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Theoretical value of radiation priming for mitigating toxicity in radiation therapy

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Abstract

Radiation toxicity is a major factor limiting therapeutic doses in oncology. Inspired by Yonezawa's studies of radioadaptive survival in mice, we adopt an empirical approach because the complexity of the human body makes comprehensive biophysical analysis currently impractical. Even complete knowledge of cellular interactions would not necessarily explain whole-system responses. A previously developed model described adaptive biological responses to time-dependent irradiation using a damped-oscillator analogy, but employed a limited set of response curves without a specific biological basis. The present study generalizes this model by introducing a biologically relevant inverted Gompertzian-like response shape, with potential applications in biology and oncology. The resulting model suggests that radiation training (priming) through low, gradually increasing doses of total-body irradiation could improve tolerance to subsequent therapeutic irradiation, potentially allowing doses up to five times those conventionally administered. Very preliminary estimates based on the existing evidence indicate a training period of approximately six weeks and a cumulative priming dose of up to about 600 cGy (such a dose is lethal if given acutely—but if fractionated over several weeks, even without the assumed adaptive protection, it should not cause acute effects). If validated in animal models and subsequent clinical trials, this approach may significantly enhance the effectiveness of radiation therapy by enabling the safe administration of higher therapeutic doses.

Keywords: Oncology; Fractionation; Yonezawa effect; Hormesis; Adaptive protection

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1. Introduction

Ionizing radiation occupies a central place in modern oncology. Radiation therapy (RT) is used in the treatment of approximately 60% of cancer patients, either as the principal therapeutic modality or in combination with surgery, chemotherapy, immunotherapy, and other treatments.[1] Its clinical value derives from the ability of ionizing radiation to damage malignant cells and thereby achieve local or regional tumor control. At the same time, radiation is not absolutely selective: healthy tissues within or near the treatment volume are also exposed. Consequently, RT effectiveness depends not only on the radiation sensitivity of the tumor but also on the tolerance of surrounding normal tissues. The need to achieve sufficient tumor control while avoiding unacceptable injury to healthy organs defines the therapeutic window within which radiation treatment must operate.

Considerable technological progress has improved radiation delivery precision. Modern imaging, computerized treatment planning, dose fractionation, and increasingly conformal irradiation techniques allow clinicians to concentrate the prescribed dose more precisely within the target volume. Nevertheless, these advances do not eliminate radiation toxicity. Normal-tissue reactions remain an important constraint on total dose, dose per fraction, irradiated volume, and the overall treatment schedule.[2] Acute adverse effects may interrupt treatment or reduce patients' quality of life, whereas delayed damage may appear months or years after irradiation. Moreover, the dose required for reliable tumor control may approach or exceed the tolerance of nearby healthy tissues. Thus, even when radiation delivery is geometrically accurate, the patient's biological response may still limit treatment effectiveness.

Most approaches to improving the therapeutic window focus on delivering a higher dose to the tumor while reducing healthy-tissue exposure. A complementary approach is to modify the patient's biological response. If the tolerance of healthy tissues to radiation could be temporarily increased without a comparable increase in tumor radioresistance, higher therapeutic doses might become feasible. This possibility is particularly relevant when tumor control is limited by the tolerance of critical organs or by the cumulative systemic effects of treatment. The question is therefore not limited to how radiation can be delivered more precisely. It also concerns whether the organism can be prepared to withstand irradiation more effectively.

In this context, relatively low radiation doses are of particular interest. Low-dose irradiation has usually been discussed in relation to radiation protection and stochastic risk, but it may also possess therapeutic or conditioning potential. Sakamoto *et al.*[3] investigated the combination of low-dose and high-dose irradiation in lymphoma treatment and reported favorable clinical effects. More recently, Kojima *et al.*[4] described the use of low-dose ionizing radiation in case studies involving both malignant and non-malignant diseases. Although the available evidence is limited and the underlying mechanisms remain insufficiently understood, these studies suggest that low-dose irradiation may serve not merely as a reduced form of conventional RT but as an adjunctive intervention capable of modifying the biological response to subsequent treatment.

