Radiation adaptive response and cancer: From the statistical physics point of view

Krzysztof W. Fornalski*
National Centre for Nuclear Research (NCBJ), ulica A. Sołtana 7, 05-400 Otwock-Świerk, Poland
and Ex-Polon Laboratory, ulica Podleśna 81a, 05-552 Łazy, Poland

(Received 3 October 2018; revised manuscript received 2 February 2019; published 26 February 2019)

Elements of statistical physics formalism were applied to mutagenic and carcinogenic processes associated with cellular DNA; these are lesion (damage) creation, mutation creation, and cellular neoplastic (cancer) transformation. The probabilities of all state changes were strictly related to potential barrier heights between energetic states of DNA molecules. Barriers can be modified when radiation adaptive response mechanisms are applied, which are associated with a radiobiological quantity called radiosensitivity. It was discussed that radiosensitivity is determined by the cell's response to radiation resulting in three potential dose-response scenarios: linear, threshold, or hormetic. The type of dose-response is of critical importance in the development of radiation protection standards and individual radiation risk assessment. It is shown that the different scenarios describe different limits of the same underlying phenomena and the cell can respond in a linear, threshold, or hormetic way regarding its radiosensitivity. Finally, the dissipative adaptation mechanism is discussed in the context of proliferating cancer cells.

DOI: 10.1103/PhysRevE.99.022139

I. INTRODUCTION

The radiation adaptive response is a biophysical phenomenon which may appear in organisms irradiated by low doses of ionizing radiation. This effect stimulates natural mechanisms responsible for antioxidants, apoptosis, immune system, and DNA repair processes, reducing the risk of neoplastic transformation of irradiated cell(s) [1–4]. There are many ways in which the adaptive response can be presented. The easiest way for experimenters is when the adaptive response is associated with a small priming radiation dose that reduces a significant portion of the detrimental effects of a higher challenging dose; this is called the priming dose effect [5]. The radiation adaptive response may be a special case among the wider adaptation processes of every living organism [6].

The concept that the general dose-response relationship for low doses of ionizing radiation is potentially nonlinear has a crucial importance for existing radiation protection standards. In fact, one can observe many scientific discussions worldwide as to which model of radiation risk curve should be the appropriate one [4,7–9]:

(a) linear dependence (so-called linear no-threshold model, LNT, which assumes that all radiation implies some risk of cancer induction),

(b) threshold dependence (which assumes that radiation is dangerous only above some exact value),

(c) hormetic dependence (which assumes that low doses of ionizing radiation are beneficial for an organism's health).

The discussion of which model is better has been ongoing for years. However, the important point is that each model claims to have experimental data which support it; therefore, it is hard to clearly state which one is the only possible solution [10].

Each of the three dose-response models has its own supporters, experimental data, and many mathematical or biophysical concepts to explain it. For example, one can simulate an irradiated cell's behavior using a stochastic or analytic approach [11–14]. Also, a physical formalism from pure thermodynamics can be applied to predict organism response to irradiation [15]. However, the biggest challenge would be to create a more general model which can join all three completely different relationships into a single one.

A few years ago, England proposed a concept of life creation associated with "dissipative adaptation in driven self-assembly" [6,16,17]. There is a fundamental biophysical difference between living organisms and, for example, a group of carbon atoms. Living organisms deal much better with obtaining energy from the environment and releasing it as heat (dissipation). In England's theory, when a group of atoms is exposed to an external energy source, such as from the sun, ionizing radiation, or chemical reactions, and surrounded by a thermal bath (e.g., atmosphere or ocean), it will gradually be transformed to spread out more and more energy. Under certain conditions, matter will inevitably acquire some fundamental physical properties that are identical with life [18]. The essence of England's theory is the generalization of the second law of thermodynamics for particle systems with specific features. These systems are strongly dependent on an external energy source, such as from an electromagnetic wave, and release the heat to the surrounding thermal bath. Each living organism can be treated as such a system—and these systems change over time [6,16,17].

The overall system's behavior (namely, self-replication or aging) becomes more and more irreversible [16,17]. It can then be shown that the course of evolution is more likely, which assumes obtaining more energy from the environment

*krzysztof.fornalski@gmail.com

and dissipating it to the mentioned surrounding thermal bath. Self-replication, which is the process responsible for the evolution of life on Earth, is one of the mechanisms by which the system can increase the amount of energy dissipated over time. The most effective way to receive energy is to create its own copies due to the quick growth of young organisms and the highly energetic process of multiplication. Apart from self-replication, the second method of effective energy dissipation is the creation of more complex organizational structures. The living organism—in comparison with a nonliving group of atoms—is better at acquiring and releasing energy (e.g., solar). Under certain conditions, matter will be spontaneously organized to obtain minimal energy [6,16,17].

This paper examines the radiation adaptive response as applied to the lesion creation (namely, prompt postradiation damage of DNA molecule) and mutation creation (namely, stable unrepaired damage of DNA molecule) mechanisms. The study uses some elements of the statistical physics formalism applied by England and colleagues [6,16,17]. It is shown that this point of view sufficiently explains the physical basics of the radiation adaptive response mechanism and presents some additional elements to the biophysics of the process of cancer induction (neoplastic transformation).

