Radiobiological Models

Hyperboost Training Course Model-based Data Analysis for Clinical Applications

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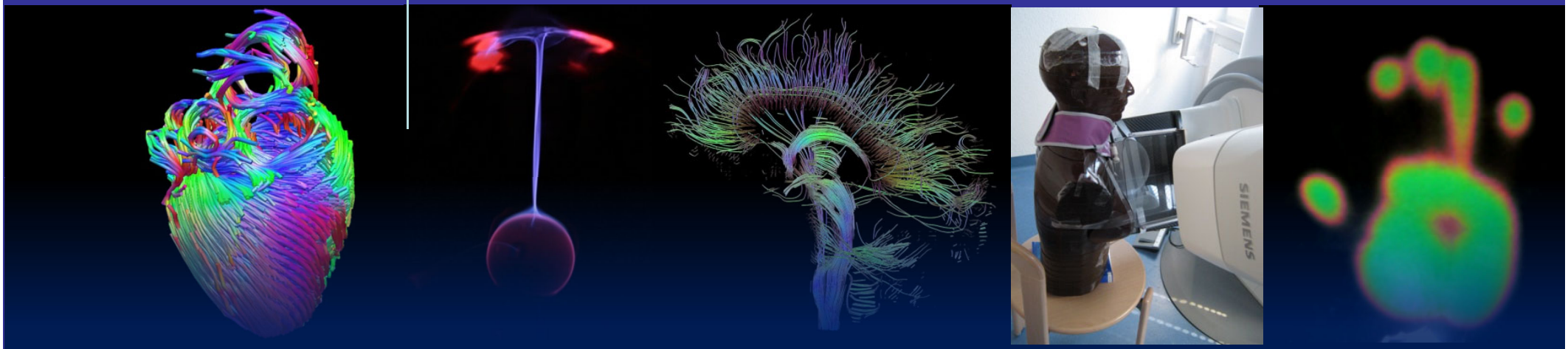
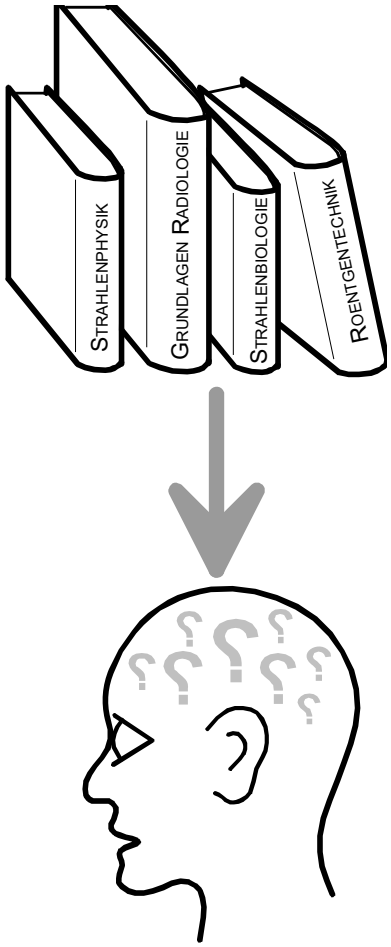
Medical Biophysics Group ZHAW
2024



CONTENT MBDA



Model-based data analysis for clinical application – Modelling and Biological Systems:

Day 1

0920-1100: Modelling and Biological Systems
1320-1400: Using Graphical Model Editors
1400-1450: Using Python for Model Fitting

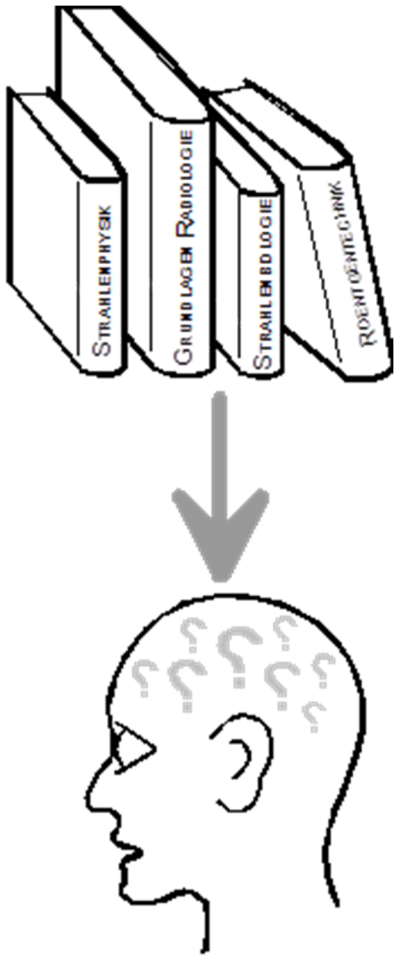
Day 2

1110-1200: Biokinetic / Biodynamic Modelling (→ Lab2: Model-based Data Analysis of PET Images)

Day3

0900-1100: Radiobiological Models

Content



Modelling Survival

- LQ- / LQL- Type Models
- Transient Biological Dose Equivalent TDBE
- MHR Model

TCP & NTCP

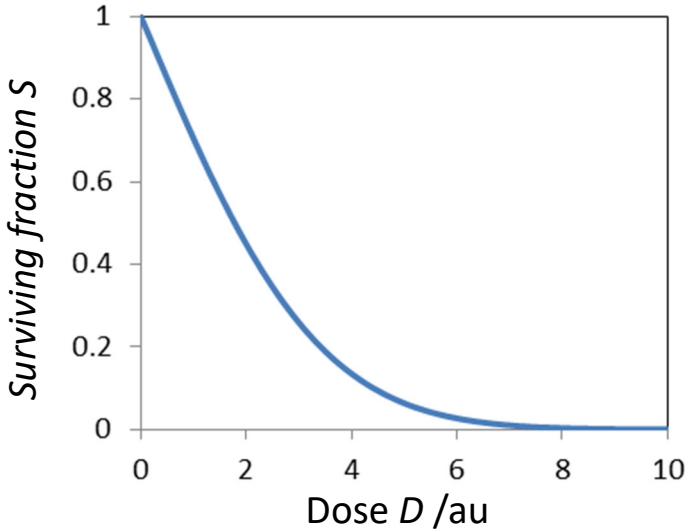
Learning Objectives

Students are able

- to describe the limitations of the LQ model
- to explain the differences between data-descriptive and dynamic ("mechanistic") models
- to understand the different assumptions for dynamic models
- to use dynamic radiobiological models for data fitting
- to calculate TCP from survival data
- to model TCP/NTCP

Modelling Survival

LQ Models



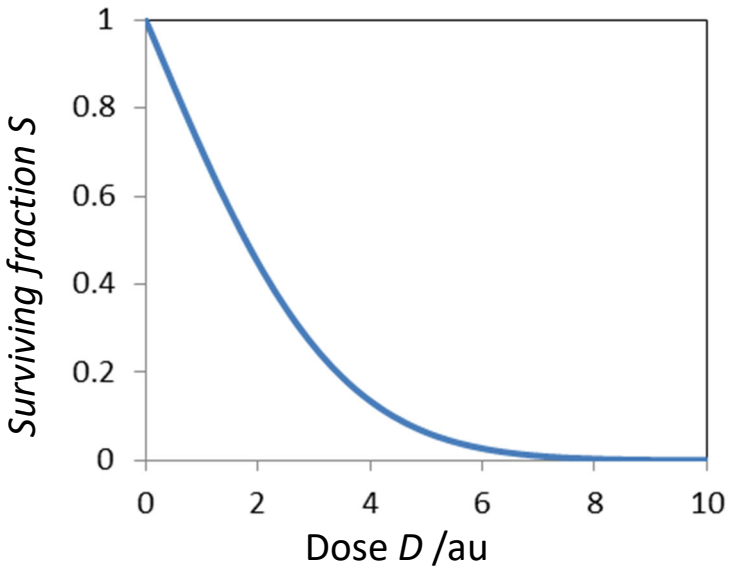
Linear-quadratic (LQ) models: Often used for anticancer treatments using chemo- or radiation therapy.

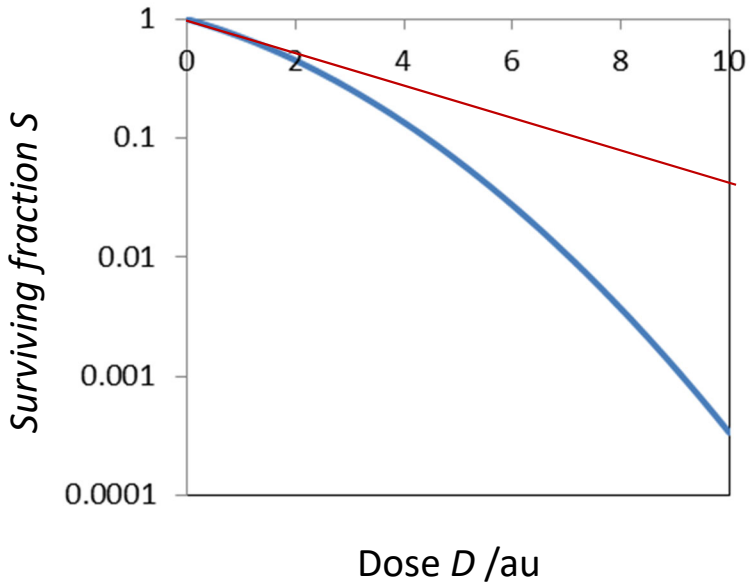
- Survival (surviving fraction of cancer cells *S*) is modelled as function of the dose *D*:

$$S = \frac{N}{N_0} = e^{-(\alpha D + \beta D^2)}$$

Fig.9. Surviving fraction *S* as a function of the dose *D* with a linear quadratic model (linear scales).

LQ Models





$$S = \frac{N}{N_0} = e^{-(\alpha D + \beta D^2)}$$

$$\ln S = -\left(\alpha D + \beta D^2\right)$$

Fig.10. Surviving fraction *S* as a function of the dose *D* with a linear quadratic model, left: linear scale, right: log-scale; α = 0.3 / au; β = 0.05 / au^2.

Radiation Biology: Cellular Effects

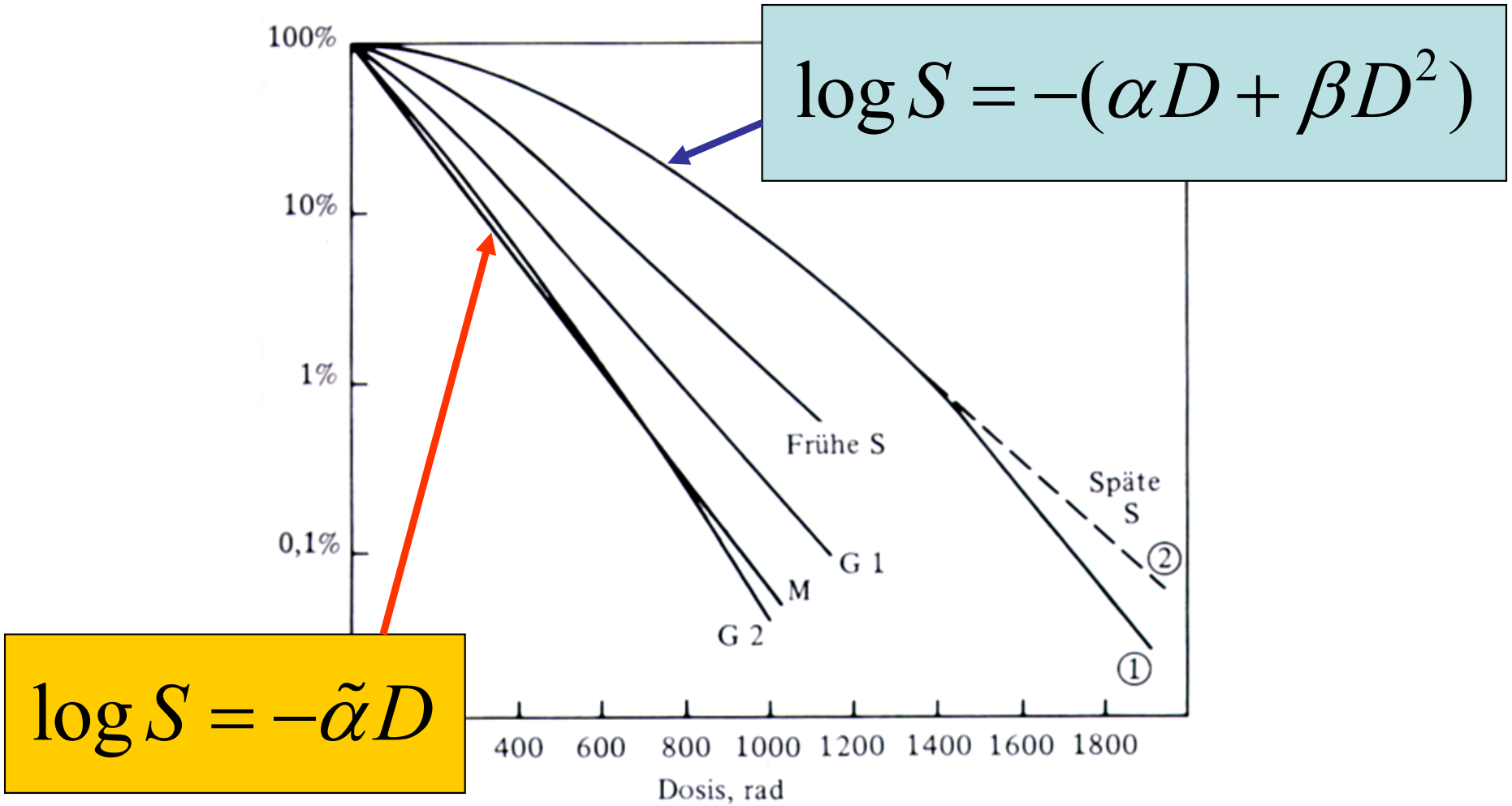


Fig.20. Survival for CHO cells after irradiation with 250 keVp photons (Fritz-Niggli, 1997; from Sinclair, 1968)

LQ Radiosensitivity Model Parameters

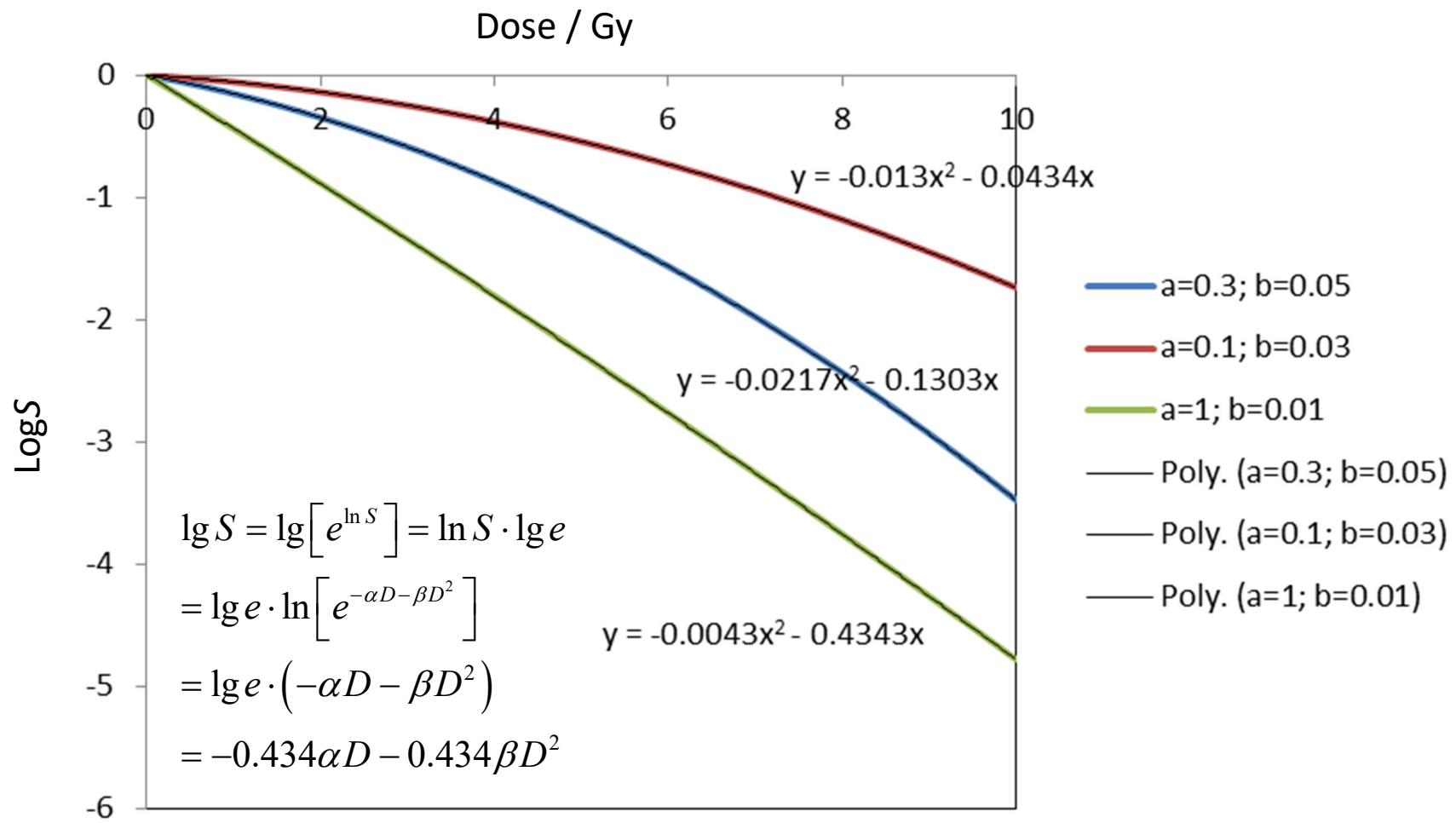
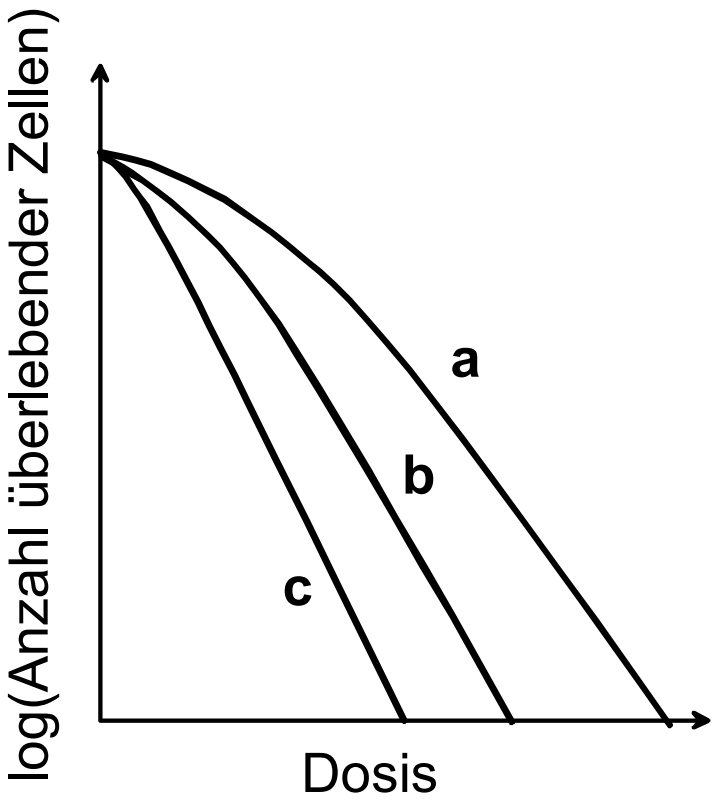


Fig.20. Survival for different α- and β-values.

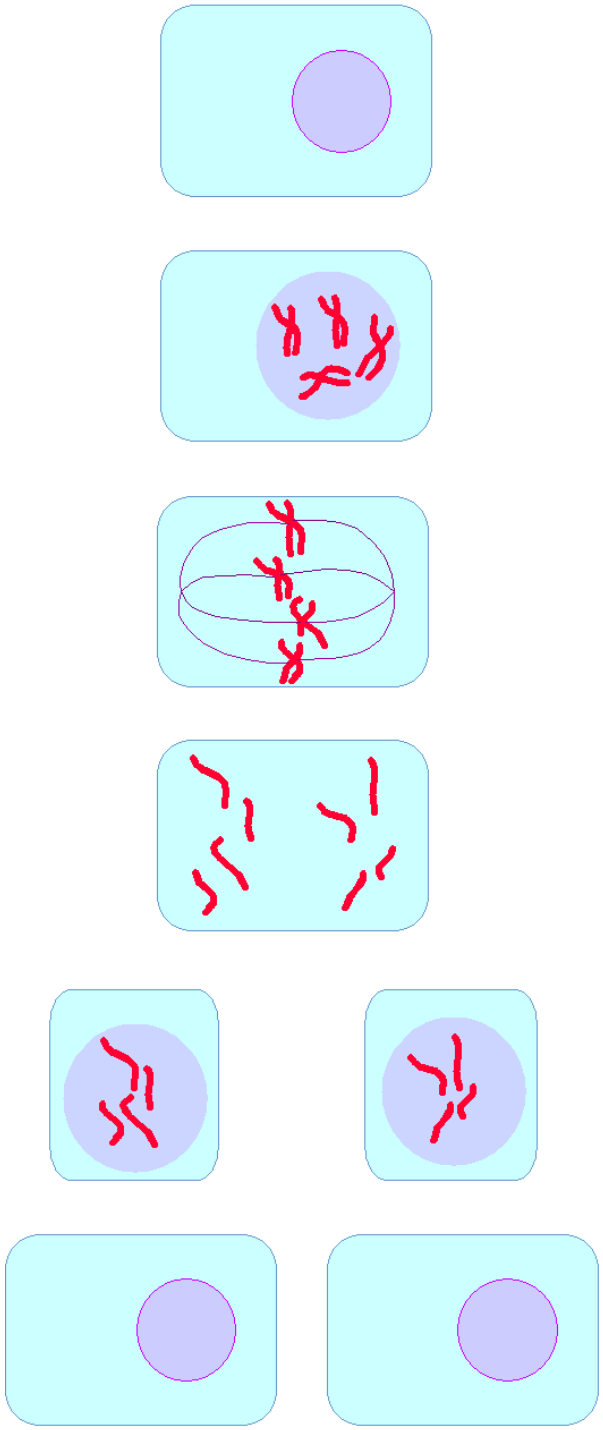
Radiation Biology: Cellular Effects



Survival after irradiation is not only a characteristics of cell lines but also strongly influenced by the cell cycle.

- (a) late S-phase.
- (b) early S-phase.
- (c) during mitosis, similar response can be observed for high-LET radiation in all phases.

Fig.16. Cell cycle dependency of survival



G2 - Phase

Beginn der Mitose
(Prophase P)

Mitose
(Metaphase M)

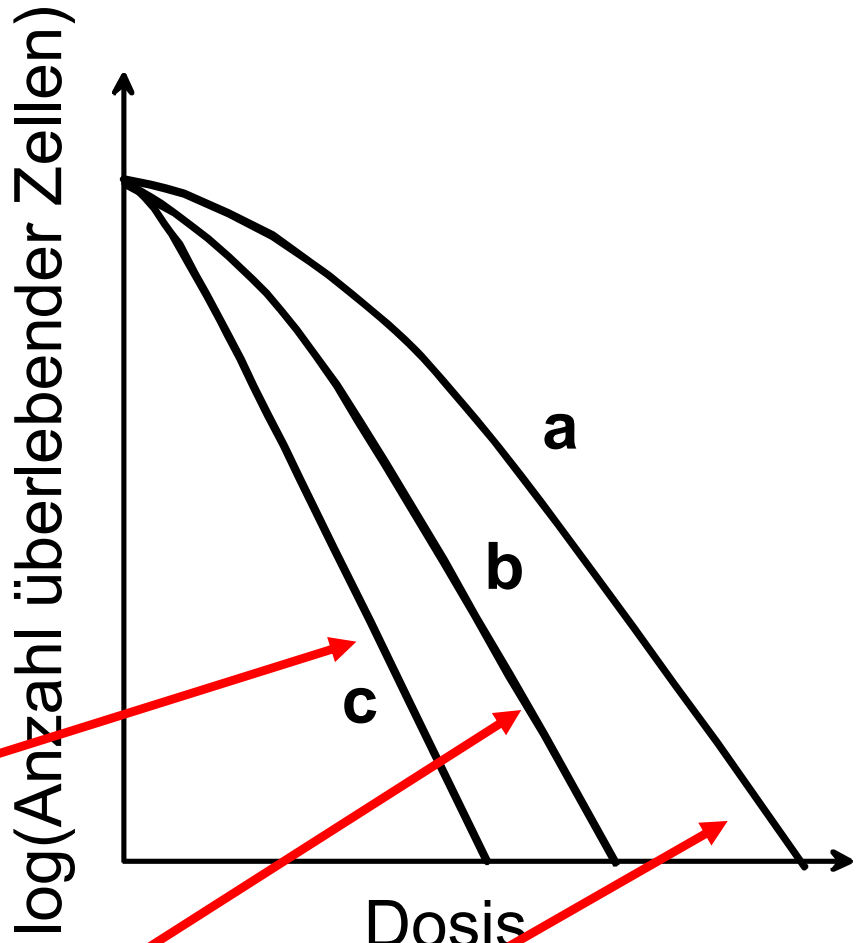
Mitose
(Anaphase)

Mitose
(Telophase)

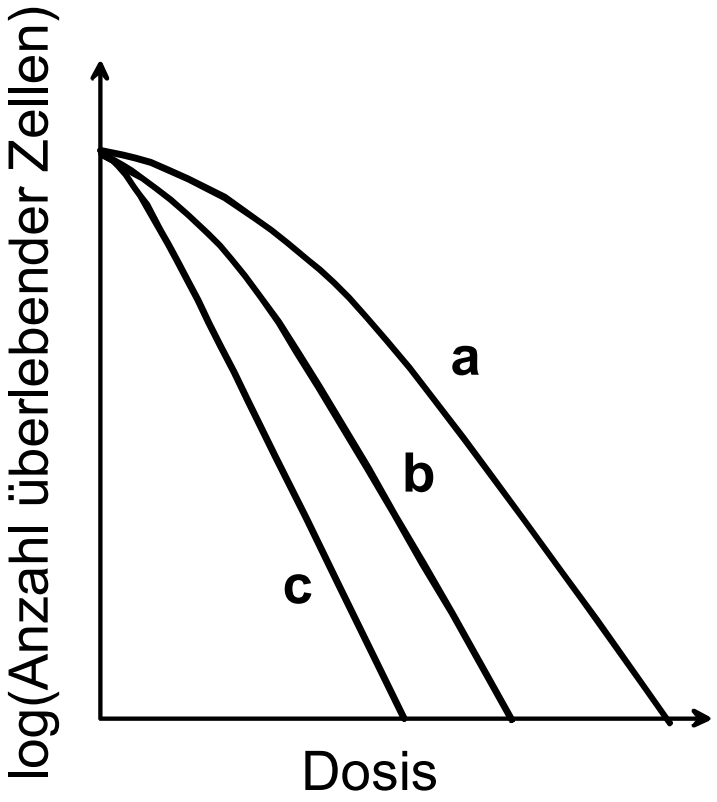
Cytokinese

G1-Phase

S-Phase
(DNA-Synthese)



Radiation Biology: Cellular Effects



Reasons for this observations?