The proposed use of low-dose irradiation as a preparatory intervention is related to the broader phenomenon of adaptive response, sometimes discussed under the concept of radiation hormesis. The core hypothesis is that a relatively small initial stress may activate protective, reparative, or compensatory processes, thereby altering the response to a later, larger stress. In radiotherapy, such an effect could be interpreted as radiation priming or radiation training. A preliminary irradiation would not be intended to destroy the tumor directly. Rather, it would induce a systemic adaptive state in which healthy tissues—or the organism as a whole—could withstand a greater subsequent radiation burden. This concept differs from ordinary dose fractionation: instead of merely allowing recovery between therapeutic fractions, it seeks to cumulatively increase the patient's resistance before administering the principal therapeutic dose.

Experimental support for this possibility can be traced to Yonezawa's[5] studies of radio-adaptive survival in mice. In these experiments, a subgroup of animals received low-dose irradiation before being exposed to a substantially higher radiation dose. The survival rate of the pre-irradiated mice was significantly higher than that of animals that received the high dose without preliminary irradiation. These findings indicate that the biological consequences of a given radiation dose may depend not only on its magnitude but also on the organism's previous irradiation history. In other words, the response to successive doses may not be obtained by simply adding the effects of each dose independently. The first irradiation may alter the state of the system and thereby change its response to later exposure.

Translating this observation into a clinically useful procedure presents several difficulties. The intensity, timing, and duration of the adaptive response must be characterized, and the priming dose must remain sufficiently low to avoid irreversible damage. At the same time, it must be high enough to produce a meaningful adaptive effect. The interval between priming and therapeutic irradiation is also important: irradiation administered too early may occur before the adaptive response develops, whereas excessive delay may allow the protective state to decay. Furthermore, individual differences in radiosensitivity may substantially affect the optimal schedule. Any proposed treatment protocol must therefore account for both dose dependence and time dependence, while maintaining an adequate safety margin.

Smirnova and Yonezawa[6] proposed a mathematical model intended to explain the experimental phenomenon. Their model represented the relevant biological processes using 13 first-order differential equations and about 50 parameters. Such a detailed formulation may provide insight into possible mechanisms, but its complexity limits its practical application when many parameters cannot be determined reliably for an individual patient.

Microdosimetric models, developed by Leonard,[7] instead relate adaptation to stochastic energy-deposition events in sensitive cellular volumes. He describes activation thresholds, dose-rate dependence, and the development and fading of protection between priming and challenge exposures. This provides a physical basis for dose–timing calculations, although biological activation and repair parameters remain experimentally determined. Repair-kinetic models extend the framework by allowing irradiation to modify DNA-repair efficiency and antioxidant activity, thereby representing competition between damage induction and inducible protection.[8] Fornalski *et al.*[9] later developed a more compact theoretical approach that analyzed separate detrimental effects and quantified the influence of the priming dose. Krasowska *et al.*[10] extended this framework to repeated priming and variable dose-rate exposures, emphasizing endpoint-specific calibration and the limitations of assuming additive adaptive signals. Collectively, these models provide tools for experimental design and hypothesis testing; they do not yet establish a generally validated method for prescribing human priming doses.

The above studies demonstrate the importance of mathematical modeling, but they also reveal the need for models that retain the essential dynamics of adaptive response while using a relatively small number of interpretable parameters.

The human body is a complex dynamical system. Its response to irradiation emerges from interactions among cells, tissues, organs, repair processes, immune responses, and systemic regulatory mechanisms. An exhaustive description of individual-cell behavior may therefore be insufficient to predict the organism's response as a whole. In such circumstances, an empirical or phenomenological model may be useful even when it does not represent every underlying biological mechanism explicitly. A simple model can identify general relationships among dose, time, damage, recovery, and adaptation and can generate testable predictions regarding potentially useful irradiation schedules.

Analogies with comparatively simple physical systems may be especially valuable for this purpose. In the present work, the evolution of the organism's radiation resistance is represented by analogy with a damped oscillator. Acute irradiation produces an initial deterioration, followed by a compensatory response that may temporarily raise the organism's strength above its pre-irradiation level before it gradually returns toward equilibrium. Successive radiation pulses may then be coordinated so that the adaptive effects accumulate without crossing the threshold of irreversible damage. The model is extended by introducing an inverted Gompertzian-like dose-dependence function and is used to explore a possible radiation-training schedule. The objective is not to claim clinical validation of radiation priming, but to formulate a transparent empirical framework that clarifies the assumptions, identifies the critical parameters, and provides a basis for future experimental and clinical investigation.

