Mathematical Biosciences 245 (2013) 282–298

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

# Optimal policies of non-cross-resistant chemotherapy on Goldie and Coldman's cancer model

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ARTICLE INFO

*Article history:*
Received 26 November 2012
Received in revised form 19 July 2013
Accepted 26 July 2013
Available online 6 August 2013

*Keywords:*
Goldie and Coldman's model
Drug resistance
Optimal cancer treatment

ABSTRACT

Mathematical models can be used to study the chemotherapy on tumor cells. Especially, in 1979, Goldie and Coldman proposed the first mathematical model to relate the drug sensitivity of tumors to their mutation rates. Many scientists have since referred to this pioneering work because of its simplicity and elegance. Its original idea has also been extended and further investigated in massive follow-up studies of cancer modeling and optimal treatment.

Goldie and Coldman, together with Guaduskas, later used their model to explain why an alternating non-cross-resistant chemotherapy is optimal with a simulation approach. Subsequently in 1983, Goldie and Coldman proposed an extended stochastic based model and provided a rigorous mathematical proof to their earlier simulation work when the extended model is approximated by its quasi-approximation. However, Goldie and Coldman's analytic study of optimal treatments majorly focused on a process with symmetrical parameter settings, and presented few theoretical results for asymmetrical settings. In this paper, we recast and restate Goldie, Coldman, and Guaduskas' model as a multi-stage optimization problem. Under an asymmetrical assumption, the conditions under which a treatment policy can be optimal are derived. The proposed framework enables us to consider some optimal policies on the model analytically. In addition, Goldie, Coldman and Guaduskas' work with symmetrical settings can be treated as a special case of our framework. Based on the derived conditions, this study provides an alternative proof to Goldie and Coldman's work. In addition to the theoretical derivation, numerical results are included to justify the correctness of our work.



## 1. Introduction

Chemotherapy has been widely used in the treatment of tumor cells. One of the major obstacles to achieving satisfactory treatment outcomes is the emergence of drug resistance. Mutants have become resistant to the applied agents. This resistance is inherited by daughter cells during mitosis and could lead to the incurability. Researchers have identified and studied several mechanisms relating to the development of resistance. For instance, genetic alternation can lead the loss or gain of functions for particular proteins. A protein that serves as a receptor with diminished function can reduce the rate of drug transport into the cell. The gain of function by a protein involved in repairing the drug-induced damage can increase a mutant's tolerance against drug toxicity. Both of these changes can reduce the sensitivity of mutants to applied agents [1].

Based on biological observations and studies, researchers have developed several mathematical models to further investigate the drug resistance problems. In particular, in 1979, Goldie and Coldman proposed the first model relating the drug sensitivity of tumors to their mutation rates [2]. This ground-breaking work subsequently simulated massive studies in cancer modeling and optimal treatment. Kimmel, Axelrod and other researchers proposed models to consider the gene amplification [3–8]. Cojocaru and Agur considered a model of a cell-cycle-phase-specific drug [9]. Swierniak and Smieja investigated the optimal therapy under drug resistance based on optimal control theory [10]. Murray and Coldman studied the effects of heterogeneity on optimal therapy [11]. Wodarz and Komarova developed a stochastic model to elucidate the relevance of tumor size, turnover rate and the number of drugs used in the combination therapy to treatment success [12,13]. Combination of two drugs to improve therapy of chronic myeloid leukemia was considered in [14]. Gaffney explored the age structure and rest phases in modeling adjuvant chemotherapy scheduling [15,16]. Jackson and Byrne considered a model to study the drug resistance and vasculature in solid tumor [17]. The details and more relevant work can be referred to the articles [18–22].

In a follow-up paper published by Goldie, Coldman, and Guaduskas in 1982 [23], they used their original model and a simulation method to explain why alternating non-cross-resistant chemotherapy is optimal when two agents are used in the therapy.

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http://dx.doi.org/10.1016/j.mbs.2013.07.020

Later in 1983, they proposed an extended model that included the stochastic nature of the resistance phenomena [24]. When considering the quasi-approximation of their extended model, they offered a rigorous proof to justify their earlier simulation of the optimality of alternating non-cross-resistant chemotherapy.

However, the proof presented by Goldie and Coldman is based on the assumption that both agents have equal efficacies. With this symmetrical assumption, an optimal treatment policy likely will not favor any one of the applied agents, and thus, an alternating policy is optimal. However, Goldie and Coldman presented few theoretical results regarding asymmetrical cases. Therefore, this study presents the original model of Goldie and Coldman as a multi-stage decision-making problem. Under a weaker assumption, this study presents the conditions under which a treatment policy is optimal. The proposed work provides a possible theoretical extension of the Goldie and Coldman model to asymmetrical cases. The symmetrical assumption of the Goldie and Coldman model can be treated as a special case in the proposed framework and henceforth, this study provides an alternative proof to their 1983 work [24]. The derivations presented in this study show that the alternative policy can also be optimal in a special asymmetrical case. In addition to the theoretical derivations, the following discussion includes numerical results to justify the correctness of the proposed method.

## 2. The model framework

In this section, we briefly review and restate Goldie, Coldman, and Guaauskas' model [23]. Suppose that the chemotherapy is applied to a tumor consisting of three phenotypes of cells: $R_1$, $R_2$ and $S$. This chemotherapy includes two various drugs. The $R_1$ phenotype is resistant to the first drug, but sensitive to the second drug. The $R_2$ phenotype is resistant to the second drug, but sensitive to the first drug. The $S$ phenotype is sensitive to both drugs. Mutations may occur during the tumor growth process. This model is based on the assumption that an $S$ type cell can mutate to either a $R_1$ or $R_2$ type cell. Both $R_1$ and $R_2$ type cells can mutate to a new phenotype of cells: $R_{1,2}$. An $R_{1,2}$ type cell is resistant to both drugs. Furthermore, it is assumed that the drug resistance is caused by one single mutational event. No resistance is acquired through a dynamic process such as the multi-step gene amplification considered [3,7]. Initially, the doubly resistant cell does not exist in the tumor. When it appears, the patient's cancer becomes incurable. Therefore, the goal of the therapy is to administer the two available drugs to minimize the probability of the occurrence of $R_{1,2}$ type cells.

Consider a $n$-cycle treatment problem. Each cycle consists of two phases: the treatment phase and the growth phase. During each treatment phase, one drug is introduced to eliminate the targeted tumor cells. For example, if the first drug is applied, a proportion of cells sensitive to this drug (in this case, $R_2$ and $S$ type cells) will be eliminated. During the growth phase, the duplication of tumor cells causes tumor growth. The following sections present a detailed description of each phase.

### 2.1. The treatment phase

During the treatment phase, drugs are applied to eliminate tumor cells. For simplicity, in Goldie and Coldman's model, the effect of drug-intervention is assumed to be instantaneous. That is, upon the application of the drugs, a proportion of cells sensitive to the applied drug is immediately eliminated. A drug's cell cycle specificity as [9] is not considered in details in this framework. The fraction of survival is determined based on the log-kill law [1]. This law can be understood from the solution thermodynamics. In a solution of drug molecules, only those molecules with sufficient kinetic energy and the right orientation interact with the target cells. These interactions are stochastic in nature, and the survival probability of target cells can be stated as the following equation [1].

$$log(P_{survival}) = -\beta D,$$

where $\beta$ is a drug and target cell dependent constant and $D$ is the dosage level. The log-scale survival probability is negatively proportional to the dosage level. A greater dosage level leads to a lower survival probability. The following discussion is based on the assumption that the dosage levels of both drugs remain fixed throughout the entire treatment process. Moreover, always consider the expected residual population size. In other words, if the survival probability $P_{survival} = \frac{1}{k^2}$ and the initial population size is $N_0$, the residual population size after treatment is $\frac{1}{k^2} \cdot N_0$. For ease of presentation, $k^2$ is referred as the log-kill constant of the applied drug against the target cell.

Suppose that the initial sizes of the $R_1, R_2$, and $S$ type cells are $R_1(N_0)$, $R_2(N_0)$, and $S(N_0)$, respectively. Let $R_1(N)$, $R_2(N)$, and $S(N)$ denote the sizes of the $R_1$, $R_2$, and $S$ type cells at the end of the treatment phase. Suppose that the log-kill constants for the first drug against $R_2$ and $S$ type cells are ${k_{1,r}}^2$ and ${k_{1,s}}^2$, respectively. The log-kill constants for the second drug against $R_1$ and $S$ type cells are ${k_{2,r}}^2$ and ${k_{2,s}}^2$. The variation in the number before and after treatment can be calculated using the following equations.

After the first drug is applied, we have the following relationship:

$$R_1(N) = R_1(N_0),$$
$$R_2(N) = \frac{1}{k_{1,r}^2} R_2(N_0)$$

and

$$S(N) = \frac{1}{k_{1,s}^2} S(N_0).$$

Similarly, after the second drug is applied, we have the following relationship:

$$R_1(N) = \frac{1}{k_{2,r}^2} R_1(N_0),$$
$$R_2(N) = R_2(N_0)$$

and

$$S(N) = \frac{1}{k_{2,s}^2} S(N_0).$$

### 2.2. The growth phase

During the growth phase, cells may duplicate and the entire population grows. Assume that all types of cells duplicate at the same rate. Let the doubling time of the population be $d$ days. Let the duration of each growth phase be $d'$ days and let the initial size of the population before a growth phase be $N_0$. At the end of the growth phase, the size of population reaches $N$. At this point, $N_0$ and $N$ can be related with the following equation

$$N = N_0 \cdot 2^{\frac{d'}{d}}. \quad (1)$$

Suppose that the initial sizes of the $R_1$, $R_2$, and $S$ type cells are $R_1(N_0)$, $R_2(N_0)$, and $S(N_0)$, respectively. Let $R_1(N)$, $R_2(N)$, and $S(N)$ denote the sizes of the $R_1$, $R_2$, and $S$ type cells at the end of the growth phase. Assume that no doubly resistant $R_{1,2}$ cells appear during the entire growth phase. In this case, $N_0 = R_1(N_0) + R_2(N_0) + S(N_0)$. and $N = R_1(N) + R_2(N) + S(N)$. Because mutations from $S$ type cells

to $R_1$ or $R_2$ type cells may occur, various types of cells do not increase proportionally. The following theorem describes the dynamics of the mutations and duplications, and provides essential formulae to compute $R_1(N)$, $R_2(N)$, and $S(N)$.

**Theorem 2.1.** *Let $\alpha_1$ denote the spontaneous mutation rate from an S type cell to an $R_1$ type cell, and $\alpha_2$ denote the spontaneous mutation rate from an S type cell to an $R_2$ type cell. Let $\Delta N$ denote the increase of the population size. Suppose that when $\Delta N \to 0$, the increase of $R_1$ and $R_2$ type cells follows the following equations:*

$$R_1(N_0+\Delta N) = R_1(N_0) + \frac{R_1(N_0)}{N_0}\Delta N + \alpha_1\left(1-\frac{R_1(N_0)}{N_0}-\frac{R_2(N_0)}{N_0}\right)\Delta N + o\left(\Delta N^2\right) \quad (2)$$

*and*

$$R_2(N_0+\Delta N) = R_2(N_0) + \frac{R_2(N_0)}{N_0}\Delta N + \alpha_2\left(1-\frac{R_1(N_0)}{N_0}-\frac{R_2(N_0)}{N_0}\right)\Delta N + o\left(\Delta N^2\right). \quad (3)$$

*Then, $R_1(N)$, $R_2(N)$, and $S(N)$ can be obtained with the following equations:*

$$R_1(N) = \frac{N}{N_0}R_1(N_0) + \frac{\alpha_1}{\alpha_1+\alpha_2}S(N_0)\frac{N}{N_0}\left(1-\left(\frac{N}{N_0}\right)^{-\alpha_1-\alpha_2}\right), \quad (4)$$

$$R_2(N) = \frac{N}{N_0}R_2(N_0) + \frac{\alpha_2}{\alpha_1+\alpha_2}S(N_0)\frac{N}{N_0}\left(1-\left(\frac{N}{N_0}\right)^{-\alpha_1-\alpha_2}\right) \quad (5)$$

*and*

$$S(N) = S(N_0)\cdot\left(\frac{N}{N_0}\right)^{1-\alpha_1-\alpha_2}. \quad (6)$$

**Proof.** See Appendix A. □

When $\Delta N$ is very small, the second term on the right hand side of Eq. (2) shows that the duplication of $R_1$ type cells is proportional to $\frac{R_1(N_0)}{N_0}$. The third term indicates that a portion $\alpha_1(1-\frac{R_1(N_0)}{N_0}-\frac{R_2(N_0)}{N_0})$ of $S$ type cells mutates to $R_1$ type cells. The assumptions in Eqs. (2) and (2) are extended from the original idea of [2], in which Goldie and Coldman considered only one type of resistant cells. When considering the case of two types of resistant cells in [23], they introduced some approximations to their derivations, but did not explicitly describe how they obtained these expressions.

The results of Eqs. (4)–(6) can be obtained by solving a system of differential equations, and are therefore exact expressions. The following section presents the formula to evaluate the probability that no doubly resistant cells appear.

### 2.3. Probability of occurrence of no double resistance

The Goldie, Coldman, and Guaauskas-model is based on the assumption that only $R_1$ and $R_2$ type cells can mutate to $R_{1,2}$ type cells (i.e., An $S$ type cell can mutate to an $R_1$ or an $R_2$ type cell, but can not directly mutate to an $R_{1,2}$ type cell). Let the mutation rates from an $S$ type cell to an $R_1$ or an $R_2$ type cell be $\alpha_1$ and $\alpha_2$, respectively. The following lemma and theorem present the underlying assumptions of the mutation process and the probability that no doubly resistant cells are present.

**Lemma 2.2.** *During the growth phase, let the population size grow from N to $N+\Delta N$ with $\Delta N \to 0$. Suppose that no mutations from an $R_1$ type or an $R_2$ type cell to an $R_{1,2}$ type cell occur during this period. Let the mutation rate from an S type cell to an $R_1$ type cell be $\alpha_1$, and let the mutation rate from an S type cell to an $R_2$ type cell be $\alpha_2$. The increase of $R_1$ type cells caused by the duplication of $R_1$ type cells is*

$$\Delta R_{1,dup}(N)\cdot\Delta N = \left(\frac{dR_1(N)}{dN} - \alpha_1\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\right)\Delta N$$

*and the increase of $R_2$ type cells caused by the duplication of $R_2$ type cells is*

$$\Delta R_{2,dup}(N)\cdot\Delta N = \left(\frac{dR_2(N)}{dN} - \alpha_2\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\right)\Delta N.$$

**Proof.** The number of $R_1$ type cells may increase caused by the duplication of $R_1$ type cells themselves or the mutations from $S$ type cells to $R_1$ type cells. When no mutations from $R_1$ type cells to $R_{1,2}$ type cells occur as the population size grows from $N$ to $N+\Delta N$, the increase of $R_1$ type cells can be calculated as

$$\begin{aligned} &R_1(N+\Delta N) - R_1(N) - \alpha_1\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\Delta N \\ &\cong \left(\frac{dR_1(N)}{dN} - \alpha_1\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\right)\Delta N. \end{aligned}$$

Similarly,

$$\begin{aligned} &R_2(N+\Delta N) - R_2(N) - \alpha_2\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\Delta N \\ &\cong \left(\frac{dR_2(N)}{dN} - \alpha_2\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\right)\Delta N. \end{aligned}$$ □

This lemma appears in the appendix of [23]. However, Goldie, Coldman, and Gudauskas considered that the number of $R_1$ and $R_2$ type cells is much smaller compared with the number of $S$ type cells. Therefore, $1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}$ is approximately 1 in their expressions. Because $R_{1,2}$ type cells are present during the process $R_1$ type or $R_2$ type cells duplicate, these relationships can be used to calculate the probability that no mutations to $R_{1,2}$ type cells will occur.

