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# Random Threshold Model: A Low-Dose Radiation-Induced Risk Assessment Approach Considering Individual Susceptibility to Cancer

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## Abstract

**Objectives:** The linear no-threshold (LNT) model, which has been used for radiation protection purposes, was developed based on the assumption that exposure to even a small amount of radiation may cause cancer. However, although it is known in carcinogenesis that there is variation in radiation sensitivity among individuals, the LNT model does not adequately consider radiosensitive subgroups. In this paper, we represent susceptibility to contract cancer by radiation exposure by means of the threshold of a dose-response function, introduce an assumption that the thresholds are random to represent the variation of the radiosensitivity among individuals in a susceptible subgroup. We propose a novel method, the random threshold (RT) model, for determining the safe dose limit for the subgroup to protect cancer-susceptible individuals from radiation exposure. **Conclusion:** The proposed method is illustrated by targeting *ATM* gene (a cancer-susceptible gene) mutation carriers as a radiosensitive subgroup. For cancer risk associated with low-dose radiation exposure, the contribution of radiosensitivity cannot be ignored, thus the RT model would be more suitable for risk protection for radiosensitive subgroups instead of the LNT model. We also notice that it could be widely applicable for risk protection of not only low-dose radiation but also environmental pollutants.

## Keywords

Ataxia-telungiectasia mutation, cancer susceptibility, Linear no-threshold model, radiation protection, threshold model

## Introduction

Cancer incidence is a probabilistic event. Let $Pr(D|E = d)$ be the conditional probability of an individual in a population to contract cancer ($D$) over lifetime when exposed dose $d$ of radiation ($E = d$). Note that this probability is also called a dose-response function in $d$. The excess relative risk (ERR) of cancer by exposing dose $d$ of radiation is defined by

$$ERR(d) = (Pr(D|E = d) - Pr(D|E = 0))/Pr\,(D|E = 0).$$

The linear no-threshold (LNT) model may be expressed in terms of the ERR as follows:

$$ERR^*(d) = \beta d \tag{1}$$

where $d$ is dose and $\beta$ is given constant. The model has been widely used to protect cancer risks of radiation exposure even at low doses (<100 mSv), following the 2007 recommendations of the International Commission on Radiological Protection (ICRP).[1]

This model was developed based on the traditional assumption that every increment of radiation dose, no matter how small, constitutes an increased cancer risk for human.[2,3]

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The value of $\beta$ is specified depending on situations at risk; in particular, $\beta = 0.055$ (/Sv) has been recommended to protect the risk of general public by the ICRP publication 103.[1]

Against the LNT model, the European Commission points the possibility that no cancer is induced until the exposure to certain amount of radiation that is called the threshold.[4] Let $x_0$ be the threshold, then the dose-response function with threshold $x_0$ may be expressed by

$$h(d,x_0) = \begin{cases} c & \text{if } d < x_0 \\ c(1+g(d-x_0)) & \text{if } d > x_0 \end{cases}. \quad (2)$$

for any $d$, where $c$ is a positive (>0) constant often called the background effect, $g(d)$ is an increasing function in $d$, satisfying $g(0) = 0$ . We call the model threshold model with threshold $x_0$.

The ERR of this model may be expressed by

$$ERR(d) = \begin{cases} 0 & \text{if } d < x_0 \\ g(d-x_0) & \text{if } d > x_0 \end{cases}.$$

It is well known in cancer induction that there is variation in radiation sensitivity among individuals, depending on sex, age, genetic background, lifestyle such as smoking, and exposures to other agents.[5,6] Thus, we consider in this study a subgroup of susceptible individuals by radiation exposure in a population and propose a method to determine a safe dose limit for their radiological protection.

In this paper, we first show, in next section, how we represented the susceptibility to developing cancer following radiation exposure by setting a threshold for a dose-response function. Then, the threshold must be distributed over the targeted subgroup, since it is a gathering of individuals. Thus, it would be reasonable to treat $x_0$ in equation (2) as the realization of random variable $X$ distributed across the subgroup. We call this the "random threshold (RT) model" and advocate for its application to protect a susceptible subgroup of individuals from the risk of radiation exposure and subsequent development of cancer. The novel model for determining a safe dose limit for a susceptible subgroup of individuals who may develop cancer is introduced in Section 3. It uses the lower percentile of the distribution of the threshold, instead of the ERR. The application of the RT method to mutation carriers of the *ATM* gene, which is linked to cancer susceptibility, is detailed in Section 4, to illustrate the proposed method. Finally, we discuss the RT model and its application in Section 5.