II. STATISTICAL PHYSICS OF DNA LESION CREATION

Let us consider the quasi-isolated physical system (isolated during some period of time τ), where the surrounding matter (isolation) is transparent to the ionizing radiation and heat exchange only. It is an assumed approximation of the chromosome with DNA particles, namely, atoms of the DNA molecule. It is important to note that this purely physical model of the DNA treated all DNA atoms (namely, sugar, phosphate bonds, and purine and pyrimidine bases forming a helical structure) as single physical particles. In the first stage, those particles can be found in two simplified physical states: x_i, which represents the nondamaged DNA particle, and x_j, which represents the particle in the lesion state. The corresponding energies are E_i and E_j, respectively, where $E_i \geqslant E_j$. Both states can be degenerated and N_i particles are expected in x_i, and N_j in the x_j state, where $N_j \ll N_i$ (DNA lesion is assumed to be a rare event). One can additionally assume that the natural potential barrier $E_R > \max(E_i, E_j)$ exists between both states, which prevents DNA from forming spontaneous lesions.[1]

In the special case where $E_i = E_j$, the situation is symmetrical (equilibrium): the probability of a particle's spontaneous state change can be presented using the Boltzmann distribution [6,19],

$$r_{i\to j} = r^0_{ij}\, e^{-\beta(E_{R,ij}-E_i)}, \tag{1}$$

where $r^0_{ij} = r^0_{ji}$ because $E_{R,ij} = E_{R,ji}$ and $E_i = E_j$. The consequence of the presented symmetry is that the probability of the particle found in its ith state can be simply presented as

$$p(x_i) \sim e^{-\beta E_i}, \tag{2}$$

where the system's temperature $T = (k_B\,\beta)^{-1}$. It may be concluded with a balance equation,

$$\frac{p(x_i)}{p(x_j)} = \frac{r_{j\to i}}{r_{i\to j}}, \tag{3}$$

which is presented in a symmetrical case [see Appendix A for the proof of Eq. (3)].

England [17] and Perunov *et al.* [6] concluded that the equilibrium state can create the driving force and the DNA particle from the x_i state can make a spontaneous jump to the state x_j because of thermal fluctuations creating sinusoidal oscillations of $E(t)$ and $E_R(t)$. This statistical irreversibility implies that the energy of the oscillated side (e.g., E_j) will be lower at the moment of the jump, and that the positive value of heat can be dissipated into the surrounding reservoir (thermal bath) (see Appendix B for detailed calculations). This makes the connection between heat dissipation and the irreversibility of DNA particle maintenance and its repair processes.

Regardless of the oscillations mentioned above, the existence of the symmetry and the balance represents the situation where lesion creation and repair mechanisms in the DNA have the same probability. However, in the general situation, it is not the case—usually it is much easier to damage DNA than to repair it ($r_{i\to j} > r_{j\to i}$), which is a consequence of the second law of thermodynamics. Thus, in that more complicated situation, $E_i > E_j$ and the symmetry is broken ($r^0_{ij} \neq r^0_{ji}$); see Fig. 1.

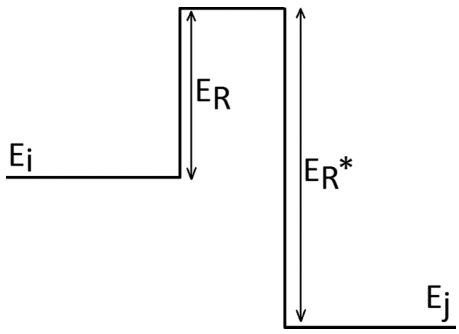

FIG. 1. Two possible states of particles in the DNA chain: nondamaged (E_i) and damaged (E_j), so-called lesion state. The potential barrier is represented by E_R.

All of the parameters presented above can be described as

$$E_i = n\,E_j, \text{ where } n > 1 \text{ and } n \in \mathbf{R},$$

$$E_R = h\,E_i = n\,h\,E_j, \text{ where } h > 0 \text{ and } h \in \mathbf{R},$$

$$E^*_R = E_R + E_i - E_j = n\,h\,E_j + n\,E_j - E_j = E_j(n\,h + n - 1) \equiv E_j\theta,$$

which are schematically presented in Fig. 1. Important observation should be given to the parameter $\theta = n\,h + n - 1$, which represents the general correlation of potential barrier height with both energy levels.

[1]Every one of the 10 000 or so genes in a human DNA molecule has a spontaneous mutation rate, different for each gene. The effect of ionizing radiation can change those rates.

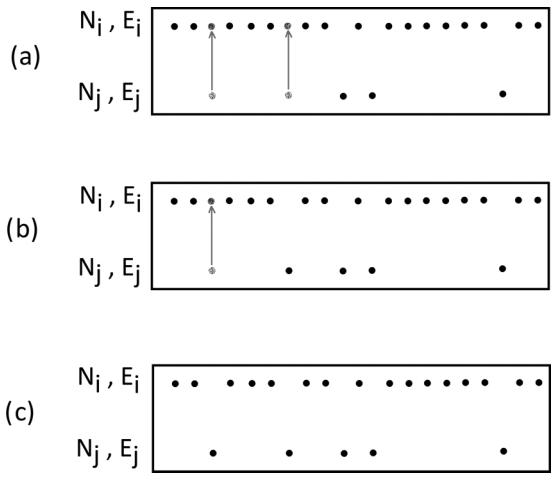

FIG. 2. The simplified model of the DNA and three possible scenarios of DNA exemplary lesion repair: (a) beneficial (hormetic) effect, where two lesions were repaired (two gray arrows) because of the good efficiency of the repair enzymes, (b) neutral effect, where a single lesion was repaired (gray arrow), and (c) detrimental effect, where no lesions were repaired because of the poor efficiency of the repair enzymes.

The situation presented above seems to be natural: the DNA molecule uses physical forces and the organism's repair mechanisms which keep all DNA particles together. This mechanism fails, e.g., when the organism dies. In that situation, the stochastic drift makes DNA unstable and, finally, its structure disappears. It can be deduced afterwards that the creation of life is strictly connected with the second law of thermodynamics [6,16,17].

