Radiation dose estimation through the gamma-H2AX protein

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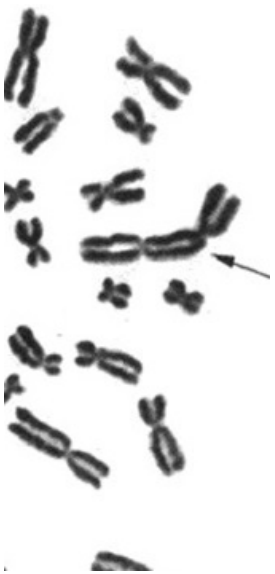
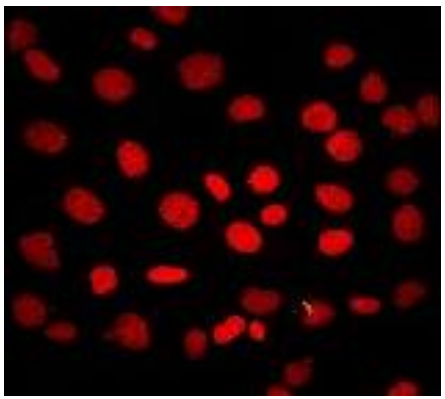
Radiation biodosimetry

- Radiation incident leading to (potentially) exposed inviduals
- Contracted radiation dose can be estimated restrospetively by exploiting the radiation-induced change in certain biomarkers
- 'Gold–standard': Dicentric chromosomes (resulting from unsuccessful DNA–damage response)
- However: time– and work–intensive and expensive methodology



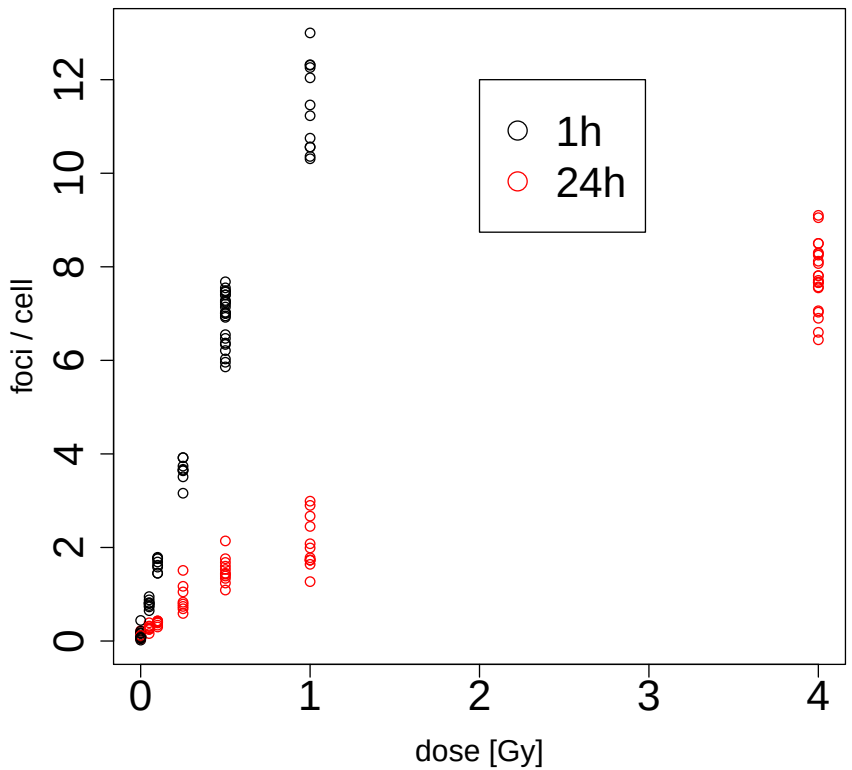
γ-H2AX as radiation biomarker

- Biomarkers based on proteins have recently emerged as a quicker and cheaper alternative
- The H2AX–histone responds to radiation–induced double strand breaks with phosphorylation, in this state then referred to as γ–H2AX
- γ–H2AX foci can be counted manually (immunofluorescence microscopy) or automated (flow cytometers)