## Susceptibility and Threshold

Let $Pr(D|E = d, A)$ be the conditional probability of individual $A$ to develop cancer ($D$) when exposed dose $d$ of radiation ($E = d$). $A$'s risk ratio of cancer when exposed dose $d$ of radiation relative to no radiation exposed is defined by

$$R(d|A) = Pr(D|E = d, A)/\, Pr(D|E = 0, A) \quad (3)$$

We call individual $A$ is more susceptible to develop cancer than individual $B$ if and only if $R(d|A) > R(d|B)$ for any $d > 0$.

$Pr(D|E = d, A)$ is also a dose-response function in $d$ of individual $A$ to develop cancer. We suppose the following model for this function from (2);

$$Pr(D|E = d, A) = \begin{cases} C_A & \text{if } d < d_A \\ C_A(1+g(d-d_A)) & \text{if } d > d_A \end{cases} \quad (4)$$

where $d$ is dose and $C_A$ is a background effect of individual $A$; and $g(d)$ is an increasing function in $d$ with $g(0) = 0$ and is assumed not depend on individual $A$. We have the following proposition which shows the sensitivity of an individual may be represented by the threshold. The proof of the proposition is given in Appendix 1.

**Proposition 1.** Suppose that individual $B$ also follows the dose-response function (4) with $C_A$ and $d_A$ replaced by $C_B$ and $d_B$. Then, individual $A$ is more susceptible than individual $B$ to develop cancer if and only if $d_A < d_B$.

## Protection for a Radiosensitive Subgroup

### Dose Response Function in the Subgroup

Let $S$ be a radiosensitive subgroup of individuals who generate cancer based on the dose-response function (2). When the radiosensitivity among individuals in $S$ is taken into account, it would be natural to consider $x_0$ in (2) an observed value of random variable $X$. Let $X$ follows a probability density function (pdf) $f(x)$ over $S$. Then the dose-response function for an individual in $S$ is given by the expectation of $h(d,X)$ given in (2) with respect to $X$; that is

$$h(d) = E(h(d;X)) = c\left(1 + \int_0^d g(d-x)f(x)dx\right),$$

We approximate $g(d)$ by a linear function $g(d) = \beta^* d$ in low-dose region.

Then, $h(d)$, ERR and the risk ratio, denoted by $R(d)$, is given, respectively, by

$$\begin{aligned} h(d) &= c(1+\beta^*\left(dF(d) - \int_0^d xf(x)dx\right), \\ ERR^*(d) &= \beta^*\left(dF(d) - \int_0^d xf(x)dx\right) \\ R(d) &= 1 + \beta^*\left(dF(d) - \int_0^d xf(x)dx\right), \end{aligned} \quad (5)$$

where $F(d)$ is the cumulative distribution function (cdf) of $X$.

Upon setting $f(x)$, we could apply these functions to make a cancer risk assessment for individuals in $S$ in a traditional way, but we do not do so in this paper; instead, we propose a

novel idea that takes into account the sensitivity of individuals in $S$ to cancer following radiation exposure.

## The Safe Dose Limit for Sensitive Individuals in the Subgroup

Suppose that the distribution function of the threshold has been completely established. First, we recall that the threshold was defined as the minimal amount of radiation exposure that causes cancer in an individual base. Thus, its distribution over subgroup $S$ may be recognized as the distribution of safe dose limits over the subgroup; in other words, a new *dose-response function* is introduced in $S$ whose "dose" corresponds to the safe dose limit and whose "response" is related to the percentage of individuals in $S$ who develop cancer. Recall also that the threshold was identified with the susceptibility to cancer; which makes it possible to order linearly these individuals' susceptibility, from the most susceptible to least susceptible. Thus, the "dose" in the dose-response function may be also recognized as the sensitivity to cancer.

Our goal is to determine a safe dose limit for individuals in $S$ who might develop cancer, taking into account their susceptibilities. To achieve this, we establish a strategy that ignores $p$% of individuals who are more susceptible than others, to protect the remaining (1-$p$)% individuals in $S$ from developing cancer. The strategy is mathematically realized by using $d_p$ defined by

$$d_p = F^{-1}(p)$$

as the safe dose limit for individuals in subgroup $S$ (see Figure 1), where $F(d)$ is the distribution function of the threshold and $p$ is a pre-determined safe level that must be selected based on the consensus of communities.

