Electronic Supplementary Material:

Online Resource 1

Journal Instructions
Submission
Supply all supplementary material in standard file formats.
Please include in each file the following information: article title, journal name, authornames; affiliation and e-mail address of the corresponding author.
Text and Presentations
Submit your material in PDF format; .doc or .ppt files are not suitable for long-termviability.
Spreadsheets
Spreadsheets should be submitted as .csv or .xlsx files (MS Excel).
Numbering
If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.
Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”.
Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.
Captions
For each supplementary material, please supply a concise caption describing the content of the file.
Processing of supplementary files
Electronic supplementary material will be published as received from the author without any conversion, editing, or reformatting.

Supplementary Material for the article “Synergy theory for murine Harderian gland tumorigenesis after irradiation by mixtures of high-energy ionized atomic nuclei.” REBP.

Edward Huang, Yimin Lin, Mark Ebert, Dae Woong Ham, Claire Yunzhi Zhang, others???, Rainer K. Sachs[1,2]
sachs@math.berkeley.edu.

Parts

Online Resource 1, part 2

ion	*L*	*Z*	*β**	MeV/u	comments
H1	0.4	1	0.614	250	Chang
He4	1.6	2	0.595	228	Alpen
Ne20	25	10	0.813	670	Chang
Si28	70	14	0.623	260	Chang
Ti48	100	22	0.876	1000	Chang
Fe56	195	26	0.793	600	Alpen
Fe56	195	26	0.793	600	Chang
Fe56	250	26	0.654	300	Alpen
Nb93	464	43	0.793	600	Chang
La139	953	57	0.791	593	Alpen

Chang LET at mouse, Alpen at entering beam. Exception Alpen Entering beam changed to 195 since the data sets were found to be combinable, and were combined, in

Online Resource 1, part 3.

New one-ion models were used instead of recent models based on modifications of Katz' amorphous track structure approach {Katz, 1988. Quantitative Mathematical Models in Radiation Biology`, ed. J. Kiefer. #235;Cucinotta, 1999 #230;Goodhead, 2006 #231;Cucinotta, 2010 #44;Cucinotta, 2013 #138;Chang, 2016 #115;Cucinotta, 2017 #257}. There were a number of reasons we considered new models, as follows.

First, it has often been argued, e.g. in {Goodhead, 2006 #231}, that when applied to experiments with complex biological targets the amorphous track structure approach loses some of the simplicity, elegant agreement with data, and biophysical credibility which it has when applied to experiments where the targets are emulsions or viruses.

Second, NTE are conceptually completely different from delta rays as regards transmitting influences from a directly hit cell to neighboring cells {Hatzi, 2015 #269}. NTE involve endogenous cell signaling. We saw no reason why the biophysical reasoning that leads to the amorphous track structure models should be relevant to NTE.

Third, the HZE models in {Cucinotta, 2017 #257} contain a factor interpreted as due to cell killing; we felt that the factor implicitly assumes cell repopulation after cell killing is strongly biased against

repopulation of tumorigenic cells whereas unbiased repopulation or repopulation with the opposite bias is more likely to occur {Sachs, 2005 #70}.

Fourth, some models in {Cucinotta, 2017 #257} use an adjustable parameter that regression found to be not significantly different from zero even at the largest p-level, $p \leq 0.1$ usually considered. We reasoned that since the hazard function formalism automatically takes into account the constraint that prevalence $\leq 100\%$, one might, in the interests of parsimony (i.e. Occam's razor), be able to find models with fewer adjustable parameters, all significantly different from zero.

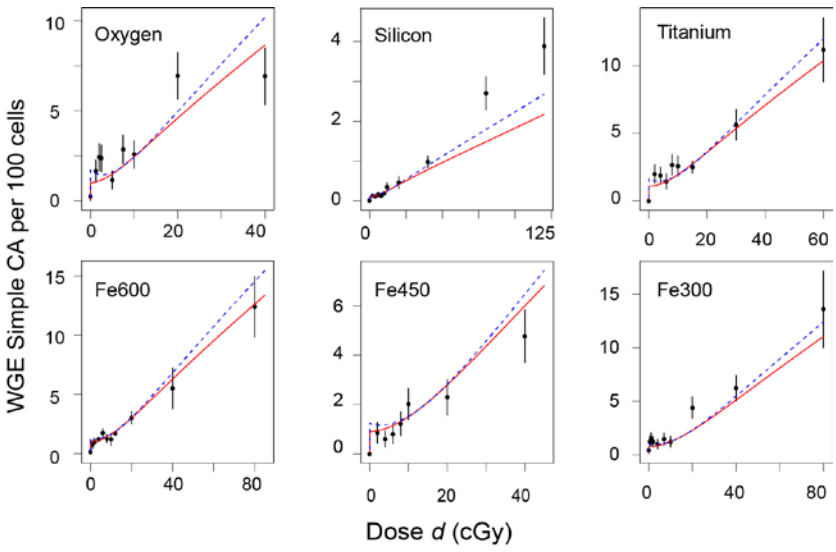
Fifth, we felt models which used discontinuous jumps in effect level should either be replaced by stochastic process models or by non-stochastic models with continuous values, first derivatives and second derivatives – postulating that an infinitesimal dose increment can produce a finite jump in effect conflates stochastic process models and deterministic models in an unusual way.

Sixth, the comparatively elementary version of IEA used in this paper assumes monotonic increasing one-ion DERs, while some previous models allow dose regions where the one-ion DERs are decreasing instead. Using one-ion DERs that are not monotonic increasing at all doses of interest would have required a far-reaching generalization of the elementary IEA formalism {Ham, 2017 #507}, more challenging computationally than necessary for the present paper's explanation of synergy theory.

However, all these arguments do not rule out the possibility that the amorphous track structure approach may have important advantages over the one-ion DERs we used here, for example perhaps much better goodness of fit for published and upcoming murine HG tumorigenesis data. Balanced comparisons have not yet been carried out.

Fig. 3.1. One-ion DERs. 8-panels with data and error bars

The figure will look similar to the following but will refer to HG prevalence instead of the chromosome aberration data shown in this placeholder and will contain 8 panels for the 7 HZE ions in our present database instead and our low LET DER instead of the 6 panels shown in the place holder.



Online Resource 1, part 4.

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 one-ion DERs are initialized from these hazard functions as user-written functions following the hazard function equation Eq. (2.2.4.1). These resulting one-ion DERs 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 IEA to mixtures of $N \geq 2$ one-ion DERs, with at most one low-LET DER. calculate_complex_id takes an argument to specify use of either the NTE+TE or the TE-alone model. Calculation of $I(d)$ requires construction of an R vector dE with elements corresponding to the derivative of each one-ion DER curve as a function of dose. A one-dimensional root finder uniroot is used to find the incremental effect of each one-ion DER. We construct dI, a vector corresponding to the numerical derivative of $I(d)$ with respect to

mixture dose *d* by applying Eq. (2.3.4.1) to each element of **d**E. A numerical ODE integrator from deSolve is used to integrate dI with a Radau method to return a R list of mixture DER entries.

Confidence intervals for the calculated IEA baseline mixture DER *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 dose from multivariate distributions determined during one-ion DER fitting. Our MC simulations use 500 total parameter samples over each selected dose point. These samples are drawn with the rmvnorm function from the mvtnorm package. An IEA dose effect relation is calculated at each selected dose point 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.

Online Resource 1, Bibliography