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THE RELATIVE BIOLOGIC EFFECTIVENESS VERSUS LINEAR ENERGY TRANSFER CURVE AS AN OUTPUT-INPUT RELATION FOR LINEAR CELLULAR SYSTEMS

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Abstract. Experiments have established that different radiation types have different magnitudes of biological response. When biological response is defined in terms of the Relative Biologic Effectiveness (RBE) and different radiation type is characterized by Linear Energy Transfer (LET), the plot of the RBE versus LET (RBE-LET) curve shows RBE to increase with increasing LET, to reach a maximum, and to decrease with further increasing LET. Perhaps due to the descriptive nature of biology, most quantitative models for the RBE-LET curve ignore the reality of the underlying molecular biology. On the other hand, the molecular basis for the RBE-LET curve is not completely known despite recent efforts.

Here we introduce a differential equation formulation for a signal-and-system model that sees cells as systems, different radiation types as input, and cellular responses as output. Because of scant knowledge of the underlying biochemical network, the current version is necessarily a work in progress. It explains the RBE-LET curve using not just input parameters but also systems internal state parameters. These systems internal state parameters represent parts of a biochemical network within a cell. Although multiple biochemical parts may well be involved, the shape of the RBE-LET curve is reproduced when only three system parameters are related to three biochemical parts: the molecular machinery for DNA double strand break repair; the molecular pathways for handling oxidative stress; and the radiolytic products of the cellular water.

Despite being a simplified "toy model," changes in the systems state parameters lead to model curves that are refutable in a modern molecular biology laboratory. As the parts in the biochemical network of the radiation response are being further elucidated, this model can incorporate new systems state parameters to allow a more accurate fit.

1. **Background.** Since experiments on cultured mammalian cells were first reported in the early 1960s [1], the pattern of biological response to different radiation type has been found to be similar for many cell lines [2, 3]. In these studies, customary practice defines the magnitude of biological response in terms of the ratio $RBE = \frac{Dose(referenceradiation)}{Dose(testradiation)}$ for a given endpoint [4]. The "reference radiation"

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is commonly the external photon beam. The radiation types themselves are characterized by LET, which is defined as the average energy locally imparted to an incremental distance traversed by an incident particle in a medium [4]. In terms of the RBE and LET thus defined, these experiments showed that the RBE-LET curve ascends to a maximum for LET in the range of 100-200 eV/nm, then decreases with further increasing LET.

RBE values from such experiments have had limited medical use for a number of reasons, the chief one being a lack in basic understanding of the biology underlying the RBE-LET curve. This lack of knowledge contributes to the indifference among those in the medical community, who have extensive clinical experience with the "reference" external photon beam, and who doubt the benefits of nonconventional and exotic radiation therapy. Historically, at a few physics laboratories that conducted clinical research, a pragmatic approach incorporates RBE values as a part of a "weighting factor" to relate the biological effectiveness of a particular radiation to the "reference" photon beam. The choice of the right RBE value and "weighting factor" is largely dependent on the clinical experience of the physician. Such an empirical approach, however, can lead to negative outcomes, such as the case for fast-neutron therapy. Thus, recent worldwide interest in hospital-based ion-beam radiation therapy calls for a rigorous effort to understand the biological basis of the RBE-LET curve.

While the physiological state of the irradiated cells are known to play a major role [5, 6], explanations for the RBE-LET curve generally omit the physiology of the radiation response, and permit mainly physical parameters describing the incident radiation beam. Recent molecular biology applications have begun to corroborate the essence of radiosensitivity to be the collective response of biochemical networks when cells are irradiated. Despite these efforts, the molecular basis of the RBE-LET curve remains not completely known [7].

In this paper, a mathematical model is derived for the RBE-LET curve. This model sees cells as systems, with different radiation types as input, and biological responses as output. A result of the model is a mathematical expression for the systems response as a function not only of the radiation's spatial interaction pattern, but importantly also a function of three systems state parameters. These state parameters represent the main biochemical parts that underlie the physiology of the RBE-LET curve. Since the underlying biology is not well understood, the derivation is not based on mathematical formulation of a conservation statement but rather is loosely motivated by the empirical linear-quadratic relation between cell survival and radiation dose (in the range 0-5 J/kg). The linear-quadratic relation provides two of three systems state parameters in this signal-and-system model. One of these state parameters, the coefficient of the quadratic term, was proposed [8] and is widely understood to represent DNA repair. The coefficient of the linear term—as far as we are aware—is not understood to have corresponding radiobiological significance. This, however, should not prevent us from proposing it, after some deliberation, to represent cellular redox state. The third system parameter will be introduced here to take into account the radiation effect in aqueous medium, which is 70%-80% of the cellular chemical composition. The input radiation track is described as a random pulse train using Fourier analysis [9], rather than cluster analysis.