H2AX calibration data from PHE

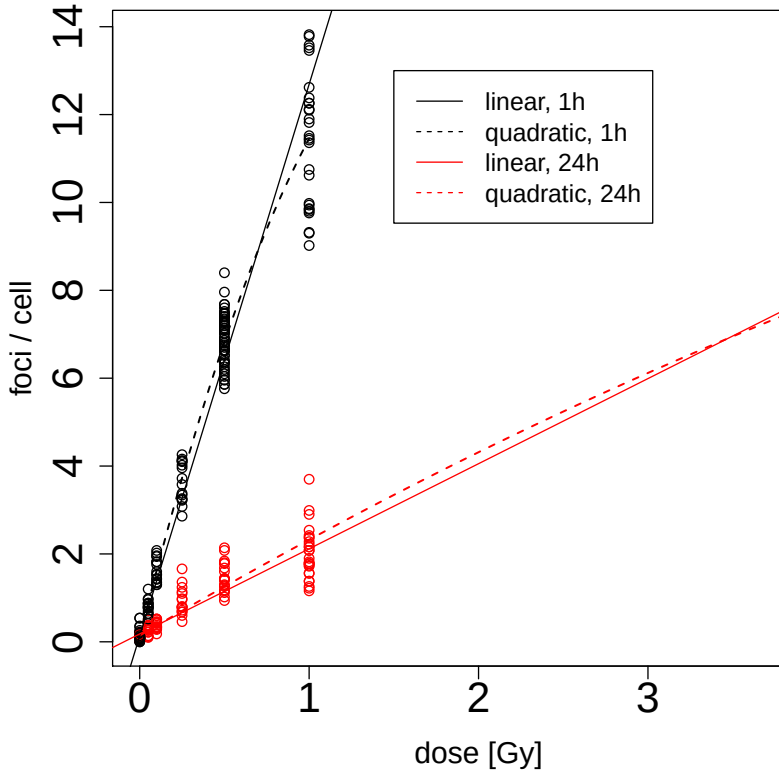
Foci 'yield' (that is foci/cell, out of 500 sample cells) versus design dose:



- 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

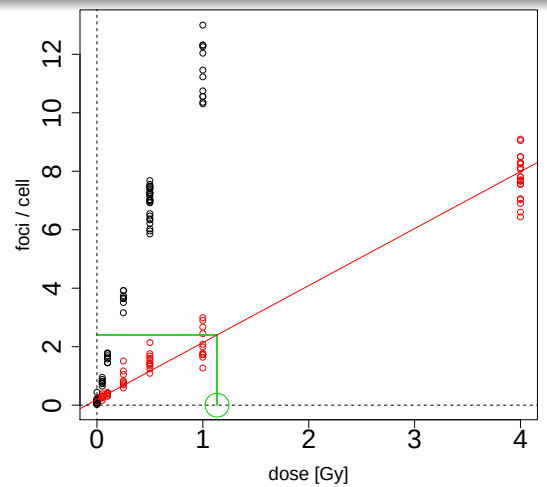
- Given calibration data (x_i, y_i), with x=dose, y =yield
- Count data (Poisson) regression with mean function $A+Bx$, gives estimates $\hat{A}$, $\hat{B}$
- Huge overdispersion ($\hat{\phi} \approx 60$!)
- Quasi-likelihood approach needed to obtain correct parameter standard errors



Dose estimation

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

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



- UQ via delta–method:

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

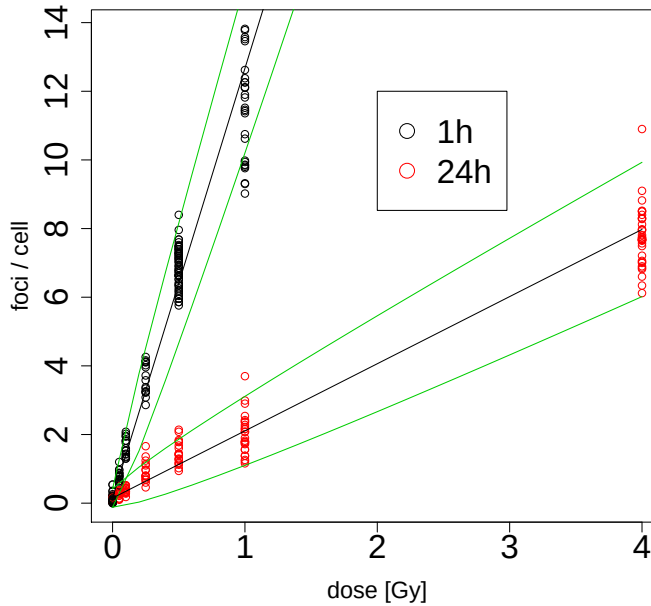
- This accounts for intra– and inter–individual variation, but still requires calibration curve to be ‘correct’

