Statistical modelling in biological dosimetry

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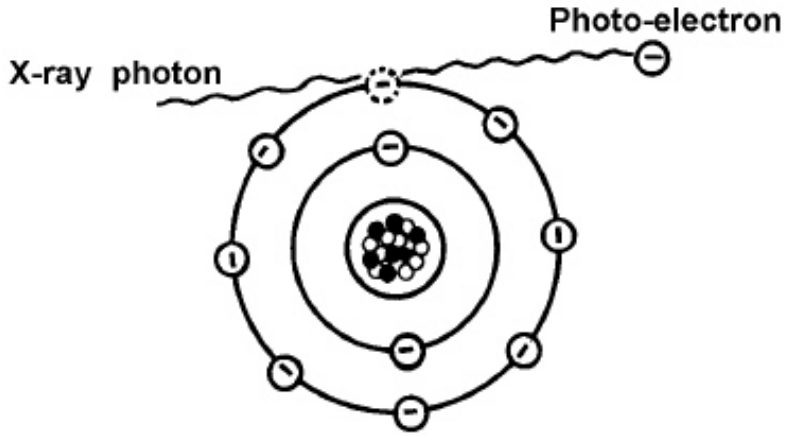
with thanks to E. Ainsbury, S. Barnard, D. Endesfelder, M. Higueras, and Y. Cai

Limerick, 8 November 2024

Radiation

Radiation is energy in the form of waves or particles that travels through space or some material (includes heat, radio waves, light,...)



When we talk about radiation, we often mean ionizing radiation (α and β particles, γ–rays, X–rays, neutrons...), which carries enough energy to ionize atoms or molecules. Ionizing radiation can cause serious damage to cells, tissues, and DNA.

Dosimetry

Dosimetry is the measurement of the absorbed dose delivered by ionizing radiation. The absorbed dose is measured in Gy (Joules per kg).

This talk will focus on biological dosimetry, short biodosimetry.

Biological dosimetry is based on biomarkers that measure either the damage caused by ionizing radiation (such as counts of aberrant chromosomes per cell) or the (damage-repair) response by the cell to the radiation exposure (through proteins). In either case, this (typically) produces count data.

Dicentric chromosomes

Example: Calibration (laboratory) data for dicentric chromosomes

Frequencies of dicentric chromosomes in $n = 4400$ lymphocyte cells after *in vitro* 'whole body' exposure with 200 kV X-rays.

	y_{ij}								
x_i	0	1	2	3	4	5	6	7	n_i
1	1715	268	15	2	0	0	0	0	2000
2	638	298	56	8	0	0	0	0	1000
3	247	225	85	37	6	0	0	0	600
4	99	129	92	52	21	5	2	0	400
5	48	88	97	99	36	25	5	2	400

- x_i: dose (in Gy) used to irradiate blood sample i, $i = 1, \dots 5$.
- y_{ij}: counts of dicentric aberrations in j-th cell of blood sample i, $j = 1, \dots n_i$.

These are count data, so a natural choice for the response distribution is Poisson, that is

$$f(y_{ij}|x_i) = e^{-\lambda_i} \frac{\lambda_i^{y_{ij}}}{y_{ij}!}$$

where

$$\lambda_i = E(y_{ij}|x_i)$$

is some parametric model for the dose-response relationship. For parameter estimation, firstly set up the likelihood function:

$$L = \prod_{i,j} f(y_{ij}|x_i) = \prod_{i,j} e^{-\lambda_i} \frac{\lambda_i^{y_{ij}}}{y_{ij}!} \propto \prod_i e^{-n_i\lambda_i} \lambda_i^{\sum_j y_{ij}}$$

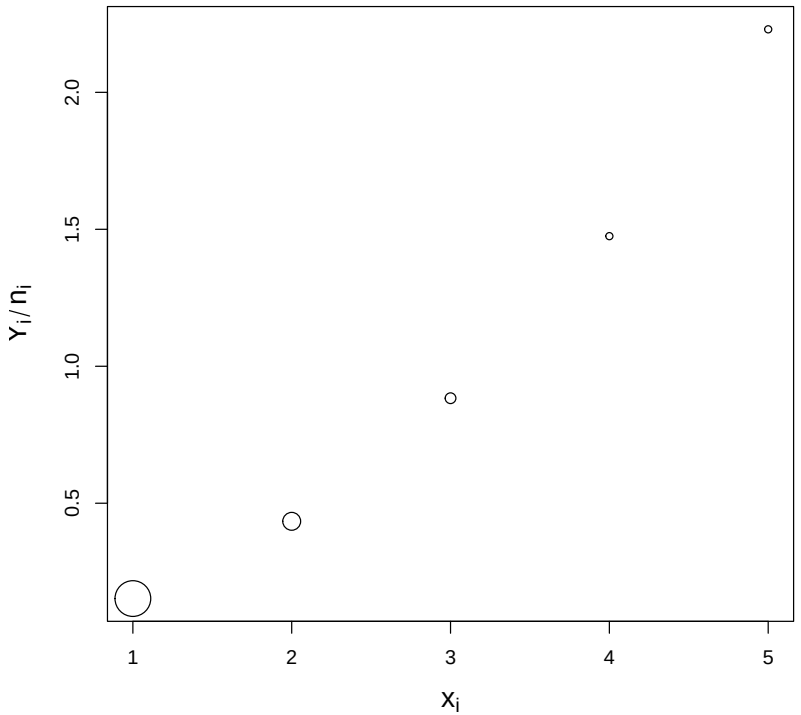
Hence, one can conveniently work at the *aggregated data* level, with data $(x_i, Y_i) = (x_i, \sum_{j=1}^{n_i} y_{ij})$.

Aggregated data

Let $Y_i = \sum_j y_{ij}$. Then the aggregated data are:

x_i	n_i	Y_i
1.0	2000	304
2.0	1000	434
3.0	600	530
4.0	400	590
5.0	400	892

Graphically, with circle size $\propto n_i$:



'Empirical dose-response curve'; this may be linear or quadratic, but in this context never exponential...

Poisson regression with identity link

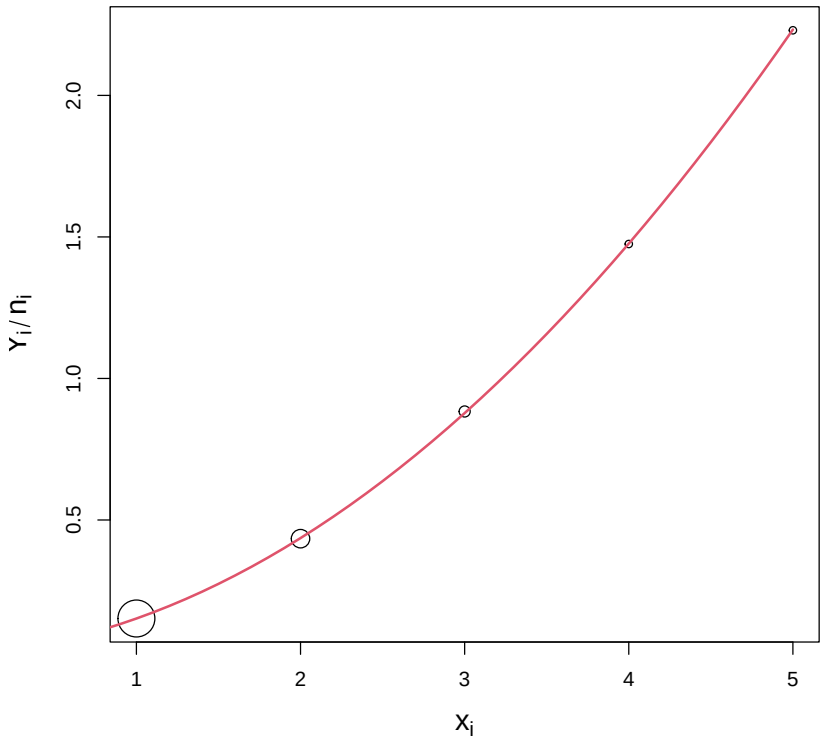
Model in terms of aggregated data: $Y_i \sim \text{Pois}(n_i \lambda_i)$ with

$$\lambda_i \equiv E(Y_i|x_i)/n_i = \beta_0 + \beta_1 x_i + \beta_2 x_i^2.$$

Fitted dose-response curve from Poisson regression,

$$\hat{\lambda}_i = \hat{\beta}_0 + \hat{\beta}_1 x_i + \hat{\beta}_2 x_i^2.$$

This curve (estimated from laboratory data) serves as calibration curve for the dose-estimation problem.



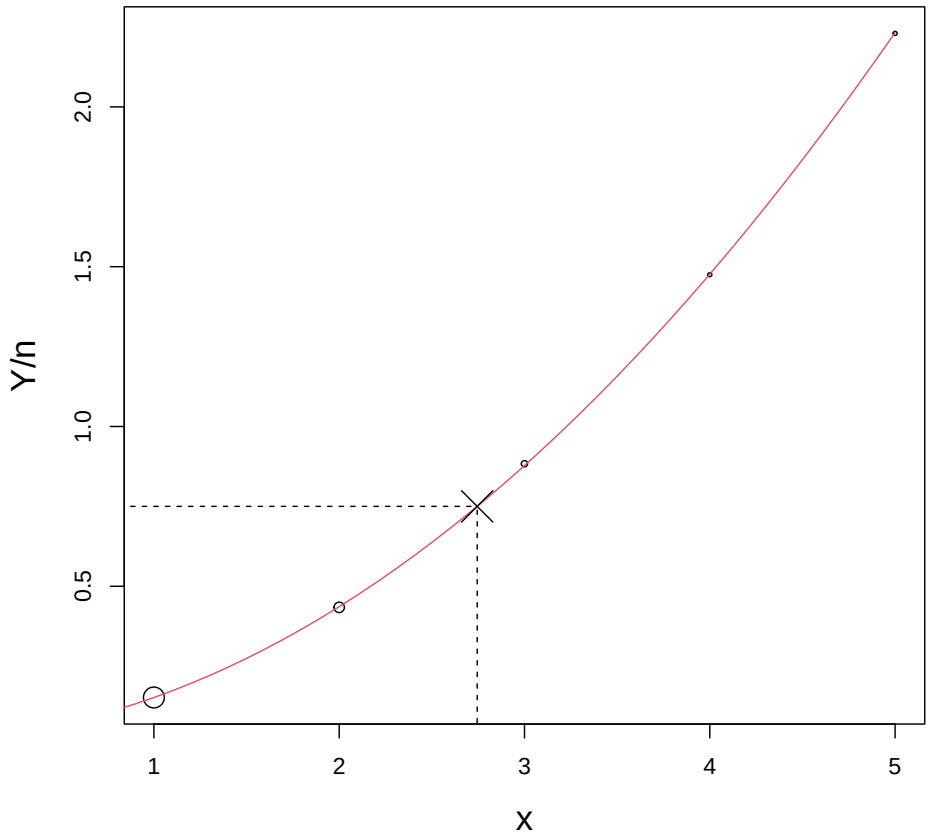
Inverse regression

Dose estimation is an inverse regression problem:

- We have a model for the dicentric count, Y_i, given dose x_i.
- In practice, we want to estimate x_i given Y_i.