- Activation of repair pathways!
- (a & b) homologues recombination HR) and Non-Homologues End Joining (NHEJ)
- (c) NHEJ

Fig.16. Cell cycle dependency of survival

Cellular Repair: HR vs. NHEJ

DNA repair after damage:

- Homologues Recombination (HR)
- Non-Homologies End-Joining (NHEJ)
- …

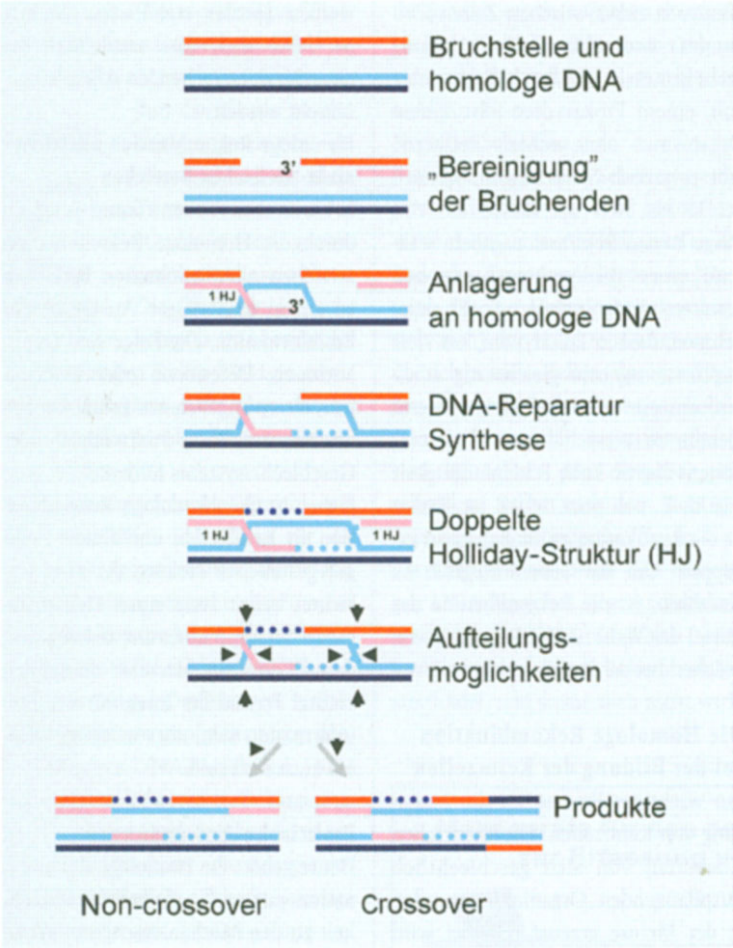
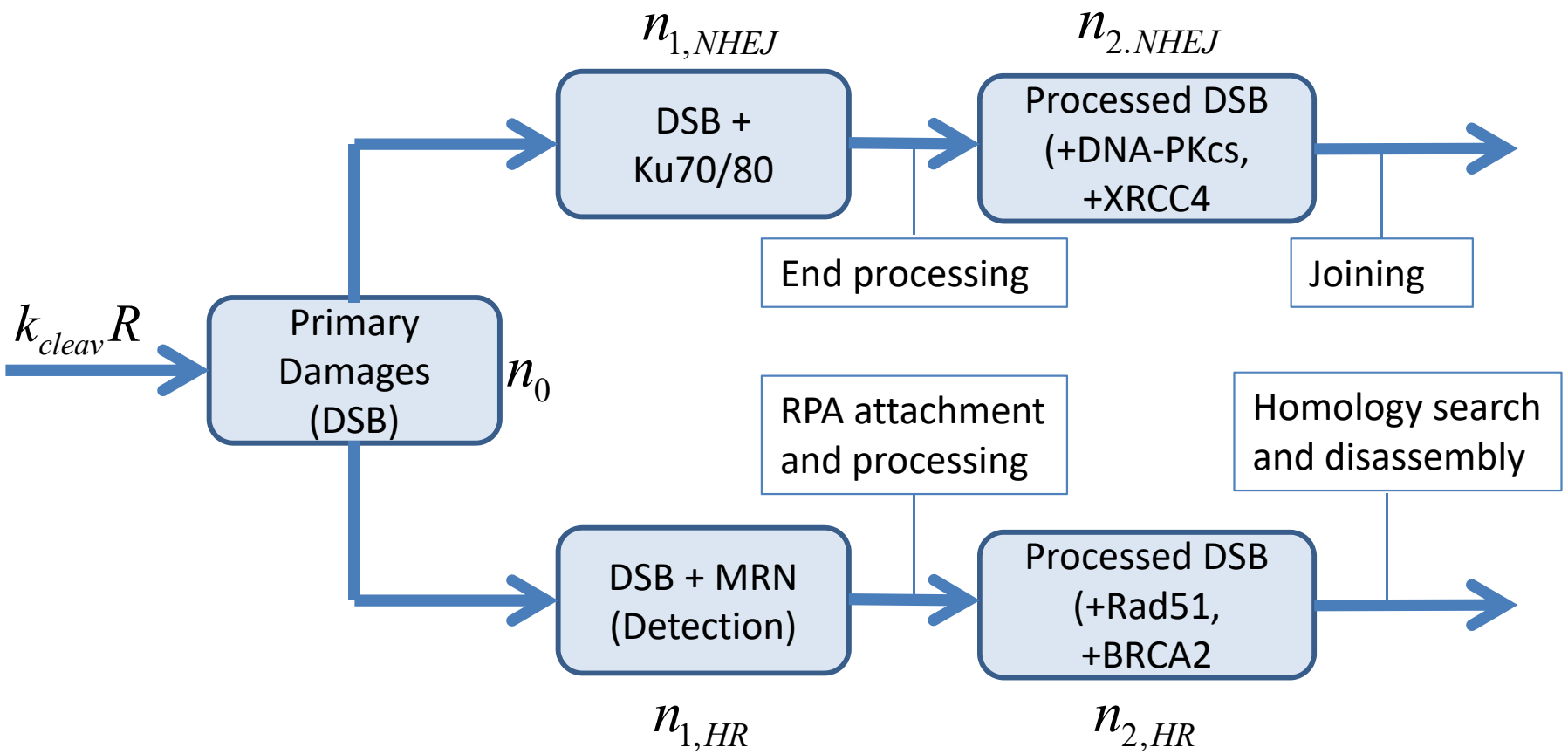


Fig.18. Homologues Recombination (Bencsik-Theilen et al. Strahlenschutzpraxis 4 / 2010)

Cellular Repair: HR vs. NHEJ



Schulz N, Chaachouay H, Nytko KJ, Weyland MS, Roos M, Füchslin RM, Guscetti F, Scheidegger S, Rohrer Bley C (2017): Dynamic In Vivo Profiling of DNA Damage and Repair after Radiotherapy Using Canine Patients as a Model. Int J Mol Sci 2017, 18, 1176; doi:10.3390/ijms18061176

Radiation Biology: Cellular Effects

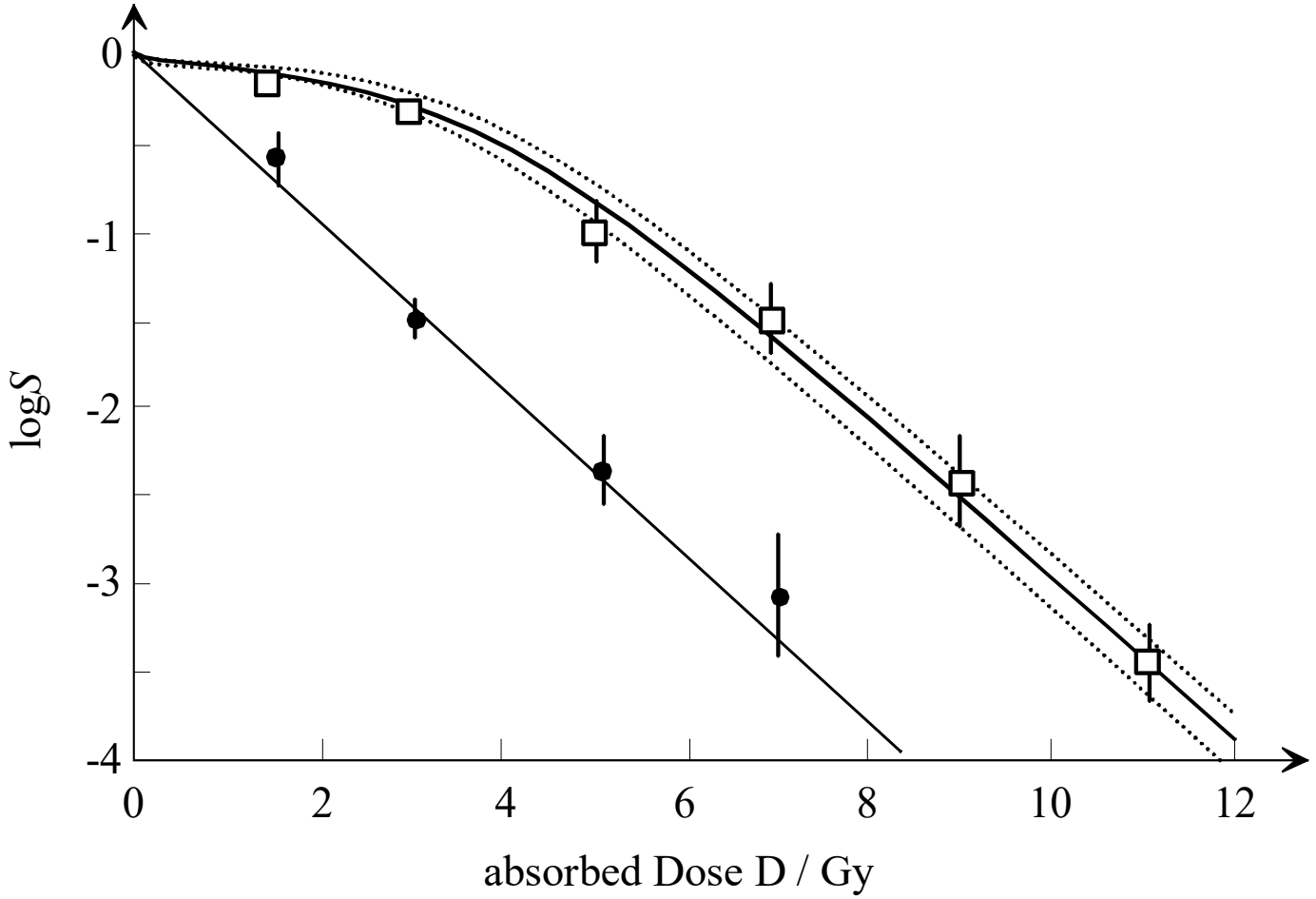
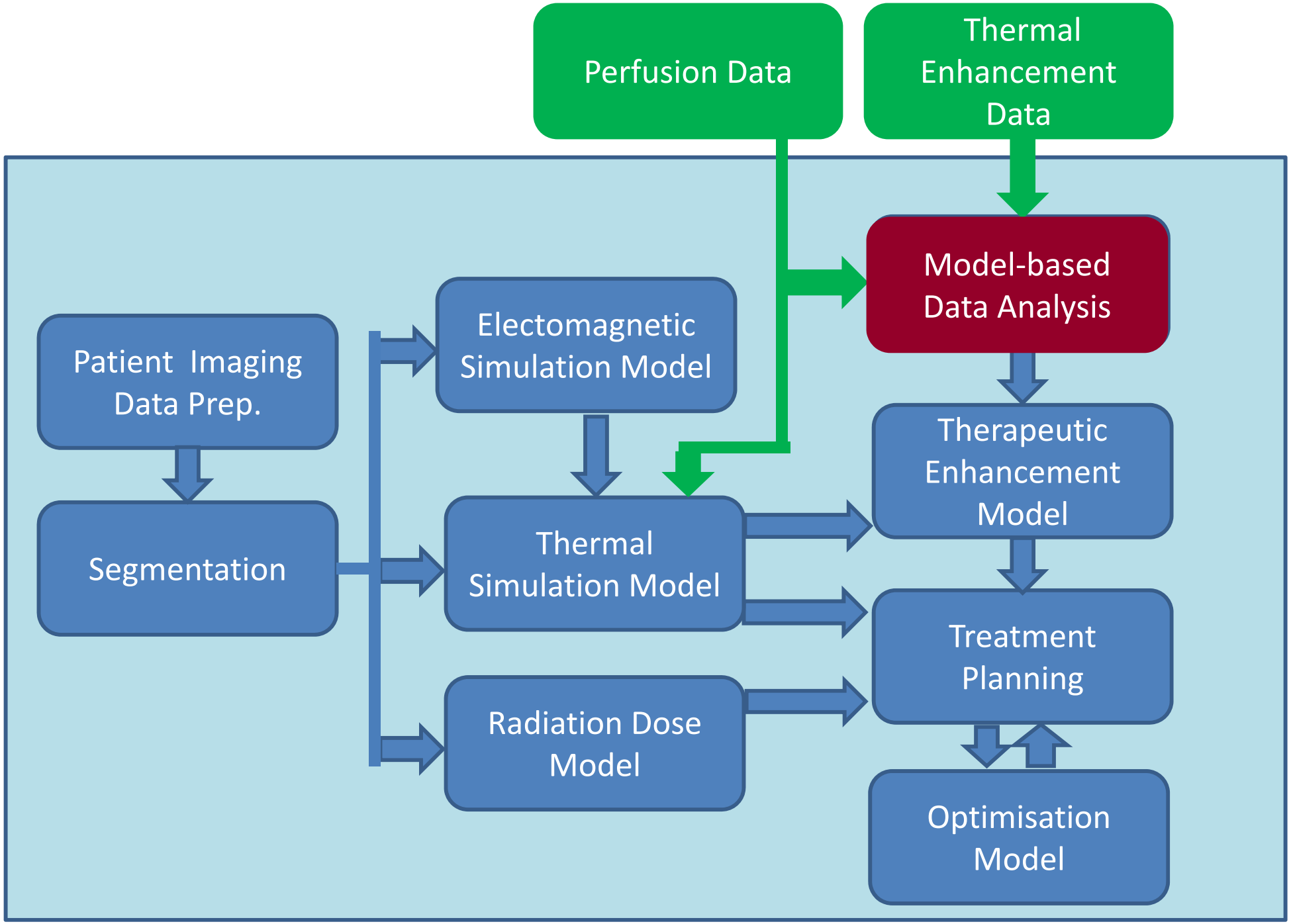
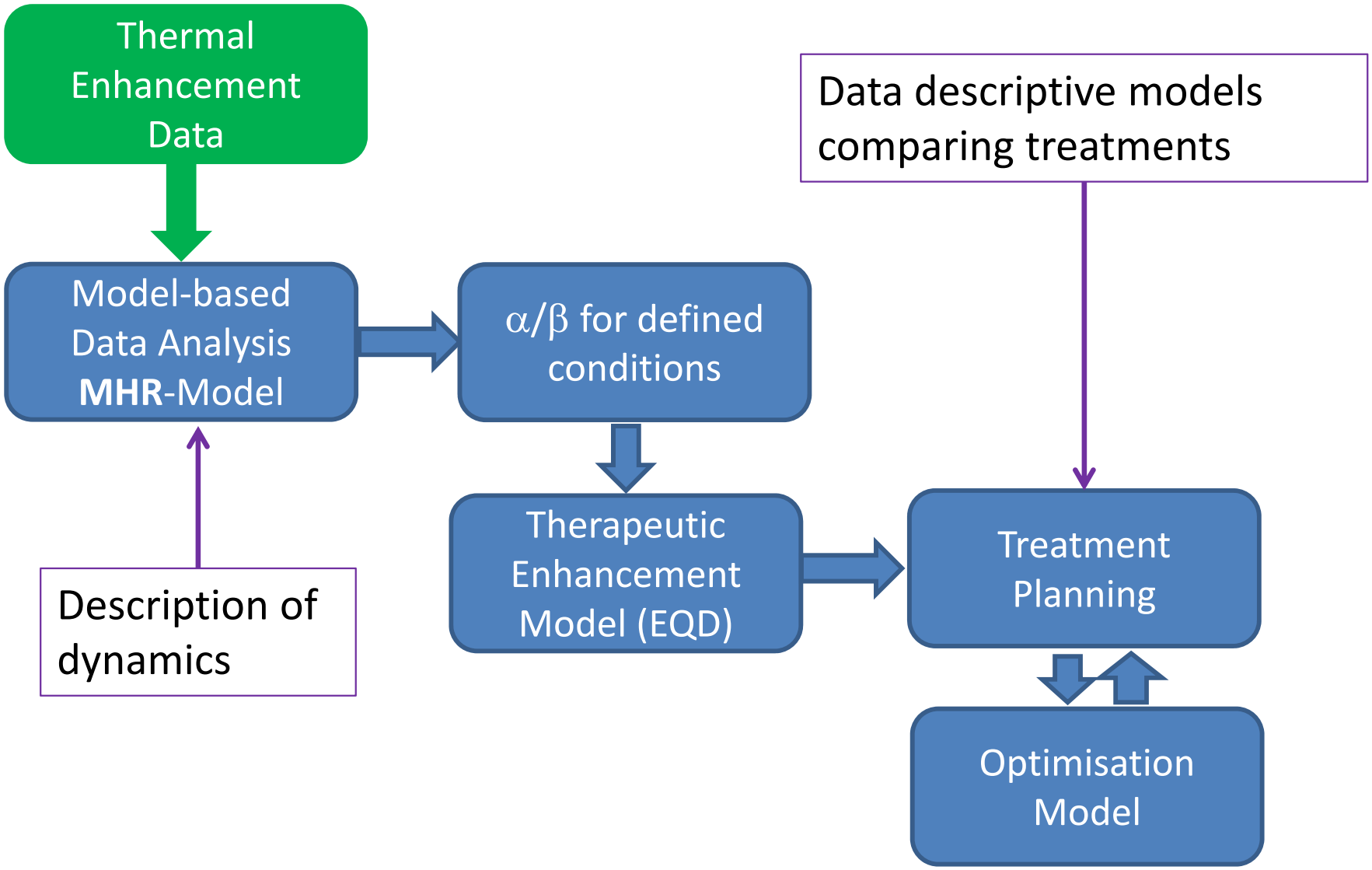


Fig.21. p53(+/+) vs. p53(-/-) murine embrionic fibroblast (Data from Harrigan et al.; Fits by Scheidegger et al., CMMM, 2013)


Perfusion Data
Thermal Enhancement Data
Model-based Data Analysis
Patient Imaging Data Prep.
Electomagnetic Simulation Model
Therapeutic Enhancement Model
Segmentation
Thermal Simulation Model
Treatment Planning
Radiation Dose Model
Optimisation Model

Combining MHR Model with TP Model



BED?

EQD??

EUD???

TBDE???

Biological Equivalent Dose BED

Assumption: LQ model; *d* = dose per fraction

$$\lim_{d\to 0}\left(n\cdot(\alpha d+\beta d^2)\right)=nd\cdot\alpha=BED\cdot\alpha$$

$$=\left[-\log S\right]_{LDR}\rightarrow BED=\frac{\left[-\log S\right]_{LDR}}{\alpha}$$

$$BED=\frac{-\log S}{\alpha}=\frac{n\cdot(\alpha d+\beta d^2)}{\alpha}=nd\cdot\left[1+\frac{\beta d}{\alpha}\right]$$

Biological Equivalent Dose BED

Incompete repair; *d* = dose per fraction

$$BED = nd \cdot \left[1 + \frac{(1+h) \cdot \beta d}{\alpha} \right]$$

With an incomplete – repair –factor *h*, for 2 subsequent fractions and 1st-order repair kinetics:

$$h = e^{-\gamma t}$$

Repair and repopulation can be included in a
much more elegant and flexibel way by using kinetic dose model
→ TBDE!

Equivalent Dose EQD

Assumption: LQ model; *d* = dose per fraction, *D* = total dose

$$EQD_2 \cdot (\alpha + \beta \cdot 2\text{Gy}) = D \cdot (\alpha + \beta d)$$

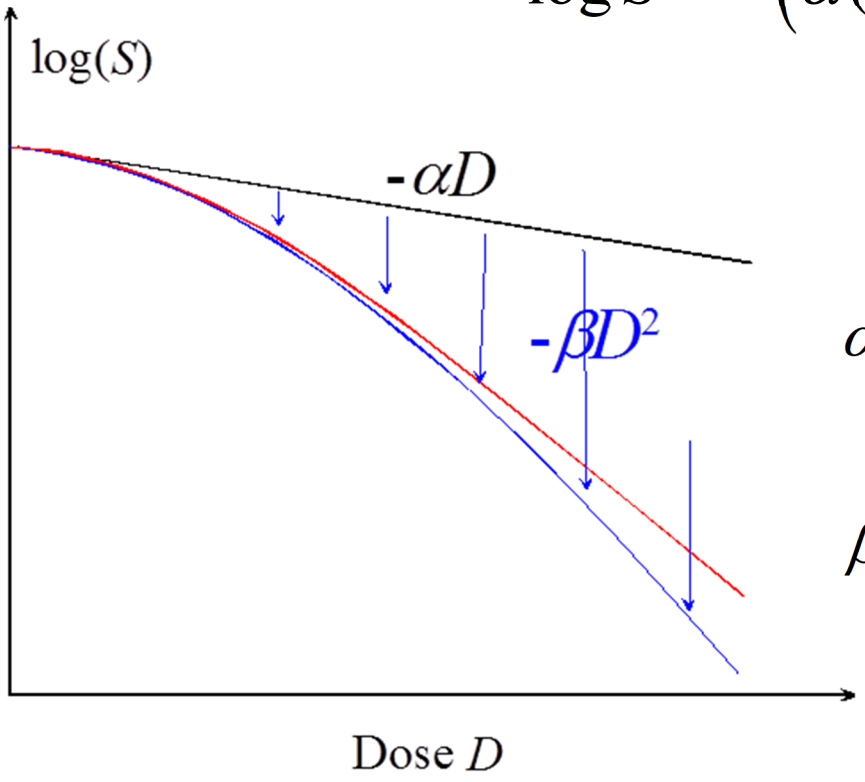
$$EQD_2 = D \cdot \left(\frac{\alpha + \beta d}{\alpha + \beta \cdot 2\text{Gy}} \right)$$

$$EQD_2 = D \cdot \left(\frac{(\alpha + \beta d) \cdot \frac{1}{\beta}}{(\alpha + \beta \cdot 2\text{Gy}) \cdot \frac{1}{\beta}} \right) = D \cdot \left(\frac{\frac{\alpha}{\beta} + d}{\frac{\alpha}{\beta} + 2\text{Gy}} \right)$$

LQ – based Model – Using Data – Descriptive Models

Van Leeuwen et al. (2017): *Int J Hyperth* 33, 160-169.

$$\log S = -\left(\alpha(T, t_{\text{int}}) \cdot D + \beta(T, t_{\text{int}}) \cdot D^2\right)$$



$$\alpha(T, t_{\text{int}}) = \alpha_{37} \cdot \exp\left[\frac{T-37}{41-37} \cdot \ln\left[\frac{\alpha_{41}}{\alpha_{37}}\right] \cdot e^{-\mu t_{\text{int}}}\right]$$

$$\beta(T, t_{\text{int}}) = \beta_{37} \cdot \exp\left[\frac{T-37}{41-37} \cdot \ln\left[\frac{\beta_{41}}{\beta_{37}}\right] \cdot e^{-\mu t_{\text{int}}}\right]$$

EQD for HT

Leeuwen et al. (2017): *Int J Hyperth* 33, 160-169.

$$EQD_{RT} = \frac{\alpha(T, t_{\text{int}}) \cdot D + G\beta(T, t_{\text{int}}) \cdot D^2}{\alpha_{37} + \beta_{37} \cdot d_{ref}}$$

Assumption:
Complete repair between fx, no repair during fx, $G \rightarrow 1/n$, $D/n = d_{ref}$

Including direct cytotoxicity → additive cell killing:

$$EQD_{RT} = \frac{\alpha(T, t_{\text{int}}) \cdot D + G\beta(T, t_{\text{int}}) \cdot D^2 + \ln S_{dc}}{\alpha_{37} + \beta_{37} \cdot d_{ref}}$$

EQD for HT and Direct Cytotoxicity

$$\frac{dN}{dt} = -k(T) \cdot N \rightarrow S_{dc} = \frac{N}{N_0} = e^{-k(T) \cdot t_{tr}}$$

$$\ln S_{dc} = -k(T) \cdot t_{tr}$$

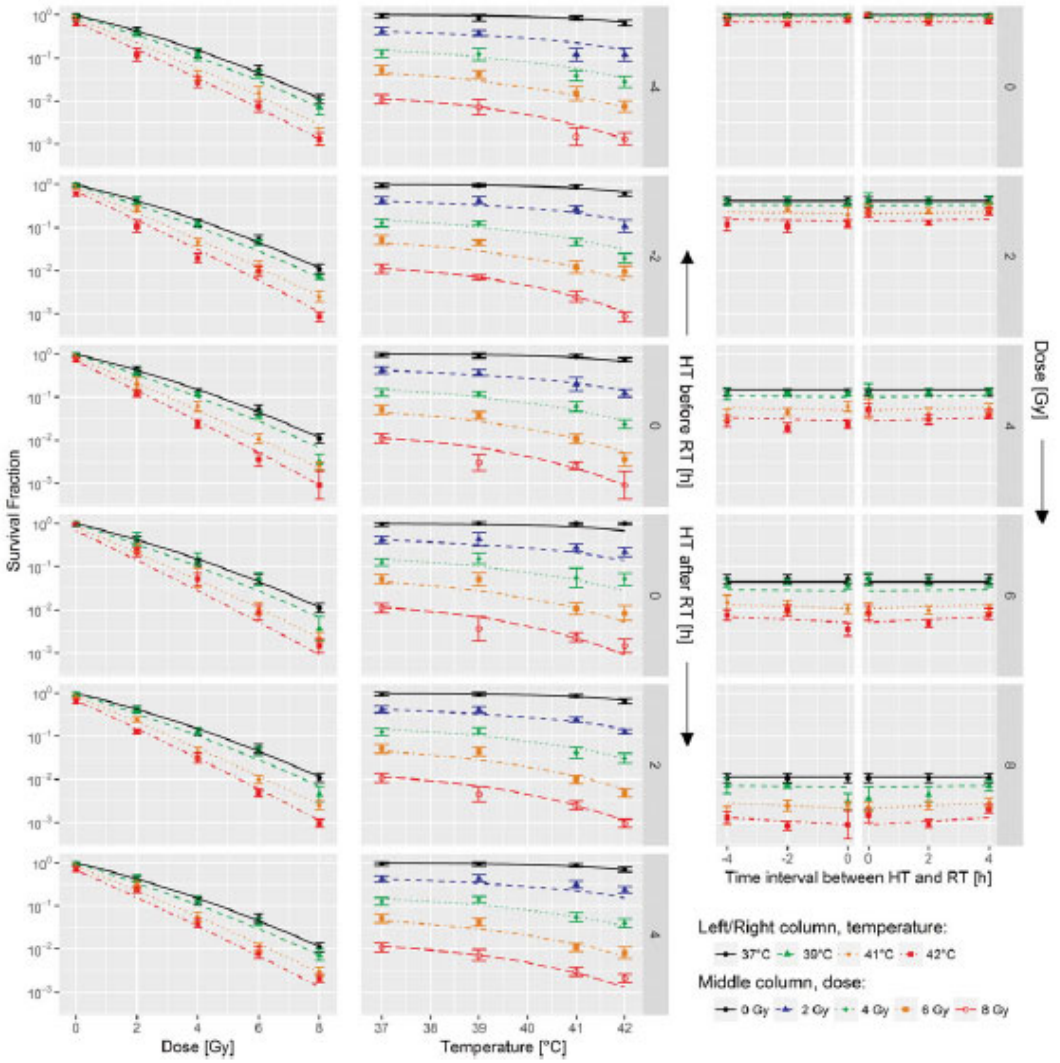
For fixed treatment / heating time t_{tr}:

$$k(T) \cdot t_{tr} \rightarrow A(T) \cdot e^{f(\Delta S, \Delta H, T)}$$

$$EQD_{RT} = \frac{\alpha(T, t_{\text{int}}) \cdot D + G\beta(T, t_{\text{int}}) \cdot D^2 + A(T) \cdot e^{f(\Delta S, \Delta H, T)}}{\alpha_{37} + \beta_{37} \cdot d}$$

Leeuwen et al. (2017): *Int J Hyperth* 33, 160-169; modified

Pro and Cons of Modified LQ Model(s)



+ established framework

+ α/β values can be extracted from data in-vitro

+ α/β values can be extracted from data in-vitro

+ α/β values can be compared with clinical data by TCP models

- Inclusion of non-linear kinetics, non-exponential repopulation, advanced repair models and ecoystem dynamics very not straight foreward

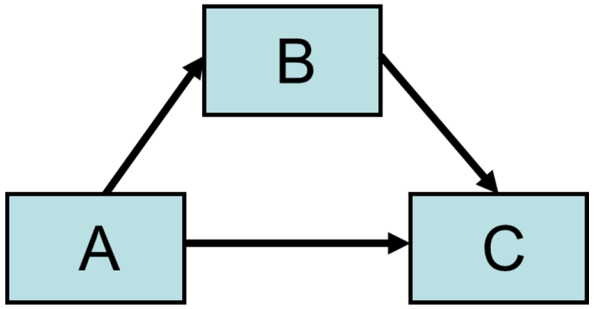
- α/β values determination for all conditions and tumours difficult

- Do not allow a full insight into the dynamics of the biological system

Leeuwen et al. (2017): *Int J Hyperth* 33, 160-169.

