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.

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# Synergy analysis for mouse Harderian gland radiation tumorigenesis induced by mixed beams whose individual components are nuclei in the galactic cosmic ray spectrum

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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 linear-combination 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 baseline, recently introduced to replace the simple effect additivity baseline, 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*, the following: (a)new IDERs that use a recently published hazard function equation; (b) corresponding incremental effect additivity baseline MIXDERs; and (c), 95% confidence intervals, calculated taking parameter correlations into account, for the new baseline MIXDERs. We give evidence 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

The following acronyms are comparatively unfamiliar but are often used in this paper are

* HG Harderian Gland. An organ found in many rodents
* IDER Individual Dose-Effect Relation, for a single agent or single mixture component
* MIXDER Mixture Dose-Effect Relation
* 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” respectively are used to refer to negative or positive second derivatives respectively when analyzing IDER graphs (Fig. 1.1.1). “Low dose” usually refers to doses between 0 and 2 cGy; “very low dose” usually 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 published data on mouse Harderian Gland (HG) radiogenic tumorigenesis after exposure to ions in the galactic cosmic ray (GCR) spectrum; relevant references include [Fry, Powers-Risius, Alpen et al. 1983; Fry, Powers-Risius, Alpen et al. 1985; Curtis, Townsend, Wilson et al. 1992; Alpen, Powers-Risius, Curtis et al. 1993; Alpen, Powers-Risius, Curtis et al. 1994; Chang, Cucinotta, Bjornstad et al. 2016; Siranart, Blakely, Cheng et al. 2016]. The paper emphasizes *in silico* analyses of the following: the data; new individual dose-effect relations (IDERs) for the data; and the possibility that a mixture of such ions could induce an effect different from the effect anticipated using the IDERs of the mixture components, i.e. could involve synergy or antagonism.

### 1.3. Synergy Theory

Synergy theories use baseline mixture dose-response relations (MIXDERs) that define absence of synergy and absence of antagonism. Often it is taken for granted that simple effect additivity gives the baseline: using the dose which each component contributes to the total mixture dose one calculates from the IDER of that component the effect the component would contribute if acting by itself, then one simply adds all these effects; a deviation + or – from the sum is taken to indicate synergy or antagonism. As summarized in rrr it has been known for a very long time that if mixture components have highly curvilinear IDERs instead of being approximately liear-no-thresholdin a mixtureeffect additivity As reviewed in rrr the apparently obvious linear combination simple effect additivity baseline MIXDER for a mixed radiation field whose individual components are ions in the data set; and 95% confidence intervals, calculated taking parameter correlations into account, for the new baseline MIXDERs.

## 2. Mathematical and Computational Methods

### 2.1. Open-Source, Freely Available Programs; fill in Edward’s paragraph

### 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

(2.2.3.1) *E*=1-exp(-*H*).

Motivate: Automatically incorporates upper limit 1 without needing to add extra parameters

*E* is IDER (section 2.2.1) iff *H* is IDER.

If *H* LNT then slope of *E* at d=0 is the constant H slope.

### 2.3. IDERs Used in This Paper

#### 2.3.1. Motivations

Cuc/Cacao 17 didn’t fully exploit the advantages of their clever hazard function formula.

#### 2.3.2. IDERs: Functional Forms

For HZE\_TE:

(2.3.2.1) *H*=-.01[*aate1* x *L* x *d* x exp(-*aate2* x *L*)]

Here: *H* is the hazard function; aate1 is an adjustable parameter with dimensions μm Gy-1 keV-1 (Edward: explain Eq. (2.3.2.1)

For 1-parameter low LET model: bet= 0.15204 0.01239 12.28 p=9.21e-08 \*\*\*

For 2-parameter low LET model:

# LOW.m <- nls(HG ~ .0275 +(1-deficit)\*(1-exp(-bet \* dose.1)), #####here our motivation for taking deficit=0

# data = dfrL,

# weights = NWeight,

# start = list(deficit=.5,bet = .5))

# summary(LOW.m) # gives deficit -0.09349 with p=0.8273, beta=0.13488, p=0.0809. Therefore take deficit=0.

### 2.4. Synergy Analysis

## 3. Results

### 3.1. IDERs

#### 3.1.1. Calibrated Parameters

#### 3.1.2

## Bibliography

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).

1. Alpen EL, P Powers-Risius, SB Curtis and R DeGuzman. "Tumorigenic potential of high-Z, high-LET charged-particle radiations." Radiat Res **136**(3): 382-391. (1993).

2. Alpen EL, P Powers-Risius, SB Curtis, R DeGuzman and RJ Fry. "Fluence-based relative biological effectiveness for charged particle carcinogenesis in mouse Harderian gland." Adv Space Res **14**(10): 573-581. (1994).

3. 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).

4. Curtis SB, LW Townsend, JW Wilson, P Powers-Risius, EL Alpen and RJ Fry. "Fluence-related risk coefficients using the Harderian gland data as an example." Adv Space Res **12**(2-3): 407-416. (1992).

5. Fry RJ, P Powers-Risius, EL Alpen and EJ Ainsworth. "High-LET radiation carcinogenesis." Radiat Res Suppl **8**: S188-195. (1985).

6. Fry RJ, P Powers-Risius, EL Alpen, EJ Ainsworth and RL Ullrich. "High-LET radiation carcinogenesis." Adv Space Res **3**(8): 241-248. (1983).

7. 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).