数理解析研究所講究録
第 1974 巻 2015 年 101-117



# Switching Solutions of a Hybrid System describing Intermittent Androgen Suppression Therapy of Prostate Cancer

東北大学大学院理学研究科　蛭子くるみ
KURUMI HIRUKO
Mathematical Institute,
Tohoku University

## 1 Introduction

The paper is denoted to some remarks on the result obtained in [11].

Prostate cancer is one of the deadly disease 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. In 1941, Huggins and Hodges ([9]) 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 ([19]), and the therapy is called Continuous Androgen Suppression therapy. However, during several years of the CAS therapy, the relapse of prostate tumor often occurs ([4]). The fact was also verified mathematically by [13] and [14]. It is known that there exist Androgen-Dependent cells (AD cells) and Androgen-Independent cells (AI cells) in prostate tumors. AI cells are considered as one of the causes for the relapse. Although AD cells can not proliferate under the androgen suppressed condition, AI cells are not sensitive to androgen suppression and can still proliferate under the androgen poor condition ([2], [16]). Thus the relapse of prostate tumors is caused by progression to androgen independent cancer due to emergence of AI cells. Since prostate cancer cells produce large amount of Prostate-Specific Antigen, the serum PSA is utilized as a good biomarker for prostate cancer. This means that the level corresponds to the total number of cancer cells or the size of tumor.

In order to prevent or prolong the relapse of prostate tumors, Intermittent Androgen Suppression therapy was proposed and has been studied clinically by many researchers (e.g., see [1], [3], [6], [17], and references therein). Recently the IAS therapy is becoming a major in hormonal therapy for prostate cancer. The typical feature of the clinical phenomenon is stated as follows:

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

In order to comprehend qualitative property of prostate tumors under the IAS therapy, several mathematical models were proposed and has been studied in the mathematical literature, for instance, hybrid ODE models ([8], [10], [12], [18], and references therein), hybrid PDE models ([7], [15], [20], [21], [22]). Due to the feature (i), an unknown binary function, denoting the treatment state, appears in the models. The discontinuity of the binary function is the cause of the difficulty of the models. To the best of our knowledge, there is no result proving that the binary function switches in the hybrid PDE models. The purpose of this paper is to prove the existence of a solution with the switching property for a hybrid PDE model.

In the present paper, we focus on the feature (i) and the following:

(ii) There is the competition interaction between AD cells and AI cells in prostate tumors.

From these features (i) and (ii), Y. Tao, Q. Guo, and K. Aihara proposed a mathematical model describing the IAS therapy for prostate cancer ([20]). They regarded the prostate tumor as a densely packed radially symmetric three dimensional sphere. Moreover they formulated the serum PSA level as the radius of tumor. In our previous paper ([11]), we analyzed the following model which is based on the model proposed in [20]:

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

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

$$
\begin{aligned}
P(u,a) &= \{f_1(a) - f_2(a) - c_1 + (c_1+c_2)u\}\,u(1-u),\\
F(u,a) &= f_1(a)u + \{f_2(a) - (c_1+c_2)u\}\,(1-u).
\end{aligned}
$$

The unknown functions in (P) are the androgen concentration $a$, the volume fraction of AD cells $u$, the advection velocity of the cancer cells $v$, the radius of the tumor $R$, and the treatment state $S$. Since we regard the prostate tumor as a densely packed radially symmetric three dimensional sphere, the unknowns $u$ and $v$ are radially symmetric functions with radial variable $\rho$.

Positive 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.

Here we remark that the condition of $S$ in (P) is a concise form. Indeed, the feature (i) is formulated precisely as follows: $S(t)\in\{0,1\}$ and

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

We will state our previous result in [11]. To begin with, let $f_1:[0,a_*]\to\mathbb{R}$ and $f_2:[0,a_*]\to\mathbb{R}$ satisfy

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

$$\text{(A1)} \qquad f_1(a_*) - f_2(a_*) - c_1 > 0,$$
$$\text{(A2)} \qquad f_1(0) - f_2(0) + c_2 > 0.$$

Remark that (A0) is a natural assumption in the clinical point of view. We considered the initial data $(u_0, R_0, a_0, S_0)$ satisfying the following:

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

where $0 < \alpha < 1$, and $B_1 := \{x \in \mathbb{R}^3 \mid |x| < 1\}$. Under these setting, we obtained the following result:

**Theorem 1.1.** *Assume that $f_i$ and $c_i$ satisfy* (A0), (A1), *and* (A2). *Let $S_0 = 0$ and $(u_0, R_0, a_0)$ satisfy* (IC) *and $u_0 > 0$. Then, for a suitable pair $(r_0, r_1)$ with $0 < r_0 \le R_0 < r_1 < \infty$, the system* (P) *has a unique classical solution $(u, v, R, a, S)$ satisfying the following:*

(i) $(u, v, R, a) \in C^{2+\alpha,1+\alpha/2}(B_1 \times \mathbb{R}_+) \times (C^{1+\alpha,\alpha/2}(B_1 \times \mathbb{R}_+) \cap C^1(B_1 \times \mathbb{R}_+)) \times C^1(\mathbb{R}_+) \times C^{0,1}(\mathbb{R}_+)$;

(ii) *There exists a strictly monotone increasing sequence $\{t_j\}_{j=0}^\infty$ with $t_0 = 0$ and $t_j \to \infty$ as $j \to \infty$ such that, for any $j \in \mathbb{N} \cup \{0\}$, $a \in C^1((t_j, t_{j+1}))$ and*

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

(iii) *There exist positive constants $C_1 < C_2$ such that the solution $R(t)$ satisfies*

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

In the clinical point of view, Theorem 1.1 means that, if a patient has the prostate tumor with the properties corresponding to (A0), (A1), and (A2), then we can set appropriate thresholds $r_0$ and $r_1$ such that the IAS therapy will be successful on the patient.

Since we considered only the case with $S_0 = 0$ in [11], we are interested in the following problem:

**Problem 1.1.** *Does there exist a "switching solution" of* (P) *with appropriate thresholds $0 < r_0 < r_1 < \infty$ and $S_0 = 1$? Moreover what is the dynamical aspect of the switching solution?*

In order to give an answer to Problem 1.1, we impose the following assumption on $u_0$:

$$\text{(1.1)} \qquad \min_{\rho \in [0,1]} u_0(\rho, t) > \frac{c_1 + c_2}{g(0) + c_1 + 2c_2}.$$

Then we obtain the following result:

**Theorem 1.2.** *Assume that $f_i$ and $c_i$ satisfy* (A0), (A1), *and* (A2). *Let $S_0 = 1$ and $(u_0, R_0, a_0)$ satisfy* (IC) *and* (1.1). *Then, for a suitable pair $(r_0, r_1)$ with $0 < r_0 < R_0 \le r_1 < \infty$, the system* (P) *has a unique classical solution $(u, v, R, a, S)$ satisfying the following:*

(i) $(u, v, R, a) \in C^{2+\alpha, 1+\alpha/2}(B_1 \times \mathbb{R}_+) \times (C^{1+\alpha, \alpha/2}(B_1 \times \mathbb{R}_+) \cap C^1(B_1 \times \mathbb{R}_+)) \times C^1(\mathbb{R}_+) \times C^{0,1}(\mathbb{R}_+)$;

(ii) *There exists a strictly monotone increasing sequence* $\{t_j\}_{j=0}^{\infty}$ *with* $t_0 = 0$ *and* $t_j \to \infty$ *as* $j \to \infty$ *such that, for any* $j \in \mathbb{N} \cup \{0\}$, $a \in C^1((t_j, t_{j+1}))$ *and*

$$S(t) = \begin{cases} 1 & \textit{for} \quad t \in [t_{2j}, t_{2j+1}), \\ 0 & \textit{for} \quad t \in [t_{2j+1}, t_{2j+2}); \end{cases}$$

(iii) *There exist positive constants* $K_1 < K_2$ *such that the solution* $R(t)$ *satisfies*

$$K_1 \le R(t) \le K_2 \quad \textit{for any} \quad t \ge 0.$$

Theorem 1.2 means that, if a prostate tumor has the properties corresponding to (A0)–(A2) and (1.1), then we can start the IAS therapy with the medication by setting appropriate thresholds $0 < r_0 < r_1 < \infty$. Moreover, then the IAS therapy will be successful on the patient.