Beyond Data Descriptive Models: Dynamic Radiobiological Models

Modelling in Radio-Oncology: LQ-Type Models



The model of Carlone et al.[1] is based on the following assumptions:

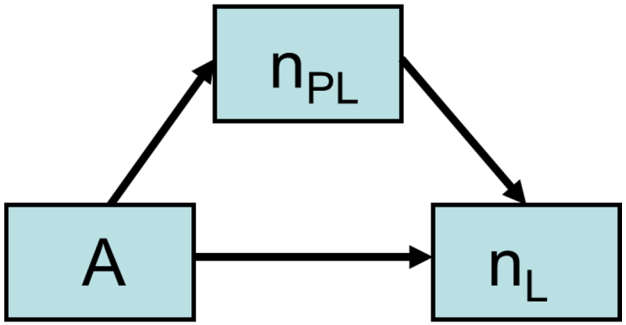
- There are *A* potential target sites
- Radiation-induced hits can be either sub-lethal or lethal
- Sub-lethal hits can be repaired

$$\frac{dB}{dt} = 2pR - \mu B - pR\varepsilon B$$

$$\frac{dC}{dt} = \alpha R + pR\varepsilon B$$

[1]Carlone MC, Wilkins D, Raaphorst GP. The modified linear-quadratic model of Guerrero and Li can be derived from amechanistic basis and exhibits linear-quadratic-linear behaviour. *Phys. Med. Biol*. 2005;**50**:L9-13

Modelling in Radio-Oncology: LQ-Type Models



The LPL - model of Curtis[2] is based on a comparable approach:

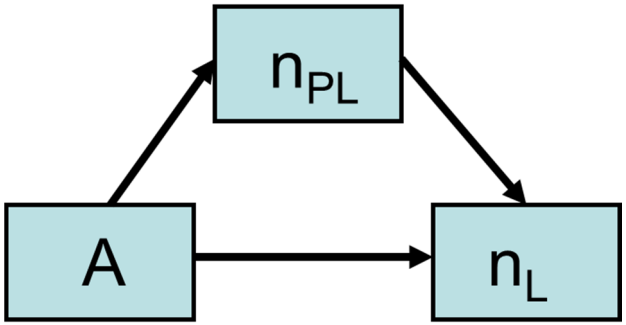
- There are *A* potential target sites
- Radiation-induced hits can be either sub-lethal or lethal
- Sub-lethal hits can be repaired

$$\frac{dn_{PL}}{dt} = \eta_{PL} \cdot R - \varepsilon_{PL} \cdot n_{PL} - \varepsilon_{2PL} \cdot n_{PL}^2$$

$$\frac{dn_L}{dt} = \eta_L \cdot R + \varepsilon_{2PL} \cdot n_{PL}^2$$

[2]Curtis SB. Lethal and potentially lethal lesions induced by radiation – A Unified Repair Model. *Radiat. Res*. 1986;**106**:252-70.

Modelling in Radio-Oncology: LQ-Type Models



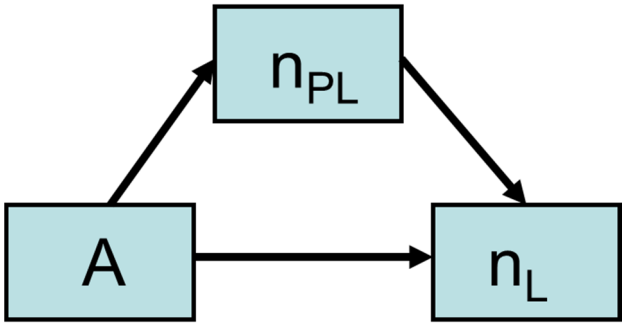
The LPL - model described the number of hits. Therefore, the survival has to be calculated via a statistical approach (Poisson):

$$\frac{dn_{PL}}{dt} = \eta_{PL} \cdot R - \varepsilon_{PL} \cdot n_{PL} - \varepsilon_{2PL} \cdot n_{PL}^2$$

$$\frac{dn_L}{dt} = \eta_L \cdot R + \varepsilon_{2PL} \cdot n_{PL}^2$$

$$S = e^{-n_L(t+t_r) - n_{PL}(t+t_r)}$$

Modelling in Radio-Oncology: LQ-Type Models



The delay time t_r is introduced because the transient amount of hits do not reflect the number of hits after repair!

A second disadvantage of this category of models is the fact that they do not directly describe the population dynamics, which becomes important when looking to tissue – an immune system interactions.

$$S = e^{-n_L(t+t_r)-n_{PL}(t+t_r)}$$

$$\log S = \log\left(e^{-n_L(t+t_r)-n_{PL}(t+t_r)}\right) =$$

$$= \left(-n_L(t+t_r) - n_{PL}(t+t_r)\right)/\ln(10)$$

Modelling in Radio-Oncology: LQ-Type Models

Γ-LQ model (dynamic LQ-model using a kinetic TBDE sub-model)

$$\frac{dN}{dt} = -(\alpha + 2\beta D) \cdot N \cdot R$$

$$R \cdot dt = dD$$

$$\rightarrow \quad \frac{dN}{N} = -(\alpha + 2\beta D) \cdot dD$$

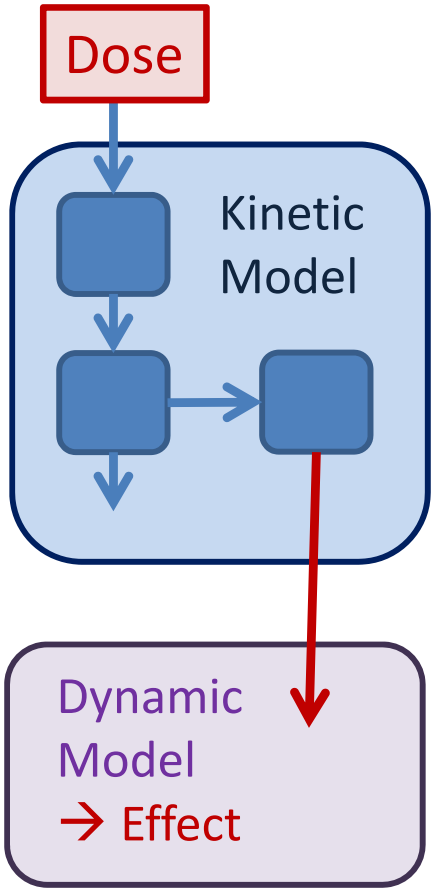
$$\int (dN / N) = -\int (\alpha + 2\beta D) \cdot N \cdot dD = -(\alpha D + \beta D^2)$$

$$= \ln\left(N(D) / N_0 \right)$$

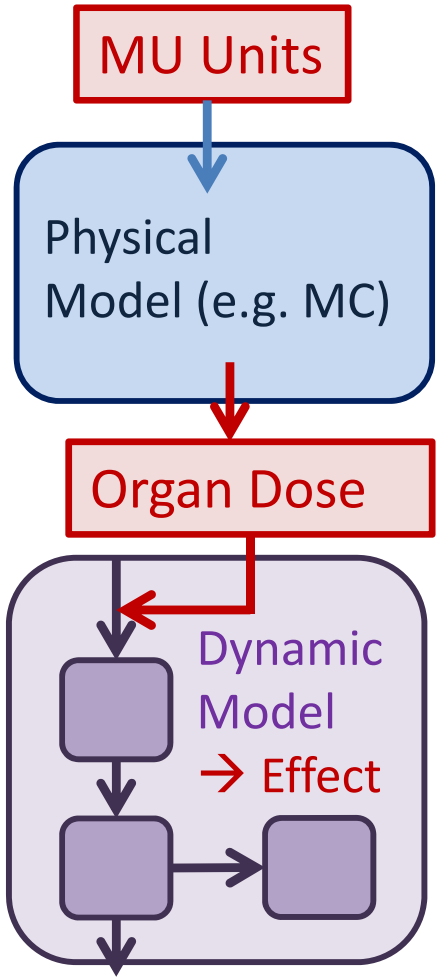
Dose?

Modelling Therapies

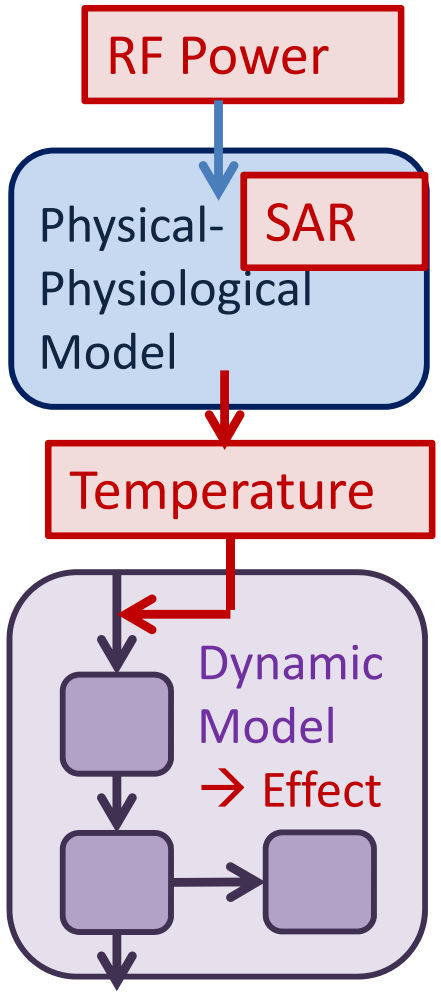
Pharmacology



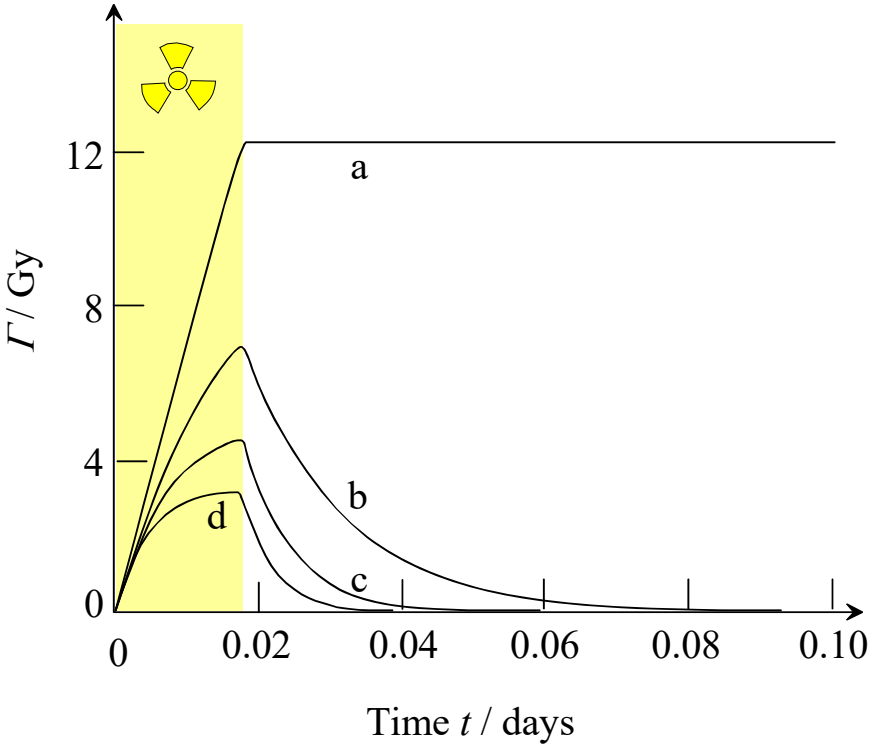
Radiation Therapy



Hyperthermia



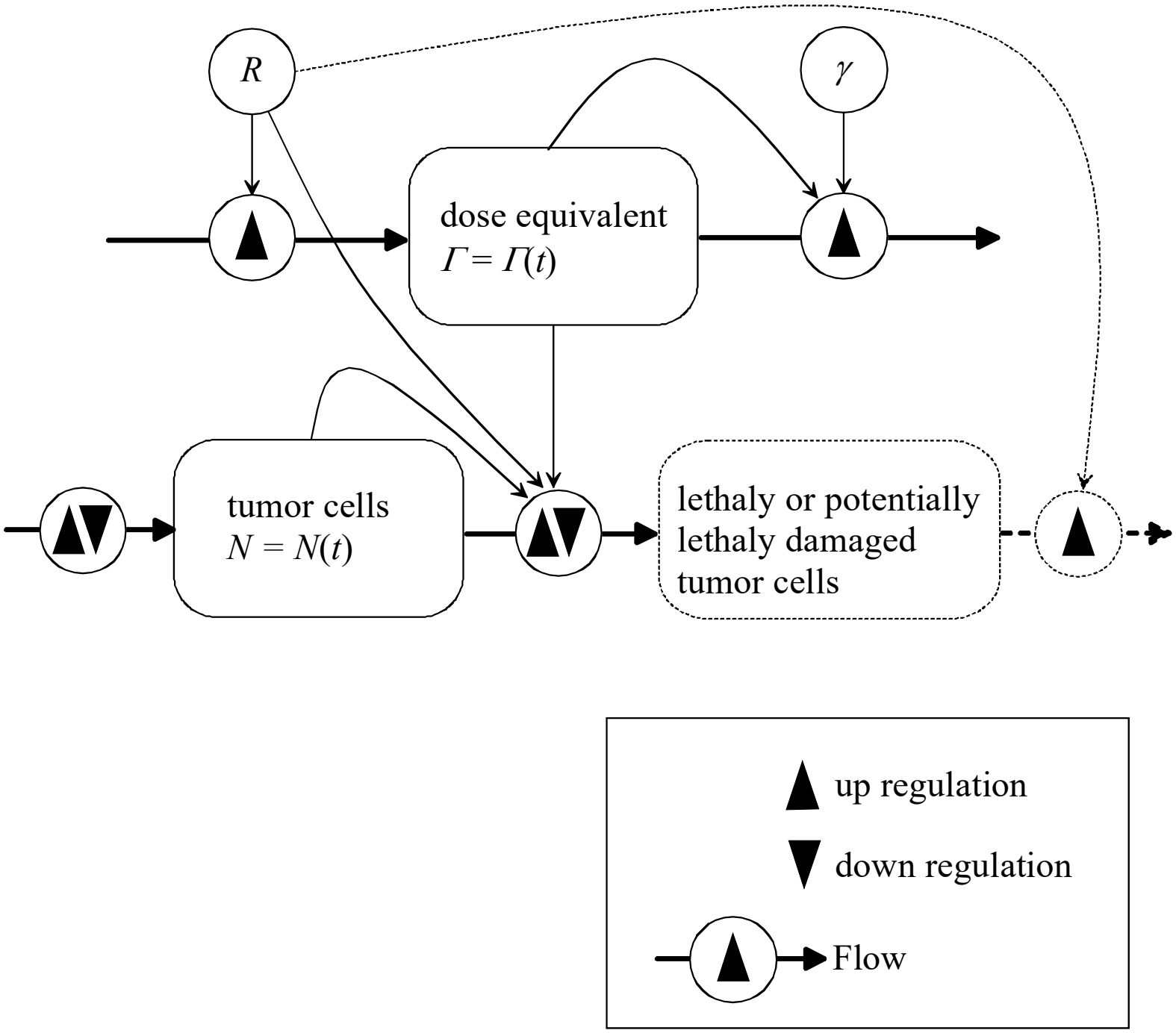
Modelling in Radio-Oncology: LQ-Type Models



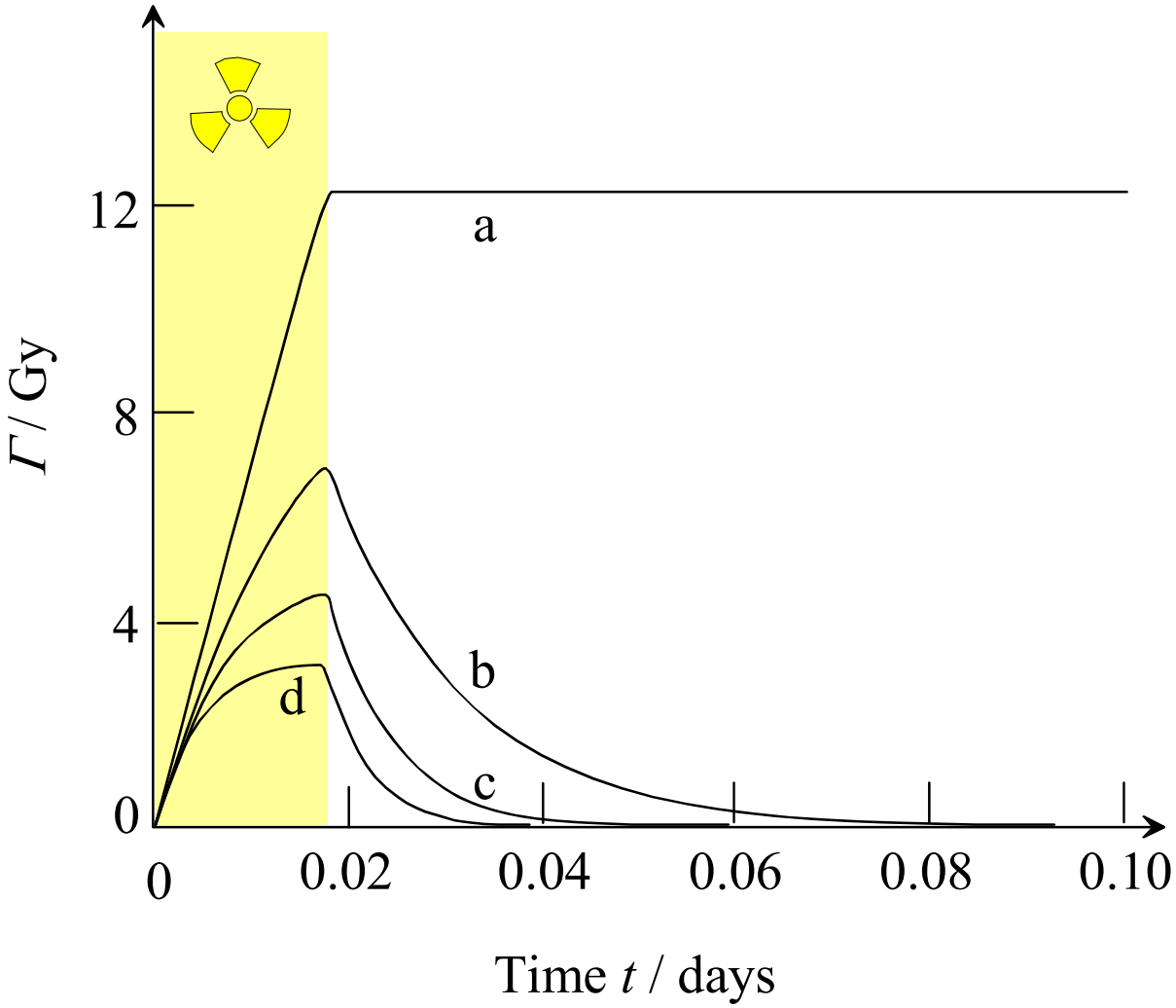
The Γ-LQ model[3] is based on a different approach:

- TBDE describes a dose equivalent Γ which is proportional to the transient biological damage

[3]Scheidegger S, Lutters G, Bodis S (2011): A LQ-based kinetic model formulation for exploring dynamics of treatment response of tumours in patients. *Z. Med. Phys*. **21**,164–173


R
γ
dose equivalent
Γ = Γ(t)
tumor cells
N = N(t)
lethaly or potentially
lethaly damaged
tumor cells
up regulation
down regulation
Flow

Radiation Biology: Cellular Effects



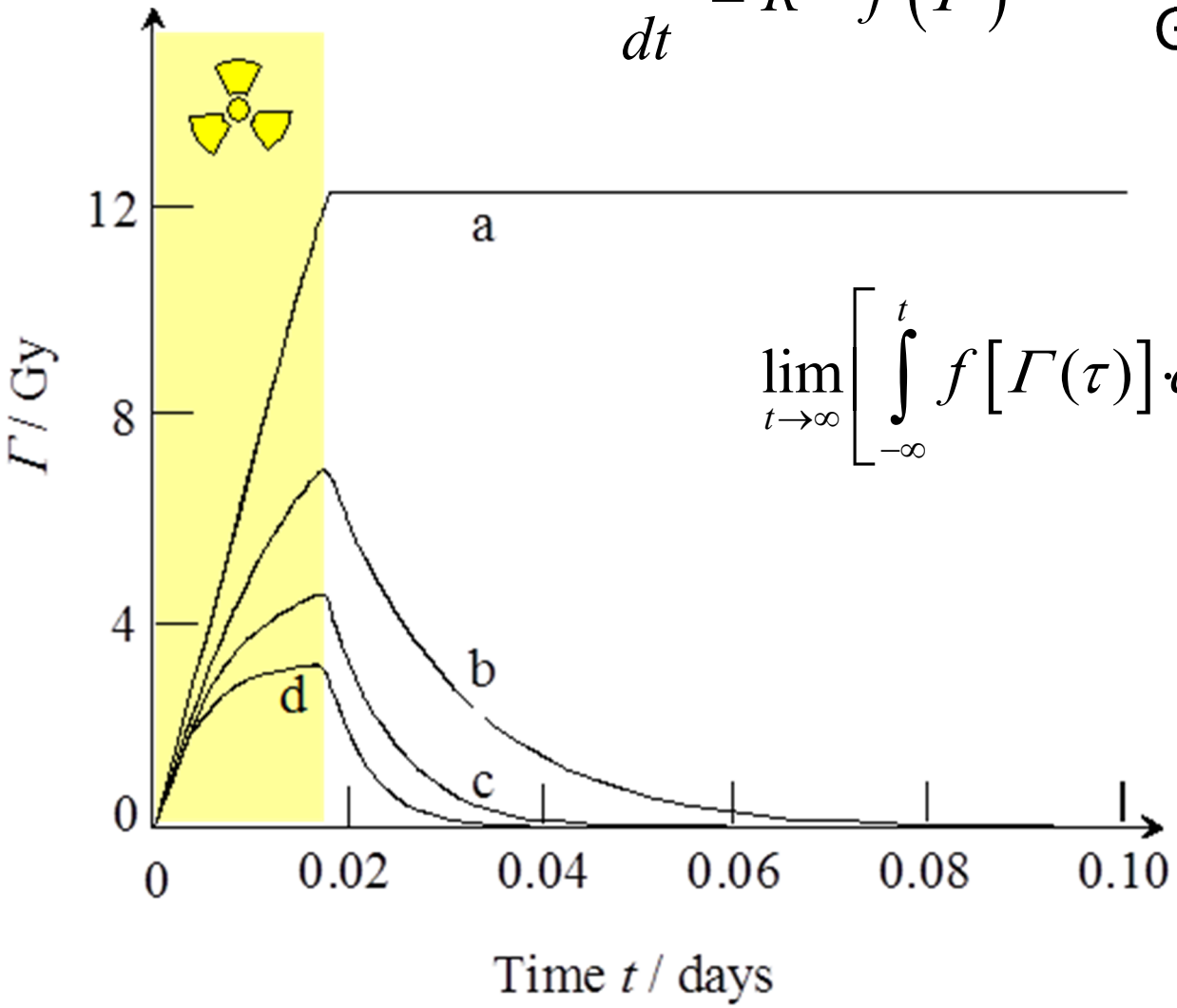
To include repair as a dynamic process into the dose-effect relationship, a Transient Biological Dose Equivalent (TBDE) can be defined, allowing a straightforward modelling.

MHR Model: Transient Radiation Dose Γ

$$\frac{d\Gamma}{dt} = R - f(\Gamma)$$

TBDE Γ is calibrated in Gy:

$$\lim_{t\to\infty}\left[\int_{-\infty}^{t} f\left[\Gamma(\tau)\right]\cdot d\tau\right] = \lim_{t\to\infty}\left[D(t)\right] = D_{tot}$$



Scheidegger et al. (2011), *Z Med Phys* 21, 164-173

Modelling in Radio-Oncology: LQ-Type Models

Γ-LQ model (dynamic LQ-model using a kinetic TBDE sub-model): Substitution of the absorbed dose *D* by Γ(TBDE)

$$\frac{dN}{dt} = -(\alpha + 2\beta D) \cdot N \cdot R$$

$$\frac{dN}{dt} = -(\alpha + 2\beta \Gamma) \cdot N \cdot R$$

Modelling in Radio-Oncology: LQ-Type Models

For the TBDE sub-model, a kinetic description for repair (e.g. 1st or 2nd – order) has to be selected:

$$\frac{dN}{dt} = -(\alpha + 2\beta\Gamma) \cdot N \cdot R$$

$$\frac{d\Gamma}{dt} = R - f(\Gamma)$$

$$\frac{d\Gamma}{dt} = R - \gamma\Gamma$$

$$\frac{d\Gamma}{dt} = R - \tilde{\gamma}\Gamma^2$$

Modelling in Radio-Oncology: LQ-Type Models

$$\frac{dN}{dt} = -(\alpha + 2\beta\Gamma) \cdot N \cdot R$$

$$\frac{d\Gamma}{dt} = R - f\left(\Gamma\right)$$

Normalization of Γ:

$$\lim_{t\to\infty}\left[\int_{-\infty}^{t} f\left(\Gamma(\tau)\right)\cdot d\tau\right] = \lim_{t\to\infty}\left[D(t)\right] = D_{tot}$$

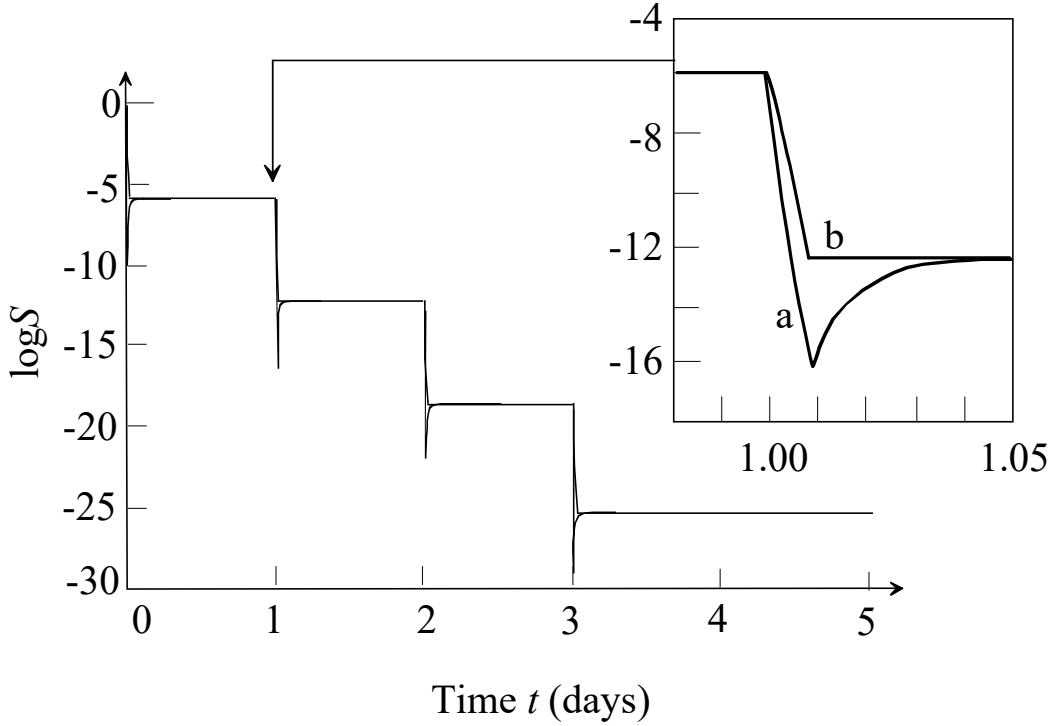
Modelling in Radio-Oncology: LQL-Type Models

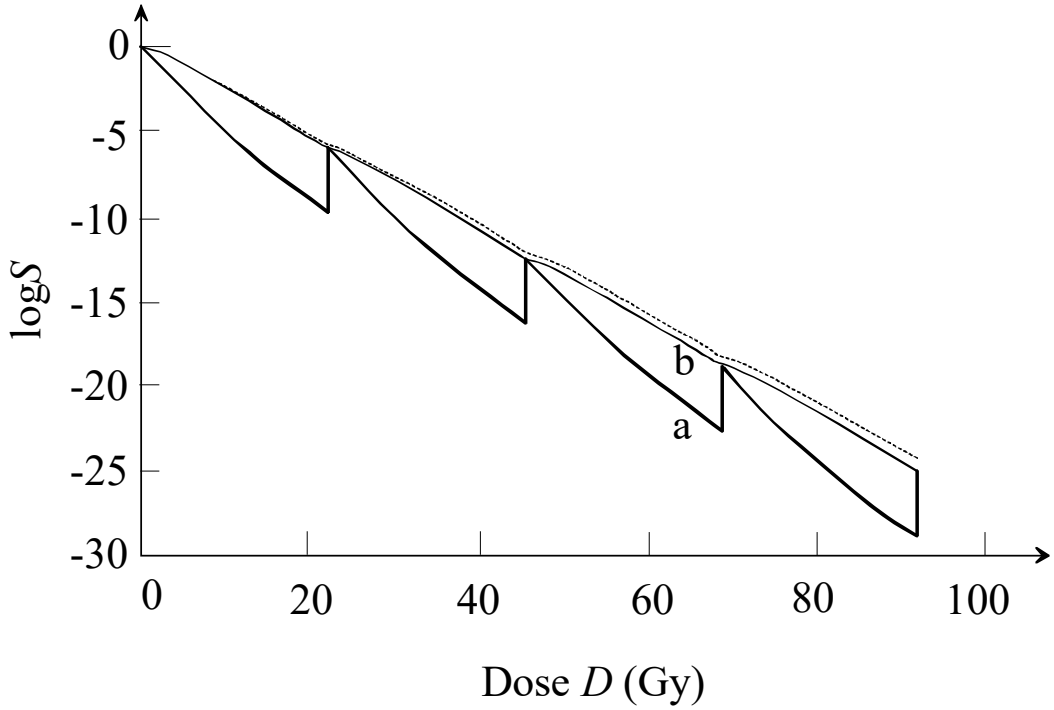
Slope of log*S* @ high doses (for Γ-LQ and Carlone models for 2nd order kinetics (for details see Scheidegger et al., *Z Med Phys* **21**, 164-173):

