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Application of Lotka–Volterra Equations for Homeostatic Response to an Ionizing Radiation Stressor

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Abstract: Every living organism is a physical, complex system which can be modeled by nonlinear dynamical equations in some very narrowed cases. Here we discuss the adoption and potential application of Lotka–Volterra equations (with damping) to simulate, on a very general level, an organism's response to a dose of ionizing radiation. The step-by-step calculations show how such modeling can be applied to practically every living thing affected by some external stressor. It is presented that Lotka–Volterra prey–predator equations can successfully model the homeostasis (equilibrium) state of the living matter, with balance between detrimental and beneficial factors which interact in the system. It was shown that too large of a radiation dose can break the damping process, making the system unstable, which is analogous to the irreversible transformation of the irradiated cell/organism. On the contrary, too low of a radiation dose makes the damping factor slightly negative, which means that some nonzero low level of ionizing radiation is the most optimal for an organism's homeostasis.

Keywords: Lotka–Volterra; prey–predator; homeostasis; radiation; carcinogenesis; low dose

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1. Introduction

The homeostatic behavior of the living system is a set of internal actions which balance and equilibrate all detrimental and positive interactions which create a stable situation over time. However, in some cases, the strong disturbance of that stable system (e.g., through a strong external stressor, like chemicals or ionizing radiation) can activate an adequate response, which can interact via a positive or detrimental way, which finally results in getting back to stable homeostasis or breaking the whole system (e.g., organism death, cancer transformation, cancer growth or even cancer metastasis) [1]. Therefore, this approach can be used in the context of cancer risk assessment related to external stressors.

The general problem of proper assessment of the cancer risk related to the dose or concentration of a potentially harmful (oncogenic) substance (the mentioned stressor) has been the subject of many scientific studies for years. While for high doses the matter seems simple (cancer risk increases with the dose), for small doses the resultant of various processes occurring there is not a foregone conclusion, and thus the postulated linearity is broken. For example, in toxicology and ecology, many cases are known where low doses of certain substances can have a positive effect on the body, while high doses will only have a negative effect [2,3]. Understanding these mechanisms and attempting mathematical description seems to be very important for the correct calculation of cancer risk.

The correlation between the cancer risk assessment and the proposed model can be identified with three mechanisms (or applications): The first one can be connected with the simple damage-repair competition: is the repair process successful or not? The second case may describe the cancer (neoplastic) transformation of a single cell with an accumulated number of oncogenic mutations. Such accumulation is a main trigger of cancer transformation, which is an irreversible cliff-effect process. The third application of the proposed model is an existing cancer cell which tries to break the immune cage to start the growing process and, finally—the metastasis [4]. All those mentioned cases can

be generally described as the strong irreversible disturbance of the homeostasis state, but some practical applications suggest that basic Lotka–Volterra equations are too simple to fully adapt them for description of the reality [4].

One of the most interesting oncogenic factors to be considered in the mentioned situations is the ionizing radiation. The global radiation protection standards assume a linear model—i.e., a linear nonthreshold (LNT) increase in cancer risk (so-called radiation risk) with the dose. However, there are a large number of studies that clearly show the collapse of this linearity in the low-radiation dose area [5]. Independently of the conducted experimental research, analytical methods and biophysical models are also being developed which try to find a solution to the problem of low doses of radiation. One approach is to use ecological modeling.

Ecological modeling is a well-known method of population risk analysis in some polluted environments because organisms' response can drive their adaptation and evolution [3]. One of the possible solutions in that analysis is a Leslie matrix, which is a discrete, age-structured model of population growth that is very famous in population ecology [6]. For example, a Leslie matrix was successfully used for nonhuman population behavior modeling related to ionizing radiation where the individual radiosensitivity was taken into consideration [7]. This radioecological approach can show a nonlinear response to the dose rate of chronic exposure of some population, which is called a "radiation exposure population effect" [8]. Analogically, the Allee effect can be explained using a similar point of view [9,10]. Another way of analysis can be performed by physical methods (nonlinear dynamics), for example by the Lotka–Volterra equations (so-called prey–predator ecological model) in two ways: a more complicated one with a consumer competition mechanism for ecosystems and population dynamics [11], or a simplified one with classical Lotka–Volterra equations [12]. The latter case is developed and described below in detail in relation not to the population dynamics but to a single organism (or cell) where prey and predator processes are used as an analogue to detrimental and beneficial processes, respectively.

Below, one can find the methodology of the classical Lotka–Volterra equations' application for an organism's disturbance. Next, the implementation of a damping factor was added to simulate the homeostasis state of the system and its further disturbance.

2. Methodology: Living System's Disturbance and Lotka–Volterra Equations

In a normal (healthy) organism, the jostling process between detrimental and beneficial processes keep the system stable (balance or homeostasis). In the special case of ionizing radiation as a detrimental factor, one can rewrite the simple homeostatic balance equation as

$$P_C \approx P_H \tag{1}$$

where P_C corresponds to the probability function of detrimental (cancerous) effects' influence, while P_H means beneficial (hormetic) effects' influence. Both probability functions can change over time:

$$\begin{cases} \frac{dP_C}{dt} = \varepsilon_C \, P_C \\ \frac{dP_H}{dt} = \varepsilon_H \, P_H \end{cases} \tag{2}$$

This is, however, not the final set of equation of the analyzing problem. The crucial importance should be put on ε_C and ε_H parameters, which can be presented in their simplest form as:

$$\begin{cases} \varepsilon_C = \alpha_C \, D \\ \varepsilon_H = -\alpha_H \, D + \beta_H \, D^2 \end{cases} \tag{3}$$

where $\varepsilon_C > 0$ corresponds to the linear growth with the analyzed substance dose (e.g., ionizing radiation), while $\varepsilon_H < 0$ corresponds to low doses only (for $D < \alpha_H/\beta_H$), which is consistent with the hormetic effect. In general, the hormetic relationship can be J-shaped (as mentioned) or U-shaped (for $\varepsilon_H = \alpha_H - \beta_H \, D + \gamma_H \, D^2$). Of course, those relationships are valid only for $D > 0$. In other words: both relationships in Equation (3) are responsible for the proper signal dynamics: ε_C for the detrimental signal change with dose P_C and ε_H

for the beneficial signal change with dose P_H. The overall response of the organism is a joint effect of both beneficial and detrimental processes, and will be discussed later.

An increase in cancerogenic processes, P_C, however, causes an increase in beneficial ones (P_H) to protect the system. And the opposite: a large quantity of P_H causes a reduction in P_C. This is analogical to the prey–predator phenomena, which can be described by the Lotka–Volterra equations as [12]

$$\begin{cases} \frac{dP_C}{dt} = (\varepsilon_C - k_C P_H)\, P_C \\ \frac{dP_H}{dt} = (\varepsilon_H + k_H P_C)\, P_H \end{cases} \tag{4}$$

where predators consume preys, and an increase in the number of preys (P_C) causes an increase in the number of predators (P_H). Additionally, the ε_C and ε_H parameters correspond to the dose-response model of detrimental and beneficial factors, respectively. This approach was described in the previous study in the context of the ionizing radiation's influence on the evolution of species [12].