Inverse regression

For instance, assume a patient has been admitted to hospital due to potential radiation exposure. A sample of $n_* = 200$ lymphocytes was analyzed, yielding $Y_* = 150$ dicentrics.



Dose estimation from calibration curve

Mathematically, this is not a big problem. Assume the observed ratio of dicentrics ('yield') is $y_* = Y_*/n_*$. Then we have

$$y_* = \hat{\beta}_0 + \hat{\beta}_1 x + \hat{\beta}_2 x^2$$

which can be solved wrt x as

$$\hat{x}_* = \frac{-\hat{\beta}_1 + \sqrt{\hat{\beta}_1^2 - 4\hat{\beta}_2(\hat{\beta}_0 - y_*)}}{2\hat{\beta}_2}$$

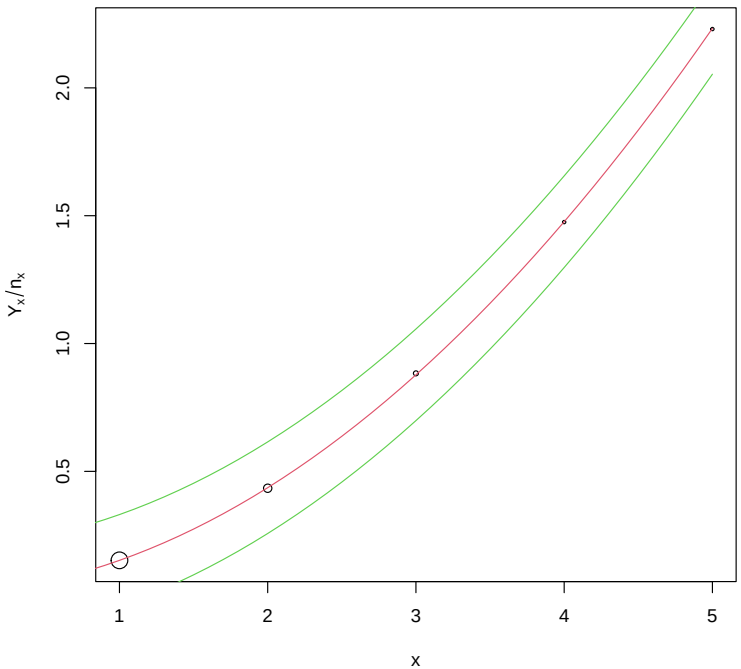
With $y_* = 150/200 = 0.75$, this gives

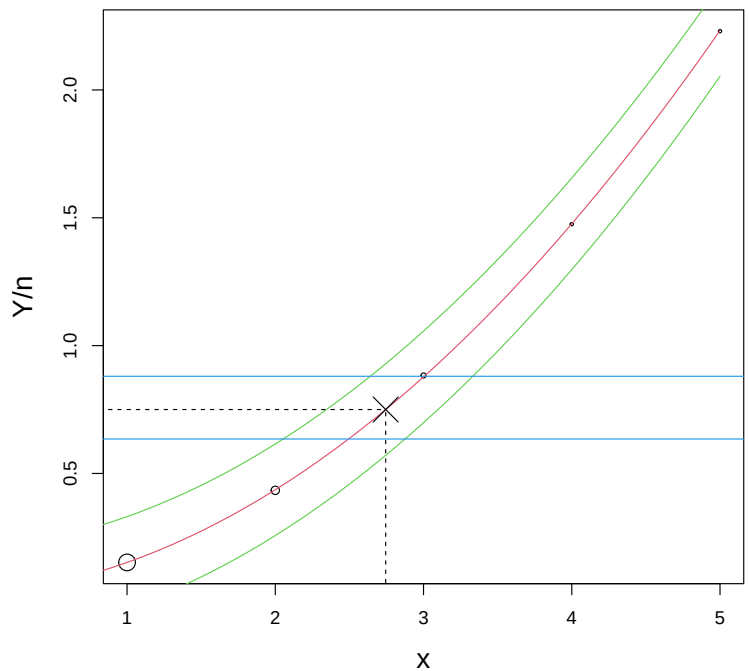
$$\hat{x}_* = 2.745.$$

Uncertainty

Of course, this estimation is not *exact*. There is uncertainty...

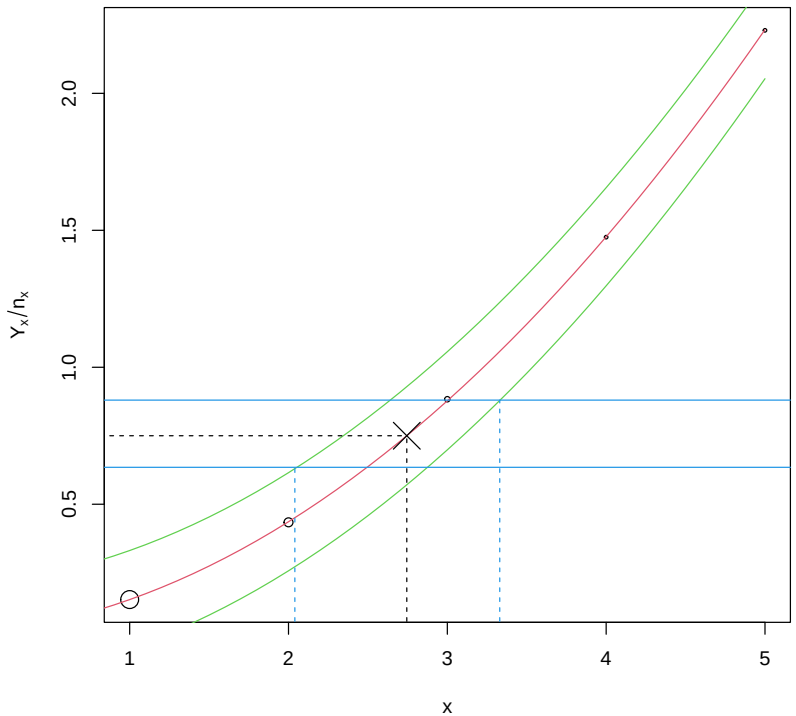
- ...due to the estimation of the calibration curve;
- ...due to random variation of Y_*, given x_*.





Uncertainty bounds

Combine the two sources of uncertainty ('Merkle's method', 1983):



Here, a 95% confidence interval for the 'true' dose, x_*, is given as $[2.04, 3.33]$.

Official uncertainty assessment routine suggested by the International Atomic Energy Agency (IAEA, 2011).

A (semi-)Bayesian approach to UQ (Higueras et al, 2015)

Estimate *in vitro* dose-response curve $\hat{\lambda}(x)$ as before.

For the (potentially) exposed patient, count dicentrics, Y_*, in a sample of n_* cells, yielding 'test data likelihood'

$$L(Y_*|\lambda, n_*) \propto e^{-n_*\lambda}\lambda^{Y_*}$$

where $\lambda = \beta_0 + \beta_1 x + \beta_2 x^2$, and x representing dose. Assume a prior density $p(x, \lambda) = \phi(\lambda|x)p(x)$, where $\phi(\lambda|x) \sim N(\hat{\lambda}(x), \mathrm{Var}(\hat{\lambda}(x)))$. Use Bayes's theorem to obtain posterior density for (λ, x):

$$p(\lambda, x|Y_*) \propto L(Y_*|\lambda, n_*)p(x, \lambda)$$

Integration over λ gives *calibrative density of* x:

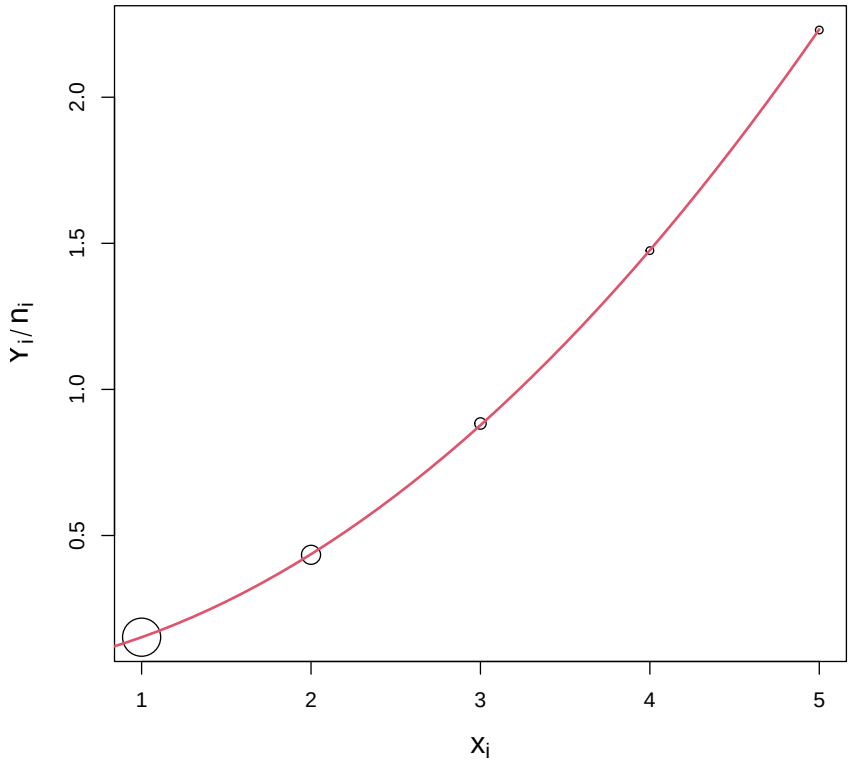
$$p(x|Y_*) \propto p(x) \int L(Y_*|\lambda, n_*)\phi(\lambda|x)\, d\lambda$$

Integral has explicit solution via Hermite distribution.