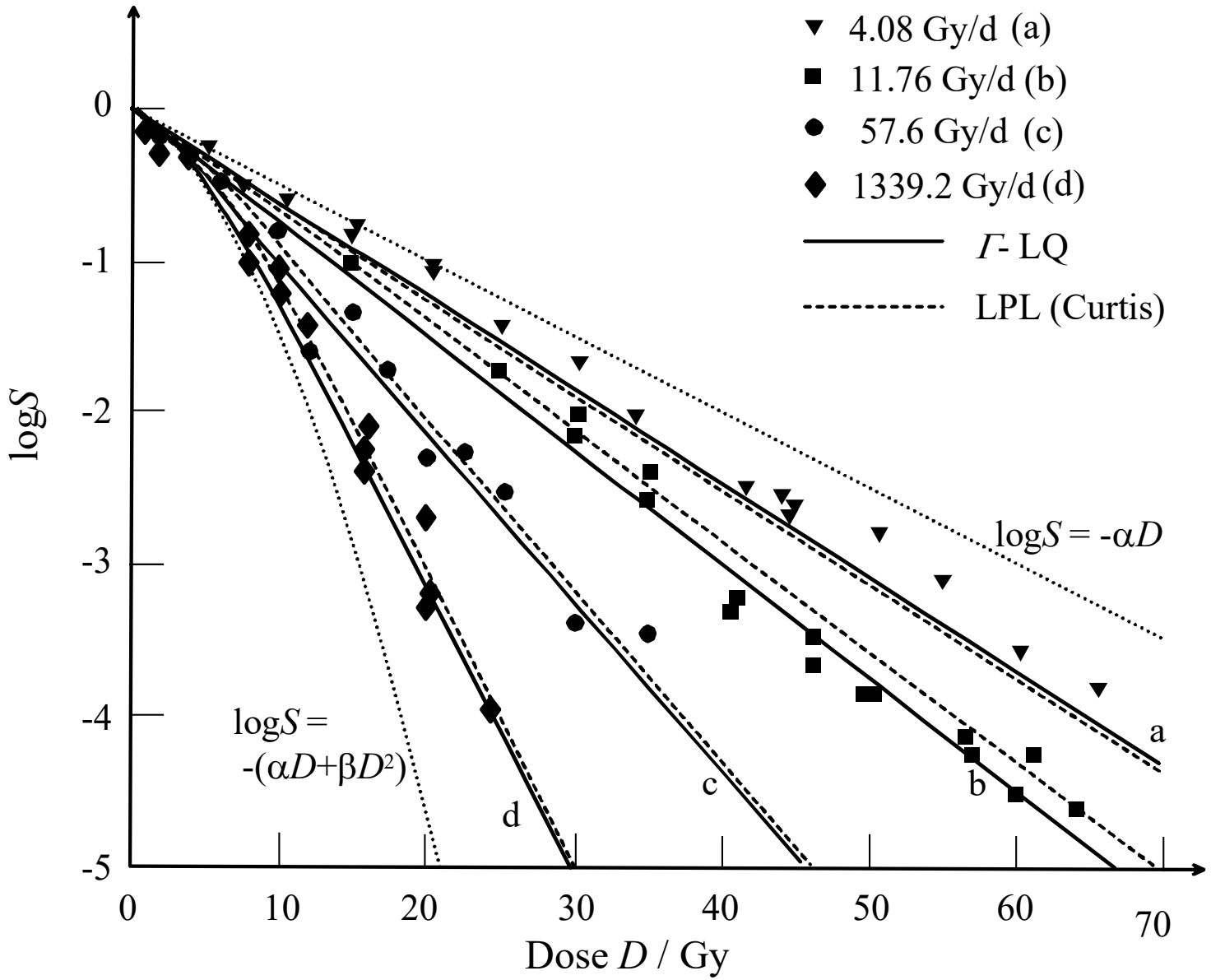
$$\alpha + \frac{2\beta R}{\mu + pR\varepsilon} = \alpha + 2\beta\Gamma_{eq}$$

$$\tilde{\gamma} = \frac{\left(\mu + p\varepsilon R\right)^2}{R} = \frac{\mu^2}{R} + p^2\varepsilon^2 R + 2\mu p\varepsilon$$

Completely different models exhibit the same results (LQL)!!! → **Interpretation???**

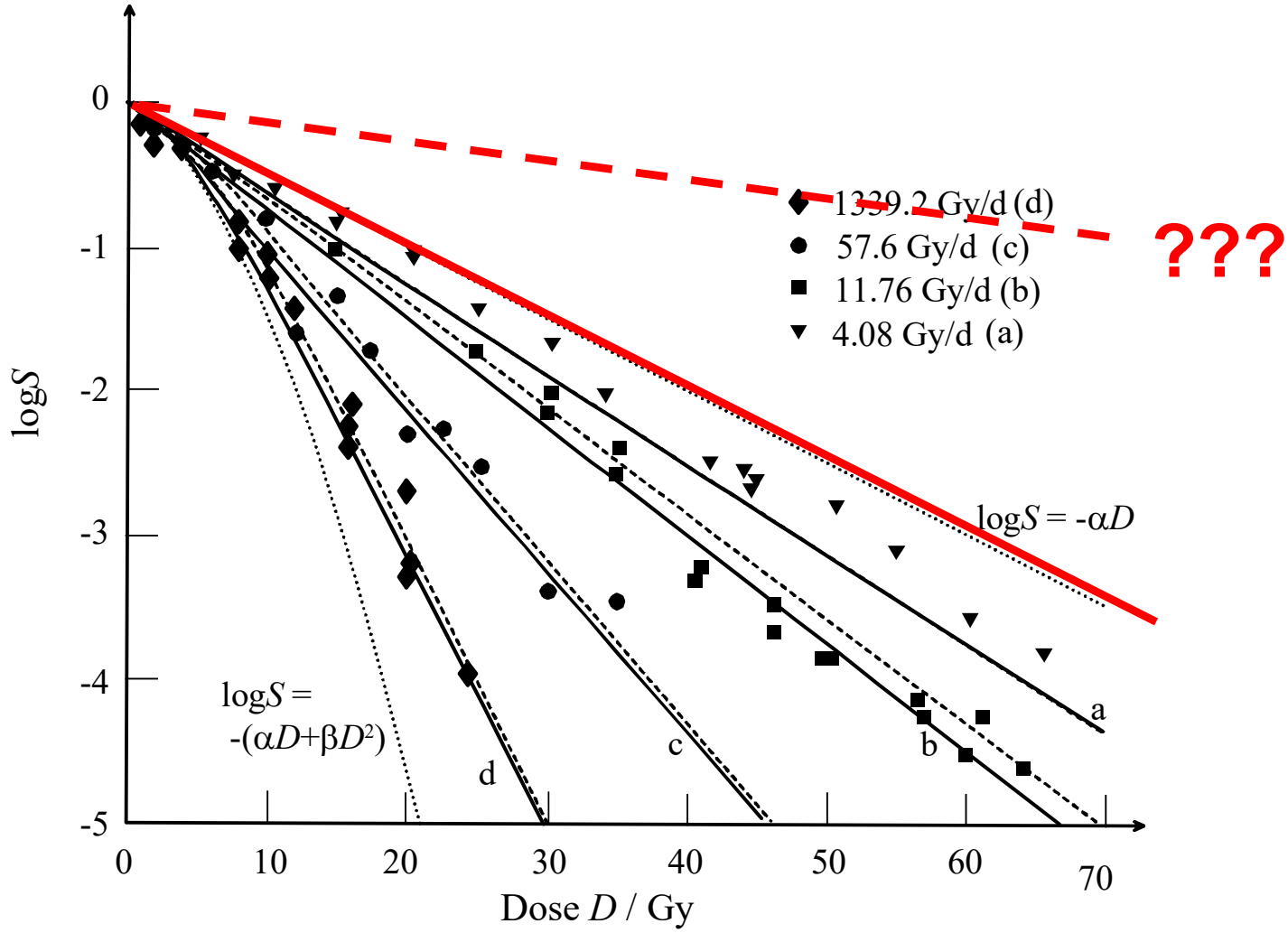

0
-5
-10
-15
-20
-25
-30
logS
0
1
2
3
4
5
Time t (days)
-4
-8
-12
-16
1.00
1.05
a
b


0
-5
-10
-15
-20
-25
-30
logS
0
20
40
60
80
100
Dose D (Gy)
a
b



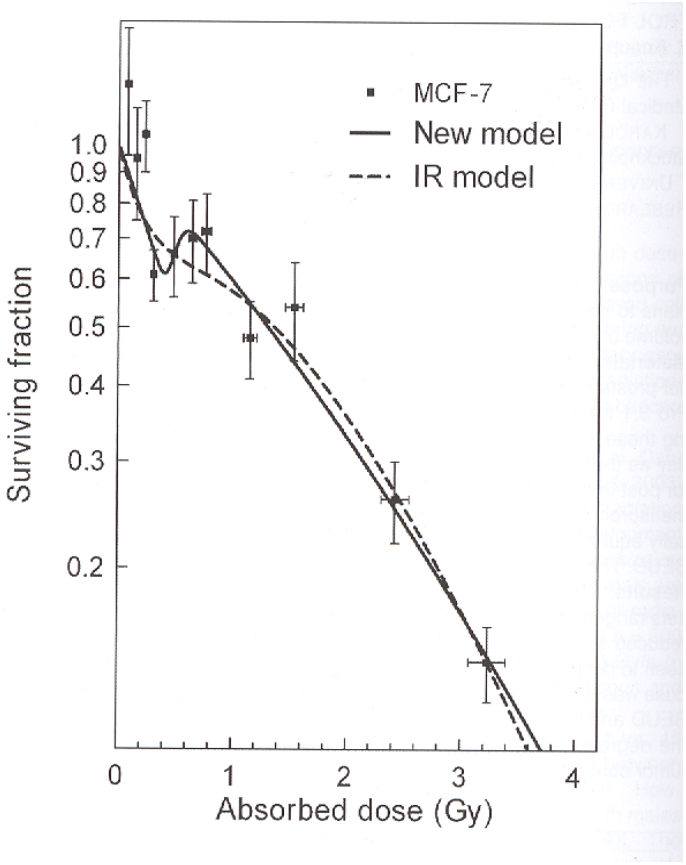
Dose rate dependency of survival and Low Dose Rate (LDR) and vDLR limits (Schedegger et al. Z. Med. Phys, 2011)

Radiation Biology: Cellular Effects



Dose rate dependency of survival and Low Dose Rate (LDR) and vDLR limits (Schedegger et al. Z. Med. Phys, 2011)

Modelling in Radio-Oncology: LQ-Type Models



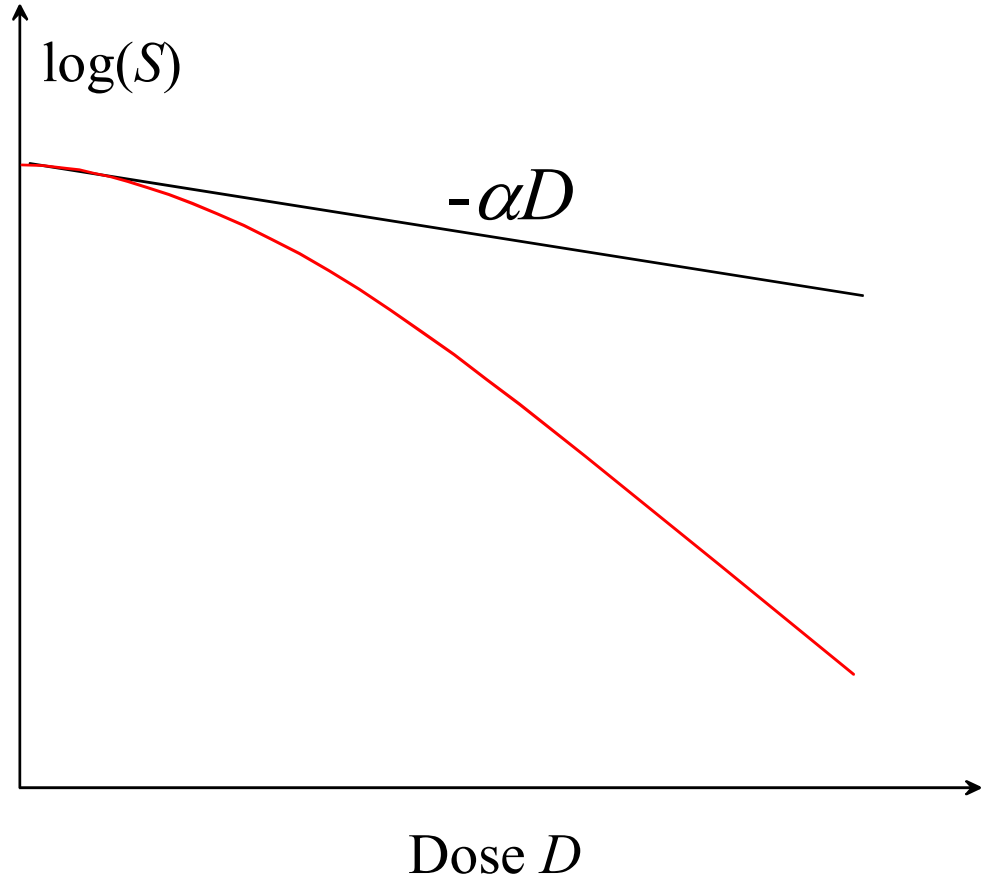
Limits of dynamic LQ-type models: Low dose hypersensitivity

- Initially higher cell killing (@ low doses)
- With increasing dose decreasing cell killing
- Induced repair models (e.g. IR model of Guirado Llorente et al.[4]

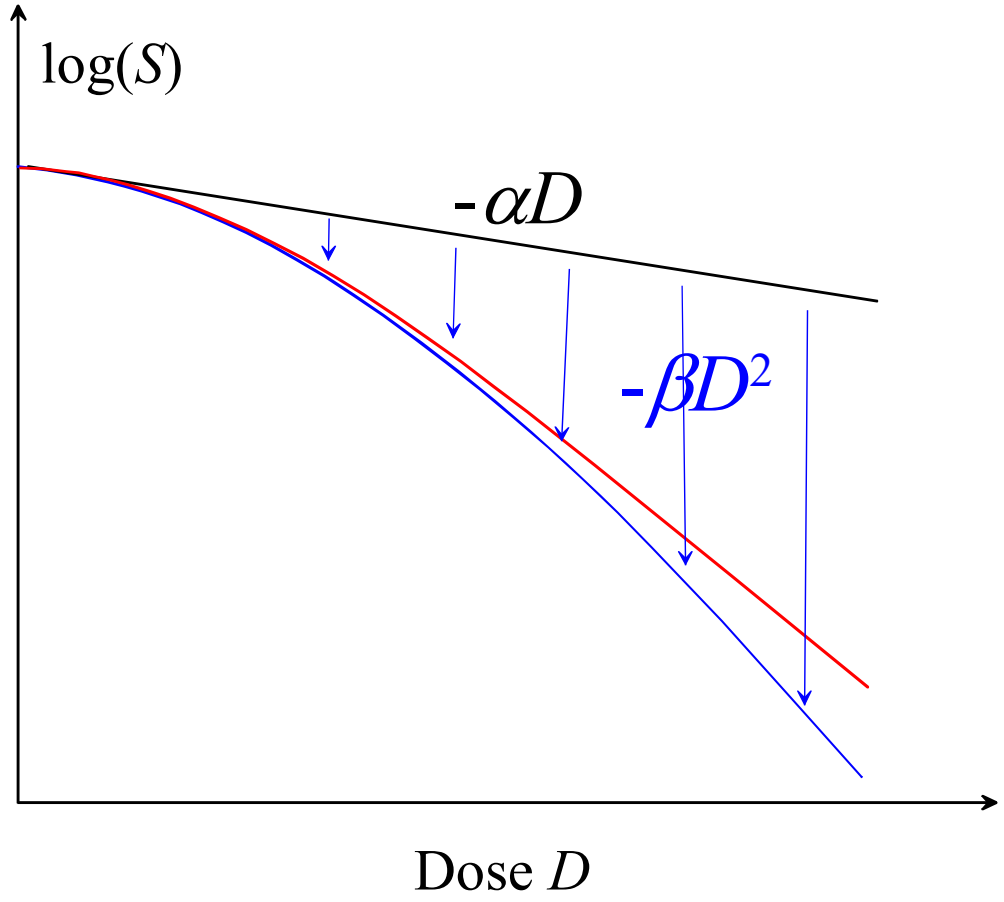
---

[4]Guirado Llorente, D., Aranda, M., Ortiz Seidel, M., Mesa Pérez, J.A., Vega Fernandez J.M.D.L., Martinez Luna, R.J., Zamora Ardoy, L.I., Villalobos Torres, M., Lallena, A.M.: Low dose hypersensitivity in mulicellular tumour spheroids. Radiother. Oncol. 96 (2010), Supl. 1, 607-8.

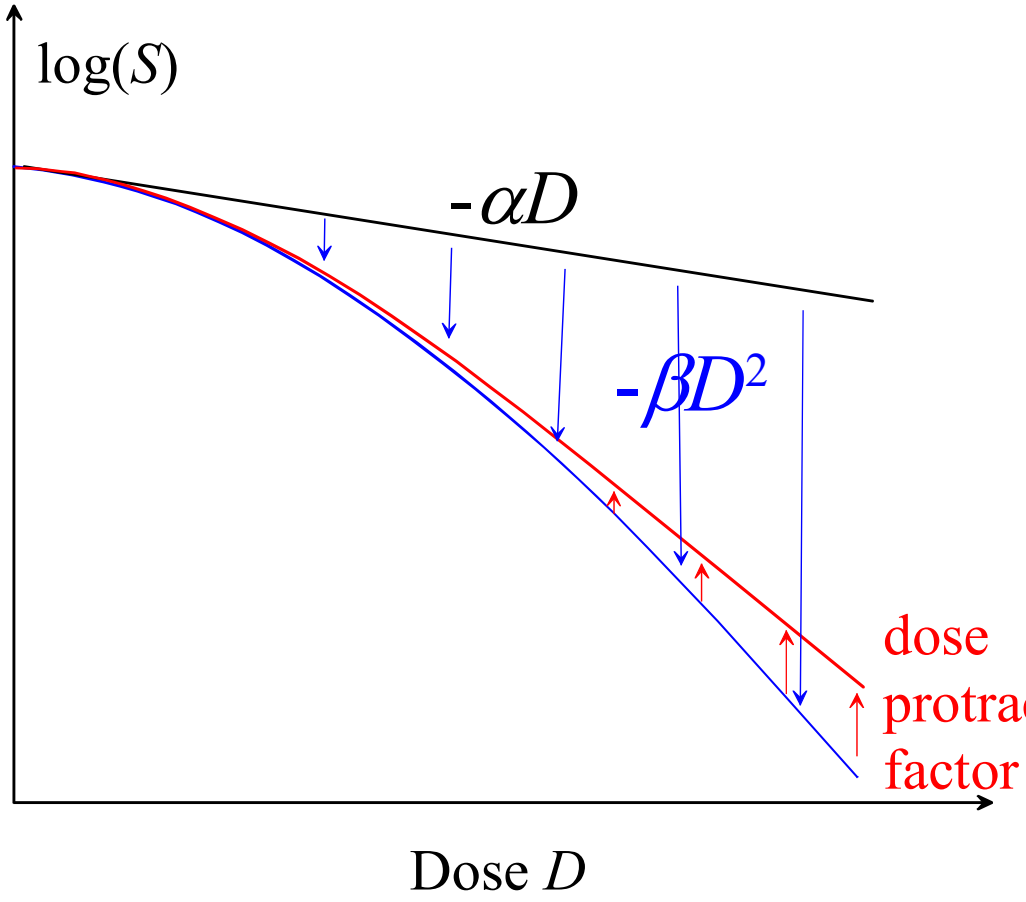
Modelling in Radio-Oncology: LQ-Type Models



Modelling in Radio-Oncology: LQ-Type Models



Modelling in Radio-Oncology: LQ-Type Models

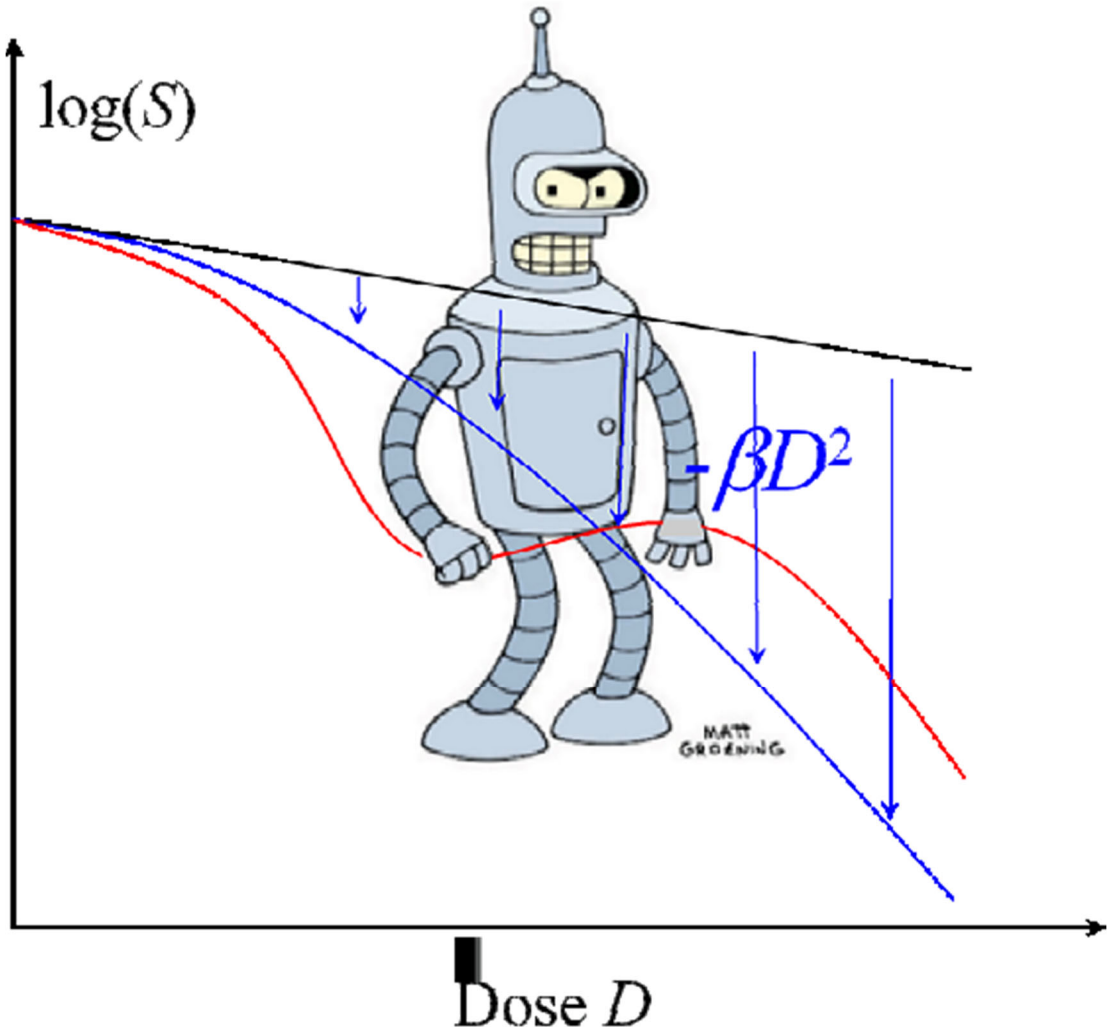


$$\log S = -\left(\alpha D + G\beta D^2\right)$$

$$G = \left(\frac{2}{D^2}\right)\int_{-\infty}^{\infty} R(t)dt \int_{-\infty}^{t} e^{-\lambda\cdot(t-\tau)} R(\tau)d\tau$$

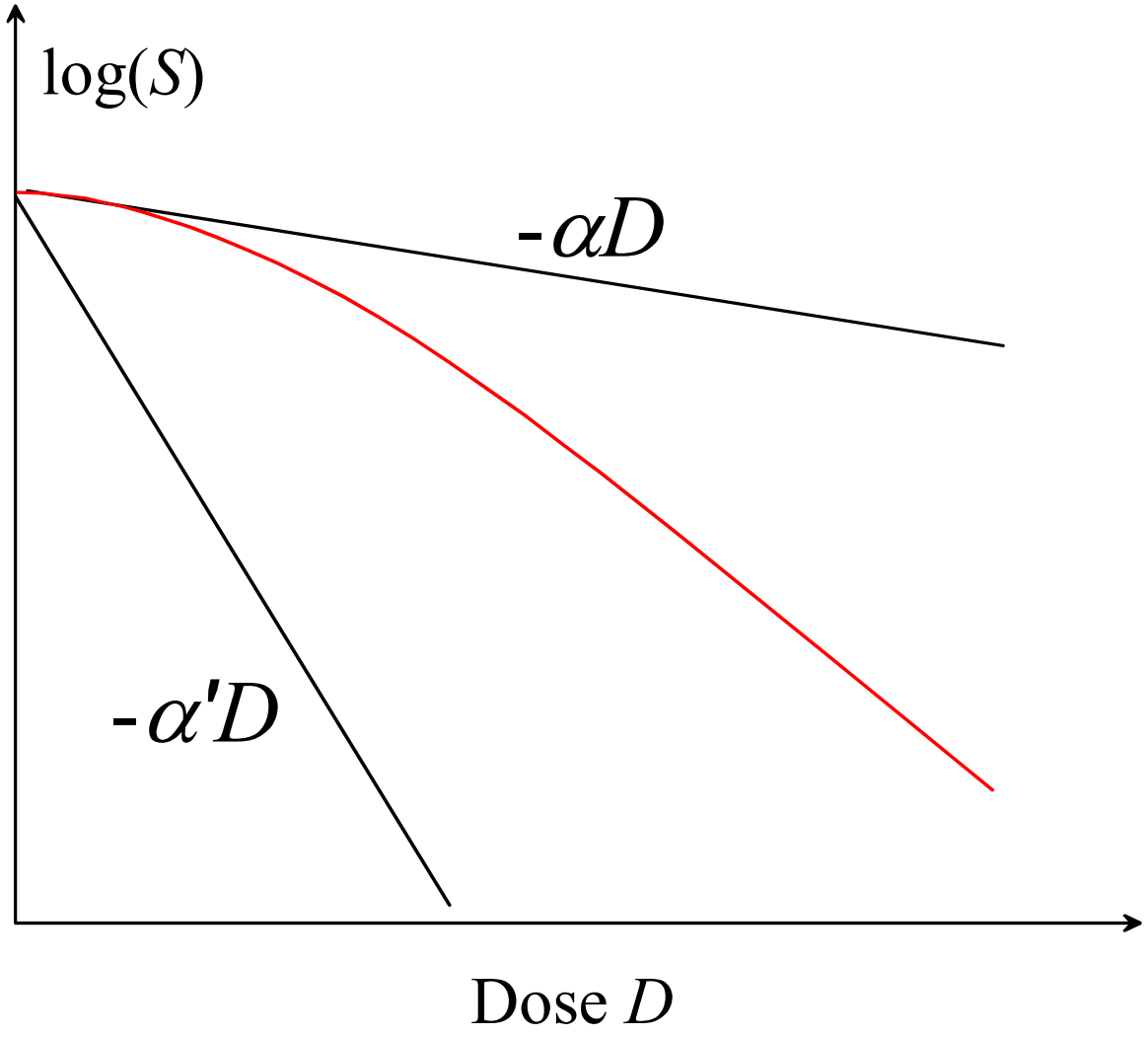
Generalized Lea-Catchside-Factor G: Kellerer AM, Rossi HH. The theory of dual radiation action. Curr Top Radiat Res. 1972;8:85–158.

