equiv 1$ yields $V_2(t) > 0$ for any $t \ge 0$ and setting $\widetilde{V}_2(t) := 1/V_2(t)$, we observe from (25) that

$$\frac{d\widetilde{V}_2}{dt}(t) \le \{g(a(t)) + c_2\}\widetilde{V}_2(t) - 3\{g(a(t)) + c_2\}. \tag{32}$$

Applying Gronwall's inequality to (32), we have

$$\widetilde{V}_2(t) \le 3 + \big(\widetilde{V}_2(0) - 3\big) \exp\Big[\int_0^t \{g(a(s)) + c_2\}\, ds \Big].$$

Since

$$\begin{aligned} \int_0^t \{g(a(s)) + c_2\}\, ds &= \int_0^{s_1} \{g(a(s)) + c_2\}\, ds + \int_{s_1}^t \{g(a(s)) + c_2\}\, ds \\ &\le (g(a_0) + c_2)s_1 - \{-g(a(s_1)) - c_2\}(t - s_1) \to -\infty \quad \text{as} \quad t \to \infty, \end{aligned}$$

one can verify that $\limsup_{t\to\infty} \widetilde{V}_2(t) \le 3$. On the other hand, since $w \le 1$ yields $\widetilde{V}_2(t) \ge 3$ in $[0, \infty)$, we find $\liminf_{t\to\infty} \widetilde{V}_2(t) \ge 3$. Thus we have $\lim_{t\to\infty} \widetilde{V}_2(t) = 3$ and then

$$\|w(\cdot, t) - 1\|_{L^\infty(B_1)} \to 0 \quad \text{as} \quad t \to \infty. \tag{33}$$

By way of $u + w \equiv 1$, it follows from (33) that for any ε with

$$0 < \varepsilon < \frac{f_2(s_1)}{-g(0) + c_1 + c_2}, \tag{34}$$

there exists $T_1 > s_1$ such that

$$\|u(\cdot, t)\|_{L^\infty(B_1)} < \varepsilon \quad \text{for any} \quad t > T_1. \tag{35}$$

In what follows, let $t > T_1$. Since R satisfies

$$R(t) = R_0 \exp\Big[\int_0^{T_1} v(1, s)\, ds \Big] \exp\Big[\int_{T_1}^{t} v(1, s)\, ds \Big], \tag{36}$$

it is sufficient to estimate the integrals in the right-hand side of (36). We observe from the continuity of $v(1, \cdot)$ that

$$\int_0^{T_1} v(1, s)\, ds \ge -C T_1$$

for some $C > 0$. Moreover, we obtain

$$\begin{aligned}
\int_{T_1}^{t} v(1, s)\, ds &= \int_{T_1}^{t} \int_0^1 F(u(\rho, s), a(s)) \rho^2 \, d\rho\, ds \\
&\ge \int_{T_1}^{t} \int_0^1 [-\{-g(a(t)) + c_1 + c_2\} u + f_2(a(T_1))] \rho^2 \, d\rho\, ds \\
&\ge \frac{1}{3} \{-(-g(0) + c_1 + c_2)\varepsilon + f_2(a(s_1))\}(t - T_1).
\end{aligned}$$

Hence, it follows from (34) and (35) that $\liminf_{t\to\infty} R(t) = \infty$.

Next we turn to the case (ii). By the assumption (A0) and the monotonicity of $f_i(a(\cdot))$, there exists $s_2 \ge 0$ such that

$$f_2(a(t)) > 0, \quad g(a(t)) < 0, \quad \text{for any} \quad t \ge s_2.$$

Recalling $V_1(t) > 0$ in $[0, \infty)$ and setting $\widetilde{V}_1(t) := 1/V_1(t)$, we reduce (24) to

$$\frac{d\widetilde{V}_1}{dt}(t) \geq -g(a(t))\widetilde{V}_1 - 3\{-g(a(t)) + c_1 + c_2\}.$$

Since it follows from the same argument as in (i) that

$$\widetilde{V}_1(t) \geq e^{-\int_0^t g(a(s))\,ds} \left[3(g(0) - c_1 - c_2) \int_0^t e^{\int_0^s g(a(\tau))\,d\tau} ds + \widetilde{V}_1(0) \right], \tag{37}$$

we estimate the integral in the right-hand side of (37). Noting that $a(\cdot)$ is monotone decreasing, we use the change of variable $a(s) = z$, and then

$$\begin{aligned}\int_0^t g(a(s))\,ds &= -\frac{1}{\gamma}\int_{a_0}^{a(t)} \frac{g(z)}{z}\,dz = -\frac{1}{\gamma}\int_{a_0}^{a(t)} \left[\frac{g(0)}{z} + g'(\tilde{z}) \right] dz \\ &\leq -\frac{g(0)}{\gamma}\log\frac{a(t)}{a_0} + \frac{a_0}{\gamma}\|g'\|_\infty,\end{aligned} \tag{38}$$

where $\tilde{z} \in (\,0, a_0\,)$. Combining (37) with (38), we obtain

$$\begin{aligned}\widetilde{V}_1(t) \geq& \left(\frac{a(t)}{a_0}\right)^{\frac{g(0)}{\gamma}} \left[3(g(0) - c_1 - c_2) \int_0^\infty \left(\frac{a_0}{a(s)}\right)^{\frac{g(0)}{\gamma}} ds + \widetilde{V}_1(0) e^{-\frac{a_0}{\gamma}\|g'\|_\infty} \right] \\ \geq& \left(\frac{a(t)}{a_0}\right)^{\frac{g(0)}{\gamma}} \left[\frac{-3(-g(0) + c_1 + c_2)}{-g(0)} + \widetilde{V}_1(0) e^{-\frac{a_0}{\gamma}\|g'\|_\infty} \right].\end{aligned}$$

Under (A0) and (31), the inequality implies that $\widetilde{V}_1 \to \infty$ as $t \to \infty$, i.e., $V_1(t) \to 0$ as $t \to \infty$. Thus for any ε with

$$0 < \varepsilon < \frac{f_2(a(s_2))}{-g(0) + c_1 + c_2}, \tag{39}$$

there exists $T_2 \geq s_2$ such that

$$\|u(\cdot, t)\|_{L^\infty(B_1)} < \varepsilon \quad \text{for any} \quad t > T_2. \tag{40}$$

By virtue of (39) and (40), we have

$$\begin{aligned}\int_{T_2}^t v(1, s)\,ds &\geq \int_{T_2}^t \int_0^1 \{-(-g(0) + c_1 + c_2)u + f_2(a(T_2))\}\rho^2\,d\rho\,ds \\ &\geq \frac{1}{3}\{-(-g(0) + c_1 + c_2)\varepsilon + f_2(a(s_2))\}(t - T_2).\end{aligned}$$

Thus we see that $\liminf_{t\to\infty} R(t) = \infty$ along the same line as in (i). □

Next we give the asymptotic behavior of solutions to (P) with $r_0 = 0$ and $S_0 = 1$.

Theorem 3.3 *Let* $r_0 = 0$. *Let* (u_0, R_0, a_0, S_0) *satisfy* (IC) *and* $S_0 = 1$. *Assume that*

$$g(0) + c_2 > 0 \tag{41}$$

and

$$\min_{\rho\in[0,1]} u_0(\rho) > 1 - \frac{g(0) + c_2}{g(0) + c_1 + 2c_2}. \tag{42}$$

Then the solution (u, v, R, a, S) *of* (P) *satisfies* $R(t) \to 0$ *as* $t \to \infty$.

Proof Recalling that $S \equiv 1$ under (P) with $r_0 = 0$ and $S_0 = 1$, and using (A0), we find $s_3 \geq 0$ such that

$$f_1(a(t)) < 0 \quad \text{for any} \quad t \geq s_3. \tag{43}$$

Let $\overline{w}$ be the solution of the following initial value problem:

$$\begin{cases} \dfrac{d\overline{w}}{dt}(t) = -\{g(a(t)) + c_2\}\overline{w}(t) + \{g(a(t)) + c_1 + 2c_2\}\overline{w}(t)^2, \\ \overline{w}(0) = 1 - \min\limits_{\rho\in[0,1]} u_0(\rho). \end{cases}$$

Then Lemma 2.4 asserts that

$$0 \leq w(\rho, t) \leq \overline{w}(t) \quad \text{for any} \quad (\rho, t) \in [0, 1] \times [0, \infty), \tag{44}$$

i.e., $\overline{w}$ is a supersolution of w. Since $w_0 \not\equiv 0$, the relation (44) implies $\overline{w}(t) > 0$ for any $t \geq 0$. Setting $\omega := 1/\overline{w}$, we see that ω is expressed by

$$\omega = e^{\int_0^t \{g(a(s))+c_2\}\,ds}\left[-\int_0^t \{g(a(s)) + c_1 + 2c_2\}e^{-\int_0^s \{g(a(\tau))+c_2\}\,d\tau} ds + \frac{1}{\overline{w}(0)} \right].$$

Here we have

$$\begin{aligned} &\int_0^t \{g(a(s)) + c_1 + 2c_2\}e^{-\int_0^s \{g(a(\tau))+c_2\}\,d\tau}\, ds \\ &= \int_0^t \{g(a(s)) + c_2\}e^{-\int_0^s \{g(a(\tau))+c_2\}\,d\tau} ds + (c_1 + c_2)\int_0^t e^{-\int_0^s \{g(a(\tau))+c_2\}\,d\tau} ds \\ &\leq -e^{-\int_0^t \{g(a(\tau))+c_2\}\,d\tau} + 1 + (c_1 + c_2)\int_0^t e^{-\{g(0)+c_2\}s}\, ds \\ &\leq 1 + \frac{c_1 + c_2}{g(0) + c_2}\left(1 - e^{-\{g(0)+c_2\}t}\right) \leq \frac{g(0) + c_1 + 2c_2}{g(0) + c_2}. \end{aligned}$$