**Theorem 2.3.** *During the growth phase, an $R_1$ or an $R_2$ type cell may mutate to an $R_{1,2}$ type cell with mutation rates $\alpha_{1,2}$ and $\alpha_{2,1}$, respectively. Let $P_{no\text{-}resist}(N)$ denote the probability that no $R_{1,2}$ type cell is present when the total population size is N. Let $P_{no\text{-}resist}(N'|N)$ denote the probability that no $R_{1,2}$ type cell is present when the total population size is $N'$ conditioned on that no $R_{1,2}$ type cell being present when the total population size is N. If the population size increases from N to $N+\Delta N$ with $\Delta N \to 0$ during the growth phase and the probability of that no doubly resistant cells generated is*

$$P_{no\text{-}resist}(N+\Delta N|N) = 1-\alpha_{1,2}\cdot\Delta R_{1,dup}(N)\cdot\Delta N - \alpha_{2,1}\cdot\Delta R_{2,dup}(N)\cdot\Delta N + O(\Delta N^2), \quad (7)$$

*then the probability of no doubly resistant cell being present is*

$$P_{no\text{-}resist}(N) = \exp\left(-\alpha_{1,2}(R_1(N)-R_1(N_0)) - \alpha_{2,1}(R_2(N)-R_2(N_0)) + \frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}(S(N)-S(N_0))\right). \quad (8)$$

**Proof.** See Appendix B. □

The expression in Eq. (7) is based on the non-homogeneous Poisson process assumption [25] introduced in [2,23]. This Poisson type process is based on the implicit assumption that the probabil-

ity of simultaneous occurrence of two mutational events is negligible (i.e. $O(\Delta N^2)$) as $\Delta N$ approaches zero. Therefore, simultaneous mutations to $R_1$ (or $R_2$) and to $R_{1,2}$ are neglected. Moreover, in contrast to a typical Poisson process, the increase in the number of cells $\Delta N$ serves as the time counter in this mutation process. The intensity function of the mutation from $R_1$ type cells to $R_{1,2}$ type cells is $\alpha_{1,2} \cdot \Delta R_{1,dup}(N)$. Therefore, the probability of no $R_{1,2}$ type cells being generated by the mutation of $R_1$ type cells is $1 - \alpha_{1,2} \cdot \Delta R_{1,dup}(N) + O(\Delta N^2)$. Similarly, the probability of no $R_{1,2}$ type cells being generated by the mutation of $R_2$ type cells is $1 - \alpha_{2,1} \cdot \Delta R_{2,dup}(N) + O(\Delta N^2)$. Because these two events are assumed to be independent, the probability of no $R_{1,2}$ type cells generated as the population increases from $N$ to $N + \Delta N$ is the product of $1 - \alpha_{1,2} \cdot \Delta R_{1,dup}(N) + O(\Delta N^2)$ and $1 - \alpha_{2,1} \cdot \Delta R_{2,dup}(N) + O(\Delta N^2)$ indicated in Eq. (7). One thing worth mentioning is that the intensity function depends on $R_1(N)$ (or $R_2(N)$) because the occurrence of mutations to $R_{1,2}$ type cells depends on the number of $R_1(N)$ (or $R_2(N)$) within the entire tumor cell population.

## 3. The optimal *n*-cycle treatment problem

The previous section presents the details of the treatment and the growth phases in one cycle. During the treatment phase, a drug is applied to reduce the tumor size. Thereafter, the tumor grows during the growth phase. Mutations from either $R_1$ or $R_2$ type cells to $R_{1,2}$ type cells might occur during this phase. The growth process described in Theorem 2.1 assumes that no doubly resistant cell presents. The probability for such an event occurring can be evaluated, and it serves as the measure of good treatment outcomes. An optimal $n$-cycle treatment problem is to select optimal treatment options for each cycle to maximize the probability of the non-occurrence of doubly resistant cells throughout the entire $n$ cycles. This section provides the formulation of this problem and the following section provides a close-form solution to this problem under certain assumptions.

To ease the following presentation, first consider several notations. Consider an $n$-cycle treatment process with an initial population of cells. The population size varies when the population experiences various drug interventions and growth phases at different cycles. Therefore, the population size can be viewed as a function of treatment options and settings of growth phases. Let $N_0^{(i)}$, $\bar{N}_0^{(i)}$ and $\bar{N}^{(i)}$ denote the population sizes before the treatment, after the treatment, and after the growth phase of the $i$th cycle. These population sizes can be expressed as

$$N_0^{(i)} = N_0^{(i)}(T_1, \ldots T_{i-1}, G_1, \ldots G_{i-1}),$$
$$\bar{N}_0^{(i)} = \bar{N}_0^{(i)}(T_1, \ldots T_i, G_1, \ldots G_{i-1})$$

and

$$\bar{N}^{(i)} = \bar{N}^{(i)}(T_1, \ldots T_i, G_1, \ldots G_i).$$

The term $T_i$ represents the treatment option of the $i$th treatment phase and $G_i$ represents the settings of the $i$th growth phase. In the following, we assume that the duration of each growth phase is $d'$ (Fig. 1). Growth and mutation are spontaneous and are not affected by external forces. Therefore, we suppress variables $G_i$. The term $T_i$ is 1 or $-1$ for $i = 1 \ldots n$. Each $T_i$ represents the first or second drug selected as the treatment option in the $i$th cycle, respectively. For simplicity, our expression will include $T_i$ explicitly only when necessary. Moreover, we denote $(T_1, \ldots T_i)$ as $T_{1\to i}$ for notational convenience.

The following discussion presents the formulation of the $n$-cycle treatment problem. The entire treatment process can be formulated as an optimization problem. Briefly speaking, a population initially consists of $N_0^{(1)}$ cells. During the treatment and the growth phases of each cycle, the population size may decrease and then increase because of the implementation of drug therapy followed by cell duplication. An $S$ type cell may mutate to a $R_1$ or $R_2$ type cell with rates $\alpha_1$ and $\alpha_2$, respectively. An $R_1$ or $R_2$ type cell can further mutate to a doubly resistant $R_{1,2}$ type cell with rates $\alpha_{1,2}$ and $\alpha_{2,1}$ Fig. 2.

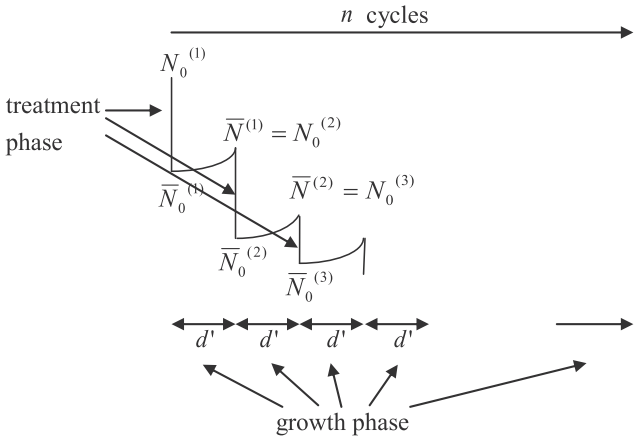


**Fig. 1.** Treatment and growth phase.

### 3.1. Treatment phase at the ith cycle

Suppose that the log-kill constants for the first drug against $R_2$ and $S$ type cells are $k_{1,r}{}^2$ and $k_{1,s}{}^2$, respectively. The log-kill constants for the second drug against $R_1$ and $S$ type cells are $k_{2,r}{}^2$ and $k_{2,s}{}^2$, respectively. During the $i$th cycle, denote the treatment option $T_i = 1$ if the first drug is applied and $T_i = -1$ if the second drug is applied. Let $N_0^{(i)}$ and $\bar{N}_0^{(i)}$ be the population sizes before and after the treatment of the $i$th treatment phase. The variation in the number of $R_1$, $R_2$, and $S$ type cells before and after treatment can be calculated using the following equations:

$$R_1\left(\bar{N}_0^{(i)}\right) = (k_{2,r})^{(T_i-1)} \cdot R_1\left(N_0^{(i)}\right), \tag{9}$$

$$R_2\left(\bar{N}_0^{(i)}\right) = (k_{1,r})^{(-T_i-1)} \cdot R_2\left(N_0^{(i)}\right) \tag{10}$$

and

$$S\left(\bar{N}_0^{(i)}\right) = (k_{2,s})^{(T_i-1)} \cdot (k_{1,s})^{(-T_i-1)} \cdot S\left(N_0^{(i)}\right). \tag{11}$$

In Eq. (9), the notation $(k_{2,r})^{(T_i-1)}$ denotes $k_{2,r}$ with power $(T_i - 1)$. Eqs. (10) and (11) apply similar notations.

### 3.2. Growth phase at the ith cycle

Let $\bar{N}_0^{(i)}$ and $\bar{N}^{(i)}$ be the population sizes before and after growth of the $i$th growth phase. The variation in the number of $R_1$, $R_2$ and $S$ type cells before and after growth can be calculated using the following equations. Eqs. (1) and (4)–(6) lead to the following:

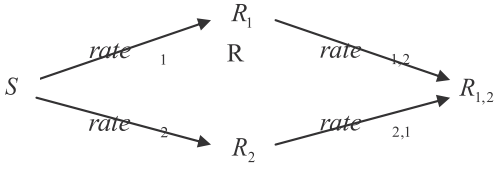


**Fig. 2.** Mutation rates.

$$R_1(\bar{N}^{(i)}) = 2^{\frac{d'}{d}} R_1\left(\bar{N}_0^{(i)}\right) + \frac{\alpha_1}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(i)}\right) 2^{\frac{d'}{d}} \left(1 - \left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right), \quad (12)$$

$$R_2(\bar{N}^{(i)}) = 2^{\frac{d'}{d}} R_2\left(\bar{N}_0^{(i)}\right) + \frac{\alpha_2}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(i)}\right) 2^{\frac{d'}{d}} \left(1 - \left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right), \quad (13)$$

and

$$S(\bar{N}^{(i)}) = S\left(\bar{N}_0^{(i)}\right) \cdot \left(2^{\frac{d'}{d}}\right)^{1-\alpha_1-\alpha_2}. \quad (14)$$

### 3.3. Optimal n-cycle treatment problem

The objective of an optimal $n$-cycle treatment problem is to select one of two available drugs as the treatment option for each cycle to maximize the probability of no doubly resistant cells appearing throughout the entire $n$ cycles. The following theorem states this formulation.

**Theorem 3.1.** *The evaluation of the probability that no doubly resistant cell appears can be obtained from Eq. (8). The overall optimization problem can be expressed as*

$$\begin{aligned}\max_{T_i, i=1\ldots n} P_{no\text{-}resist}^{n\text{-}cycle} = \max_{T_i, i=1\ldots n} \exp\Bigg(\sum_{i=1}^{n}\Big(&-\alpha_{1,2}\left(R_1\left(\bar{N}^{(i)}(T_{1\to i-1}, T_i)\right)\right.\\ &\left.-R_1\left(\bar{N}_0{}^{(i)}(T_{1\to i-1}, T_i)\right)\right) - \alpha_{2,1}\left(R_2\left(\bar{N}^{(i)}(T_{1\to i-1}, T_i)\right)\right.\\ &\left.-R_2\left(\bar{N}_0{}^{(i)}(T_{1\to i-1}, T_i)\right)\right) + \frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}\left(S\left(\bar{N}^{(i)}(T_{1\to i-1}, T_i)\right)\right.\\ &\left.-S\left(\bar{N}_0{}^{(i)}(T_{1\to i-1}, T_i)\right)\right)\Big)\Bigg), \end{aligned} \quad (15)$$

*where $T_i$ is 1 or −1* to represent the first or second drug selected as the treatment option in the ith treatment phase. The objective function $P_{no\text{-}resist}^{n\text{-}cycle}$ *is the probability that no doubly resistant cell will appear during the n-cycle treatment process.*

This theorem can be easily proved by recursively applying Eq. (8). Because an exponential function is a strictly increasing function, this problem is equivalent to the following problem:

$$\begin{aligned}\min_{T_i, i=1\ldots n} \sum_{i=1}^{n}\Bigg(&\alpha_{1,2}\left(R_1\left(\bar{N}^{(i)}(T_{1\to i-1}, T_i)\right) - R_1\left(\bar{N}_0{}^{(i)}(T_{1\to i-1}, T_i)\right)\right)\\ &+\alpha_{2,1}\left(R_2\left(\bar{N}^{(i)}(T_{1\to i-1}, T_i)\right) - R_2\left(\bar{N}_0{}^{(i)}(T_{1\to i-1}, T_i)\right)\right)\\ &-\frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}\left(S\left(\bar{N}^{(i)}(T_{1\to i-1}, T_i)\right) - S\left(\bar{N}_0{}^{(i)}(T_{1\to i-1}, T_i)\right)\right)\Bigg). \end{aligned} \quad (16)$$

This problem can be further expressed as the following problem. Appendix C presents the details of these derivations.

$$\begin{aligned}\min_{T_i, i=1\ldots n} \sum_{i=1}^{n}\Bigg(&\left(2^{\frac{d'}{d}}-1\right)\left(\alpha_{1,2}k_{2,r}^{T_i-1}R_1\left(N_0{}^{(i)}(T_{1\to i-1})\right)\right.\\ &\left.+\alpha_{2,1}k_{1,r}^{-T_i-1}R_2\left(N_0{}^{(i)}(T_{1\to i-1})\right)\right) + \frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{(\alpha_1+\alpha_2)(1-\alpha_1-\alpha_2)}\\ &\left(2^{\frac{d'}{d}} - 2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}} - (\alpha_1+\alpha_2)\left(2^{\frac{d'}{d}}-1\right)\right)\cdot k_{2,s}^{T_i-1}k_{1,s}^{-T_i-1}S\left(N_0{}^{(i)}(T_{1\to i-1})\right)\Bigg). \end{aligned} \quad (17)$$

It can be noted that the objective function of this optimization problem is expressed as a function of $T_{1\to i-1}$, and $T_i$ in the last expression. The following section shows that with a given $T_{1\to i-1}$, if $T_i$ is properly chosen at each cycle, then the treatment process can be optimized.

## 4. Optimal therapy under equal efficacy assumptions

In this section, we assume that the first and second drugs have the same efficacy on $S$ type cells. In other words, their kill constants against $S$ type cells $k_{1,s}{}^2$ and $k_{2,s}{}^2$ are equivalent to $k_s{}^2$. This assumption is used to derive the analytical solution to the optimal treatment problem.

Because both drugs have the same log-kill constant against $S$ type cells, the objective function of the optimization problem can be expressed as

$$\begin{aligned}\min_{T_i, i=1\ldots n} \sum_{i=1}^{n}\Bigg(&\left(2^{\frac{d'}{d}}-1\right)\left(\alpha_{1,2}k_{2,r}^{T_i-1}R_1\left(N_0{}^{(i)}(T_{1\to i-1})\right) + \alpha_{2,1}k_{1,r}^{-T_i-1}R_2\left(N_0{}^{(i)}(T_{1\to i-1})\right)\right)\\ &+\frac{(\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1})\left(2^{\frac{d'}{d}} - 2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}} - (\alpha_1+\alpha_2)\left(2^{\frac{d'}{d}}-1\right)\right)k_s^{-2}S\left(N_0{}^{(i)}(T_{1\to i-1})\right)}{(\alpha_1+\alpha_2)(1-\alpha_1-\alpha_2)}\Bigg). \end{aligned} \quad (18)$$

Eqs. (11) and (14) show that

$$S(N_0^{(i)}) = \left(\left(2^{\frac{d'}{d}}\right)^{1-\alpha_1-\alpha_2} k_s^{-2}\right)^{i-1} \cdot S\left(N_0^{(1)}\right).$$

Based on this relation, the objective function in Eq. (18) can be simplified as

$$\min_{T_i, i=1\ldots n} \sum_{i=1}^{n}\left(\left(2^{\frac{d'}{d}}-1\right)\left(\alpha_{1,2}k_{2,r}^{T_i-1}R_1\left(N_0{}^{(i)}(T_{1\to i-1})\right) + \alpha_{2,1}k_{1,r}^{-T_i-1}R_2\left(N_0{}^{(i)}(T_{1\to i-1})\right)\right)\right). \quad (19)$$

Dropping the positive constant $2^{\frac{d'}{d}} - 1$ leads to the following equivalent objective function:

$$\min_{T_i, i=1\ldots n} \sum_{i=1}^{n}\left(\alpha_{1,2}k_{2,r}^{T_i-1}R_1\left(N_0{}^{(i)}(T_{1\to i-1})\right) + \alpha_{2,1}k_{1,r}^{-T_i-1}R_2\left(N_0{}^{(i)}(T_{1\to i-1})\right)\right).$$

The optimal policy under this equal efficacy but not fully symmetric assumption is described in the following lemma and theorem. They partially solve the general $n$-cycle treatment problem and represent the major results of this paper. Goldie, Coldman and Gudauskas' work is a special case of this assumption, as described in the following section.