Modelling in Radio-Oncology: LQ-Type Models

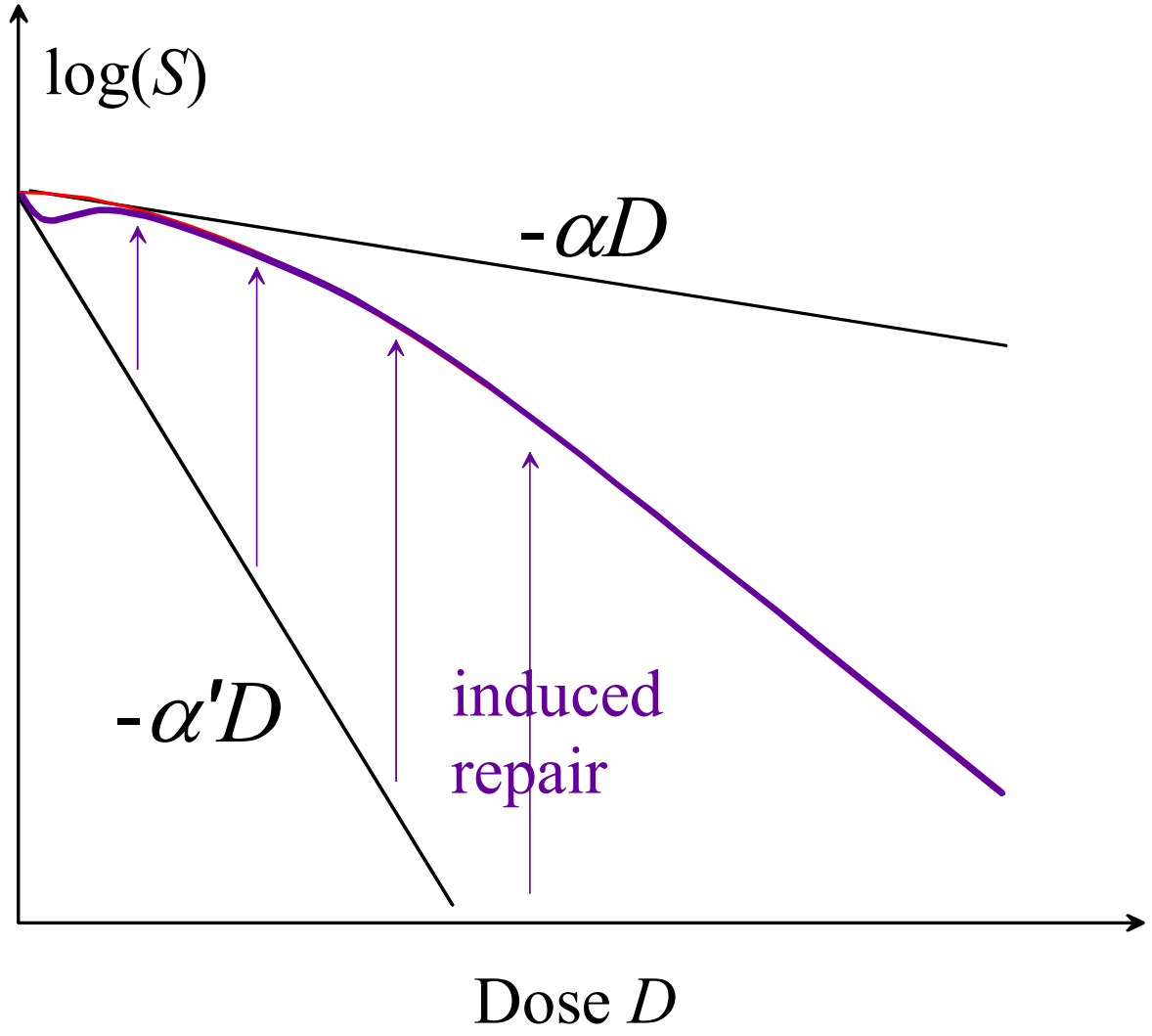


… The Wrong Approach?

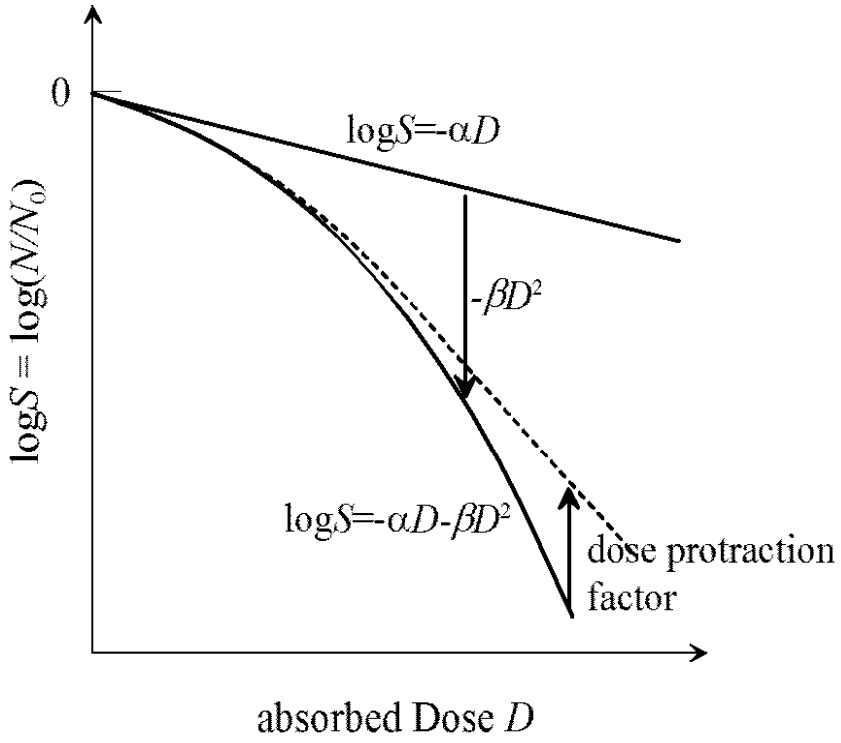
Modelling in Radio-Oncology: Induces-Repair



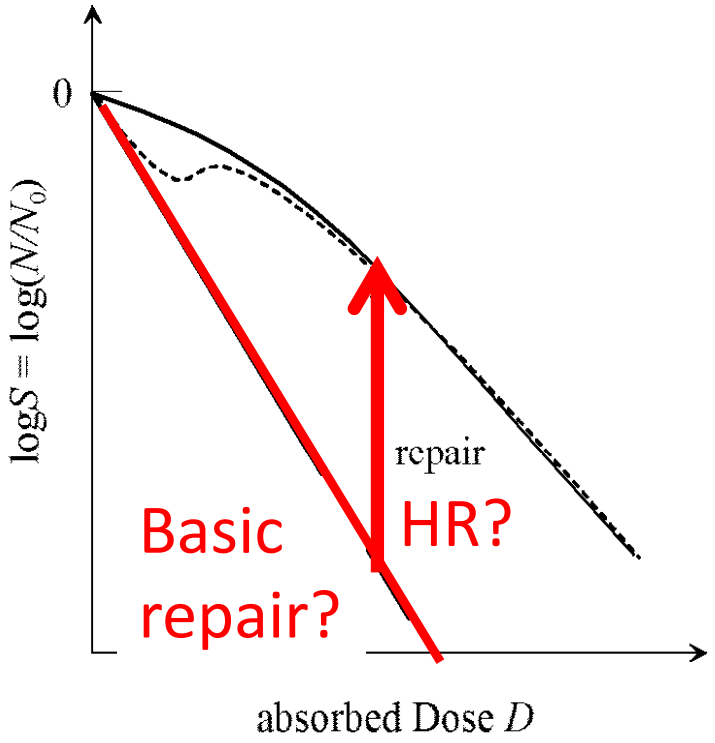
Modelling in Radio-Oncology: Induces-Repair



Modelling in Radio-Oncology: Induces-Repair



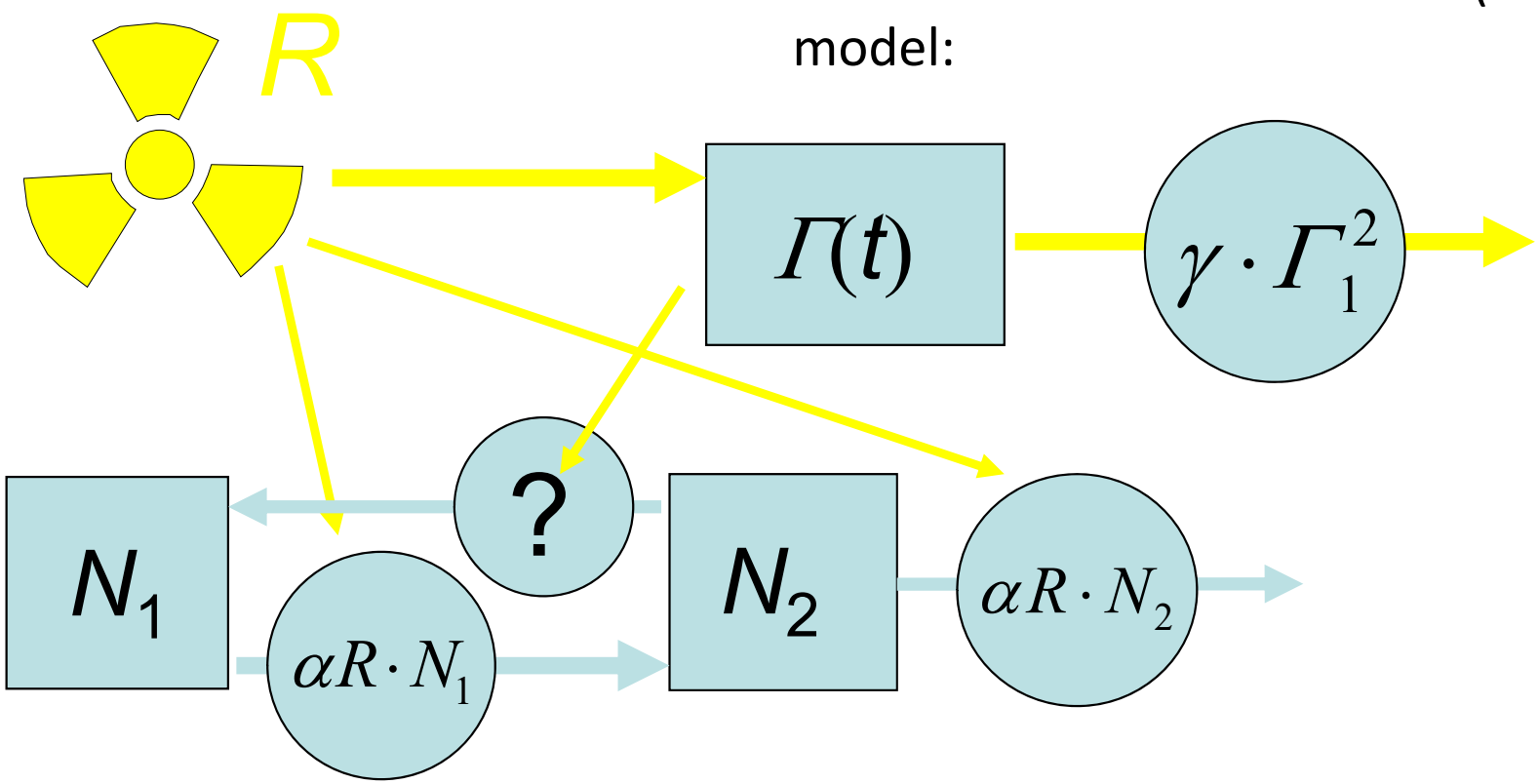
(a)



(a) Corresp. to observations of cell cycle dependent radiosensitivity

Modelling in Radio-Oncology: Induced Repair

The basic idea of a TBDE – IR (Γ-IR[5]) model:



[5]Scheidegger S., Füchslin R.M. (2011): Kinetic model for dose equivalent – an efficient way to predict systems response of irradiated cells. Proc. of ASIM 2011 (full papers, ISBN 978-3-905745-44-3)

Γ-IR - Model:

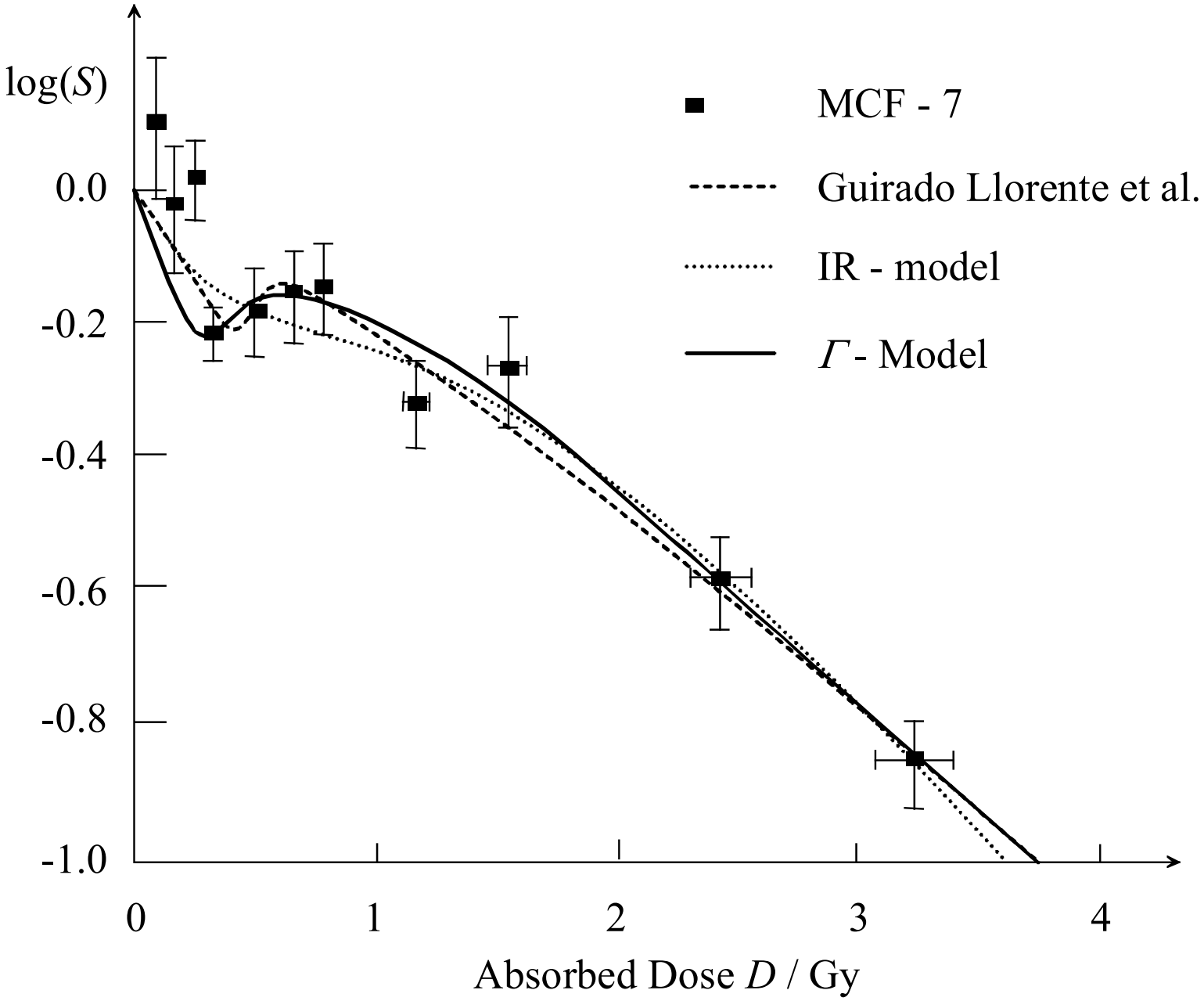
• in principle no β- term required, but a second population

$$\frac{dN_1}{dt} = -\alpha \cdot R \cdot N_1 + \Theta(\Gamma, N_2)$$

$$\frac{dN_2}{dt} = \alpha \cdot R \cdot (N_1 - N_2) - \Theta(\Gamma, N_2)$$

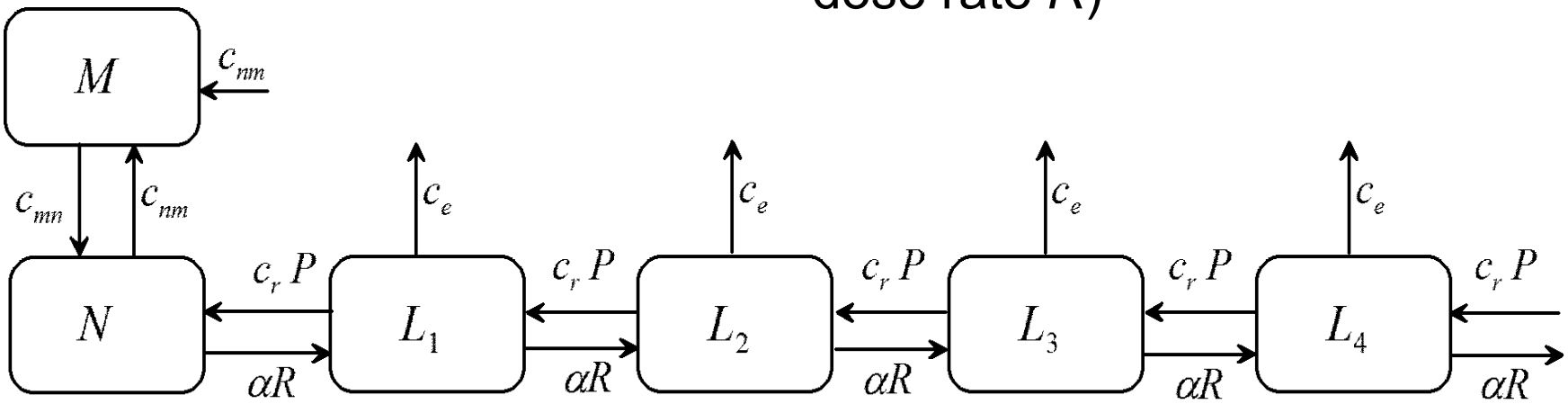
$$\Theta(\Gamma, N_2) = \vartheta \cdot e^{-\kappa \cdot (\Gamma - \Gamma_C)^2} \cdot N_2$$

Low Dose Hypersensitivity



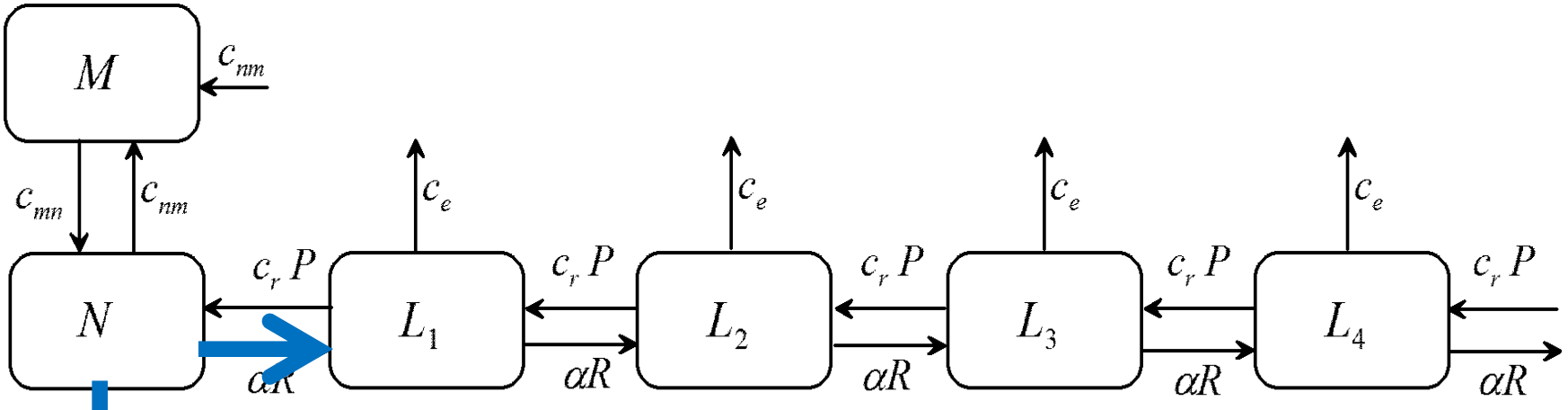
Multi-Hit Repair (MHR) Model

- *N*,*M*: No. of tumour cells in the mitotic cycle
- L_i: No. Of tumour cells with i radiation induced (‘’severe’’) hits (hit induction proportional to dose rate *R*)



Scheidegger S, Fuchs HU, Zaugg K, Bodis S, Füchslin RM (2013): *Computational and Mathematical Methods in Medicine*, 2013, http://dx.doi.org/10.1155/2013/587543

MHR Model



$$\left[\frac{dN}{dt}\right]_{rad} = -\alpha R \cdot N$$

R: Dose rate

$$\left[\frac{dN}{dt}\right]_{dc} = -k(T) \cdot N$$

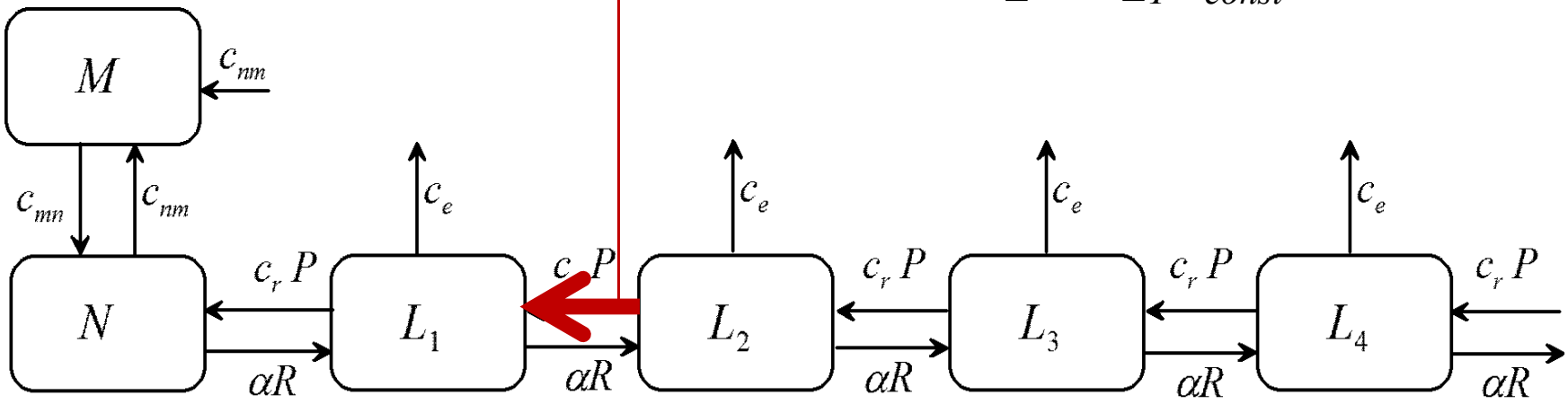
+ direct heat-induced cytotoxicity

MHR Model: Repair Probability

$$\frac{dL_2}{dt} = -c_r P \cdot L_2$$

P: Repair probability

$$\left[\frac{\partial P}{\partial \Lambda}\right]_{\Gamma=const} = -\mu_\Lambda P$$



MHR Model: Repair Probability

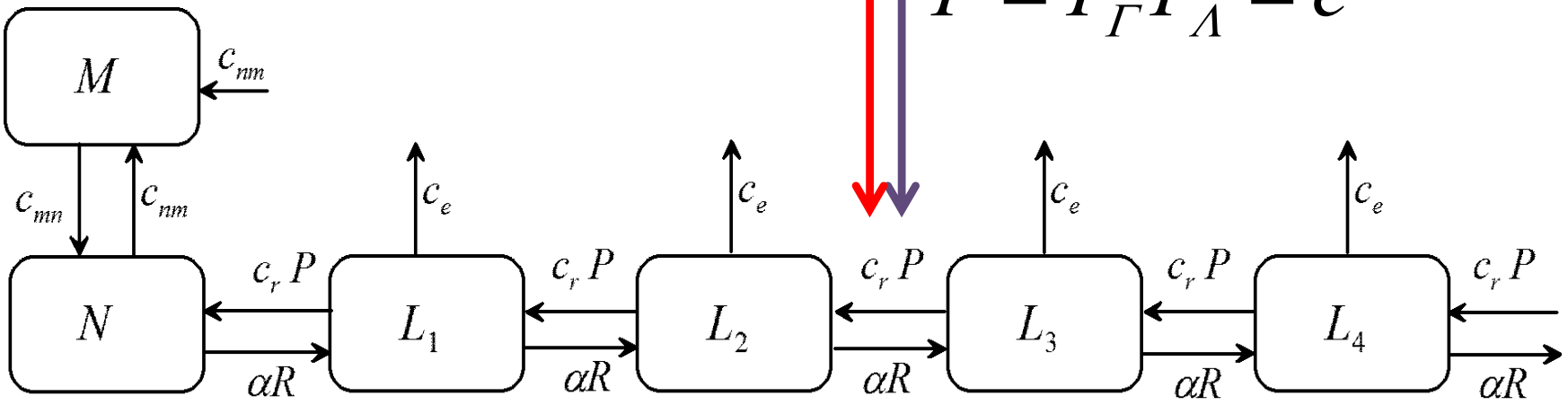
Radiation

$$\left[\frac{\partial P}{\partial \Gamma}\right]_{\Lambda=const} = -\mu_{\Gamma} P$$

Heat

$$\left[\frac{\partial P}{\partial \Lambda}\right]_{\Gamma=const} = -\mu_{\Lambda} P$$

$$P = P_{\Gamma} P_{\Lambda} = e^{-(\mu_{\Gamma}\Gamma + \mu_{\Lambda}\Lambda)}$$



MHR model (IR part): basic concept

DNA damage

$$\frac{dN}{dt} = -\alpha R N + c_r e^{-(\mu_\Gamma \Gamma)} \cdot L_1$$

$$\frac{dL_1}{dt} = \alpha R N - \left(\alpha R + c_r e^{-(\mu_\Gamma \Gamma)} + c_e\right) \cdot L_1 + c_r e^{-(\mu_\Gamma \Gamma)} \cdot L_2$$

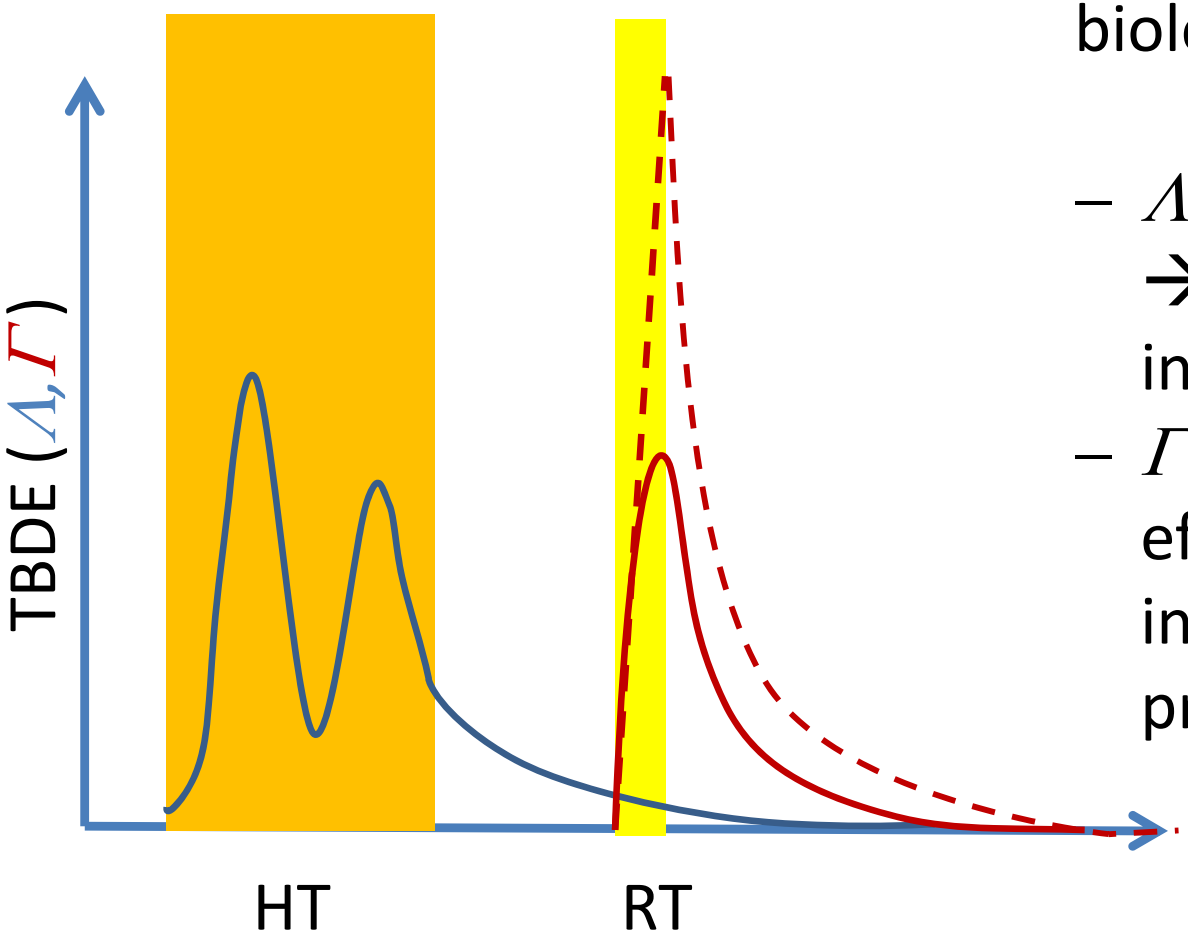
$$\frac{dL_k}{dt} = \alpha R L_{k-1} - \left(\alpha R + c_r e^{-(\mu_\Gamma \Gamma)} + c_e\right) \cdot L_k + c_r e^{-(\mu_\Gamma \Gamma)} \cdot L_{k+1}$$

$$\frac{d\Gamma}{dt} = R - f(\Gamma)$$

$$\lim_{t\to\infty}\left[\int_{-\infty}^{t} f\left(\Gamma(\tau)\cdot\right)d\tau\right] = \lim_{t\to\infty}\left[D(t)\right] = D_{tot}$$

Protein damage

Concept behind Transient Biological Dose Equivalent



TBDE proportional to biological effect:

- Λ: thermal effects →repair protein inactivation
- Γ: radiation-induced effects → damage induction on repair proteins

Scheidegger S, Fuchs HU, Füchslin RM (2014): *NOLTA* 2014, 168-171.