A (semi-)Bayesian approach to UQ (Higueras et al, 2015)

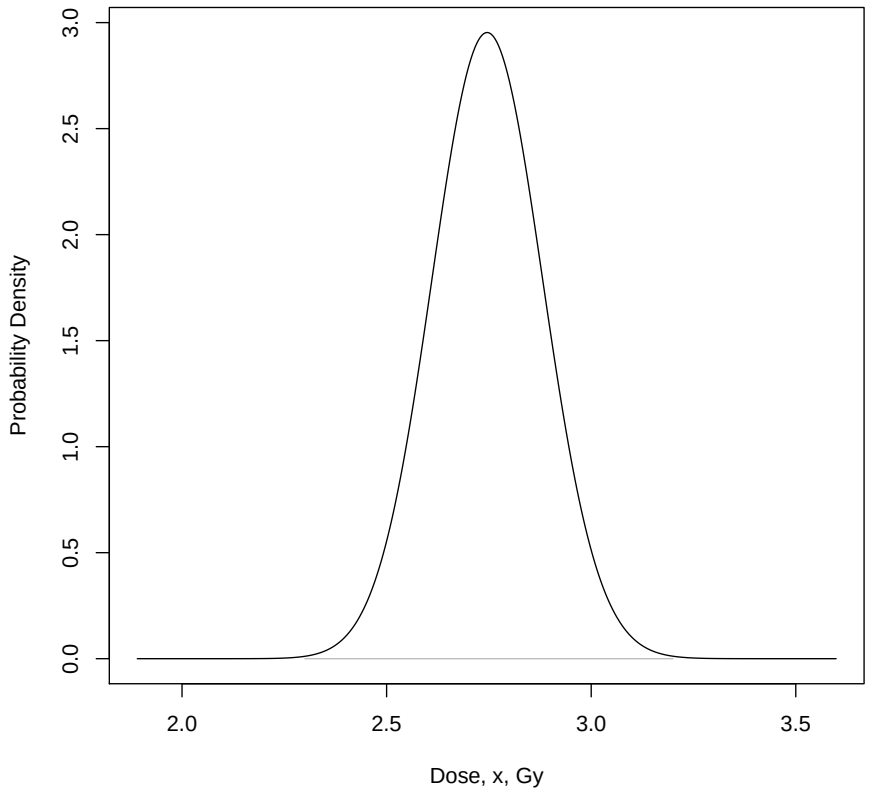
Consider again the example before: Patient sample with $n_* = 200$, $Y_* = 150$.

Use the same estimated dose–response curve, $\hat{\lambda}_i = \hat{\beta}_0 + \hat{\beta}_1 x_i + \hat{\beta}_2 x_i^2$, as before:



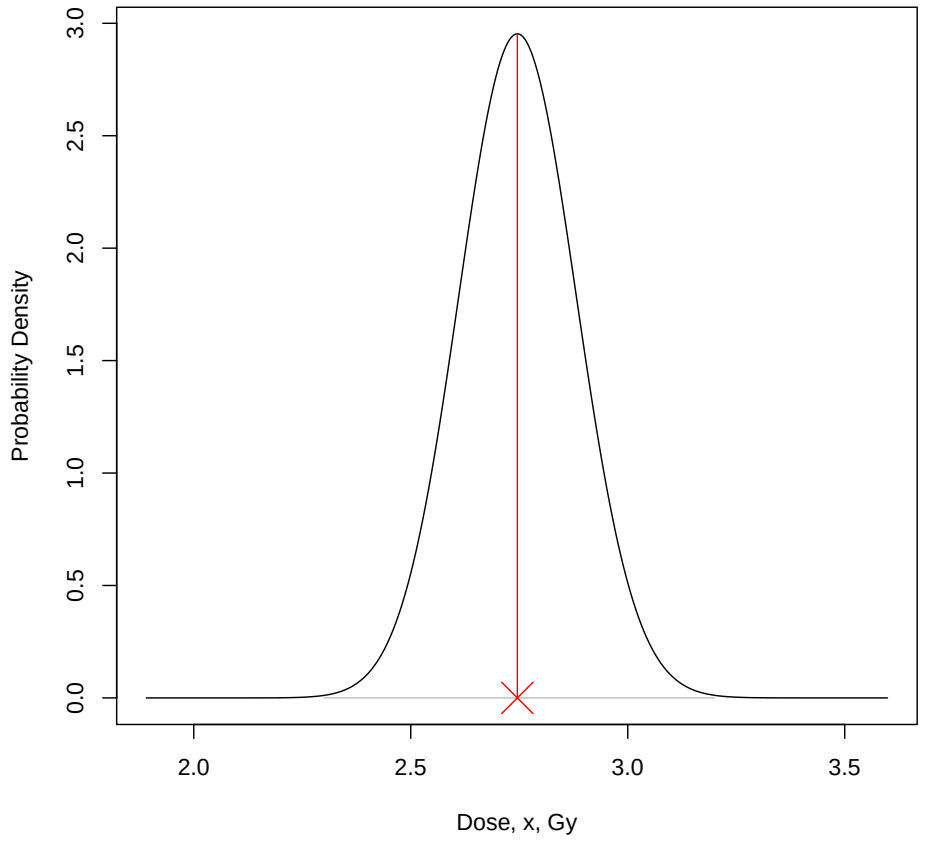
A (semi-)Bayesian approach to UQ (Higueras et al, 2015)

Calibrative density for 'true' dose x, using R package **radir**:



A (semi-)Bayesian approach to UQ (Higueras et al, 2015)

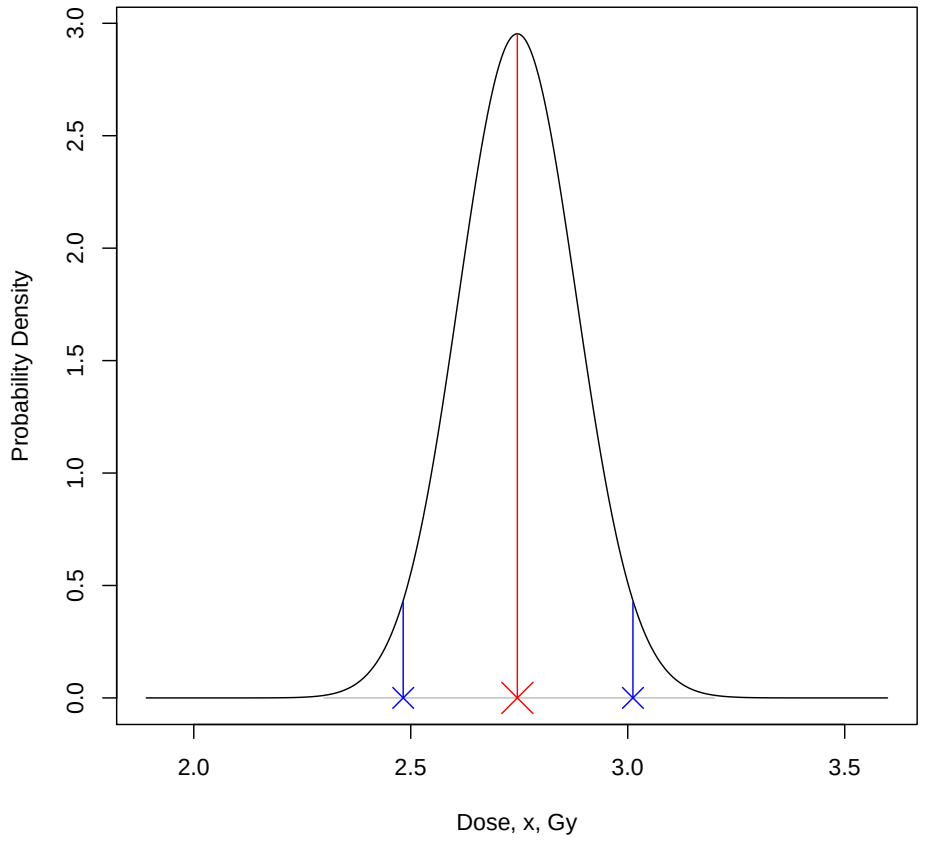
Dose estimate: Mode of calibrative density:



$$\hat{x}_* = 2.75.$$

A (semi-)Bayesian approach to UQ (Higueras et al, 2015)

Uncertainty assessment: 95% Credible intervals



$CI = [2.48, 3.01]$.

Compare Merkle:
$[2.04, 3.33]$.

Properties of the dicentric assay

Generally considered as "gold-standard" for biological dosimetry.

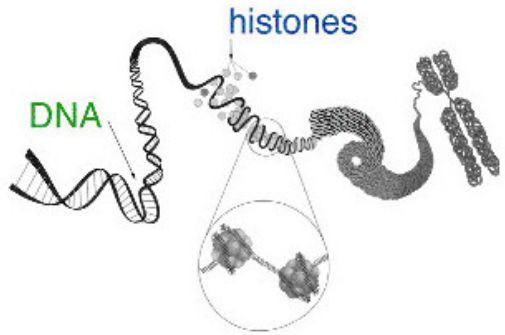
- Little inter-individual or inter-lab variation;
- Little overdispersion (hence Poisson model is appropriate);
- can be adapted to deal with partial body exposures;
- well supported by software.

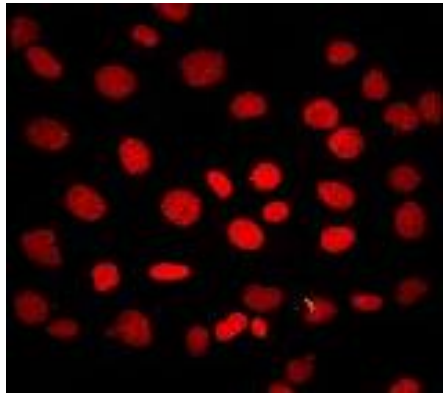
However, some disadvantages:

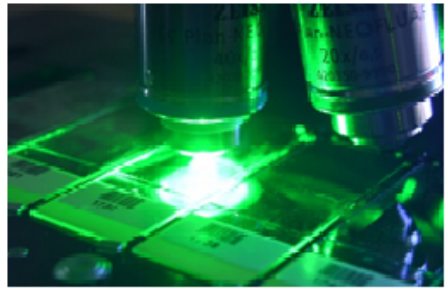
- Need to wait 2 to 3 days until metaphase in mitosis;
- Need experienced cytogeneticists for the ‘scoring’ of aberrations;
- Potential biases (cell death, repair).

Alternative biomarker: The γ-H2AX foci assay

- Histones are proteins which help to package the DNA double helix.
- Following radiation-induced double strand breaks, the H2AX histone phosphorylates, in this state referred to as γ-H2AX.
- The resulting foci can be counted manually or in a semi-automated way, using immunofluorescence microscopy.
- Typically, one examines a sample of 500-2000 (blood) cells on a given 'slide' and then records the number of foci per cell.