Since it follows from (41) that

$$\liminf_{t\to\infty} \exp\left[\int_0^t \{g(a(s)) + c_2\}\, ds \right] \geq \liminf_{t\to\infty} \exp\left[(g(0) + c_2)t\right] = \infty,$$

we observe from (42) that $\lim_{t\to\infty}\omega(t)=\infty$, i.e., $\lim_{t\to\infty}\overline{w}(t)=0$, where we used the positivity of $\overline{w}$. With the aid of (44), for any ε with

$$0<\varepsilon<\frac{-f_1(a(s_3))}{-g(0)}, \tag{45}$$

there exists $T_3>s_3$ such that

$$\|w(\cdot,t)\|_{L^\infty(B_1)}<\varepsilon \quad \text{for any} \quad t>T_3.$$

Recalling $u=1-w$ and using the same argument as in the proof of Theorem 3.2 (i), we can verify that

$$\begin{aligned} R(t) &\le R_0 e^{CT_3} e^{\int_{T_3}^t v(1,s)\,ds} \le R_0 e^{CT_3}\exp\Big[\int_{T_3}^t \{-g(a(s))w+f_1(a(s))\}\,ds\Big] \\ &\le R_0 e^{CT_3}\exp\Big[\frac{1}{3}\{-g(0)\varepsilon+f_1(s_3)\}(t-T_3)\Big]. \end{aligned}$$

Then (45) yields $\limsup_{t\to\infty}R(t)=0$. □

We turn to the case of (P) with $r_1=\infty$ and $S_0=0$. We note that (P) with $r_1=\infty$ and $S_0=0$ describes the behavior of prostate tumor under non-medication.

Theorem 3.4 *Let* $r_1=\infty$. *Let* (u_0,R_0,a_0,S_0) *satisfy* (IC) *and* $S_0=0$. *We suppose that one of the following assumptions holds*:
(i) $f_1(a_*)-c_1>0$; (ii) $f_2(a_*)-c_2>0$; (iii) $g(a_*)-c_1>0$;
(iv) $-g(a_*)+c_1>0$, $f_2(a_*)>0$, *and*

$$\max_{\rho\in[0,1]}u_0(\rho)<\frac{-g(a_*)+c_1}{-g(a_*)+2c_1+c_2}; \tag{46}$$

(v) $g(a_*)+c_2>0$ *and*

$$\min_{\rho\in[0,1]}u_0(\rho)>1-\frac{g(a_*)+c_2}{g(a_*)+c_1+2c_2}\exp\Big[-\frac{a_*}{\gamma}\|g'\|_\infty\Big].$$

Then the solution (u,v,R,a,S) *of* (P) *satisfies* $R(t)\to\infty$ *as* $t\to\infty$.

Proof We prove the case (i). Remark that $S\equiv 0$ yields the monotonicity of $a(t)$, especially that of $f_i(a(t))$. Under the assumption (i), we find $s_4\ge 0$ such that $f_1(a(t))-c_1>0$ for any $t\ge s_4$. Since it follows from (22) that

$$\frac{dU}{dt}\ge\{f_1(a(t))-c_1\}U(t) \quad \text{for any} \quad t\ge 0,$$

making use of Gronwall's inequality and the monotonicity of $f_1(a(\cdot))$, we find

$$\begin{aligned} U(t) &\geq U(s_4)\exp\Big[\int_{s_4}^{t}\{f_1(a(s))-c_1\}\,ds\Big] \\ &\geq U(s_4)\exp\left[\{f_1(a(s_4))-c_1\}(t-s_4)\right] \quad \text{for any} \quad t\geq s_4. \end{aligned}$$

Consequently we see that

$$\liminf_{t\to\infty}\frac{4}{3}\pi R^3(t)=\liminf_{t\to\infty}\{U(t)+W(t)\}\geq\liminf_{t\to\infty}U(t)=\infty.$$

Regarding the other cases, we obtain the conclusion along the same line as in the proof of Theorem 3.2. □

By the same argument as in the proof of Theorem 3.3, we obtain the following:

Theorem 3.5 *Let $r_1=\infty$. Let (u_0, R_0, a_0, S_0) satisfy* (IC) *and $S_0=0$. Assume that*

$$-g(a_*)+c_1>0, \quad f_2(a_*)<0, \tag{47}$$

and (46). *Then the solution (u, v, R, a, S) of* (P) *satisfies $R(t)\to 0$ as $t\to\infty$.*

4 Proof of the Main Theorem

The purpose of this section is to prove the existence of a switching solution of (IAS) and investigate its property under the assumption (A0)–(A2). Here we note that (A1) and (A2) are written as $g(a_*)-c_1>0$ and $g(0)+c_2>0$, respectively, where g was defined by (26). For this purpose, we may deal with (P) instead of (IAS), for the solution of (P) constructed in Sect. 2 also satisfies (IAS). In the following, we fix (u_0, R_0, a_0, S_0) satisfying (IC), $u_0>0$, and $S_0=0$, arbitrarily.

To begin with, we shall study the behavior of solutions of (P) with $S\equiv 0$. More precisely, for each "initial data" $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$, we consider the following system:

$$\begin{cases} \dfrac{d\tilde{a}}{dt}(t)=-\gamma(\tilde{a}(t)-a_*) & \text{in} \quad \mathbb{R}_+, \\ \partial_t\tilde{u}(\rho,t)-\mathscr{L}'(\tilde{v},\tilde{R})\tilde{u}(\rho,t)=P(\tilde{u}(\rho,t),\tilde{a}(t)) & \text{in} \quad I_\infty, \\ \tilde{v}(\rho,t)=\dfrac{1}{\rho^2}\displaystyle\int_0^\rho F(\tilde{u}(r,t),\tilde{a}(t))r^2\,dr & \text{in} \quad I_\infty, \\ \dfrac{d\widetilde{R}}{dt}(t)=\tilde{v}(1,t)\widetilde{R}(t) & \text{in} \quad \mathbb{R}_+, \\ \partial_\rho\tilde{u}(\rho,t)\big|_{\rho\in\{0,1\}}=0, \quad \dfrac{\tilde{v}(\rho,t)}{\rho}\Big|_{\rho=0}=\dfrac{1}{3}F(\tilde{u}(0,t),\tilde{a}(t)), & \text{in} \quad \mathbb{R}_+, \\ \tilde{a}(0)=\tilde{a}_0, \;\; \tilde{u}(\rho,0)=\tilde{u}_0(\rho), \;\; \widetilde{R}(0)=\widetilde{R}_0, & \text{in} \quad I, \end{cases} \tag{P0}$$

where the operator $\mathscr{L}'$ was defined by (8). We characterize the time variable in terms of the solution $\tilde{a}(\cdot)$ to (P0). Recalling that f_1 is monotone, we define a function $\tau_0 : (\,0,\, f_1(a_*) - f_1(\tilde{a}_0)\,] \to [\,0, \infty\,)$ as

$$\tau_0(\varepsilon) = \tilde{a}^{-1}(f_1^{-1}(f_1(a_*) - \varepsilon)), \tag{48}$$

where $\tilde{a}^{-1}$ and f_1^{-1} denote the inverse functions of $\tilde{a}$ and f_1, respectively. Note that, since $\tilde{a}(t) \uparrow a_*$ as $t \to \infty$, $\varepsilon \downarrow 0$ is equivalent to $\tau_0(\varepsilon) \to \infty$.

From now on, we will follow the notation $\|\cdot\|_\infty$ defined in (30).

Lemma 4.1 *Assume that there exist constants* $A \in (\,0, 1\,)$ *and* $\kappa \in (\,0, a_*\,)$ *such that* $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$ *satisfies* (IC) *and the following*:

$$\min_{\rho\in[\,0,1\,]} \tilde{u}_0(\rho) \geq A; \tag{49}$$

$$\tilde{a}_0 \leq \kappa. \tag{50}$$

Then there exists a strictly monotone increasing continuous function

$$\Gamma_0(\varepsilon; A, \kappa) : (\,0,\, f_1(a_*) - f_1(0)\,] \to \mathbb{R}_+$$

with $\Gamma_0(\varepsilon; A, \kappa) \downarrow 0$ *as* $\varepsilon \downarrow 0$ *such that the solution of* (P0) *satisfies*

$$\|\tilde{u}(\cdot, \tau_0(\varepsilon)) - 1\|_{L^\infty(B_1)} \leq \Gamma_0(\varepsilon; A, \kappa) \quad \text{in} \quad (\,0,\, f_1(a_*) - f_1(\tilde{a}_0)\,].$$

Proof Let us consider

$$\begin{cases} \dfrac{d\overline{w}}{dt} = -(g(\tilde{a}(t)) - c_1)(1 - \overline{w})\overline{w}, \\ \overline{w}(0) = 1 - \min\limits_{\rho\in[\,0,1\,]} \tilde{u}_0(\rho). \end{cases} \tag{51}$$