The presented approach, here given by Equation (4), seems to be a good approximation of the system's behavior, where the competition between detrimental and beneficial factors keeps the system in a meta-stable state. In that situation, the homeostatic balance equation, given here by Equation (1), is maintained; however, regular fluctuations are observed when one factor dominates over another one, and vice versa (see Figure 1).

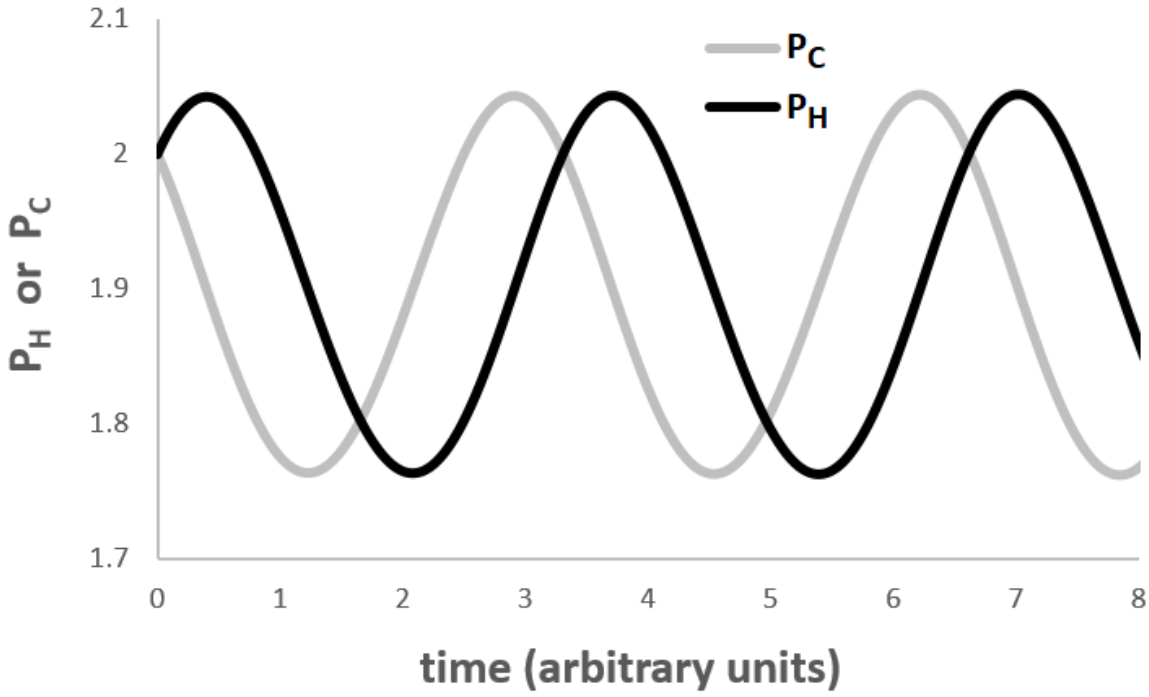


Figure 1. The time-related solution of Lotka–Volterra Equation (4) for exemplary in-put values of $\varepsilon_C = 2.1$, $\varepsilon_H = -2.1$ and $k_C = k_H = 1$.

Equation (4) can be rewritten in a time-independent form as

$$\frac{dP_C}{dP_H} = \frac{P_C}{P_H} \frac{\varepsilon_C - k_C P_H}{\varepsilon_H + k_H P_C} \tag{5}$$

which results in the closed curves characteristic to the Lotka–Volterra equations (phase space).

Next, the Equation (5) can be rewritten in a splitting variables form:

$$\frac{k_C P_H - \varepsilon_C}{P_H}\, dP_H + \frac{k_H P_C + \varepsilon_H}{P_C}\, dP_C = 0 \tag{6}$$

The solution of Equation (6) is a function $P_H(P_C)$ or $P_C(P_H)$, which creates the curve in $P_H - P_C$ phase space. In the situation when $\frac{\varepsilon_C}{k_C} \approx -\frac{\varepsilon_H}{k_H}$, the phase space is a circle (thus, Equation (1) is maintained) (see, for example, Figure 2). For the ideal condition of $P_H = P_C$, the phase space is a single point only, with coordinates of $(P_H, P_C) = \left(\frac{\varepsilon_C}{k_C}, -\frac{\varepsilon_H}{k_H}\right)$ (local extremum–critical point) (see Appendix A for details). Of course, a more probable case is that the solution would be fluctuating around this critical point (oscillations with the frequency $\omega = i\sqrt{\varepsilon_C \varepsilon_H}$, see Appendix A), which is the real situation of the jostling process between detrimental and beneficial factors in the mentioned system. Those oscillations can be, however, damped to zero when an additional "damping factor" is implemented into the Lotka–Volterra equations.