The most critical point in the above discussion is in the specification of the distribution of the threshold, which is illustrated below.

## Specifying the Distribution of the Threshold

We suppose pdf $f(x)$ of the threshold belongs to the family of gamma distributions with parameters $k$ and $\lambda$ given as follows:

$$f(x) = \frac{\lambda^{k}}{\Gamma(\mathrm{k})} x^{k-1} \exp(-\lambda \mathrm{x}).$$

It is known that the family of gamma distributions takes various shapes depending on the values of $k$ and $\lambda$, and that waiting time until "death" in life testing is a random variable that is frequently modeled with a gamma distribution.[7]

*Specifying Unknown Parameters of the Gamma Distribution.* The existence of radiosensitive subgroups is of particular interest in radiotherapy and has been the subject of several studies, such as the Women's Environmental, Cancer, and Radiation Epidemiology (WECARE) study.[8] Most of those studies are population-based case-control studies, in which the relative risks (RR) in intervals $(d_i, d_{i+1}), i = 1, 2, \cdots (d_1 < d_2 < \cdots)$ are respectively evaluated and the first interval that makes the RR significant is identified. We may use the information to assess values of parameters of the gamma-distribution under the following assumptions:

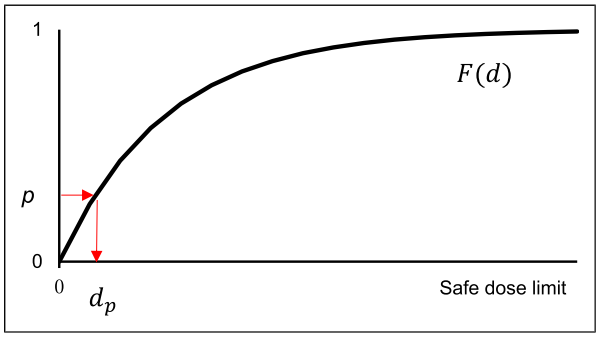


**Figure 1.** The distribution function of the threshold ($F(d)$) and the safe dose limit ($d_p$) for pre-determined risk level $p$.

**Assumption 1.** The left edge $\mathrm{d}_1^*$ of the interval $(\mathrm{d}_1^*, \mathrm{d}_2^*)$ that made RR the first significant is located at the lower Q x 100% point of the distribution of the threshold.

**Assumption 2.** The given value of RR in the interval $(d_1^*, d_2^*)$ that made RR the first significant is attained at the mid-point of the interval.

From Assumption 1, it follows that

$$Q = \int_0^{d_1^*} f(x|k,\lambda)dx = F\left(\lambda d_1^* \middle| k, 1\right)$$

where $F(x|k,1)$ is the cdf of $f(x|k,1)$. Thus, letting $a_Q(k)$ be the constant that satisfies $Q = F(a_Q(k)|k,1)$, we have

$$\lambda = a_Q(k)/d_1^*. \tag{6}$$

Next, let $d_0$ be the midpoint of the interval $(d_1^*, d_2^*)$ that made RR the first significant and $r_0$ be the given value of RR over the interval. Since it is known in a case of rare disease that the RR in a case-control study is a good estimate of the risk ratio in follow-up framework, we have the following approximation from Assumption 2 by replacing $R(d_0)$ in (5) by $r_0$;

$$r_0 \approx 1 + \beta^* \left( d_0 F(d_0|k,\lambda) - \frac{k}{\lambda} F(d_0|k+1,\lambda) \right) \tag{7}$$

The derivation of the formula is given in Appendix 2. An algorithm to determine $k$, $\lambda$ and $\beta^*$ that satisfies equations (6) and (7) is given in Appendix 3.

*Choice of Q.* Recall that $Q$ is the proportion of patients who have had onset of cancer by the exposure of dose less than $d_1^*$, the edge of interval $(d_1^*, d_2^*)$ that made the RR first significant. Thus, $d_1^*$ could be larger than the threshold of the deterministic

effect (harmful tissue reactions), which is defined as the dose that results in about 1% incidence,[8] and we propose to use $Q = 0.5\%\ or\ 1\%$ (see Discussion section). Smaller $Q$ makes the safety dose limit more conservative.