By way of Lemma 2.4, one can easily verify that $\overline{w}$ is a supersolution of $1 - \tilde{u}$. Solving (51) and setting $t = \tau_0(\varepsilon)$, we find

$$\omega(\tau_0(\varepsilon)) = 1 + (\omega(0) - 1)\exp\Big[\int_0^{\tau_0(\varepsilon)} \{g(\tilde{a}(s)) - c_1\}\,ds\,\Big],$$

where $\omega = 1/\overline{w}$. From the change of variable $\tilde{a}(s) = z$, we have

$$\begin{aligned} \int_0^{\tau_0(\varepsilon)} \{g(\tilde{a}(s)) - c_1\}ds &= -\frac{1}{\gamma}\int_{\tilde{a}_0}^{\tilde{a}(\tau_0(\varepsilon))}\Big[\,\frac{g(z) - g(a_*)}{z - a_*} + \frac{g(a_*) - c_1}{z - a_*}\,\Big]dz \\ &\geq -\frac{\tilde{a}(\tau_0(\varepsilon)) - \tilde{a}_0}{\gamma}\|g'\|_\infty + \frac{g(a_*) - c_1}{\gamma}\log\frac{a_* - \tilde{a}_0}{a_* - \tilde{a}(\tau_0(\varepsilon))} \\ &\geq -\frac{a_*}{\gamma}\|g'\|_\infty + \frac{g(a_*) - c_1}{\gamma}\log\frac{a_* - \tilde{a}_0}{a_* - \tilde{a}(\tau_0(\varepsilon))}, \end{aligned} \tag{52}$$

where we used (A1) in the last inequality. Therefore, using (49) and (50), we define the required function $\Gamma_0(\varepsilon; A, \kappa)$ as follows:

$$\overline{w}(\tau_0(\varepsilon)) \leq \Big[1 + Ae^{-\frac{a_*}{\gamma}\|g'\|_\infty} \Big(\frac{a_* - \kappa}{a_* - f_1^{-1}(f_1(a_*) - \varepsilon)} \Big)^{\frac{g(a_*)-c_1}{\gamma}} \Big]^{-1} =: \Gamma_0(\varepsilon; A, \kappa).$$

This completes the proof. □

Lemma 4.2 *Under the same assumption as in Lemma 4.1, there exists a constant $\varepsilon_1 \in (0, f_1(a_*))$, independent of $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$, such that the solution of* (P0) *satisfies*

$$\frac{d\widetilde{R}}{dt}(\tau_0(\varepsilon)) > 0 \quad \textit{for any} \quad \varepsilon \in (0, \varepsilon_1].$$

Proof Since $d\widetilde{R}/dt$ is written by

$$\frac{d\widetilde{R}}{dt}(t) = \widetilde{R}(t)\tilde{v}(1,t) = \widetilde{R}(t)\int_0^1 F(\tilde{u}(\rho,t), \tilde{a}(t))\rho^2\, d\rho, \tag{53}$$

we observe that the sign of $d\widetilde{R}/dt$ is determined by that of the integral in (53). In particular, we focus on the sign of F. From $\partial_z^2 F(z,\alpha) = 2(c_1 + c_2) > 0$, we find

$$\begin{aligned} F(z,\alpha) &> F(1,\alpha) + \partial_z F(1,\alpha)(z-1) \\ &\geq F(1,\alpha) + \partial_z F(1,a_*)(z-1) =: y(z;\alpha) \quad \text{in} \quad [0,1) \times [0, a_*], \end{aligned} \tag{54}$$

where we used the monotonicity of $\partial_z F(1,\alpha) = g(\alpha) - c_1 - c_2$ in the second inequality. Here, noting the positivity of $\partial_z F(1, a_*)$, we denote by $z_0(\alpha)$ the zero point of $y(z;\alpha)$ given by

$$z_0(\alpha) = \frac{-F(1,\alpha) + \partial_z F(1,a_*)}{\partial_z F(1,a_*)}.$$

Since (48) yields that

$$F(1, \tilde{a}(\tau_0(\varepsilon))) = f_1(a_*) - \varepsilon > 0 \quad \text{for any} \quad \varepsilon \in (0, f_1(a_*)), \tag{55}$$

we see that

$$z_0(\tilde{a}(\tau_0(\varepsilon))) < 1, \quad y(1, \tilde{a}(\tau_0(\varepsilon))) > 0, \quad \text{for all} \quad \varepsilon \in (0, f_1(a_*)). \tag{56}$$

Then, for each $\varepsilon \in (0, f_1(a_*))$, we observe from (56) that $y(z, \tilde{a}(\tau_0(\varepsilon))) \geq 0$ for all $z \in [z_0(\tilde{a}(\tau_0(\varepsilon))), 1]$. Combining the fact with (54)–(55), we infer that

$$F(z, \tilde{a}(\tau_0(\varepsilon))) > 0 \ \text{ for all } \ z \in [z_0(\tilde{a}(\tau_0(\varepsilon))), 1], \ \text{ if } \ \varepsilon \in (0, f_1(a_*)). \tag{57}$$

In order to complete the proof of Lemma 4.2, it is sufficient to prove the claim: there exists a constant $\varepsilon_1 \in (0, f_1(a_*))$, independent of $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$, such that the solution $(\tilde{u}, \tilde{v}, \widetilde{R}, \tilde{a})$ of (P0) satisfies

$$\min_{\rho \in [0,1]} \tilde{u}(\rho, \tilde{a}(\tau_0(\varepsilon))) \geq z_0(\tilde{a}(\tau_0(\varepsilon))) \quad \text{for any} \quad \varepsilon \in (0, \varepsilon_1].$$

Indeed, combining the claim with (57), we clearly obtain the conclusion. We shall show the claim by way of Lemma 4.1. Since $z_0(\tilde{a}(\tau_0(f_1(a_*))) = 1$ and

$$z_0(\tilde{a}(\tau_0(\varepsilon))) \downarrow z_0(a_*) < 1, \quad 1 - \Gamma_0(\varepsilon; A, \kappa) \uparrow 1, \quad \text{as} \quad \varepsilon \downarrow 0,$$

from the monotonicity of $z_0(\tilde{a}(\tau_0(\varepsilon)))$ and $1 - \Gamma_0(\varepsilon; A, \kappa)$, we find a constant $\tilde{\varepsilon}_1 \in (0, f_1(a_*))$ uniquely, independent of $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$, such that

$$1 - \Gamma_0(\varepsilon; A, \kappa) \geq z_0(\tilde{a}(\tau_0(\varepsilon))) \quad \text{for any} \quad \varepsilon \in (0, \tilde{\varepsilon}_1]. \tag{58}$$

Recalling (50) implies that $f_1(\kappa) \geq f_1(\tilde{a}_0)$ and setting $\varepsilon_1 := \min\{\tilde{\varepsilon}_1, f_1(a_*) - f_1(\kappa)\}$, we observe from (58) and Lemma 4.1 that

$$\min_{\rho \in [0,1]} \tilde{u}(\rho, \tilde{a}(\tau_0(\varepsilon))) \geq 1 - \Gamma_0(\varepsilon; A, \kappa) \geq z_0(\tilde{a}(\tau_0(\varepsilon))) \quad \text{for any} \quad \varepsilon \in (0, \varepsilon_1].$$

Then the claim holds true and we have completed the proof. □

Lemma 4.3 *Let* $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0) = (u_0, R_0, a_0)$. *Then there exist monotone decreasing functions* M^- *and* M^+ *defined on* $(0, f_1(a_*) - f_1(0)]$ *such that the solution of* (P0) *satisfies*

$$R_0 \exp M^-(\varepsilon) \leq \widetilde{R}(\tau_0(\varepsilon)) \leq R_0 \exp M^+(\varepsilon) \quad \textit{in} \quad (0, f_1(a_*) - f_1(a_0)], \tag{59}$$

where the second inequality is strict for any $\varepsilon \in (0, f_1(a_*) - f_1(a_0))$. *Moreover,* M^- *and* M^+ *satisfy the following*:

$$-\infty < M^-(\varepsilon) \leq M^+(\varepsilon) < \infty \quad \textit{in} \quad (0, f_1(a_*) - f_1(0)]; \tag{60}$$

$$\lim_{\varepsilon \downarrow 0} M^-(\varepsilon) = \infty. \tag{61}$$

Proof Since $\widetilde{R}(\tau_0(\varepsilon))$ is given by

$$\widetilde{R}(\tau_0(\varepsilon)) = R_0 \exp\left[\int_0^{\tau_0(\varepsilon)} \tilde{v}(1, s)\, ds \right] \quad \text{in} \quad (0, f_1(a_*) - f_1(a_0)], \tag{62}$$

we will estimate the integral in (62). To this aim, setting $\tilde{w} = 1 - \tilde{u}$, we decompose the integral as follows:

$$\int_0^{\tau_0(\varepsilon)} \tilde{v}(1,s)\,ds = (c_1 + c_2)\int_0^{\tau_0(\varepsilon)}\int_0^1 \tilde{w}^2\rho^2\,d\rho ds \tag{63}$$
$$- \int_0^{\tau_0(\varepsilon)}\int_0^1 \left[g(\tilde{a}(s)) + c_1 + c_2\right]\tilde{w}\rho^2\,d\rho ds + \frac{1}{3}\int_0^{\tau_0(\varepsilon)} f_1(\tilde{a}(s))\,ds =: I_1 + I_2 + I_3.$$

First we construct M^-. Regarding I_1, it follows from Jensen's inequality that

$$I_1 \geq \frac{c_1 + c_2}{3}\int_0^{\tau_0(\varepsilon)}\left(\int_0^1 \tilde{w}\rho^2\,d\rho\right)^2 ds =: \frac{c_1 + c_2}{27}\int_0^{\tau_0(\varepsilon)} \mathscr{W}(s)^2\,ds. \tag{64}$$

Employing a differential inequality in (25), we see that $\mathscr{W}$ satisfies

$$\mathscr{W}(s) \geq \frac{1}{1 + \left(\frac{1}{\mathscr{W}(0)} - 1\right)\exp\left[\int_0^s \{g(\tilde{a}(\tau)) + c_2\}\,d\tau\right]}. \tag{65}$$