2. Materials and methods

We report the results of a theoretical modeling study—more specifically, an empirical mathematical investigation that extends a previously developed damped-oscillator model of the adaptive biological response to time-dependent irradiation. The purpose of the model is not to provide a detailed representation of the biochemical and cellular mechanisms involved. Instead, it offers a low-dimensional phenomenological framework to describe the organism's principal response features and to examine the possible cumulative effects of radiation pulses administered according to different temporal schedules.

2.1. Low-dose radiation response as damped-oscillator evolution

A mathematical model describing the biological response to irradiation with an arbitrary temporal profile was previously developed.[11,12] The model is based on an analogy with a damped oscillator. In physics, a damped oscillator is a system that, after being displaced from equilibrium, undergoes oscillatory motion whose amplitude gradually decreases because energy is dissipated. Familiar examples include a mass attached to a spring and a swinging pendulum subjected to friction. In the present context, the analogy is phenomenological rather than mechanistic: the organism is not assumed to behave literally as an oscillator.

The model characterizes resistance to acute radiation effects with a single state variable, which may be termed "organism strength" or "resistance to illness." This variable represents an aggregate measure of the organism's capacity to withstand radiation-induced damage. It may be associated with measurable biological characteristics such as hematopoietic recovery, immune activity, antibody production, DNA repair, or other protective and compensatory processes. However, no unique correspondence with any individual biological parameter is assumed.

The model incorporates several intuitive assumptions. Acute irradiation initially reduces organism strength; this deterioration is followed by a compensatory response that may temporarily raise resistance above its pre-irradiation level. Without further irradiation, the response gradually decays toward equilibrium. Subsequent radiation pulses

act on the organism in its current state and may therefore produce effects different from those of an identical first pulse. This simplified framework enables the qualitative and quantitative investigation of radiation adaptation without requiring a complete theory of the underlying biological mechanisms.

First, we define two formal parameters u and τ. Their correspondence to physical parameters is discussed later. u is the dimensionless excess of the organism's strength. The zero value $u = 0$ is defined as corresponding to the initial organism's strength before irradiation, and $u = x$ corresponds $(x+1)$-fold radiation resistance of the organism. For example, $u = 3$ corresponds to four-fold radiation resistance. τ is the dimensionless time measured in units of the characteristic time T_0. The model assumes the following regarding the organism's strength evolution over time:

(i) The time evolution of the organism's strength is mathematically analogous to a mass on a spring with a damper (Figure 1A). After displacement from equilibrium due to acute irradiation, the organism undergoes one oscillation with the so-called time constant (characteristic time) T_0, as shown in Figure 1B, and then its strength asymptotically approaches equilibrium. Such one-oscillation evolution is referred to as "critical damping."

(ii) Following acute irradiation (radiation pulse), the organism's strength experiences an initial drop (degradation) proportional to the radiation dose.

(iii) The organism's response after acute irradiation is also proportional to the radiation dose. While both the response and strength degradation exhibit proportionality to the initial dose, the assumption of critical oscillation suggests that the strength eventually surpasses its pre-irradiation level.

(iv) Upon subsequent radiation pulses of the same dose, both the strength and its time-derivative exhibit similar discontinuities as observed after the first pulse (Figure 1C).

Under the premise of the aforementioned assumptions, the prospect of enhancing a patient's radioresistance emerges. The enhancement is expected to be achieved through the implementation of "radiation training" involving a well-coordinated sequence of acute irradiations (fractions). Figure 1 exemplifies the impact of such fractionation, demonstrating that after the second pulse, the organism's strength u attains a maximum of 0.8; this corresponds to an 80% increase in the dose that can be administered to the patient without causing irreversible damage (elaborated upon in the subsequent section).