Curve validation

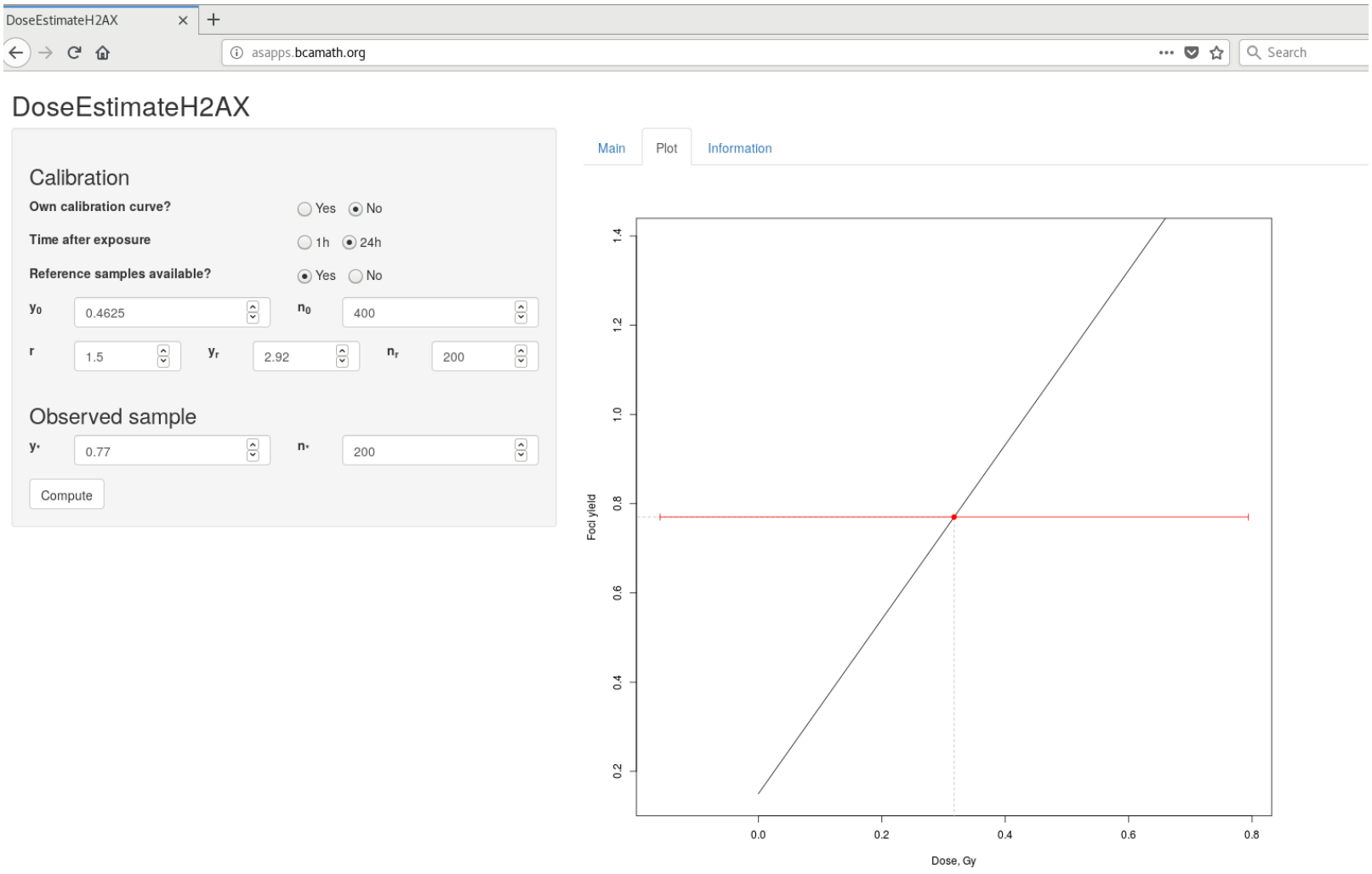
Complication: The calibration curve may vary with laboratory, scorer, equipment etc. Hence, a given calibration curve needs to be validated before use.

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



Web applet


DoseEstimateH2AX
asapps.bcamath.org
Search
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
Observed sample
y*
0.77
n*
200
Compute
Main
Plot
Information
Foci yield
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0.0
0.2
0.4
0.6
0.8
Dose, Gy

Summary

We believe to have solved the questions regarding

- ... the incorporation of overdispersion
- ... the validation of the calibration curve
- ... the quantification of uncertainty in this process

Open questions are

- Is the dispersion a 'universal property of foci counts', or a feature of the scoring mechanism?
- Partial body exposure cannot be easily identified since overdispersion will be present either way

Future directions

- Combinations of Biomarkers
  Idea: Use quick and cheap (but potentially high variance) biomarkers such as H2AX for the triage step, and a more precise biomarker (such as the dicentric assay) as a second step, depending on the first outcome. Bayesian approach favorable here.

- Why always estimate 'dose'?
  There is some fixation in the community on always estimating *dose*. Why not triage directly based on the H2AX count? This removes need for inverse regression, and reduces uncertainties. Could be dealt with easily through ordinal logistic regression.

References

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