Let us imagine that a single DNA lesion appeared in the chromosome ($N_i \to N_i - 1$ and $N_j \to N_j + 1$) because of a natural or artificial reason, such as ionizing radiation. After some period of time, special repair enzymes (naturally occurring in all living cells) try to repair this single particular DNA lesion. Three scenarios can be considered afterward: (a) the beneficial (hormetic) effect, where two lesions were repaired (this new one and some old one) because of the good efficiency of repair enzymes, (b) the neutral effect, where this single lesion was repaired, and (c) the detrimental effect, where no lesions were repaired because of poor efficiency of the repair enzymes; see Fig. 2. Other scenarios (such as the repair of three lesions in one step) are assumed to be very rare and thus they can be omitted.

One has to note that the three presented scenarios are well known [10] (see Sec. I). The situation when a beneficial effect appears corresponds to the radiation hormesis, where the low doses of ionizing radiation can stimulate organism(s) for better DNA lesion repair and, finally, cancer risk reduction [20]. The neutral effect [Fig. 2(b)] corresponds to the threshold model, where repair mechanisms work quite well and the negative effect can appear only when some certain dose is exceeded. The last scenario, namely, the detrimental effect [Fig. 2(c)], can be related to the linear no-threshold (LNT) model where no repair mechanisms are assumed during some period of time, τ, and every dose is related to the cancer risk. The LNT model is a base for the international radiation protection standards [10].

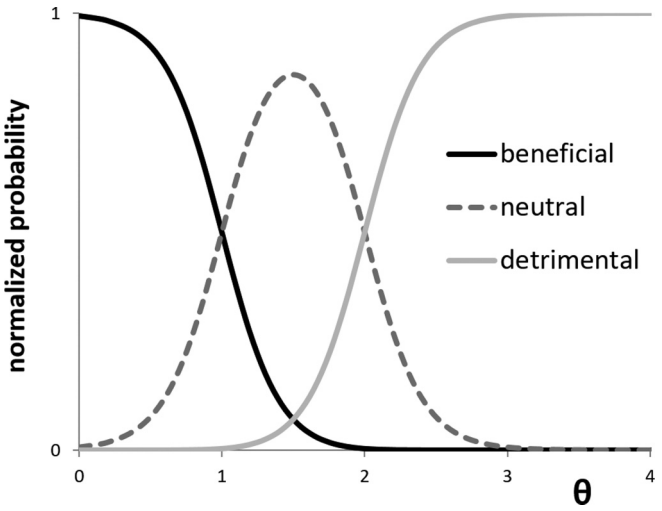

FIG. 3. The normalized probabilities from Eqs. (4)–(6) present that for $\theta \in (0, 1)$ the beneficial scenario dominates, for $\theta \in (1, 2)$ the neutral scenario wins, and for $\theta > 2$ the detrimental scenario prevails; all scenario mechanisms are presented in Fig. 2. This proves that the type of cell's response to radiation depends on the individual radiosensitivity (see, also, Fig. 6).

From the statistical physics point of view, in the first scenario [beneficial effect; Fig. 2(a)] the probability of two lesions repair equals

$$p_{2j\to 2i} = p_0\, e^{-2\beta(E_R^* - E_j)} = p_0\, e^{-2\beta E_j(\theta-1)}; \tag{4}$$

and analogically for the neutral effect [Fig. 2(b)],

$$p_{j\to i} = p_0\, e^{-\beta E_j(\theta-1)}, \tag{5}$$

and for the detrimental effect [Fig. 2(c)],

$$p_{j\to j} = p_0\, e^{-\beta E_j}. \tag{6}$$

In the next step, one can compare each probability or just calculate the relative values of them as presented below,

$$\begin{aligned} \frac{p_{j\to i}}{p_{j\to j}} &= e^{-\beta E_j(\theta-2)}, \\ \frac{p_{j\to i}}{p_{2j\to 2i}} &= e^{\beta E_j(\theta-1)}, \\ \frac{p_{2j\to 2i}}{p_{j\to j}} &= e^{-2\beta E_j(\theta-\frac{3}{2})}, \end{aligned} \tag{7}$$

and conclude that for $\theta \in (0, 1)$ the beneficial scenario dominates, for $\theta \in (1, 2)$ the neutral scenario wins, and for $\theta > 2$ the detrimental scenario prevails. This result can be more easily observed for normalized probabilities, i.e., when each probability would be divided by the summarized probability; see Fig. 3. The next conclusion is that the θ parameter (which is a function of n and h parameters) is strictly related to the cell's susceptibility to repair process(es). In the special case of radiation as a driving field of that system, the θ parameter can be proportional to the radiosensitivity—the radiobiological quantity which describes the individual (cell or organism) susceptibility to ionizing radiation influence. The relationship between the cell's beneficial or detrimental response and its radiosensitivity is still under much scientific investigation; however, some experimental evidence shows that

radio-sensitive organisms exhibit a detrimental response, while radio-resistant ones exhibit a beneficial response [21–23].

Those findings are in agreement with Fig. 3 and θ as the parameter related to radiosensitivity. Additionally, the typical radiosensitivity distribution among individuals is described by a nonsymmetrical quasi-Gaussian curve, where the long and flat tail[2] is located on the high radio-sensitive side [24]. This is also consistent with Fig. 3, where for large and very large values of the θ parameter ($\theta > 3$), only the detrimental response dominates.

Regardless of the radiosensitivity, the θ parameter is strictly connected with the height of the potential barrier E_R and any manipulation of θ means the manipulation of the internal cell's protection mechanisms. In general, the mechanism responsible for DNA maintenance depends on many parameters, but in the scenario described above one can narrow them to radiosensitivity, time, and radiation dose only. In particular, the biophysical phenomena called radiation adaptive response can be responsible for the potential barrier(s) change with time and dose [11–13].