2.2. Description of the parameters

If the radiation dose is sufficiently high, the organism may sustain damage that cannot be fully compensated by normal repair and recovery processes. In this model, such damage corresponds to a persistent reduction in "organism strength," including a decreased ability to resist infections, recover from tissue injury, maintain hematopoietic

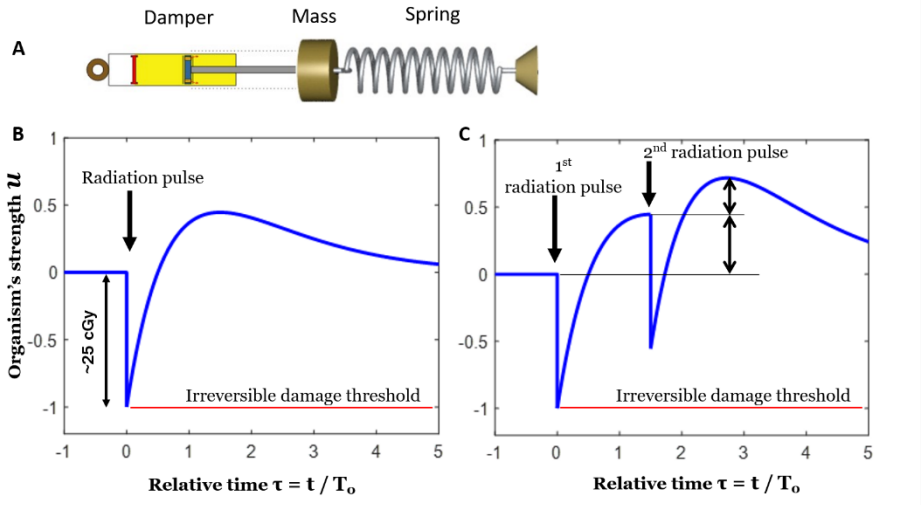


Figure 1. The damped oscillator mechanical analogy (A) and time evolution of the organism's strength described by the model after single-pulse (B) and double-pulse (C) irradiation. According to the proposed model, if the irradiation dose is increased above about 25 cGy, the body will suffer irreversible damage. T_0 is the time constant, or characteristic time of the system, hypothesized to be of the order of two weeks.

function, and respond to additional physiological stresses. We assume a critical dose above which the response can no longer be considered fully reversible. This dose is denoted by D (damage).

As a first approximation, we associate this critical level with the onset of acute subclinical effects and assume D (damage) = 25 cGy.[13] A similar value has been identified as a possible threshold for radiation-induced cancer in analyses of atomic-bomb survivors.[14] Nevertheless, these observations involve different biological endpoints and should not be interpreted as demonstrating a single universal threshold. Acute tissue injury, hematopoietic suppression, adaptive response, and radiation carcinogenesis are distinct phenomena governed by different mechanisms and timescales.

The value of 25 cGy should therefore be regarded only as an approximate calibration parameter. It is not claimed to represent a sharply defined boundary between harmless and harmful exposure, nor is it expected to apply identically to every individual or irradiation condition. Its purpose is to establish the characteristic dose scale needed to investigate general trends predicted by the model. Throughout the remainder of the paper, we assume that D (damage)=25 cGy corresponds to $u = -1$, as illustrated in Figure 1. Radiation dose is then expressed in dimensionless form as the physical dose divided by D (damage). This normalization allows the mathematical results to be interpreted independently of the particular numerical estimate selected for the critical dose.

The second principal calibration parameter concerns time. We assume the characteristic time T_0 required for the organism to develop and subsequently lose a radiation-induced adaptive response is approximately two weeks, i.e., $T_0 \sim 2$ weeks. This estimate aligns with practical observations in RT, where many acute adverse effects develop and subside over periods of several weeks.[2] The characteristic time should not be interpreted as the duration of a single molecular or cellular process. Rather, it represents an aggregate timescale encompassing injury, signaling, repair, compensatory proliferation, immune activity, and systemic recovery.

Historical observations of acute radiation syndrome following the atomic bombings of Japan provide an additional indication of the relevant timescale. Deaths associated with acute radiation injury began approximately one week after exposure, reached their highest frequency after roughly three weeks, and declined substantially within six to eight weeks.[15] These observations are valuable because the victims did not benefit from modern specialized treatment for radiation injury. Their outcomes therefore reflect, to a considerable extent, the natural progression of injury and recovery. Nevertheless, the heterogeneous doses, combined injuries, and difficult post-bombing conditions prevent these observations from serving as a precise calibration dataset.