Thus we hope that the results give a guideline for the patient who will be treated by the IAS therapy. On the other hand, our assumptions are written in terms of the properties of the tumor, namely, net grows rate and competition coefficients. Therefore we also hope that the result can be utilized for judging whether the IAS therapy is applicable for the patient or not.

In the clinical point of view, it is important to keep the size of tumor as small as possible. We state the difference between Theorem 1.1 and Theorem 1.2:

**Corollary 1.1.** *Assume that* $f_i$ *and* $c_i$ *satisfy* (A0), (A1), *and* (A2). *Let* $(u_0, R_0, a_0, S_0)$ *satisfy* (IC), *and*

$$\min_{\rho \in [0,1]} u_0(\rho) \ge \max\left\{1 - \frac{1}{2}\frac{g(0) + c_2}{g(0) + c_1 + 2c_2}, \ \frac{-g(0) + c_1 + c_2}{2(c_1 + c_2)}\right\}. \tag{1.2}$$

*Then, for a suitable pair* $(r_0, r_1)$ *with* $0 < r_0 < r_1 < \infty$, *there exists a unique classical solution* $(u, v, R, a, S)$ *of* (P) *satisfying the following: There exist positive constants* $K_1 \le C_1 < C_2 \le K_2$ *such that, for* $t \ge 0$, *the solution* $R(t)$ *satisfies*

$$\begin{cases} K_1 \le R(t) \le K_2 & \textit{if} \quad S_0 = 0, \\ C_1 \le R(t) \le C_2 & \textit{if} \quad S_0 = 1. \end{cases}$$

Remark that

$$\frac{c_1 + c_2}{g(0) + c_1 + 2c_2} \le \max\left\{1 - \frac{1}{2}\frac{g(0) + c_2}{g(0) + c_1 + 2c_2}, \ \frac{-g(0) + c_1 + c_2}{2(c_1 + c_2)}\right\}.$$

Thus the assumption (1.2) includes the assumption (1.1). Corollary 1.1 means that if we set $S_0 = 1$, a patient having the prostate tumor with the properties corresponding to (A0), (A1), (A2), (1.1), and "(1.2)" may keep the radius of the tumor $R$ small in comparison to the case of $S_0 = 0$.

## 2 Dynamical aspect of switching solutions

The purpose of this section is to prove the existence of a switching solution of (P) and give its property.

Throughout this section, we assume (A0), (A1), and (A2). Remark that (A1) and (A2) are respectively written as $g(a_*) - c_1 > 0$ and $g(0) + c_2 > 0$, where $g(z) := f_1(z) - f_2(z)$. Moreover, we consider the initial data $(u_0, R_0, a_0, S_0)$ satisfying (IC) and (1.1).

From now on, we denote by $C^{2\kappa+\alpha,\kappa+\beta}(Q_T)$ ($\kappa \in \mathbb{N} \cup \{0\}$, $0 < \alpha < 1$, $0 < \beta < 1$) Holder space on $Q_T$ (for the precise definition, see [5]).

In order to prove Theorem 1.2, we have to construct a short time existence of (P). In [11], we have proved the following:

**Theorem 2.1.** *Let* $(u_0, R_0, a_0, S_0)$ *be an initial data satisfying* (IC). *Then there exists* $T > 0$ *such that the system* (P) *has a unique solution* $(u, v, R, a, S)$ *satisfying* $S(t) = S_0$ *in* $[0, T)$ *and*

$$(u, v, R, a) \in C^{2+\alpha,1+\alpha/2}(Q_T) \times (C^{1+\alpha,\frac{\alpha}{2}}(Q_T) \cap C^1(Q_T)) \times C^1([0,T)) \times C^1([0,T)),$$

*where* $Q_T := B_1 \times [0, T)$.

We shall prove Theorem 1.2 by employing the function $a(\cdot)$, describing a concentration of androgen, as a parameter instead of the time valuable $t$. We characterize the time variable in terms of $a(\cdot)$ under $S = 1$. Indeed, recalling $f_1' > 0$, let us define a function $\tau_1 : (0, f_1(a_*) - f_1(0)) \to \mathbb{R}$ as

$$a(\tau_1(\delta)) = f_1^{-1}(f_1(0) + \delta). \tag{2.1}$$

Note that, since $a(t) \downarrow 0$ as $t \to \infty$ under $S = 1$, $\delta \downarrow 0$ is equivalent to $\tau_1(\delta) \to \infty$.

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

$$\|h\|_\infty := \sup_{z \in [0,a_*]} |h(z)|. \tag{2.2}$$

Set

$$V_1(t) := \int_0^1 u(\rho, t)\rho^2 \, d\rho.$$

In the following, we state several lemmas without proof. For the proof of the lemmas, see [11].

**Lemma 2.1.** *Let* $(u_0, R_0, a_0, S_0)$ *satisfy* (IC). *Suppose that there exist constants*

$$A \in \left( \frac{c_1 + c_2}{g(a_*) + c_1 + 2c_2}, 1 \right) \quad \text{and} \quad \kappa \in (0, a_*) \tag{2.3}$$

*such that for a pair* $(\tilde{\delta}_0, \tilde{\delta}_1)$ *with* $0 < \tilde{\delta}_1 < \tilde{\delta}_0 < f_1(a_*) - f_1(0)$ *the solution* $(u, v, R, a, S)$ *of* (P) *satisfies*

$$\min_{\rho \in [0,1]} u(\rho, \tau_1(\tilde{\delta}_0)) \geq A, \tag{2.4}$$

$$a(\tau_1(\tilde{\delta}_0)) \geq \kappa, \tag{2.5}$$

$$S(\tau_1(\delta)) \equiv 1 \quad \text{in} \quad (\tilde{\delta}_1, \tilde{\delta}_0]. \tag{2.6}$$

*Then there exists a monotone increasing function* $\Gamma_1(\delta; A, \kappa) \in C([0, f_1(a_*) - f_1(0)])$ *with* $\Gamma_1(s; A, \kappa) \downarrow 0$ *as* $s \downarrow 0$ *such that*

$$u(\cdot, \tau_1(\delta)) \geq \max\left\{ \min_{\rho \in [0,1]} u(\rho, \tau_1(\tilde{\delta}_0)),\ 1 - \Gamma_1(\delta; A, \kappa) \right\} \quad \text{in} \quad [\tilde{\delta}_1, \tilde{\delta}_0].$$

**Lemma 2.2.** *Let* $(u_0, R_0, a_0, S_0)$ *satisfy* (IC). *Suppose that there exist constants* $A$ *and* $\kappa$ *with* (2.3) *such that for a pair* $(\tilde{\delta}_0, \tilde{\delta}_1)$ *with* $0 < \tilde{\delta}_1 < \tilde{\delta}_0 < f_1(a_*) - f_1(0)$ *the solution* $(u, v, R, a, S)$ *of* (P) *satisfies* (2.4), (2.5), (2.6),

$$a(\tau_1(\tilde{\delta}_1)) \le f_1^{-1}(0), \tag{2.7}$$

*and*

$$\min_{\rho\in[0,1]} u(\rho, \tau_1(\tilde{\delta}_1)) \ge \frac{-g(0) + c_1 + c_2}{2(c_1 + c_2)}. \tag{2.8}$$

*Then there exists a positive constant* $\tilde{\delta} \in [\tilde{\delta}_1, \min\{\tilde{\delta}_0, -f_1(0)\}]$ *such that*

$$\frac{dR}{dt}(\tau_1(\delta)) < 0 \quad in \quad [\tilde{\delta}_1, \tilde{\delta}].$$