Furthermore, the same argument as in (52) yields

$$\int_0^s \{g(\tilde{a}(\tau)) + c_2\}\,d\tau \leq \frac{g(a_*) + c_2}{\gamma}\log \mathscr{T}_{a_0}(\tilde{a}(s)), \tag{66}$$

where

$$\mathscr{T}_{z_1}(z_2) := \frac{a_* - z_1}{a_* - z_2}. \tag{67}$$

Hence, combining (64) with (65)–(66), we have

$$I_1 \geq \frac{c_1 + c_2}{27}\int_0^{\tau_0(\varepsilon)}\left[\,1 + \left[\,\frac{1}{\mathscr{W}(0)} - 1\,\right]\mathscr{T}_{a_0}(\tilde{a}(s))^{\frac{g(a_*)+c_2}{\gamma}}\,\right]^{-2} ds =: I_{11}.$$

Changing the variable

$$\eta = 1 + \left(\frac{1}{\mathscr{W}(0)} - 1\right)\mathscr{T}_{a_0}(\tilde{a}(s))^{\frac{g(a_*)+c_2}{\gamma}}$$

and setting

$$\eta_0 := \frac{1}{\mathscr{W}(0)}, \quad \eta_\varepsilon := 1 + \left(\frac{1}{\mathscr{W}(0)} - 1\right)\mathscr{T}_{a_0}(\tilde{a}(\tau_0(\varepsilon)))^{\frac{g(a_*)+c_2}{\gamma}},$$

we can define $M_1^- : (0, f_1(a_*) - f_1(a_0)] \to \mathbb{R}$ as follows:

$$
\begin{aligned}
I_{11} &= C_1 \int_{\eta_0}^{\eta_\varepsilon} \frac{d\eta}{(\eta-1)\eta^2} \ge C_1 \left[\log \frac{\eta_0(\eta_\varepsilon - 1)}{\eta_\varepsilon(\eta_0 - 1)} - \frac{1}{\eta_0} \right] \\
&= - C_1 \left[\log \left[\mathscr{U}_0 + (1 - \mathscr{U}_0) \mathscr{T}_{a_0}(\tilde{a}(\tau_0(\varepsilon)))^{-\frac{g(a_*)+c_2}{\gamma}} \right] + 1 - \mathscr{U}_0 \right] \\
&\ge - C_1 \left[\log \left[1 + (1 - \mathscr{U}_0) \mathscr{T}_{\kappa_0}(\tilde{a}(\tau_0(\varepsilon)))^{-\frac{g(a_*)+c_2}{\gamma}} \right] + 1 - \mathscr{U}_0 \right] =: M_1^-(\varepsilon),
\end{aligned}
$$

where $C_1 = (c_1 + c_2)/(27(g(a_*) + c_2))$, and

$$
\mathscr{U}(s) := 3 \int_0^1 \tilde{u}(\rho, s)\, \rho^2 \, d\rho, \quad \mathscr{U}_0 := \mathscr{U}(0), \quad \kappa_0 := \max\{a_0, f_1^{-1}(0)\}. \tag{68}
$$

Regarding I_2, it follows from $\tilde{w} = 1 - \tilde{u}$ that

$$
I_2 \ge - \frac{g(a_*) + c_1 + c_2}{3} \int_0^{\tau_0(\varepsilon)} \{1 - \mathscr{U}(s)\} \, ds.
$$

Using (24) and the same calculation as in (66), we have

$$
\mathscr{U}(s) \ge \left[1 + (\mathscr{U}_0^{-1} - 1) \mathscr{T}_{a_0}(\tilde{a}(s))^{-\frac{g(a_*)-c_1}{\gamma}} \right]^{-1}.
$$

Then, by the same argument as in the derivation of M_1^-, we obtain

$$
\begin{aligned}
I_2 &\ge - \frac{g(a_*) + c_1 + c_2}{3} \int_0^{\tau_0(\varepsilon)} \frac{\left(\mathscr{U}_0^{-1} - 1\right) \mathscr{T}_{a_0}(\tilde{a}(s))^{-\frac{g(a_*)-c_1}{\gamma}}}{1 + (\mathscr{U}_0^{-1} - 1) \mathscr{T}_{a_0}(\tilde{a}(s))^{-\frac{g(a_*)-c_1}{\gamma}}} \, ds \\
&= \frac{1}{3} \frac{g(a_*) + c_1 + c_2}{g(a_*) - c_1} \log \left[\mathscr{U}_0 + (1 - \mathscr{U}_0) \mathscr{T}_{a_0}(\tilde{a}(\tau_0(\varepsilon)))^{-\frac{g(a_*)-c_1}{\gamma}} \right] \\
&\ge \frac{1}{3} \frac{g(a_*) + c_1 + c_2}{g(a_*) - c_1} \log \mathscr{U}_0 =: M_2^-(\varepsilon).
\end{aligned}
$$

It follows from the same argument as in (52) that

$$
\begin{aligned}
I_3 &= \frac{f_1(a_*)}{3\gamma} \log \mathscr{T}_{a_0}(\tilde{a}(\tau_0(\varepsilon))) - \frac{1}{3\gamma} \int_{a_0}^{\tilde{a}(\tau_0(\varepsilon))} f'(\tilde{z}) \, dz \\
&\ge \frac{f_1(a_*)}{3\gamma} \log \mathscr{T}_{\kappa_0}(\tilde{a}(\tau_0(\varepsilon))) - \frac{a_*}{3\gamma} \| f_1' \|_\infty =: M_3^-(\varepsilon),
\end{aligned} \tag{69}
$$

where $\tilde{z} \in (a_0, a_*)$. Setting $M^-(\varepsilon) = \sum_{i=1}^3 M_i^-(\varepsilon)$ and recalling (48), we see that M^- is well-defined on $(0, f_1(a_*) - f_1(a_0)]$.

We shall derive M^+. Since $\tilde{w} = 1 - \tilde{u} \le 1$, the same argument as in M_2^- yields

$$\begin{aligned} I_1 &\le (c_1 + c_2) \int_0^{\tau_0(\varepsilon)} \int_0^1 \tilde{w}\rho^2 \, d\rho ds = \frac{c_1 + c_2}{3} \int_0^{\tau_0(\varepsilon)} \{1 - \mathscr{U}(s)\} \, ds \\ &\le -\frac{1}{3} \frac{c_1 + c_2}{g(a_*) - c_1} \log \left[\mathscr{U}_0 + (1 - \mathscr{U}_0) \mathscr{T}_{a_0}(\tilde{a}(\tau_0(\varepsilon)))^{-\frac{g(a_*)-c_1}{\gamma}} \right] \\ &\le -\frac{1}{3} \frac{c_1 + c_2}{g(a_*) - c_1} \log \mathscr{U}_0 =: M_1^+(\varepsilon). \end{aligned}$$

Regarding I_2, we have

$$I_2 \le -\frac{g(0) + c_1 + c_2}{3} \int_0^{\tau_0(\varepsilon)} \mathscr{W}(s) \, ds \le 0 =: M_2^+(\varepsilon).$$

Eliminating the negative term from the first line in (69), we find

$$I_3 \le \frac{f_1(a_*)}{3\gamma} \log \mathscr{T}_{a_0}(\tilde{a}(\tau_0(\varepsilon))) \le \frac{f_1(a_*)}{3\gamma} \log \mathscr{T}_0(\tilde{a}(\tau_0(\varepsilon))) =: M_3^+(\varepsilon),$$

where the first inequality is followed from the monotonicity of f_1, and it is strict for any $\varepsilon \in (0, f_1(a_*) - f_1(a_0))$. Setting $M^+(\varepsilon) := \sum_{i=1}^3 M_i^+(\varepsilon)$, we observe that $M^+(\varepsilon)$ is well-defined on $(0, f_1(a_*) - f_1(a_0)]$.

From the definition of M^- and M^+, we see that (59) and (61) hold true. Moreover, thanks to $\tilde{a}(\tau_0(\varepsilon)) = f_1^{-1}(f_1(a_*) - \varepsilon)$, we infer that M^- and M^+ can be extended on $(0, f_1(a_*) - f_1(0)]$ and (60) holds. This completes the proof. □

Lemma 4.4 *Let $M^\pm : (0, f_1(a_*) - f_1(0)] \to \mathbb{R}$ be the functions constructed by Lemma 4.3. Let $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$ satisfy*

$$\int_0^1 \tilde{u}_0(\rho)\rho^2 \, d\rho \ge \int_0^1 u_0(\rho)\rho^2 \, d\rho, \tag{70}$$

$$\tilde{a}_0 \le \kappa_0, \tag{71}$$

and (IC)*, where κ_0 is defined by* (68)*. Then the solution of* (P0) *satisfies*

$$\widetilde{R}_0 \exp M^-(\varepsilon) \le \widetilde{R}(\tau_0(\varepsilon)) \le \widetilde{R}_0 \exp M^+(\varepsilon) \quad \text{in} \quad (0, f_1(a_*) - f_1(\tilde{a}_0)], \tag{72}$$

where the second inequality is strict for any $\varepsilon \in (0, f_1(a_*) - f_1(\tilde{a}_0))$.