Both D (damage) and T_0 are expected to vary among individuals. Differences in age, health status, genetic radiosensitivity, prior treatment, irradiated volume, dose rate, and the condition of the hematopoietic and immune systems may considerably alter the response. Variations of several tens of percent appear plausible. For example, the United States Department of Defense reports that the dose associated with a 30% probability of nausea and vomiting—an early manifestation of acute radiation syndrome—lies between approximately 75 and 125 cGy.[16] This range is higher than the assumed D (damage), but the two values represent different endpoints: the former concerns a defined probability of clinically apparent symptoms, whereas the latter is intended to characterize the onset of subclinical and potentially cumulative damage.

The assumed values are also substantially higher than doses commonly discussed in connection with hormesis, typically around 10 cGy.[17] Responses at very low and substantially higher doses may involve different balances among damage, repair, adaptation, and tissue failure; simple extrapolation between these ranges is therefore inappropriate. In any future clinical application, the model parameters would need to be personalized and determined before treatment. The values adopted here serve only as provisional reference values for exploring the model and illustrating possible irradiation schedules.

2.3. Dose dependence of the adaptive response

The dose dependence of the adaptive response is crucial. Using the mass-spring-damper analogy, the dose dependence describes how the spring loses elasticity as it is stretched. We do not know this dose dependence, but we hypothesize that the functional law does not vary a lot from person to person. In previous work, three hypotheses for functional dependency were suggested,[12] while none of them could be associated with a reasonable radiobiological mechanism. Here, we propose a general form of such dependency based on an inverted Gompertzian-like shape, which is widely used in adaptive response modeling.[9] Several other threshold functions (binary and sigmoid) have also been tried with no significant difference in results. The cumulative function was selected since it was compatible with the model, while its derivative (Gompertz curve) was not.

Mathematically, the Gompertz distribution has two parameters. We parametrized it differently from the canonical form, choosing one parameter as the "effective

dose" at which the adaptive response drops to 50% (the "spring's" elasticity drops to 50% of its initial value). We denote this parameter as ED_{50} (loosely analogous to LD_{50}). The second parameter is the canonical Gompertz parameter η, which likely has no biological meaning but describes the width of the shape. Figure 2 presents inverted Gompertzian-like shapes for four values of η. More mathematical details are given in the Appendix; for a thorough description of the model, the reader is referred to the previous works.[11,12]

Notably, the function in Figure 1 is "strength," while the function in Figure 2 is the dose-dependence function. Dose dependence describes, mechanically speaking, how the spring loses elasticity as it is stretched.

3. Results

As mentioned earlier in the introduction, RT side effects are significant. While dose fractionation is commonly used to reduce these side effects, no training has been reported for this purpose. With whole-body low-dose irradiation, the aim is to enhance the body's resistance to radiation without affecting the tumor's resistance, since tumors receive much higher radiation doses during RT than healthy tissues.

In the context of our model, a crucial practical concern is achieving a high value of $u = u^{\text{target}}$ without surpassing the "red line" of irreversible damage, as illustrated in Figure 3 ($u = -1$). In practice, certain safety margins should be considered, and thus, the minimum allowable level of u should be set above the value of $u = -1$, corresponding to the previously mentioned D (damage).

We propose the following heuristic approach as a solution. The suggested irradiation schedule involves three distinct stages:

(i) Initial total-body irradiation with a relatively low dose, approximately 25 cGy.
(ii) Subsequent daily irradiation for τ_{rad} days, starting with even lower doses that increase exponentially over time.
(iii) A treatment pause, during which we anticipate the development of an adaptive response, making the patient's organism (but hopefully not the tumor) more resistant to radiation. While cancer cells usually have different radiosensitivity, we anticipate that the tumor does not become more radioresistant because adaptive response is a systemic feature of the whole organism, not a particular tissue or tumor. This expectation is also based on Sakamoto's results showing better clinical outcomes when combining low- and high-dose irradiation compared with high-dose alone.[3]

To some extent, the system behaves like a spring being gradually stretched until $\tau < \tau_{rad}$, and then released when the irradiation is halted at $\tau = \tau_{rad}$ (the analogy is only qualitative). The outcomes are presented in Figure 3.