**Lemma 2.3.** *Let* $(u_0, R_0, a_0, S_0)$ *satisfy* (IC). *Assume that there exists a pair* $(\tilde{\delta}_0, \tilde{\delta}_1)$ *with* $0 < \tilde{\delta}_1 < \tilde{\delta}_0 < f_1(a_*) - f_1(0)$ *such that the solution* $(u, v, R, a, S)$ *of* (P) *satisfies* (2.6) *and*

$$\min_{\rho\in[0,1]} u(\rho, \tau_1(\tilde{\delta}_0)) > \frac{c_1 + c_2}{g(0) + c_1 + 2c_2}. \tag{2.9}$$

*Then, for* $(u(\cdot, \tau_1(\tilde{\delta}_0)), a(\tau_1(\tilde{\delta}_0)))$, *there exist functions*

$$\Psi^-(\delta) := \Psi^-(\delta; \omega_1, \omega_2) = \Psi^-(\delta; \min_{\rho\in[0,1]} u(\rho, \tau_1(\tilde{\delta}_0)), a(\tau_1(\tilde{\delta}_0)))(0, f_1(a_*) - f_1(0)) \to \mathbb{R},$$
$$\Psi^+(\delta) := \Psi^+(\delta; \omega_3, \omega_4) = \Psi^+(\delta; \min_{\rho\in[0,1]} u(\rho, \tau_1(\tilde{\delta}_0)), a(\tau_1(\tilde{\delta}_0)))(0, f_1(a_*) - f_1(0)) \to \mathbb{R},$$

*satisfying the following:*

(i) $\Psi^-$ *and* $\Psi^+$ *are monotone increasing functions defined on* $(0, f_1(a_*) - f_1(0))$ *with* $\lim_{\delta\downarrow 0} \Psi^+(\delta) = -\infty$;

(ii) *It holds that* $-\infty < \Psi^-(\delta) \le \Psi^+(\delta) < \infty$ *in* $[\tilde{\delta}_1, \tilde{\delta}_0]$, *in particular,*

$$R(\tau_1(\tilde{\delta}_0)) \exp[\Psi^-(\delta)] \le R(\tau_1(\delta)) \le R(\tau_1(\tilde{\delta}_0)) \exp[\Psi^+(\delta)] \quad in \quad [\tilde{\delta}_1, \tilde{\delta}_0].$$

Next, we define the time variable in terms of $a(\cdot)$ under $S = 0$ by the same manner as in (2.1). Recalling $f_1' > 0$, let us define a function $\tau_0 : (0, f_1(a_*) - f_1(0)) \to \mathbb{R}$ as

$$a(\tau_0(\varepsilon)) = f_1^{-1}(f_1(a_*) - \varepsilon). \tag{2.10}$$

Note that, since $a(t) \uparrow a_*$ as $t \to \infty$ under $S = 0$, $\varepsilon \downarrow 0$ is equivalent to $\tau_0(\varepsilon) \to \infty$.

**Lemma 2.4.** *Let* $(u_0, R_0, a_0, S_0)$ *satisfy* (IC). *Assume that there exists a pair* $(\tilde{\varepsilon}_0, \tilde{\varepsilon}_1)$ *with* $0 < \tilde{\varepsilon}_1 < \tilde{\varepsilon}_0 < f_1(a_*) - f_1(0)$ *such that the solution* $(u, v, R, a, S)$ *of* (P) *satisfies*

$$S(\tau_0(\varepsilon)) \equiv 0 \quad in \quad (\tilde{\varepsilon}_1, \tilde{\varepsilon}_0]. \tag{2.11}$$

*Then it holds that*

$$\min_{\rho\in[0,1]} u(\rho, \tau_0(\varepsilon)) \ge \min_{\rho\in[0,1]} u(\rho, \tau_0(\tilde{\varepsilon}_0)) \quad in \quad [\tilde{\varepsilon}_1, \tilde{\varepsilon}_0].$$

**Lemma 2.5.** *Let* $(u_0, R_0, a_0, S_0)$ *satisfy* (IC). *Assume that there exists a pair* $(\tilde{\varepsilon}_0, \tilde{\varepsilon}_1)$ *with* $0 < \tilde{\varepsilon}_1 < \tilde{\varepsilon}_0 < f_1(a_*) - f_1(0)$ *such that the solution* $(u, v, R, a, S)$ *of* (P) *satisfies* (2.11) *and*

$$\min_{\rho\in[0,1]} u(\rho, \tau_0(\tilde{\varepsilon}_0)) \geq \frac{-\frac{1}{2}f_1(a_*) + g(a_*) + c_1 + c_2}{g(a_*) + c_1 + 2c_2}, \tag{2.12}$$

$$a(\tau_0(\tilde{\varepsilon}_1)) \geq f_1^{-1}(\tfrac{1}{2}f_1(a_*)). \tag{2.13}$$

*Then it holds that*

$$\frac{dR}{dt}(\tau_0(\varepsilon)) > 0 \quad in \quad [\tilde{\varepsilon}_1, \min\{\tilde{\varepsilon}_0, \tfrac{1}{2}f_1(a_*)\}].$$

**Lemma 2.6.** *Let* $(u_0, R_0, a_0, S_0)$ *satisfy* (IC). *Suppose that there exists a pair* $(\tilde{\varepsilon}_0, \tilde{\varepsilon}_1)$ *with* $0 < \tilde{\varepsilon}_1 < \tilde{\varepsilon}_0 < f_1(a_*) - f_1(0)$ *such that the solution* $(u, v, R, a, S)$ *of* (P) *satisfies* (2.11). *Then, for* $(u(\cdot, \tau_0(\tilde{\varepsilon}_0)), a(\tau_0(\tilde{\varepsilon}_0)))$, *there exist functions*

$$\Phi^-(\varepsilon) := \Phi^-(\varepsilon;\, \sigma_1,\, \sigma_2) = \Phi^-(\varepsilon;\, V_1(\tau_0(\tilde{\varepsilon}_0)),\, a(\tau_0(\tilde{\varepsilon}_0))) : (0, f_1(a_*) - f_1(0)) \to \mathbb{R},$$
$$\Phi^+(\varepsilon) := \Phi^+(\varepsilon;\, \sigma_3,\, \sigma_4) = \Phi^+(\varepsilon;\, V_1(\tau_0(\tilde{\varepsilon}_0)),\, a(\tau_0(\tilde{\varepsilon}_0))) : (0, f_1(a_*) - f_1(0)) \to \mathbb{R},$$

*satisfying the following*:

(i) $\Phi^-$ *is a monotone decreasing function with* $\lim_{\varepsilon\downarrow 0} \Phi^-(\varepsilon) = \infty$;

(ii) *It holds that* $-\infty < \Phi^-(\varepsilon) \leq \Phi^+(\varepsilon) < \infty$ *in* $[\tilde{\varepsilon}_1, \tilde{\varepsilon}_0]$, *in particular,*

$$R(\tau_0(\tilde{\varepsilon}_0)) \exp[\Phi^-(\varepsilon)] \leq R(\tau_0(\varepsilon)) \leq R(\tau_0(\tilde{\varepsilon}_0)) \exp[\Phi^+(\varepsilon)] \quad in \quad [\tilde{\varepsilon}_1, \tilde{\varepsilon}_0].$$

We are in a position to the prove Theorem 1.2.

*Proof of Theorem* 1.2.

We prove Theorem 1.2 by a modification of that in [11].

[Step 1] The key of the proof is to construct "comparison functions" of $R(t)$. Thus we start the proof with preparation for the construction.