Proof In the same manner as in the proof of Lemma 4.3, we see that (59) replaced (M^-, M^+, a_0) by $(\tilde{M}^-, \tilde{M}^+, \tilde{a}_0)$ holds true, where $\tilde{M}^-$ and $\tilde{M}^+$ are respectively determined by M^- and M^+, replaced (u_0, a_0) by $(\tilde{u}_0, \tilde{a}_0)$. Since (70) and (71) imply that

$$\tilde{\mathscr{U}}_0 := 3\int_0^1 \tilde{u}_0(\rho)\rho^2\,d\rho \ge 3\int_0^1 u_0(\rho)\rho^2\,d\rho = \mathscr{U}_0$$

and

$$\mathscr{T}_{\kappa_0}(\alpha) \le \mathscr{T}_{\tilde{a}_0}(\alpha) \le \mathscr{T}_0(\alpha) \quad \text{for any} \quad \alpha \in [\,0, a_*\,],$$

we find

$$\tilde{M}^+(\varepsilon) \le M^+(\varepsilon), \quad \tilde{M}^-(\varepsilon) \ge M^-(\varepsilon), \quad \text{in} \quad (\,0, f_1(a_*) - f_1(0)\,].$$

Thus we obtain (72). □

In order to investigate the behavior of solutions of (P) with $S \equiv 1$, for each "initial data" $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$, we consider the following system:

$$\begin{cases} \dfrac{d\tilde{a}}{dt}(t) = -\gamma\tilde{a}(t) & \text{in} \quad \mathbb{R}_+, \\ \partial_t\tilde{u}(\rho,t) - \mathscr{L}'(\tilde{v},\tilde{R})\tilde{u}(\rho,t) = P(\tilde{u}(\rho,t),\tilde{a}(t)) & \text{in} \quad I_\infty, \\ \tilde{v}(\rho,t) = \dfrac{1}{\rho^2}\displaystyle\int_0^\rho F(\tilde{u}(r,t),\tilde{a}(t))r^2\,dr & \text{in} \quad I_\infty, \\ \dfrac{d\widetilde{R}}{dt}(t) = \tilde{v}(1,t)\widetilde{R}(t) & \text{in} \quad \mathbb{R}_+, \\ \partial_\rho\tilde{u}(\rho,t)\big|_{\rho\in\{0,1\}} = 0, \quad \dfrac{\tilde{v}(\rho,t)}{\rho}\Big|_{\rho=0} = \dfrac{1}{3}F(\tilde{u}(0,t),\tilde{a}(t)), & \text{in} \quad \mathbb{R}_+, \\ \tilde{a}(0) = \tilde{a}_0, \ \ \tilde{u}(\rho,0) = \tilde{u}_0(\rho), \ \ \widetilde{R}(0) = \widetilde{R}_0, & \text{in} \quad I. \end{cases} \tag{P1}$$

We characterize the time variable in terms of the solution $\tilde{a}(\cdot)$ to (P1). Following the same manner as in (48) and recalling the monotonicity of f_1, we define a function $\tau_1 : (\,0, f_1(\tilde{a}_0) - f_1(0)\,] \to [\,0,\infty\,)$ as

$$\tau_1(\delta) = \tilde{a}^{-1}(f_1^{-1}(f_1(0)+\delta)). \tag{73}$$

Since $\tilde{a}(t) \downarrow 0$ as $t \to \infty$, $\delta \downarrow 0$ is equivalent to $\tau_1(\delta) \to \infty$.

Lemma 4.5 *Let* $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$ *satisfy* (IC) *and*

$$\min_{\rho\in[\,0,1\,]} \tilde{u}_0(\rho) > 1 - \frac{g(0)+c_2}{g(0)+c_1+2c_2} =: 1 - C_g. \tag{74}$$

Then the solution $(\tilde{u}, \tilde{v}, \widetilde{R}, \tilde{a})$ *of* (P1) *satisfies*

$$\min_{\rho\in[\,0,1\,]} \tilde{u}(\rho,\tau_1(\delta)) \ge \min_{\rho\in[\,0,1\,]} \tilde{u}_0(\rho) \quad \textit{in} \quad (\,0, f_1(\tilde{a}_0) - f_1(0)\,].$$

Proof Recalling that (A2) and (74) respectively correspond to (41) and (42), we can construct the supersolution $\overline{w}$ of $\tilde{w} = 1 - \tilde{u}$ along the same argument as in the proof of Theorem 3.3. Using the change of variable $\tilde{a}(t) = z$, we have

$$\overline{w}(\tau_1(\delta)) \leq \left[\frac{1}{C_g} + \left[\frac{1}{\overline{w}(0)} - \frac{1}{C_g} \right] \left[\frac{\tilde{a}_0}{f_1^{-1}(f_1(0) + \delta)} \right]^{\frac{g(0)+c_2}{\gamma}} \right]^{-1} =: \Gamma_1(\delta)$$

for any $\delta \in (\, 0,\ f_1(\tilde{a}_0) - f_1(0)\,]$. Then $\underline{u} := 1 - \Gamma_1$ is a subsolution of $\tilde{u}$. In particular, the monotonicity of $\Gamma_1(\cdot)$ gives us the conclusion. □

Next we construct an analogue of Lemma 4.2 for (P1). To this aim, we note that

$$F(z, \alpha) = (c_1 + c_2) \left(z - K^*(\alpha)\right)^2 - (c_1 + c_2)K^*(\alpha) + f_2(\alpha),$$

where

$$K^*(\alpha) := \frac{-g(\alpha) + c_1 + c_2}{2(c_1 + c_2)}. \tag{75}$$

Lemma 4.6 *Let* $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$ *satisfy* (IC), (74), *and the following*:

$$\min_{\rho \in [0,1]} \tilde{u}_0(\rho) \geq K^*(0); \tag{76}$$

$$\tilde{a}_0 > f_1^{-1}(0). \tag{77}$$

Then the solution $(\tilde{u}, \tilde{v}, \widetilde{R}, \tilde{a})$ *of* (P1) *satisfies*

$$\frac{d\widetilde{R}}{dt}(\tau_1(\delta)) < 0 \quad \textit{for any} \quad \delta \in (\, 0, -f_1(0)\,).$$

Proof In order to verify the sign of $d\widetilde{R}/dt$, we use a similar way in Lemma 4.2, i.e., focus on the sign of $F(\tilde{u}, \tilde{a})$. First we note that (77) is equivalent to $f_1(\tilde{a}_0) > 0$. Recalling the relation $(\, 0, -f_1(0)\,) \subset (\, 0,\ f_1(\tilde{a}_0) - f_1(0)\,]$, we find

$$F(1, \tilde{a}(\tau_1(\delta))) = f_1(\tilde{a}(\tau_1(\delta))) = f_1(0) + \delta < 0 \quad \text{in} \quad (\, 0, -f_1(0)\,). \tag{78}$$

Since (A2) implies $K^*(0) < 1$, the monotonicity of $K^*(\cdot)$ and (78) asserts that

$$F(z, \alpha) < 0 \quad \text{for any} \quad z \in [\, K^*(0), 1\,] \times (\, 0, -f_1(0)\,). \tag{79}$$

By virtue of (74), we can apply Lemma 4.5 to the solution $\tilde{u}$ and then (76) implies that

$$\min_{\rho\in[0,1]} \tilde{u}(\rho, \tau_1(\delta)) \geq \min_{\rho\in[0,1]} \tilde{u}_0(\rho) \geq K^*(0) \quad \text{for any} \quad \delta \in (0, f_1(\tilde{a}_0) - f_1(0)]. \tag{80}$$

Therefore we have completed the proof. □

Lemma 4.7 *Let* $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$ *satisfy*

$$\min_{\rho\in[0,1]} \tilde{u}_0(\rho) \geq 1 - \frac{1}{2}C_g, \tag{81}$$

$$\tilde{a}_0 \geq f_1^{-1}(0), \tag{82}$$

and (IC). *Then there exist monotone increasing functions* L^- *and* L^+ *defined on the interval* $(0, f_1(a_*) - f_1(0)]$, *independent of* $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$, *such that the solution of* (P1) *satisfies*

$$\widetilde{R}_0 \exp L^-(\delta) \leq \widetilde{R}(\tau_1(\delta)) \leq \widetilde{R}_0 \exp L^+(\delta) \quad in \quad (0, f_1(\tilde{a}_0) - f_1(0)], \tag{83}$$

in particular, the first inequality in (83) *is strict in* $(0, f_1(\tilde{a}_0) - f_1(0))$. *Moreover,* L^- *and* L^+ *satisfy the following*:

$$-\infty < L^-(\delta) \leq L^+(\delta) < \infty \quad in \quad (0, f_1(a_*) - f_1(0)]; \tag{84}$$

$$\lim_{\delta\downarrow 0} L^+(\delta) = -\infty. \tag{85}$$

Proof Along the same line as in the proof of Lemma 4.3, we will estimate the following:

$$I_1 + I_2 + I_3 := (c_1 + c_2)\int_0^{\tau_1(\delta)}\int_0^1 \tilde{w}^2\rho^2\, d\rho - \int_0^{\tau_1(\delta)}\int_0^1 (g(\tilde{a}(s)) + c_1 + c_2)\tilde{w}\rho^2\, d\rho ds + \frac{1}{3}\int_0^{\tau_1(\delta)} f_1(\tilde{a}(s))\, ds,$$

where $\tilde{w} = 1 - \tilde{u}$. First, since $I_1 \geq 0$, we set $L_1^-(\delta) \equiv 0$. Using the supersolution $\overline{w}$ of $\tilde{w}$ constructed in the proof of Theorem 3.3 and its estimate, we observe from (81) that

$$I_2 \geq -\frac{g(a_*) + c_1 + c_2}{3}\int_0^{\tau_1(\delta)} \overline{w}(s)\, ds \geq -\frac{g(a_*) + c_1 + c_2}{3}C_g\int_0^{\tau_1(\delta)} \exp\left[-\int_0^s \{g(\tilde{a}(\tau')) + c_2\}\, d\tau'\right] ds. \tag{86}$$