*Error bounds of the assessed safe dose limit.* Often the dose interval that made RR the first significant in case-control studies are identified with small sample sizes, and the RR over the interval is provided with 95% CI to represent its uncertainties. The proposed safe dose limit depends on the RR, thus it has also uncertainties. These uncertainties may be evaluated by using the CI of the RR as follows: Replace the value of $r_0$ in (5) by the value of its upper and lower bounds, respectively, and apply the same algorithm as given above. The resulting interval assesses uncertainties of the proposed safe dose limit. We call them U-limit and L-limit.

## Application to the *ATM* Gene Carriers

There are several known radiation susceptible subgroups to generate cancer in a population.[5,6] Among them we focus on the subgroup $S$ = {Any rare *ATM* missense variant carriers predicted to be deleterious to induce cancer} in the WECARE study[8] and illustrate the proposed methodology.

There are cancer-susceptible gene carriers in the healthy population, such as carriers of the ataxia-telangiectasia mutated (*ATM*) gene. The *ATM* gene was first reported to be the causative gene of ataxia-telangiectasia in 1995.[9] Ataxia-telangiectasia is a rare autosomal recessive genetic disorder characterized by cerebellar ataxia, telangiectasia, susceptibility to infection, and radiosensitivity. Carriers of the *ATM* gene have been estimated to comprise approximately 1% of the general population.[10] In 1987, Swift and co-workers reported that for heterozygotes responsible for ataxia-telangiectasia, the RR of cancer was estimated to be 2.3 for men and 3.1 for women in the US white population.[11] Female *ATM* carriers are considered to have an approximately 2.3-fold higher risk of developing breast cancer than non-carriers.[12]

### *Women's Environmental, Cancer, and Radiation Epidemiology (WECARE) Study*

The WECARE study was an international population-based case-control study; the 708 case subjects were women with contralateral breast cancer, and the 1397 control subjects were women with unilateral breast cancer matched to the case subjects on age, follow- up time, registry reporting region, and race and/or ethnicity.[8] The exposed radiation dose of each subject was estimated by examining past medical records; it was reported that the mean dose received to the contralateral breast was 1.2 Gy (SD = 0.7).[8] Statistical analysis was conducted by logistic regressions. It was reported that women in the WECARE study who carried any rare *ATM* missense variant predicted to be deleterious and who received radiation therapy for their first cancer, had a significantly elevated risk of contralateral breast cancer compared with unexposed women who carried the same deleterious missense variant; RR = 5.3, 95% CI: (1.6 ,17.3) in dose range 0.01-0.99 Gy; RR = 5.8, 95% CI: (1.8, 19.0) in dose range ≥1.0 Gy (see Bernstein, et al[8]). Thus, the existence of such radiosensitive *ATM* carriers should not be ignored in dose limit setting for radiation protection purposes.[13]

### *Threshold Distribution and the Safe Dose Limit of ATM Gene Carriers*

Targeting subgroup $S$ = {carriers of any rare *ATM* missense variant predicted to be deleterious}, we apply the proposed method to assess the safe dose limit for individuals in $S$ by using the results given by the WECARE study.

The WECARE study gave RR = 5.3 and 95% CI= (1.6, 17.3) that was significant in dose interval (0.01, 0.99) (Gy). Thus, by considering 1 Gy is almost equivalent to 1 Sv, we may put $d_0 = 500$ (mSv), $d_1^* = 10$ (mSv), and $r_0 = 5.3$. Setting $k = 0.1$ as the initial value for $k$ in Step 1 and $\delta = 0.001$ in Step 3 and applying the algorithm given in Appendix 2, we may determine values of parameters $k$, $\lambda$ and $\beta^*$; and then compute the safe dose limit.

The results are listed in Table 1 when $Q = 0.5\%, 1\%$ and risk levels 0.01, 0.001, 0.0001 and 0.00005. In the case of LNT, we put $\beta = 0.055$ in (1). The U-limit and L-limit are also listed in Table 1.