2. **Methods & results.** Physical systems are often described by mathematical models that can approximate how the system will respond to a given input. Frequently these models relate the input to the output by means of a differential equation in which the system response is the unknown function in the differential equation and the input appears as a forcing term. Most often the equations are derived by expressing some empirical physical law in terms of the input and output. Such models are prevalent in classical applied mathematics but are only now beginning to appear in modeling biological processes. This is a result of the fact that biological processes tend to be much more complex than physical examples like circuits and elastic systems and the empirical laws governing biological systems are, as yet, either unknown or are poorly understood. Nevertheless, the characteristic shape of a typical RBE-LET curve suggests the existence of a particular form of mathematical model for the biological response of a cell system to radiation input.

We consider a single incident particle passing through a cellular medium of thickness $0 \leq x \leq L$. The case history of the particle's primary interaction with the medium is denoted by $I(x)$ and is modeled as a sequence of random pulses at locations denoted by x_k with transferred energy ε_k associated with the spike, i.e.,

$$I(x) = \sum_{k=1}^{K} \varepsilon_k \delta(x - x_k). \tag{1}$$

We can choose a Fourier representation for the input $I(x)$ of the form

$$I(x) = \sum_{n=0}^{\infty} J_n e^{in\pi x/L} \tag{2}$$

with $J_n = \frac{1}{L}\int_0^L I(z)e^{-in\pi z/L}dz = \frac{1}{L}\sum_{k=1}^{K} \varepsilon_k e^{in\pi x_k/L}$. Note that $J_0 = \frac{1}{L}\sum_{k=1}^{K} \varepsilon_k$ represents the input energy per unit length and, as such, is directly analogous to LET. It carries information about the spatial average of the input energy. The coefficients J_n for $n>0$ are also quantities having the same units as LET but are associated with periodic oscillation of frequency $\omega_n = \frac{n\pi}{L}$and are interpreted as the portion of the total input energy that is concentrated in the frequency ω_n. They provide information about the spatial distribution of energy transfer. It should be noted incidentally that LET, like J_0, by itself gives no information about the spatial pattern of input energy. When used with the assumption that there is a certain amount of energy transfer per interaction, however, LET becomes a useful tool to describe the spatial pattern of input energy. For example, assuming an energy transfer per interaction of 60 eV, an α-particle with LET 120 eV/nm would have an average spacing of 120 eV/60 eVnm=2/nm [4]. Evidently, LET/energy transfer/event and ω_n are analogous quantities in that they both are measures of the spatial pattern of energy transfer.

The microscopic energy state of the medium, denoted by $\varepsilon(x)$, can be similarly expressed as a Fourier representation

$$\varepsilon(x) = \sum_{n=0}^{\infty} G_n e^{in\pi x/L} = \sum_{n=0}^{\infty} G_n e^{i\omega_n x}. \tag{3}$$

In the absence of a clear understanding of the mechanisms involved, a heuristic explanation of the model is based on the empirical linear-quadratic fit to survival data

$$\frac{S}{S_0} = e^{-\alpha D - \beta D^2}.$$

In this relation, S is survival after a dose D; S_0 is survival at D=0; α and β are positive constants. Next, we define radiosensitive response as $r = -\ln \frac{S}{S_0} = \ln \frac{1}{SF}$, where $SF = \frac{S}{S_0}$is the surviving fraction. The linear-quadratic relation becomes

$$r = \alpha D + \beta D^2. \tag{4}$$

D is defined by $D = \frac{\Delta E}{\Delta m}$, with ΔE as the medium's energy in a mass Δm. Note that relation (4) expresses the fact that the response r is an increasing function of dose D and that this increasing function can be approximated with a linear term αD, plus a quadratic correction term βD^2, to account for experimentally observed deviations from a linear relation. Given the current level of experimental precision, a two-term approximation is sufficient.