In Figure 3, we assumed the dimensionless dose parameter $ED_{50} = 24$, which is hypothesized to correspond to about 600 cGy of absorbed dose. We hypothesize that the adaptive dose response is actually described by the values of η about 0.0001–0.01 since such curves (Figure 2) have a similar shape to the inverted dose response of radiation carcinogenesis observed in the survivors of the

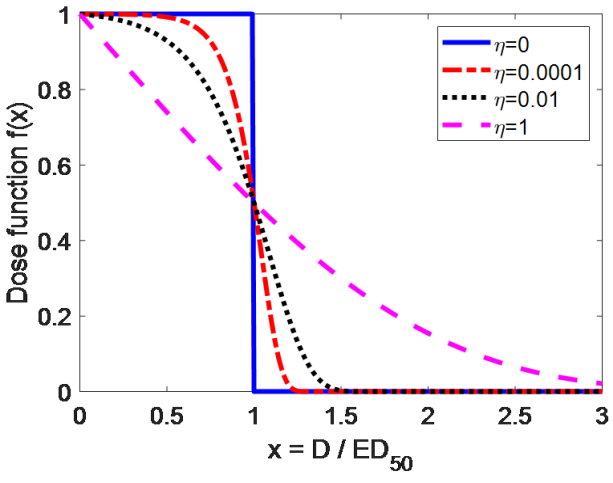


Figure 2. Four hypothetical dose functions of the organism's adaptive response corresponding to four values of η of inverted Gompertzian-like shape. ED_{50} is the "effective dose" when the adaptive response decreases to 50%. The parameter η likely has no biological meaning; it describes the width of the shape.

atomic bombing of Japan. But even for $\eta = 1$, it might be possible to achieve above fivefold increase in the patient's radioresistance.[14]

The optimal training duration is expected to be around two characteristic time units (Figure 3). Assuming T_0 = 14 days would require four weeks of total-body irradiation, plus an additional two weeks to allow adaptive protection to build up. Whether delaying RT treatment by 6 weeks is clinically acceptable goes beyond the scope of this discussion. The estimated total-body dose is approximately ED_{50}, i.e., about 600 cGy as discussed above.

4. Discussion

We propose modeling the time evolution of the adaptive protective response to radiation by analogy with a damped oscillator, such as a mechanical system consisting of a mass attached to a spring and a damper. In this analogy, irradiation initially displaces the organism from its equilibrium state by reducing its capacity to withstand injury. The subsequent biological response acts as a compensatory process that may temporarily increase the organism's resistance above its original level. In the absence of additional irradiation, this increased resistance gradually decays, and the system returns toward equilibrium. Although the analogy is deliberately simplified, it captures three essential features of the hypothesized response: initial radiation-induced deterioration, delayed adaptive overcompensation, and gradual relaxation.

The principal advantage of this theoretical approach is that it describes the response using only a few parameters. These include a characteristic damage dose, a characteristic response time, the magnitude of the adaptive effect, and the shape of the dose-dependence function. The parameters were estimated approximately from existing knowledge of acute radiation effects in humans and animals. They should not be interpreted as universal biological constants. Rather, they provide provisional scales that allow the consequences of different irradiation schedules to be investigated. Future experiments will be required to determine their actual distributions, correlations, and dependence on factors such as age, health status, irradiated volume, dose rate, and individual radiosensitivity.

Using the model, we propose a practical approach to improving RT effectiveness through controlled radiation priming. The central idea is to administer a sequence of relatively low total-body doses before the principal therapeutic irradiation. Each priming dose would initially decrease organism strength but would subsequently induce an adaptive response. If the timing and magnitude of the successive doses are properly selected, each additional exposure would occur while some protection induced by the preceding exposures remained present. The cumulative response could then raise the patient's tolerance to subsequent therapeutic irradiation while avoiding the anticipated threshold of irreversible damage.

