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

1.1. Terminology

1.2. Scope of Paper

1.3. Synergy Analysis

2. Mathematical and Computational Methods

2.1. Open-Source, Freely Available Programs

Unless otherwise stated, all software employed 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 Git-based online version control repository GitHub. The script is freely offered for use or modification under the GNU General Public License v3.0. There is no warranty on the script, implied or otherwise.

2.2. IDERs and Hazard Functions: General Approach [almost always use toy examples for 1st year 1-variable calculus audience]

2.2.1. Basic Properties

Notation. dose d, effect E. Related notations are: $E(d : \mathbf{p})$ where d is dose and $\mathbf{p}$ is a vector of adjustable parameters that are calibrated by regression from the data; $E_j(d_j; \mathbf{p_j})$ when discussiong a mixture whose j^{th} component contributed dose d_j to the total mixture dose, with $j = 1, 2, \ldots, N$; and $E(d; \mathbf{p}; L)$ when LET L is used instead of an integer label j.

2.2.2. Hazard Functions

2.3. IDERs Used in This Paper (will be Long sub-section with various subdivisions)

2.3.1. Motivations

2.3.2. IDERs: Functional Forms

2.4. Synergy Analysis (will be long sub-section with various subdivisions)

2.4.1. Distribution of Mixture Dose Between Mixture Components

2.4.2. Simple versus Incremental Additivity

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 computational methods and functions is as follows. Various datasets on Harderian gland tumorgenesis are first implemented as R dataframe structures. Non-linear least square models are fitted over these dataframes using the Gauss-Newton algorithm. Coefficients extracted from the models 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 in Section 2.2.3. These resulting IDERs encompass various particle 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 or 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 $d(I)$ by applying Equation (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 are found through Monte Carlo simulations. For each value of a vector of dose points, a user-written function `generate_ci` initializes a vector of N random parameter value samples from a Gaussian distribution normalized to a NTE or TE model. These samples are drawn with the `rmvnorm` function from the `mvtnorm` package. Another vector of effect values is calculated at that dosage for each set of sample parameters with `calculate_complex_id`. A 95% confidence interval is constructed from the sorted effect values. The naive confidence intervals are also computed within `generate_ci` by implementing a set of parameters two standard deviations above and below the mean values and evaluating `calculate_complex_id` for each dose point according to those parameters.

Works Cited

1. Bennett PV, NC Cutter and BM Sutherland. “Split-dose exposures versus dual ion exposure in human cell neoplastic transformation.” Radiat Environ Biophys 46(2): 119-123. (2007).

2. Chang PY, FA Cucinotta, KA Bjornstad, J Bakke, CJ Rosen, N Du, . . . EA Blakely. “Harderian Gland Tumorigenesis: Low-Dose and LET Response.” Radiat Res 185(5): 449-460. (2016).

3. Cucinotta FA and LJ Chappell. “Non-targeted effects and the dose response for heavy ion tumor induction.” Mutat Res 687(1-2): 49-53. (2010).

4. Norbury JW, W Schimmerling, TC Slaba, EI Azzam, FF Badavi, G Baiocco, . . . CJ Zeitlin. “Galactic cosmic ray simulation at the NASA Space Radiation Laboratory.” Life Sci Space Res (Amst) 8: 38-51. (2016).

5. Siranart N, EA Blakely, A Cheng, N Handa and RK Sachs. "Mixed Beam Murine Harderian Gland Tumorigenesis: Predicted Dose-Effect Relationships if neither Synergism nor Antagonism Occurs." Radiat Res 186(6): 577-591. (2016).