**Lemma 4.1.** *Let $T_{1\to i-1}$ be chosen as an arbitrary $\bar{T}_{1\to i-1}$ during the first $i-1$ treatment phases. Denote $T_i^*$ and $T_i^{**}$ as alternative options for the ith treatment phase. The following relationship holds:*

*If*

$$\begin{aligned}&\alpha_{1,2}k_{2,r}^{T_i^*-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) + \alpha_{2,1}k_{1,r}^{-T_i^*-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\\ &\leqslant \alpha_{1,2}k_{2,r}^{T_i^{**}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) + \alpha_{2,1}k_{1,r}^{-T_i^{**}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right), \end{aligned}$$

*then*

$$\begin{aligned}&\alpha_{1,2}k_{2,r}^{T_{i+1}-1}R_1\left(N_0{}^{(i+1)}(\bar{T}_{1\to i-1}, T_i^*)\right) + \alpha_{2,1}k_{1,r}^{-T_{i+1}-1}R_2\left(N_0{}^{(i+1)}(\bar{T}_{1\to i-1}, T_i^*)\right)\\ &\leqslant \alpha_{1,2}k_{2,r}^{T_{i+1}-1}R_1\left(N_0{}^{(i+1)}(\bar{T}_{1\to i-1}, T_i^{**})\right)\\ &\quad + \alpha_{2,1}k_{1,r}^{-T_{i+1}-1}R_2\left(N_0{}^{(i+1)}(\bar{T}_{1\to i-1}, T_i^{**})\right) \end{aligned}$$

*for both $T_{i+1} = 1$ and $T_{i+1} = -1$.*

**Proof.** See Appendix D. □

**Theorem 4.2.** *In an n-cycle treatment process, the optimal treatment options for minimizing the probability of the occurrence of doubly resistant cells $R_{1,2}$ can be determined as follows. For $i = 1$, the optimal treatment option is*

$$T_1^* = \arg\min_{T_1}\left(\alpha_{1,2}k_{2,r}^{T_1-1}R_1\left(N_0{}^{(1)}\right) + \alpha_{2,1}k_{1,r}^{-T_1-1}R_2\left(N_0{}^{(1)}\right)\right). \quad (20)$$

*Suppose that the optimal treatment options of the first $(i-1)$th cycles have been determined to be $T_{i-1}^*$. The optimal treatment option for ith cycle is*

$$T_i^* = \arg\min_{T_i}\left(\alpha_{1,2}k_{2,r}^{T_i-1}R_1\left(N_0^{(i)}(T_{1\to i-1}=T_{1\to i-1}^*)\right)\right.$$
$$\left.+\alpha_{2,1}k_{1,r}^{-T_i-1}R_2\left(N_0^{(i)}(T_{1\to i-1}=T_{1\to i-1}^*)\right)\right). \quad (21)$$

**Proof.** This theorem can be proved by induction. For $i=1$, it is obvious that

$$T_1^* = \arg\min_{T_1}\left(\alpha_{1,2}k_{2,r}^{T_1-1}R_1\left(N_0^{(1)}\right)+\alpha_{2,1}k_{1,r}^{-T_1-1}R_2\left(N_0^{(1)}\right)\right).$$

Let $i=k$ be true. We have

$$T_k^* = \arg\min_{T_k}\left(\alpha_{1,2}k_{2,r}^{T_k-1}R_1\left(N_0^{(k)}(T_{1\to k-1}=T_{1\to k-1}^*)\right)+\alpha_{2,1}k_{1,r}^{-T_k-1}R_2\right.$$
$$\left.\times\left(N_0^{(k)}(T_{1\to k-1}=T_{1\to k-1}^*)\right)\right).$$

This in turn implies that

$$\Rightarrow \alpha_{1,2}k_{2,r}^{T_k^*-1}R_1\left(N_0^{(k)}(T_{1\to k-1}=T_{1\to k-1}^*)\right)$$
$$+\alpha_{2,1}k_{1,r}^{-T_k^*-1}R_2\left(N_0^{(k)}(T_{1\to k-1}=T_{1\to k-1}^*)\right)$$
$$\leqslant \alpha_{1,2}k_{2,r}^{T_k-1}R_1\left(N_0^{(k)}(T_{1\to k-1}=T_{1\to k-1}^*)\right)$$
$$+\alpha_{2,1}k_{1,r}^{-T_k-1}R_2\left(N_0^{(k)}(T_{1\to k-1}=T_{1\to k-1}^*)\right)$$

for any $T_k$. By Lemma 4.1,

$$\alpha_{1,2}k_{2,r}^{T_{k+1}-1}R_1\left(N_0^{(k+1)}(T_{1\to k}=T_{1\to k}^*)\right)$$
$$+\alpha_{2,1}k_{1,r}^{-T_{k+1}-1}R_2\left(N_0^{(k+1)}(T_{1\to k}=T_{1\to k}^*)\right)$$
$$\leqslant \alpha_{1,2}k_{2,r}^{T_{k+1}-1}R_1\left(N_0^{(k+1)}(T_{1\to k-1}^*,T_k)\right)$$
$$+\alpha_{2,1}k_{1,r}^{-T_{k+1}-1}R_2\left(N_0^{(k+1)}(T_{1\to k-1}^*,T_k)\right).$$

This corresponds to the $(k+1)$th term in the summation of the objective function. To optimize the treatment process up to the $(k+1)$th cycle, it is only necessary to select the treatment option at the $(k+1)$th cycle as

$$T_{k+1}^* = \arg\min_{T_{k+1}}\left(\alpha_{1,2}k_{2,r}^{T_{k+1}-1}R_1\left(N_0^{(k+1)}(T_{1\to k}=T_{1\to k}^*)\right)+\alpha_{2,1}k_{1,r}^{-T_{k+1}-1}\right.$$
$$\left.R_2\left(N_0^{(k+1)}(T_{1\to k}=T_{1\to k}^*)\right)\right). \qquad \square$$

The following example demonstrates that the method described in Theorem 4.2 can obtain optimal treatment options. In Table 1, the treatment options for each cycle are chosen based on Theorem 4.2. The options in Table 2 represent another sequence of treatment options that does not satisfy the condition specified in Theorem 4.2. It can be observed that the probability of the non-occurrence of $R_{1,2}$ type cells in Table 2 is less than that of Table 1.

**Example 1.**
Let the doubling time of the population be $d=36$ days, the duration of each growth phase be $d'=21$ days, and the initial total size be $N=10^{10}$. The log-kill constants are ${k_{1,r}}^2=225$, $k_{2,r}^2=1225$, and ${k_{1,s}}^2=k_{2,s}^2\equiv k_s^2=4$. The mutation rates are set to be $\alpha_1=10^{-4.5}$, $\alpha_{2,1}=10^{-5}$, $\alpha_2=10^{-7}$, and $\alpha_{1,2}=10^{-6.5}$. Assume that the population starts with one $S$ type cell, and that no doubly resistant cells are present during the period that the population increases to $N=10^{10}$. The expected sizes of $R_1$ and $R_2$ can be computed as

$$R_1\left(N_0^{(1)}\right)=\frac{\alpha_1}{\alpha_1+\alpha_2}N(1-N^{-\alpha_1-\alpha_2})=7278754.7155,$$

$$R_2\left(N_0^{(1)}\right)=\frac{\alpha_2}{\alpha_1+\alpha_2}N(1-N^{-\alpha_1-\alpha_2})=23017.4434$$

and

$$S\left(N_0^{(1)}\right)=10^{10}-R_1\left(N_0^{(1)}\right)-R_2\left(N_0^{(1)}\right)=9992698228.$$

The probability that no doubly resistant cells are present is

$$\exp\left(-\alpha_{1,2}R_1\left(N_0^{(1)}\right)-\alpha_{2,1}R_2\left(N_0^{(1)}\right)+\frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}\left(S\left(N_0^{(1)}\right)-1\right)\right)$$
$$=0.08874434.$$

Table 1 and Table 2 present summaries of the details of a 10-cycle treatment problem with two sequences of treatment options. The results in these tables confirm the correctness of Theorem 4.2.

## 5. Optimal therapy under equal mutation rates

Goldie, Coldman and Gudauskas' work can be viewed as special cases of Theorem 4.2. They consider two cases with symmetrical parameter settings such that alternating therapy is optimal [23,24]. Both cases require that the initial sizes of $R_1$ and $R_2$ satisfying the condition that $R_1\left(N_0^{(1)}\right)=R_2\left(N_0^{(1)}\right)$ and the log kill constants ${k_{1,r}}^2$, $k_{2,r}^2$, $k_{1,s}^2$ and ${k_{2,s}}^2$ are equivalent. In case 1, the mutation rates $\alpha_1$, $\alpha_2$, $\alpha_{1,2}$ and $\alpha_{2,1}$ are assumed to be equivalent. In case 2, the assumptions on mutation rates are relaxed as $\alpha_1=\alpha_2$ and $\alpha_{1,2}=\alpha_{2,1}$. The following theorems restate Goldie, Coldman and Gudauskas' results on symmetrical cases based on our formulation. Details of two numerical examples are provided based on our previously derived formulae. These examples reconfirm the correctness of Goldie, Coldman and Gudauskas' work on symmetrical cases.

**Table 1**
The log-kill constants ${k_{1,r}}^2=225$, $k_{2,r}^2=1225$ and the mutation rates $\alpha_1=10^{-4.5}$, $\alpha_{2,1}=10^{-5}$, $\alpha_2=10^{-7}$, and $\alpha_{1,2}=10^{-6.5}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)})=R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)})=R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)})=S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | −1 | 143.7779 | 23017.4434 | 2498174556.9603 | 48074.3641 | 34638.5416 | 3742984607.6829 | 0.88898526 | 0.07889241 |
| 2 | 1 | 48074.3641 | 0.0231 | 935746151.9207 | 89956.7773 | 56.7235 | 1402017098.2766 | 0.99135534 | 0.07821041 |
| 3 | −1 | 1.7769 | 56.7235 | 350504274.5691 | 6717.4707 | 106.2234 | 525156299.0201 | 0.99930279 | 0.07815588 |
| 4 | −1 | 0.1327 | 106.2234 | 131289074.7550 | 2515.3778 | 167.1089 | 196708826.6894 | 0.99931563 | 0.07810240 |
| 5 | 1 | 2515.3778 | 0.0001 | 49177206.6724 | 4710.9238 | 2.9794 | 73681611.6835 | 0.99954557 | 0.07806691 |
| 6 | −1 | 0.0931 | 2.9794 | 18420402.9209 | 353.0295 | 5.5800 | 27599066.0493 | 0.99996335 | 0.07806404 |
| 7 | −1 | 0.0070 | 5.5800 | 6899766.5123 | 132.1932 | 8.7785 | 10337836.3935 | 0.99996403 | 0.07806124 |
| 8 | 1 | 132.1932 | 0.0000 | 2584459.0984 | 247.5779 | 0.1566 | 3872263.6885 | 0.99997611 | 0.07805937 |
| 9 | −1 | 0.0049 | 0.1566 | 968065.9221 | 18.5531 | 0.2933 | 1450441.4176 | 0.99999807 | 0.07805922 |
| 10 | −1 | 0.0004 | 0.2933 | 362610.3544 | 6.9473 | 0.4613 | 543294.6914 | 0.99999811 | 0.07805907 |

**Table 2**
The log-kill constants ${k_{1,r}}^2 = 225$, $k_{2,r}^2 = 1225$ and the mutation rates $\alpha_1 = 10^{-4.5}$, $\alpha_{2,1} = 10^{-5}$, $\alpha_2 = 10^{-7}$, and $\alpha_{1,2} = 10^{-6.5}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)}) = R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)}) = R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)}) = S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 7278754.7155 | 0.0153 | 2498174556.9603 | 10953668.6417 | 151.3662 | 3742984607.6829 | 0.31665894 | 0.02810169 |
| 2 | −1 | 216.3688 | 151.3662 | 935746151.9207 | 18250.8043 | 283.4821 | 1402017098.2766 | 0.99810679 | 0.02804849 |
| 3 | 1 | 18250.8043 | 0.0002 | 350504274.5691 | 34060.1175 | 21.2344 | 525156299.0201 | 0.99671496 | 0.02795635 |
| 4 | −1 | 0.6728 | 21.2344 | 131289074.7550 | 2516.1870 | 39.7693 | 196708826.6894 | 0.99973885 | 0.02794905 |
| 5 | 1 | 2516.1870 | 0.0000 | 49177206.6724 | 4712.1363 | 2.9793 | 73681611.6835 | 0.99954545 | 0.02793634 |
| 6 | −1 | 0.0931 | 2.9793 | 18420402.9209 | 353.0295 | 5.5798 | 27599066.0493 | 0.99996336 | 0.02793532 |
| 7 | 1 | 353.0295 | 0.0000 | 6899766.5123 | 661.1294 | 0.4180 | 10337836.3935 | 0.99993621 | 0.02793354 |
| 8 | −1 | 0.0131 | 0.4180 | 2584459.0984 | 49.5315 | 0.7829 | 3872263.6885 | 0.99999486 | 0.02793339 |
| 9 | 1 | 49.5315 | 0.0000 | 968065.9221 | 92.7592 | 0.0586 | 1450441.4176 | 0.99999105 | 0.02793314 |
| 10 | −1 | 0.0018 | 0.0586 | 362610.3544 | 6.9495 | 0.1098 | 543294.6914 | 0.99999928 | 0.02793312 |

### 5.1. The mutation rates $\alpha_1 = \alpha_2 = \alpha_{1,2} = \alpha_{2,1}$

**Theorem 5.1.** *Under the assumptions of Theorem 4.2, if the conditions* $R_1\left(N_0^{(1)}\right) = R_2\left(N_0^{(1)}\right)$, *the log kill constants* ${k_{1,r}}^2 = k_{2,r}^2 = k_{1,s}^2 = k_{2,s}^2$ *and the mutation rates* $\alpha_1 = \alpha_2 = \alpha_{1,2} = \alpha_{2,1}$ *are satisfied, the alternating treatment policy is optimal to problem (15). In other words,* $T_{i+1} = -T_i$ *for* $i = 1$ *to* $n - 1$.

**Proof.** See Appendix E. □

In the following, we reproduce Goldie, Coldman and Gudauskas' example. The numerical results are computed with formulae derived in this paper and henceforth are slightly different compared with results stated in [23]. It can be observed that the alternating policy is optimal.

**Example 2.**
Let the doubling time of the population be $d = 36$ days, the duration of each growth phase be $d' = 21$ days, and the initial population size be $N = 10^{10}$. The log-kill constants are ${k_{1,r}}^2 = k_{2,r}^2 = k_{1,s}^2 = k_{2,s}^2 = 100$, and the mutation rates are $\alpha_1 = \alpha_2 = \alpha_{1,2} = \alpha_{2,1} = 10^{-6}$. We assume that the population starts with one $S$ type cell. Suppose that during the process that the population size increases to $N = 10^{10}$, no doubly resistant cells present. Then, the expected sizes of $R_1$ and $R_2$ can be computed as

$$R_1\left(N_0^{(1)}\right) = \frac{\alpha_1}{\alpha_1+\alpha_2}N(1 - N^{-\alpha_1-\alpha_2}) = 230253.2075,$$

$$R_2\left(N_0^{(1)}\right) = \frac{\alpha_2}{\alpha_1+\alpha_2}N(1 - N^{-\alpha_1-\alpha_2}) = 230253.2075$$

and

$$S\left(N_0^{(1)}\right) = 10^{10} - R_1\left(N_0^{(1)}\right) - R_2\left(N_0^{(1)}\right) = 9999539494.$$

The probability that no doubly resistant cells are present is

$$\exp\left(-\alpha_{1,2}R_1\left(N_0^{(1)}\right) - \alpha_{2,1}R_2\left(N_0^{(1)}\right) + \frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}\left(S\left(N_0^{(1)}\right) - 1\right)\right) = 0.643709.$$

A 10-cycle treatment problem with three different sequences of treatment options are presented in Tables 3–5, respectively. It can be observed that the alternating policy in Table 5 has the greatest probability of the non-occurrence of double resistance. Henceforth, it is the optimal strategy.