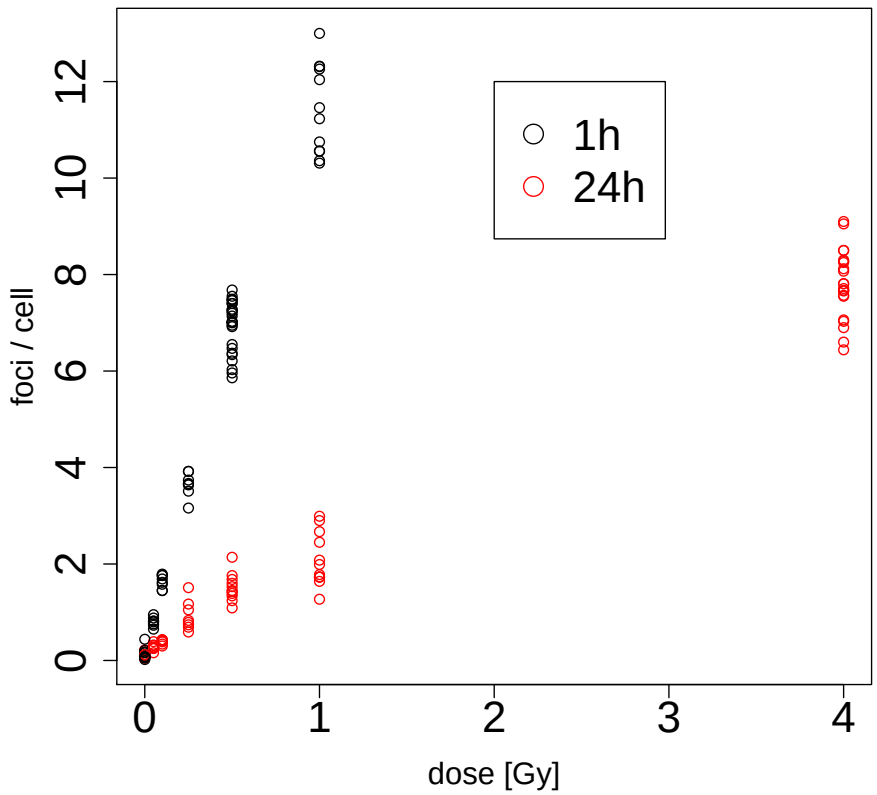






H2AX calibration data from PHE (now UKHSA)

Foci yield (that is foci/cell, out of 500 sample cells) versus design dose:



- Strong (linear?) dose–response relationship; strong decay from 1h to 24h after exposure
- H2AX-based dose estimation has to happen within 24 hours of exposure!
- Considerable variation, so Uncertainty Quantification crucial

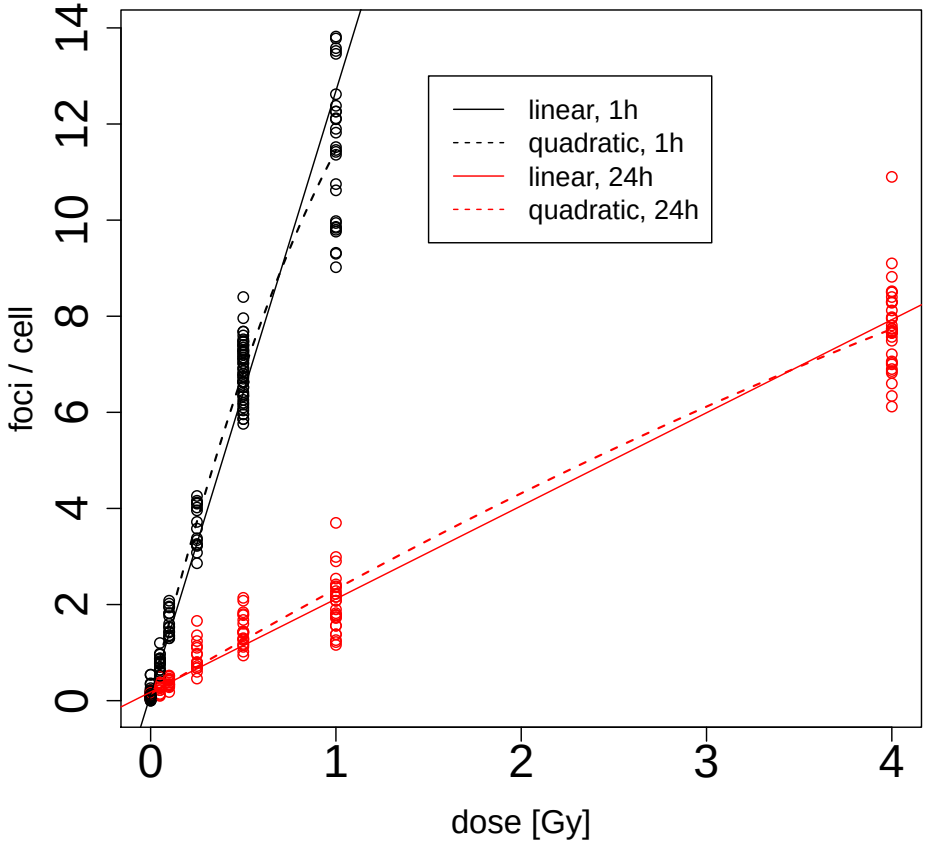
Calibration curve estimation

Denote again Y_i the total foci count from n_i cells for slide i, $i = 1, \ldots, k$.

As before, one can easily fit linear [or quadratic] curves

$$\begin{aligned} \lambda_i &\equiv E(Y_i|x_i)/n_i \\ &= A + Bx_i \,[+Cx_i^2]. \end{aligned}$$

Linear calibration curves appear sufficient for this assay.



Overdispersion

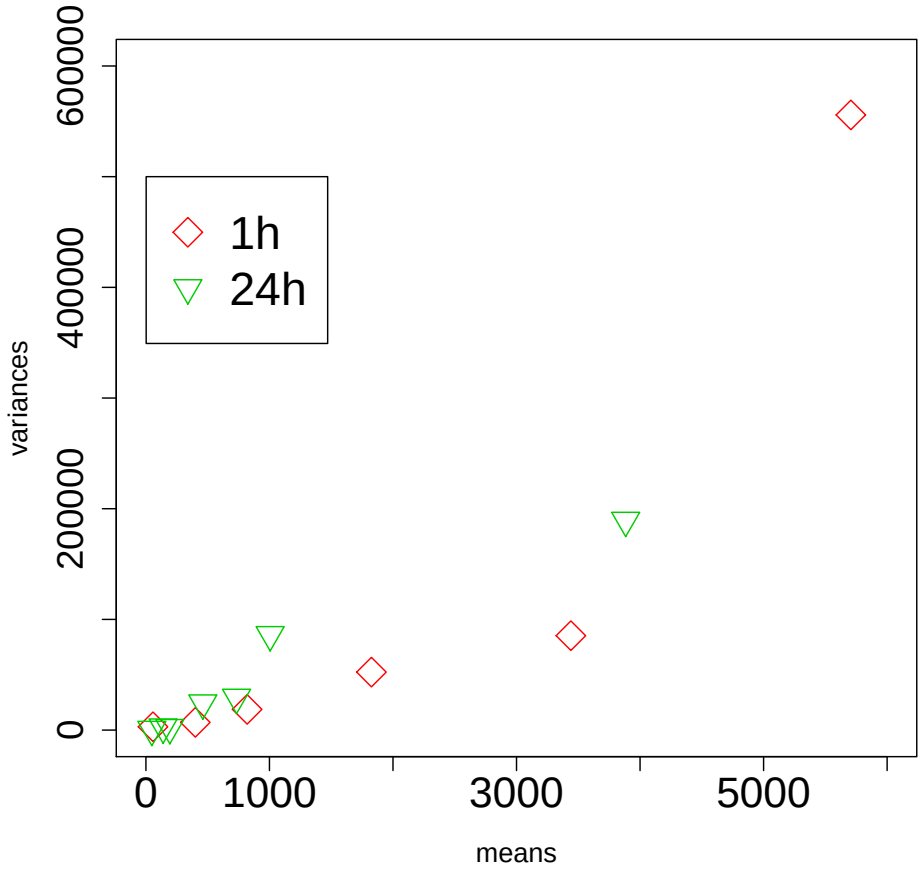
However, variance-to-mean ratio (dispersion) now $>> 1$!

In fact, linear-model based dispersion estimate

$$\hat{\phi} = \text{Deviance}/(N-2),$$

with $N = \sum_{i=1}^{k} n_i$, gives:

time	1h	24h
$\hat{\phi}$	57.91	54.26



- Overdispersed linear Poisson model

$$E(Y_i|x_i) = An_i + B(n_i x_i); \qquad \text{Var}(Y_i|x_i) = \phi E(Y_i|x_i)$$

Score equations for this model

$$\frac{1}{\phi}\sum_{i=1}^{k}\begin{pmatrix} 1 \\ x_i \end{pmatrix}(Y_i - n_i\lambda_i)/\lambda_i = \begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

... so the estimates of A and B do not depend on ϕ!

