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Shot noise in radiobiological systems

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ABSTRACT

As a model for human tissue, this report considers the rate of free radical generation in a dilute solution of water in which a beta-emitting radionuclide is uniformly dispersed. Each decay dissipates a discrete quantity of energy, creating a large number of free radicals in a short time within a small volume determined by the beta particle range. Representing the instantaneous dissipated power as a train of randomly-spaced pulses, the time-averaged dissipated power $\bar{\boldsymbol{p}}$ and rate of free radical generation $\bar{\boldsymbol{g}}$ are derived. The analogous result in the theory of electrical circuits is known as the shot noise theorem. The reference dose of X-rays D_{ref} producing an identical rate of free radical generation and level of oxidative stress is shown a) to increase with the square root of the absorbed dose, D, and b) to be far larger than D. This finding may have important consequences for public health in cases where the level of shot noise exceeds some noise floor corresponding to equilibrium biological processes. An estimate of this noise floor is made using the example of potassium-40, a beta-emitting radioisotope universally present in living tissue.

The three principal types of ionizing radiation (alpha, beta, and gamma) cover a continuum from densely to sparsely ionizing. Because the spatial distribution of ionization events is different in each case, even for equal quantities of deposited energy, for each variety of ionizing radiation the interaction with living tissue is of different character. In general, different biological outcomes result. This observation motivates the definition of the relative biological effectiveness (RBE) of types of ionizing radiation other than gamma and X-rays, RBE $= D_{ref}/D$. According to this definition, D represents the absorbed dose of alpha or beta particles (in Grays), while D_{ref} represents that dose of 250 kV X-rays required to produce the same biological effect caused by the dose D (Hall, 1994). The radiation weighting factors W_R applied to radiation protection are abstracted from measurements of RBE in a simple manner to allow practical application. For beta particles, the focus of this paper, $W_R = 1$.

The linear no-threshold (LNT) framework holds that doses are strictly additive, with the risk of cancer increasing uniformly with accumulating dose (BEIR VII, 2006). In this view, the distribution of dose with time is not important and has no biological effect. It is firmly established, however, that the free radical products of radiolysis by ionizing radiation have short lifetimes in the range from nanoseconds to milliseconds. This presents a paradox. While the spatial distribution of ionization events is accounted for by the definition of RBE, there appears to be no attempt within the LNT framework to account for the temporal distribution of ionization products on very short time scales.

This shortcoming of the LNT framework may be addressed by deriving the time-averaged rate of free radical generation, $\bar{g}$, along with the reference dose of X-rays duplicating that rate of free radical generation, D_{ref}. The quantity $\bar{g}$ describes the production of free radicals in near-instantaneous bursts of thousands, locally disrupting the equilibrium between pro-oxidant and anti-oxidant molecular species and creating a state of significant oxidative stress. Oxidative stress has numerous adverse health effects, including cancer (Sies, 1993). The reference dose calculation assumes that the rate of free radical generation is uniquely determined by the dissipated power, regardless of radiation quality. This is unlikely to be generally true, but should be a good approximation in many instances.

As a model of human tissue, consider a dilute solution of water in which a beta-emitting radionuclide is uniformly dispersed. Each emitted beta particle possesses an energy E_o equal to the expected value of the beta particle kinetic energy distribution, on the order of 100 keV–1 MeV. The range of beta particles in water is given by the phenomenological expression (Katz and Penfold, 1952)

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$$R = (4.12mm)E_o^{1.265-0.0954\ln[E_o]}, \tag{1}$$

with E_o specified in MeV. For $E_o = 0.350$ MeV, Eqn. (1) predicts a range of about 1 mm.

The chain of events following the absorption of a fast charged particle may be separated into four distinct temporal stages: the physical stage, the physicochemical stage, the stage of non-homogeneous chemistry, and finally the biological stage (Azzam et al., 2012). The ionizations and excitations defining the beta particle track during the physical stage reorganize very rapidly without diffusion during the physicochemical stage, ending about 1 picosecond after beta particle emission. The track structure at this instant is inhomogeneous and contains a high concentration of radiolysis products, including a number of free radicals n_{fr} on the order of 1–10 thousand or more.

The chemical disturbance existing at the end of the physico-chemical stage is completely contained within a limited volume defined by the beta particle range. Therefore the average rate of emission (that is, the activity), N, should properly be normalized to a volume of approximately $V = 4\pi R^3/3$. Having established a proper length scale, one must then also select an appropriate time scale τ. A principal concern is the indirect effect describing damage to DNA caused by the highly-reactive hydroxyl radical $OH^{\blacksquare}$. It is estimated that two-thirds of all DNA lesions caused by ionizing radiation are due to hydroxyl radicals, which have a lifetime in living tissue on the order of $\tau = 1$ ns (Bacq and Alexander, 1961). The free radical lifetime limits the speed of the chemical response to dissipated power, a behavior expressed mathematically by definition of a bandwidth of response, B. The bandwidth is related to the time scale by $B = 1/2\pi\tau$.