MHR Model: Transient Thermal Dose Λ

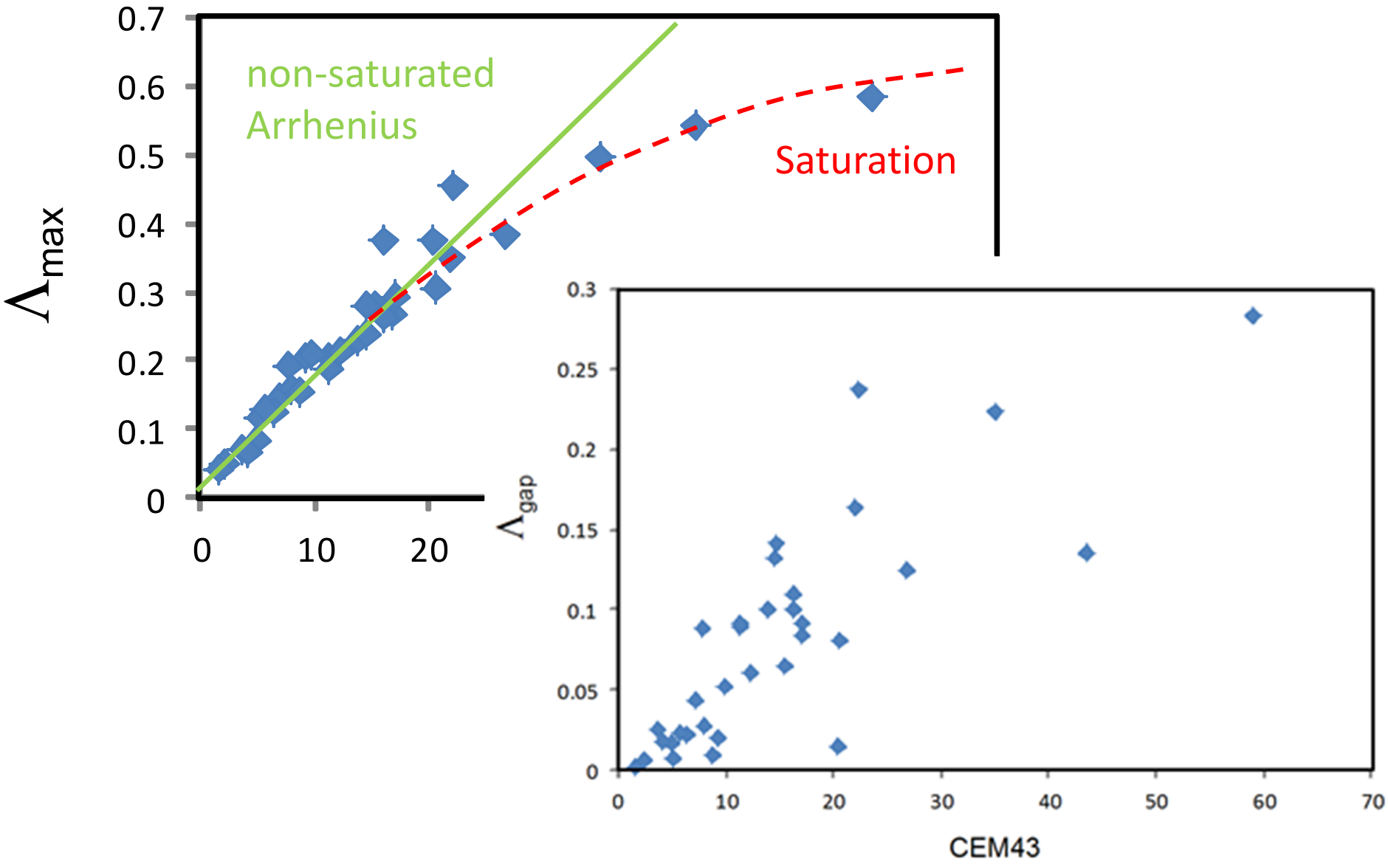
$$\frac{d\Lambda}{dt} = k_1 \Upsilon - k_2 \Lambda$$

$$\frac{d\Upsilon}{dt} = -k_1 \Upsilon + k_2 \Lambda \ ;$$

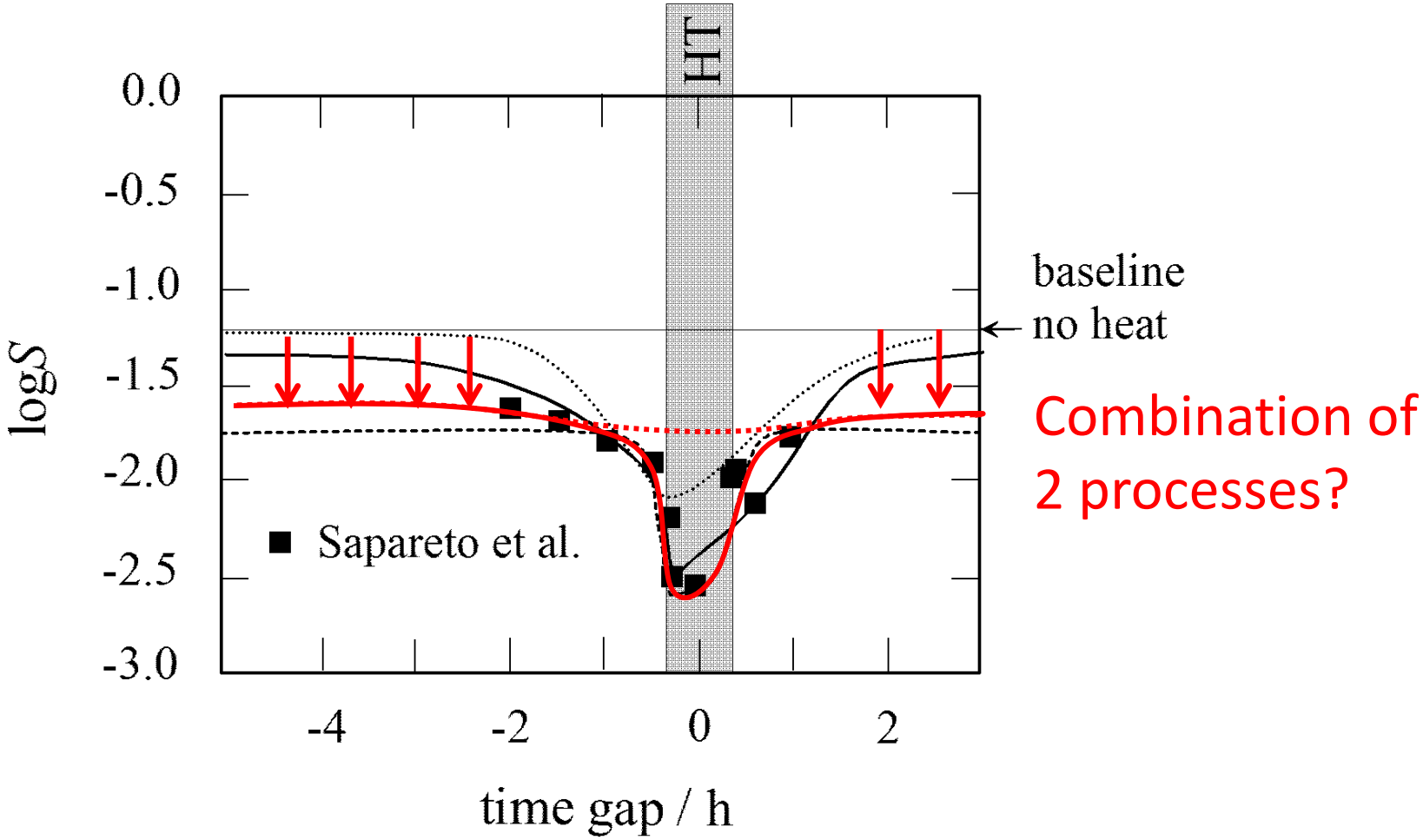
$$k_1 = \kappa \cdot e^{-\frac{E_a}{RT}}$$

- Transient (dynamic) thermal dose Λ describes protein-related impact on cellular repair capacity.
- It is based on data in vitro and biophysical aspects of heat-stability of proteins (E_a ~1000-2200 kJ/mol for T < 43°C)
- Describes only protein inactivation in a small temperature range and goes into saturation for high temperatures and long heating time - **additive cell killing is not included**!

CEM43° vs. Λ – Clinical Data

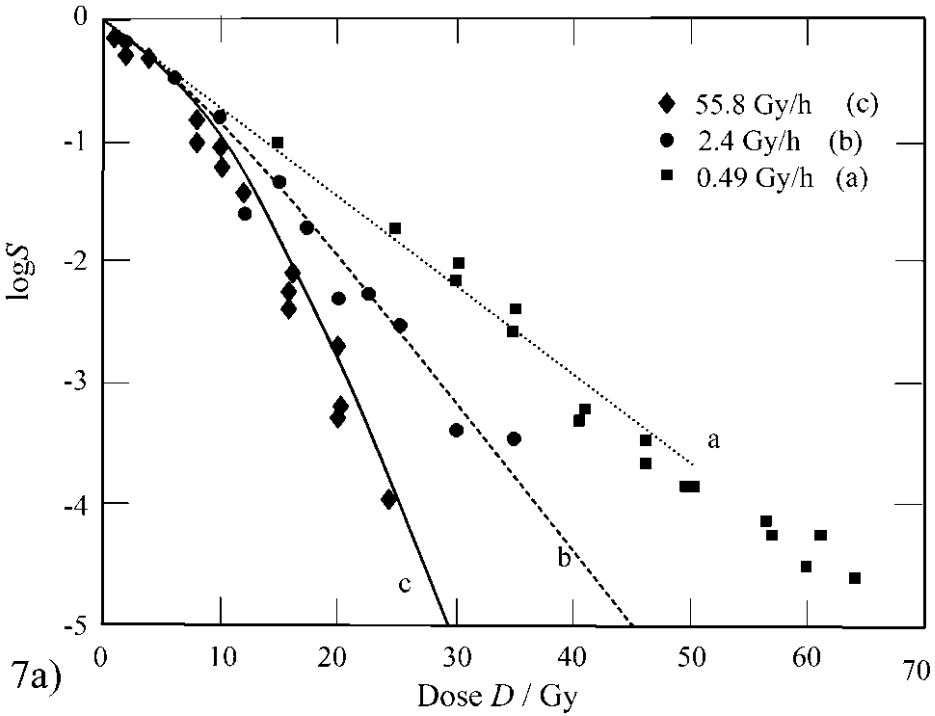


Modelling the synergistic effect of HT-RT: MHR-Approach: Time Gap between RT and HT

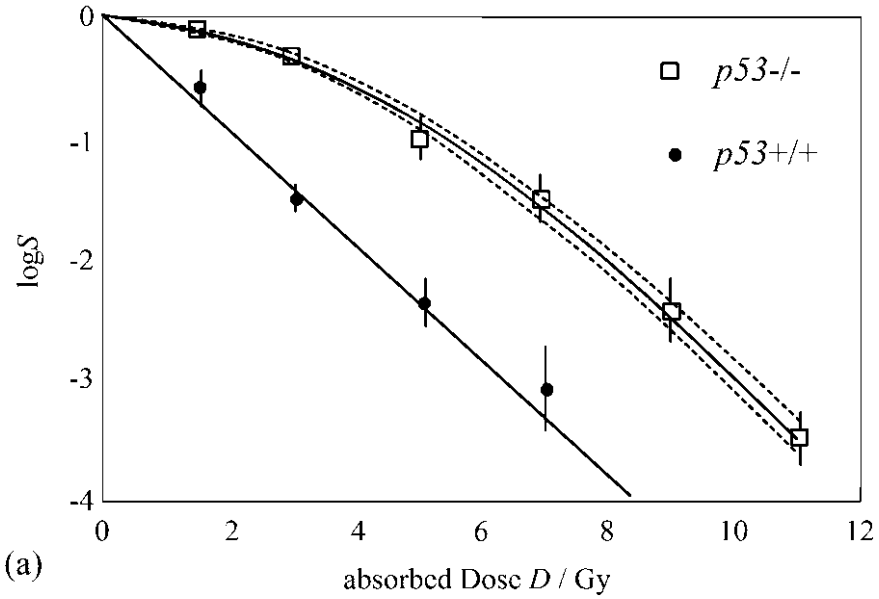


Scheidegger S, et al. (2013): *Computational and Mathematical Methods in Medicine*, 2013, http://dx.doi.org/10.1155/2013/587543

Dose rate dependence, apoptotic vs non-apoptotic cell death

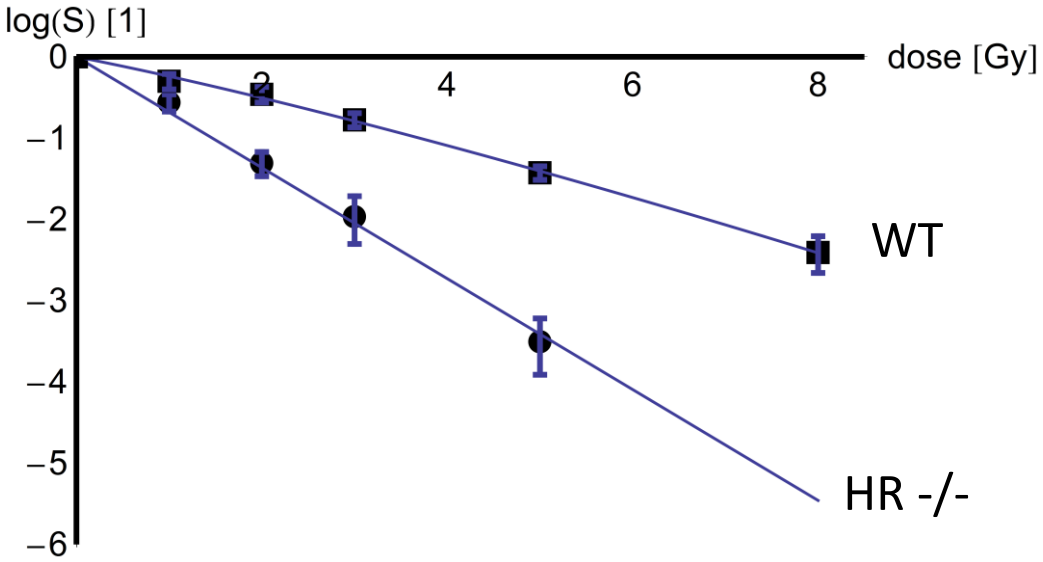


Fit of experimental data from Wells & Bedford, *Radiat Res* **94**, 105-34: C3H10T1/2 cells

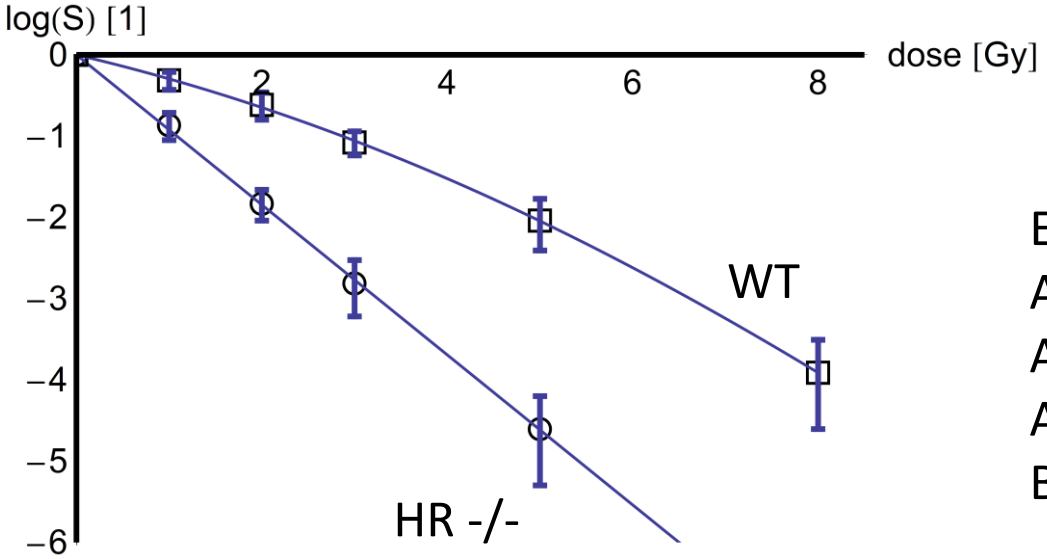


Apoptotic (p53+/+) and non-apoptotic (p53-/-) cell death: Experimental data from Harrigan Hardenberg P, et al., *Int J Radiat Oncol Bio Phys* **43**(3), 601-5

Fitting CHO data (photons and protons): HR deficient vs. HR non-deficient cell lines

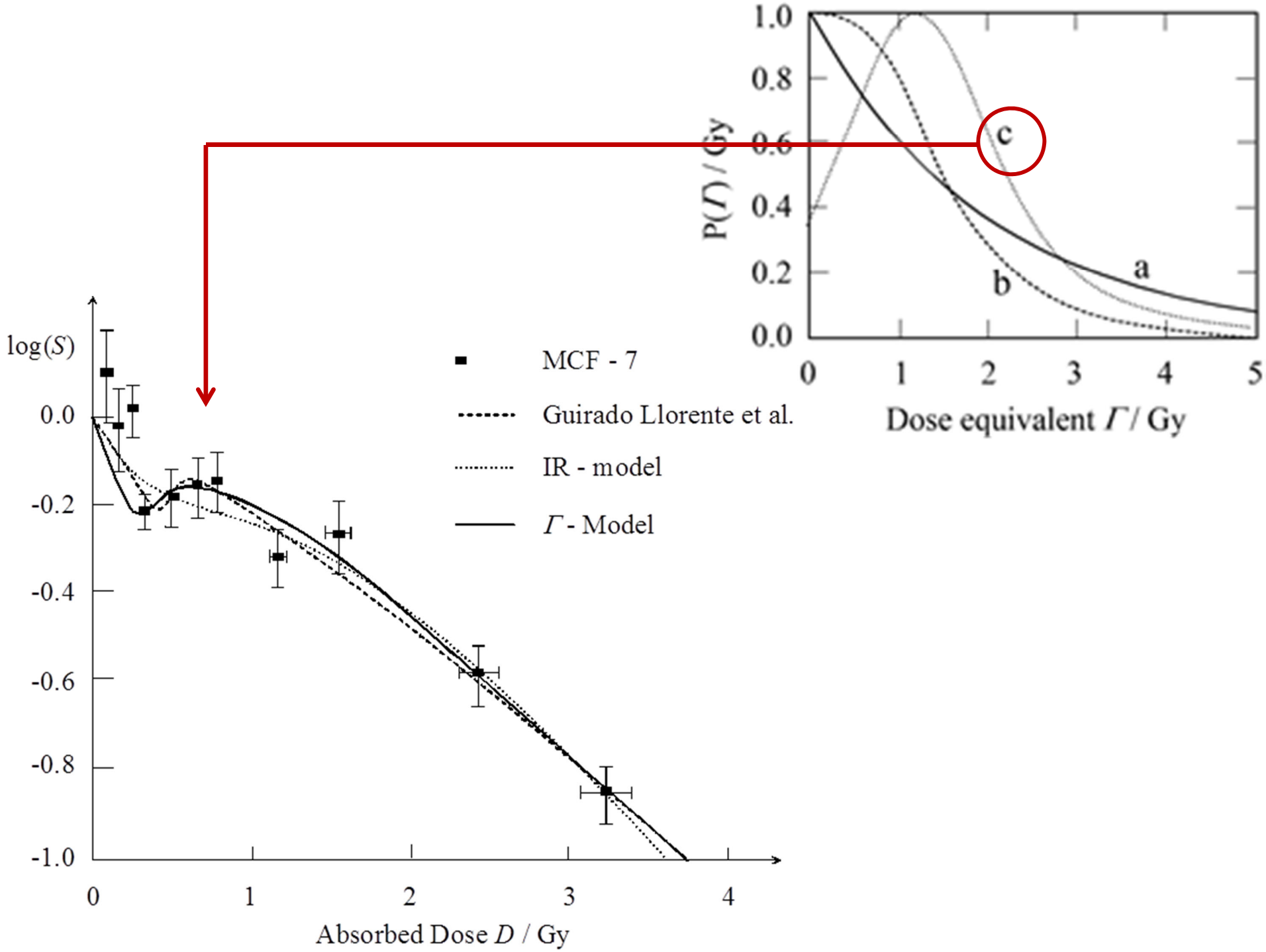


CHO cells irradiated with photons

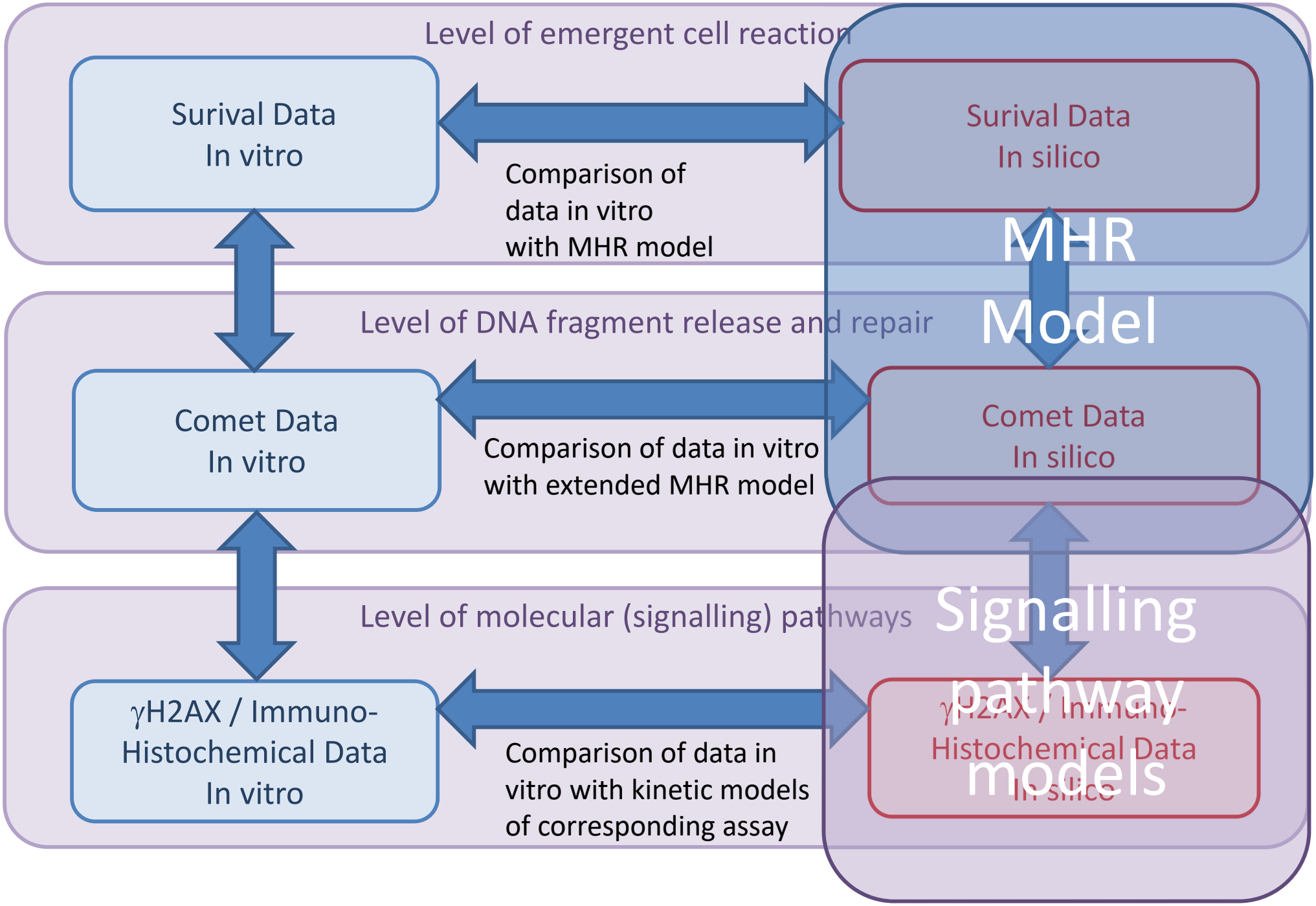


CHO cells irradiated with protons

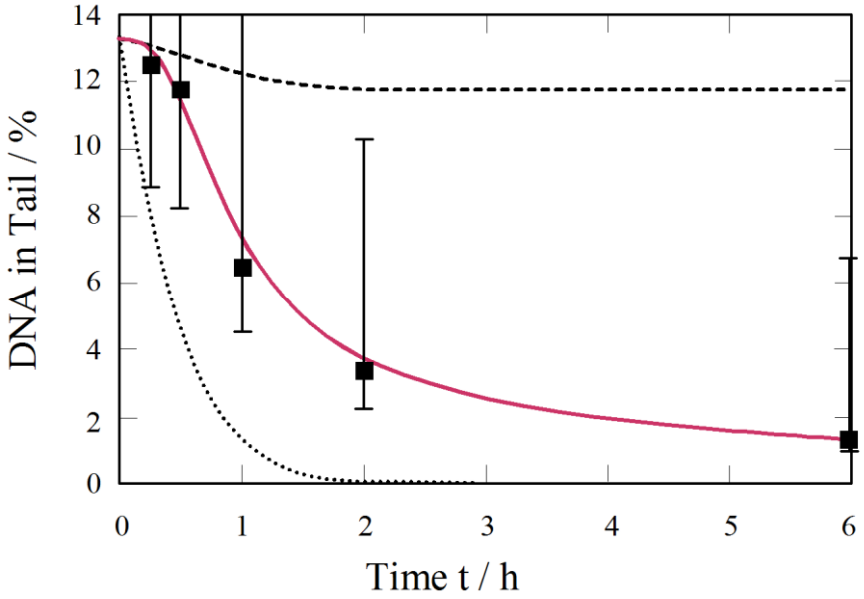
Experimental data: Grosse N, Fontana AO, Hug EB, Lomax A, Coray A, Augsburger M, Paganetti H, Sartori AA, Pruschy M: Int J Radiation Oncol Biol Phys, 88 (2014) 1, 175-181

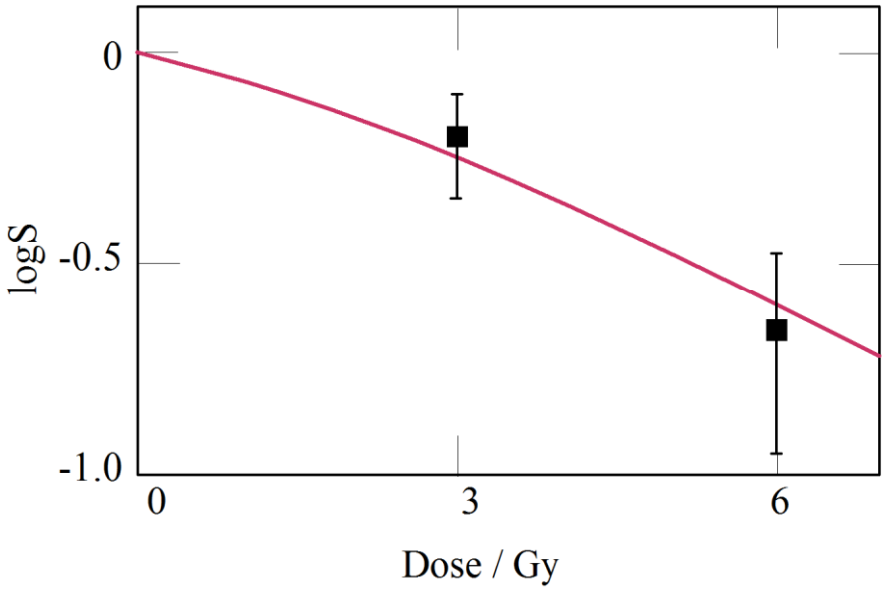

log(S)
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
0
1
2
3
4
Absorbed Dose D / Gy
MCF - 7
Guirado Llorente et al.
IR - model
Γ - Model
P(Γ) / Gy
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Dose equivalent Γ / Gy
a
b
c

Survival and Comets:
Multi Assay Fitting using MHR Model


Level of emergent cell reaction
Surival Data
In vitro
Comparison of
data in vitro
with MHR model
Surival Data
In silico
MHR
Model
Level of DNA fragment release and repair
Comet Data
In vitro
Comparison of data in vitro
with extended MHR model
Comet Data
In silico
Level of molecular (signalling) pathways
Signalling
pathway
models
γH2AX / Immuno-
Histochemical Data
In vitro
Comparison of data in
vitro with kinetic models
of corresponding assay
γH2AX / Immuno-
Histochemical Data
In silico