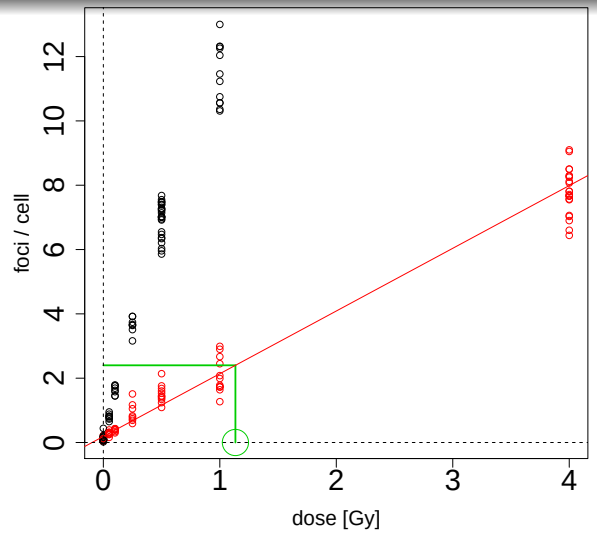
- However, standard errors do depend on ϕ, namely

$$SE(\hat{A}) = \sqrt{\hat{\phi}}\,\text{SE}_P(\hat{A}); \qquad \text{SE}(\hat{B}) = \sqrt{\hat{\phi}}\,\text{SE}_P(\hat{B}).$$

Dose estimation

Inverse regression: For a new yield y_*, one has

$$\hat{x}_* = \frac{y_* - \hat{A}}{\hat{B}}.$$



UQ via delta–method:

$$\begin{aligned} SE^2(\hat{x}_*) &\approx \left(\frac{\partial \hat{x}_*}{\partial \hat{A}}\right)^2 SE^2(\hat{A}) + \left(\frac{\partial \hat{x}_*}{\partial \hat{B}}\right)^2 SE^2(\hat{B}) + \left(\frac{\partial \hat{x}_*}{\partial y_*}\right)^2 SE^2(y_*) \\ &= \frac{1}{\hat{B}^2} SE^2(\hat{A}) + \frac{(y_* - \hat{A})^2}{\hat{B}^4} SE^2(\hat{B}) + \frac{1}{\hat{B}^2} \frac{\hat{\phi} y_*}{n_*} \end{aligned}$$

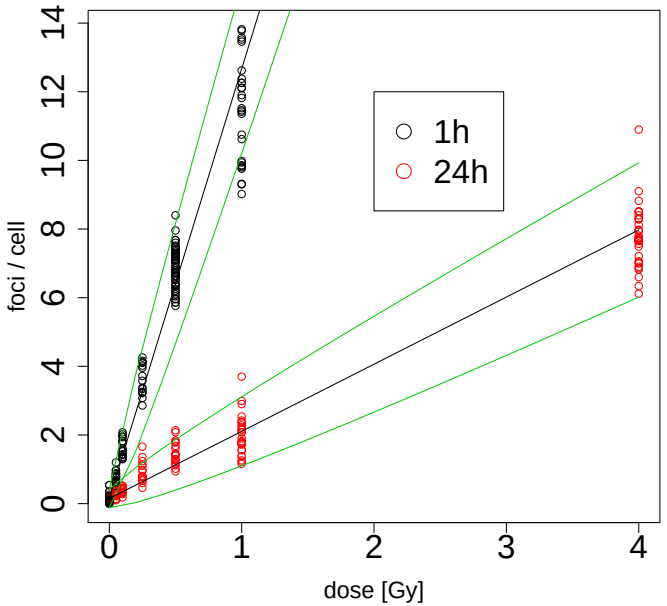
This accounts for intra– and inter–individual variation, but still requires calibration curve to be ‘correct’

Curve validation

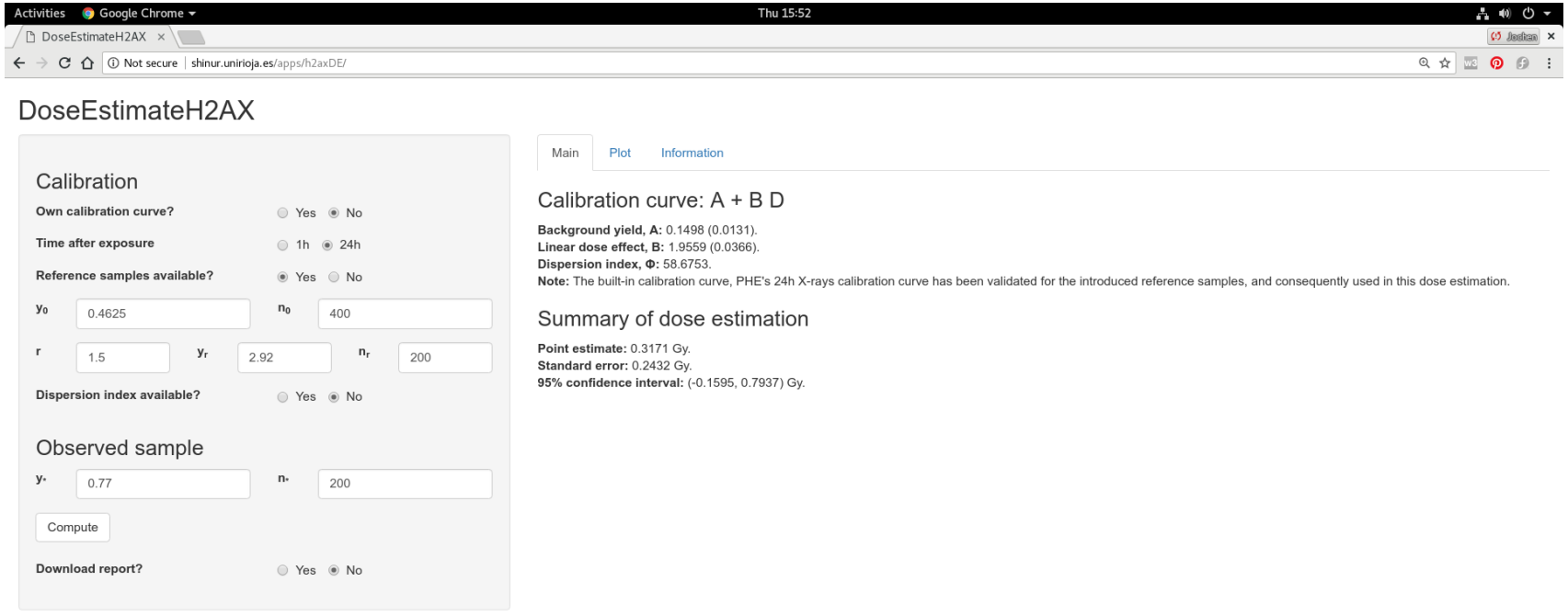
Complication: The calibration curve may vary with laboratory, scorer, equipment etc. Hence, a given calibration curve needs to be validated before use.

Before examining a patient sample, lab should irradiate two reference samples at 0Gy and 1.5Gy and compare yields with prediction interval:

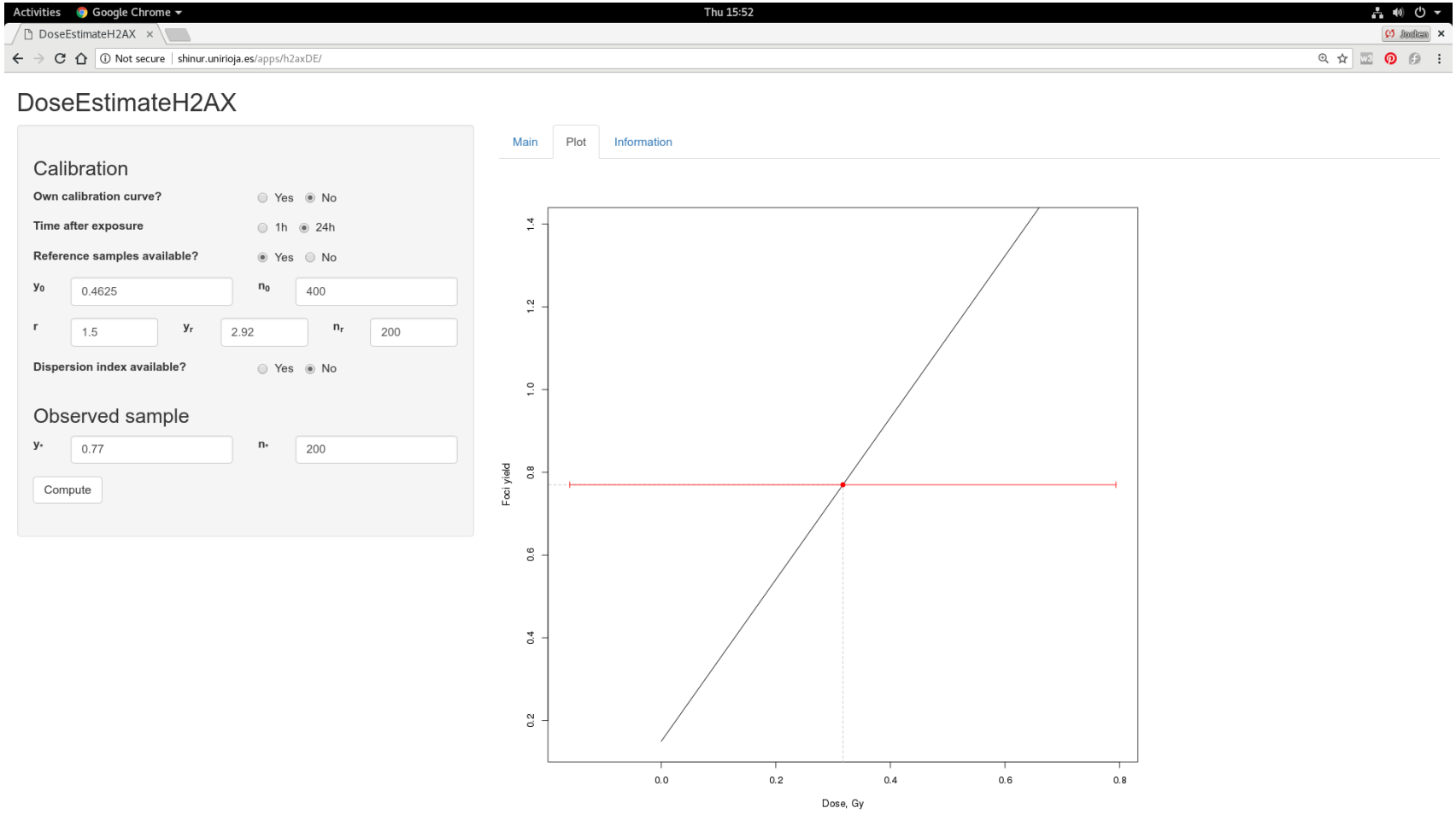
- If inside, validated
- If outside, a new calibration curve can be computed from the reference samples which still allows dose estimation, albeit at a higher variance (Einbeck et al, 2018)



Web applet


Activities
Google Chrome
Thu 15:52
DoseEstimateH2AX
Jochen
Not secure
shinur.unirioja.es/apps/h2axDE/
DoseEstimateH2AX
Calibration
Own calibration curve?
Yes
No
Time after exposure
1h
24h
Reference samples available?
Yes
No
y0
0.4625
n0
400
r
1.5
yr
2.92
nr
200
Dispersion index available?
Yes
No
Observed sample
y*
0.77
n*
200
Compute
Download report?
Yes
No
Main
Plot
Information
Calibration curve: A + B D
Background yield, A: 0.1498 (0.0131).
Linear dose effect, B: 1.9559 (0.0366).
Dispersion index, Φ: 58.6753.
Note: The built-in calibration curve, PHE's 24h X-rays calibration curve has been validated for the introduced reference samples, and consequently used in this dose estimation.
Summary of dose estimation
Point estimate: 0.3171 Gy.
Standard error: 0.2432 Gy.
95% confidence interval: (-0.1595, 0.7937) Gy.