It is important to note that the variables r, D, and LET are macroscopic variables in the sense that they are descriptive of the system as a whole as opposed to the variables *I(x)* and *ε(x)*, which vary with position and are accordingly referred to as microscopic variables. We define now one additional microscopic variable *p(x)*, the microscopic response which, like the other microscopic variables, has a Fourier representation of the form

$$p(x) = \sum_{n=0}^{\infty} P_n e^{in\pi x/L} = \sum_{n=0}^{\infty} P_n e^{i\omega_n x}.$$

By analogy with the linear-quadratic relation (4) between r and D, we assume a similar two-term relation between P_n, the frequency domain representation for microscopic response p, and the frequency variable ω_n,

$$P_n = A\,(i\omega_n)\,G_n + B\,(i\omega_n)^2\,G_n. \tag{5}$$

This assumption is motivated by the observation that the radiosensitive response is affected by the spatial pattern of energy transfer events and while this information is missing in the standard interpretation of LET, the frequency domain descriptions contain information about the discrete nature of energy transfer. It is reasonable to suppose then that P_n and ω_n should be the dependent and independent variables in the relationship expressing how response varies with LET. The relation (5) asserts then that local response is an increasing function of locally deposited energy but the dependence, like the linear-quadratic relation (4), is not a simple linear relation.

The relation (5) between P_n and G_n is equivalent to the following relation between $p(x)$ and $\varepsilon(x)$

$$p = A\frac{d\varepsilon}{dx} + B\frac{d^2\varepsilon}{dx^2}. \tag{6}$$

Here we have made note of the fact that (3) implies that the derivatives of $\varepsilon(x)$ have representations $\frac{d\varepsilon}{dx} = \sum_{n=0}^{\infty} i\omega_n G_n e^{i\omega_n x}$and $\frac{d^2\varepsilon}{dx^2} = \sum_{n=0}^{\infty} -\omega_n^2 G_n e^{i\omega_n x}$ so that the linear and quadratic terms on the right side of (5) are the coefficients in the frequency domain representations for the first and second derivatives of $\varepsilon(x)$.

Because most cellular composition is water, a fraction of the energy $\varepsilon(x)$ is related to the energy involved in producing radiolytic products. Although those radicals and molecular products that escape a spur would make a significant contribution to cell death, within a spur, most of the radiolytic products are reconverted to water [10]. This fraction is assumed to make no contribution to cell death. It follows that cell death is related to the net energy given by $I(x) - C\varepsilon(x)$, with C denotes the fraction making no contribution to cell kill. If *p(x)* is assumed to be proportional

to the net energy, $I(x) - C\varepsilon(x)$, then (6) reduces to

$$I(x) = C\varepsilon(x) + A\frac{d\varepsilon}{dx} + B\frac{d^2\varepsilon}{dx^2}. \tag{7}$$

Here C has dimensions of $[1/energy]$ and the dimensions for A and B must be $[length/energy]$ and $[length^2/energy]$, respectively.

A deterministic random pulse train is a realization (i.e., outcome) of a Poisson stochastic process, and not of the stochastic process itself. Because of this, equation (7) is not a stochastic differential equation, but rather a 2^{nd} order ordinary differential equation on the interval $0 \leq x \leq L$. It is encouraging that the assumption (5) leads naturally to the classic form of input-output model (7).

In view of (2) and (3), equation (7) is equivalent to an algebraic equation relating G_n to J_n in the complex plane,

$$J_n = (C + iA\omega_n - B\omega_n)\, G_n.$$

Using this result in combination with (5) leads to the following expression relating radiobiological response to the spatial pattern of a single microscopic radiation track,

$$P_n = \frac{i\omega_n A - \omega_n^2 B}{C + i\omega_n A - \omega_n^2 B} J_n.$$

And the related expression for the magnitudes

$$|P_n| = \frac{\sqrt{(A\omega_n)^2 + (B\omega_n^2)^2}}{\sqrt{(C - B\omega_n^2)^2 + (A\omega_n)^2}} |J_n|. \tag{8}$$

Now P_n is the frequency domain representation of local response *p(x)*, which is a microscopic variable. The macroscopic variable analogous to *p(x)* could be called "cumulative radiosensitive response" $q(x)$, and could be defined as a spatial average as $q(x) = \frac{1}{L}\int_0^x p(z)dz =$ cumulative response up to depth $x \leq L$. Then $\frac{dq}{dx} = \frac{1}{L}p(x)$ and if the Fourier coefficient of $q(x)$ is Q_n then $i\omega_n Q_n = \frac{1}{L}P_n$, which is to say

$$|Q_n| = \frac{1}{L|\omega_n|} \frac{\sqrt{(A\omega_n)^2 + (B\omega_n^2)^2}}{\sqrt{(C - B\omega_n^2)^2 + (A\omega_n)^2}} |J_n|. \tag{9}$$

In terms of systems engineering terminology, the ratio $|Q_n/J_n|$ represents the system gain in response to a random pulse train radiation input.