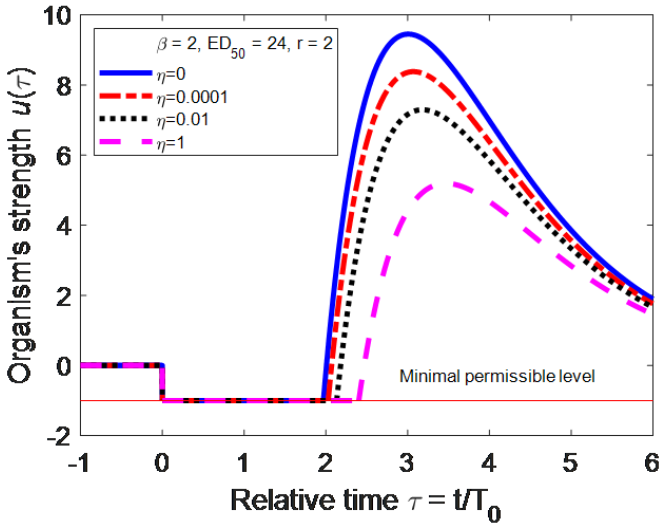


Figure 3. Values of the organism's strength $u(\tau)$ after radiation training. The value $u(\tau) = 0$ corresponds to the normal level. The value $u(\tau) = -1$ corresponds to the minimal permissible level; a normal person can sustain D (damage) (which we assume to be about 25 cGy) before the strength falls to $u(\tau) = -1$. If $u(\tau)$ reaches the value of $u(\tau) = 1$ then $u(\tau) + 1 = 2$ and the patient can absorb a radiation dose of 2×D (damage) (twice the normal). The value $u(\tau) = 5$ ($\eta = 1$) corresponds to a 6-fold increase in radioresistance.

The calculations suggest that gradually increasing priming doses may be preferable to a sequence of equal doses. At the start of the procedure, before adaptive protection has developed, the patient would receive a comparatively small dose. Later doses could increase as the modeled organism's strength rises. This way, the irradiation schedule would adjust to the patient's changing state rather than be determined solely by a fixed fractionation rule. The procedure can be viewed as a form of radiation training in which a controlled sequence of stresses is intended to strengthen the response to a later, substantially greater stress.

For the provisional parameters' values used in this study, the model predicts that organism strength might increase sufficiently to permit a therapeutic dose several times greater than the dose tolerated without priming, possibly approaching a fivefold increase under favorable conditions. The corresponding radiation-training period is estimated to be approximately six weeks, including about four weeks of gradually increasing irradiation followed by an additional recovery interval during which the adaptive response approaches its maximum. The cumulative total-body priming dose may reach approximately 600 cGy. These values are outputs of the theoretical model and should not be interpreted as a recommended clinical protocol. In particular, a cumulative total-body dose of this magnitude raises substantial safety concerns and would require rigorous experimental justification. However, a 600 cGy dose is lethal if administered acutely; if fractionated over several weeks, it should not cause acute effects, even without the assumed adaptive protection.

The present model is considerably simpler than the model proposed by Smirnova and Yonezawa,[6] which includes 13 first-order differential equations and approximately 50 parameters. Such a detailed formulation may describe a broader range of biological processes, but the large number of parameters makes empirical calibration difficult, particularly for individual patients. Our phenomenological model deliberately sacrifices biological detail for transparency and practical interpretability. It is also simpler than the approach developed by Fornalski *et al.*[9] The most important distinction, however, is not merely mathematical simplicity. The present analysis directly examines whether the adaptive-response concept might be translated into a time-dependent priming schedule relevant to RT.

In this context, the treatment scenario reported by Sakamoto *et al.*[3] is particularly noteworthy. Sakamoto and colleagues employed 10 irradiation fractions with a cumulative dose of approximately 150 cGy, administered several times per week. Their objectives and biological endpoints differed from those considered here: their work concerned the therapeutic effects of combining low-dose and high-dose irradiation, whereas the present model focuses primarily on short-term adaptive changes in normal-tissue tolerance. Nevertheless, the repeated low-dose exposures in their protocol may be viewed as conceptually related to radiation training. The reported findings provide limited empirical support for the proposition that the biological effect of a sequence of doses cannot necessarily be inferred by simply adding the effects of the individual exposures.

Our proposed schedule differs from the Sakamoto protocol in two important respects. First, it begins with lower doses because adaptive protection is assumed to be absent at the start of treatment. Second, the priming dose increases gradually as the modeled organism strength rises. Daily irradiation may provide more precise control over the response than irradiation administered only several times per week, although this assumption must be tested experimentally. The optimal frequency would depend on the characteristic adaptation and recovery times and could differ substantially among individuals.