Table 1 shows that

i. The safe dose limit assessed by the RT model gets stringent as $Q$ increases for each risk level. For example, to protect one woman among 10,000 unilateral breast cancer patients of *ATM* carriers from contracting contralateral breast cancer, the table shows that the safe dose limit assessed by the RT model is 1.11 mSv with L and U-limit (0.38, 1.75), 0.55 mSv with L and U-limit (0.100, 0.954), respectively, when $Q = 0.5\%\ and\ 1\%$; while that of the LNT model is 1.82 mSv. Note that even U-limits at this risk level are all smaller than the safety limit of the LNT model.
ii. The safe dose limit assessed by the RT model gets smaller as the risk level becomes stricter, but the speed of decrement is slow, compared to that of the LNT model.
iii. Note that the current safe dose limit for general public recommended by the ICRP is 1 mSv/year.[1] It corresponds to 5 individuals generating cancer per year among 100,000 general public if one applies the LNT model with the consideration of the dose and dose-rate effectiveness factor (DDREF).[1] Similar modification might be needed, but safe dose limits assessed by the RT model in Table 1 are all smaller than 1 mSv.

**Table 1.** Values of $k$, $\lambda$ and Safe Dose Limits.

| | | | | Safe Dose Limits (mSv) Risk levels | | | |
|---|---|---|---|---|---|---|---|
| RT model | k | λ | β* | 0.01 | 0.001 | 0.0001 | 0.00005 |
| Q = 0.5% | 1.8 | 0.0072 | 0.016 | 14.89 | 4.03 | 1.11 | 0.756 |
| L-limit | 1.2 | 0.0013 | 0.009 | 13.77 | 2.60 | 0.38 | 0.214 |
| U-limit | 2.3 | 0.0161 | 0.046 | 17.89 | 4.85 | 1.75 | 1.295 |
| Q = 1% | 1.6 | 0.0072 | 0.015 | 10.04 | 2.33 | 0.550 | 0.359 |
| L-limit | 1.0 | 0.0010 | 0.006 | 9.97 | 1.00 | 0.100 | 0.050 |
| U-limit | 2.0 | 0.0149 | 0.045 | 10.05 | 3.05 | 0.954 | 0.673 |
| LNT model | | | | 181.82 | 18.18 | 1.82 | 0.91 |

## Discussion

Showing that the individual difference of susceptibility leads to the variation of threshold of dose-response function, we introduced in this paper the RT model and proposed a method to determine a safe dose limit based on the model to protect subgroup of radiosensitive individuals from developing cancer.

The keystone of the method is the specification of the distribution of the threshold. We developed a method for the specification under assumptions (A1) and (A2). Of these two assumptions, (A2) would be easily acceptable, but it might not easy to accept (A1). Instead of (A1) we may use the following information;

**(B1)** The annual risk of contralateral breast cancer in the US over the 25 years follow-up period was 0.37% (https://www.cancer.org), that is $\Pr(D) = 0.0037$.

**(B2)** From Bernstein et al[8] that reported results of the WECARE study, the proportion of patients exposed dose less than $d_1^*$ is $14/37$ among case subjects and $14/46$ among control subjects. Expressing the case subjects by $D$ and control subjects by $D^c$, these proportions are expressed by conditional probabilities $Pr(d < d_1^* | D^C) = 14/37$ and $Pr(d < d_1^* | D^C) = 14/46$. Applying Bay's rule, we have

$$Q = \frac{Pr(\mathrm{d} < d_1^* | \mathrm{D}) Pr(D)}{Pr(\mathrm{d} < d_1^* | \mathrm{D}) \Pr(\mathrm{D}) + \Pr(\mathrm{d} < d_1^* | D^c) \Pr(D^c)}.$$

Since $Pr(D)$ is extremely small compared to $Pr(D^C)$, we may approximate $Q$ by

$$Q \approx \frac{Pr(d < d_1^* | D)}{Pr(d < d_1^* | D^c)} Pr(D),$$

We find $Q = 0.005$ by plugging the information from (B1) and (B2) into the equation. This strengthens our reasoning for recommending the selection of $Q = 0.5\%$ for use in the study. Uncertainty of estimates in a published paper is treated by 95% CI, we also developed L and U-limits to treat the uncertainty of the assessed safe dose limit, by extrapolating those 95% CI in the published paper, so that one may take those limits into account when determining the safe dose limits.

This method, which takes individual difference of susceptibility into account, would be useful in considering dose limits for public and occupational exposures for subgroups that exhibit high susceptibility. In addition, there remains the possibility that dose limits will be established for medical exposure in the future, in which case the present model may prove useful. On the other hand, it may be necessary to note the possibility of inadequate treatment due to overestimation of risk, notwithstanding the L and U-limits developed in the present paper.