III. RADIATION ADAPTIVE RESPONSE MECHANISM

The dose- and time-related probability function for the radiation adaptive response effect appearance was proposed a few years ago [11–13],

$$p_{AR} = \gamma D^2 t^2 \, e^{-\alpha_1 D - \alpha_2 t}, \tag{8}$$

where D is the single-pulsed absorbed dose received t time ago, and γ, α_1, α_2 are calibration constants. In a more general situation, Eq. (8) can be written in its continuous form related to the dose rate ($\dot{D}$) and the cell's age (T) [11,12],

$$p_{AR} = \gamma \int_{t=0}^{T} \dot{D}^{\mu} \, (T-t)^{\delta} \, e^{-\alpha_1 \dot{D} - \alpha_2 (T-t)} \, dt. \tag{9}$$

The probability function of the adaptive response given by Eq. (8) [or (9)] can reduce the value of E_R by $E_{AR} = c\, E_R\, p_{AR}$. Thus, the potential barrier from Fig. 1 can achieve new values E'_R and E'^{*}_R which are related to the old ones as

$$\begin{aligned} E'_R &= E_R \mp E_{AR} = (n\,h \mp n\,h\,c\,p_{AR})\, E_j, \\ E'^{*}_R &= E^{*}_R \mp E_{AR} = (\theta \mp n\,h\,c\,p_{AR})\, E_j, \end{aligned} \tag{10}$$

where c^{-1} denotes the maximal possible value of the p_{AR} distribution, and then $cp_{AR} \in \langle 0, 1\rangle$, which concludes that the strongest adaptive response mechanism can reduce E'_R to zero when $x_j \to x_i$, and strengthen it ($2E_R$) in the opposite direction ($x_i \to x_j$). Additionally, by applying Eq. (10) to the way of thinking from the previous section, one can write $\theta' = \theta - n\,h\,c\,p_{AR}$.

Analyzing all new probabilities analogical to Eqs. (4)–(6), where $\theta \to \theta'$, one can observe that their absolute values increase with time and reach a maximum as the distribution of p_{AR}. After a very long time, the situation becomes the same as described in the previous section because $\lim_{t\to\infty} p_{AR} = 0$.

[2]One has to note that this long tail is connected with the hyper radiosensitivity, which is a quite rare effect [34].

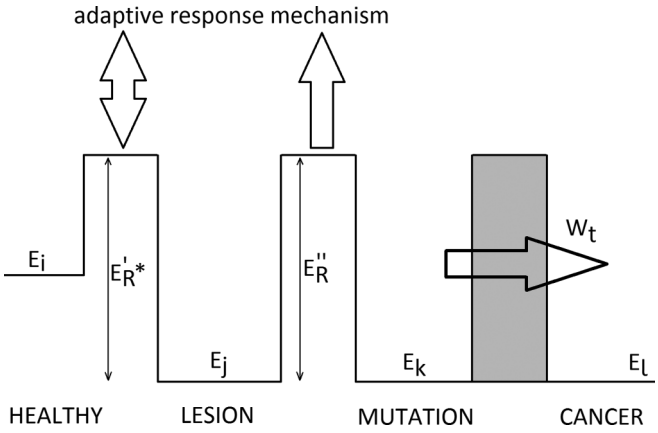

FIG. 4. The general scheme of the cancer induction process assuming that the E_i level corresponds to the energy of a nondamaged particle in DNA (denoted as the x_i state), E_j to its lesion state (x_j) energy, E_k to mutation state (x_k) energy, and E_l to cancer state (x_l) energy. The additional work W_t is related to cancer transformation of the mutated cell. The adaptive response mechanism, here represented by the vertical arrows, works as follows: it lowers the first potential barrier when $x_j \to x_i$ (repair of one lesion) and increases this barrier in the opposite direction ($x_i \to x_j$, namely, lesion creation); additionally, it increases the second barrier for $x_j \to x_k$ (stable mutation creation). It is assumed that the adaptive response mechanism has no influence to the last stage of cancer induction, namely, $x_k \to x_l$.

However, the relationship presented in Fig. 3 does not change significantly, which means that the radiation adaptive response mechanism temporarily helps in the DNA repairing process.

The last conclusion can be deduced also from the fact that analogically to the previous section, the beneficial and neutral responses have the same probability ($p'_{2j\to 2i} = p'_{j\to i}$) for $\theta' = 1$, and similarly for the neutral and detrimental probabilities ($p'_{j\to i} = p'_{j\to j}$) for $\theta' = 2$.

The adaptive response mechanism is also presented in the next step of the carcinogenesis process, namely, the mutation induction. The mutation of DNA results from the unrepaired or the improperly repaired lesion, as well as due to errors during DNA replication. In that situation, the particle transverses to the new state x_k, where, however, it does not change its energy ($E_j = E_k$). Thanks to that, Eqs. (1)–(3) can be applied here with E''_R related to the adaptive response as well. The adaptive response, however, increases the potential barrier to protect the organism from mutation occurrence (Fig. 4) [1–3]. Thus, the probability of mutation creation from a single lesion can be described as

$$p_{j\to k} = p_0 \, e^{-\beta E''_R}. \tag{11}$$

One has to note, however, that up to the recent radiobiological data, the opposite situation is forbidden (no mutation repair exists) [25,26], so the path $j \to k$ is strictly irreversible ($p_{k\to j} \approx 0$). From the purely physical point of view, however, the inverse probability cannot equal zero but is very small, which is connected with additional biological work (B) protecting mutations from repair processes, and therefore $p_{k\to j} \sim \exp[-\beta(E''_R + B)]$. The analogical process can be found in many statistical physics textbooks: the probability that the lake would be frozen in the middle of a hot summer is extremely low, but higher than zero.