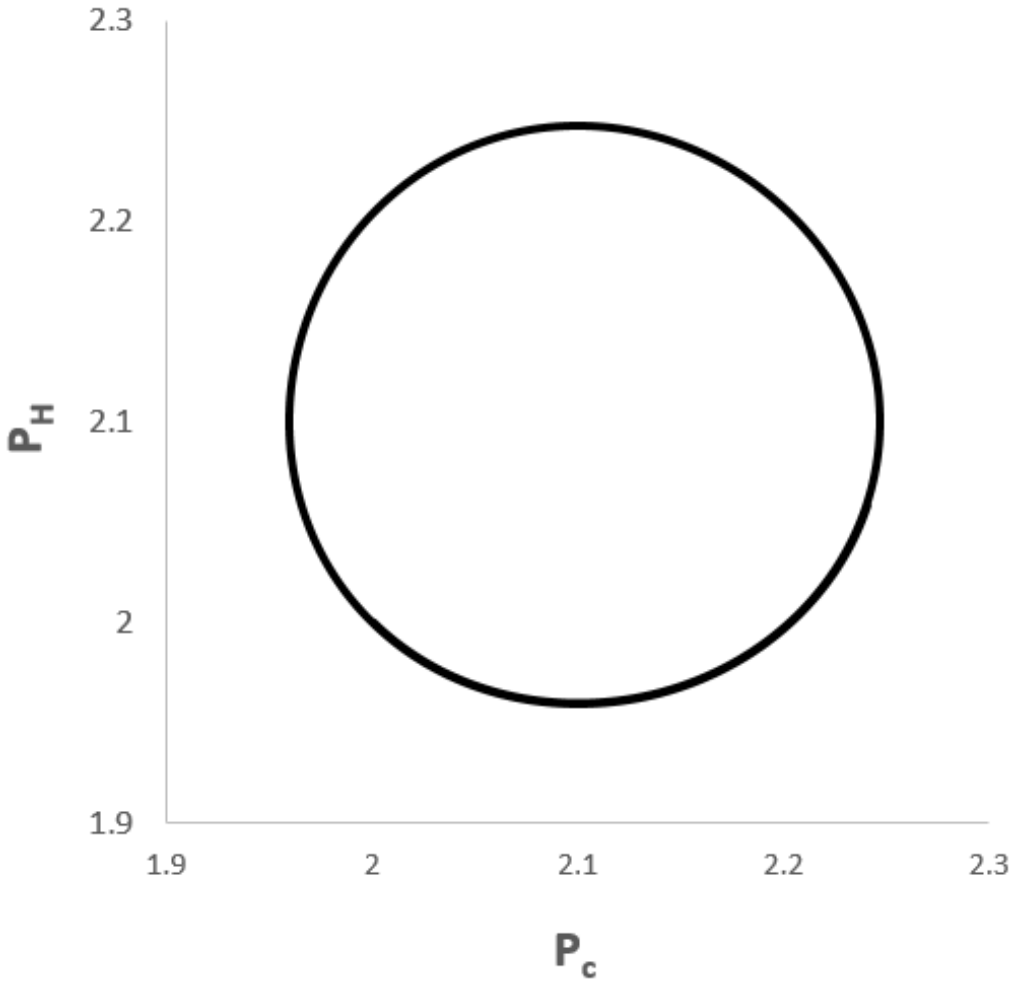


Figure 2. The phase space of P_H and P_C functions, given by Equation (4) for exemplary data from Figure 1. One can observe the regular oscillation of P_H and P_C functions, which is another representation of periodic functions in Figure 1.

3. Damping Processes and Homeostatic Balance Equation

The jostling process between detrimental and beneficial factors described in the previous section is stable over time. However, in a real situation, many disturbances of the system exist. After such a disturbance and creation of a detrimental pulse, the system naturally goes back to stable conditions due to additional dumping mechanism(s). This situation was recently simulated by the damped harmonic oscillator [13] related to the adaptive response phenomenon, which is a good analogy to the mentioned situation.

In the case of Lotka–Volterra equations, one needs to implement damping terms into Equation (4), which creates their new forms as

$$\begin{cases} \frac{dP_C}{dt} = (\varepsilon_C - k_C P_H)\, P_C - \mu_C P_C^2 \\ \frac{dP_H}{dt} = (\varepsilon_H + k_H P_C)\, P_H - \mu_H P_H^2 \end{cases} \tag{7}$$

with damping parameters (factors) μ_C and μ_H (which shall be generally lower than $\{k\}$ to keep the damping process not too strong). In this situation, the shape of functions given by Equation (7) and originally presented in Figure 1 (without damping) became the ones in Figure 3. Similarly, the perfect circle from Figure 2 became spiral (see Figure 4), which goes to the critical point. This reasoning can allow us to make analogous calculations like Equations (5)–(9), which are much more complicated, but one can use a simpler solution and find that Equation (7) stabilizes for $t \to \infty$, where $\frac{dP_C}{dt} = \frac{dP_H}{dt} = 0$. Therefore, after a long time, one obtains stable values of

$$P_H = \frac{\mu_C \varepsilon_H + k_H \varepsilon_C}{k_H k_C + \mu_C \mu_H} \tag{8}$$

and

$$P_C = \frac{\mu_H \varepsilon_C - k_C \varepsilon_H}{k_H k_C + \mu_C \mu_H} \tag{9}$$

The proposed damping factors, μ_C and μ_H, were selected as the simplest constant values. This is rather a simplification of the reality, where such processes, which are analogous to the damping, can be described by some function. Indeed, both μ factors are dependent on many variables (like age), which makes the damping process more complicated. For simplicity, to show a more qualitative approach, both μ factors are assumed to be constant values.

One has to note that the exact conditions determine which probability factor, P_C or P_H, will dominate after damped fluctuations (Figure 3). Let us focus on the special condition of homeostatic balance (equilibrium, namely, $P_C = P_H$, see Equation (1)), which generates the equation of

$$\frac{\varepsilon_C}{\varepsilon_H} = \frac{\mu_C + k_C}{\mu_H - k_H} \tag{10}$$

This equation can be rewritten in a different form, as

$$\theta = \frac{\mu + k_C}{\mu - k_H} \tag{11}$$

which joins both dynamic factors (k_C is responsible for an decrease in detrimental processes due to beneficial processes, and k_H is responsible for an increase in beneficial processes due to detrimental processes, see Equation (4)) and damping factors, which can be assumed to be equal both for detrimental and beneficial processes, i.e., $\mu = \mu_C = \mu_H$. The coefficient θ is negative for low doses (where $\varepsilon_H < 0$ and $\mu < k_H$), which was presented in Figure 5 for $\mu = 0.1$. One can call the Equation (11) a homeostatic balance equation with a damping factor [12]. Please note that the plateau in Figure 5 represents the quasistable situation where detrimental and beneficial factors fluctuate around a stable point (which is finally reached). The strong disturbance in the balance equation creates a cliff-like effect which is observed on the right side of Figure 5.

An analogical (but clearer) effect can be observed in the shape of the $\mu(D)$ function, which can be obtained after some calculation from Equations (3) and (11) (where $\theta^{-1} = (\beta_H D - \alpha_H)/\alpha_C$) (see Figure 6). This function, which connects radiation dose and damping factor, shows an interesting thing: the damping factor is slightly negative for the lowest doses, and positive for medium ones. This area is analogical to the plateau from Figure 5. However, the mentioned negative value for the lowest doses seems to be unexpected but has a strong basis: too low a radiation stressor (e.g., below natural back-

ground) is not natural, and makes the μ factor slightly negative. Indeed, many experimental findings showed that a loo-low background radiation makes organisms weaker [14,15].

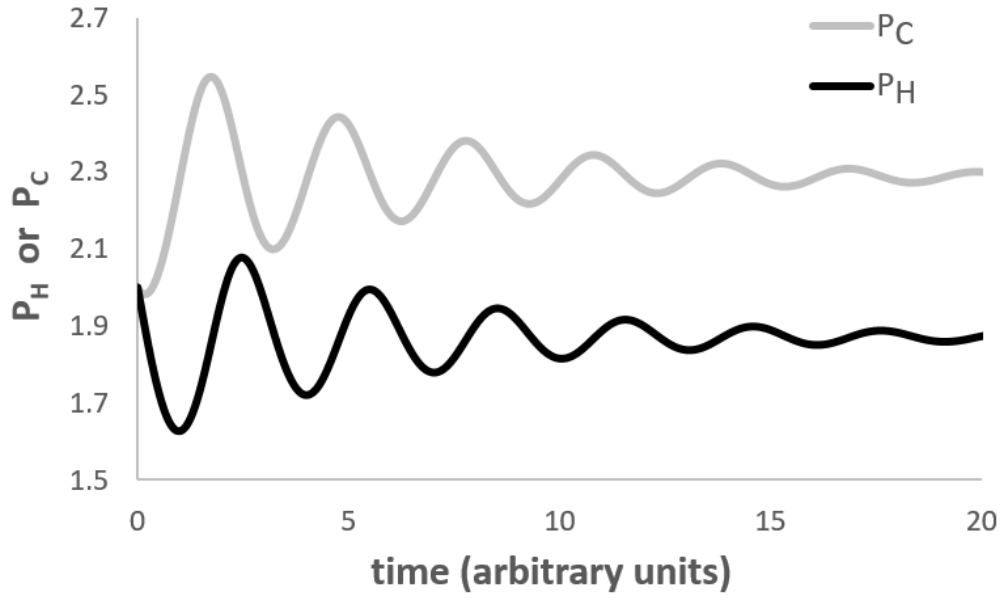


Figure 3. The conditions presented originally in Figure 1 but with additional damping parameters $\mu_C = \mu_H = 0.1$ (see Equation (7)). In this exact case, the P_C finally dominates, which generates higher risk of cancer induction in the organism.