Web applet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DoseEstimateH2AX
Calibration
Own calibration curve?
Yes
No
Time after exposure
1h
24h
Reference samples available?
Yes
No
y0
0.4625
n0
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2.92
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Dispersion index available?
Yes
No
Observed sample
y*
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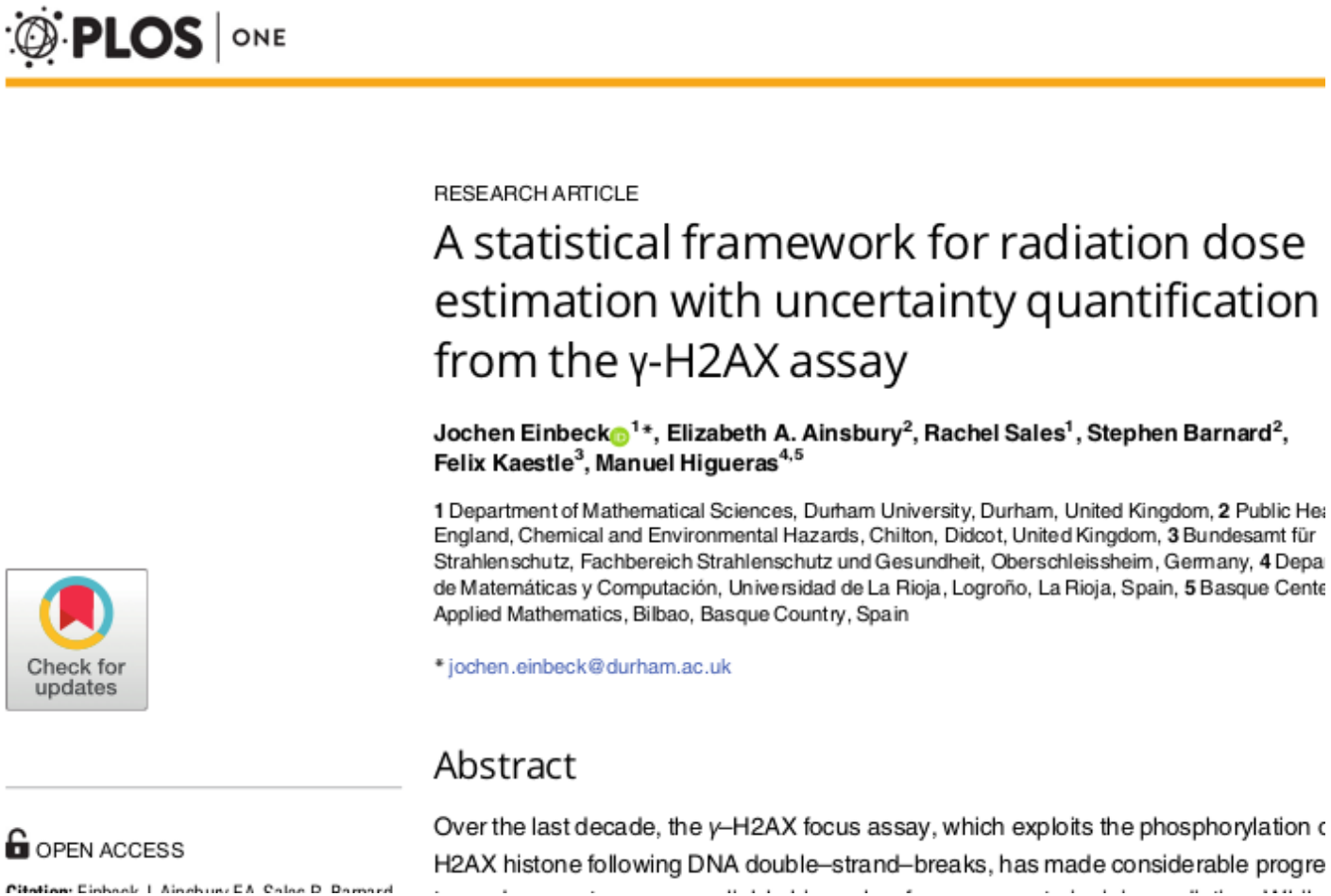
n*
200
Compute
Main
Plot
Information
Foci yield
Dose, Gy
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0.0
0.2
0.4
0.6
0.8

Dosimetry with the γ-H2AX assay



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RESEARCH ARTICLE

A statistical framework for radiation dose estimation with uncertainty quantification from the γ-H2AX assay

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Abstract

Over the last decade, the γ–H2AX focus assay, which exploits the phosphorylation o H2AX histone following DNA double–strand–breaks, has made considerable progre

Raw and aggregated data

Why is the dispersion value (≈ 60) such high?

Calibration data from dosimetry units usually come in one of two forms:

Raw data (columns with all counts for a given slide)

	A	B	C	D	E	F	G
1		0.75 Gy			1.5 Gy		
2	Control	30%	60%	100%	30%	60%	100%
3	0	4	1	3	9	4	7
4	0	0	1	3	0	1	7
5	0	0	1	2	0	5	3
6	0	0	1	3	0	0	1
7	0	5	0	5	1	0	5
8	0	3	4	2	6	0	5
9	0	0	3	3	1	7	7
10	0	0	1	1	0	4	7
11	0	0	3	7	0	0	7
12	0	2	4	5	0	0	8
13	0	0	6	4	6	0	7

Aggregated data (one row for slide, with averaged foci count)

A	B	C	D	E
Donor	Cond	n	Average	dose
1	B	50	7.52	0.5
4	C	10	8.4	4
5	B	50	7.28	0.5
6	C	40	10.9	4
7	C	10	6.9	4
9	D	50	0.14	0
9	E	50	7.1	0.5
9	F	46	8.5	4
10	D	26	0.538462	0
10	D	50	7.6	0.5
10	F	30	7.66	4
11	D	50	0.14	0

Accordingly one would use raw or aggregated data for the model fitting including the dispersion estimation.

Data aggregation and dispersion (From PhD dissertation A. Errington)

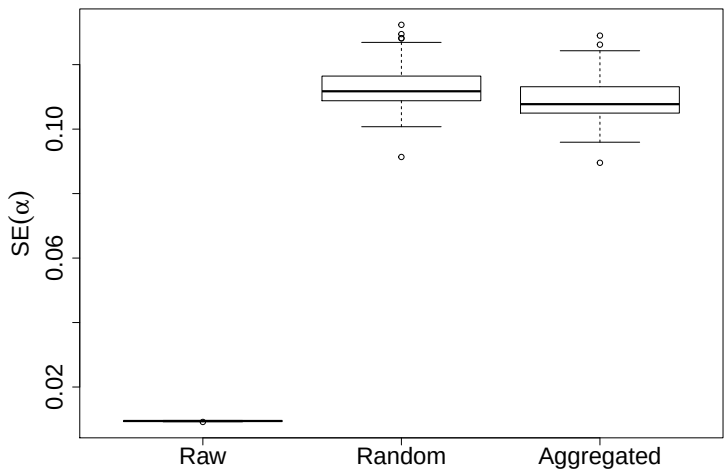
Of course, if one has the raw data available, then we can also aggregate them, and fit both (raw and aggregated data models) to compare.

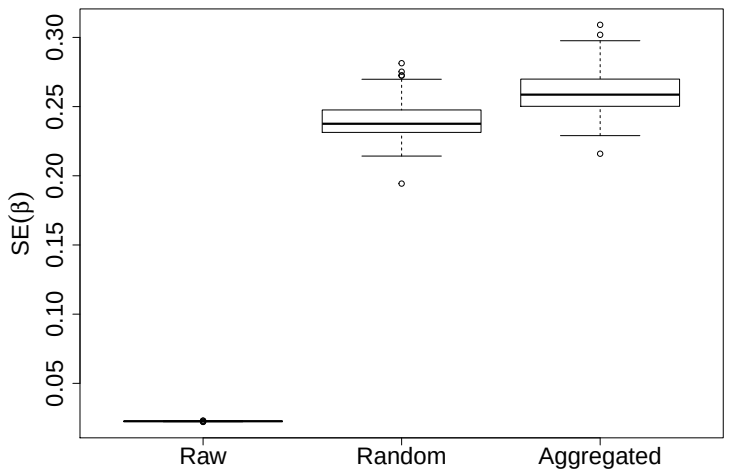
	Raw		Aggregated	
	PHE-Foci1	BfS-Foci	PHE-Foci1	BfS-Foci
$(\hat{\beta}_0, \hat{\beta}_1)$	(0.766, 1.700)	(2.011, 5.746)	(0.766, 1.700)	(2.011, 5.746)
$(\mathrm{SE}(\hat{\beta}_0), \mathrm{SE}(\hat{\beta}_1))$	(0.042, 0.058)	(0.009, 0.023)	(0.213, 0.298)	(0.102, 0.248)
$\hat{\phi}$	1.444	1.223	37.70	147.99
$\mathrm{SE}[\hat{\phi}]$	0.049	0.004	37.70	0.16
ν	1198	233218	2	114
$\chi^2_{\nu,0.95}/\nu$	1.068	1.005	2.996	1.227

Table 6.1 Parameter estimates along with their associated standard errors and dispersion estimates obtained from each model. The last row gives the critical value that $\hat{\phi}$ would be compared with in a Poisson goodness-of-fit test at the 5% level of significance.

Data aggregation and dispersion (From PhD dissertation A. Errington)

While these high dispersion estimates are clearly biased, they do correct a problem which sits elsewhere, namely unaccounted correlations in the raw data structure. Fitting raw data models naively will lead to incorrect results:





We suggest to either use the aggregated model for calibration curve fitting, or a raw data model with random effects for slides.

Data aggregation and dispersion

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Int. J. Biostat. 2022; 18(1): 183–202

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The effect of data aggregation on dispersion estimates in count data models

https://doi.org/10.1515/ijb-2020-0079

Received May 29, 2020; accepted April 21, 2021; published online May 7, 2021

Abstract: For the modelling of count data, aggregation of the raw data over certain subgroups or predictor configurations is common practice. This is, for instance, the case for count data biomarkers of radiation exposure. Under the Poisson law, count data can be aggregated without loss of information on the Poisson parameter, which remains true if the Poisson assumption is relaxed towards quasi-Poisson. However, in biodosimetry in particular, but also beyond, the question of how the dispersion estimates for quasi-Poisson models behave under data aggregation have received little attention. Indeed, for real data sets featuring unexplained heterogeneities, dispersion estimates can increase strongly after aggregation, an effect which we will demonstrate and quantify explicitly for some scenarios. The increase in dispersion estimates implies an inflation of the parameter standard errors, which, however, by comparison with random effect models, can be shown to serve a corrective purpose. The phenomena are illustrated by γ-H2AX foci data as used for instance in radiation biodosimetry for the calibration of dose-response curves.