IV. CANCER TRANSFORMATION

The mutated cell can undergo neoplastic transformation and turn into a cancerous one when several single mutations accumulate in its DNA [13,25]. This process is, however, quite different to those described earlier (namely, energetic changes of the particle) and it is hard to say about, e.g., the next state of the single particle, x_l. Therefore, the energy of particles in the cancerous state remains the same as in the mutation state ($E_k = E_l$) because the cancer transformation means that the whole cell (meant as a physical complex system) undergoes this transformation without physical change of the DNA molecule. The transformation, however, starts from the exact number of oncogenic mutations in DNA, which is equal to the number of particles in the mutation state, N_k. Thus, it is not possible to calculate the probability of cancer (neoplastic) transformation for a single particle only ($p_{k\to l}$) since the whole cell would undergo transformation (even if other DNA particles, $N_i + N_j$, are in different states, such as nondamaged ones). From the purely physical modeling point of view, one can focus on all mutated ones only (N_k) as initiators of the process. Therefore, the probability that N_k mutations are enough for the initiation of the neoplastic transformation process can be given by a sigmoidal relationship based on biological data [27–29]. This relationship can be strictly correlated with the appropriate cancer creation model which can be based on the phase transition theory or catastrophe theory [14]. As mentioned in the cited studies [13,14], this function is therefore well described by the sigmoidal Avrami-Mehl equation with critical index ξ,

$$p_A(N_k) \sim 1 - e^{-\text{const } N_k^{\xi}}. \tag{12}$$

However, Eq. (12) describes the probability that N_k mutations allow the system (cell) for cancer transformation, but the immunological defense (represented by potential barrier E_R''') together with additional transformation work W_t (Fig. 4) also play an important role. The W_t parameter can be strictly correlated with additional mechanisms and/or detrimental agents responsible for the increase in the probability of cancer transformation. Thus, in the described situation of the single cell DNA only, W_t can be treated as an external work which changes the physical phase of the whole system (cell). Finally, the cancer transformation of the whole mutated cell can be described by the probability of

$$p_t \sim p_A(N_k)\, e^{-\beta(E_R''' - W_t)}. \tag{13}$$

The extension of the second law of thermodynamics proposed by Crooks [30] combined time-reversal symmetry and energy conservation. Thanks to that, the relative probabilities of different paths can be presented as

$$\frac{p_{i\to j\to k\to l}}{p_{l\to k\to j\to i}} = e^{\beta\, \Delta Q(i\to j\to k\to l)}, \tag{14}$$

assuming that the trajectory $i \to j \to k \to l$ is more likely than the opposite one. This extension of the second law was successfully applied to the theory of self-replication [16]. The basis for that is the statement that statistical irreversibility of the process (here, the cancer creation) "implies thermodynamic constraints for the fueling of systems that make copies of themselves" [17]. In this special case, the cancer cells have a great ability of replication, which follows England's theory.

The numerator from the left-hand side of Eq. (14) can be presented in a more general way [6] as $\pi_\tau[\boldsymbol{x}(t)|\boldsymbol{x}(0);\lambda(t)]$—the probability density for microtrajectories, "that expresses how likely one would be to observe the system progressing through a given series of subsequent arrangements $\boldsymbol{x}(t)$ over time τ" [6], where $\lambda(t)$ denotes to some driving field. In the case presented above, that field can correspond to the general carcinogenic mechanism.

Analyzing Eq. (14), it is worth noting that it strictly relates to the θ parameter[3] —the result of the likelihood ratio is monotonically increasing with the increase of θ. It means that the probability of cancer creation, and therefore the heat dissipation, increases with θ. This is connected with the detrimental response preference for high values of θ (Fig. 3), which seems to be quite natural.

When the radiation adaptive response mechanism is taken into consideration, the results are substantially different: there is no consistent dependence on θ, but both parameters creating θ, namely, n and h, need to be analyzed separately—Eq. (14) increases when n increases, and it decreases when h increases. This is a result of the adaptive response mechanism which drives both potential barriers (Fig. 4) and moves them up or down regarding the direction of the particle jump. Nevertheless, the main conclusion is that the adaptive response is a complex and hard to predict mechanism which has a great but still not fully known role in cancer induction.

V. DISCUSSION

This paper describes the physical basics for lesion and mutation creation in a living cell's DNA, which is the initial step for cancer (neoplastic) transformation. This process can be reduced by the radiation adaptive response mechanism due to enhancement of the cellular repair processes. These mechanism(s) may be associated with individual radiosensitivity (or radioresistance).

The role of the adaptive response has been studied worldwide among radiation protection experts. The linear no-threshold (LNT) model of radiogenic cancer creation is used by many in radiation protection, especially by regulators. This model, however, does not take into consideration any mechanism which break the linearity, and phenomena such as adaptive response are simply omitted there. Therefore, the LNT has been strongly criticized by many physicians, radiobiologists, toxicologists, and radiation biophysicists [10], so two more models need to be discussed: hormetic (occurs where some positive influence of low doses of ionizing radiation is observed) and threshold (occurs where no dose response is observed until a certain dose level is achieved). The adaptive response was taken by these into consideration.

If the strength of the adaptive response is dependent on individual radiosensitivity, then the general response to radiation is strictly dependent on this parameter. Thus, the organism can respond in a linear, threshold, or hormetic

[3]But this special case relationship is independent of the h change, and all changes of θ are connected with changes of n only.

way with respect to the actual value of radiosensitivity—or, generally, the effectiveness of DNA repair represented here by the θ parameter (Fig. 3). Finally, radio-sensitive individuals can respond in a more linear (detrimental) way, while radio-resistant individuals can respond in a more hormetic (beneficial) way because repair processes (enhanced by the adaptive response) are much stronger there. Assuming that individual radiosensitivity exhibits a Gaussian distribution [24], one can assume that the majority of the population will respond with a threshold, while the remaining population (located on both tails) will respond with hormesis or a linear response. Similar relationships have been observed in other experimental findings [21,22]. Additionally, some theoretical models found that this finding seems to be natural from the evolutionary point of view [31].