### 5.2. The mutation rates $\alpha_1 = \alpha_2$ and $\alpha_{1,2} = \alpha_{2,1}$

**Theorem 5.2.** *Under the assumptions of Theorem 4.2, if the conditions* $R_1\left(N_0^{(1)}\right) = R_2\left(N_0^{(1)}\right)$, *the log kill constants* ${k_{1,r}}^2 = k_{2,r}^2 \equiv k_r^2$, $k_{1,s}^2 = k_{2,s}^2 \equiv k_s^2$ *and the mutation rates* $\alpha_1 = \alpha_2 \equiv \alpha_1$, $\alpha_{1,2} = \alpha_{2,1} \equiv \alpha_{1,2}$ *are satisfied, the alternating treatment policy is optimal to the problem (15). In other words,* $T_{i+1} = -T_i$ *for* $i = 1$ *to* $n - 1$.

**Proof.** See Appendix E. □

A 10-cycle treatment problem is presented in Tables 6–8. Options in Tables 6 and 7 do not satisfy conditions in Theorem 5.1. Options in Table 8 are obtained with the method stated in Theorem 5.1. It can be observed that the probability of the non-occurrence of $R_{1,2}$ type cells is maximized under alternating treatment policy. Therefore, it is optimal.

**Example 3.**
Let the doubling time of the population be $d = 36$ days, the duration of each growth phase be $d' = 21$ days, and the initial population size $N$ be $10^{10}$. The log-kill constants are set to be ${k_{1,r}}^2 = k_{2,r}^2 \equiv k_r^2 = 144$, $k_{1,s}^2 = k_{2,s}^2 \equiv k_s^2 = 100$ and the mutation rates are set to be $\alpha_1 = \alpha_2 = 10^{-6}$, $\alpha_{1,2} = \alpha_{2,1} = 10^{-5.5}$. We assume that the population starts with one $S$ type cell. Furthermore, assume that no doubly resistant cells are present during the process that the population size increases to $N = 10^{10}$. The expected sizes of $R_1$ and $R_2$ can be computed as

$$R_1\left(N_0^{(1)}\right) = \frac{\alpha_1}{\alpha_1+\alpha_2}N(1 - N^{-\alpha_1-\alpha_2}) = 230253.2075,$$

**Table 3**
The log-kill constants ${k_{1,r}}^2 = k_{2,r}^2 = 100$, and the mutation rates $\alpha_1 = \alpha_2 = \alpha_{1,2} = \alpha_{2,1} = 10^{-6}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)}) = R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)}) = R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)}) = S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 230253.2075 | 2302.5321 | 99995394.9359 | 345050.5894 | 3510.4792 | 149823686.7292 | 0.89055922 | 0.57326169 |
| 2 | 1 | 345050.5894 | 35.1048 | 1498236.8673 | 516992.6476 | 53.5054 | 2244817.0858 | 0.84201372 | 0.48269421 |
| 3 | 1 | 516992.6476 | 0.5351 | 22448.1709 | 774613.7562 | 0.8153 | 33634.2261 | 0.77288782 | 0.37306847 |
| 4 | 1 | 774613.7562 | 0.0082 | 336.3423 | 1160609.2729 | 0.0124 | 503.9436 | 0.67977357 | 0.25360209 |
| 5 | 1 | 1160609.2729 | 0.0001 | 5.0394 | 1738949.0871 | 0.0002 | 7.5506 | 0.56082867 | 0.14222732 |
| 6 | −1 | 17389.4909 | 0.0002 | 0.0755 | 26054.7972 | 0.0003 | 0.1131 | 0.99137213 | 0.14100020 |
| 7 | −1 | 260.5480 | 0.0003 | 0.0011 | 390.3809 | 0.0004 | 0.0017 | 0.99987018 | 0.14098190 |
| 8 | −1 | 3.9038 | 0.0004 | 0.0000 | 5.8491 | 0.0006 | 0.0000 | 0.99999805 | 0.14098162 |
| 9 | −1 | 0.0585 | 0.0006 | 0.0000 | 0.0876 | 0.0010 | 0.0000 | 0.99999997 | 0.14098162 |
| 10 | −1 | 0.0009 | 0.0010 | 0.0000 | 0.0013 | 0.0014 | 0.0000 | 1.00000000 | 0.14098162 |

**Table 4**
The log-kill constants $k_{1,r}{}^2 = k_{2,r}^2 = 100$, and the mutation rates $\alpha_1 = \alpha_2 = \alpha_{1,2} = \alpha_{2,1} = 10^{-6}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)}) = R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)}) = R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)}) = S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 230253.2075 | 2302.5321 | 99995394.9359 | 345050.5894 | 3510.4792 | 149823686.7292 | 0.89055922 | 0.57326169 |
| 2 | 1 | 345050.5894 | 35.1048 | 1498236.8673 | 516992.6476 | 53.5054 | 2244817.0858 | 0.84201372 | 0.48269421 |
| 3 | 1 | 516992.6476 | 0.5351 | 22448.1709 | 774613.7562 | 0.8153 | 33634.2261 | 0.77288782 | 0.37306847 |
| 4 | −1 | 7746.1376 | 0.8153 | 336.3423 | 11606.0929 | 1.2217 | 503.9436 | 0.99614708 | 0.37163107 |
| 5 | −1 | 116.0609 | 1.2217 | 5.0394 | 173.8949 | 1.8305 | 7.5506 | 0.99994156 | 0.37160935 |
| 6 | −1 | 1.7389 | 1.8305 | 0.0755 | 2.6055 | 2.7427 | 0.1131 | 0.99999822 | 0.37160869 |
| 7 | 1 | 2.6055 | 0.0274 | 0.0011 | 3.9038 | 0.0411 | 0.0017 | 0.99999869 | 0.37160820 |
| 8 | 1 | 3.9038 | 0.0004 | 0.0000 | 5.8491 | 0.0006 | 0.0000 | 0.99999805 | 0.37160748 |
| 9 | 1 | 5.8491 | 0.0000 | 0.0000 | 8.7638 | 0.0000 | 0.0000 | 0.99999709 | 0.37160640 |
| 10 | −1 | 0.0876 | 0.0000 | 0.0000 | 0.1313 | 0.0000 | 0.0000 | 0.99999996 | 0.37160638 |

**Table 5**
The log-kill constants $k_{1,r}{}^2 = k_{2,r}^2 = 100$, and the mutation rates $\alpha_1 = \alpha_2 = \alpha_{1,2} = \alpha_{2,1} = 10^{-6}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)}) = R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)}) = R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)}) = S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 230253.2075 | 2302.5321 | 99995394.9359 | 345050.5894 | 3510.4792 | 149823686.7292 | 0.89055922 | 0.57326169 |
| 2 | −1 | 3450.5059 | 3510.4792 | 1498236.8673 | 5170.8251 | 5260.6835 | 2244817.0858 | 0.99653698 | 0.57127647 |
| 3 | 1 | 5170.8251 | 52.6068 | 22448.1709 | 7747.4974 | 78.8348 | 33634.2261 | 0.99740051 | 0.56979144 |
| 4 | −1 | 77.4750 | 78.8348 | 336.3423 | 116.0815 | 118.1189 | 503.9436 | 0.99992211 | 0.56974706 |
| 5 | 1 | 116.0815 | 1.1812 | 5.0394 | 173.9257 | 1.7698 | 7.5506 | 0.99994157 | 0.56971377 |
| 6 | −1 | 1.7393 | 1.7698 | 0.0755 | 2.6059 | 2.6517 | 0.1131 | 0.99999825 | 0.56971278 |
| 7 | 1 | 2.6059 | 0.0265 | 0.0011 | 3.9045 | 0.0397 | 0.0017 | 0.99999869 | 0.56971203 |
| 8 | −1 | 0.0390 | 0.0397 | 0.0000 | 0.0585 | 0.0595 | 0.0000 | 0.99999996 | 0.56971201 |
| 9 | 1 | 0.0585 | 0.0006 | 0.0000 | 0.0877 | 0.0009 | 0.0000 | 0.99999997 | 0.56971199 |
| 10 | −1 | 0.0009 | 0.0009 | 0.0000 | 0.0013 | 0.0013 | 0.0000 | 1.00000000 | 0.56971199 |

**Table 6**
The log-kill constants $k_{1,r}{}^2 = k_{2,r}^2 \equiv k_r^2 = 144$,and the mutation rates $\alpha_1 = \alpha_2 = 10^{-6}$, $\alpha_{1,2} = \alpha_{2,1} = 10^{-5.5}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)}) = R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)}) = R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)}) = S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 230253.2075 | 1598.9806 | 99995394.9359 | 345050.5894 | 2456.3431 | 149823686.7292 | 0.69390704 | 0.17231628 |
| 2 | 1 | 345050.5894 | 17.0579 | 1498236.8673 | 516992.6476 | 26.4657 | 2244817.0858 | 0.58056497 | 0.10004080 |
| 3 | 1 | 516992.6476 | 0.1838 | 22448.1709 | 774613.7562 | 0.2890 | 33634.2261 | 0.44278554 | 0.04429662 |
| 4 | 1 | 774613.7562 | 0.0020 | 336.3423 | 1160609.2729 | 0.0032 | 503.9436 | 0.29504571 | 0.01306953 |
| 5 | 1 | 1160609.2729 | 0.0000 | 5.0394 | 1738949.0871 | 0.0000 | 7.5506 | 0.16059477 | 0.00209890 |
| 6 | −1 | 12076.0353 | 0.0000 | 0.0755 | 18093.6092 | 0.0001 | 0.1131 | 0.98115067 | 0.00205933 |
| 7 | −1 | 125.6501 | 0.0001 | 0.0011 | 188.2624 | 0.0001 | 0.0017 | 0.99980202 | 0.00205893 |
| 8 | −1 | 1.3074 | 0.0001 | 0.0000 | 1.9589 | 0.0001 | 0.0000 | 0.99999794 | 0.00205892 |
| 9 | −1 | 0.0136 | 0.0001 | 0.0000 | 0.0204 | 0.0002 | 0.0000 | 0.99999998 | 0.00205892 |
| 10 | −1 | 0.0001 | 0.0002 | 0.0000 | 0.0002 | 0.0003 | 0.0000 | 1.00000000 | 0.00205892 |

**Table 7**
The log-kill constants $k_{1,r}{}^2 = k_{2,r}^2 \equiv k_r^2 = 144$, and the mutation rates $\alpha_1 = \alpha_2 = 10^{-6}$, $\alpha_{1,2} = \alpha_{2,1} = 10^{-5.5}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)}) = R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)}) = R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)}) = S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 230253.2075 | 1598.9806 | 99995394.9359 | 345050.5894 | 2456.3431 | 149823686.7292 | 0.69390704 | 0.17231628 |
| 2 | 1 | 345050.5894 | 17.0579 | 1498236.8673 | 516992.6476 | 26.4657 | 2244817.0858 | 0.58056497 | 0.10004080 |
| 3 | 1 | 516992.6476 | 0.1838 | 22448.1709 | 774613.7562 | 0.2890 | 33634.2261 | 0.44278554 | 0.04429662 |
| 4 | −1 | 5379.2622 | 0.2890 | 336.3423 | 8059.7868 | 0.4332 | 503.9436 | 0.99155881 | 0.04392270 |
| 5 | −1 | 55.9707 | 0.4332 | 5.0394 | 83.8614 | 0.6490 | 7.5506 | 0.99991112 | 0.04391880 |
| 6 | −1 | 0.5824 | 0.6490 | 0.0755 | 0.8726 | 0.9724 | 0.1131 | 0.99999806 | 0.04391871 |
| 7 | 1 | 0.8726 | 0.0068 | 0.0011 | 1.3074 | 0.0101 | 0.0017 | 0.99999861 | 0.04391865 |
| 8 | 1 | 1.3074 | 0.0001 | 0.0000 | 1.9589 | 0.0001 | 0.0000 | 0.99999794 | 0.04391856 |
| 9 | 1 | 1.9589 | 0.0000 | 0.0000 | 2.9350 | 0.0000 | 0.0000 | 0.99999691 | 0.04391843 |
| 10 | −1 | 0.0204 | 0.0000 | 0.0000 | 0.0305 | 0.0000 | 0.0000 | 0.99999997 | 0.04391842 |

$$R_2\left(N_0{}^{(1)}\right) = \frac{\alpha_2}{\alpha_1+\alpha_2} N(1 - N^{-\alpha_1-\alpha_2}) = 230253.2075$$

and

$$S\left(N_0{}^{(1)}\right) = 10^{10} - R_1\left(N_0{}^{(1)}\right) - R_2\left(N_0{}^{(1)}\right) = 9999539494.$$

The probability that no doubly resistant cell are present is

$$\exp\left(-\alpha_{1,2}R_1\left(N_0{}^{(1)}\right) - \alpha_{2,1}R_2\left(N_0{}^{(1)}\right) + \frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}\left(S\left(N_0{}^{(1)}\right)-1\right)\right) = 0.24832761.$$

The details of the example are provided in Tables 6–8.

**Table 8**
The log-kill constants ${k_{1,r}}^2 = k_{2,r}^2 \equiv k_r^2 = 144$, and the mutation rates $\alpha_1 = \alpha_2 = 10^{-6},\ \alpha_{1,2} = \alpha_{2,1} = 10^{-5.5}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)}) = R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)}) = R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)}) = S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 230253.2075 | 1598.9806 | 99995394.9359 | 345050.5894 | 2456.3431 | 149823686.7292 | 0.69390704 | 0.17231628 |
| 2 | −1 | 2396.1846 | 2456.3431 | 1498236.8673 | 3591.1281 | 3681.2639 | 2244817.0858 | 0.99238161 | 0.17100351 |
| 3 | 1 | 3591.1281 | 25.5643 | 22448.1709 | 5380.6262 | 38.3168 | 33634.2261 | 0.99431706 | 0.17003170 |
| 4 | −1 | 37.3655 | 38.3168 | 336.3423 | 55.9851 | 57.4106 | 503.9436 | 0.99988075 | 0.17001143 |
| 5 | 1 | 55.9851 | 0.3987 | 5.0394 | 83.8829 | 0.5974 | 7.5506 | 0.99991116 | 0.16999632 |
| 6 | −1 | 0.5825 | 0.5974 | 0.0755 | 0.8728 | 0.8950 | 0.1131 | 0.99999814 | 0.16999601 |
| 7 | 1 | 0.8728 | 0.0062 | 0.0011 | 1.3077 | 0.0093 | 0.0017 | 0.99999861 | 0.16999577 |
| 8 | −1 | 0.0091 | 0.0093 | 0.0000 | 0.0136 | 0.0140 | 0.0000 | 0.99999997 | 0.16999577 |
| 9 | 1 | 0.0136 | 0.0001 | 0.0000 | 0.0204 | 0.0001 | 0.0000 | 0.99999998 | 0.16999576 |
| 10 | −1 | 0.0001 | 0.0001 | 0.0000 | 0.0002 | 0.0002 | 0.0000 | 1.00000000 | 0.16999576 |

## 6. Optimal therapy under unequal mutation rates

Results in Section 5 can be anticipated since the role of type $R_1$ and $R_2$ are symmetrical in Theorems 5.1 and 5.2. The treatment process does not favor either the first drug or the second drug and henceforth alternating therapy is the optimal policy. In this section, we consider a special case with asymmetrical parameter settings. In this special case, the log kill constants are set to be ${k_{1,r}}^2 = k_{2,r}^2 = k_r^2,\ k_{1,s}^2 = k_{2,s}^2 = k_s^2$ and the mutation rates are set to be $\alpha_1 = \alpha_{2,1} \equiv \alpha_1, \alpha_2 = \alpha_{1,2} \equiv \alpha_2$. It can shown that the alternating therapy is still optimal in this case. Besides a proof to the theorem stated in the following, we provide an intuitive explanation to why it is valid.

**Theorem 6.1.** *Under the assumptions of Theorem 4.2, if the conditions* $\alpha_2 R_1\left(N_0^{(1)}\right) = \alpha_1 R_2\left(N_0^{(1)}\right)$, *the log kill constants* ${k_{1,r}}^2 = k_{2,r}^2 \equiv k_r^2$, $k_{1,s}^2 = k_{2,s}^2 \equiv k_s^2$ *and the mutation rates* $\alpha_1 = \alpha_{2,1} \equiv \alpha_1,\ \alpha_2 = \alpha_{1,2} \equiv \alpha_2$ *are satisfied, the alternating treatment policy is optimal to the problem (15). In other words,* $T_{i+1} = -T_i$ *for* $i = 1$ *to* $n - 1$.