Let $(u_0, R_0, a_0, S_0)$ satisfy (IC) and (1.1). To begin with, using the functions derived in Lemma 2.6, we define the functions $M^\pm : (0, f_1(a_*) - f_1(0)) \to \mathbb{R}$ as follows:

$$\begin{cases} M^-(\varepsilon) := \inf\limits_{(\sigma_1,\sigma_2)\in\mathcal{M}} \Phi^-(\varepsilon;\, \sigma_1,\, \sigma_2), \\ M^+(\varepsilon) := \sup\limits_{(\sigma_3,\sigma_4)\in\mathcal{M}} \Phi^+(\varepsilon;\, \sigma_3,\, \sigma_4), \end{cases} \tag{2.14}$$

where

$$\mathcal{M} := \{(x_1, x_2) \in \mathbb{R}^2 \mid A_0 \leq 3x_1 \leq 1,\ 0 \leq x_2 \leq f_1^{-1}(0)\},$$

with

$$A_0 := \max\left\{\frac{c_1 + c_2}{g(0) + c_1 + 2c_2}, \frac{-g(0) + c_1 + c_2}{2(c_1 + c_2)}, \frac{-\frac{1}{2}f_1(a_*) + g(a_*) + c_1 + c_2}{g(a_*) + c_1 + 2c_2}\right\}. \tag{2.15}$$

On the other hand, making use of the functions given by Lemma 2.3, we define $L^\pm$ : $(0, f_1(a_*) - f_1(0)) \to \mathbb{R}$ as follows:

$$\begin{cases} L^-(\delta) := \inf\limits_{(\omega_1,\omega_2)\in\mathcal{L}} \Psi^-(\delta;\, \omega_1,\, \omega_2), \\ L^+(\delta) := \sup\limits_{(\omega_3,\omega_4)\in\mathcal{L}} \Psi^+(\delta;\, \omega_3,\, \omega_4), \end{cases} \tag{2.16}$$

where

$$\mathcal{L} := \left\{ (x_1, x_2) \in \mathbb{R}^2 \mid \min_{\rho\in[0,1]} u_0(\rho) \le x_1 \le 1,\, \kappa_1 \le x_2 \le a_* \right\},$$

with

$$\kappa_1 := \min\{a_0, f_1^{-1}(\tfrac{1}{2}f_1(a_*))\}. \tag{2.17}$$

Indeed $M^\pm$ and $L^\pm$ are given by

$$\begin{aligned}
M^-(\varepsilon) =& -\frac{c_1+c_2}{3(g(a_*)+c_2)}\log\left[1+(1-A_0)\left[\frac{a_*-f_1^{-1}(f_1(a_*)-\varepsilon)}{a_*-f_1^{-1}(0)}\right]^{\frac{g(a_*)+c_2}{\gamma}}\right] \\
&-\frac{1}{3}\frac{c_1+c_2}{g(a_*)+c_2}(1-A_0)+\frac{f_1(a_*)}{3\gamma}\log\left(\frac{a_*-f_1^{-1}(0)}{a_*-f_1^{-1}(f_1(a_*)-\varepsilon)}\right) \\
&-\frac{1}{3}\frac{g(a_*)+c_1+c_2}{g(a_*)-c_1}\log\left[1+\left[\frac{1}{A_0}-1\right]\exp\left[\frac{a_*}{\gamma}\|g'\|_\infty\right]\right]-\frac{a_*}{3\gamma}\|f_1'\|_\infty,
\end{aligned}$$

$$\begin{aligned}
M^+(\varepsilon) =& \frac{1}{3}\frac{c_1+c_2}{g(a_*)-c_1}\log\left(1+\left(\frac{1}{A_0}-1\right)\exp\left[\frac{a_*}{\gamma}\|g'\|_\infty\right]\right) \\
&+\frac{f_1(a_*)}{3\gamma}\log\left(\frac{a_*}{a_*-f_1^{-1}(f_1(a_*)-\varepsilon)}\right),
\end{aligned} \tag{2.18}$$

$$\begin{aligned}
L^-(\delta) =& -\frac{1}{C_L}+\frac{1}{C_L}\left[\frac{f_1^{-1}(f_1(0)+\delta)}{a_*}\right]^{\frac{g(0)+c_2}{\gamma}}+\log\left[\frac{f_1^{-1}(f_1(0)+\delta)}{a_*}\right]^{\frac{-f_1(0)}{3\gamma}}, \\
L^+(\delta) =& \frac{3}{2}\frac{1}{C_L^2}\frac{(g(0)+c_2)(c_1+c_2)}{(g(a_*)+c_1+c_2)^2}+\frac{-f_1(0)}{3\gamma}\log\left(\frac{f_1^{-1}(f_1(0)+\delta)}{\kappa_1}\right)+\frac{a_*}{\gamma}\|f_1'\|_\infty,
\end{aligned} \tag{2.19}$$

where

$$C_L := 3\left(\frac{1}{1-\min_{\rho\in[0,1]}u_0(\rho)}-\frac{g(0)+c_1+2c_2}{g(0)+c_2}\right)\frac{g(0)+c_2}{g(a_*)+c_1+c_2}.$$

[Step 2] Let us fix an upper threshold $r_1 \in [R_0, \infty)$ arbitrarily. We shall show that, for a suitable $r_0 \in (0, R_0)$, the following holds: if there exists a time $t^*$ such that

$$R(t^*) = r_0, \quad f_1(a(t^*)) < \frac{1}{2}f_1(a_*), \quad \lim_{t\uparrow t^*} S(t) = 1, \quad S(t^*) = 0, \tag{2.20}$$

and

$$\min_{\rho\in[0,1]} u(\rho, t^*) > \frac{-\frac{1}{2}f_1(a_*)+g(a_*)+c_1+c_2}{g(a_*)+c_1+c_2}, \tag{2.21}$$

then, there exists a time $t_* > t^*$ such that

$$R(t_*) = r_1, \quad f_1(a(t_*)) \ge \frac{1}{2}f_1(a_*), \quad \lim_{t\uparrow t_*} S(t) = 0, \quad S(t_*) = 1. \tag{2.22}$$

Let $\varepsilon_0 := f_1(a_*) - f_1(a(t^*))$, i.e., $a(\tau_0(\varepsilon_0)) = a(t^*)$. Remark that (2.20) implies

$$\varepsilon_0 > \frac{1}{2}f_1(a_*). \tag{2.23}$$

Here we claim that there exists a constant $\beta_1 \in (0, \varepsilon_0)$ such that

$$R(\tau_0(\beta_1)) = r_1 \quad \text{and} \quad R(\tau_0(\varepsilon)) > r_1 \quad \text{in} \quad (\beta_1, \varepsilon_0]. \tag{2.24}$$

Suppose not $R(\tau_0(\varepsilon)) \neq r_1$ for any $\varepsilon \in (0, \varepsilon_0)$. Then the assumptions (2.20) and (2.21) indicate that Lemma 2.6 holds for $\tilde{\varepsilon}_0 = \varepsilon_0$ and $\tilde{\varepsilon}_1 = 0$, and then

$$R(\tau_0(\varepsilon)) \to \infty \quad as \quad \varepsilon \downarrow 0.$$

This is a contradiction. Thus (2.24) holds.