Note that the proposed method could be widely applicable, not only for low-dose radiation risk assessment, but also for the risk assessment of environmental pollutants where it is reported, for example, that genetic variants impact the sensitivity to ambient air pollution in pediatric patients with asthma.[14] Also note that the current low-dose risk assessment is limited to assessing the risk that is measured by the increase in annual excess incidences when the fixed amount of the dose is exposed throughout the year.

One of the limitations of this study is the assumption of Gamma distribution for the threshold. It is uncertain even now whether it is true for the case of human, while the distribution is often used for assessing the risks of environmental pollutants to generate cancer in animal experiments. We hope that further investigations, such as epidemiological and biological studies, could validate our model and may shed light on the need for radiation-induced risk assessment approaches considering individual susceptibility to cancer.

## Conclusion

Conventional models were accompanied by significant limitations in risk assessment for radiation sensitive subgroups. In this study, we developed the RT model as one way to assess risk for cancer susceptible subgroups and illustrated it using the example of *ATM* gene carriers. This model would have versatility for risk assessment of various susceptible groups.

## Appendix 1 (Proof of Proposition 1)

The RR of individual $A$ to develop cancer may be represented as follows:

$$R(d|A) = \begin{cases} 1 & \text{if } 0 < d < d_A \\ 1 + g(d - d_A) & \text{if } d > d_A \end{cases},$$

where $g(d)$ is a monotone increasing function in $d$ that satisfies $g(0) = 0$.

Thus, if $d_A < d_B$, we have $R(d|A) - R(d|B) > 0$ for any $d > 0$, and

$$R(d|A) - R(d|B) = \begin{cases} 0 & \text{if } d < d_A \\ g(d - d_A) & \text{if } d_A < d < d_B \\ g(d_B - d_A) & \text{if } d_B < d \end{cases}.$$

By contrast, suppose that individual $A$ is more susceptible than individual $B$, so that $R(d|A) \geq R(d|B)$ for any $> 0$. Then, if $d_A > d_B$, we must have $1 + g(d - d_A) < 1 + g(d - d_B)$, since $g(d)$ is a monotone increasing function in $d$. However, this inequality contradicts $R(d|A) \geq R(d|B)$, thus $d_A \leq d_B$.

## Appendix 2 (Derivation of equation (7))

Denoting the pdf of Gamma distribution with parameters $k$ and $\lambda$ by $f(x; k, \lambda)$, and its cumulative distribution function by $F(x; k, \lambda)$, we have

$$\int_0^{d_0} xf(x; \mathrm{k}, \lambda)dx = \frac{\Gamma(k+1)}{\Gamma(k)} \frac{1}{\lambda} \int_0^{d_0} \frac{\lambda^{k+1}}{\Gamma(k)} x^{(k+1)-1} \exp(-\lambda x)dx$$
$$= \frac{k}{\lambda} F(d_0; k+1, \lambda).$$

Thus, we have equation (7), since $R(d_0) \cong r_0$.

## Appendix 3 (Algorithm to determine $k$, $\lambda$ and $\beta^*$)

Parameters $k$, $\lambda$ and $\beta^*$ that satisfy (6) and (7) may be determined under the assumptions (A1) and (A2) by the following algorithm:

**Step1:** Give an initial value for $k$ and compute $a_0(k) = F^{-1}(Q|k, 1)$ and $\lambda$ by (6).
**Step2:** Compute

$$\beta(k) = (r_0 - 1)/(d_0 F(d_0|k, \lambda) - (k/\lambda)F(d_0|k+1, \lambda))$$

**Step3:** Increase $k$ to $k$+0.01 and repeat the same steps until $\beta(k) - \beta(k + 0.01) \leq \delta$ is satisfied, where $\delta$ is a pre-given small constant, and select the smallest $k$ that first satisfies the inequality and fix $\lambda$ by (6) and set $\beta^* = \beta(k)$ for the value of $\beta^*$.

**Note:** $\beta(k)$ is a decreasing function in $k$ and converges to its asymptote quickly as $k$ increases; see Figure S1.

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### Author Contributions

Conceptualization, T.Y. and H.F.; Methodology, T.Y.; Investigation, T.Y.; Writing—original draft preparation, T.Y.; Writing—review and editing, H.F.; Project administration, H.F.; Funding acquisition, H.F. All authors have read and agreed to the published version of the manuscript.

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### Data Availability Statement

All data generated or analyzed during this study are included in this published article.

### Supplemental Material

Supplemental material for this article is available online.

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