**Proof.** See Appendix F. □

It is worth mentioning that the condition $\alpha_2 R_1\left(N_0^{(1)}\right) = \alpha_1 R_2\left(N_0^{(1)}\right)$ is a mild assumption. If we assume that a population starts with one $S$ type cell and the population grows without the appearance of $R_{1,2}$ type cells, this condition is satisfied at the starting point of the $n$-cycle treatment process. Moreover, with $\alpha_1 \neq \alpha_2$ in this case, $S$ type cells mutate to $R_1$ and $R_2$ type cells with various rates. However, this asymmetrical setting can be offset by the effect of that $R_1$ type cells mutate to $R_{1,2}$ with rate $\alpha_2$ and $R_2$ type cells mutate to $R_{1,2}$ with rate $\alpha_1$. Therefore, the parameter settings can be viewed as symmetrical in a broad sense represented in Fig. 3 and the alternating therapy is still optimal. The following example is used to illustrate Theorem 6.1.

**Example 4.**
Let the doubling time of the population be $d = 36$ days, the duration of each growth phase be $d' = 21$ days, and the population size $N$ be $10^{10}$. The log-kill constants are set to be ${k_{1,r}}^2 = k_{2,r}^2 \equiv k_r^2 = 144,\ k_{1,s}^2 = k_{2,s}^2 \equiv k_s^2 = 100$ and the mutation rates are set to be $\alpha_1 = \alpha_{2,1} = 10^{-6},\ \alpha_2 = \alpha_{1,2} = 10^{-5}$. We assume that the population starts with one $S$ type cell. Furthermore, assume that no doubly resistant cells present during the process that the population size increases to $N = 10^{10}$. The expected sizes of $R_1$ and $R_2$ can be computed as

$$R_1\left(N_0^{(1)}\right) = \frac{\alpha_1}{\alpha_1 + \alpha_2} N(1 - N^{-\alpha_1 - \alpha_2}) = 230229.3513,$$

$$R_2\left(N_0^{(1)}\right) = \frac{\alpha_2}{\alpha_1 + \alpha_2} N(1 - N^{-\alpha_1 - \alpha_2}) = 2302293.5132,$$

and

$$S\left(N_0^{(1)}\right) = 10^{10} - R_1\left(N_0^{(1)}\right) - R_2\left(N_0^{(1)}\right) = 9997467477.$$

The probability that no doubly resistant cells are present is

$$\exp\left(-\alpha_{1,2} R_1\left(N_0^{(1)}\right) - \alpha_{2,1} R_2\left(N_0^{(1)}\right) + \frac{\alpha_1\alpha_{1,2} + \alpha_2\alpha_{2,1}}{1 - \alpha_1 - \alpha_2}\left(S\left(N_0^{(1)}\right) - 1\right)\right) = 0.01222056.$$

The details of a 10-cycle treatment problem are presented in Tables 9–11. Options in Tables 9 and 10 do not satisfy the conditions in Theorem 6.1. Options in Table 11 are obtained with the method in Theorem 6.1. It can be observed that the probability of non-occurrence of $R_{1,2}$ type cells is maximized with options in Table 11. Therefore, alternating therapy is optimal under this asymmetrical parameter settings.

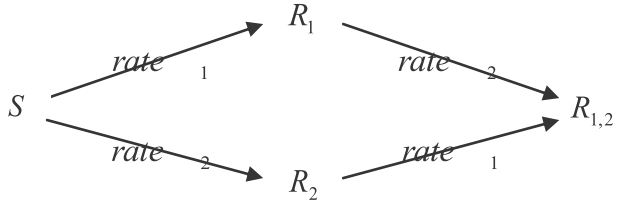


**Fig. 3.** Unequal mutate rates with $\alpha_1 = \alpha_{2,1},\ \alpha_2 = \alpha_{1,2}$.

## 7. Discussion

Since Goldie and Coldman proposed their original model, many researchers have studied its potential clinical application and model refinements. One notable study was presented by Day [26], who explored various parameter changes in the model proposed by Goldie and Coldman and their corresponding optimal policies. Day set the model parameters to a low, medium, or high value relative to a reference level in a two-drug cyclic therapy. Based on various combinations of values in different model parameters, Day considered how an optimal policy may change accordingly in 16 preselected treatment strategies. One interesting result of this study is the so-called "worst drug rule." In other words, under certain circumstances, the worst drug should be administering before administering more effective drugs. This rule attracted clinical oncologists to test its correctness.

Katouli and Komarova recently published a related study [27,28] that reinvestigates Day's work based on the model in [12,13]. In their study, two characteristics of cancer drugs are considered: potency and activity spectrum. A drug with a higher potency can kill the tumor cells susceptible to it more effectively, whereas a drug with a broader activity spectrum is effective against to broader spectrum of mutant cells. In a cyclic treatment, they considered two drugs $A$ and $B$ applied alternatively with peri-

**Table 9**
The log-kill constants ${k_{1,r}}^2 = k_{2,r}^2 \equiv k_r^2 = 144$ and the mutation rates $\alpha_1 = \alpha_{2,1} = 10^{-6}$, $\alpha_2 = \alpha_{1,2} = 10^{-5}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)}) = R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)}) = R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)}) = S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 230229.3513 | 111.0288 | 99974674.7714 | 345014.8328 | 772.0198 | 149792096.4874 | 0.31742318 | 0.00387909 |
| 2 | 1 | 345014.8328 | 0.0372 | 1497920.9649 | 516939.0731 | 9.1305 | 2244335.6001 | 0.17920290 | 0.00069514 |
| 3 | 1 | 516939.0731 | 0.0004 | 22443.3560 | 774533.4852 | 0.1366 | 33626.8896 | 0.07608196 | 0.00005289 |
| 4 | 1 | 774533.4852 | 0.0000 | 336.2689 | 1160489.0023 | 0.0020 | 503.8318 | 0.02107737 | 0.00000111 |
| 5 | 1 | 1160489.0023 | 0.0000 | 5.0383 | 1738768.8849 | 0.0000 | 7.5489 | 0.00308008 | 0.00000000 |
| 6 | −1 | 83.8527 | 0.0000 | 0.0755 | 125.6370 | 0.0000 | 0.1131 | 0.99958224 | 0.00000000 |
| 7 | −1 | 0.0061 | 0.0000 | 0.0011 | 0.0091 | 0.0001 | 0.0017 | 0.99999997 | 0.00000000 |
| 8 | −1 | 0.0000 | 0.0001 | 0.0000 | 0.0000 | 0.0001 | 0.0000 | 1.00000000 | 0.00000000 |
| 9 | −1 | 0.0000 | 0.0001 | 0.0000 | 0.0000 | 0.0002 | 0.0000 | 1.00000000 | 0.00000000 |
| 10 | −1 | 0.0000 | 0.0002 | 0.0000 | 0.0000 | 0.0002 | 0.0000 | 1.00000000 | 0.00000000 |

**Table 10**
The log-kill constants ${k_{1,r}}^2 = k_{2,r}^2 \equiv k_r^2 = 144$ and the mutation rates $\alpha_1 = \alpha_{2,1} = 10^{-6}$, $\alpha_2 = \alpha_{1,2} = 10^{-5}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)}) = R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)}) = R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)}) = S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 230229.3513 | 111.0288 | 99974674.7714 | 345014.8328 | 772.0198 | 149792096.4874 | 0.31742318 | 0.00387909 |
| 2 | 1 | 345014.8328 | 0.0372 | 1497920.9649 | 516939.0731 | 9.1305 | 2244335.6001 | 0.17920290 | 0.00069514 |
| 3 | 1 | 516939.0731 | 0.0004 | 22443.3560 | 774533.4852 | 0.1366 | 33626.8896 | 0.07608196 | 0.00005289 |
| 4 | −1 | 37.3521 | 0.1366 | 336.2689 | 55.9651 | 0.2067 | 503.8318 | 0.99981382 | 0.00005288 |
| 5 | −1 | 0.0027 | 0.2067 | 5.0383 | 0.0040 | 0.3098 | 7.5489 | 0.99999988 | 0.00005288 |
| 6 | −1 | 0.0000 | 0.3098 | 0.0755 | 0.0000 | 0.4642 | 0.1131 | 0.99999985 | 0.00005288 |
| 7 | 1 | 0.0000 | 0.0000 | 0.0011 | 0.0000 | 0.0000 | 0.0017 | 1.00000000 | 0.00005288 |
| 8 | 1 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 1.00000000 | 0.00005288 |
| 9 | 1 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 1.00000000 | 0.00005288 |
| 10 | −1 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 1.00000000 | 0.00005288 |

**Table 11**
The log-kill constants ${k_{1,r}}^2 = k_{2,r}^2 \equiv k_r^2 = 144$ and the mutation rates $\alpha_1 = \alpha_{2,1} = 10^{-6}$, $\alpha_2 = \alpha_{1,2} = 10^{-5}$.

| $i$ | $T_i$ | $R_1\left(\bar{N}_0^{(i)}\right)$ | $R_2\left(\bar{N}_0^{(i)}\right)$ | $S\left(\bar{N}_0^{(i)}\right)$ | $R_1(\bar{N}^{(i)}) = R_1\left(N_0^{(i+1)}\right)$ | $R_2(\bar{N}^{(i)}) = R_2\left(N_0^{(i+1)}\right)$ | $S(\bar{N}^{(i)}) = S\left(N_0^{(i+1)}\right)$ | $P_{no\text{-}resist}(\bar{N}^{(i)})$ | $P_{no\text{-}resist}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 230229.3513 | 111.0288 | 99974674.7714 | 345014.8328 | 772.0198 | 149792096.4874 | 0.31742318 | 0.00387909 |
| 2 | −1 | 16.6384 | 772.0198 | 1497920.9649 | 25.8370 | 1165.7973 | 2244335.6001 | 0.99952928 | 0.00387726 |
| 3 | 1 | 25.8370 | 0.0562 | 22443.3560 | 38.7253 | 0.2202 | 33626.8896 | 0.99987118 | 0.00387676 |
| 4 | −1 | 0.0019 | 0.2202 | 336.2689 | 0.0030 | 0.3320 | 503.8318 | 0.99999988 | 0.00387676 |
| 5 | 1 | 0.0030 | 0.0000 | 5.0383 | 0.0045 | 0.0001 | 7.5489 | 0.99999999 | 0.00387676 |
| 6 | −1 | 0.0000 | 0.0001 | 0.0755 | 0.0000 | 0.0001 | 0.1131 | 1.00000000 | 0.00387676 |
| 7 | 1 | 0.0000 | 0.0000 | 0.0011 | 0.0000 | 0.0000 | 0.0017 | 1.00000000 | 0.00387676 |
| 8 | −1 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 1.00000000 | 0.00387676 |
| 9 | 1 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 1.00000000 | 0.00387676 |
| 10 | −1 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 1.00000000 | 0.00387676 |

ods $\Delta_A$ and $\Delta_B$, respectively. By introducing a variety of methods, they were able to systematically and extensively consider various strategies through numerical explorations rather than limiting themselves to 16 preselected treatment strategies, as in Day's work. They proposed an important concept called "mutual strength." A two-drug cyclic therapy can achieve satisfactory probabilities of treatment success only if the two applied drugs are mutually strong. They derived two general rules for successful cyclic treatment. First, in a cyclic treatment with mutually strong drugs with a similar activity spectrum, the best treatment strategy is to apply the best drug first, but to use the worst drug for longer. Second, in a cyclic treatment with mutually strong drugs with a similar potency, the best treatment strategy is to use the less active drug first, and to use the more active drug for longer. They also discussed how the effects of cross-resistance and toxicity may change these general rules. They concluded that the worst drug may not hold. Several biological studies have reached similar conclusions for non-small-cell lung cancer [29–32].

The focus and approach of this study differ from those in the study by Katouli and Komarova. The major concern of their work is to explore the general rule, which elucidates the relationship between model parameters and optimal treatment policies, through systematic numerical analysis. Their treatment efficacy is implicitly reflected by the variation in tumor cell's death and mutation rates. Instead, the present work is a control-theory based approach. In this setting, drug administration is represented by explicit variables in the model. The maximal number of cycles $n$ can be determined by the maximal tolerable toxicity from clinic consideration. Each cycle length is assumed to be the minimal time required for the applied drugs to take full effect on the targeted tumor cells. With the imposed equally efficacy assumption against $S$ type cells, the proposed model is mathematically tractable. Specifically, Theorem 4.2 provides an explicit link between treatment options at each stage and different model parameters. Although this is less general than the model proposed by Katouli and Komarova, it produces an easily implementable rule rather than the general treatment guideline proposed by Katouli and Komarova (or by Day). The rule can be briefly stated as follows. Let $R_1(N_0^{(i)})$ and $R_2(N_0^{(i)})$ denote the size of $R_1$ and $R_2$ type cells at the $i$th cycle, respectively. Let $\alpha_{1,2}$ denote the mutation rate for $R_1$ type cells mutating to $R_{1,2}$ type cells, and $\alpha_{2,1}$ denote the mutation rate for $R_2$ type cells

mutating to $R_{1,2}$ type cells. Without treatment at the $i$th cycle, the expected size of $R_{1,2}$ type cells caused by the mutation of $R_1$ and $R_2$ type cells is $\alpha_{1,2}R_1(N_0^{(i)}) + \alpha_{2,1}R_2(N_0^{(i)})$. If the application of Drug 1 at the $i$th cycle yields the greatest reduction in this expected size of $R_{1,2}$ type cells, then the treatment option at the $i$th cycle should be Drug 1. Otherwise, the treatment option at the $i$th cycle should be Drug 2. This present work further considers that asymmetry exists both in killing constants and cell's mutation rates (serve as counterparts of potency and activity spectrum in the method of Katouli and Komarova). Optimal treatment options for each cycle under this circumstance can also be obtained by Theorem 4.2. It can be observed that, under such an asymmetrical parameter setting, an optimal treatment strategy does not necessarily consist of cycles of alternating length throughout the entire treatment process. For instance, in Table 1, Drug 2 is first used with a duration of one cycle followed by the usage of Drug 1 with a duration of one cycle. Thereafter, Drug 2 is used with a duration of two cycles followed by the usage of Drug 1 with a duration of two cycles. In contrast, some previous research only consider strategies consisting of cycles of alternating length such as Day's 16 preselected sequences of treatment options. Katouli and Komarova did little to address issues on asymmetry existing both in potency and activity spectrum in their study. Henceforth, they also focused on strategies consisting of cycles of alternating lengths $\Delta_A$ and $\Delta_B$.

Regarding aspects of modeling refinements, two important topics closely related to the present study should be considered. One is the drug's cell cycle specificity and the other is the gene amplification phenomenon. In their original work, Goldie and Coldman made two assumptions for simplification. First, their model simply assumes that a portion of cells susceptible to the applied agent are eliminated upon drug-intervention without further referring to the cell-cycle dependence of various agents. Second, a tumor cell is either completely resistant or susceptible to an anticancer agent; partial resistance is not considered. A single mutational event during the cell's duplication process can cause a susceptible cell to produce resistant progeny cells. Researchers have suggested several refinements on these simplifications based on the findings of cell cycle specificity and gene amplification. The following paragraphs present a brief discussion of the biological backgrounds of these two phenomena, the corresponding modeling and treatment approaches, some important studies and their connections to this present work.

The cell cycle refers to the sequence of phases that each cell undergoes from its birth to division. A cycle consists of the growth phase ($G_1$), DNA synthesis phase ($S$), the preparation for division phase ($G_2$), and the division phase ($M$). After division, the daughter cells can either enter the $G_1$ phase or enter a dormant phase ($G_0$). Cells in the $G_0$ phase enter $G_1$ phase again after a variable period of time [33]. From a treatment viewpoint, the cell cycle is of interest because various anticancer agents are only effective at specific phases. Different agents may perturb the cycle transition time, or hold or kill cells at specific phases. These agents can be combined into one therapy to maximize the cumulative treatment efficacy. For example, an agent may be used to hold cells in the $S$ phase and to release them when another $G_2/M$ agent achieves its maximal killing potential [20,34]. When a treatment process takes into account these cycle specific effects, the entire cell population is dissected into one, two, or three disjoint compartments [35–38]. Cells at the same phase are classified into the same compartment and they are all sensitive or resistance to one applied agent. The dynamics of the growth and death of cells in each compartment and the possible transitions between any two compartments are described by a set of ordinary differential equations. These equations may include control variables to represent how agents are administrated to control the targeted population. One performance index is used to evaluate the treatment efficacy under various usages of agents (i.e., controllers) against the cell population. The performance index usually penalizes unfavorable events, such as a large tumor population size and the side effects of the applied agents.