Since the change of variable $\tilde{a}(\tau') = s'$ yields

$$-\int_0^s \{g(\tilde{a}(\tau')) + c_2\}\, d\tau' \le \frac{g(0)+c_2}{\gamma} \log \frac{\tilde{a}(s)}{\tilde{a}_0},$$

the inequality (86) is reduced to

$$\begin{aligned} I_2 &\ge -\frac{g(a_*)+c_1+c_2}{3} C_g \int_0^{\tau_1(\delta)} \left(\frac{\tilde{a}(s)}{\tilde{a}_0}\right)^{\frac{g(0)+c_2}{\gamma}} ds \\ &\ge -\frac{C_g}{3} \frac{g(a_*)+c_1+c_2}{g(0)+c_2} \left\{1 - \left(\frac{\tilde{a}(\tau_1(\delta))}{a_*}\right)^{\frac{g(0)+c_2}{\gamma}}\right\} =: L_2^-(\delta). \end{aligned}$$

Moreover, we find

$$\begin{aligned} I_3 &= \frac{-f_1(0)}{3\gamma} \log \frac{\tilde{a}(\tau_1(\delta))}{\tilde{a}_0} + \frac{1}{3\gamma} \int_{\tilde{a}(\tau_1(\delta))}^{\tilde{a}_0} f_1'(\tilde{z})\, dz \\ &\ge \frac{-f_1(0)}{3\gamma} \log \frac{\tilde{a}(\tau_1(\delta))}{a_*} =: L_3^-(\delta), \end{aligned} \tag{87}$$

where $\tilde{z} \in (0, \tilde{a}_0)$. The last inequality is followed from the monotonicity of f_1, and it is strict for any $\delta \in (0, f_1(\tilde{a}_0) - f_1(0))$. Setting $L^-(\delta) := \sum_{i=1}^3 L_i^-(\delta)$ and recalling (73), we observe that L^- is well-defined on $(0, f_1(\tilde{a}_0) - f_1(0)]$.

Next, we derive L^+. By a similar argument as in the derivation of L_2^-, we obtain

$$\begin{aligned} I_1 &\le \frac{c_1+c_2}{3} \int_0^{\tau_1(\delta)} \overline{w}(s)^2\, ds \le \frac{c_1+c_2}{3} C_g^2 \int_0^{\tau_1(\delta)} \left(\frac{\tilde{a}(s)}{\tilde{a}_0}\right)^{2\frac{g(0)+c_2}{\gamma}} ds \\ &\le \frac{C_g}{6} \frac{c_1+c_2}{g(0)+c_1+2c_2} =: L_1^+(\delta). \end{aligned}$$

Since $I_2 \le 0$, we set $L_2^+(\delta) \equiv 0$. From the first equality in (87), we have

$$I_3 \le \frac{-f_1(0)}{3\gamma} \log \frac{\tilde{a}(\tau_1(\delta))}{f_1^{-1}(0)} + \frac{a_*}{3\gamma} \|f_1'\|_\infty =: L_3^+(\delta).$$

Setting $L^+(\delta) := \sum_{i=1}^3 L_i^+(\delta)$, we see that L^+ is well-defined on $(0, f_1(\tilde{a}_0) - f_1(0)]$.

From the definitions of L^- and L^+, it is clear that (83), (84), and (85) hold true. We have completed the proof. □

We are in the position to prove Theorem 1.1.

Proof of Theorem 1.1. To begin with, we prove the existence of switching solution of (IAS). The key of the proof is how to determine the appropriate thresholds r_0 and r_1. We divide the proof of the existence into 4 steps. Finally we shall prove a boundedness of the switching solution and its regularity.

Step 1: Fix $r_0 \in (0, \infty)$ arbitrarily. Let r_1 satisfy

$$r_1 \geq r_0 \exp\left[-L^-(-f_1(0))\right], \tag{88}$$

where remark that $L^-(-f_1(0)) < 0$. We claim the following: if $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$ satisfies

$$\min_{\rho \in [0,1]} \tilde{u}_0(\rho) \geq \underline{\omega} := \max\{K^*(0), 1 - \frac{1}{2}C_g\}, \quad \widetilde{R}_0 = r_1, \quad \tilde{a}_0 > f_1^{-1}(0), \tag{89}$$

and (IC), then there exists $\beta_1 \in (0, -f_1(0))$ such that the solution of (P1) satisfies

$$\widetilde{R}(\tau_1(\beta_1)) = r_0, \quad \frac{d\widetilde{R}}{dt}(\tau_1(\beta_1)) < 0. \tag{90}$$

Let $\delta_0 := f_1(\tilde{a}_0) - f_1(0)$, i.e., $\tilde{a}(\tau_1(\delta_0)) = \tilde{a}_0$. Remark that the third inequality in (89) yields $\delta_0 > -f_1(0)$. Since (89) allows us to apply Lemma 4.7, there exists $\beta_1' \in (0, \delta_0)$ such that

$$\widetilde{R}(\tau_1(\beta_1')) = r_0 \quad \text{and} \quad \widetilde{R}(\tau_1(\delta)) > r_0 \quad \text{for any} \quad \delta \in (\beta_1', \delta_0].$$

Moreover, we infer from (89) that Lemma 4.6 implies that

$$\frac{d\widetilde{R}}{dt}(\tau_1(\delta)) < 0 \quad \text{for any} \quad \delta \in (0, -f_1(0)).$$

Therefore it is sufficient to prove that $\beta_1' < -f_1(0)$. Then β_1' is nothing but the required constant β_1. Combining the relation (83) with (88), we have

$$r_0 = \widetilde{R}(\tau_1(\beta_1')) > r_1 \exp L^-(\beta_1') \geq r_0 \exp\left[L^-(\beta_1') - L^-(-f_1(0))\right].$$

Then the monotonicity of L^- yields $\beta_1' < -f_1(0)$.

Step 2: We shall show that, there exists $\varepsilon_1^* \in (0, f_1(a_*) - f_1(0))$ such that for any $r_0 \in (0, \infty)$ and $r_1 \geq r_0 \exp[M^+(\varepsilon_1^*)]$, the following holds: if $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0)$ satisfies

$$\min_{\rho \in [0,1]} \tilde{u}_0(\rho) \geq \mathscr{U}_0 = 3\int_0^1 u_0(\rho)\rho^2\, d\rho, \quad \widetilde{R}_0 = r_0, \quad \tilde{a}_0 < f_1^{-1}(0), \tag{91}$$

and (IC), then there exists $\beta_2 \in (0, \varepsilon_1^*)$ such that the solution of (P0) satisfies

$$\widetilde{R}(\tau_0(\beta_2)) = r_1, \quad \frac{d\widetilde{R}}{dt}(\tau_0(\beta_2)) > 0. \tag{92}$$

Let $\varepsilon_0 := f_1(a_*) - f_1(\tilde{a}_0)$, i.e., $\tilde{a}(\tau_0(\varepsilon_0)) = \tilde{a}_0$. Remark that $\varepsilon_0 > f_1(a_*)$ by the third inequality in (91). By Lemma 4.4, there exists a constant $\beta_2' \in (0, \varepsilon_0)$ such that

$$\widetilde{R}(\tau_0(\beta_2')) = r_1 \quad \text{and} \quad \widetilde{R}(\tau_0(\varepsilon)) < r_1 \quad \text{for any} \quad \varepsilon \in (\beta_2', \varepsilon_0]. \tag{93}$$

We define ε_1^* as ε_1 in Lemma 4.2 with $A = \mathscr{U}_0$ and $\kappa = f_1^{-1}(0)$, i.e.,

$$1 - \Gamma_0(\varepsilon_1^*; \mathscr{U}_0, f_1^{-1}(0)) = z_0(f_1^{-1}(f_1(a_*) - \varepsilon_1^*)). \tag{94}$$

Then Lemma 4.2 asserts that $\varepsilon_1^* \in (0, f_1(a_*))$ and

$$\frac{d\widetilde{R}}{dt}(\tau_0(\varepsilon)) > 0 \quad \text{for any} \quad \varepsilon \in (0, \varepsilon_1^*].$$

Thus it is sufficient to prove that $\beta_2' \in (0, \varepsilon_1^*)$. Then β_2' is nothing but the required constant β_2. Letting r_1 satisfy

$$r_0 \exp M^+(\varepsilon_1^*) \le r_1, \tag{95}$$

we show that $\beta_2' \in (0, \varepsilon_1^*)$. Indeed, since the relation (72) in Lemma 4.4 holds true, we observe from (95) that

$$r_0 \exp M^+(\varepsilon_1^*) \le r_1 = \widetilde{R}(\tau_0(\beta_2')) < r_0 \exp M^+(\beta_2').$$

Then the monotonicity of M^+ clearly yields $\varepsilon_1^* > \beta_2'$.

