Synergy analysis for mouse Harderian gland radiation tumorigenesis induced by mixed beams whose individual components are simulated galactic cosmic rays

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1. Introduction #Edward: to take advantage of the RR paper acceptance I rewrote abstract, all of section 1 Introduction, and most of section 2.2. I sent you a .docx with these changes because I was not sure how best to enter them. I can deal with GitHub now but am sort of drowning in multiple versions – various versions in my .docx files or on my RStudio + your .Rmd and your .pdf on GitHub. Please never change the .Rmd without immediately changing the .pdf because then I get lost. Especially because I am also writing quite a few other similar papers/proposals at the same time. Below I add a few more changes, mainly to see if I am doing what is best or at least manageable for you. Do I have to notify you by email when I make any commitment or are you automatically notified by GitHub?

1.1. Terminology

1.2. Scope of Paper

1.3. Synergy Analysis

2. Mathematical and Computational Methods

2.1. Open-Source, Freely Available Programs #Edward: this sub-section is now in great shape. Thanks.

All customized software we developed for this study are open source and freely available. We utilize the programming language R (R Core Team 2017), which is primarily designed for statistical computing and graphics. We supplement the base R software environment with "R packages" - curated R code collections loaded from the Comprehensive R Archive Network (CRAN). The specific packages used are detailed under Computation Implementation (Section 2.5.). All development of the source code was performed in RStudio, a integrated development environment for R. The current script and its past iterations are both stored on the online version control repository GitHub. The script is offered for free use or modification under the (lenient) GNU General Public License v3.0. There is no warranty on the script, implied or otherwise.

2.2. IDERs and Hazard Functions: General Approach #Edward: This whole subsection needs to be replaced by my .docx version.

2.2.1. Basic Properties

Let $E(d;\mathbf{p})$ represent an IDER with d being dose and $\mathbf{p}$ a vector of adjustable parameters that are calibrated by regression from the data. Let $E_j(d_j;\mathbf{p_j})$ be a MIXDER whose j^{th} component contributed dose d_j to the total mixture dose, with $j = 1, 2, \ldots, N$. We denote by $E(d;\mathbf{p};L)$ a MIXDER when LET L is used instead of

an integer label j. We define an IDER as standard if it satisfies the following properties. (a) $E(d = 0; \mathbf{p}) = 0$. (b) It has continuous first and second derivatives at all non-negative dosages including $d = 0$. For the time being, we also require (c): the IDER must be monotonically increasing in some half-open dose interval $[0, A_j)$. Conditions (a) and (b) are necessary by definition of an individual dose effect relationship sans background radiation effects. Condition (c) is required to calculate $I(d)$ by the original version of incremental effect additivity synergy theory {Siranart, 2016 #265}, but has since been generalized very substantially, as explained below.

2.2.2. Hazard Functions

All our essential calculations take $E(d; \mathbf{p})$ to be given by the equation $E = 1 - exp(-H)$ where $H(d; \mathbf{p})$, called the hazard function, obeys the following conditions. (a) H is 0 when $d = 0$. (b) H has continuous first and second derivatives at all non-negative dosages including $d = 0$. (c) H is convex and monotonic increasing. Note that these condtions on H hold if and only if E obeys similar conditions.

We assume $\lim_{d\to\infty} H = \infty$ which is equivalent to $\lim_{d\to\infty} E(d, \mathbf{p}) = 1$. For purposes of this paper, a curve is convex if it has a positive second derivative, which implies upward curvature. Concavity is the opposite. More general definitions are not needed here. Convexity is desired for H because the resulting IDER will have an upper limit of 1 without additional adjustable parameters.

2.3. IDERs Used in This Paper #Edward: I think my .docx also changed a lot of 2.3?

2.3.1. Motivations

For the purposes for incremental effect additivity, IDERs are ideally smooth and monotionically increasing. The hazard function utilized in Cucinotta & Cacao (2017) allows us to construct IDERs that satisfy these properties with fewer adjustable parameters than in earlier models (Ham 2017). Notably, our resulting IDER parameters are different from zero at significant levels ($p < 10^{-5}$).