Let $r_0 \in (0, R_0)$ satisfy

$$r_0 \leq R_0 \exp\left[-M^+(\tfrac{1}{2} f_1(a_*))\right]. \tag{2.25}$$

Here we note that (2.18) yields $M^+(\frac{1}{2} f_1(a_*)) > 0$. By (2.24) and (2.25), we have

$$\begin{aligned} r_1 &\leq r_0 \exp\left[M^+(\beta_1)\right] \\ &\leq R_0 \exp\left[M^+(\beta_1) - M^+(\tfrac{1}{2} f_1(a_*))\right] \leq r_1 \exp\left[M^+(\beta_1) - M^+(\tfrac{1}{2} f_1(a_*))\right], \end{aligned}$$

i.e.,

$$M^+(\beta_1) - M^+(\tfrac{1}{2} f_1(a_*)) \geq 0.$$

Since the monotonicity of $M^+$ yields $\beta_1 \leq \frac{1}{2} f_1(a_*)$ which is equivalent to

$$a(\tau_0(\beta_1)) \geq f_1^{-1}(\tfrac{1}{2} f_1(a_*)). \tag{2.26}$$

By virtue of (2.21) and (2.26), we are able to apply Lemma 2.5 for $\tilde{\varepsilon}_0 = \varepsilon_0$ and $\tilde{\varepsilon}_1 = \beta_1$. Then, recalling (2.23), we see that

$$\frac{dR}{dt}(a(\tau_0(\varepsilon))) > 0 \quad \text{in} \quad [\beta_1, \tfrac{1}{2} f_1(a_*)]. \tag{2.27}$$

The definition of $\beta_1$ and (2.27) imply that $S(\tau_0(\varepsilon))$ can be switched from 1 to 0 at $\varepsilon = \beta_1$. Combining this fact with (2.24) and (2.26), we see that (2.22) holds for $t_* = \tau_0(\beta_1)$.

[Step 3] Let us fix an upper threshold $r_1 \in [R_0, \infty)$ arbitrarily. We shall show that, if there exists a time $t_*$ such that

$$\min_{\rho \in [0,1]} u(\rho, t_*) \geq \min_{\rho \in [0,1]} u_0(\rho), \tag{2.28}$$

and (2.22) hold, then, for a suitable lower threshold $r_0 \in (0, R_0)$, there exists a time $t^*$ such that (2.20) and (2.21) hold.

Let $\delta_0 := f_1(a(t_*)) - f_1(0)$, i.e., $a(\tau_1(\delta_0)) = a(t_*)$. Remark that (2.22) implies

$$\delta_0 \geq \frac{1}{2} f_1(a_*) - f_1(0). \tag{2.29}$$

Here we claim that for each $r_0 \in (0, R_0)$, there exists a constant $\beta_0 \in (0, \delta_0)$ such that

$$R(\tau_1(\beta_0)) = r_0 \quad \text{and} \quad R(\tau_1(\delta)) > r_0 \quad \text{for any} \quad \delta \in (\beta_0, \delta_0]. \tag{2.30}$$

Suppose not, $R(\tau_1(\delta)) \neq r_0$ for any $\delta \in (0, \delta_0)$. Then the assumptions (1.1), (2.22), and (2.28) indicate that Lemma 2.3 holds for $\tilde{\delta}_0 = \delta_0$ and $\tilde{\delta}_1 = 0$, and then

$$R(\tau_1(\delta)) \to 0 \quad as \quad \delta \downarrow 0.$$

Thus we see that (2.30) holds.

Now we define $\Gamma_1^*(\delta) : (0, f_1(a_*) - f_1(0)) \to \mathbb{R}$ as

$$\Gamma_1^*(\delta) := \Gamma_1(\delta\,; \min_{\rho\in[0,1]} u_0(\rho), \kappa_1),$$

where $\Gamma_1$ is derived in Lemma 2.1 and $\kappa_1$ is given by (2.17). If $\min_{\rho\in[0,1]} u_0(\rho) < A_0$, where $A_0$ is defined in (2.15), then it follows from (2.29) and the definition of $\Gamma_1^*$ that

$$1 - \Gamma_1^*(\delta_0) \leq 1 - \Gamma_1^*(\tfrac{1}{2} f_1(a_*) - f_1(0)) \leq \min_{\rho\in[0,1]} u_0(\rho). \tag{2.31}$$

Here we use the estimate $\kappa_1 \leq f_1^{-1}(\frac{1}{2} f_1(a_*))$ in the second inequality. Since $\Gamma_1^*$ is monotone increasing, there exists $\delta_1 \leq \delta_0$ such that

$$1 - \Gamma_1^*(\delta_1) = A_0.$$

From now on, setting

$$\delta^* := \begin{cases} \min\{\delta_1, -f_1(0)\} & \text{if} \quad \min_{\rho\in[0,1]} u_0(\rho) < A_0, \\ -f_1(0) & \text{if} \quad \min_{\rho\in[0,1]} u_0(\rho) \geq A_0, \end{cases} \tag{2.32}$$

we let the lower threshold $r_0$ satisfy

$$r_0 \leq R_0 \exp\left[L^-(\delta^*)\right]. \tag{2.33}$$

We claim that

$$\beta_0 \leq \delta^* \leq -f_1(0) < \delta_0. \tag{2.34}$$

Indeed, since (1.1) and (2.28) imply that $u(\rho, \tau_1(\delta_0))$ satisfies (2.9), Lemma 2.3 can be applied for $\tilde{\delta}_0 = \delta_0$ and $\tilde{\delta}_1 = \beta_0$. Thus we observe from (2.33) that

$$r_1 \exp\left[L^-(\beta_0)\right] \leq R(\tau_1(\beta_0)) = r_0 \leq r_1 \exp\left[L^-(\delta^*)\right].$$

Then the monotonicity of $L^-$ yields $\beta_0 \leq \delta^*$. Moreover recalling the definition of $\delta^*$ and (2.29), we have $\delta^* \leq -f_1(0) < \delta_0$. Thus, we obtain the relation (2.34).

Here we show that

$$\min_{\rho\in[0,1]} u(\rho, \tau_1(\delta)) > A_0 \quad \text{in} \quad [\beta_0, \delta^*]. \tag{2.35}$$

Recalling that (1.1) and (2.28) yield (2.4) with $A = \min_{\rho\in[0,1]} u_0$, we verify that Lemma 2.1 can be applied for $\tilde{\delta}_0 = \delta_0$ and $\tilde{\delta}_1 = \beta_0$. Then, for any $\delta \in [\beta_0, \delta_0]$,

$$\min_{\rho\in[0,1]} u(\rho, \tau_1(\delta)) \geq \max\left\{ \min_{\rho\in[0,1]} u(\rho, \tau_1(\delta_0)),\ 1 - \Gamma_1(\delta; \min_{\rho\in[0,1]} u_0(\rho), f_1^{-1}(\tfrac{1}{2} f_1(a_*))) \right\}. \tag{2.36}$$

Thus it is sufficient to show that the right-hand side in (2.36) is bounded from below by $A_0$. Indeed, if $\min_{\rho\in[0,1]} u_0 \geq A_0$, then it follows from (1.1) and (2.28) that

$$\min_{\rho\in[0,1]} u(\rho, \tau_1(\delta_0)) \geq A_0.$$

On the other hand, if $\min_{\rho\in[0,1]} u_0(\rho) < A_0$, the monotonicity of $\Gamma_1^*$ and (2.34) yield that

$$1 - \Gamma_1(\delta; \min_{\rho\in[0,1]} u_0(\rho), f_1^{-1}(\tfrac{1}{2}f_1(a_*))) \geq 1 - \Gamma_1^*(\delta) \geq 1 - \Gamma_1^*(\delta^*) \geq A_0 \quad \text{in} \quad [\beta_0, \delta^*].$$

Hence we get (2.35). Setting $t^* = \tau_1(\beta_0)$, we see that (2.35) implies (2.21).

Finally, we turn to the proof of (2.20) with $t^* = \tau_1(\beta_0)$. To begin with, we prove that

$$\frac{dR}{dt}(\tau_1(\delta)) < 0 \quad \text{in} \quad [\beta_0, \delta^*]. \tag{2.37}$$

It follows from (2.34) and the definition of $\tau_1(\cdot)$ that $a(\tau_1(\beta_0)) \leq f_1^{-1}(0)$. Combining the fact with (2.35), we can apply Lemma 2.2 for $\tilde{\delta}_0 = \delta_0$ and $\tilde{\delta}_1 = \beta_0$. Thus we obtain (2.37). Therefore $S$ switches from 1 to 0 at the time $\tau_1(\beta_0)$. Moreover, since $f_1(a(\tau_1(\beta_0))) \leq 0$ and $f_1(a_*) > 0$, we can easily check that (2.20) holds for $t^* = \tau_1(\beta_0)$.