Step 3: We shall prove that, there exists $\varepsilon_0^* \in (0, f_1(a_*) - f_1(0))$ such that for any $r_0 \in (0, \infty)$ and $r_1 \ge R_0 \exp M^+(\varepsilon_0^*)$, the following holds: if $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0) = (u_0, R_0, a_0)$, then there exists $\beta_0 \in (0, \varepsilon_0^*)$ such that the solution of (P0) satisfies the following:

$$\widetilde{R}(\tau_0(\beta_0)) = r_1, \quad \frac{d\widetilde{R}}{dt}(\tau_0(\beta_0)) > 0; \tag{96}$$

$$\min_{\rho \in [0,1]} \tilde{u}(\rho, \tau_0(\beta_0)) \ge \max\{\underline{\omega}, \mathscr{U}_0\}, \quad \tilde{a}(\tau_0(\beta_0)) > f_1^{-1}(0). \tag{97}$$

Setting $\tilde{\varepsilon}_1$ as ε_1 in Lemma 4.2 with $A = \min_{\rho \in [0,1]} u_0(\rho)$ and $\kappa = a_0$, we have

$$\frac{d\widetilde{R}}{dt}(\tau_0(\varepsilon)) > 0 \quad \text{for any} \quad \varepsilon \in (0, \tilde{\varepsilon}_1] \quad \text{with} \quad \tilde{\varepsilon}_1 \in (0, f_1(a_*)).$$

By way of the function Γ_0^* defined by

$$\Gamma_0^*(\varepsilon) := \Gamma_0(\varepsilon; \min\{\min_{\rho \in [0,1]} u_0(\rho), \underline{\omega}\}, \max\{a_0, f_1^{-1}(0)\}),$$

we define $\tilde{\varepsilon}_2$ as follows:

$$1 - \Gamma_0^*(\tilde{\varepsilon}_2) = \max\{\underline{\omega}, \mathscr{U}_0, 1 - \Gamma_0^*(f_1(a_*) - f_1(0))\}. \tag{98}$$

From now on, we set $\varepsilon_0^* := \min\{\tilde{\varepsilon}_1, \tilde{\varepsilon}_2\}$ and let r_1 satisfy $r_1 \geq R_0 \exp M^+(\varepsilon_0^*)$. Let $\varepsilon_0' := f_1(a_*) - f_1(a_0)$, i.e., $\tilde{a}(\tau_0(\varepsilon_0')) = a_0$. With the aid of Lemma 4.3, we find a constant $\beta_0' \in (0, \varepsilon_0')$ such that (93) holds for $\beta_2' = \beta_0'$. Noting that the latter relation in (97) is equivalent to $\beta_0' < f_1(a_*)$ and recalling $\varepsilon_0^* \leq \tilde{\varepsilon}_1 < f_1(a_*)$, we have $\beta_0' < \varepsilon_0^*$. The same argument as in Step 2 implies that

$$R_0 \exp M^+(\varepsilon_0^*) \leq r_1 = \tilde{R}(\tau_0(\beta_0')) < R_0 \exp M^+(\beta_0'),$$

where the last inequality is followed from Lemma 4.3. Then the monotonicity of M^+ gives us the required relation. Finally we prove the former relation in (97). Thanks to the monotonicity of Γ_0, we observe from Lemma 4.1 that, for any $\varepsilon \in [\beta_0', \tilde{\varepsilon}_2]$,

$$\min_{\rho \in [0,1]} \tilde{u}(\rho, \tau_0(\varepsilon)) \geq 1 - \Gamma_0(\varepsilon; \min_{\rho \in [0,1]} u_0(\rho), a_0) \geq 1 - \Gamma_0^*(\varepsilon) \geq \max\{\underline{\omega}, \mathcal{U}_0\}.$$

Therefore β_0' is nothing but the required constant β_0.

Step 4: We shall prove that, for a suitable pair of theresholds (r_0, r_1), the system (P) has a unique solution with the property (i) in Theorem 1.1. Fix $r_0 \in (0, \infty)$ and let r_1 satisfy

$$r_1 \geq \max\left\{R_0 \exp M^+(\varepsilon_0^*), r_0 \exp M^+(\varepsilon_1^*), r_0 \exp\left[-L^-(-f_1(0))\right]\right\}. \tag{99}$$

We note that (99) yields $\max\{r_0, R_0\} < r_1$, for M^+ is positive in $(0, f_1(a_*) - f_1(0)]$.

With the aid of Step 3, there exist $\beta_0 \in (0, \varepsilon_0^*)$ and a unique solution $(\tilde{u}, \tilde{v}, \widetilde{R}, \tilde{a})$ of (P0) with $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0) = (u_0, R_0, a_0)$ such that (96) and (97) hold. Since β_0 is uniquely determined, setting $(u, v, R, a) = (\tilde{u}, \tilde{v}, \widetilde{R}, \tilde{a})$ in $\bar{I} \times [0, t_1]$, we observe from (96) and the proof of Theorem 3.1 that (u, v, R, a, S) is a unique solution of (P) in $\bar{I} \times [0, \tau_0(\beta_0))$ such that $S(t) = 0$ in $[0, t_1)$ and $S(t)$ switches from 0 to 1 at t_1, where $t_1 := \tau_0(\beta_0)$.

Since (96)–(97) asserts that (89) holds for $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0) = (u, R, a)|_{t=t_1}$, it follows from Step 1 that there exist $\beta_1 \in (0, -f_1(0))$ and a unique solution $(\tilde{u}_1, \tilde{v}_1, \widetilde{R}_1, \tilde{a}_1)$ of (P1), with $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0) = (u, R, a)|_{t=t_1}$, satisfying (90). Since β_1 is uniquely determined, setting $(u, v, R, a) = (\tilde{u}_1, \tilde{v}_1, \widetilde{R}_1, \tilde{a}_1)$ in $\bar{I} \times [t_1, t_2]$ and $S(t) = 1$ in $[t_1, t_2)$, we deduce from (90) and the proof of Theorem 3.1 that (u, v, R, a, S) is a unique solution of (P) in $\bar{I} \times [0, t_2)$ satisfying the following: $S(t) = 1$ in $[t_1, t_2)$; $S(t)$ switches from 1 to 0 at t_2, where t_2 is the time determined by $\tau_1(\beta_1)$.

Here we claim that (91) holds for $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0) = (u, R, a)|_{t=t_2}$. Since (96)–(97) implies that $\min_{\rho \in [0,1]} u(\rho, t_1) \geq \max\{\underline{\omega}, \mathcal{U}_0\}$, we infer from Lemma 4.5 that

$$\min_{\rho \in [0,1]} u(\rho, t_2) \geq \max\{\underline{\omega}, \mathcal{U}_0\}.$$

Thus the claim holds true. Then it follows from Step 2 that there exist $\beta_2 \in (0, \varepsilon_1^*)$ and a unique solution $(\tilde{u}_2, \tilde{v}_2, \widetilde{R}_2, \tilde{a}_2)$ of (P0), with $(\tilde{u}_0, \widetilde{R}_0, \tilde{a}_0) = (u, R, a)|_{t=t_2}$, satisfying (92). Thanks to the uniqueness of β_2, setting

$$(u, v, R, a) = (\tilde{u}_2, \tilde{v}_2, \widetilde{R}_2, \tilde{a}_2) \quad \text{in} \quad \bar{I} \times [\, t_2, t_3\,],$$

where t_3 is the time determined by $\tau_0(\beta_2)$, we deduce from the same argument as above that (u, v, R, a, S) is a unique solution of (P) in $\bar{I} \times [\, 0, t_3\,)$ satisfying the following: $S(t) = 1$ in $[\, t_2, t_3\,)$; $S(t)$ switches from 0 to 1 at t_3.

In order to apply Step 1 again, we verify that $u(\cdot, t_3)$ satisfies the first property in (89). Combining Lemma 4.4 with (99), we see that

$$R_0 \exp M^+(\varepsilon_0^*) \le r_1 = \widetilde{R}_2(\tau_0(\beta_2)) < r_0 \exp M^+(\beta_2) \le R_0 \exp M^+(\beta_2), \quad (100)$$

and then the monotonicity of M^+ yields $\varepsilon_0^* > \beta_2$. Recalling the monotonicity of Γ_0 and using Lemma 4.1, we have for any $\varepsilon \in [\, \beta_2, \varepsilon_0^*\,]$

$$\begin{aligned}\min_{\rho \in [\,0,1\,]} u(\rho, \tau_0(\varepsilon)) &\ge 1 - \Gamma_0(\varepsilon; \max\{\underline{\omega}, \mathscr{U}_0\}, f_1^{-1}(0)) \\ &\ge 1 - \Gamma_0^*(\varepsilon) \ge 1 - \Gamma_0^*(\varepsilon_0^*) \ge \max\{\underline{\omega}, \mathscr{U}_0\}.\end{aligned}$$

Thus Step 1 is applicable again. Therefore we can construct inductively a solution of (P) with the property (i) in Theorem 1.1.