2.3.2. IDERs: Functional Forms #Edward: This subsection is basically in pretty good shape; thanks

Three IDER variants in this paper are implemented to reflect differing particle types and modeling approaches. We describe the effects of individual HZE particles with IDERs corresponding to the TE approach and the NTE approach. The functional form of the HZE, NTE hazard function is as follows:

$$H = 0.01 * [aa1 * L * d * exp(-aa2 * L) + (1 - exp(-\phi * d)) * kk1] \quad (2.3.2.1)$$

Here, $aa1$ and $aa2$ are adjustable parameters with respective dimensions μm Gy^{-1} keV^{-1} and μm keV^{-1} and $kk1$ is dimensionless. #Edward: added this line

Additionally, the HZE, TE hazard function appears as:

$$H = -0.01[aate1 * L * d * exp(-aate2 * L)] \quad (2.3.2.2)$$

Here, $aate1$ and $aate2$ are adjustable parameters with respective dimensions μm Gy^{-1} keV^{-1}. #Edward: corrected this line.

Lastly, we describe an IDER for low-LET ions. We do not use the hazard function to construct this IDER. (#egh note to Ray - why don't we used a NTE/TE model to describe low-LET IDERs?) #Edward: From now on I will use "egh" instead of "Edward". The NTE term is proportional to L for small L; in our data the two low LET ions have such small LET that the NTE contribution is negligible. Later I plan the following. Calibrate kk1 from HZE data at non-zero doses. Then add to $I_{low-LET}$ for the low LET ions a term for NTE effects that depends on L but holds kk1 fixed at its already calibrated value so there is no additional adjustable constant involved.

$$I_{low-LET}(d) = 1 - exp(-\beta * d) \quad (2.3.2.3)$$

#egh: When I have time I will add a motivation here for why we did not, unlike previous models, add a quadratic term in the exponent. Also, please rename this beta as alpha or alpha_{low-LET} because that is what radiobiologists always use for termsa linear in dose.

2.4. Synergy Analysis

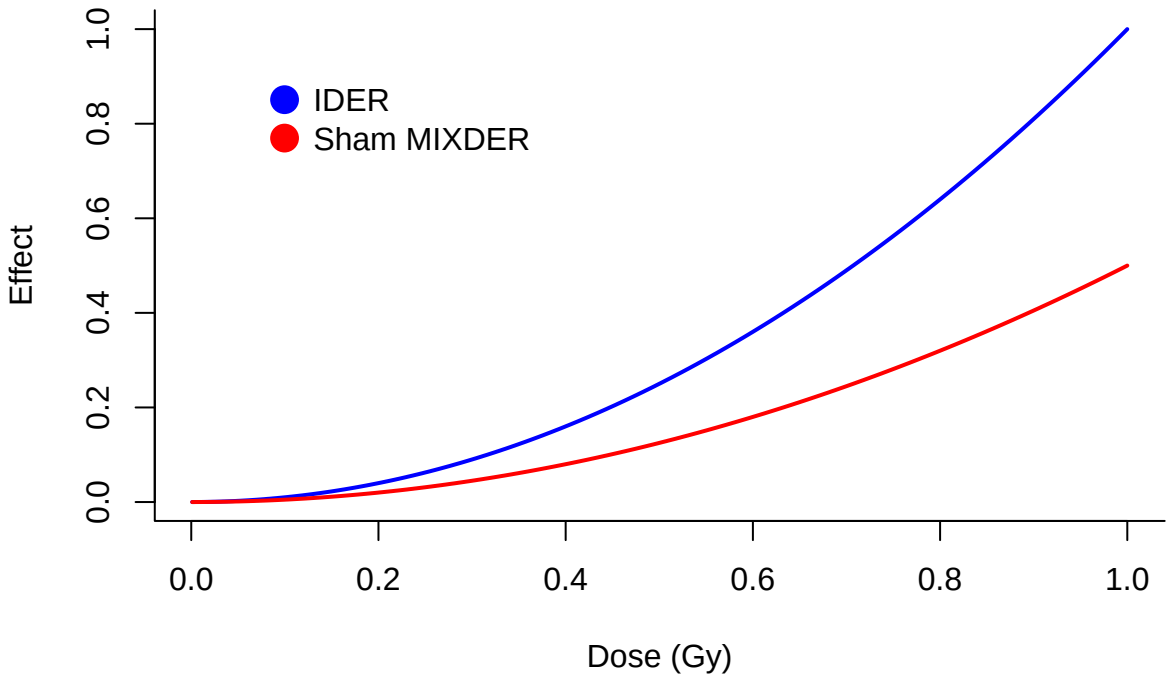
2.4.1. Distribution of Mixture Dose Between Mixture Component

A mixed radiation field consists of $N \geq 2$ components. Each component independently has a dose-effect relation consisting of background and radiogenic contributions. We define an IDER as the radiogenic contribution from a component. Thus by definition IDERs are zero when dose is zero.