[Step 4] We shall prove that, for a suitable pair $(r_0, r_1)$, the system (P) has a unique solution with the property (ii) in Theorem 1.2. In the following, we let $r_1 \in [R_0, \infty)$ and let $r_0$ satisfy

$$r_0 < \min\left\{R_0 \exp\left[-M^+(\tfrac{1}{2}f_1(a_*))\right], R_0 \exp\left[L^-(\delta^*)\right]\right\}. \tag{2.38}$$

To begin with, we claim that the solution $(u, R, a, S)$, starting from the initial data $(u_0, R_0, a_0, S_0)$ with $S_0 = 1$, (IC), and (1.1), satisfies the following: (i) There exists $t_1 > 0$ such that $S$ is switched from 1 to 0 at $t = t_1$; (ii) The solution $(u, R, a, S)$ satisfies (2.20) and (2.21) with $t^* = t_1$. In Step 3, we set $t_* = 0$ and replace (2.22) and (2.28) to

$$R(0) = R_0, \quad S(0) = 1. \tag{2.39}$$

Let $\delta_0' := f_1(a_0) - f_1(0)$, i.e., $a(\tau_1(\delta_0')) = a_0$. Then the same argument as in Step 3 yields that there exists $\beta_0' \in (0, \delta_0')$ such that

$$R(\tau_1(\beta_0')) = r_0 \quad \text{and} \quad R(\tau_1(\delta)) > r_0 \quad \text{in} \quad (\beta_0', \delta_0'].$$

Here we claim that $\delta^* \geq \beta_0'$. Indeed, since we can apply Lemma 2.3 for $\tilde{\delta}_0 = \delta_0'$ and $\tilde{\delta}_1 = \beta_0'$, we infer from (2.38) that

$$R_0 \exp\left[L^-(\beta_0')\right] \leq R(\tau_1(\beta_0')) = r_0 \leq R_0 \exp\left[L^-(\delta^*)\right].$$

Then the monotonicity of $L^-$ yields $\delta^* \geq \beta_0'$.

Next we show that (2.21) holds for $t^* = \tau_1(\beta_0')$. Indeed, recalling Lemma 2.1 can be applied for $\tilde{\delta}_0 = \delta_0'$ and $\tilde{\delta}_1 = \beta_0'$, it follows from the same argument as in Step 3 that

$$u(\rho, \tau_1(\delta)) \geq A_0 \quad \text{in} \quad [\beta_0', \min\{\delta_0', \delta^*\}]. \tag{2.40}$$

Finally, it follows from $\delta^* \geq \beta_0'$ and (2.40), that Lemma 2.2 can be applied for $\tilde{\delta}_0 = \delta_0'$ and $\tilde{\delta}_1 = \beta_0'$. Then we see that

$$\frac{dR}{dt}(\tau_1(\beta_0')) < 0.$$

Therefore $S$ switches from 1 to 0 at the time $\tau_1(\beta_0')$. Moreover (2.20) holds for $t^* = \tau_1(\beta_0')$. Indeed, we have

$$f_1(a(\tau_1(\beta_0'))) \leq f_1(a(\tau_1(\delta^*))) \leq f_1(a(\tau_1(-f_1(0)))) = 0 < \frac{1}{2}f_1(a_*).$$

By virtue of Step 2, we see that there exists a time $t_2 > t_1$ such that $S$ switches from 0 to 1 at $t = t_2$. Since we observe from Lemma 2.1 that

$$\min_{\rho\in[0,1]} u(\rho, t_1) \geq \min_{\rho\in[0,1]} u_0(\rho),$$

Lemma 2.4 indicates that $u$ satisfies (2.28) with $t_* = t_2$.

Step 3 asserts that there exists a time $t_3 > t_2$ such that $S$ switches from 1 to 0 at $t = t_3$. Moreover the solution $(u, R, a, S)$ satisfies (2.20) and (2.21) at $t^* = t_3$. Therefore we can prove the property (ii) in Theorem 1.2 inductively.

[Step 5] Finally we prove the property (i) in Theorem 1.2. By the property (ii), we obtain the time sequence $\{t_j\}_{j=0}^{\infty}$. We define sequences $\{\delta_0^{2j}\}_{j=0}^{\infty}$, $\{\varepsilon_0^{2j+1}\}_{j=0}^{\infty}$, and $\{\beta_j\}_{j=0}^{\infty}$ inductively. Let $\delta_0^0 := f_1(a_0) - f_1(0)$, i.e., $\tau_1(\delta_0^0) = t_0 = 0$. Set

$$\beta_0 := f_1(a(t_1)) - f_1(0). \tag{2.41}$$

By the definition of $\tau_1$, the relation (2.41) is equivalent to $a(\tau_1(\beta_0)) = a(t_1)$. We set

$$\varepsilon_0^1 := f_1(a_*) - f_1(0) - \beta_0.$$

The definitions of $\tau_0$ and $\tau_1$ yield $a(\tau_0(\varepsilon_0^1)) = a(\tau_1(\beta_0))$. Since $a(\cdot)$ is monotone in $[0, t_1]$, it holds that $\tau_1(\beta_0) = t_1 = \tau_0(\varepsilon_0^1)$. Next we set

$$\beta_1 := f_1(a_*) - f_1(a(t_2)), \tag{2.42}$$

$$\delta_0^2 := f_1(a_*) - f_1(0) - \beta_1. \tag{2.43}$$

Then we observe from (2.42) and (2.43) that $a(\tau_0(\beta_1)) = a(t_2)$ and $a(\tau_1(\delta_0^2)) = a(\tau_0(\beta_1))$. The monotonicity of $a(\cdot)$ in $[t_1, t_2]$ gives us the relation $\tau_0(\beta_1) = \tau_1(\delta_0^2)$. Along the same manner as above, we define inductively $\varepsilon_0^{2j-1}$, $\delta_0^{2j}$, and $\beta_j$ for each $j \geq 2$ as follows:

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

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

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

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

$$R(\tau_1(\beta_{2j})) = r_0, \ \ R(t) > r_0 \ \text{ and } \ S(t) \equiv 1 \ \text{ on } \ [\tau_1(\delta_0^{2j}), \tau_1(\beta_{2j})), \tag{2.44}$$

$$R(\tau_0(\beta_{2j+1})) = r_1, \ \ R(t) < r_1 \ \text{ and } \ S(t) \equiv 0 \ \text{ on } \ [\tau_0(\varepsilon_0^{2j+1}), \tau_0(\beta_{2j+1})). \tag{2.45}$$

To begin with, we give the lower and upper bounds of $R$ when $S \equiv 1$, i.e., in each interval $[\tau_1(\delta_0^{2j}), \tau_1(\beta_{2j}))$. Let us fix $j \in \mathbb{N}$ arbitrarily. Then, Lemma 2.3, the monotonicity of $L^+$, and (2.44) yield that

$$r_0 < R(\tau_1(\delta)) \leq r_1 \exp\left[L^+(\delta)\right] \leq r_1 \exp\left[L^+(\delta_0^{2j})\right] \quad \text{on} \quad (\beta_{2j}, \delta_0^{2j}]. \tag{2.46}$$

On the other hand, by (2.45) and Lemma 2.6, we find

$$M^-(\beta_{2j-1}) \leq \log\left(\frac{r_1}{r_0}\right).$$

Since $M^-(\varepsilon)$ is monotone and diverges to $\infty$ as $\varepsilon \downarrow 0$, there exists a constant $\hat{\varepsilon} \in (0, \beta_{2j-1}]$ being independent of $j$ such that

$$M^-(\hat{\varepsilon}) = \log\left(\frac{r_1}{r_0}\right).$$

Thereafter, setting

$$\hat{\delta} := f_1(a_*) - f_1(0) - \hat{\varepsilon},$$

we obtain the relation $\hat{\delta} \geq \delta_0^{2j}$. Indeed, the relation is followed from

$$f_1(0) + \hat{\delta} = f_1(a_*) - \hat{\varepsilon} \geq f_1(a_*) - \beta_{2j-1} = f_1(0) + \delta_0^{2j}. \tag{2.47}$$

Since $j \in \mathbb{N}$ is arbitral, we observe from (2.46) and the relation $\hat{\delta} \geq \delta_0^{2j}$ that

$$r_0 < R(\tau_1(\delta)) \leq r_1 \exp\left[L^+(\hat{\delta})\right] \quad \text{on} \quad (\beta_{2j}, \delta_0^{2j}] \tag{2.48}$$

for any $j \in \mathbb{N}$. Regarding the case of $j = 0$, the relation $R_0 \leq r_1$ and (2.46) imply (2.48) for $j = 0$.