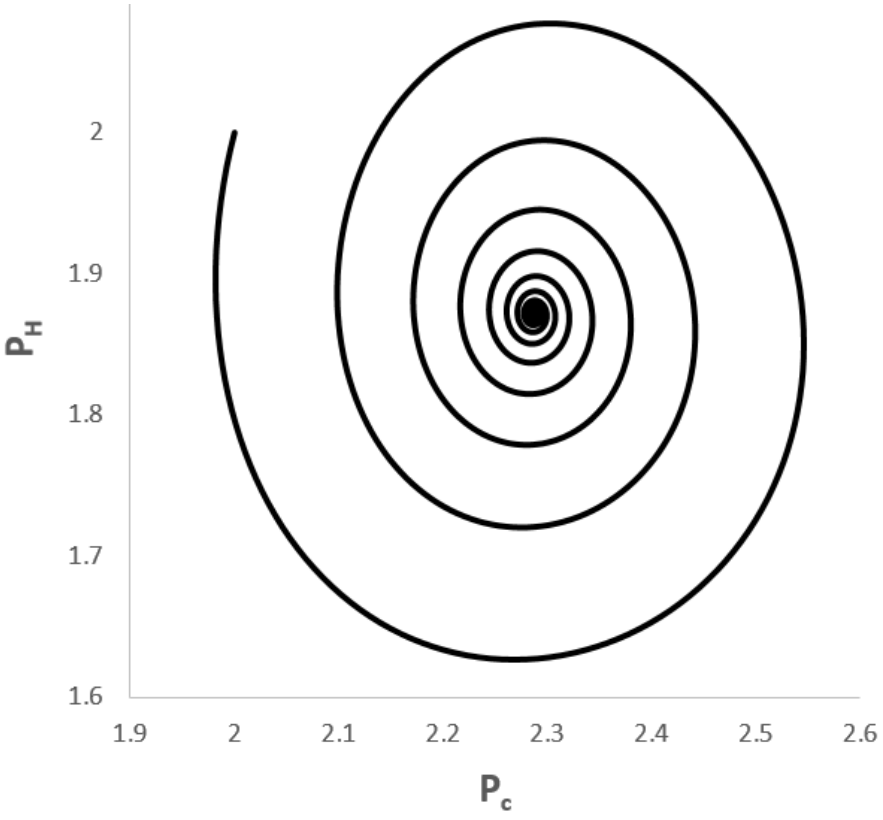


Figure 4. The analogy to Figure 2 but with conditions from Figure 3. The system reaches the exact conditions due to the damping process.

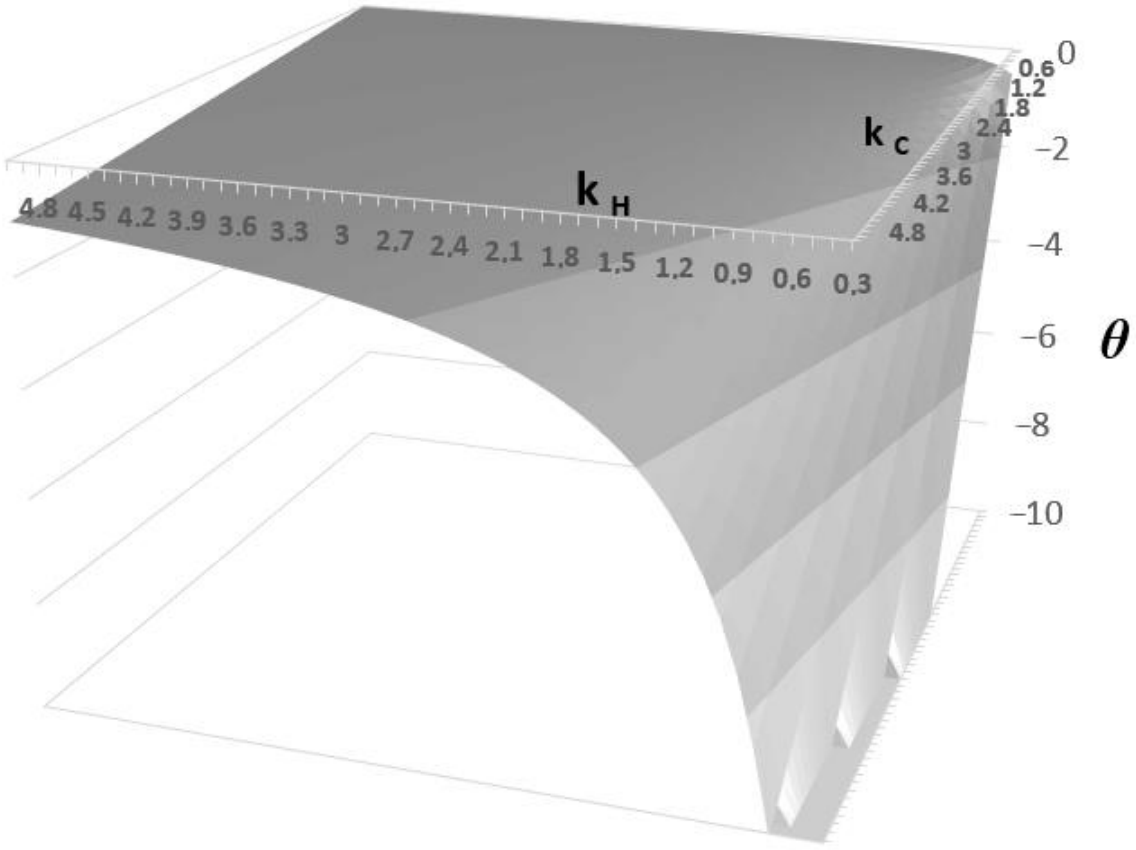


Figure 5. The visualization of Equation (11) for exemplary value $\mu = 0.1$. Each point from the presented surface corresponds to the homeostatic balance conditions (see Equation (1)). The rapid decrease on the right side represents the instability around the critical point of $k_H = \mu$. Please note that $\theta < 1$ for $k_H > \mu$.