The individual cell's radiosensitivity can be experimentally measured in many different ways using different definitions of that parameter [26]. However, the biophysical meaning of the proposed θ parameter is strictly connected with potential barriers and the ability of the cell's mechanisms to successfully prevent lesions and mutations. In particular, the first barrier ($E_R^{'*}$) is responsible mostly for the strength of molecular forces within the DNA chain, while the second barrier ($E_R^{''}$) corresponds to the repair mechanisms which protect DNA against the creation of stable mutations. Both quantities can be experimentally measured and therefore related to the definition of the θ parameter. This definition of radiosensitivity seems to be more general and has potentially higher practical applications. Of note, French scientists tried to mathematically formalize radiosensitivity factor(s), but their correlation with dose-response curves was not always consistent [23,32,33]. Anyway, many additional scientific investigations on radiosensitivity influence on the cancer risk assessment are of crucial importance. This is because the presented approach based on thermodynamics fundamentals joins all three dose-response models (which were completely different and opposed until now) into a single one using the radiosensitivity parameter as the input information. This general approach can potentially finalize the discussion between LNT and hormesis supporters [7–9] because it shows that the different models describe different limits of the same underlying phenomena.

A good example of how this approach works is presented in Fig. 5, which contains some exemplary results of the modeling of irradiated cell behavior [13]; this is the dose-response relationship, namely, the non-normalized probability of the cell's neoplastic transformation related to the absorbed dose (in arbitrary units). The typical shape of that curve (for typical radiosensitivity) is sigmoidal [13]: the curve increases very slightly, becoming quasilinear for medium doses, and saturates at high doses because of the cell's immediate death (which is not presented in Fig. 5 because it is narrowed to low and medium doses only). This is usually called the threshold model. The LNT model is represented by a straight line (also saturated for high doses), while the hormetic curve is represented by the sigmoid with the local minimum for low doses. The humpbacked curve represents hyper radiosensitivity—the cellular effect of very large radiosensitivity which is quite rare but important from the radiotherapy point of view [34]. Each scenario seen in Fig. 5 was presented using the same cell

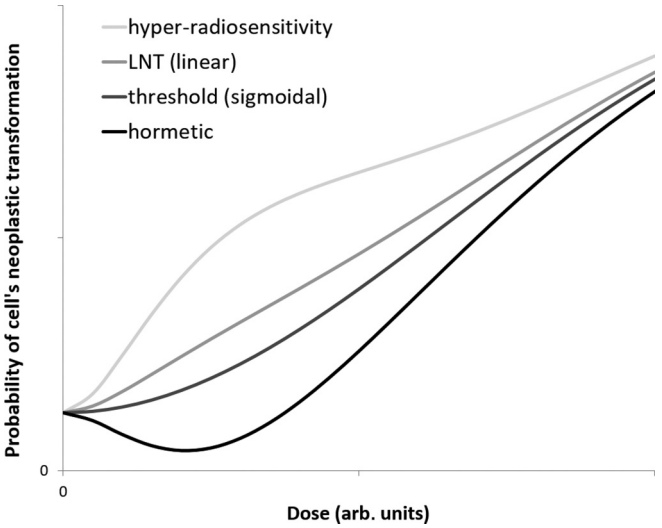

FIG. 5. The non-normalized probability of a cell's neoplastic transformation (cancer risk) as related to the absorbed dose (in arb. units). Four curves represent four different results of the modeling of single cell irradiation [13]; the curves represent (from the top to bottom): hyper-radiosensitivity model, linear (LNT) model, threshold (sigmoidal) model, and hormetic model. Each model differs from the others by the strength of the adaptive response only. One has to note that all curves start from nonzero risk point due to nonradiation sources of the total cancer risk. Additionally, the slightly nonlinear shape of the LNT model for the lowest doses is an artifact from numerical calculations. This figure is based on Ref. [35].

model [13], but with different strengths of adaptive response, which are dependent on individual radiosensitivity [35]. This is a good theoretical example of how the proposed approach

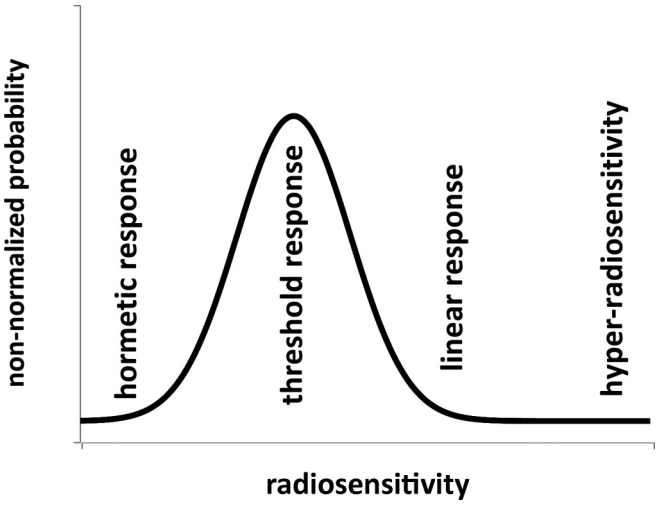

FIG. 6. The simplified scheme of the non-normalized probability distribution of individual radiosensitivity based on three mechanisms from Fig. 3, experimental findings on radiosensitivity [24], and earlier theoretical models [31]. Four different cell's responses, namely, hormetic, threshold, linear, and hyper radiosensitivity, are expressed in Fig. 5. In particular, the threshold response is characteristic for individuals with the most frequent (standard) value of radiosensitivity.

influences the probability of neoplastic transformation, which is related to cancer risk.