Step 5: We prove the property (ii) in Theorem 1.1. Using the sequence $\{t_j\}_{j=0}^{\infty}$ obtained by Step 4, we inductively define sequences $\{\varepsilon_0^{2j}\}_{j=0}^{\infty}$, $\{\delta_0^{2j+1}\}_{j=0}^{\infty}$, and $\{\beta_j\}_{j=0}^{\infty}$. Let $\varepsilon_0^0 := f_1(a_*) - f_1(a_0)$, i.e., $\tau_0(\varepsilon_0^0) = t_0 = 0$. Set

$$\beta_0 := f_1(a_*) - f_1(a(t_1)). \quad (101)$$

By the definition of τ_0, the relation (101) is equivalent to $a(\tau_0(\beta_0)) = a(t_1)$. We set

$$\delta_0^1 := f_1(a_*) - f_1(0) - \beta_0.$$

The definitions of τ_0 and τ_1 yield $a(\tau_1(\delta_0^1)) = a(\tau_0(\beta_0))$. Since $a(\cdot)$ is monotone in $[\, 0, t_1\,]$, it holds that $\tau_0(\beta_0) = t_1 = \tau_1(\delta_0^1)$. Next we set

$$\beta_1 := f_1(a(t_2)) - f_1(0); \quad (102)$$

$$\varepsilon_0^2 := f_1(a_*) - f_1(0) - \beta_1. \quad (103)$$

Then, from (102) and (103), we find $a(\tau_1(\beta_1)) = a(t_2)$ and $a(\tau_0(\varepsilon_0^2)) = a(\tau_1(\beta_1))$. The monotonicity of $a(\cdot)$ in $[\, t_1, t_2\,]$ gives us the relation $\tau_1(\beta_1) = \tau_0(\varepsilon_0^2)$. Along the same manner as above, we define inductively ε_0^{2j}, δ_0^{2j+1}, and β_j for each $j \ge 2$ as follows:

$$\beta_j := \begin{cases} f_1(a_*) - f_1(a(t_{j+1})) & \text{if } j \text{ is even}, \\ f_1(a(t_{j+1})) - f_1(0) & \text{if } j \text{ is odd}, \end{cases}$$

$$\delta_0^{2j-1} := f_1(a_*) - f_1(0) - \beta_{2j-2}, \quad \varepsilon_0^{2j} := f_1(a_*) - f_1(0) - \beta_{2j-1}.$$

We note that the monotonicity of $a(\cdot)$ in $[\,t_j, t_{j+1}\,]$ implies $\tau_0(\beta_{2j}) = \tau_1(\delta_0^{2j+1})$ and $\tau_1(\beta_{2j+1}) = \tau_0(\varepsilon_0^{2j+2})$ for each $j \in \mathbb{N} \cup \{0\}$. Then, it follows from the definitions of the sequences that, for any $j \in \mathbb{N} \cup \{0\}$,

$$R(\tau_0(\beta_{2j})) = r_1, \quad R(\tau_0(\varepsilon)) < r_1 \quad \text{and} \quad S(\tau_0(\varepsilon)) \equiv 0, \quad \text{on} \quad (\,\beta_{2j}, \varepsilon_0^{2j}\,]; \tag{104}$$

$$R(\tau_1(\beta_{2j+1})) = r_0, \quad R(\tau_1(\delta)) > r_0 \quad \text{and} \quad S(\tau_1(\delta)) \equiv 1, \quad \text{on} \quad (\,\beta_{2j+1}, \delta_0^{2j+1}\,]. \tag{105}$$

We give the lower and upper bounds of R when $S \equiv 0$, i.e., for the case of (104). We note that, for the case of $j = 0$, it clearly follows from Lemma 4.3 that

$$R_0 \exp M^-(f_1(a_*) - f_1(a_0)) \le R(\tau_0(\varepsilon)) < r_1 \quad \text{on} \quad (\,\beta_0, \varepsilon_0^0\,], \tag{106}$$

where the first inequality was obtained by the monotonicity of M^-. For any $j \in \mathbb{N}$, we observe from Lemma 4.3 that

$$r_0 \exp M^-(\varepsilon_0^{2j}) \le r_0 \exp M^-(\varepsilon) \le R(\tau_0(\varepsilon)) < r_1 \quad \text{on} \quad (\,\beta_{2j}, \varepsilon_0^{2j}\,]. \tag{107}$$

Here, by (105) and Lemma 4.7, we find $\log(r_0/r_1) \le L^+(\beta_{2j-1})$. Since $L^+(\delta)$ is monotone and diverges to $-\infty$ as $\delta \downarrow 0$, there exists $\hat{\delta} \in (\,0, \beta_{2j-1}\,]$, independent of j, such that $L^+(\hat{\delta}) = \log(r_0/r_1)$. Thus, setting $\hat{\varepsilon} := f_1(a_*) - f_1(0) - \hat{\delta}$, we obtain

$$f_1(a_*) - \hat{\varepsilon} = f_1(0) + \hat{\delta} \le f_1(0) + \beta_{2j-1} = f_1(a_*) - \varepsilon_0^{2j}, \quad \text{i.e.,} \quad \hat{\varepsilon} \ge \varepsilon_0^{2j}. \tag{108}$$

Since $j \in \mathbb{N}$ is arbitral, we observe from (107) and (108) that

$$r_0 \exp M^-(\hat{\varepsilon}) \le R(\tau_0(\varepsilon)) < r_1 \quad \text{on} \quad (\,\beta_{2j}, \varepsilon_0^{2j}\,] \quad \text{for any} \quad j \in \mathbb{N}. \tag{109}$$

In particular, we see that

$$r_0 = R(\tau_0(\varepsilon_0^{2j})) \ge r_0 \exp M^-(\varepsilon_0^{2j}) \ge r_0 \exp M^-(\hat{\varepsilon}). \tag{110}$$

Next, we derive the lower and upper bounds of R when $S \equiv 1$, i.e., for the case of (105). For any $j \in \mathbb{N} \cup \{0\}$, we observe from (105) and Lemma 4.7 that

$$r_0 < R(\tau_1(\delta)) \le r_1 \exp L^+(\delta) \le r_1 \exp L^+(\delta_0^{2j+1}) \quad \text{on} \quad (\,\beta_{2j+1}, \delta_0^{2j+1}\,], \tag{111}$$

where the last inequality was followed from the monotonicity of L^+. Here, it follows from (104) and Lemma 4.3 that $M^-(\beta_{2j}) \le \log(r_1/\min\{R_0, r_0\})$. Since $M^-(\varepsilon)$ is monotone and diverges to ∞ as $\varepsilon \downarrow 0$, there exists $\bar{\varepsilon} \in (\,0, \beta_{2j}\,]$, independent of j, such that $M^-(\bar{\varepsilon}) = \log(r_1/\min\{R_0, r_0\})$. Setting $\bar{\delta} := f_1(a_*) - f_1(0) - \bar{\varepsilon}$, we deduce from a similar argument as in (108) that the relation $\bar{\delta} \ge \delta_0^{2j+1}$ holds. Combining the fact with (111), we have

$$r_0 < R(\tau_1(\delta)) \le r_1 \exp L^+(\bar{\delta}) \quad \text{on} \quad (\beta_{2j+1}, \delta_0^{2j+1}] \quad \text{for any} \quad j \in \mathbb{N} \cup \{0\}. \tag{112}$$

In particular, we see that

$$r_1 = R(\tau_1(\delta_0^{2j+1})) \le r_1 \exp L^+(\delta_0^{2j+1}) \le r_1 \exp L^+(\bar{\delta}). \tag{113}$$

Consequently, by virtue of (106), (109)–(110), and (112)–(113), we conclude that the property (ii) in Theorem 1.1 holds for

$$C_1 = \min\{R_0 \exp M^-(f_1(a_*) - f_1(a_0)), r_0 \exp M^-(\hat{\varepsilon})\}, \quad C_2 = r_1 \exp L^+(\bar{\delta}).$$

Step 6: Finally we prove the regularity of the switching solution constructed by the above arguments. The equation of a implies

$$\left| \frac{da}{dt}(t) \right| = |\gamma(a_* - a(t)) - \gamma a_* S(t)| \le 2\gamma a_* \quad \text{in} \quad [0, \infty) \setminus \{t_j\}_{j=0}^{\infty}.$$

Fix $j \in \mathbb{N}$ arbitrarily. Then, for any t and s with $t_{j-1} \le t < t_j < s < t_{j+1}$, we have

$$\begin{aligned} |a(t) - a(s)| &\le |a(t) - a(t_j)| + |a(t_j) - a(s)| \\ &= \left| \frac{da}{dt}(\tau_1) \right| |t - t_j| + \left| \frac{da}{dt}(\tau_2) \right| |t_j - s| \le 4\gamma a_* |t - s|, \end{aligned} \tag{114}$$

where $\tau_1 \in (t, t_j)$ and $\tau_2 \in (t_j, s)$. Since j is arbitrary, we see that $a \in C^{0,1}(\mathbb{R}_+)$.

We consider the following initial boundary problem:

$$\begin{cases} \partial_t \tilde{u}(\rho, t) - \mathscr{L}'(\tilde{v}, \tilde{R})\tilde{u} = P(\tilde{u}(\rho, t), a(t)) & \text{in } I_\infty, \\ \tilde{v}(\rho, t) = \dfrac{1}{\rho^2} \displaystyle\int_0^\rho F(\tilde{u}(r, t), a(t)) r^2 \, dr & \text{in } I_\infty, \\ \dfrac{d\tilde{R}}{dt}(t) = \tilde{v}(1, t)\tilde{R}(t) & \text{in } \mathbb{R}_+, \\ \partial_\rho \tilde{u}(0, t) = \partial_\rho \tilde{u}(1, t) = 0, \quad \dfrac{\tilde{v}}{\rho}\Big|_{\rho=0} = \dfrac{1}{3} F(\tilde{u}(0, t), a(t)) & \text{in } \mathbb{R}_+, \\ \tilde{u}(\rho, 0) = u_0(\rho), \quad \tilde{R}(0) = R_0, & \text{in } I. \end{cases} \tag{$\mathscr{P}$}$$

Since $a \in C^{0,1}(\mathbb{R}_+)$, the proofs of Lemma 2.3 and Theorem 3.1 indicate that $(\mathscr{P})$ has a unique solution $(\tilde{u}, \tilde{v}, \tilde{R})$ in the class

$$C^{2+\alpha, 1+\frac{\alpha}{2}}(Q_\infty) \times (C^{1+\alpha, \frac{\alpha}{2}}([0, 1) \times \mathbb{R}_+) \cap C^1([0, 1) \times \mathbb{R}_+)) \times C^1(\mathbb{R}_+).$$

Recalling that (u, v, R), which is obtained by Step 4, also satisfies $(\mathscr{P})$, we observe from the uniqueness that $(\tilde{u}, \tilde{v}, \tilde{R}) = (u, v, R)$ in Q_∞. We obtain the conclusion. □

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