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

Yimin Lin, Edward Greg Huang, Mark Ebert, Dae Woong Ham, and Rainer K. Sachs

3 October 2017

1. Introduction

1.1. Terminology

There will be a number of acronyms in this paper. The main ones are the following, with less familiar but here often used ones, such as IDER and MIXDER, in bold-face and underlined. AIVP Autonomous ODE Initial Value Problem (Section sss below) GCR Galactic Cosmic Rays (or Galactic Cosmic Radiation). Occurs above low earth orbit. HG Harderian Gland. An organ found in many rodents HZE ion High Z and E (charge and energy) atomic nuclei, almost fully ionized IDER Individual Dose-Effect Relation, for a single agent or single mixture component MIXDER Mixture Dose-Effect Relation L=LET Linear Energy Transfer, stopping power, LET ∞ LNT Linear-No-Threshold. A straight line through the origin (dose=0, effect=0) NTE Non-Targeted Effect(s) due to inter-cellular interactions. 'Bystander' effect(s) ODE Ordinary Differential Equation TE Targeted Effect(s). Standard radiobiology action due to a direct hit or near miss In the paper: "concave" and " convex" are used, as illustrated in Fig. fff below, to refer to second derivatives when analyzing IDER graphs; "low dose" usually refers to doses between 0 and 2 cGy; "very low dose" refers to doses between 0 and 5 mGy; and "ultra low dose" refers to doses <1 mGy. More details on terminology and a summary of the mathematical symbols used are in sub-section A1 of the supplementary materials.

1.2. Scope of Paper

NASA has been concerned about possible synergy when mixed radiation fields produce biological damage (reviewed, e.g., in [Norbury et al. 2016],[Siranart et al. 2016], [Ham et al. 2017rrr]). There is evidence that synergy sometimes occurs (e.g. [Bennett et al. 2007]). We will here use mathematical synergy analyses of earlier and proposed experiments on mouse Harderian Gland (HG) radiogenic tumorigenesis after exposure to mixtures whose components simulate GCR. There is evidence that HZE ions probably induce NTE due to inter-cellular interactions [Cucinotta and Chappell 2010; Chang et al. 2016], so we will use $I(d)$

1.3. Synergy Analysis

1.3.1. A Brief History of Synergy Theory

Lots more stuff here

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 with RStudio, a free open source 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: General Approach [almost always use toy examples for 1st year 1-variable calculus audience]

2.2.1. General Requirements on IDERS

Notation. dose. labeled by index or by biophysical parameters. contain adjustable parameters IDERs defined and C2 on half open interval [0,infinity) of dose axis. 0 at dose 0. $E < 1$ for all doses.

2.2.2. Concave/Convex Terminology as Regards Second Derivatives

Use a 3-panel Figure with concave, convex, and inflection point IDERs to illustrate the following items. Suppose $d2E/dd2 < 0$ for all doses in an open interval, then E is (strictly) "concave" for all such doses; > 0 (strictly) convex. Inflection point. Aside: convex graphs have a much more general definition in mathematics [give reference] but here we will only need the above.

2.2.3. The Hazard Function Equation

$E = 1 - exp(-H)$. Motivate E is IDER (section 2.2.1) iff H is IDER.

2.2.4. Standard IDERs and IDERs Defined by an Autonomous Initial Value Problem (AIVP IDERs)

Standard: given as functions of dose, explicit using "elementary" functions or high-quality numerical. AIVP: $dE/dd = F(E)$; $E(0) = 0$; insist, as a mild condition on F, that there be a unique solution C2 at and near dose 0. Motivate at length. Important Innovation.

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

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

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 contruct 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 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 (x) to each element of `dE`. A numerical ODE integrator from `deSolve` is used to integrate `dI` to return a R list of dose-effect coordinates.

Confidence intervals for the calculated baseline MIXDER are found through Monte Carlo simulations (more to be added).

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).