Estimation of dose and time

- The γ-H2AX assay has a strong time-dependency. Ideally, we could estimate simultaneously exposure time and dose.
- Basic idea: If one had TWO measurements of foci yield at unknown points but with known time distance, one has two pieces of information to work out dose and exposure time from the relevant equations.
- Our work takes the premise that, for a given lab, two lab-specific calibration curves at *any* time points are available, and that the physical decay mechanism between measurement points is universal (not lab-specific).

Linking calibration curves with foci decay

We know from the literature that γ-H2AX foci decay follows a double-exponential law.

Hence a suitable model is

$$y = a + bt + d(Ae^{ut} + Be^{vt}) \tag{1}$$

where a, b, A, B, u, v are constants.

Assume further that we have two patient samples available (considered as realizations of model (1)), at time points t_0 and $t_0 + \Delta$, with known Δ.

The values t_0 are d are to be inferred.

Find values for a, b, A, B, u, v.

The parameters u and v are determined by the physical decay mechanism and hence we fix them at $u = -0.35$ and $v = -0.018$ (Horn et al, 2011).

The parameters a, b, A, B are related to the absolute magnitude of foci observed, and hence are lab-specific. We can obtain them by equating the calibration curves $y_t = a_t + d \times b_t$, for $t = t_1, t_2$ to the model equation:

- For the 'background radiation'
$$a_t = a + bt$$
- For the dose-dependent part
$$b_t = Ae^{-0.35t} + Be^{-0.018t}$$

  Note these are two equations each, at $t = t_1, t_2$.

Estimating time and dose

For the actual dose and time estimation,

- set up a system of two equations of type (1) with our two yield measurements at times t_0 and $t_0 + \Delta$,
- solve this system for d and t_0, for which we use the Mathematica solver “NSolve".

Example for PHE data

The calibration curves of the previously shown PHE data

$$y_1 = 0.13 + 12.56d$$

$$y_{24} = 0.18 + 1.94d$$

lead to the system of equations

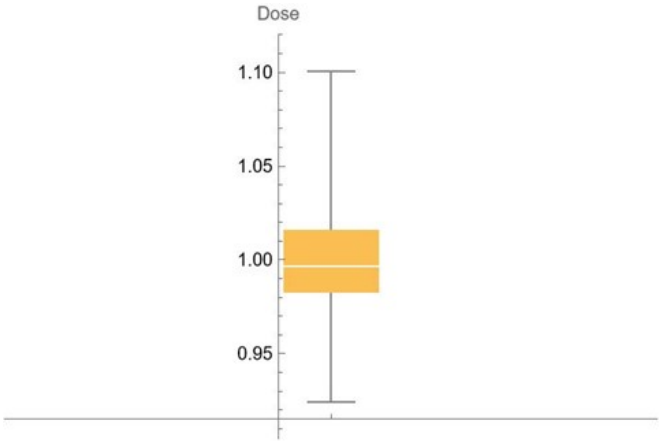
$$\begin{aligned} y_t &= 0.13 + 0.0021t + d(13.62e^{-0.35t} + 3.01e^{-0.018t}) \\ y_{t+\Delta} &= 0.13 + 0.0021(t+\Delta) + d(13.62e^{-0.35(t+\Delta)} + 3.01e^{-0.018(t+\Delta)}) \end{aligned}$$

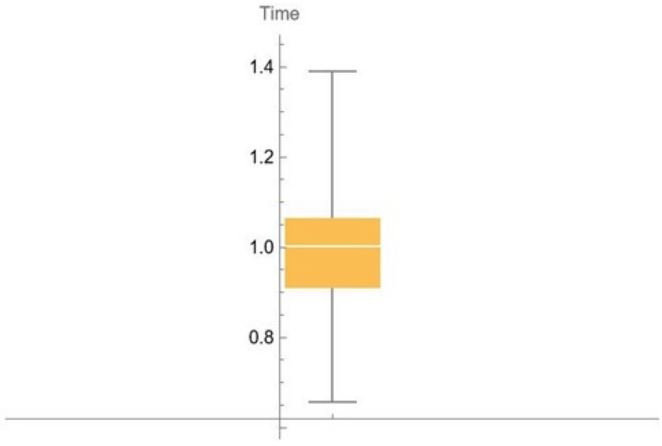
which can be solved for any two yields y_t, $y_{t+\Delta}$ at unknown times t, $t+\Delta$ with known Δ.

Simulation (from MSc dissertation Y. Cai)

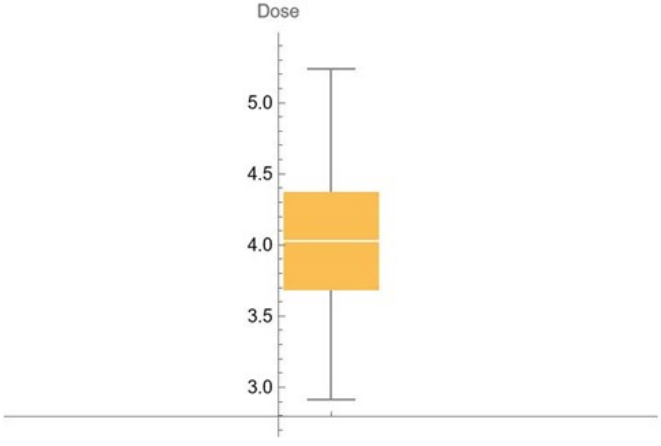
100 NB count data sets simulated from y_1, y_{24} ($\phi = 50$, $n = 500$)