Cancer incidence as a result of exposure to ionizing radiation is often the most important and frequently discussed topic in the literature, being presented using all possible models: the linear, threshold, and hormetic dose responses. The process of carcinogenesis exhibits a strong irreversibility, which can be explained based on the principles of thermodynamics. Application of the second law of thermodynamics proves, however, that this process needs a lot of energy, which is then dissipated into the environment. More than that, cancer cells replicate very fast and on a large scale.

The cell which has low susceptibility to repair processes (high radiosensitivity) responds to radiation mostly in a detrimental way [23]. The higher the radiosensitivity, the more probable the response is a detrimental one. This stronger detrimental response causes a higher probability of cancer (neoplastic) transformation and higher heat dissipation to the surrounding bath (environment) and to the higher entropy production. This is consistent with the conclusions of Crooks [30] and England [17] about the second law of thermodynamics because "accelerating a process of assembly should cost more in dissipated work" [17].

ACKNOWLEDGMENTS

The author wishes to thank Prof. Charles L. Sanders for valuable remarks on biology and all linguistic corrections. Additional thanks to Gary L. Hoe, Prof. Ludwik Dobrzyński (National Centre for Nuclear Research, Poland), and Prof. Agata Fronczak (Faculty of Physics, Warsaw University of Technology, Poland) for all additional remarks and comments.

APPENDIX A

The proof of Eq. (3) for the symmetrical case ($E_{R,ij} = E_{R,ji}$, because $E_i = E_j$) is

$$r_{i\to j} \sim \frac{e^{-\beta E_{R,ij}}}{e^{-\beta E_i}} = e^{-\beta E_{R,ij}} \times e^{\beta E_i} => \frac{r_{i\to j}}{r_{j\to i}} = \frac{e^{-\beta E_{R,ij}} \times e^{\beta E_i}}{e^{-\beta E_{R,ji}} \times e^{\beta E_j}} = \frac{e^{-\beta E_j}}{e^{-\beta E_i}} = \frac{p(x_j)}{p(x_i)}.$$

APPENDIX B

Based on the calculations presented by Perunov *et al.* [6], one can apply them to the situation presented in this paper. Let us imagine the situation where the potential barrier and the energy of the x_j state oscillate with the amplitude $0.5E_R$:

$$E_R(t) = E_R - \tfrac{1}{2}E_R\cos(\omega t),$$
$$E_j(t) = -\tfrac{1}{2}E_R\cos(\omega t), \tag{B1}$$

where $\omega \gg {}^1/_\tau \gg r$ and it was assumed that $E_i(t) = \text{const}$ and $E_j = 0$ in the basic state. Thus, the probability of particle jump is given by

$$r_{i\to j}(t) = r_{ij}^0\, e^{-\beta[E_R - \frac{1}{2}E_R\cos(\omega t)]}. \tag{B2}$$

One can note that for $\beta E_R \gg 1$, the barrier becomes smaller and the probability $r_{i\to j}(t)$ increases. The maximal value of the mentioned probability is reached for $\cos(\omega t) = 1$, where

$$r_{i\to j}^{\max} = r_{ij}^0\, e^{-\frac{1}{2}\beta E_R}. \tag{B3}$$

The relation with the probability where there are no oscillations,

$$\frac{r_{i\to j}^{\max}}{r_{i\to j}^{\text{no osc.}}} = e^{\frac{1}{2}\beta E_R} > 1, \tag{B4}$$

which results in the particle drift from x_i to x_j when oscillations exist. Additionally, when one calculates the average probability

$$\overline{r_{i\to j}} = \frac{\omega}{2\pi}\int_0^{\frac{2\pi}{\omega}} r_{i\to j}(t)dt = r_{ij}^0\, e^{-\beta E_R}\, I_0\left(\frac{1}{2}\beta E_R\right), \tag{B5}$$

where I_0 corresponds to the Bessel function, it can be clearly seen that Eq. (B5) is higher than the probability of no oscillations,

$$r_{i\to j}^{\text{no osc.}} = r_{ij}^0\, e^{-\beta E_R} < \overline{r_{i\to j}}, \tag{B6}$$

which supports the previous conclusion. Just for formal reasons, let us check the minimal value of the mentioned probability [$\cos(\omega t) = -1$] to find that

$$\frac{r_{i\to j}^{\min}}{r_{i\to j}^{\text{no osc.}}} = \frac{e^{-\frac{3}{2}\beta E_R}}{e^{-\beta E_R}} = e^{-\frac{1}{2}\beta E_R} < 1, \tag{B7}$$

which is obvious.

To conclude, the presented situation described that the particle can drift to the E_j state, which is connected with positive entropy production to the surrounding environment,

$$\Delta S = \beta\Delta Q_{i\to j} = \tfrac{1}{2}\beta E_R. \tag{B8}$$

[1] S. Wolf, The adaptive response in radiobiology: Evolving insights and implications, Environ. Health Perspect. **106**(Suppl. 1), 277 (1998).

[2] L. E. Feinendegen, The role of adaptive responses following exposure to ionizing radiation, Human Exper. Toxicol. **18**, 426 (1999).

[3] R. E. J. Mitchel, The dose window for radiation-induced protective adaptive responses, Dose Resp. **8**, 192 (2010).

[4] Ch. L. Sanders, *Radiobiology and Radiation Hormesis* (Springer, New York, 2017).

[5] M. T. B. Toossi, S. A. Dehkordi, M. Sankian, H. Azimian, M. N. Amiri, and S. Khademi, Effects of adaptive response

induced by low-dose ionizing radiation on immune system in spleen lymphocytes of BALB/C mice, Eur. J. Med. Phys. **32**, 244 (2016).