Radiation Biology: Cellular Effects

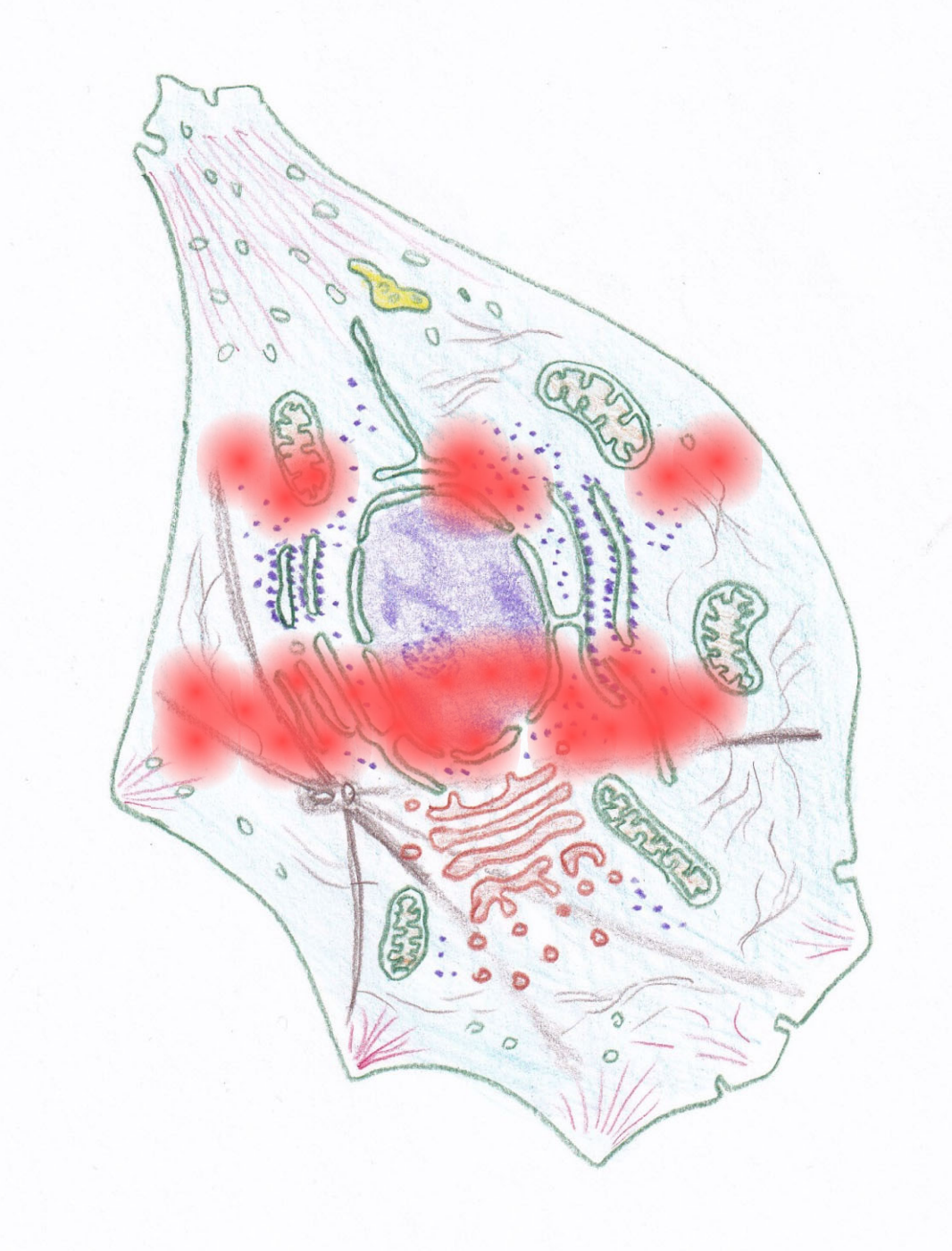




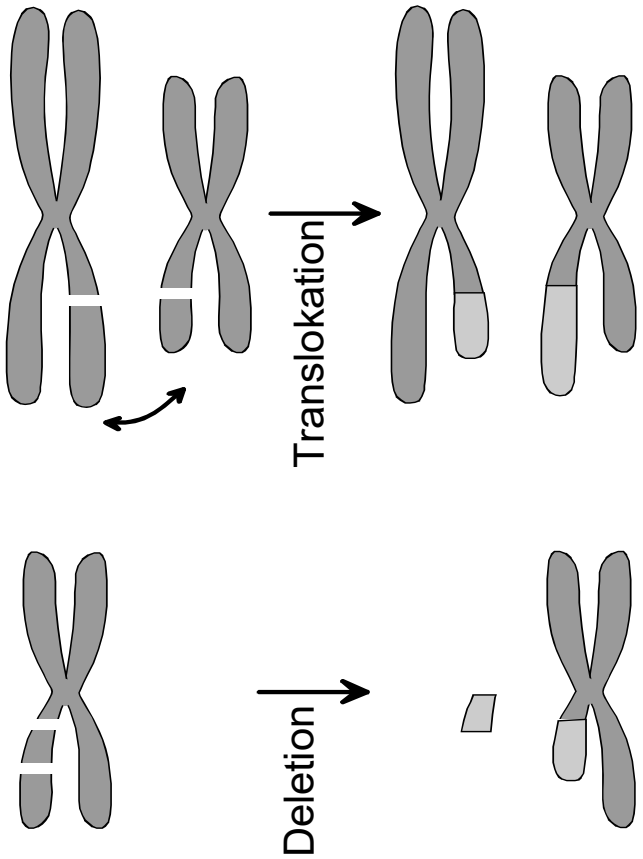
COMET: DNA Damage ⟷ Survival of Sarcoma Cells

Analysis in vitro and – for time resolved Comet –
ex vivo (canine tumor biopsy material)!

What is considered by a hit?



Radiation Biology: Cellular Effects



Isolated radiation-induced chemical modifications on the DNA may have little impact (isolated single strand breaks) Double strand breaks can be associated with severe damages and mutation, leading to cell death or carcinogenesis. Interestingly, most of the double strand breaks are repaired and cannot be considered as severe radiation-induced hits (s. MHR model).

Fig.5. Translocation and deletion on chromosomes

Radiation Biology: Cellular Effects

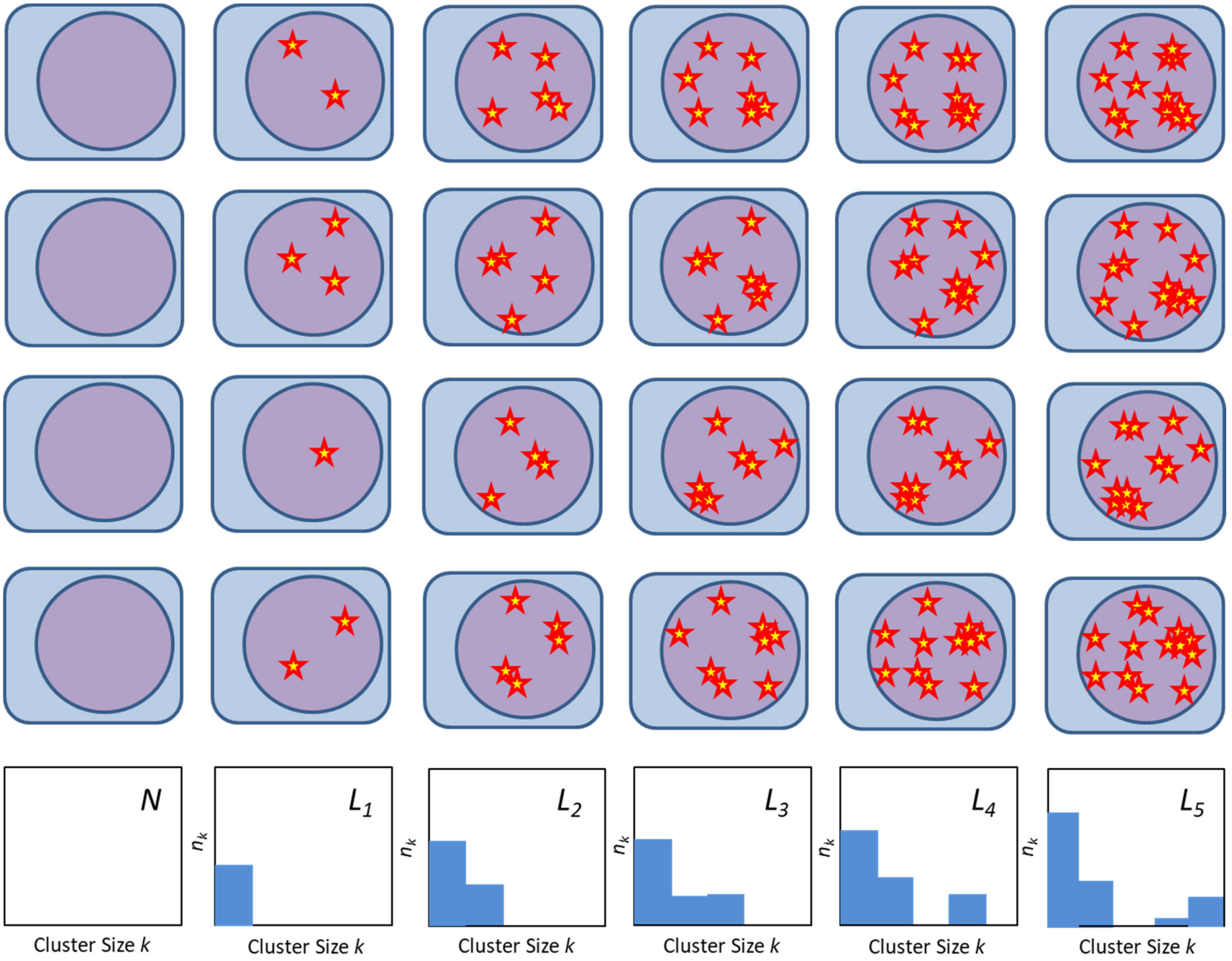
In case that a hit is considered a Double Strand Break (DSB), the linear induction rate is expected to be linear with dose (Rothkamm et al. 2015; Durante et al. 2013).

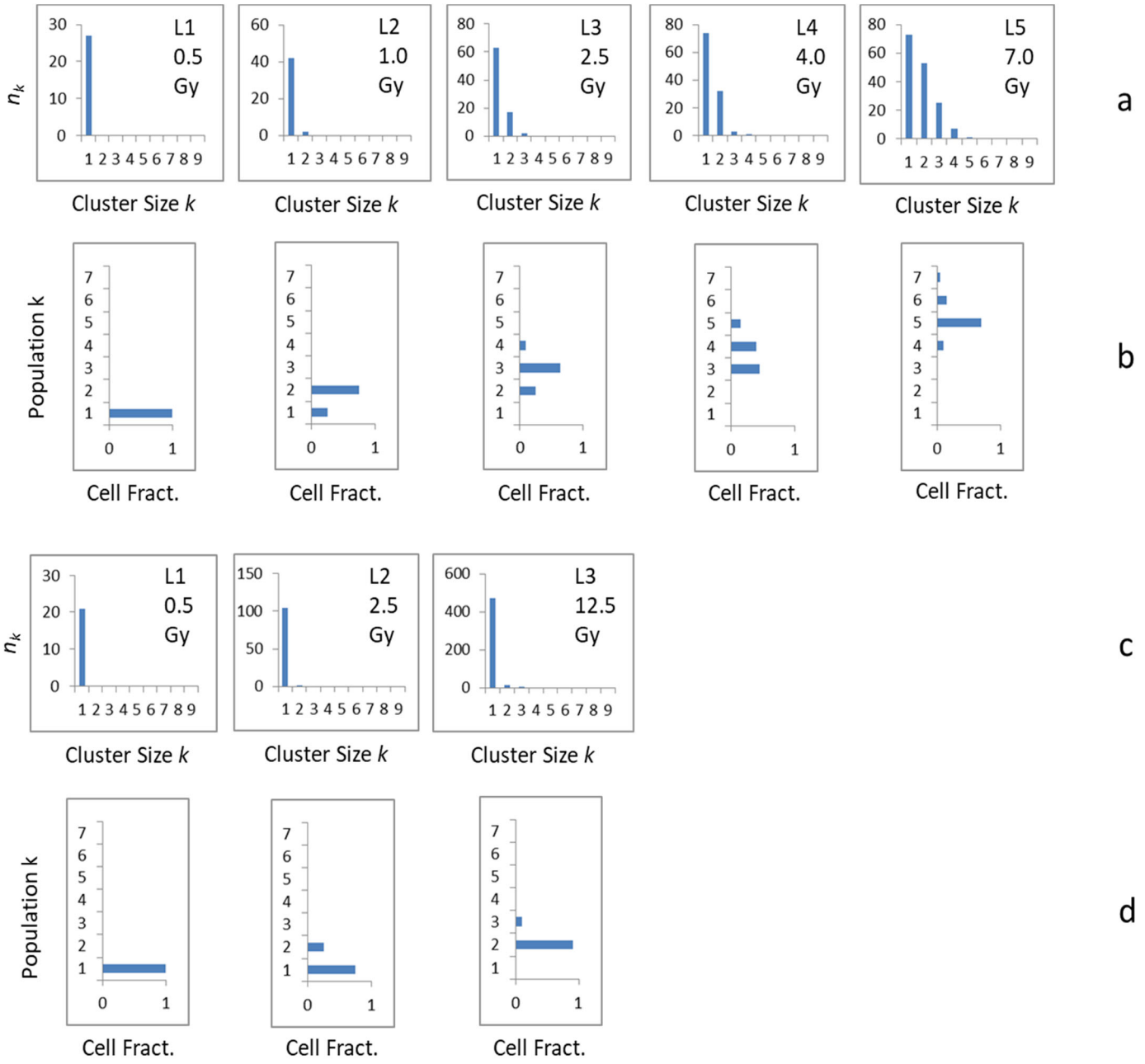
This is in agreement with the linear hit induction rate in the MHR model. Based on the data provided by Rothkamm et al. (Rothkamm et al. 2003), 30-40 DSB can be expected at 1 Gy.

Durante M, Bedford JS, Chen DJ, Conrad S, Cornforth MN, Natarajan AT, van Gent DC, Obe G. (2013): From DNA damage to chromosome aberrations: joining the break. Mutat Res 30, 756(1-2): 5-13. doi: 10.1016/j.mrgentox.2013.05.014

Rothkamm K, Barnard S, Moquet J, Ellender M, Rana Z, Burdak-Rothkamm S (2015): DNA damage foci: Meaning and significance. Environmental and Molecular Mutagenesis, 56(6), 491–504. https://doi.org/10.1002/em.21944

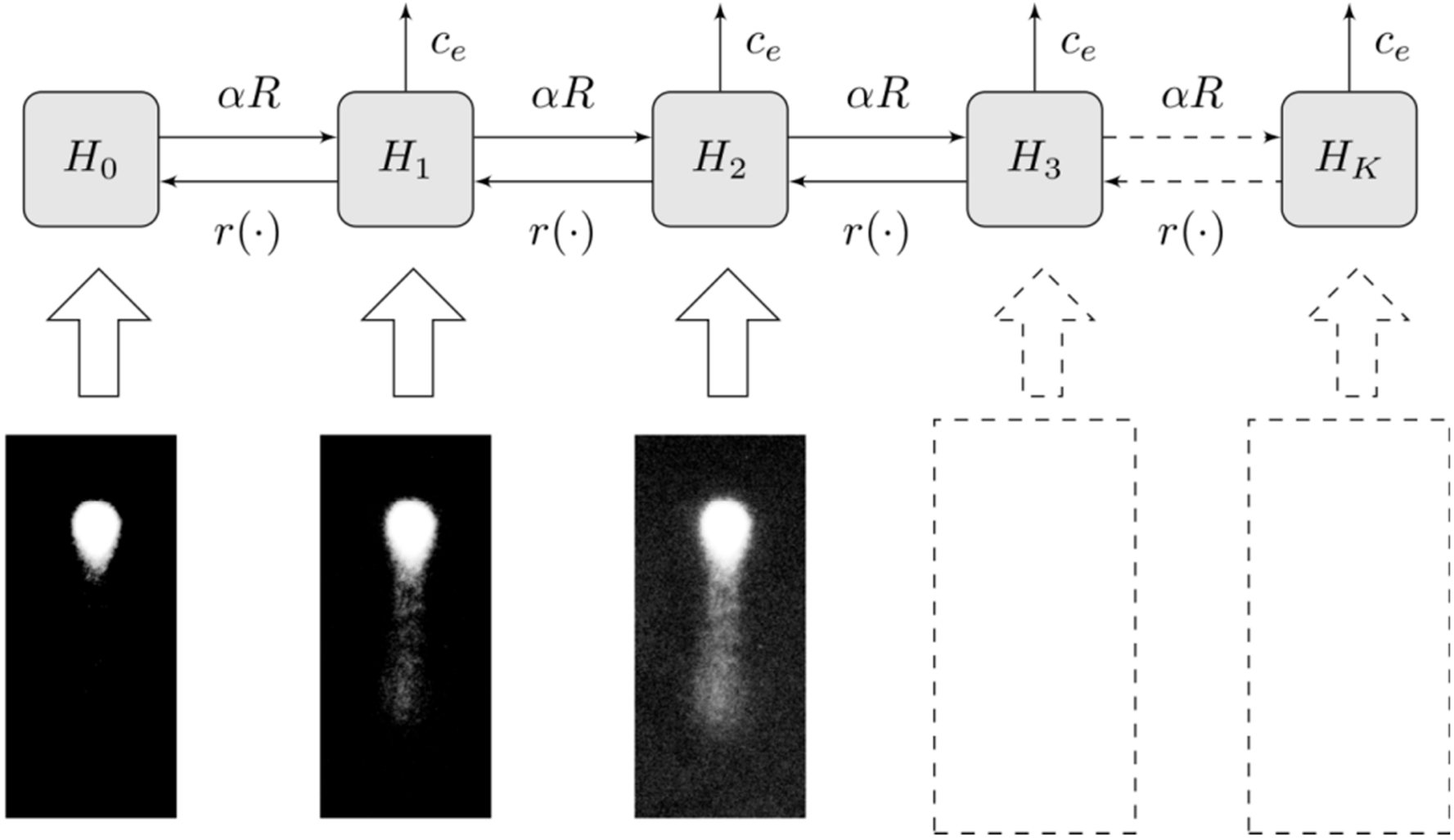
MHR Model: Cluster Hypothesis





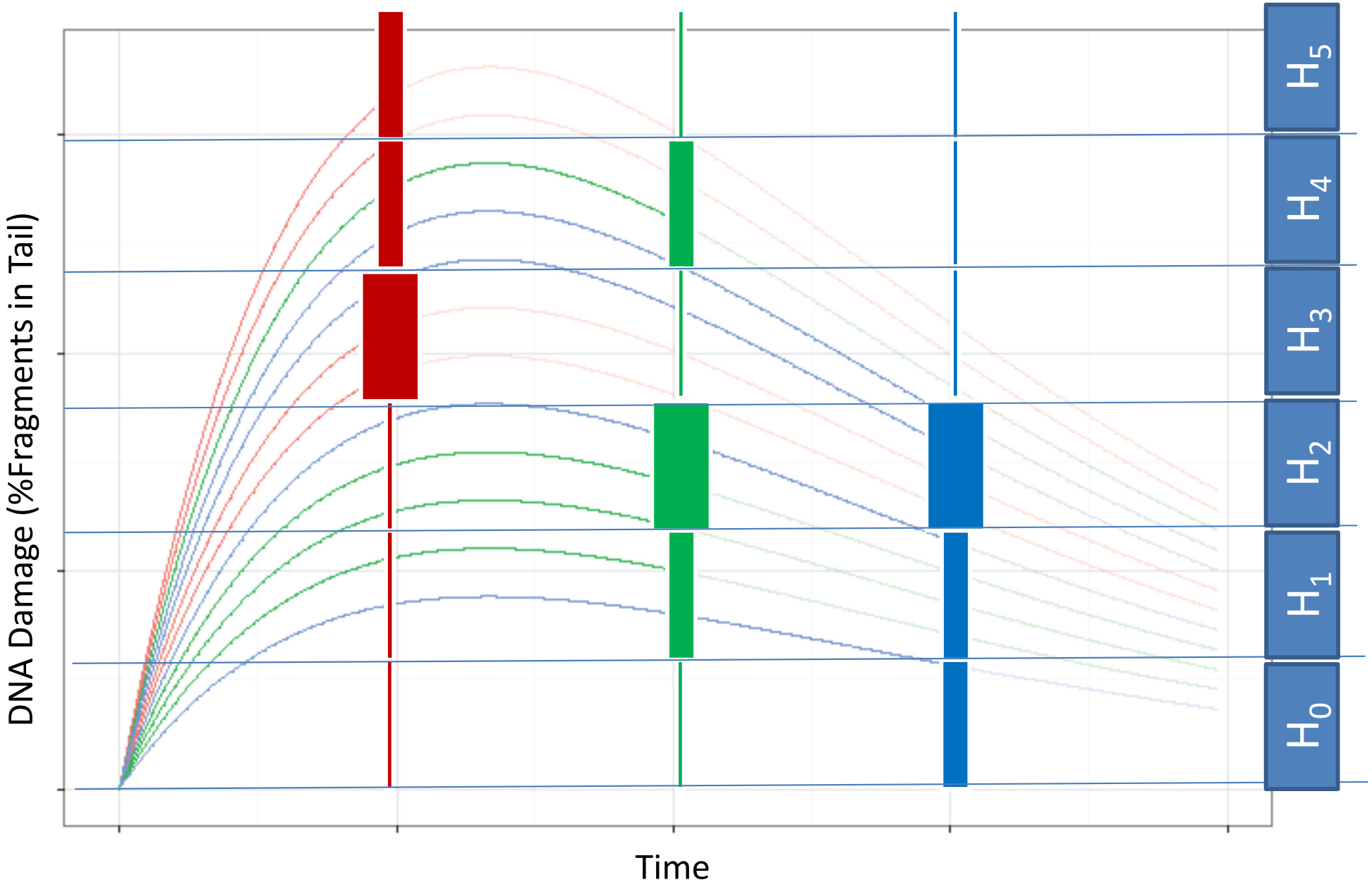
Distributions of clusters with k hits in a cell (a,c) and distributions of the number of cells in the different populations L_k (b,d): (a,b) 196 potential target sites and (c,d) 10^4 target sites.

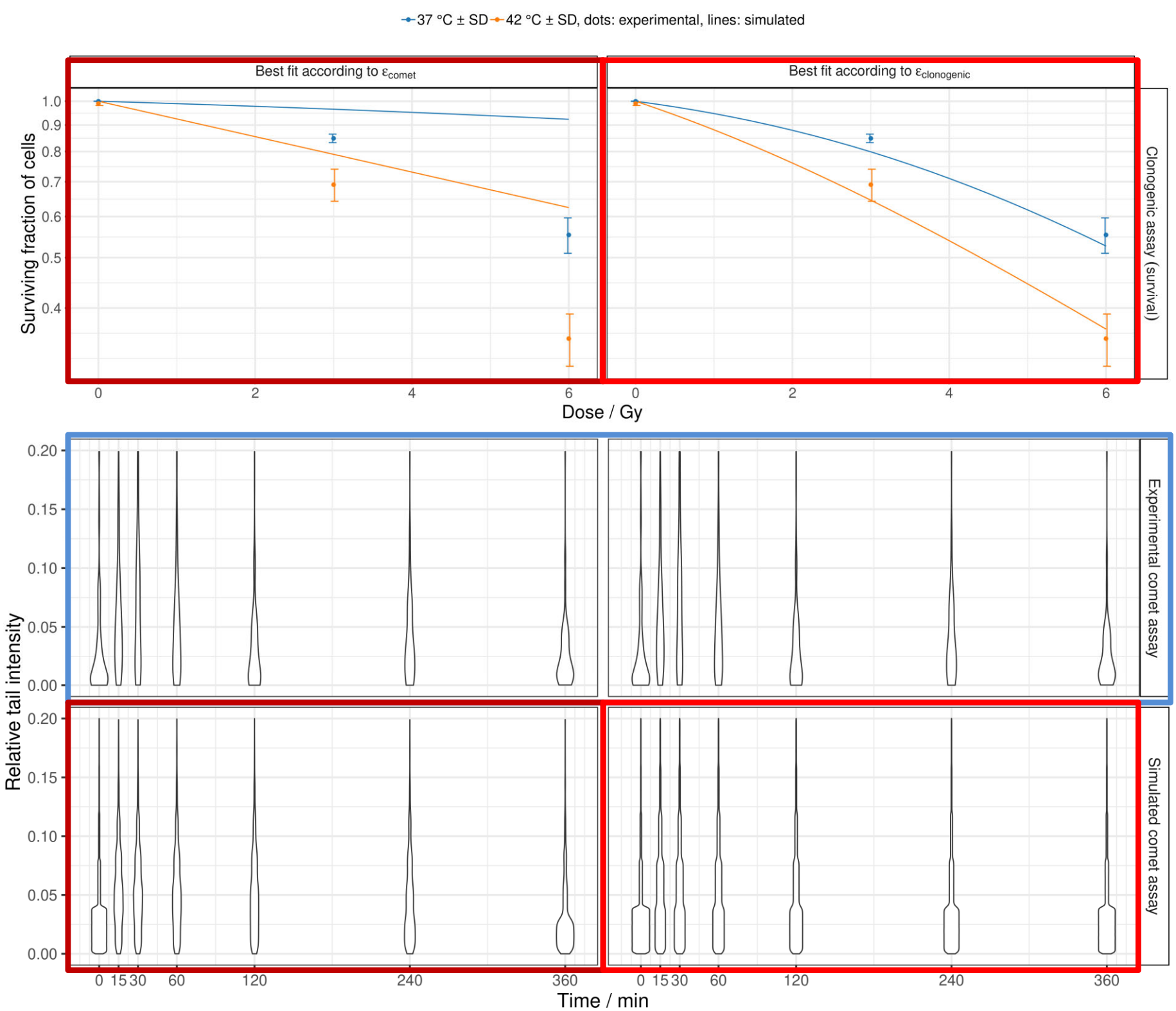
Mapping Comets to a Population Histogram



Weyland et al. (2020): *Computational and Mathematical Methods in Medicine*, 2020, https://dx.doi.org/10.1155/5972594

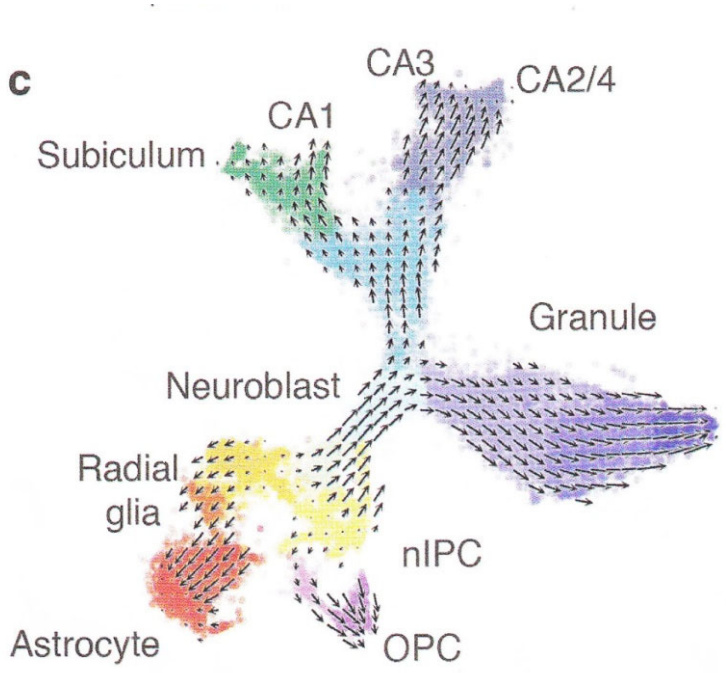
Comet Assay: Looking at the DNA Damage

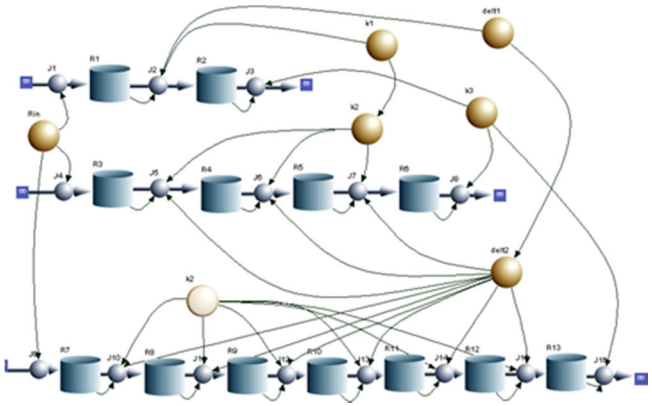


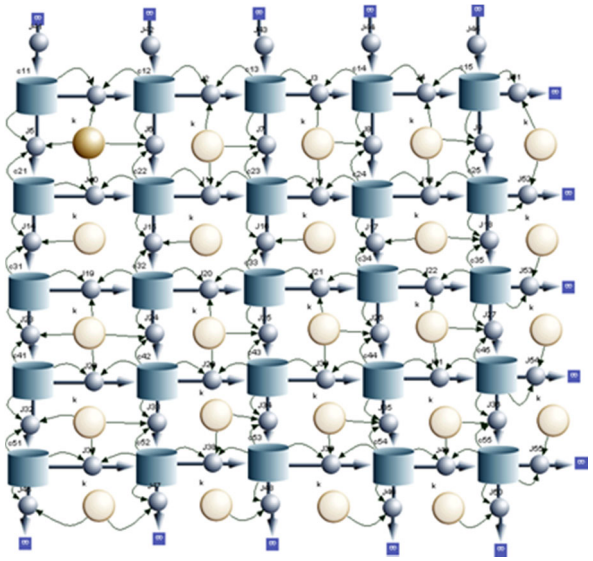

37 °C ± SD
42 °C ± SD, dots: experimental, lines: simulated
Best fit according to ε_{comet}
Best fit according to $\varepsilon_{clonogenic}$
Clonogenic assay (survival)
Surviving fraction of cells
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
2
4
6
Dose / Gy
Experimental comet assay
Simulated comet assay
Relative tail intensity
0.20
0.15
0.10
0.05
0.00
0
15
30
60
120
240
360
Time / min