A major uncertainty concerns the biological mechanisms underlying the adaptive response. Radiation-induced signaling, DNA repair, antioxidant activity, immune modulation, hematopoietic recovery, and compensatory cellular proliferation may all contribute, but their relative importance remains unclear.[18] Moreover, mechanisms that dominate after very low doses may not remain effective at higher doses. Existing experimental and clinical observations indicate that adaptive responses can occur,[3-6] but do not show that such responses appear consistently or reach the magnitude predicted by the model.

Another clinically decisive uncertainty is whether priming can increase the radioresistance of normal tissues without producing a comparable increase in tumor radioresistance. The model treats adaptation as a systemic property of the organism and implicitly assumes that healthy tissues will respond differently from the tumor. This assumption is plausible because malignant tissues frequently exhibit altered repair, signaling, and regulatory processes, but it cannot be accepted without direct evidence. If priming protects the tumor to the same extent as normal tissues, the therapeutic advantage would be eliminated. Experimental studies must therefore measure the responses of both healthy and malignant tissues under identical priming conditions.

The proposed approach should first be investigated in controlled animal experiments. Such studies should determine the dependence of the response on priming dose,

dose rate, interval between exposures, cumulative dose, and time before the therapeutic challenge. They should also evaluate hematological, immunological, histological, and survival endpoints and establish whether the adaptive effect differs between healthy tissues and tumors. Only after reproducible protection has been demonstrated, and the absence of enhanced tumor radioresistance has been established, could carefully designed clinical investigations be considered.

The main limitation of the present work is therefore its theoretical and phenomenological nature. The characteristic time, damage threshold, response magnitude, and dose-dependence function are only approximate. The model represents the organism by a single state variable and consequently does not distinguish among organs, tissues, or biological mechanisms. Individual variability may be considerably greater than assumed, and some patients may exhibit little or no adaptive response. Accordingly, the predicted fivefold increase in radiation tolerance, the six-week training period, and the cumulative priming dose of approximately 600 cGy must be regarded as very preliminary hypotheses, far from established therapeutic possibilities. Another central limitation of our approach is the possibility of enhanced tumor radioresistance as discussed above. Nevertheless, even if a substantial adaptive increase occurred only in a limited subgroup of patients, radiation priming could potentially widen the therapeutic window and enable more effective treatment.

5. Conclusion

The reported study suggests that adaptive biological response to time-dependent irradiation can be described using a generalized damped-oscillator framework incorporating an inverted Gompertzian-like response shape. Based on this mathematical model, radiation training, or priming, using low, gradually increasing total-body irradiation doses may offer a practical approach to improving RT protocols. Despite all the uncertainties and limitations discussed above, such priming could potentially increase patients' tolerance to subsequent therapeutic irradiation, possibly allowing higher treatment doses than those currently used. Very preliminary estimates based on existing evidence indicate a training period of about six weeks and a cumulative priming dose of up to 600 cGy (such a dose is lethal if administered acutely, but if fractionated over several weeks, even without the assumed adaptive protection, it should not cause acute effects). If validated in animal models and subsequent clinical trials, this approach may significantly enhance the effectiveness of RT by enabling the safe administration of higher therapeutic doses.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable. No empirical dataset was generated or analyzed in this theoretical/modeling study.

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Appendix

The cumulative distribution function of the Gompertz distribution is described by **Equation A1**:

$$F\left(x;\eta,b\right)=1-\exp\left[-\eta\left(e^{bx}-1\right)\right] \tag{A1}$$

We used the inverted form (**Equation A2**):

$$F_{inv}\left(x;\eta,b\right)=\exp\left[-\eta\left(e^{bx}-1\right)\right] \tag{A2}$$

The function $F_{inv}\left(x;\eta,b\right)$ yields $f\left(x\right)=0.5$ when

$$x=\frac{1}{b}\ln\left(1+\frac{\ln 2}{\eta}\right) \tag{A3}$$

Therefore,

$$ED_{50}=\frac{1}{b}\ln\left(1+\frac{\ln 2}{\eta}\right) \tag{A4}$$

and

$$b=\frac{1}{ED_{50}}\ln\left(1+\frac{\ln 2}{\eta}\right) \tag{A5}$$

Correspondingly, taking ED_{50} and η as the two parameters instead of η and b, we can calculate b and $F_{inv}\left(x;\eta,b\right)$.