[6] N. Perunov, R. A. Marsland, and J. L. England, Statistical Physics of Adaptation, Phys. Rev. X **6**, 021036 (2016).

[7] K. L. Mossman, The LNT Debate in Radiation Protection: Science vs. Policy, Dose Resp. **10**, 190 (2012).

[8] W. Weber and P. Zanzonico, The controversial linear no-threshold model, J. Nuclear Med. **58**, 7 (2017).

[9] J. A. Siegel and B. Sacks, Eliminating use of the linear no-threshold assumption in medical imaging, J. Nuclear Med. **58**, 1014 (2017).

[10] Ch. L. Sanders, *Radiation Hormesis and the Linear-No-Threshold Assumption* (Springer, New York, 2010).

[11] K. W. Fornalski, Mechanistic model of the cells irradiation using the stochastic biophysical input, Int. J. Low Radiat. **9**, 370 (2014).

[12] K. W. Fornalski, L. Dobrzyński, and J. M. Reszczyńska, Modelling of the Radiation Carcinogenesis: The Analytic and Stochastic Approaches, *Extended Abstracts Fall 2015*, Trends in Mathematics series, Research Perspectives CRM Barcelona Vol. 7 (Springer, New York, 2017), pp. 95–101.

[13] L. Dobrzyński, K. W. Fornalski, Y. Socol, and J. M. Reszczyńska, Modeling of irradiated cell transformation: dose- and time-dependent effects, Radiat. Research **186**, 396 (2016).

[14] L. Dobrzyński, K. W. Fornalski, J. Reszczyńska, and M. K. Janiak, Modelling cell reactions to ionizing radiation–from a lesion to a cancer, arXiv:1902.06172.

[15] Y. P. Chukova, Radiation hormesis in the light of the laws of quantum thermodynamics, Presentation at RAD 2018 Conference, available in: http://rad2018.rad-conference.org.

[16] J. L. England, Statistical physics of self-replication, J. Chem. Phys. **139**, 121923 (2013).

[17] J. L. England, Dissipative adaptation in driven self-assembly, Nat. Nanotechnol. **10**, 919 (2015).

[18] N. Wolchover, A New Physics Theory of Life, Quanta Magazine, January 22, 2014, https://www.quantamagazine.org/a-new-thermodynamics-theory-of-the-origin-of-life-20140122/#.

[19] C. W. Gardiner, *Handbook of Stochastic Methods*, 3rd ed. (Springer, New York, 2003).

[20] Y. Shibamoto and H. Nakamura, Overview of biological, epidemiological, and clinical evidence of radiation hormesis, Int. J. Mol. Sci. **19**, 2387 (2018).

[21] D. Weixia, F. Yinghua, C. Deqing, and C. Jianping, Study on radio-sensitivity and adaptive response of AT cells by using chromosome aberrations. Chin. J. Radiol. Med. Protect. **25**, 225 (2005).

[22] E. Khandogina and G. Mutovin, Adaptive response and radiosensitivity at low doses, Radioprotection **43**, 5 (2008).

[23] M. Bourguignon, N. Foray, C. Colin, and E. Pauwels, Individual radiosensitivity: A key issue in radiation protection, Int. J. Low Radiat. **9**, 52 (2013).

[24] NG Burnet, J Johansen, I Turesson, J Nyman, and J. H. Peacock, 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 (Pred. Oncol.) **79**, 606 (1998).

[25] *Summary of low-dose radiation effects on health*, UNSCEAR Report 2010, Annex F, available in: http://www.unscear.org/unscear/en/publications/2010.html.

[26] E. J. Hall and A. J. Giaccia, *Radiobiology for the Radiologist*, 7th ed. (Lippincott Williams & Wilkins, Philadelphia, PA, 2012).

[27] M. J. Renan, How many mutations are required for tumourigenesis? Implications from human cancer data, Mol. Carcinogenesis **7**, 139 (1993).

[28] W. C. Hahn and R. A. Weinberg, Rules for making human tumour cells, N. Engl. J. Med. **347**, 1593 (2002).

[29] B. Vogelstein, N. Papadopoulos, V. E. Velculescu, S. Zhou, L. A. Diaz Jr., and K. W. Kinzler, Cancer genome landscapes, Science **339**, 1546, (2013)

[30] G. E. Crooks, Entropy production fluctuation theorem and the nonequilibrium work relation for free energy differences, Phys. Rev. E **60**, 2721 (1999).

[31] K. W. Fornalski, Radiation and evolution: From Lotka-Volterra equation to balance equation, Int. J. Low Radiat. **10**, 222 (2016).

[32] L. Bodgi, A. Granzotto, C. Devic, G. Vogin, A. Lesne, J. F. Bottollier-Depois, J. M. Victor, M. Maalouf, G. Fares, and N. A Foray, Single formula to describe radiation-induced protein relocalization: Towards a mathematical definition of individual radio-sensitivity, J. Theor. Biol. **333**, 135 (2013).

[33] C. Devic, M. L. Ferlazzo, and N. Foray, Influence of individual radio-sensitivity on the adaptive response phenomenon: Toward a mechanistic explanation based on the nucleo-shuttling of ATM protein, Dose Response **16**, 1 (2018).

[34] I. Seth, M. C. Joiner, and J. D. Tucker, Cytogenetic low-dose hyperradiosensitivity is observed in human peripheral blood lymphocytes, Int. J. Radiat. Oncol. Biol. Phys. **91**, 82 (2015).

[35] K. W. Fornalski, *Radiation biophysics: cancer risk for low doses of ionizing radiation* (in Polish), Presentation during the Nuclear Physics Seminar at the Faculty of Physics, University of Warsaw (2018), doi: 10.13140/RG.2.2.35484.54409.