Radioactive decay is known to be a random process governed by Poisson statistics. The probability of n decays occurring within any normalizing volume V during uniform intervals of time is given by the Poisson distribution

$$P(n) = \frac{N^n}{n!}e^{-N} \tag{2}$$

The Poisson probability distribution makes explicit the physical reality that decays occur only in discrete, individual units. Beyond a certain point it is therefore not appropriate to extrapolate chemical or biological outcomes linearly downward from high activities, since individual decay events cannot be further divided. The shot noise formalism, which describes a noise process present in electronic circuits under low excitation (Schottky, 1918), provides the correct, mathematically rigorous, template for this extrapolation.

To motivate the discussion of the shot noise theorem, consider the emission of a single beta particle from an ensemble of radioactive atoms in solution. The beta particle kinetic energy is dissipated in the surrounding medium within a time less than 10 ps (10^{-11} s). Values of $E_o = 350$ keV and $V = 4$ mm^3 are assumed. Examining only the 10 ps interval, the average power dissipated by this single decay is at least 5.6 mW. Because the normalizing volume has a mass of 4 mg, the power density ($\rho = p/m$) has a value of $\rho = 1400$ W/kg. By contrast, the dose due to this single decay is 14 nGy.

For the physical situation in which a series of decays occur at random times in accordance with Eqn. (2), the doses due to individual decay events are strictly additive and are linearly related to the activity according to the equation

$$D = \frac{E_o}{m}NT, \tag{3}$$

where m is the mass of the normalizing volume and T is the interval of time considered. There is no straightforward description of the dissipated power (either average or instantaneous), since the physical situation features extremely brief intervals of relatively high power dissipation, interrupted by long (and random) intervals of zero dissipation. This situation is illustrated schematically in Fig. 1. The derivation of Carson's Theorem for the power spectral density of a random pulse train presented below follows that given in a standard text (Buckingham, 1983). Carson's Theorem is the basis of the shot noise formalism.

The dissipation of power within the normalizing volume is modeled as a train of random pulses, each with amplitude E_o:

$$p_T(t) = \sum_{k=1}^{K} E_o\delta(t - t_k). \tag{4}$$

In Eqn. (4), δ represents the Dirac delta function, possessing infinitesimal width and unit area, while the t_k comprise a set of random variables representing pulse emission times. The amplitude of each pulse equals E_o, the expected value of the beta particle energy. Energy lost to X-rays generated by radiative processes amounts to only about 1% of E_o and is ignored. Because the Fourier transform of an infinitesimally narrow pulse is the DC response $1(\omega)$, the power spectral density of the random pulse train Eqn. (4) is

$$S(\omega) = \lim_{T\to\infty} \frac{2|1(\omega)|^2 E_o^2}{T} \sum_{k,m=1}^{K} \left\langle e^{-i\omega(t_k - t_m)} \right\rangle. \tag{5}$$

In Eqn. (5), T is the duration of the pulse train, ω is the angular frequency, i is the imaginary unit, k and m are indices, and the brackets indicate an ensemble average value. The sum may be evaluated by splitting it up into two separate terms, those for which $k = m$, as well as those terms for which $k \neq m$. The result is known as Carson's Theorem,

$$S(\omega) = 2NE_o^2|1(\omega)|^2 + 4\pi N^2 E_o^2 \delta(\omega). \tag{6}$$

The time-averaged dissipated power follows by integration of the power spectral density Eqn. (6). If the activity is large ($N \gg \tau^{-1}$), the time-averaged dissipated power is linear with the activity. This result is consistent with the LNT framework. However, for low activity (mathematically, $N \ll \tau^{-1}$) one obtains

$$\bar{p} = E_o\sqrt{NB}. \tag{7}$$

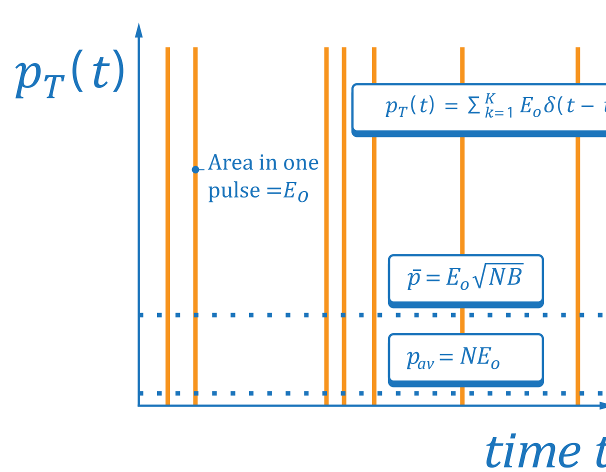

Fig. 1. Random pulse train illustrating instantaneous power dissipation in the model tissue, along with the average power and shot noise power (dashed lines).