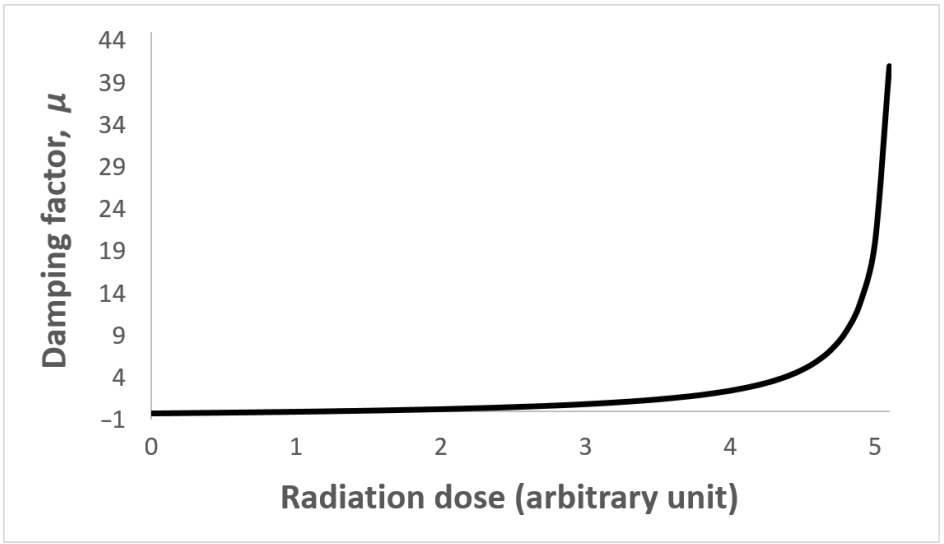


Figure 6. The damping factor (parameter), μ, in the function of radiation dose, D (given in arbitrary units). The $\mu(D)$ function is calculated from Equation (3) and (11) for exemplary parameters: $k_C = k_H = 1$, $\alpha_C = 2.1$, $\alpha_H = 3.1$ and $\beta_H = 1$. Please note that the damping factor is a response of the cell/organism to a given stressor (here: radiation), which allows the homeostasis (equilibrium) state. However, for high doses, the system is unstable (critical point), which causes an irreversible transformation of the irradiated cell/organism.

On the contrary, as one can see on the right side of Figure 6, the damping factor incidentally grows up for higher doses, which means that the system is near the critical point above which the equilibrium is no longer possible; this is an irreversible transformation of an irradiated cell (e.g., cell death, cancer transformation, stable mutation, etc.).

4. Practical Examples

As precisely described in previous sections, a living system's homeostasis is the result of a jostling process between positive (hormetic) and negative (detrimental) actions. This can create the regular fluctuations around the homeostatic equilibrium [1,12], sometimes spread over many generations [16,17], which can be described by the presented simplified model.

There are several experimental findings which are consistent with the proposed model on a very general level. Generally, many low-dose radiation studies show that the linearity in the dose-response function is broken [5], while the linear no-threshold (LNT) model can be applied to medium and high doses only. This suggests that some form of equilibrium exists between radiation's harmful effects and the organism's response (e.g., adaptive response) in the low-dose region—so this is the case which is described by the presented model. This homeostatic equilibrium is represented by the plateau (like in Figure 5 or Figure 6) in the radiation risk function in the low-dose range, which is widely discussed in the textbook by Sanders [5]. In other words: the equilibrium (homeostasis) is maintained for low doses, because the external stressor (here: the ionizing radiation) is too weak to disturb its balance. However, a high external stressor can simply destroy the equilibrium (homeostasis), which is usually described by the linear (LNT) model in a dose-response risk assessment function used, e.g., in radiation protection worldwide.

One has to note that Equation (11) and Figure 5 represent an infinite number of solutions for the simple homeostatic balance condition $P_C = P_H$ (Equation (1)). Moreover, the ratio from the left-hand side of Equation (10) does not need to be a constant value to keep the balance condition valid. This means that the beneficial or detrimental model's strength is just one, but not the only, condition for radiation risk assessment.

This process can be presented in practice on widely scattered dose-response data of radioactive gas radon influence on the risk of lung cancer. As one can see in Figure 7, the radon risk values are distributed unsymmetrically, with a maximal value around 1 (which means no risk). This means that most of the collected results show homeostatic behavior of the organism(s).

An analogical situation can be observed when epidemiological data on the dose-response relationship collected in the textbook of Sanders [5] are presented in the analogical plot (see Figure 8). This time, the data were spread over all types of cancers, because generally, the model does not focus on one type of cancer, but can be applied wider.

Other examples cover the process of cellular carcinogenesis as a rapid phase transition process [18], or the quasi-Gaussian distributions of individual radiosensitivity, which is strictly connected with the strength of the organism's response [19–21], but the detailed explanation of this can be found in the literature [22].

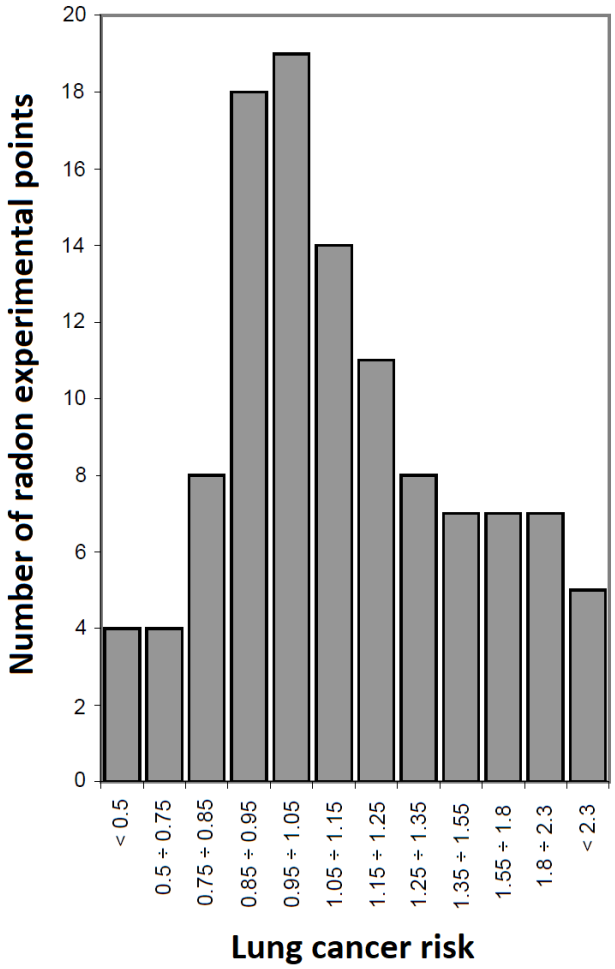


Figure 7. Lung cancer risk distribution of 112 data points from 28 independent radon studies [23]. The average risk equals 0.98 ± 0.01.