2.4.2. Simple versus Incremental Additivity

Simple effect additivity (SEA) synergy theory carries weaknesses that incremental effect additivity attempts to address. SEA notably has the tendency to defy what is known as the "sham mixture principle". Suppose that there exists a single-agent beam with dose d that is described by an IDER I. The principle asserts that synergy theory applied to a sham mixture of $I(d_1), \ldots, I(d_i), \ldots, I(d_n)$, such that $\sum_{i=1}^{n} d_i = d$, would yield a MIXDER M equivalent to I. < add plots and discuss examples > . As an example, assume that we have an IDER $i(d)$ such that $i = d^2$ and SEA MIXDER $m(d) = 2 * i(d/2)$ such that m is a mixture of two identical i components. According to the sham mixture principle, for any arbitrary dose d_j, $i(d_j) = 2 * i(d_j/2)$. However, this is trivially false, as shown in Fig. 2.4.1.

Figure 2.4.1: Simple Effect Additivity Applied to Sham Mixture



Notice that MIXDER $n * i(d/n)$ increases much more slowly than $i(d)$ in fig. 2.4.1. This is characteristic for sham mixtures of convex IDERs because SEA fails to take into account the rate at which an IDER rises. Alternatively, when SEA is applied to a sham mixture of concave IDERs, the resulting MIXDER tends to rise much faster than the lone IDER. This characteristic of SEA is indicative of flawed synergy analyses for actual mixtures. One of the greatest advantages of incremental effect additivity (IEA) over SEA is that IEA does not violate the sham mixture principle. IEA avoids the pitfalls of SEA estimates by analysing

the linear relation between a dose increment and the resulting effect increment. An ordinary differential equation is constructed from these analyses and solved to find the resulting MIXDER. We can guarantee that the MIXDER for each mixture is unqiue because ODEs only have one unique solution. This approach has become very practical in light of modern computing advances.

2.5. Computational Implementation

The data are sourced from Chang et al. (2016) and Alpen et al. (1993, 1994) and implemented as R dataframes throughout the calculations. A number of R packages from the CRAN repository were used, notably `stats` for non-linear regression, `deSolve` for solving differential equations, `mvtnorm` for Monte Carlo simulations, and `ggplot2` for plotting.

Our computational workflow with respect to R methods and functions is as follows. Various datasets on Harderian gland tumorgenesis are first implemented as R dataframe structures. Inverse variance weighted non-linear least square models are fitted over these dataframes using the Gauss-Newton algorithm inside the function `nls` from the package `stats`. Coefficients extracted from the models with `coef` are used to construct hazard functions in the form of a user-written R function. Standardized IDERs are initialized from these hazard functions as user-written functions following the hazard function equation Eq. (2.2.2.1). These resulting IDERs encompass various 1-ion beam variants (HZE, low-LET) and effect models (TE, NTE + TE).

Computing $I(d)$ involves calling a user-written R function `calculate_complex_id` that applies incremental effect additivity to mixtures of $N \geq 2$ IDERs, with at most one low-LET IDER. `calculate_complex_id` takes an argument to specify use of either the NTE+TE or the TE model. Calculation of $I(d)$ requires construction of an R vector `dE` with elements corresponding to the derivative of each IDER curve as a function of dose. A one-dimensional root finder `uniroot` is used to find the incremental effect of each IDER. We construct `dI`, a vector corresponding to the numerical derivative of $I(d)$ with respect to mixture dose d by applying Eq. (2.2.2.1) to each element of `dE`. A numerical ODE integrator from `deSolve` is used to integrate `dI` with a Radau method to return a R list of dose-effect coordinates.

Confidence intervals for the calculated baseline MIXDER $I(d)$ are found through Monte Carlo (MC) simulations. A vector of total-mixture dose points is chosen. For each MC iteration, a user-written function `generate_ci` initializes a vector of random parameter value samples for a particular dosage from multivariate distributions determined during IDER fitting. Our MC simulations use 500 total parameter samples over all selected dose points. These samples are drawn with the `rmvnorm` function from the `mvtnorm` package. An $I(d)$ dose effect relation is calculated at that dosage with `calculate_complex_id` and the sample parameters. When the MC step is completed a 95% confidence interval is constructed at each dose point sorted by effect size. The naive confidence intervals are also computed within `generate_ci` by choosing parameters using each parameter marginal distribution instead of using variance-covariance matrices.

Works Cited

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