Yellow hilite: notes from Sachs to Sachs

This is an outline, with cryptic notes that need verbal explanations when we meet, for learning to write a paper for radiobiologists – a strictly optional, very time consuming if applied to a whole section like Methods or Results, very instructive for you guys (per se and as regards understanding our eventual paper), and very useful for me. For at least the next month This outline, and anything you guys write for the paper, will be subject to major changes, as I learn more about the paper by writing the paper. This outline starts with a table of contents and a fairly coherent fragment of the Introduction. The rest is merely a guess at subsections of the Methods sections some hasty notes, mainly to myself, and the start of a bibliography that hopefully can be improved before we meet though I just got another "urgent" NASA assignment a couple of minutes ago.

Table of Contents

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

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Abstract [at present 250 words]:

Synergy analysis compares the dose-effect relationship of an agent mixture, such as a mixed radiation field, to the individual dose-effect relationships (IDERs) of the mixture components. When components of a mixture have highly curvilinear IDERs it is not appropriate to define synergy as a deviation of an observed mixture dose effect relationship (MIXDER) from the baseline no synergy/antagonism MIXDER obtained by simply adding IDER values. If high charge and energy ions induce non-targeted tumorigenesis effects, corresponding IDER are highly curvilinear at low doses, simple effect additivity MIXDERs are inappropriate baselines, and a replacement is needed for planning and interpreting mixture experiments. The incremental effect additivity theory, recently introduced to replace the simple effect additivity theory, is suitable for mathematical synergy analysis even if some mixture components have highly curvilinear IDER.

This paper uses previously published experimental information on murine Harderian gland tumorigenesis following exposure to 1-ion beams simulating components of the galactic cosmic radiation field. The paper studies, *in silico*, new IDERs that use a recently published hazard function equation and new incremental effect additivity baseline MIXDERs with 95% confidence intervals that take parameter correlations into account. We suggest that the approach improves on previous theoretical studies of the same data.

We also argue that experiments using ion mixtures intentionally simplified to facilitate biophysical insights, e.g. synergy analyses, are important. They should, in our opinion, be continued in parallel with experiments that use mixtures intentionally made complicated and designated as “representative” of conditions encountered by astronauts above low earth orbit.

288 words in a Cuc paper abstract. In this paper we describe revisions to the NASA Space Cancer Risk (NSCR) model focusing on updates to probability distribution functions (PDF) representing the uncertainties in the radiation quality factor (QF) model parameters and the dose and dose-rate reduction effectiveness factor (DDREF). We integrate recent heavy ion data on liver, colorectal, intestinal, lung, and Harderian gland tumors with other data from fission neutron experiments into the model analysis. In an earlier work we introduced distinct QFs for leukemia and solid cancer risk predictions, and here we consider liver cancer risks separately because of the higher RBE’s reported in mouse experiments compared to other tumors types, and distinct risk fac- tors for liver cancer for astronauts compared to the U.S. population. The revised model is used to make predictions of fatal cancer and circulatory disease risks for 1-year deep space and International Space Sta- tion (ISS) missions, and a 940 day Mars mission. We analyzed the contribution of the various model pa- rameter uncertainties to the overall uncertainty, which shows that the uncertainties in relative biological effectiveness (RBE) factors at high LET due to statistical uncertainties and differences across tissue types and mouse strains are the dominant uncertainty. NASA’s exposure limits are approached or exceeded for each mission scenario considered. Two main conclusions are made: 1) Reducing the current estimate of about a 3-fold uncertainty to a 2-fold or lower uncertainty will require much more expansive animal carcinogenesis studies in order to reduce statistical uncertainties and understand tissue, sex and genetic variations. 2) Alternative model assumptions such as non-targeted effects, increased tumor lethality and decreased latency at high LET, and non-cancer mortality risks from circulatory diseases could significantly increase risk estimates to several times higher than the NASA limits.

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

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 C^2 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 $d^2E/dd^2 < 0$ 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 C^2 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)

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