In order to see that equation (9) is, in fact, equivalent to an equation relating RBE to LET, note that in principle radiosensitive response could be determined either by taking the ratio of effects produced by the same radiation dose, or by taking the ratio of doses required to produce the same effect [11]. Since the International Commission on Radiological Units and Measurement took the lead in defining RBE as a ratio of doses [12], this definition became widely used. However, at least one measure based on ratio of effects has been shown experimentally to describe the same phenomenon as RBE: it increases with increasing LET to reach a maximum, then decreases as LET increases further [13]. This measure, defined as $\frac{1}{SF}$ at 2 J/kg, would be identical to the measure $r = \ln\left(\frac{1}{SF}\right)$, when the survival point is chosen at 2 J/kg. Evidently, both the ratios $|Q_n/J_n|$and RBE are equivalent measures of response magnitude. Consequently, the output-input relation (9) and the conventional RBE versus LET curve are two equivalent descriptions of the same

phenomenon. The output-input relation (9) is plotted against experimental data reported by Aoki et al [13] in Figure 1.

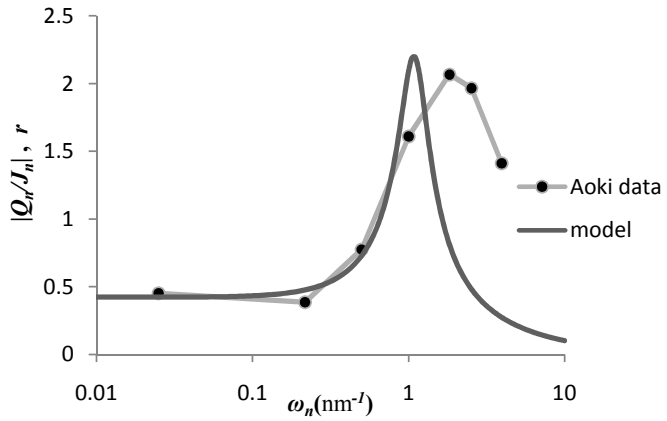


FIGURE 1. Comparison between model and data taken from reference [13]. The model curve is a plot of $Q_n/J_n(\omega_n, A, B, C) = Q_n/J_n(\omega_n, 0.4, 0.8, 0.95)$. The data points (•) represent frequencies 0.025/nm, 0.217/nm, 0.5/nm, 1/nm, 1.83/nm, 2.53/nm, 3.95/nm on the ω_n-axis. Assuming 60 eV/interaction, these frequencies correspond respectively, to the reference 200 kV x-ray with LET 1.5 eV/nm, and carbon beams with LETs 13 eV/nm, 30 eV/nm, 60 eV/nm, 110 eV/nm, 152 eV/nm, and 237 eV/nm. On the vertical axis, values correspond to both Q_n/J_n and $r = ln(1/SF2)$, where 1/SF2 data were taken from reference [13].

3. **Discussion.**

3.1. **The systems.** This derivation of the output-input relation (9) provides an explanation of the RBE-LET curve in terms of a "top-down" systems engineering approach similar to the classical approach used in the study of shot noise in electronic systems [14] (Fig. 2). This model sees cells as systems consisting of a biochemical network with multiple parts, the collective response of which culminates in the physiological outcome. The systems approach, an intuitive understanding the shape of the experimental RBE-LET curve, and the empirical linear-quadratic relation, are the main ingredients that allow us to make a guess for an analytical form of the systems response relation (9). This first approximation to the shape of the experimental RBE-LET curve assumes three biochemical parts represented by three systems state parameters A, B, and C. Although it is narrower and sharper, the model curve (Fig. 1) has the characteristic shape of the experimental curve [13]. The assumption of only three biochemical parts is necessarily tenuous, especially with the background of incomplete knowledge on the molecular basis of the RBE-LET curve. The broader shape of the experimental curve, in fact, hints at a more complex biochemical network consisting of many more biochemical parts. This wider shape can be shown to fit a curve of a modified relation (9) (to be reported), that assumes more than three systems state parameters to represent more than three underlying biochemical parts.