Next, we show the lower and upper bounds of $R$ when $S \equiv 0$, i.e., in each interval $[\tau_0(\varepsilon_0^{2j+1}), \tau_0(\beta_{2j+1}))$. Let us fix $j \in \mathbb{N} \cup \{0\}$ arbitrarily. Then, by Lemma 2.6, the monotonicity of $M^-$, and (2.45), we see that

$$r_0 \exp\left[M^-(\varepsilon_0^{2j+1})\right] \leq r_0 \exp\left[M^-(\varepsilon)\right] \leq R(\tau_0(\varepsilon)) < r_1 \quad \text{on} \quad (\beta_{2j+1}, \varepsilon_0^{2j+1}]. \tag{2.49}$$

On the other hand, by (2.44) and Lemma 2.3, we find

$$\log\left(\frac{r_0}{r_1}\right) \leq L^+(\beta_{2j}).$$

Since $L^+(\delta)$ is monotone and diverges to $-\infty$ as $\delta \downarrow 0$, there exists a constant $\bar{\delta} \in (0, \beta_{2j}]$ being independent of $j$ such that

$$L^+(\bar{\delta}) = \log\left(\frac{r_0}{r_1}\right).$$

If we set

$$\bar{\varepsilon} := f_1(a_*) - f_1(0) - \bar{\delta}, \tag{2.50}$$

then the relation $\bar{\varepsilon} \geq \varepsilon_0^{2j+1}$ holds by a similar argument as in (2.47). Recalling that $j$ is arbitral, this relation and (2.49) indicate that

$$r_0 \exp\left[M^-(\bar{\varepsilon})\right] \leq R(\tau_0(\varepsilon)) < r_1 \quad \text{on} \quad (\beta_{2j+1}, \delta_0^{2j+1}] \tag{2.51}$$

for any $j \in \mathbb{N} \cup \{0\}$.

By Lemma 2.3 and the relation $\hat{\delta} \geq \delta_0^{2j}$, we have

$$r_1 = R(\tau_1(\delta_0^{2j})) \leq r_1 \exp\left[L^+(\delta_0^{2j})\right] \leq r_1 \exp\left[L^+(\hat{\delta})\right],$$

where we use the monotonicity of $L^+$ in the last inequality. This implies $L^+(\hat{\delta}) \geq 0$. On the other hand, it follows from Lemma 2.6 and the relation $\bar{\varepsilon} \geq \varepsilon_0^{2j+1}$ that

$$r_0 = R(\tau_0(\varepsilon_0^{2j+1})) \geq r_0 \exp[M^-(\varepsilon_0^{2j+1})] \geq r_0 \exp[M^-(\bar{\varepsilon})],$$

where the last inequality is followed from the monotonicity of $M^-$. Thus we find $M^-(\bar{\varepsilon}) \leq 0$. Combining these facts with (2.48) and (2.51), we see that the property (i) in Theorem 1.2 holds for

$$C_1 = r_0 \exp[M^-(\bar{\varepsilon})], \quad C_2 = r_1 \exp[L^+(\hat{\delta})]. \tag{2.52}$$

Regarding the regularity of $u$, $v$, and $a$, we omit the proof (for the proof, see [11]). We complete the proof. □

We close this paper with the proof of Corollary 1.1.

*Proof of Corollary* 1.1. In the proof of Theorem 1.1, using the functions derived by Lemma 2.3 and Lemma 2.6, we defined the functions $\mathfrak{M}^{\pm}, \mathfrak{L}^{\pm} : (0, f_1(a_*) - f_1(0)) \to \mathbb{R}$ as follows:

$$\begin{cases} \mathfrak{M}^-(\varepsilon) := \inf\limits_{(\sigma_1,\sigma_2)\in\mathcal{M}'} \Phi^-(\varepsilon;\, \sigma_1,\, \sigma_2), \\ \mathfrak{M}^+(\varepsilon) := \sup\limits_{(\sigma_3,\sigma_4)\in\mathcal{M}'} \Phi^+(\varepsilon;\, \sigma_3,\, \sigma_4), \end{cases} \quad \begin{cases} \mathfrak{L}^-(\delta) := \inf\limits_{(\omega_1,\omega_2)\in\mathcal{L}'} \Psi^-(\delta;\, \omega_1,\, \omega_2), \\ \mathfrak{L}^+(\delta) := \sup\limits_{(\omega_3,\omega_4)\in\mathcal{L}'} \Psi^+(\delta;\, \omega_3,\, \omega_4), \end{cases} \tag{2.53}$$

where

$$\mathcal{M}' := \{(x_1, x_2) \mid 3V_1(0) \leq 3x_1 \leq 1,\ 0 \leq x_2 \leq \kappa_0'\}, \tag{2.54}$$

with $\kappa_0' := \max\{a_0, f_1^{-1}(0)\}$, and

$$\mathcal{L}' := \{(x_1, x_2) \mid \underline{\omega} \leq x_1 \leq 1,\ \kappa_1' \leq x_2 \leq a_*\}$$

with

$$\underline{\omega} := \max\left\{1 - \frac{1}{2}\frac{g(0) + c_2}{g(0) + c_1 + 2c_2},\ \frac{-g(0) + c_1 + c_2}{2(c_1 + c_2)}\right\},\ \kappa_1' := \min\{a_0, f_1^{-1}(0)\}.$$

In the proof of Theorem 1.2, we replace $A_0$ by

$$A_0' := \max\{A_0, 3V_1(0)\}.$$

We consider an upper and lower threshold satisfying

$$r_0 \leq \min\left\{R_0 \exp\left[-M^+(\tfrac{1}{2}f_1(a_*))\right], R_0 \exp\left[L^-(\delta^*)\right]\right\}, \tag{2.55}$$

$$r_1 \geq \max\left\{R_0 \exp\left[\mathfrak{M}^+(\varepsilon^*)\right], R_0 \exp\left[-\mathfrak{L}^-(-f_1(0))\right]\right\}, \tag{2.56}$$

where $\varepsilon^*$ is a positive constant (for the precise definition of $\varepsilon^*$, see [11]).

Under (2.55)-(2.56), Theorem 1.1 implies that, if $S_0 = 0$, then the system (P) has a unique switching solution satisfying

$$K_1 \leq R(t) \leq K_2,$$

where

$$K_1 = r_0 \exp[\mathfrak{M}^-(\bar{\varepsilon}')], \quad K_2 = r_1 \exp[\mathfrak{L}^+(\hat{\delta}')],$$

with

$$\mathfrak{L}^+(f_1(a_*) - f_1(0) - \bar{\varepsilon}') = \log\left(\frac{r_0}{r_1}\right), \quad \mathfrak{M}^-(f_1(a_*) - f_1(0) - \hat{\delta}') = \log\left(\frac{r_1}{r_0}\right). \tag{2.57}$$

On the other hand, the proof of Theorem 1.2 asserts that, if $S_0 = 1$, then the system (P) has a unique switching solution satisfying

$$C_1 \le R(t) \le C_2,$$

where $C_1$ and $C_2$ are given by (2.52).
In the following, we shall prove

$$K_1 \le C_1, \quad C_2 \le K_2. \tag{2.58}$$

Here we note that

$$M^- \ge \mathfrak{M}^-, \quad M^+ \le \mathfrak{M}^+, \quad L^- \ge \mathfrak{L}^-, \quad L^+ \le \mathfrak{L}^+. \tag{2.59}$$

For, it holds that $\mathcal{M} \subset \mathcal{M}'$ and $\mathcal{L} \subset \mathcal{L}'$.