In these cell-cycle-specific treatment problems, the optimal control theory framework can be used to study how agents should be administrated to maximize the performance index. Analytical solutions to these problems can be analyzed using the celebrated Pontryagin Maximum Principle [39,40]. Two types of candidates can be obtained from this principle: a bang-bang strategy or a singular strategy. In the context of anticancer therapy, a bang-bang strategy corresponds to a treatment protocol in which the maximal dose level or no agents are applied alternatively over the entire treatment period. A singular strategy refers to a treatment protocol in which the dose level of applied agents varies over the entire treatment period. Previous research [41–44] has shown that irregular structures, such as a multiplicity of solutions or periodic trajectories, may be present in these control problems, and further investigation on the optimality of solutions is required. The Legendre–Clebsch condition or Goh conditions can be used to rule out the optimality of singular strategy [45,46]. Sufficient conditions on the local optimality for bang-bang strategies to these problems may be obtained by constructing differentiable solutions to the Hamilton–Jacobi–Bellman equation with the method of characteristics [47–50].

Gene amplification refers to the process in which cells acquire additional gene copies in their division process [51,52]. During mitotic cell division, the DNA content of a cell is generally first duplicated and then evenly distributed to two of its daughter cells. This mechanism ensures that the DNA content in each cell is the same from generation to generation. However, the genome of tumor cells might evolve, leading to an increased number of copies of genes, and thus conferring a greater level of resistance to chemotherapeutic drugs [53,54]. This process could also be reversible. In certain populations, tumor cells with additional copies of genes can lose their increased copies of genes and thus gradually have less resistance to chemotherapeutic agents[55,56]. Therefore, depending on whether the additional copies of genes can persist from generation to generation after the selective agents are removed, gene amplification may be unstable or stable.

Researchers have also used stochastic models with multiple compartments [3–8] to study these evolutionary processes. The concept behind this approach is to stratify the entire tumor cell population into several subpopulations according to the number of the amplified genes, and hence, the levels of resistance to chemotherapeutic drugs in each subpopulation. The lifespan of cells and the transition probability between any two subpopulations (with each represented as one compartment in the model) are properly specified to capture the population's evolutionary behavior. Kimmel and Axelrod [3] analyzed a discrete-time model to elucidate the asymptotic properties of an unstable gene amplification process. If the gene is not extinct, they proved that the limit distribution of the number of gene copies exists under intervention of selective agents. Another study has presented similar work on modeling stable gene amplification as a multitype Galton–Watson process [57].

An optimization framework can also be used to study therapy based on evolving resistance modeling with multiple compartments. Swierniak and Smieja presented an interesting study on this topic [10]. They considered an infinite dimensional compartment model and treat the cell cycle specificity and gene amplification in one unified model. They applied a decomposition technique to make it possible to analyze the

dynamical properties of their system. When drug intervention is considered as a controller in their model, the necessary condition of the optimal control can be obtained by transforming the original model into an integro-differential system. From methodological viewpoints, the presented approach in this paper is similar to the research in [10,20]. The optimal treatment problem is formulated as a discrete control problem and the solution stated in Theorem 4.2 is obtained with dynamical programming approach. A future extension to the present work should take the effects of gene amplification and cell-cycle specificity into account. A similar implementable rule should be derived when these effects are represented as multi-type/multiple compartment models as the work in [20]. Moreover, if the assumption of equal efficacy against $S$ type cells is invalid in these models, how this implementable rule may change needs to be studied. This further analysis will bring the present work closer to realistic situations.

## Appendix A. Proof of Theorem 2.1

The objection of this section is to prove Theorem 2.1. First, we calculate the formula of $R(N)$.

### A.1. The formula of $R(N)$

Consider that $N$ is approximated as a continuous variable. The sizes $R_1(N)$ and $R_2(N)$ may be expanded about the point $N$ by Taylor's theorem as follows:

$$R_1(N+\Delta N) = R_1(N) + \frac{dR_1(N)}{dN}\Delta N + o\left(\Delta N^2\right)$$

and $R_2(N+\Delta N) = R_2(N) + \frac{dR_2(N)}{dN}\Delta N + o\left(\Delta N^2\right)$.

If the tumor population grows by $\Delta N$, an expected increase $\frac{R_1(N)}{N}\Delta N$ due to the duplication of $R_1$ type cells and an expected increase $\alpha_1\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\Delta N$ due to the mutations of $S$ to $R_1$ type cells will contribute to the increase of $R_1$ type cells. Therefore, the expected number of $R_1$ type cells is

$$R_1(N+\Delta N) = R_1(N) + \frac{R_1(N)}{N}\Delta N + \alpha_1\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\Delta N + o\left(\Delta N^2\right).$$

Similarly,

$$R_2(N+\Delta N) = R_2(N) + \frac{R_2(N)}{N}\Delta N + \alpha_2\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\Delta N + o\left(\Delta N^2\right).$$

Dividing both sides of the equality by $\Delta N$ and taking limit $\Delta N \to 0$ yield

$$\frac{dR_1(N)}{dN} = \frac{R_1(N)}{N} + \alpha_1\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right) = (1-\alpha_1)\frac{R_1(N)}{N} - \alpha_1\frac{R_2(N)}{N} + \alpha_1, \tag{A1}$$

and $$\frac{dR_2(N)}{dN} = \frac{R_2(N)}{N} + \alpha_2\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right) = (1-\alpha_2)\frac{R_2(N)}{N} - \alpha_2\frac{R_1(N)}{N} + \alpha_2. \tag{A2}$$

Let $R(N) = R_1(N) + R_2(N)$ and $\alpha = \alpha_1 + \alpha_2$. Adding Eqs. (A1) and (A2) leads to

$$\frac{dR(N)}{dN} = (1-\alpha)\frac{R(N)}{N} + \alpha.$$

This implies

$$\frac{dR(N)}{dN} + \frac{\alpha-1}{N}R(N) = \alpha \Rightarrow \frac{dR(N)}{dN}\cdot e^{\int_{N_0}^{N}\frac{\alpha-1}{N}dN} + \frac{\alpha-1}{N}R(N)\cdot e^{\int_{N_0}^{N}\frac{\alpha-1}{N}dN} = \alpha\cdot e^{\int_{N_0}^{N}\frac{\alpha-1}{N}dN} \Rightarrow \frac{d}{dN}\left(R(N)\cdot e^{\int_{N_0}^{N}\frac{\alpha-1}{N}dN}\right) = \alpha\cdot e^{\int_{N_0}^{N}\frac{\alpha-1}{N}dN}$$

$$\Rightarrow R(N)\cdot e^{\int_{N_0}^{N}\frac{\alpha-1}{N}dN} = \int \alpha\cdot e^{\int_{N_0}^{N}\frac{\alpha-1}{N}dN}dN + C.$$

Since $\int_{N_0}^{N}\frac{\alpha-1}{N}dN = (\alpha-1)\ln\frac{N}{N_0}$, we have

$$R(N) = e^{-\int_{N_0}^{N}\frac{\alpha-1}{N}dN}\left(\int \alpha\cdot e^{\int_{N_0}^{N}\frac{\alpha-1}{N}dN}dN + C\right) = \left(\frac{N}{N_0}\right)^{1-\alpha}$$

$$\left(\int \alpha\cdot\left(\frac{N}{N_0}\right)^{\alpha-1}dN + C\right) = \left(\frac{N}{N_0}\right)^{1-\alpha}\left(\frac{N^{\alpha}}{N_0^{\alpha-1}} + C\right) = N + C\left(\frac{N}{N_0}\right)^{1-\alpha}.$$

With the initial condition $R(N) = R(N_0)$ at $N = N_0$, we have

$$R(N_0) = N_0 + C\left(\frac{N_0}{N_0}\right)^{1-\alpha}.$$

It implies

$$C = R(N_0) - N_0.$$

Therefore, we have

$$R(N) = N + (R(N_0) - N_0)\left(\frac{N}{N_0}\right)^{1-\alpha}. \tag{A3}$$

### A.2. The formula of $S(N)$

Because $R(N) + S(N) = N$ and Eq. (A3), we know that

$$S(N) = N - R(N) = N - \left(N + (R(N_0) - N_0)\left(\frac{N}{N_0}\right)^{1-\alpha}\right) = S(N_0)\cdot\left(\frac{N}{N_0}\right)^{1-\alpha}.$$

### A.3. The formula of $R_1(N)$

Because Eq. (A1) and $R_1(N) + R_2(N) = R(N)$, we have

$$\frac{dR_1(N)}{dN} = (1-\alpha_1)\frac{R_1(N)}{N} - \alpha_1\frac{R(N)-R_1(N)}{N} + \alpha_1 = \frac{R_1(N)}{N} - \alpha_1\frac{R(N)}{N} + \alpha_1.$$

According to Eq. (A3), it produces

$$\frac{dR_1(N)}{dN} = \frac{R_1(N)}{N} - \alpha_1\frac{N + (R(N_0)-N_0)\left(\frac{N}{N_0}\right)^{1-\alpha}}{N} + \alpha_1 = \frac{R_1(N)}{N} - \frac{\alpha_1(R(N_0)-N_0)}{N_0^{1-\alpha}}N^{-\alpha}.$$

This implies

$$\begin{aligned}
\frac{dR_1(N)}{dN}-\frac{1}{N}R_1(N) &= -\frac{\alpha_1(R(N_0)-N_0)}{N_0^{1-\alpha}}N^{-\alpha}\\
&\Rightarrow \frac{dR_1(N)}{dN}\cdot e^{\int_{N_0}^{N}\frac{-1}{N}dN}-\frac{1}{N}R_1(N)\cdot e^{\int_{N_0}^{N}\frac{-1}{N}dN}\\
&= -\frac{\alpha_1(R(N_0)-N_0)}{N_0^{1-\alpha}}N^{-\alpha}\cdot e^{\int_{N_0}^{N}\frac{-1}{N}dN}\\
&\Rightarrow \frac{d}{dN}\left(R_1(N)\cdot e^{\int_{N_0}^{N}\frac{-1}{N}dN}\right)\\
&= -\frac{\alpha_1(R(N_0)-N_0)}{N_0^{1-\alpha}}N^{-\alpha}\cdot e^{\int_{N_0}^{N}\frac{-1}{N}dN}\\
&\Rightarrow R_1(N)\cdot e^{\int_{N_0}^{N}\frac{-1}{N}dN}\\
&= -\frac{\alpha_1(R(N_0)-N_0)}{N_0^{1-\alpha}}\int N^{-\alpha}\cdot e^{\int_{N_0}^{N}\frac{-1}{N}dN}dN+C_1.
\end{aligned}$$

It gives

$$\begin{aligned}
R_1(N) &= e^{\int_{N_0}^{N}\frac{1}{N}dN}\left(-\frac{\alpha_1(R(N_0)-N_0)}{N_0^{1-\alpha}}\int N^{-\alpha}\cdot e^{\int_{N_0}^{N}\frac{-1}{N}dN}dN+C_1\right)\\
&= \frac{N}{N_0}\left(-\frac{\alpha_1(R(N_0)-N_0)}{N_0^{1-\alpha}}\int N^{-\alpha}\cdot\frac{N_0}{N}dN+C_1\right)\\
&= \frac{N}{N_0}\left(-\frac{\alpha_1(R(N_0)-N_0)}{N_0^{1-\alpha}}N_0\frac{1}{-\alpha}N^{-\alpha}+C_1\right)\\
&= \frac{N}{N_0}\left(\frac{\alpha_1}{\alpha_1+\alpha_2}\frac{(R(N_0)-N_0)}{N_0^{-\alpha}}N^{-\alpha}+C_1\right).
\end{aligned}$$

With the initial condition $R_1(N)=R_1(N_0)$ at $N=N_0$, we have

$$\begin{aligned}
R_1(N_0) &= \frac{N_0}{N_0}\left(\frac{\alpha_1}{\alpha_1+\alpha_2}\frac{(R(N_0)-N_0)}{N_0^{-\alpha}}N_0^{-\alpha}+C_1\right)\\
&= \frac{\alpha_1}{\alpha_1+\alpha_2}(R(N_0)-N_0)+C_1.
\end{aligned}$$

It implies

$$\begin{aligned}
C_1 &= R_1(N_0)-\frac{\alpha_1}{\alpha_1+\alpha_2}(R(N_0)-N_0)\\
&= R_1(N_0)-\frac{\alpha_1}{\alpha_1+\alpha_2}(R_1(N_0)+R_2(N_0)-N_0)\\
&= \frac{\alpha_2}{\alpha_1+\alpha_2}R_1(N_0)-\frac{\alpha_1}{\alpha_1+\alpha_2}(R_2(N_0)-N_0).
\end{aligned}$$

Therefore, we have

$$\begin{aligned}
R_1(N) &= \frac{N}{N_0}\left(\frac{\alpha_1}{\alpha_1+\alpha_2}\frac{(R(N_0)-N_0)}{N_0^{-\alpha}}N^{-\alpha}+\frac{\alpha_2}{\alpha_1+\alpha_2}R_1(N_0)-\frac{\alpha_1}{\alpha_1+\alpha_2}(R_2(N_0)-N_0)\right)\\
&= \frac{N}{N_0}\left(\frac{-\alpha_1}{\alpha_1+\alpha_2}\frac{S(N_0)}{N_0^{-\alpha}}N^{-\alpha}+\frac{\alpha_2}{\alpha_1+\alpha_2}R_1(N_0)+\frac{\alpha_1}{\alpha_1+\alpha_2}(R_1(N_0)+S(N_0))\right)\\
&= \frac{N}{N_0}R_1(N_0)+\frac{\alpha_1}{\alpha_1+\alpha_2}S(N_0)\frac{N}{N_0}\left(1-\left(\frac{N}{N_0}\right)^{-\alpha_1-\alpha_2}\right).
\end{aligned}$$

### A.4. The formula of $R_2(N)$

Because $R_1(N)+R_2(N)=R(N)$ and Eq. (A4), we know that

$$\begin{aligned}
R_2(N) &= R(N)-R_1(N) = N-S(N_0)\left(\frac{N}{N_0}\right)^{1-\alpha_1-\alpha_2}\\
&\quad -\frac{N}{N_0}R_1(N_0)-\frac{\alpha_1}{\alpha_1+\alpha_2}S(N_0)\frac{N}{N_0}+\frac{\alpha_1}{\alpha_1+\alpha_2}S(N_0)\left(\frac{N}{N_0}\right)^{1-\alpha_1-\alpha_2}\\
&= \frac{N}{N_0}(R_1(N_0)+R_2(N_0)+S(N_0))\\
&\quad -\frac{N}{N_0}R_1(N_0)-\frac{\alpha_1}{\alpha_1+\alpha_2}S(N_0)\frac{N}{N_0}-S(N_0)\left(\frac{N}{N_0}\right)^{1-\alpha_1-\alpha_2}\\
&\quad +\frac{\alpha_1}{\alpha_1+\alpha_2}S(N_0)\left(\frac{N}{N_0}\right)^{1-\alpha_1-\alpha_2}\\
&= \frac{N}{N_0}R_2(N_0)+\frac{\alpha_2}{\alpha_1+\alpha_2}S(N_0)\frac{N}{N_0}\left(1-\left(\frac{N}{N_0}\right)^{-\alpha_1-\alpha_2}\right).
\end{aligned}$$

## Appendix B. Proof of Theorem 2.3

The objection of this section is to prove Theorem 2.3. According to Eq. (7) and Lemma 2.2, we know that

$$\begin{aligned}
P_{no\text{-}resist}(N+\Delta N|N) &= 1-\alpha_{1,2}\left(\frac{dR_1(N)}{dN}-\alpha_1\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\right)\Delta N\\
&\quad -\alpha_{2,1}\left(\frac{dR_2(N)}{dN}-\alpha_2\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\right)\Delta N+o(\Delta N^2).
\end{aligned}$$

Since $P_{no\text{-}resist}(N|N)=1$, we have

$$\begin{aligned}
P_{no\text{-}resist}(N+\Delta N|N) &= P_{no\text{-}resist}(N|N)\\
&\quad\cdot\left(1-\alpha_{1,2}\left(\frac{dR_1(N)}{dN}-\alpha_1\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\right)\right.\\
&\quad \Delta N-\alpha_{2,1}\left(\frac{dR_2(N)}{dN}-\alpha_2\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\right)\\
&\quad \left.\Delta N+o(\Delta N^2)\right).
\end{aligned}$$