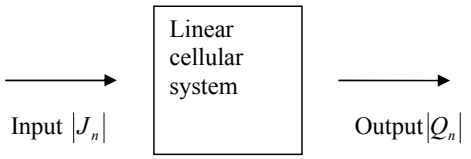


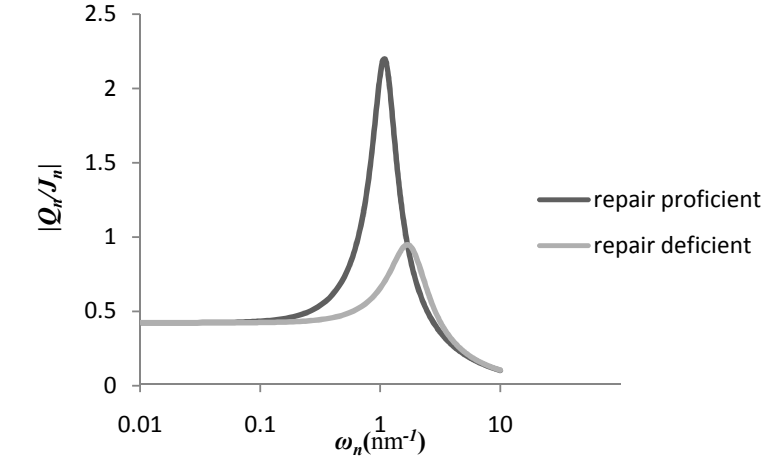
FIGURE 2. Conceptual block diagram illustrating cells as systems, the RBE-LET curve as an output-input relation, with different radiation types as input, and RBE as output.

A more pertinent question might be: Is this working model useful in the search for the molecular basis of the RBE-LET curve? After all, it is an external description of the way cells respond to different types of radiation. It has the advantage of requiring little knowledge about the internal connections between biochemical parts, which were inaccessible until the advent of molecular biology. This external description is thus incomplete precisely because the internal molecular response had remained a "black box." Nevertheless, formally plotting equation (9) for varying systems state parameters A, B, and C in (9) changes the shape of the curves in predictable ways. So, it is natural to wonder whether "tuning" the state parameters in the equation to match data for a specific radiobiological experiment can lead to new insights.

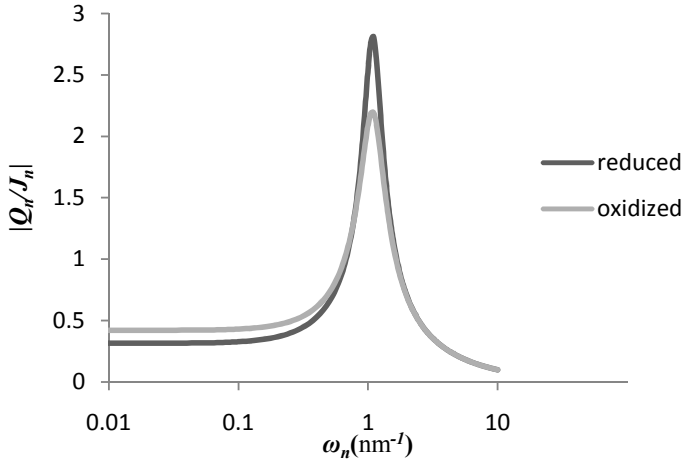
For example, if B is assumed to represent the capacity for DNA double strand break repair, with the numerically smaller value of B consistent with decreased capacity, then the output-input relation predicts that cells with reduced repair capacity will have a flattened RBE peak compared to normal cells (Fig. 3A). Indeed, laboratory data for ATM cells [15, 16], murine scid cells [17], cells with other deficient Ku76 and Ku80 subunits of the DNA-PK protein complex [18, 19], as well as ligase IV deficient cells [20]—all of which have deficiency in a protein component of the nonhomologous endjoining (NHEJ) DNA repair pathway [21]—are observed to have flattened RBE peaks compared to normal cells. Similarly, families of RBE-LET curves have been observed for systems composed of viruses and bacteriophages. These biological systems would have no repair mechanism corresponding to NHEJ repair in mammalian cells and they were found to display a flat RBE-LET curve [4]. A simple plotting exercise shows that the graph of the output-input relation (9) becomes completely flat in the limit as B tends to zero. Evidently, interpreting the state parameter B in the mathematical model to represent repair capacity suggests that biological systems with no repair capacity, such as viruses and bacteriophages should be modeled by a relation (9) with a B value which is nearly zero in order to display a completely flat RBE as a function of LET.