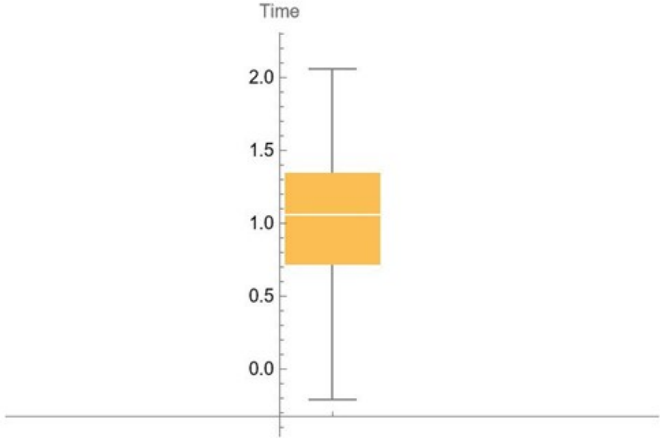
True dose
1Gy



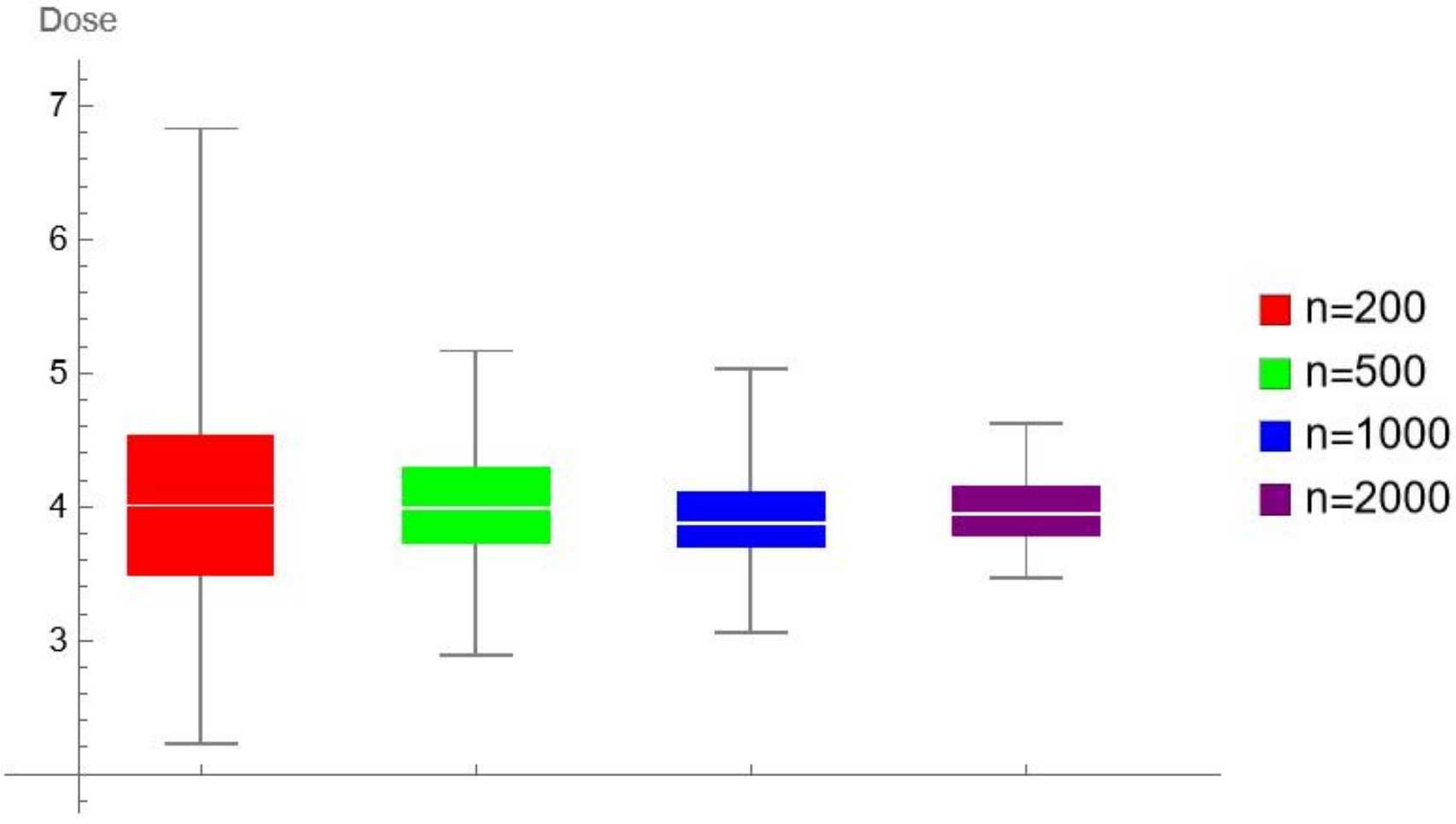


True dose
4Gg

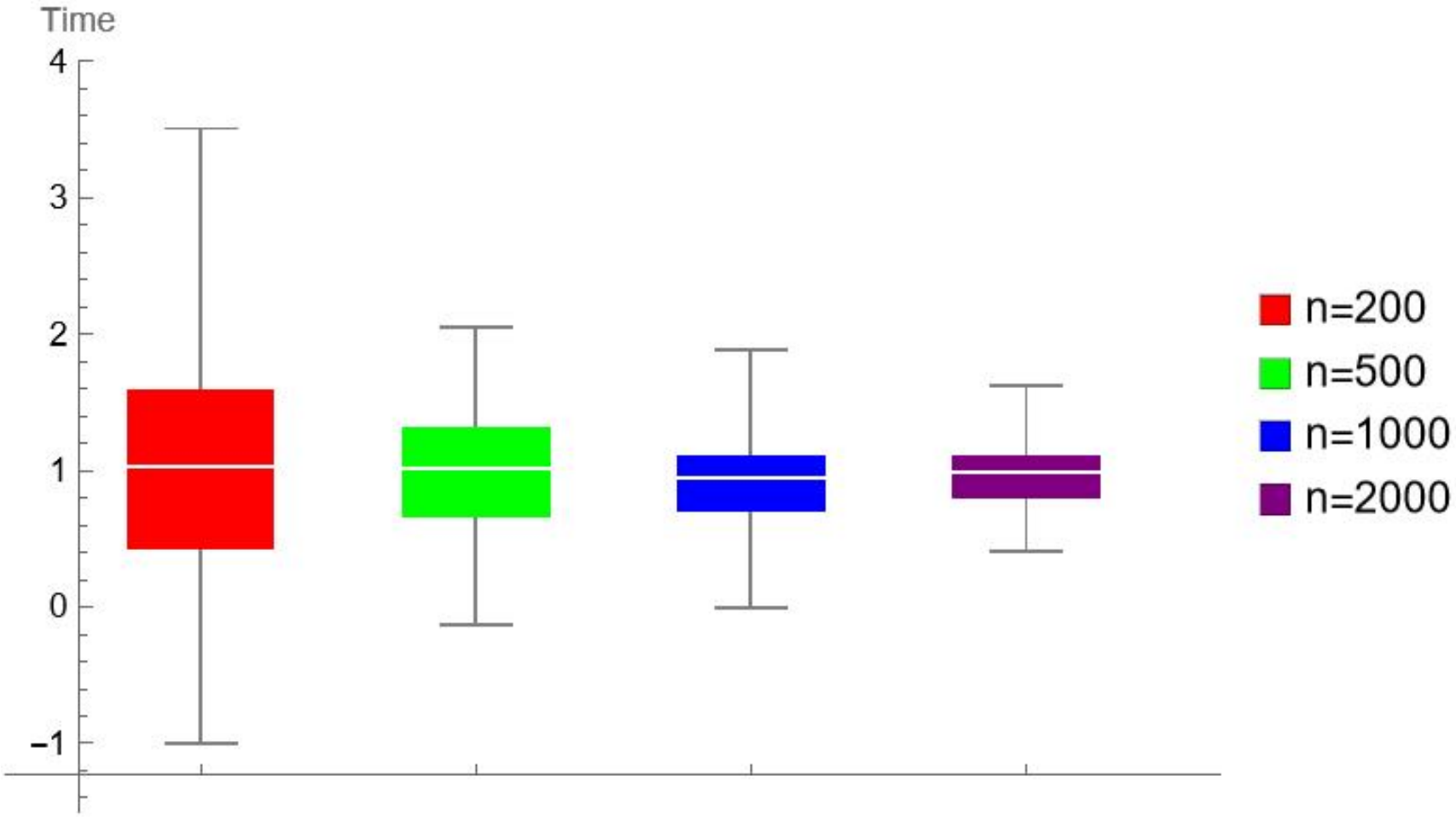




Impact of number of cells on dose estimates



Impact of number of cells on time estimates



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Abstract

In order to analyze the potential damage to the human body caused by exposure to ionizing radiation, one needs to have an estimation of the dose of radiation received by the individual. In the context of a protein-based biomarker for radiation exposure, we present here a new method that, unlike the approaches that produce the estimation with data collected at a predetermined time after exposure, allows us to estimate the dose at any time within a reasonable time interval after exposure, as well as determine the time of exposure if needed. Namely, we take existing calibration curves and generalize them using the decay mechanism of γ-H2AX foci to build a model that describes the functional relationship between the count of γ-H2AX foci in exposed blood cells and the time and dose of exposure. This model is illustrated using both real and simulated data.

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(Experimental UQ in progress...
but encounters some difficulties as numerical solvers are involved...).

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Biodose Tools

Overview

Biodose Tools (Hernández et al. 2023) is an open source project that aims to be a tool to perform all different tests and calculations needed by biological dosimetry laboratories. The app is developed using the R programming language and Shiny as a framework to offer an online, easy-to-use solution. Although the intention is to provide the application as a website, all R routines are available as an R package, which can be downloaded for improvement or personal use.

We also aim to clarify and explain the tests used and to propose those considered most appropriate. Each laboratory in its routine work should choose the most suitable method, but the project aims to reach a consensus that will help us in case of mutual assistance or intercomparisons.

The project is initially developed by RENEB association, but contributions are always welcome.

Links

View on CRAN

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Citation

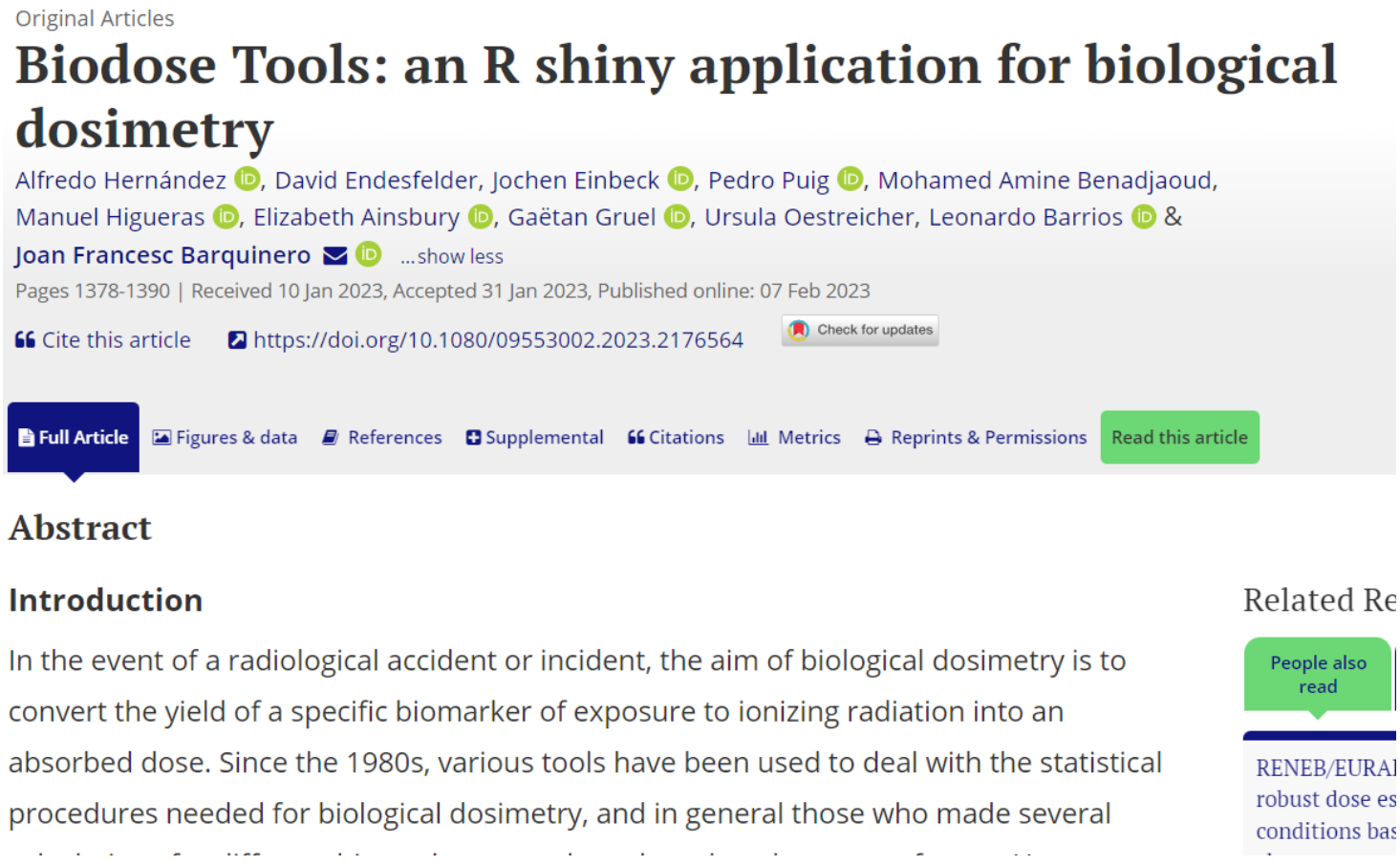
Citing biodosetools

Developers

Alfredo Hernández

Author, maintainer

Biodose Tools



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Pages 1378-1390 | Received 10 Jan 2023, Accepted 31 Jan 2023, Published online: 07 Feb 2023

Cite this article https://doi.org/10.1080/09553002.2023.2176564 Check for updates

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Abstract

Introduction

In the event of a radiological accident or incident, the aim of biological dosimetry is to convert the yield of a specific biomarker of exposure to ionizing radiation into an absorbed dose. Since the 1980s, various tools have been used to deal with the statistical procedures needed for biological dosimetry, and in general those who made several

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Biodose Tools

- available as R Shiny app, can be downloaded from CRAN or Github
- hosted and managed by the BfS, Munich
- currenty supports
  - Dicentrics
  - Translocations
  - Micronuclei
- Durham-based RA (Y. Zhang) currently working on γ-H2AX extension

Software for biodosimetric analysis:

BioDoseTools (Frequentist) dose estimation for dicentric chromosomes, micronuclei, and translocations. Available as R Shiny App: https://aldomann.shinyapps.io/biodosetools-v3/

radir (Bayesian) dose estimation, mainly for dicentric chromosomes. R package Available on CRAN: https://cran.r-project.org/package=radir

DoseEstimateH2AX (Frequentist) dose estimation for the γ-H2AX assay. Available as R Shiny App: https://shinur.unirioja.es/apps/h2axDE/

References

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Horn S et al (2011). Gamma-H2AX-based dose estimation for whole and partial body radiation exposure. *PloS ONE*, **6**(9): e25113.

Higueras M et al. (2015). A new inverse regression model applied to radiation biodosimetry. *Proc's of the Royal Society* **471**.