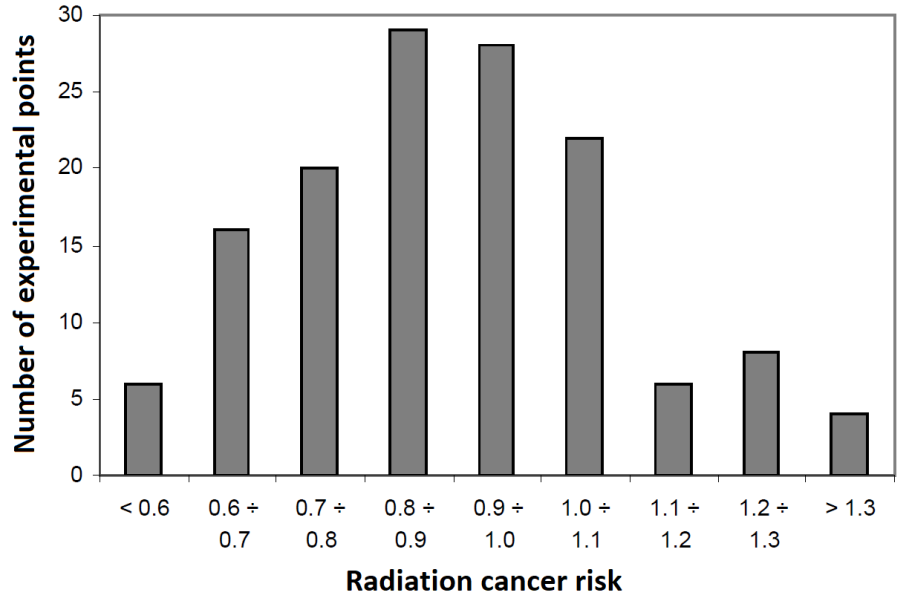


Figure 8. The distribution of 139 data points from 72 independent epidemiological studies on all types of cancer risk among people irradiated by low doses of ionizing radiation, collected by Sanders [5]. The average risk equals 0.92 ± 0.21.

5. Discussion

The proposed model presents a situation in which a healthy cell or organism (where the homeostatic balance equation is kept) can enter the carcinogenesis phase (the homeostatic balance equation is disturbed) because of the external disturbance of the system. However, contrary to the assumption adopted so far, in, for example, radiological protection, the dose-effect curve (here represented by the $\{\varepsilon\}$ parameters) is not the only factor affecting the individual cancer risk. Moreover, the presented model (in particular the damping factor, see Figure 6) shows that the risk resulting from the dose-effect curve can be effectively mitigated or, on the contrary, strengthened due to additional parameters that may be responsible for the state of the immune system of a given organism (e.g., damping factors $\{\mu\}$, or, in a more general approach, damping functions, $\{\mu(x_1, x_2, \ldots\})$.

Of course, the proposed model is quite a general one, and can be applied for different mechanisms connected with carcinogenesis processes. For example, there are three types of biological mechanisms, which can be modeled in the proposed way: the first is a damage–repair competition, the second is a mutated cell irreversible cancer (neoplastic) transformation and the third is a cancer cell multiplication/immunological cage competition [4]. In those three cases, we have some factors which act in one direction (e.g., detrimental), and some factors which act in the opposite way (e.g., beneficial). The most important thing which can be delivered from the presented model is the fact that every living organism has a different level of equilibrium where all negative and positive factors are equal. This is what is called here a balance. Any strong disturbance of that balance can make irreversible changes in the system. So, there is no one application of the model; this depends on what exactly one would like to simulate. Here, a general tool was proposed, but this can be used in many different situations and conditions.

A living organism is a physical, complex system which is very hard to model, even for one interacting factor. Indeed, Lotka–Volterra equations are relatively trivial ones and, therefore, are probably too simplified. This was pretty well discussed in the mentioned case of tumor–immune system interactions [4], where the practical case of cancer–immune system interactions is described. In this case, the Lotka–Volterra (predator-prey) equations are too simplified to model the reality, and only some general-level mechanisms can be described by that approach. Anyway, in this paper, the proposed model, which is based on the complex system physics, is able to show major processes in an irradiated cell/organism, like an adaptive response causing homeostasis (system equilibrium), a damping process which drives balance between detrimental and beneficial factors and, finally, a cliff-like effect where the dose is too high and the damping process breaks. This last situation can describe some irreversible change within the cell/organism, like stable mutation, cancer transformation or even death. Indeed, this "cliff effect" is analogous to the cancer transformation which can be described by the purely physical equations of phase transition [18,24]. Also, the breaking of the anticancer immune cage can be treated as a "cliff-like effect" process as well.

Of course, each model, even the most complicated one, is just a simplification of reality. Therefore, one can always model/simulate something in a more detailed way to find a better approximation than the proposed model. The Lotka–Volterra equations are rather simple. However, they are an example of nonlinear dynamics which, in fact, can describe some relationships on some general conceptual level. This means that those equations can properly simulate processes which are averaged over the population of interacting agents.

Thus, the proposed model is rather a conceptual one; therefore, it is hard to find a direct practical application at this stage. However, the presented paper should be treated as a useful guide on how nonlinear dynamics can work in biophysics. The reader can find an easy step-by-step application of Lotka–Volterra equations to an irradiated complex system, which also has some educational aims to demonstrate how to implement, e.g., the damping factor. Nevertheless, it is just one small step forward to understand the complex interaction of living matter with ionizing radiation.

6. Conclusions

To conclude, the proposed model is universal but high-level only. This can simulate the basic behavior of the interaction of beneficial and detrimental (cancerous) factors: usually, the equilibrium exists, and the biological homeostasis of the living system is maintained [25]. This is usually found for, e.g., low doses of external stressors, like ionizing radiation, which is too weak to break the equilibrium. However, the high dose can disturb the system and break the equilibrium; this can be treated as an analogy to, e.g., cancer transformation or tumor–immune system competition fault. This behavior is typical for a physical, complex system described by the nonlinear dynamical equations.

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Appendix A

Figure 2 shows the exemplary solution of Equation (6), which is a function of $P_H(P_C)$ or $P_C(P_H)$ (which creates the curve in $P_H - P_C$ phase space). Each point on the mentioned curve has the constant quantity:

$$C = k_H P_C + \varepsilon_H \ln P_C + k_C P_H + k_C P_H - \varepsilon_C \ln P_H \tag{A1}$$

The function C has a local extremum and the critical point for $(P_H, P_C) = \left(\frac{\varepsilon_C}{k_C}, -\frac{\varepsilon_H}{k_H}\right)$. In the situation when $\frac{\varepsilon_C}{k_C} \approx -\frac{\varepsilon_H}{k_H}$, the phase space is a circle (thus, Equation (1) is maintained). The exemplary phase space with a circle solution is presented in the mentioned Figure 2. For the ideal condition of $P_H = P_C$, the phase space is a single point only.