At the heart of this model lies its refutability by experimental manipulation of the systems state parameters using loss-of-function approaches to genes in the molecular networks underlying the RBE-LET curve. As mentioned above, reported *in vitro* studies using mutants defective in components of NHEJ repair, such as ATM, DNA-PKcs, Ku70, and Ku80—so far all showed a flattened RBE-LET curve [15-20]. Following these leads, we are exploring our loss-of-function study to genes participating in NHEJ repair. To date, seven NHEJ proteins have been identified

[21]. The first series of experiment will focus on obtaining the RBE-LET curve for cell lines deficient in XRCC4, Ligase IV, Artemis, and Cernunnos-XLF. These deficient cell lines can be mutants, or potentially knocked-down cells using RNA*i*. The hypothesis is that these deficient cell lines would display flattened RBE-LET curves when compared to repair-proficient counterparts.



Panel A



Panel B

FIGURE 3. The output-input relation for various values of the state parameters A and B. Panel A: For repair proficient cells $Q_n/J_n(\omega_n, 0.4, 0.8, 0.95)$ and repair deficient cells $Q_n/J_n(\omega_n, 0.4, 0.3, 0.95)$. Panel B: For cells in an oxidized state $Q_n/J_n(\omega_n, 0.4, 0.8, 0.95)$ and cells in reduced state $Q_n/J_n(\omega_n, 0.3, 0.8, 0.95)$.

Aerobic T1 human kidney cells with an overload of oxidative stress have been shown to have lower RBE as a function of LET when compared to hypoxic cells [22, 23]. Conversely, cells in the presence of reducing agents—such as T1 human kidney cells in the presence of the antioxidant cysteamine [24], V79 cells in the presence of

the antioxidant dimethyl sulfoxide [25], and melphalan-resistant ovarian tumor cells with elevated glutathione levels [26]—all showed higher RBE as a function of LET when compared with controls. These observations suggest the interpretation of the state parameter A as being related to the molecular capacity for cells to handle oxidative stress [27]. In this way, a numerically higher A signifies an overload of oxidative stress, so that the output-input relation (9) predicts lower RBE peaks (Fig. 3B). Thus, the molecular pathways that respond to oxidative stress may be an essential component of the molecular basis for the RBE-LET curve. Loss-of-function approach to genetic manipulations, similar to the approach proposed for NHEJ repair pathway, is also viable for the oxidative stress response pathway.

Additionally, the output-input relation suggests an explanation of variations in the RBE-LET curve when cell types are grouped by the α/β (and, analogously A/B) ratios, which form the radiobiological basis for the therapeutic use of radiation fractionation. Experiments that have led to the use of the α/β ratio, however, offer no insight for the variations [19, 28]. On the other hand, the output-input relation (9) implies that various cell types having differently-endowed capacity for NHEJ repair and molecular oxidative damage response will have different A/B ratios and correspondingly different RBE-LET curves.

In the previous paragraphs, the potential radiobiological meanings for A and B were discussed. Next, we discuss the implication of the state parameter C in relation to the capacity of cellular water to absorb radiative energy, which then becomes unavailable to cause cell damage. When the systems state parameter C is interpreted as such, an intriguing cross-over in the RBE-LET curve of aerobic cells and hypoxic cells could be explained. In the low LET range, the RBE for aerobic cells is slightly higher than hypoxic cells, while in the high LET range, the RBE for hypoxic cells is greater than the RBE for aerobic cells [22]. This cross-over can be explained by the stability of radiolytic products in the presence of molecular oxygen [10]. Specifically, the primary radiolytic radicals, the H-atom and the hydrated electron, react with molecular oxygen to form the stable superoxide radicals with long life-span (on the order of 10^{-1}seconds) and long diffusion range. In effect, oxygen decreases the non-damaging fraction of deposited energy (decreasing C), while it presents an oxidative stress (increasing A) to cells. When the output-input relation (9) is plotted with increasing A and decreasing C (Fig. 4A), it correlates with this experimental observation.