To begin with, we prove the first inequality in (2.58). Since $L^+(\delta)$ and $\mathfrak{L}^+(\delta)$ is monotone and diverges to $-\infty$ as $\delta \downarrow 0$, there exists a constant $\bar{\delta}, \bar{\delta}' \in (0, f_1(a_*) - f_1(0))$ such that

$$L^+(\bar{\delta}) = \mathfrak{L}^+(\bar{\delta}') = \log\left(\frac{r_0}{r_1}\right).$$

Then we obtain the relation $\bar{\delta} \ge \bar{\delta}'$. Indeed, the relation is followed from

$$L^+(\bar{\delta}) = \mathfrak{L}^+(\bar{\delta}') \ge L^+(\bar{\delta}')$$

and the monotonicity of $L^+$. Moreover it follows from (2.57) that

$$f_1(a_*) - f_1(0) - \bar{\varepsilon}' = \bar{\delta}'.$$

Recalling (2.50), we see that the relation $\bar{\varepsilon} \le \bar{\varepsilon}'$ holds. Then, it follows from the monotonicity of $M^-$ and $\mathfrak{M}^-$ that

$$M^-(\bar{\varepsilon}) \ge \mathfrak{M}^-(\bar{\varepsilon}').$$

The relation clearly implies $C_1 \ge K_1$.

Next we turn to the proof of the second inequality in (2.58). Since $M^-(\varepsilon)$ and $\mathfrak{M}^-(\varepsilon)$ are monotone and diverges to $\infty$ as $\varepsilon \downarrow 0$, there exist constants $\hat{\varepsilon}, \hat{\varepsilon}' \in (0, f_1(a_*) - f_1(0))$ such that

$$M^-(\hat{\varepsilon}) = \mathfrak{M}^-(\hat{\varepsilon}') = \log\left(\frac{r_1}{r_0}\right). \tag{2.60}$$

Then the monotonicity yields that $\hat{\varepsilon} \ge \hat{\varepsilon}'$. Since the same argument as above implies

$$\hat{\delta} = f_1(a_*) - f_1(0) - \hat{\varepsilon}, \quad \hat{\delta}' = f_1(a_*) - f_1(0) - \hat{\varepsilon}',$$

we have $\hat{\delta} \le \hat{\delta}'$. Thus we observe from the monotonicity of $L^+$ and $\mathfrak{L}^+$ that

$$L^+(\hat{\delta}) \le \mathfrak{L}^+(\hat{\delta}').$$

The relation is equivalent to $C_2 \le K_2$. We obtain the conclusion. □

## References


[1] K. Akakura, N. Bruchovsky, S.L. Goldenberg, P.S. Rennie, A.R. Buckley, and L.D. Sullivan, *Effects of intermittent androgen suppression on androgen-dependent tumors: apoptosis and serum prostate specific antigen*, Cancer **71** (1993), 2782–2790.

[2] F. Bladow, R.L. Vessella, K.R. Buhler, W.J. Ellis, L.D. True, and P.H. Lange, *Cell proliferation and apoptosis during prostatic tumor xenograft involution and regrowth after castration*, Int. J. Cancer **67** (1996), 785–790.

[3] N. Bruchovsky, P.S. Rennie, A.J. Coldman, S.L. Goldenberg, D. Lawson, *Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma*, Cancer Res. **50** (1990), 2275–2282.

[4] B.J. Feldman, D. Feldman, *The development of androgen-independent prostate cancer*, Nat. Rev. Cancer **1** (2001), 34–45.

[5] A. Friedman and G. Lolas, *Analysis of a mathematical model of tumor lymphangiogenesis*, Math. Models Methods Appl. Sci. **1** (2005), 95–107.

[6] M. Gleave, S. Goldenberg, N. Bruchovsky, P. Rennie, *Intermittent androgen suppression for protate cancer: rationale and clinical experience*, Prostate cancer Prostatic Dis. **1** (1998), 289–296.

[7] Q. Guo, Y. Tao, K. Aihara, *Mathematical modeling of prostate tumor growth under intermittent androgen suppression with partial differential equations*, Internat. J. Bifur. Chaos Appl. Sci. Engrg. **18** (2008), 3789–3797.

[8] Y. Hirata, N. Bruchovsky, K. Aihara, *Development of a mathematical model that predicts the outcome of hormone therapy for prostate cancer*, J. Theoret. Biol. **264** (2010), 517–527.

[9] G. Huggins and C. Hodges, Studies of prostate cancer: I. The effects of castration, oestrogen and androgen injections on serum phosphates in metastatic carcinoma of the prostate, Cancer Res. **1** (1941), 293–207.

[10] T. Hatano, Y. Hirata, H. Suzuki, K. Aihara, *Comparison between mathematical models of intermittent androgen suppression for prostate cancer*, J. Theoret. Biol. **366** (2015), 33-45.

[11] K. Hiruko, S. Okabe, *Dynamical aspects of a hybrid system describing intermittent androgen suppression therapy of prostate cancer*, preprint (2015)

[12] A. Ideta, G. Tanaka and K. Aihara, *A mathematical model of intermittent androgen suppression for prostate cancer*, J. Nonlinear Sci. **18** (2008), 593–614.

[13] T.L. Jackson, *A mathematical model of prostate tumor growth and androgen-independent relapse*, Discr. Cont. Dyn. Syst. B **4** (2004a), 187–201.

[14] T.L. Jackson, *A mathematical investigation of multiple pathways to recurrent prostate cancer: Comparison with experimental data*, Neoplasia **6** (2004b), 697–704.

[15] H.V. Jain, A. Friedman, *Modeling prostate cancer response to continuous versus intermittent androgen ablation therapy*, Discr. Cont. Dyn. Syst. B **18** (2013), 945–967.

[16] P.S. Rennie, N. Bruchovsky, and A.J. Coldman, *Loss of androgen dependence is associated with an increase in tumorigenic stem cells and resistance to cell-death genes*, J. Steroid Biochem. Mol. Biol. **37** (1990), 843–847.

[17] N. Sato, M.E. Gleave, N. Bruchovsky, P.S. Rennie, S.L. Goldenberg, P.H. Lange, and L.D. Sullivan, *Intermittent androgen suppression delays progression to androgen-independent regulation of prostate-specific antigen gene in the LNCaP prostate tumor model*, Biochem. Mol. Biol. **58** (1996), 139–146.

[18] T. Shimada and K. Aihara, *A nonlinear model with competition between prostate tumor cells and its application to intermittent androgen suppression therapy of prostate cancer*, Math. Biosci. **214** (2008), 134–139.

[19] G. Tolis, D. Ackman, A. Stellos, A. Metha, F. Labrie, A.T.A. Fazekas, A.M. Comaru-Schally, and A.V. Schally, *Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists*, Proc. Natl. Acad. Sci. USA **79** (1982), 1658–1662.

[20] Y. Tao, Q. Guo and K. Aihara, *A model at the macroscopic scale of prostate tumor growth under intermittent androgen suppression*, Math. Models Methods Appl. Sci. **12** (2009), 2177–2201.

[21] Y. Tao, Q. Guo and K. Aihara, *A mathematical model of prostate tumor growth under hormone therapy with mutation inhibitor*, J. Nonlinear Sci. **20** (2010), 219–240.

[22] Y. Tao, Q. Guo and K. Aihara, *A partial differential equation model and its reduction to an ordinary differential model for prostate tumor growth under intermittent androgen suppression therapy*. J. Math. Biol. **69** (2014) , 817–838.