But in the more probable situation, the fluctuation around the critical point denoted as $(P_H, P_C) = \left(\frac{\varepsilon_C}{k_C}, -\frac{\varepsilon_H}{k_H}\right)$, which can be visualized as in Figure 1, is analogous to the situation of the jostling process between detrimental and beneficial factors in the mentioned system. Thus, the Jacobian matrix for that case can be written as

$$J(P_C, P_H) = \begin{bmatrix} \varepsilon_C - k_C P_H & -k_C P_C \\ k_H P_H & \varepsilon_H + k_H P_C \end{bmatrix} = \begin{bmatrix} 0 & k_C \frac{\varepsilon_H}{k_H} \\ k_H \frac{\varepsilon_C}{k_C} & 0 \end{bmatrix} \tag{A2}$$

with its eigenvalues equal to $\lambda = \pm\sqrt{\varepsilon_C \varepsilon_H}$. So, the oscillations of solutions around the mentioned critical points are given with the frequency $\omega = i\sqrt{\varepsilon_C \varepsilon_H}$.

Next, assuming that the C function is a constant of motion, it would be easier to use

$$K = e^{-C} = {P_C}^{-\varepsilon_H} \, {P_H}^{\varepsilon_C} \, e^{-k_H P_C - k_C P_H} \tag{A3}$$

Which is also constant for each closed curve (orbit). For higher K, the radius of the circle (orbit) decreases, and for

$$K_{max} = \left(\frac{\varepsilon_C}{e\, k_C}\right)^{\varepsilon_C} \left(\frac{-\varepsilon_H}{e\, k_H}\right)^{-\varepsilon_H} \tag{A4}$$

the solution is a single (stable) point only, as mentioned earlier.

Now, in the phase-space plot of P_C and P_H, one can calculate the function $K(P_C,P_H)$ given by Equation (A3). It reaches a maximum value for the mentioned point $(P_H, P_C) = \left(\frac{\varepsilon_C}{k_C}, -\frac{\varepsilon_H}{k_H}\right)$, which is equal to K_{max} (see Figure A1). However, when one takes the K values going through the diagonal axis (first for $P_C = P_H$ and second, perpendicular to the first one, for

$P_H + P_C = \frac{\varepsilon_C}{k_C} - \frac{\varepsilon_H}{k_H}$), one can find the Gaussian-like distribution of K, which is nonsymmetrical for higher values (see Figure A2).

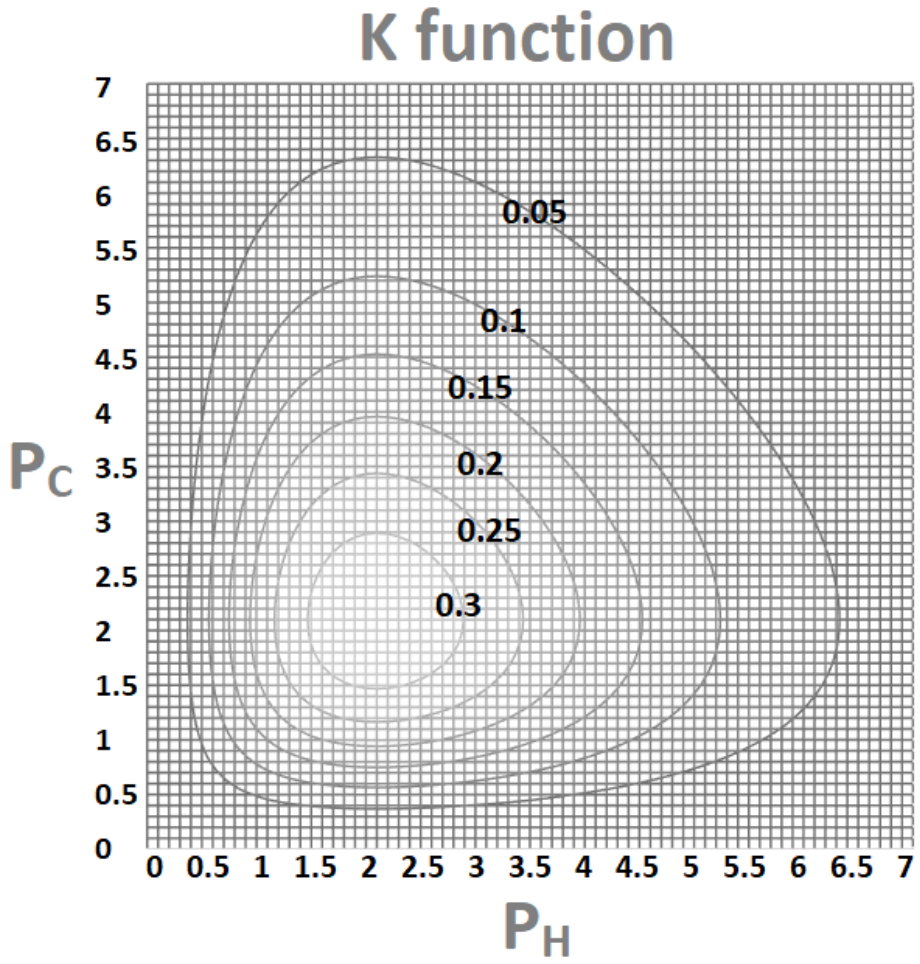


Figure A1. The K function in 3D perspective given by Equation (A3) in phase space of P_C and P_H for the same conditions as in Figure 2.

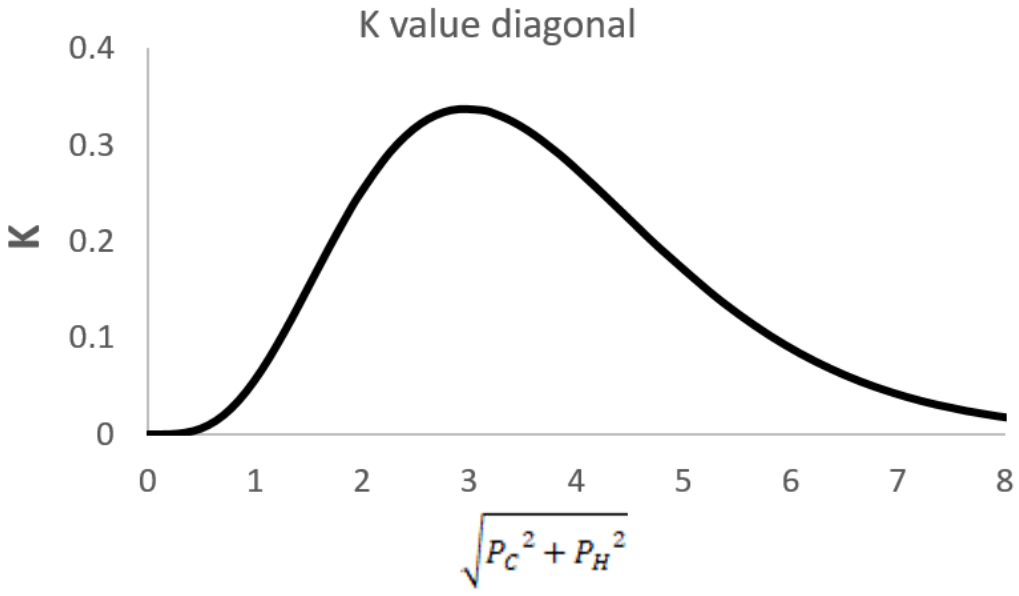


Figure A2. The K values from the diagonal axis ($P_C = P_H$) from Figure A1.