It implies

$$\begin{aligned}
\frac{P_{no\text{-}resist}(N+\Delta N|N)-P_{no\text{-}resist}(N|N)}{\Delta N} &= P_{no\text{-}resist}(N|N)\\
&\quad\cdot\left(-\alpha_{1,2}\left(\frac{dR_1(N)}{dN}-\alpha_1\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\right)\right.\\
&\quad \left.-\alpha_{2,1}\left(\frac{dR_2(N)}{dN}-\alpha_2\left(1-\frac{R_1(N)}{N}-\frac{R_2(N)}{N}\right)\right)+o(\Delta N^2)\right).
\end{aligned}$$

Given fixed $N$, let $\Delta N\to 0$ and apply the relation $S(N)=N-R_1(N)-R_2(N)$. We have

$$\begin{aligned}
\frac{dP_{no\text{-}resist}(N)}{dN} &= P_{no\text{-}resist}(N)\left(-\alpha_{1,2}\frac{dR_1(N)}{dN}-\alpha_{2,1}\frac{dR_2(N)}{dN}\right.\\
&\quad \left.+(\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1})\frac{S(N)}{N}\right).
\end{aligned}$$

This implies

$$\frac{dP_{no\text{-}resist}(N)}{dN}+\left(\alpha_{1,2}\frac{dR_1(N)}{dN}+\alpha_{2,1}\frac{dR_2(N)}{dN}-(\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1})\frac{S(N)}{N}\right)P_{no\text{-}resist}(N)=0.$$

Let

$$A(N)=\alpha_{1,2}\frac{dR_1(N)}{dN}+\alpha_{2,1}\frac{dR_2(N)}{dN}-(\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1})\frac{S(N)}{N}.$$

It processes

$$\frac{dP_{no\text{-}resist}(N)}{dN}+A(N)P_{no\text{-}resist}(N)=0.$$

It implies

$$\frac{dP_{no\text{-}resist}(N)}{dN}\cdot e^{\int_{N_0}^{N}A(N)dN}+A(N)P_{no\text{-}resist}(N)\cdot e^{\int_{N_0}^{N}A(N)dN}=0$$
$$\Rightarrow\frac{d}{dN}\left(P_{no\text{-}resist}(N)\cdot e^{\int_{N_0}^{N}A(N)dN}\right)=0\Rightarrow P_{no\text{-}resist}(N)\cdot e^{\int_{N_0}^{N}A(N)dN}=K.$$

It gives

$$\begin{aligned}P_{no\text{-}resist}(N)&=Ke^{-\int_{N_0}^{N}A(N)dN}\\&=K\exp\left(-\int_{N_0}^{N}\left(\alpha_{1,2}\frac{dR_1(N)}{dN}+\alpha_{2,1}\frac{dR_2(N)}{dN}\right.\right.\\&\quad\left.\left.-(\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1})\frac{S(N)}{N}\right)dN\right)\\&=K\exp(-\alpha_{1,2}(R_1(N)-R_1(N_0))-\alpha_{2,1}(R_2(N)-R_2(N_0))\\&\quad+(\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1})\int_{N_0}^{N}\frac{S(N)}{N}dN).\end{aligned}$$

Since

$$\begin{aligned}\int_{N_0}^{N}\frac{S(N)}{N}dN&=\int_{N_0}^{N}\left(\frac{S(N_0)}{N_0^{1-\alpha}}N^{-\alpha}\right)dN=\frac{S(N_0)}{N_0^{1-\alpha}}\frac{1}{1-\alpha}\left(N^{1-\alpha}-N_0^{1-\alpha}\right)\\&=\frac{1}{1-\alpha_1-\alpha_2}(S(N)-S(N_0)),\end{aligned}$$

we have

$$\begin{aligned}P_{no\text{-}resist}(N)=K\exp&\left(-\alpha_{1,2}(R_1(N)-R_1(N_0))-\alpha_{2,1}(R_2(N)-R_2(N_0))\right.\\&\left.+\frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}(S(N)-S(N_0))\right).\end{aligned}$$

With the initial condition $P_{no\text{-}resist}(N_0)=1$ at $N=N_0$, we have

$$\begin{aligned}P_{no\text{-}resist}(N_0)=K\exp&\left(-\alpha_{1,2}(R_1(N_0)-R_1(N_0))-\alpha_{2,1}(R_2(N_0)-R_2(N_0))\right.\\&\left.+\frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}(S(N_0)-S(N_0))\right)=1.\end{aligned}$$

It implies

$$K=1.$$

Therefore, we have

$$\begin{aligned}P_{no\text{-}resist}(N)=\exp&\left(-\alpha_{1,2}(R_1(N)-R_1(N_0))-\alpha_{2,1}(R_2(N)-R_2(N_0))\right.\\&\left.+\frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}(S(N)-S(N_0))\right).\end{aligned}$$

## Appendix C. Show that Eqs. (16) and (17) are equivalent

$$\begin{aligned}&\alpha_{1,2}\left(R_1\left(\bar{N}^{(i)}(T_{1\to i-1},T_i)\right)-R_1\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\right)\\&+\alpha_{2,1}\left(R_2\left(\bar{N}^{(i)}(T_{1\to i-1},T_i)\right)-R_2\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\right)\\&-\frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}\left(S\left(\bar{N}^{(i)}(T_{1\to i-1},T_i)\right)-S\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\right)\\&\overset{(a)}{=}\alpha_{1,2}\left(2^{\frac{d'}{d}}R_1\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)+\frac{\alpha_1\left(2^{\frac{d'}{d}}-2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}\right)}{\alpha_1+\alpha_2}\right.\\&\left.S\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)-R_1\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\right)\\&+\alpha_{2,1}\left(2^{\frac{d'}{d}}R_2\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)+\frac{\alpha_2\left(2^{\frac{d'}{d}}-2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}\right)}{\alpha_1+\alpha_2}\right.\\&\left.\times S\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)-R_2\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\right)\\&-\frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}\left(2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}S\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\right.\\&\left.-S\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\right)=\left(2^{\frac{d'}{d}}-1\right)\left(\alpha_{1,2}R_1\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\right.\\&\left.+\alpha_{2,1}R_2\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\right)+\left(\frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{\alpha_1+\alpha_2}\left(2^{\frac{d'}{d}}-2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}\right)\right.\\&\left.-\frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{1-\alpha_1-\alpha_2}\left(2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}-1\right)\right)\cdot S\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\\&=\left(2^{\frac{d'}{d}}-1\right)\left(\alpha_{1,2}R_1\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)+\alpha_{2,1}R_2\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\right)\\&+\frac{\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1}}{(\alpha_1+\alpha_2)(1-\alpha_1-\alpha_2)}\left(2^{\frac{d'}{d}}-2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}-(\alpha_1+\alpha_2)2^{\frac{d'}{d}}+(\alpha_1+\alpha_2)\right)\\&\cdot S\left(\bar{N}_0{}^{(i)}(T_{1\to i-1},T_i)\right)\overset{(b)}{=}\left(2^{\frac{d'}{d}}-1\right)\left(\alpha_{1,2}k_{2,r}^{T_i-1}R_1\left(N_0{}^{(i)}(T_{1\to i-1})\right)\right.\\&\left.+\alpha_{2,1}k_{1,r}^{-T_i-1}R_2\left(N_0{}^{(i)}(T_{1\to i-1})\right)\right)\\&+\frac{(\alpha_1\alpha_{1,2}+\alpha_2\alpha_{2,1})\left(2^{\frac{d'}{d}}-2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}-(\alpha_1+\alpha_2)\left(2^{\frac{d'}{d}}-1\right)\right)k_{2,s}^{T_i-1}k_{1,s}^{-T_i-1}}{(\alpha_1+\alpha_2)(1-\alpha_1-\alpha_2)}\\&\cdot S\left(N_0{}^{(i)}(T_{1\to i-1})\right),\end{aligned}$$

where (a) follows from Eqs. (12)–(14), and (b) follows from Eqs. (9)–(11).

Therefore, we know that the objective function in (16) and the objective function in (17) are equivalent.

## Appendix D. Proof of Lemma 4.1

*Case 1. The first drug is applied (i.e. $T_{i+1}=1$)*

$$\begin{aligned}&\alpha_{1,2}\left(k_{2,r}{}^{T_i^{**}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)-k_{2,r}^{T_i^*-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right)\\&\geqslant\alpha_{2,1}\left(k_{1,r}{}^{-T_i^*-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)-k_{1,r}^{-T_i^{**}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right)\\&\geqslant^{(a)}\alpha_{2,1}k_{1,r}^{-2}\left(k_{1,r}{}^{-T_i^*-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)-k_{1,r}^{-T_i^{**}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right),\end{aligned}$$

where (a) follows from $0\leqslant k_{1,r}^{-2}\leqslant 1$. Rearranging terms in the inequality leads to

$$\begin{aligned}&\Rightarrow\alpha_{1,2}k_{2,r}^{T_i^{**}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)+\alpha_{2,1}k_{1,r}^{-2}k_{1,r}^{-T_i^{**}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\\&\geqslant\alpha_{1,2}k_{2,r}^{T_i^*-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)+\alpha_{2,1}k_{1,r}^{-2}k_{1,r}^{-T_i^*-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right),\end{aligned}$$

*Case 2. The second drug is applied (i.e. $T_{i+1} = -1$)*

$$\begin{aligned}
&\alpha_{2,1}\left(k_{1,r}{}^{-T_i^{**}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) - k_{1,r}^{-T_i^{*}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right)\\
&\quad\geqslant \alpha_{1,2}\left(k_{2,r}{}^{T_i^{*}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) - k_{2,r}^{T_i^{**}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right)\\
&\quad\geqslant^{(b)}\alpha_{1,2}k_{2,r}^{-2}\left(k_{2,r}{}^{T_i^{*}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) - k_{2,r}^{T_i^{**}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right),
\end{aligned}$$

where (b) follows from $0 \leqslant k_{2,r}^{-2} \leqslant 1$. Rearranging terms in the inequality leads to

$$\begin{aligned}
&\Rightarrow \alpha_{1,2}k_{2,r}^{-2}k_{2,r}^{T_i^{**}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) + \alpha_{2,1}k_{1,r}^{-T_i^{**}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\\
&\quad\geqslant \alpha_{1,2}k_{2,r}^{-2}k_{2,r}^{T_i^{*}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) + \alpha_{2,1}k_{1,r}^{-T_i^{*}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right).
\end{aligned}$$

Base on the discussions in case 1 and 2, we have

$$\begin{aligned}
&\alpha_{1,2}k_{2,r}^{T_{i+1}-1}k_{2,r}^{T_i^{**}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\\
&\quad+\alpha_{2,1}k_{1,r}^{-T_{i+1}-1}k_{1,r}^{-T_i^{**}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\\
&\quad\geqslant \alpha_{1,2}k_{2,r}^{T_{i+1}-1}k_{2,r}^{T_i^{*}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\\
&\qquad+\alpha_{2,1}k_{1,r}^{-T_{i+1}-1}k_{1,r}^{-T_i^{*}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right).
\end{aligned}\tag{D1}$$

Therefore, we may have

$$\begin{aligned}
&\alpha_{1,2}k_{2,r}^{T_{i+1}-1}R_1\left(N_0{}^{(i+1)}(\bar{T}_{1\to i-1,T_i^{**}})\right) + \alpha_{2,1}k_{1,r}^{-T_{i+1}-1}R_2\left(N_0{}^{(i+1)}(\bar{T}_{1\to i-1,T_i^{**}})\right)\\
&=^{(c)}\alpha_{1,2}k_{2,r}^{T_{i+1}-1}\left(2^{\frac{d'}{d}}k_{2,r}^{T_i^{**}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) + \frac{\alpha_1}{\alpha_1+\alpha_2}\left(2^{\frac{d'}{d}} - 2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}\right)\frac{1}{k_s^2}S\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right)\\
&\quad+\alpha_{2,1}k_{1,r}^{-T_{i+1}-1}\left(2^{\frac{d'}{d}}k_{1,r}^{-T_i^{*}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) + \frac{\alpha_2}{\alpha_1+\alpha_2}\left(2^{\frac{d'}{d}} - 2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}\right)\frac{1}{k_s^2}S\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right)\\
&=2^{\frac{d'}{d}}\left(\alpha_{1,2}k_{2,r}^{T_{i+1}-1}k_{2,r}^{T_i^{**}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) + \alpha_{2,1}k_{1,r}^{-T_{i+1}-1}k_{1,r}^{-T_i^{**}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right)\\
&\quad+\frac{k_{2,r}{}^{T_{i+1}-1}\alpha_1\alpha_{1,2}+k_{1,r}^{-T_{i+1}-1}\alpha_2\alpha_{2,1}}{\alpha_1+\alpha_2}\left(2^{\frac{d'}{d}} - 2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}\right)\frac{1}{k_s^2}S\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\\
&\geqslant^{(d)}2^{\frac{d'}{d}}\left(\alpha_{1,2}k_{2,r}^{T_{i+1}-1}k_{2,r}^{T_i^{*}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) + \alpha_{2,1}k_{1,r}^{-T_{i+1}-1}k_{1,r}^{-T_i^{*}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right)\\
&\quad+\frac{k_{2,r}{}^{T_{i+1}-1}\alpha_1\alpha_{1,2}+k_{1,r}^{-T_{i+1}-1}\alpha_2\alpha_{2,1}}{\alpha_1+\alpha_2}\left(2^{\frac{d'}{d}} - 2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}\right)\frac{1}{k_s^2}S\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\\
&=\alpha_{1,2}k_{2,r}^{T_{i+1}-1}\left(2^{\frac{d'}{d}}k_{2,r}^{T_i^{*}-1}R_1\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) + \frac{\alpha_1}{\alpha_1+\alpha_2}\left(2^{\frac{d'}{d}} - 2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}\right)\frac{1}{k_s^2}S\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right)\\
&\quad+\alpha_{2,1}k_{1,r}^{-T_{i+1}-1}\left(2^{\frac{d'}{d}}k_{1,r}^{-T_i^{*}-1}R_2\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right) + \frac{\alpha_2}{\alpha_1+\alpha_2}\left(2^{\frac{d'}{d}} - 2^{(1-\alpha_1-\alpha_2)\frac{d'}{d}}\right)\frac{1}{k_s^2}S\left(N_0{}^{(i)}(\bar{T}_{1\to i-1})\right)\right)\\
&\stackrel{(c)}{=}\alpha_{1,2}k_{2,r}^{T_{i+1}-1}R_1\left(N_0{}^{(i+1)}(\bar{T}_{1\to i-1,T_i^{*}})\right) + \alpha_{2,1}k_{1,r}^{-T_{i+1}-1}R_2\left(N_0{}^{(i+1)}(\bar{T}_{1\to i-1,T_i^{*}})\right)
\end{aligned}$$

where (c) follows from Eqs. (9)–(13), and (d) follows from Eq. (D1).