3.2. **The signals.** As cells are irradiated with heavier ions (higher LET), the position of the RBE peak shifts to the right [29]. Because a greater fraction of the radiolytic products recombine and reconvert to water, densely ionizing radiations have lower radiation-chemical yield (G-values) for radicals compared to sparsely ionizing radiation [10]. When the output-input relation (9) is plotted, an increase in the state parameter C corresponding to a greater fraction of recombination and reconversion, results in the peak occurring at a higher value of LET, suggesting that our model could explain the shift of the RBE peaks with higher LET (Fig. 4B).

4. **Conclusion.** In summary, this rather heuristic formulation nonetheless leads to a "toy model" that emphasizes the reality of biology, as well as the spatial pattern of energy transfer, in producing the RBE-LET curve. This work-in-progress gives an intuitive yet clear understanding of the underlying dynamics. Perhaps its account on the biology of the radiation response unexpectedly gives a sense of coherence to diverse radiobiological observations. While being flexible enough for upgrade with

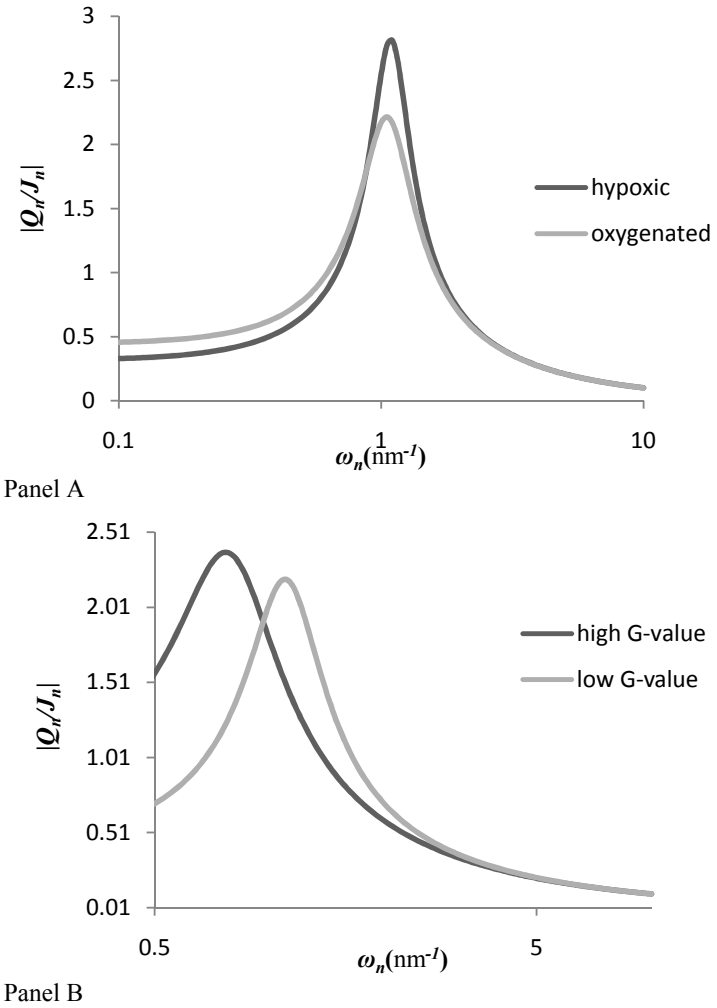


FIGURE 4. The output-input relation for various values of the state parameter C. Panel A: Predicted oxygen effect for oxygenated cells $Q_n/J_n(\omega_n, 0.4, 0.8, 0.9)$ and hypoxic cells $Q_n/J_n(\omega_n, 0.3, 0.8, 0.95)$. To the left of the peaks, there is a point where the two curves cross over each other. Panel B: Positions of the peak along the ω_n-axis for a hypothetical high-LET radiation with low G-value, $Q_n/J_n(\omega_n, 0.4, 0.8, 0.98)$; and low-LET radiation with high G-value, $Q_n/J_n(\omega_n, 0.4, 0.8, 0.95)$.

future progress, it focuses the initial search for the molecular basis of the RBE-LET curve on three biochemical parts: the NHEJ repair pathway, the machinery for handling oxidative stress, and the radiolytic products of water.

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