The conclusion of this deliberation is that the homeostatic balance state given by Equation (1) is preserved for the conditions around the K_{max}, which is the stable jostling between beneficial and detrimental factors. In the close vicinity around the K_{max}, the shape of the K distribution is quasisymmetrical (quasi-Gaussian). The slight disturbance of P_H or P_C creates the oscillations (with the frequency $\omega = i\sqrt{\varepsilon_C \varepsilon_H}$). However, the strong disturbance would break the symmetry in the K function and can create the situation for potential cancer transformation.

The K function, which joins both P_C and P_H, can be treated as a form of so-called radiosensitivity, which is usually described by quasi-Gaussian distributions with one nonsymmetrical long tail corresponding to the hyper-radiosensitivity [22,26]. However, the practical representation of the K function will not be discussed here.

References

1. Lu, S.; Wei, F.; Li, G. The evolution of the concept of stress and the framework of the stress system. *Cell Stress* **2021**, *5*, 76–85.
2. Calabrese, E. Hormesis: A revolution in toxicology, risk assessment and medicine. *EMBO Rep.* **2004**, *5* (Suppl. S1), S37–S40. [CrossRef]
3. Agathokleous, E.; Calabrese, E.J. A global environmental health perspective and optimisation of stress. *Sci. Total Environ.* **2020**, *704*, 135263.
4. Kareva, I.; Luddy, K.A.; O'Farrelly, C.; Gatenby, R.A.; Brown, J.S. Predator-Prey in Tumor-Immune Interactions: A Wrong Model or Just an Incomplete One? *Front. Immunol.* **2021**, *12*, 668221.
5. Sanders, C.L. *Radiation Hormesis and the Linear-No-Threshold Assumption*; Springer: Heidelberg, Germany; New York, NY, USA, 2010.
6. Monte, L. Characterisation of a nonlinear Leslie matrix model for predicting the dynamics of biological populations in polluted environments: Applications to radioecology. *Ecol. Model.* **2013**, *248*, 174–183.
7. Alonzo, F.; Vives i Batlle, J.; Hertel-Aas, T.; Bradshaw, C.; Vandenhove, H.; Garnier-Laplace, J. *Life History Traits, Radiosensitivity and Population Modeling: Methods to Extrapolate from Individual Endpoints to Population Dynamics*; Report no. D-No.5.2, STAR Project; European Commission: Brussels, Belgium, 2012.
8. Sazykina, T.G.; Kryshev, A.I. Simulation of population response to ionizing radiation in an ecosystem with a limiting resource—Model and analytical solutions. *J. Environ. Radioact.* **2016**, *151*, 50–57.
9. Saitanis, C.J.; Agathokleous, E. Stress response and population dynamics: Is Allee effect hormesis? *Sci.Total Environ.* **2019**, *682*, 623–628.
10. Sophia, R.J.J.; Diamond, S.L. A host-parasitoid interaction with Allee effects on the host. *Comput. Math. Appl.* **2007**, *53*, 89–103.
11. Monte, L. Predicting the effects of ionizing radiation on ecosystems by a generic model based on the Lotka-Volterra equations. *J. Environ. Radioact.* **2009**, *100*, 477–483.
12. Fornalski, K.W. Radiation and evolution: From Lotka-Volterra equation to balance equation. *Int. J. Low Radiat.* **2016**, *10*, 222–233.
13. Socol, Y.; Shaki, Y.Y.; Dobrzyński, L. Damped-oscillator model of adaptive response and its consequences. *Int. J. Low Radiat.* **2020**, *11*, 186–206.
14. Castillo, H.; Smith, G.B. Below-Background Ionizing Radiation as an Environmental Cue for Bacteria. *Front. Microbiol.* **2017**, *8*. [CrossRef]
15. Kawanishi, M.; Yagi, T. Exploration of biological phenomena of below-background natural radiation. *Nucleus* **2019**, *62*, 173–176.
16. Shi, Y.; Meng, X.; Zhang, J. Multi- and trans-generational effects of N-butylpyridium chloride on reproduction, lifespan, and pro/antioxidant status in Caenorhabditis elegans. *Sci. Total Environ.* **2021**, *778*, 146371. [PubMed]
17. Yue, W.; Mo, L.; Zhang, J. Reproductive toxicities of 1-ethyl-3-methylimidazolium bromide on Caenorhabditis elegans with oscillation between inhibition and stimulation over generations. *Sci. Total Environ.* **2021**, *765*, 144334.
18. Fornalski, K.W.; Dobrzyński, L. Modeling of single cell cancer transformation using phase transition theory: Application of the Avrami equation. *Radiat. Environ. Biophys.* **2022**, *61*, 169–175.
19. Baria, K.; Warren, C.; Roberts, S.A.; West, C.M.; Scott, D. Chromosomal radiosensitivity as a marker of predisposition to common cancers? *Br. J. Cancer* **2001**, *84*, 892–896.
20. Terzoudi, G.I.; Hatzi, V.I.; Barszczewska, K.; Manola, K.N.; Stavropoulou, C.; Angelakis, P.; Pantelias, G.E. G2-checkpoint abrogation in irradiated lymphocytes: A new cytogenetic approach to assess individual radiosensitivity and predisposition to cancer. *Int. J. Oncol.* **2009**, *35*, 1223–1230.
21. Pantelias, G.E.; Terzoudi, G.I. A standardized G2-assay for the prediction of individual radiosensitivity. *Radiother.Oncol.* **2011**, *101*, 28–34.
22. Fornalski, K.W. Radiation adaptive response and cancer: From the statistical physics point of view. *Phys. Rev. E* **2019**, *99*, 22139.
23. Fornalski, K.W.; Dobrzyński, L. Pooled Bayesian analysis of twenty-eight studies on radon induced lung cancers. *Health Phys.* **2011**, *101*, 265–273. [PubMed]
24. Davies, P.C.W.; Demetrius, L.; Tuszynski, J.A. Cancer as a dynamical phase transition. *Theor. Biol. Med. Model.* **2011**, *8*, 30.

25. Agathokleous, E. Environmental hormesis, a fundamental non-monotonic biological phenomenon with implications in ecotoxicology and environmental safety. *Ecotoxicol. Environ. Saf.* **2018**, *148*, 1042–1053.
26. Burnet, N.G.; Johansen, J.; Turesson, I.; Nyman, J.; Peacock, J.H. Describing patients' normal tissue reactions: Concerning the possibility of individualising radiotherapy dose prescriptions based on potential predictive assays of normal tissue radiosensitivity. *Int. J. Cancer* **1998**, *79*, 606.

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