## Appendix E. Proof of Theorem 5.2

Since we know that Theorem 5.1 is the special case of Theorem 5.2, we will prove Theorem 5.2 by mathematical induction only. Since $R_1\left(N_0{}^{(1)}\right) = R_2\left(N_0{}^{(1)}\right)$, in the following, we denote $R_1\left(N_0{}^{(1)}\right) = R_2\left(N_0{}^{(1)}\right) = R\left(N_0{}^{(1)}\right)$ for simplicity. According to Theorem 4.2, we know that

$$\begin{aligned}
T_i^* &= \arg\min_{T_i}\left(\alpha_{1,2}k_r^{T_i-1}R_1\left(N_0{}^{(i)}\right) + \alpha_{1,2}k_r^{-T_i-1}R_2\left(N_0{}^{(i)}\right)\right)\\
&= \arg\min_{T_i}\left(k_r{}^{T_i-1}R_1\left(N_0{}^{(i)}\right) + k_r^{-T_i-1}R_2\left(N_0{}^{(i)}\right)\right).
\end{aligned}$$

Therefore,

$$\begin{aligned}
T_1^* &= \arg\min_{T_1}\left(k_r{}^{T_1-1}R_1\left(N_0{}^{(1)}\right) + k_r^{-T_1-1}R_2\left(N_0{}^{(1)}\right)\right)\\
&= \arg\min_{T_1}\left(\left(k_r{}^{T_1} + k_r^{-T_1}\right)\left(k_r{}^{-1}R\left(N_0^{(1)}\right)\right)\right)\\
&= \arg\min_{T_1}\left(k_r{}^{T_1} + k_r^{-T_1}\right)
\end{aligned}$$

and

$$\begin{aligned}
T_2^* &= \arg\min_{T_2}\left(k_r{}^{T_2-1}R_1\left(N_0{}^{(2)}(T_1^*)\right) + k_r^{-T_2-1}R_2\left(N_0{}^{(2)}(T_1^*)\right)\right)\\
&\stackrel{(a)}{=}\arg\min_{T_2}\left(k_r{}^{T_2-1}\left(2^{\frac{d'}{d}}k_r^{T_1^*-1}R_1(N_0^{(1)}) + \frac{1}{2}S\left(\bar{N}_0^{(1)}\right)2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right)\right.\\
&\quad\left.+k_r^{-T_2-1}\left(2^{\frac{d'}{d}}k_r^{-T_1^*-1}R_2\left(N_0^{(1)}\right) + \frac{1}{2}S\left(\bar{N}_0^{(1)}\right)2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right)\right)\\
&= \arg\min_{T_2}\left(\left(k_r{}^{T_1^*+T_2} + k_r^{-T_1^*-T_2}\right)\left(2^{\frac{d'}{d}}k_r^{-2}R\left(N_0^{(1)}\right)\right)\right.\\
&\quad\left.+\left(k_r{}^{T_2} + k_r^{-T_2}\right)k_r^{-1}\frac{1}{2}S\left(\bar{N}_0^{(1)}\right)2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right)\\
&= \arg\min_{T_2}\left(k_r{}^{T_1^*+T_2} + k_r^{-T_1^*-T_2}\right) = -T_1^*
\end{aligned}$$

where (a) follows from Eq. (9), (10), (12) and (13). The statement holds for the case $i = 1$.

Suppose the statement holds for $i = 2\ldots k-1$. By Theorem 4.2, we have

$$\begin{aligned}
T_{k+1}^* &= \arg\min_{T_{k+1}}\left(k_r{}^{T_{k+1}-1}R_1\left(N_0{}^{(k+1)}(T_{1\to k}^*)\right) + k_r^{-T_{k+1}-1}R_2\left(N_0{}^{(k+1)}(T_{1\to k}^*)\right)\right)\\
&\stackrel{(a)}{=}\arg\min_{T_{k+1}}\left(k_r{}^{T_{k+1}-1}\left(2^{\frac{d'}{d}}k_r^{T_k^*-1}R_1\left(N_0^{(k)}(T_{1\to k-1}^*)\right) + \frac{1}{2}S\left(\bar{N}_0^{(k)}\right)2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right)\right.\\
&\quad\left.+k_r^{-T_{k+1}-1}\left(2^{\frac{d'}{d}}k_r^{-T_k^*-1}R_2\left(N_0^{(k)}(T_{1\to k-1}^*)\right) + \frac{1}{2}S\left(\bar{N}_0^{(k)}\right)2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right)\right)\\
&= \arg\min_{T_{k+1}}\left(\left(k_r{}^{T_k^*+T_{k+1}}R_1\left(N_0^{(k)}(T_{1\to k-1}^*)\right) + k_r^{-T_k-T_{k+1}}R_2\left(N_0^{(k)}(T_{1\to k-1}^*)\right)\right)\left(2^{\frac{d'}{d}}k_r^{-2}\right)\right.\\
&\quad\left.+\left(k_r{}^{T_{k+1}} + k_r^{-T_{k+1}}\right)k_r^{-1}\frac{1}{2}S\left(\bar{N}_0^{(k)}\right)2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right)\\
&\stackrel{(a)}{=}\arg\min_{T_{k+1}}\left(\left(k_r{}^{T_k^*+T_{k+1}}\left(2^{\frac{d'}{d}}k_r^{T_{k-1}^*-1}R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right) + \frac{1}{2}S\left(\bar{N}_0^{(k-1)}\right)2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right)\right.\right.\\
&\quad\left.\left.+k_r^{-T_k^*-T_{k+1}}\left(2^{\frac{d'}{d}}k_r^{-T_{k-1}^*-1}R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right) + \frac{1}{2}S\left(\bar{N}_0^{(k-1)}\right)2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right)\right)\left(2^{\frac{d'}{d}}k_r^{-2}\right)\right.\\
&\quad\left.+\left(k_r{}^{T_{k+1}} + k_r^{-T_{k+1}}\right)k_r^{-1}\frac{1}{2}S\left(\bar{N}_0^{(k)}\right)2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right)\\
&= \arg\min_{T_{k+1}}\left(2^{\frac{2d'}{d}}k_r^{-2}\left(k_r{}^{T_{k-1}^*+T_k^*+T_{k+1}-1}R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right) + k_r^{-T_{k-1}^*-T_k^*-T_{k+1}-1}R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right)\right.\\
&\quad+\left(k_r{}^{T_k^*+T_{k+1}} + k_r^{-T_k^*-T_{k+1}}\right)k_r^{-2}\frac{1}{2}S\left(\bar{N}_0^{(k-1)}\right)2^{\frac{2d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\\
&\quad\left.+\left(k_r{}^{T_{k+1}} + k_r^{-T_{k+1}}\right)k_r^{-1}\frac{1}{2}S\left(\bar{N}_0^{(k)}\right)2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right)\\
&= \arg\min_{T_{k+1}}\left(2^{\frac{2d'}{d}}k_r^{-2}\left(k_r{}^{T_{k-1}^*+T_k^*+T_{k+1}-1}R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right) + k_r^{-T_{k-1}^*-T_k^*-T_{k+1}-1}R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right)\right.\\
&\quad\left.+\left(k_r{}^{T_k^*+T_{k+1}} + k_r^{-T_k^*-T_{k+1}}\right)k_r^{-2}\frac{1}{2}S\left(\bar{N}_0^{(k-1)}\right)2^{\frac{2d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-2\alpha_1}\right)\right),
\end{aligned}\tag{E1}$$

where (a) follows from Eq. (9), (10), (12) and (13).

Based on the induction hypothesis, we know that $T_k^* = -T_{k-1}^*$ and

$$T_{k-1}^* = \arg\min_{T_{k-1}}\left(k_r{}^{T_{k-1}-1}R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right) + k_r^{-T_{k-1}-1}R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right).$$

Minimization problem in Eq. (E1) can be considered term by term. The minimization of the first term can be obtained as follows:

$$\begin{aligned}
&\arg\min_{T_{k+1}}\left(k_r{}^{T_{k-1}^*+T_k^*+T_{k+1}-1}R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right) + k_r^{-T_{k-1}^*-T_k^*-T_{k+1}-1}R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right)\\
&\quad= \arg\min_{T_{k+1}}(k_r{}^{T_{k+1}-1}R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right) + k_r^{-T_{k+1}-1}R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right) = T_{k-1}^*.
\end{aligned}$$

Furthermore, it can be shown that the minimization of the second term is achieved with $-T_k^*$ as follows:

$$\arg\min_{T_{k+1}}\left(k_r{}^{T_k^*+T_{k+1}} + k_r^{-T_k^*-T_{k+1}}\right) = -T_k^*.$$

Since $T_{k-1}^* = -T_k^*$, Eq. (E1) can be minimized with the choice of $T_{k+1}^* = -T_k^*$.

## Appendix F. Proof of Theorem 6.1

We will prove Theorem 5.2 by mathematical induction. Since $\alpha_2 R_1\left(N_0{}^{(1)}\right) = \alpha_1 R_2\left(N_0{}^{(1)}\right)$, in the following, we denote $\alpha_2 R_1\left(N_0{}^{(1)}\right) = \alpha_1 R_2\left(N_0{}^{(1)}\right) = \alpha R\left(N_0{}^{(1)}\right)$ for simplicity. According to Theorem 4.2, we know that

$$\begin{aligned}
T_1^* &= \arg\min_{T_1}\left(\alpha_2 k_r^{T_1-1} R_1\left(N_0{}^{(1)}\right) + \alpha_1 k_r^{-T_1-1} R_2\left(N_0{}^{(1)}\right)\right)\\
&= \arg\min_{T_1}\left(\left(k_r{}^{T_1} + k_r^{-T_1}\right)\left(k_r{}^{-1}\alpha R(N_0^{(1)})\right)\right)\\
&= \arg\min_{T_1}\left(k_r{}^{T_1} + k_r^{-T_1}\right)
\end{aligned}$$

and

$$\begin{aligned}
T_2^* &= \arg\min_{T_2}\left(\alpha_2 k_r^{T_2-1} R_1\left(N_0{}^{(2)}(T_1^*)\right) + \alpha_1 k_r^{-T_2-1} R_2\left(N_0{}^{(2)}(T_1^*)\right)\right)\\
&\overset{(a)}{=} \arg\min_{T_2}\left(\alpha_2 k_r^{T_2-1}\left(2^{\frac{d'}{d}} k_r^{T_1^*-1} R_1\left(N_0^{(1)}\right) + \frac{\alpha_1}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(1)}\right)\right.\right.\\
&\quad \left.2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\right) + \alpha_1 k_r^{-T_2-1}\left(2^{\frac{d'}{d}} k_r^{-T_1^*-1} R_2\left(N_0^{(1)}\right)\right.\\
&\quad \left.\left.+\frac{\alpha_2}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(1)}\right) 2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\right)\right)\\
&= \arg\min_{T_2}\left(\left(k_r{}^{T_1^*+T_2} + k_r^{-T_1^*-T_2}\right)\left(2^{\frac{d'}{d}} k_r^{-2}\alpha R\left(N_0^{(1)}\right)\right)\right.\\
&\quad \left.+\left(k_r{}^{T_2} + k_r^{-T_2}\right) k_r^{-1}\frac{\alpha_1\alpha_2}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(1)}\right) 2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\right)\\
&= \arg\min_{T_2}\left(k_r{}^{T_1^*+T_2} + k_r^{-T_1^*-T_2}\right) = -T_1^*
\end{aligned}$$

where (a) follows from Eq. (9), (10), (12) and (13). The statement holds for the case $i = 1$.

Suppose the statement holds for $i = 2 \ldots k-1$. By Theorem 4.2, we have

$$\begin{aligned}
T_{k+1}^* &= \arg\min_{T_{k+1}}\left(\alpha_2 k_r^{T_{k+1}-1} R_1\left(N_0{}^{(k+1)}(T_{1\to k}^*)\right)\right.\\
&\quad \left.+\alpha_1 k_r^{-T_{k+1}-1} R_2\left(N_0{}^{(k+1)}(T_{1\to k}^*)\right)\right)\\
&\overset{(a)}{=} \arg\min_{T_{k+1}}\left(\alpha_2 k_r^{T_{k+1}-1}\left(2^{\frac{d'}{d}} k_r^{T_k^*-1} R_1\left(N_0^{(k)}(T_{1\to k-1}^*)\right)\right.\right.\\
&\quad +\frac{\alpha_1}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(k)}\right) 2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\\
&\quad +\alpha_1 k_r^{-T_{k+1}-1}\left(2^{\frac{d'}{d}} k_r^{-T_k^*-1} R_2\left(N_0^{(k)}(T_{1\to k-1}^*)\right)\right.\\
&\quad \left.\left.\left.+\frac{\alpha_2}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(k)}\right) 2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\right)\right)\right)\\
&= \arg\min_{T_{k+1}}\left(\left(k_r{}^{T_k^*+T_{k+1}}\alpha_2 R_1\left(N_0^{(k)}(T_{1\to k-1}^*)\right)\right.\right.\\
&\quad \left.\left.+k_r^{-T_k^*-T_{k+1}}\alpha_1 R_2\left(N_0^{(k)}(T_{1\to k-1}^*)\right)\right)\left(2^{\frac{d'}{d}} k_r^{-2}\right)\right.\\
&\quad \left.+\left(k_r{}^{T_{k+1}} + k_r^{-T_{k+1}}\right) k_r^{-1}\frac{\alpha_1\alpha_2}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(k)}\right) 2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\right)\\
&\overset{(a)}{=} \arg\min_{T_{k+1}}\left(\left(k_r{}^{T_k^*+T_{k+1}}\alpha_2\left(2^{\frac{d'}{d}} k_r^{T_{k-1}^*-1} R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right.\right.\right.\\
&\quad \left.+\frac{\alpha_1}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(k-1)}\right) 2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\right)\\
&\quad +k_r^{-T_k^*-T_{k+1}}\alpha_1\left(2^{\frac{d'}{d}} k_r^{T_{k-1}^*-1} R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right.\\
&\quad \left.\left.\left.+\frac{\alpha_2}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(k-1)}\right) 2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\right)\right)\left(2^{\frac{d'}{d}} k_r^{-2}\right)\right.\\
&\quad \left.+\left(k_r{}^{T_{k+1}} + k_r^{-T_{k+1}}\right) k_r^{-1}\frac{\alpha_1\alpha_2}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(k)}\right) 2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\right)\\
&= \arg\min_{T_{k+1}}\left(2^{\frac{2d'}{d}} k_r^{-2}\left(k_r{}^{T_{k-1}^*+T_k^*+T_{k+1}-1}\alpha_2 R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right.\right.\\
&\quad \left.\left.+k_r^{-T_{k-1}^*-T_k^*-T_{k+1}-1}\alpha_1 R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right)\right.\\
&\quad +\left(k_r{}^{T_k^*+T_{k+1}} + k_r^{-T_k^*-T_{k+1}}\right) k_r^{-2}\frac{\alpha_1\alpha_2}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(k-1)}\right) 2^{\frac{2d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\\
&\quad \left.+\left(k_r{}^{T_{k+1}} + k_r^{-T_{k+1}}\right) k_r^{-1}\frac{\alpha_1\alpha_2}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(k)}\right) 2^{\frac{d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\right)\\
&= \arg\min_{T_{k+1}}\left(2^{\frac{2d'}{d}} k_r^{-2}\left(k_r{}^{T_{k-1}^*+T_k^*+T_{k+1}-1}\alpha_2 R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right.\right.\\
&\quad \left.\left.+k_r^{-T_{k-1}^*-T_k^*-T_{k+1}-1}\alpha_1 R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right)\right) + \left(k_r{}^{T_k^*+T_{k+1}} + k_r^{-T_k^*-T_{k+1}}\right)\\
&\quad \times k_r^{-2}\frac{\alpha_1\alpha_2}{\alpha_1+\alpha_2} S\left(\bar{N}_0^{(k-1)}\right) 2^{\frac{2d'}{d}}\left(1-\left(2^{\frac{d'}{d}}\right)^{-\alpha_1-\alpha_2}\right)\Big) \qquad \text{(F1)}
\end{aligned}$$

where (a) follows from Eq. (9).

Based on the induction hypothesis, we know that $T_k^* = -T_{k-1}^*$ and

$$T_{k-1}^* = \arg\min_{T_{k-1}}\left(\alpha_2 k_r^{T_{k-1}-1} R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right) + \alpha_1 k_r^{-T_{k-1}-1} R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right).$$

Minimization problem in Eq. (F1) can be considered term by term. The minimization of the first term can be obtained as follows:

$$\begin{aligned}
&\arg\min_{T_{k+1}}\left(k_r{}^{T_{k-1}^*+T_k^*+T_{k+1}-1}\alpha_2 R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right) + k_r^{-T_{k-1}^*-T_k^*-T_{k+1}-1}\alpha_1\right.\\
&\quad \left.R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right)\\
&= \arg\min_{T_{k+1}}\left(k_r{}^{T_{k+1}-1}\alpha_2 R_1\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right.\\
&\quad \left.+k_r^{-T_{k+1}-1}\alpha_1 R_2\left(N_0^{(k-1)}(T_{1\to k-2}^*)\right)\right) = T_{k-1}^*.
\end{aligned}$$

Furthermore, it can be shown that the minimization of the second term is achieved with $-T_k^*$ as follows:

$$\arg\min_{T_{k+1}}\left(k_r{}^{T_k^*+T_{k+1}} + k_r^{-T_k^*-T_{k+1}}\right) = -T_k^*.$$

Since $T_{k-1}^* = -T_k^*$, Eq. (F1) can be minimized with the choice of $T_{k+1}^* = -T_k^*$.

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