Interpretation of the population chain in the MHR model: “Diffusion” of cell fate probabilities?

$$\frac{dP}{dt} = \Delta\left[DP\right] - \nabla \bullet \left[\vec{F}P\right]$$

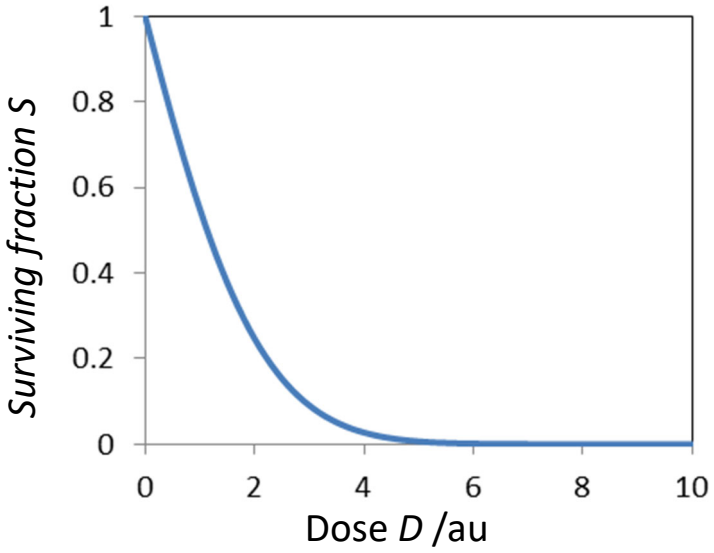


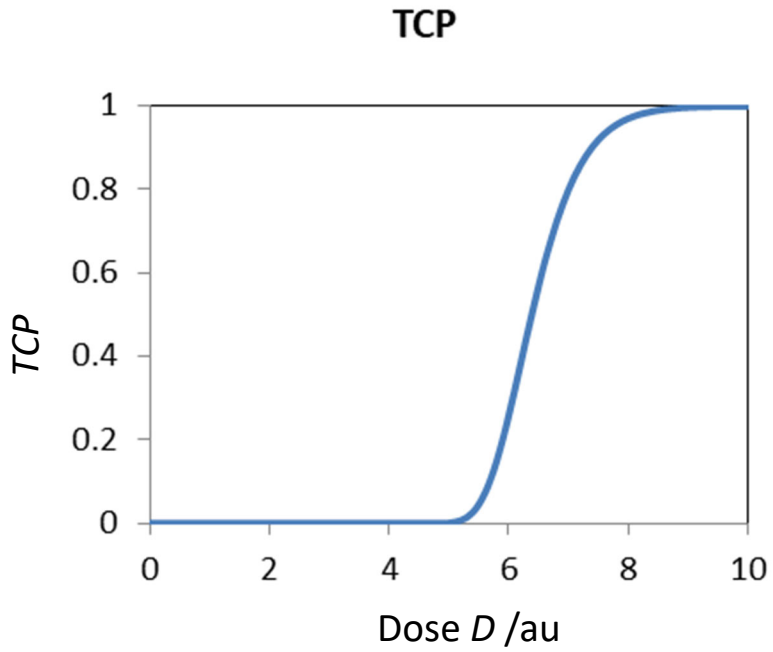




TCP & NTCP

Survival and TCP

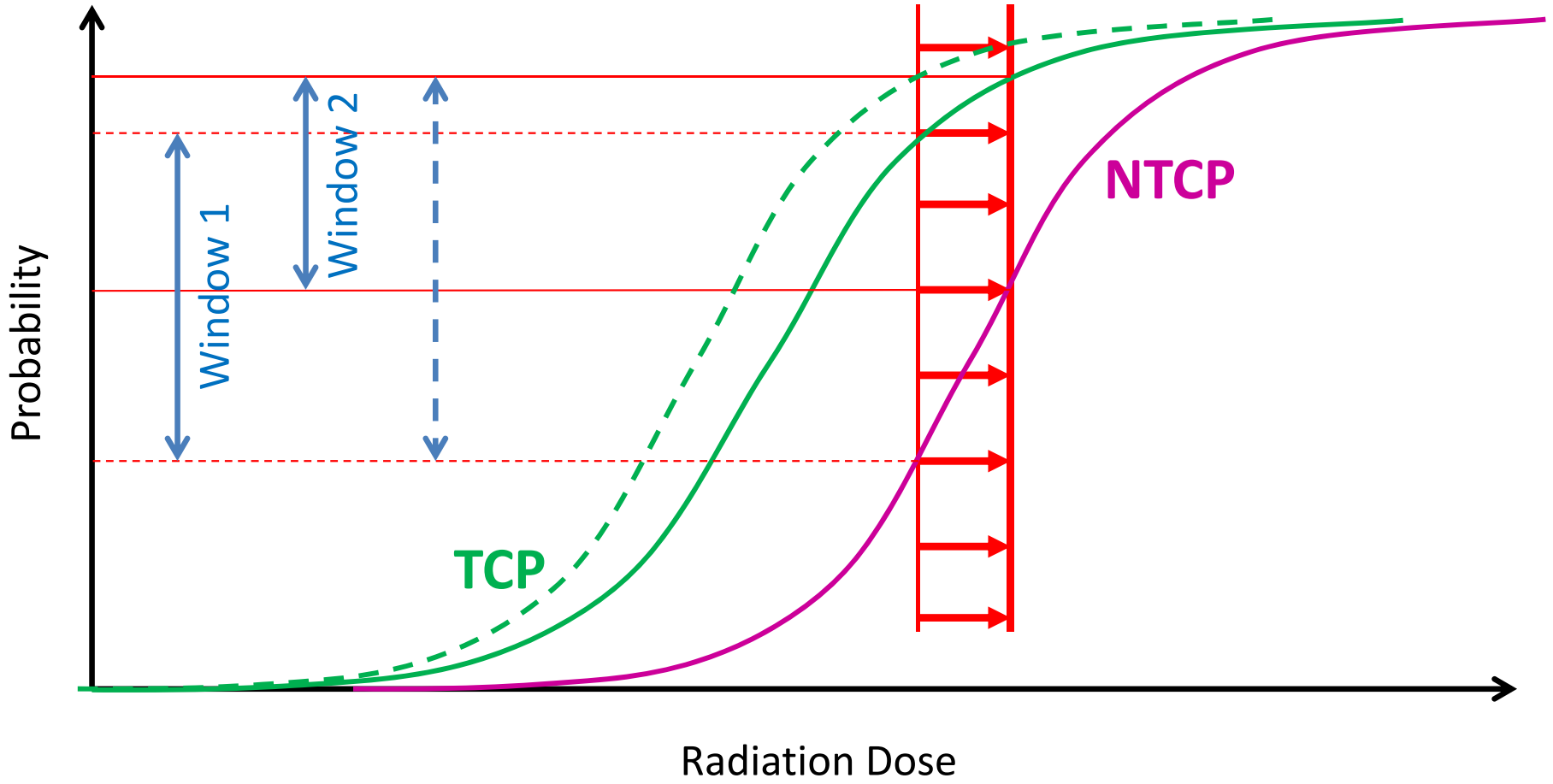




$$S = \frac{N}{N_0} = e^{-(\alpha D + \beta D^2)}$$

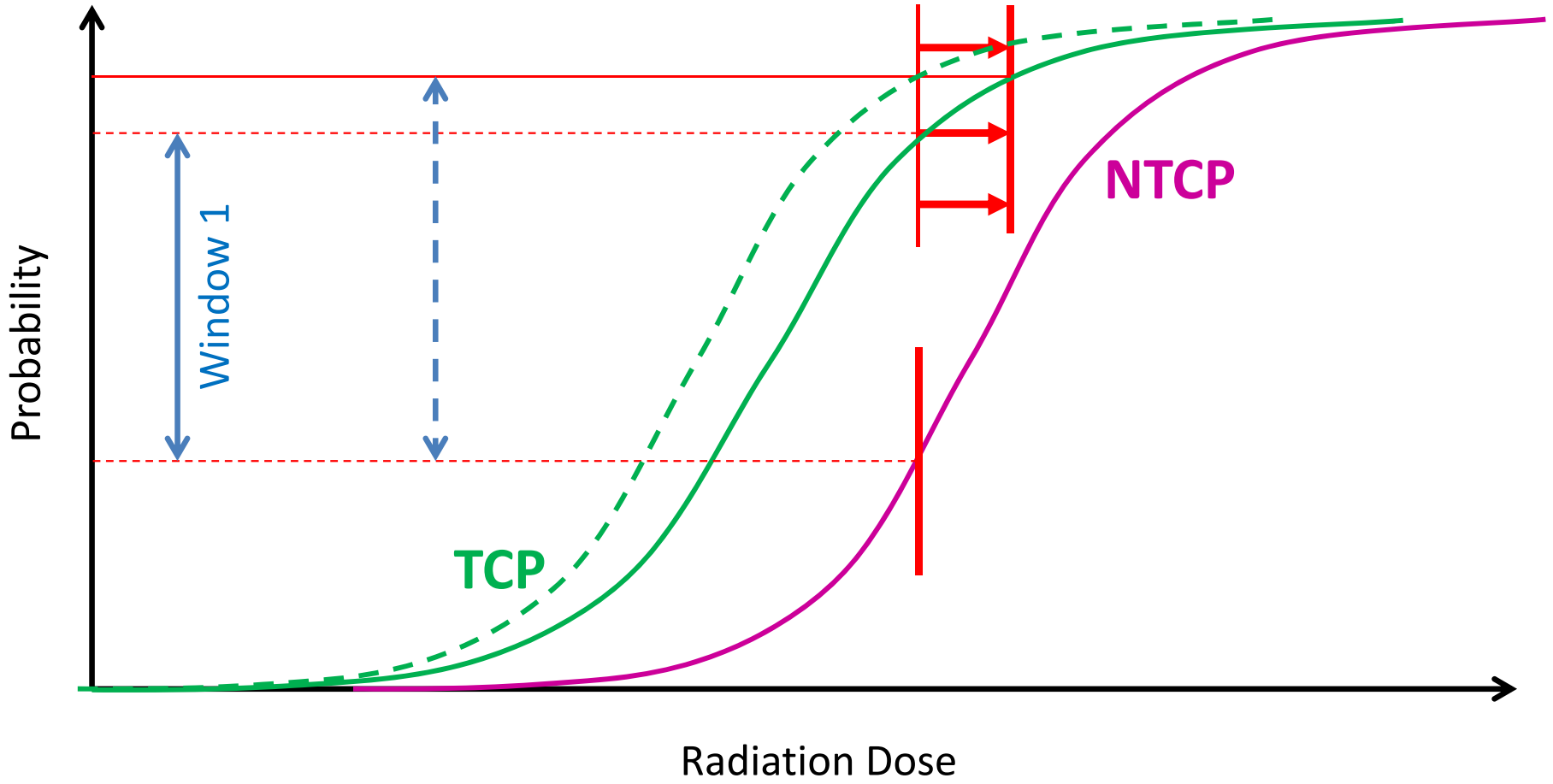
$$TCP = e^{-N} = e^{-N_0 S}$$

Fig.11. Surviving fraction *S* (left) and the Tumour Control Probability TCP (right) as a function of the dose *D*; α = 0.5 / au; β = 0.1 / au^2.; N_0 = 1000 cells (for solid tumours, N_0 can exceed 10^{12} cells!).



TCP: **T**umour **C**ontrol **P**robability

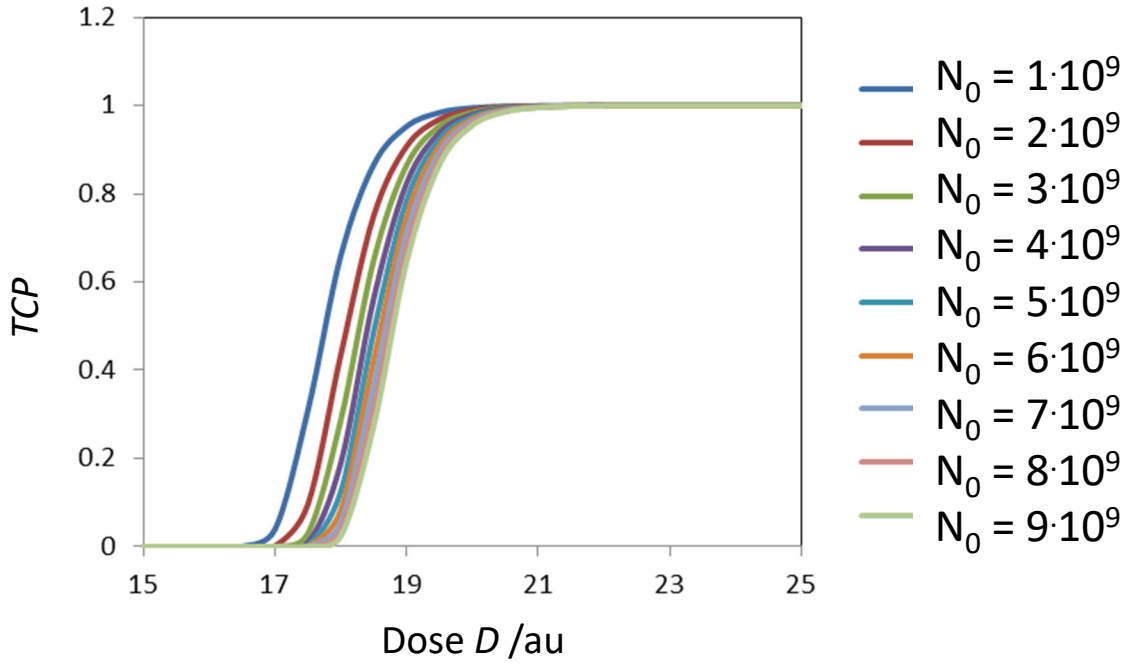
NTCP: **N**ormal **T**issue **C**omplication **P**robability



TCP: **T**umour **C**ontrol **P**robability

NTCP: **N**ormal **T**issue **C**omplication **P**robability

TCP and Tumour Volume



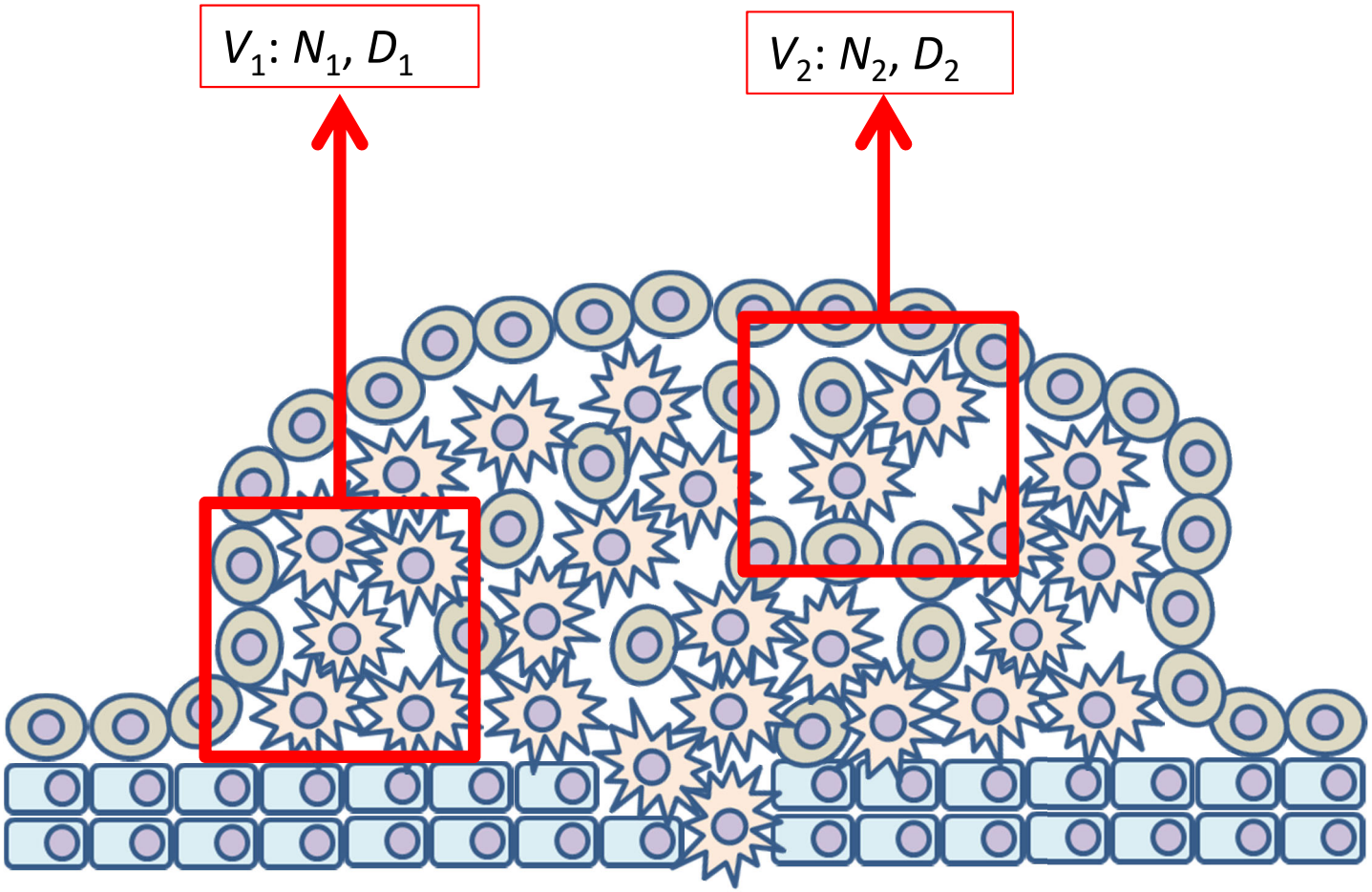
$$S = \frac{N}{N_0} = e^{-(\alpha D + \beta D^2)}$$

$$TCP = e^{-N} = e^{-N_0 S}$$

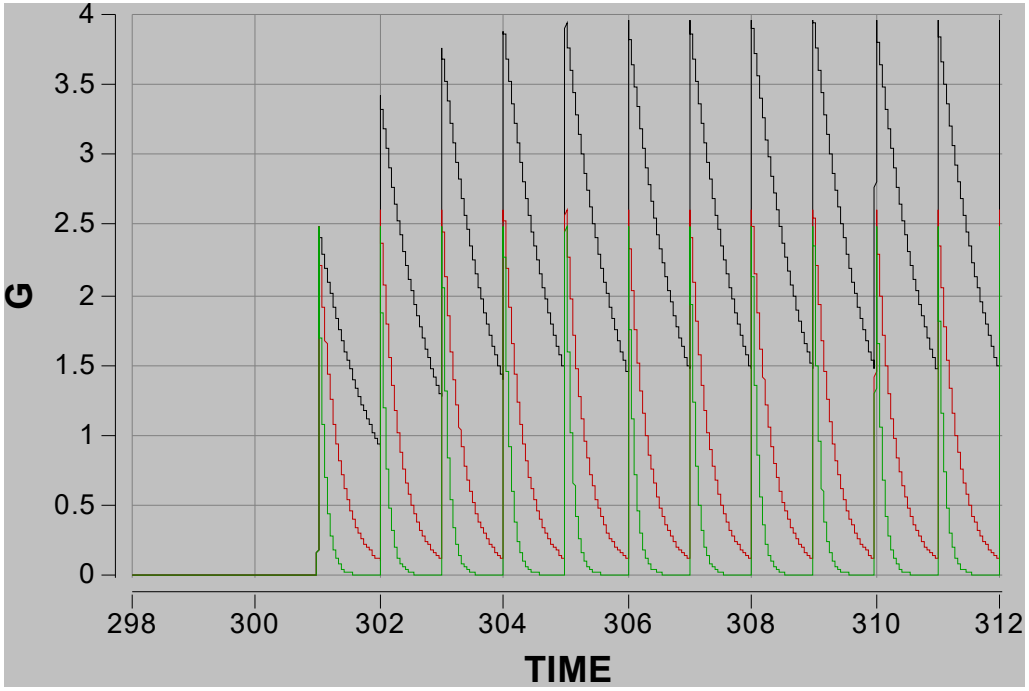
Tumour Control Probability TCP (right) as a function of the dose D; $\alpha = 0.3$ / Gy; $\beta = 0.05$ / Gy^2.; with varying N_0 (for solid tumours, N_0 can exceed 10^{12} cells!). Dose is administered in one fraction.

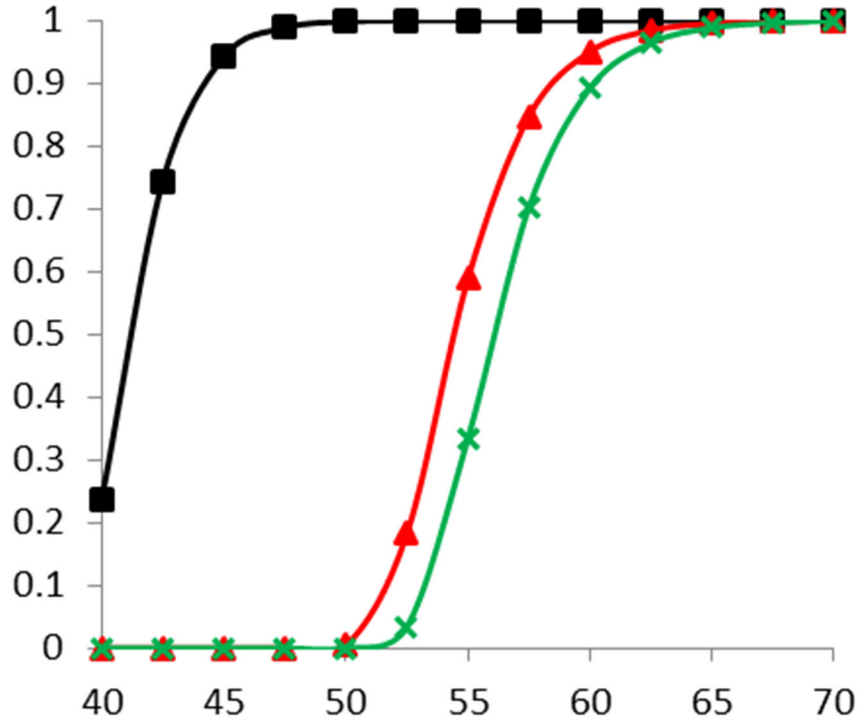
TCP and Tumour Volume

$$TCP_1 = e^{-N_1} \qquad TCP_2 = e^{-N_2} \qquad TCP_{12} = TCP_1 \cdot TCP_2$$



From Γ to TCP (Γ-LQ-Model)



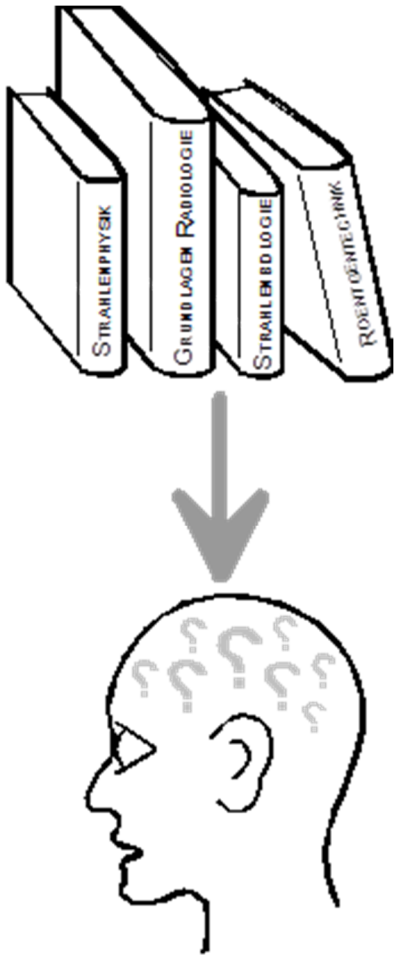


$$\frac{d\Gamma}{dt} = R - f(\Gamma)$$

Γ

$$\frac{dN}{dt} = -(\alpha + 2\beta\Gamma)\cdot RN \xrightarrow{N} TCP = e^{-N}$$

Modelling NTCP



Emami B, Lyman J, Brown A, et al. (1991): Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* **21**(1), 109–122.

Marks LB, et al. (2010): Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys .* **76**(3 Suppl): S10-S19.

Bentzen SM et al. (2010): Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): An Introduction to the Scientific Issues. *Int J Radiat Oncol Biol Phys .* **76**(3 Suppl): S3–S9.

Quantitative **A**nalysis of **N**ormal **T**issue **E**ffects in **C**linic

- Large committee of experts (n=57)
- Convened by ASTRO / AAPM
- Updated guidelines published in Red Journal supplement (vol 76, No. 3)
- 16 organ-specific papers
- Several “general principle” papers
- Present available data in a clinically useful manner

RANDALL K. TEN HAKEN, PH.D.,* LOUIS S. CONSTINE, M.D.,† AVRAHAM EISBRUCH, M.D.,‡
SØREN M. BENTZEN, PH.D.,§ JIHO NAM, M.D.,|| AND JOSEPH O. DEASY, PH.D.¶

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S10–S19, 2010

Modelling NTCP

Bentzen SM et al. (2010): *J Radiat Oncol Biol Phys* . **76**(3 Suppl): S3–S9.

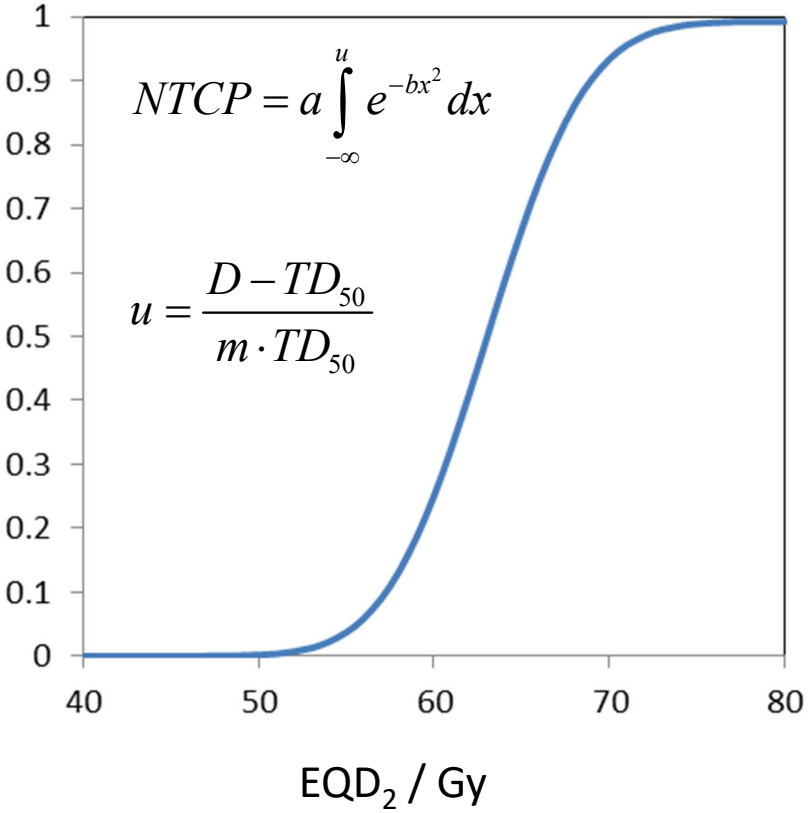
Advances in … NTCP modeling since the seminal Emami paper from 1991 are reviewed:

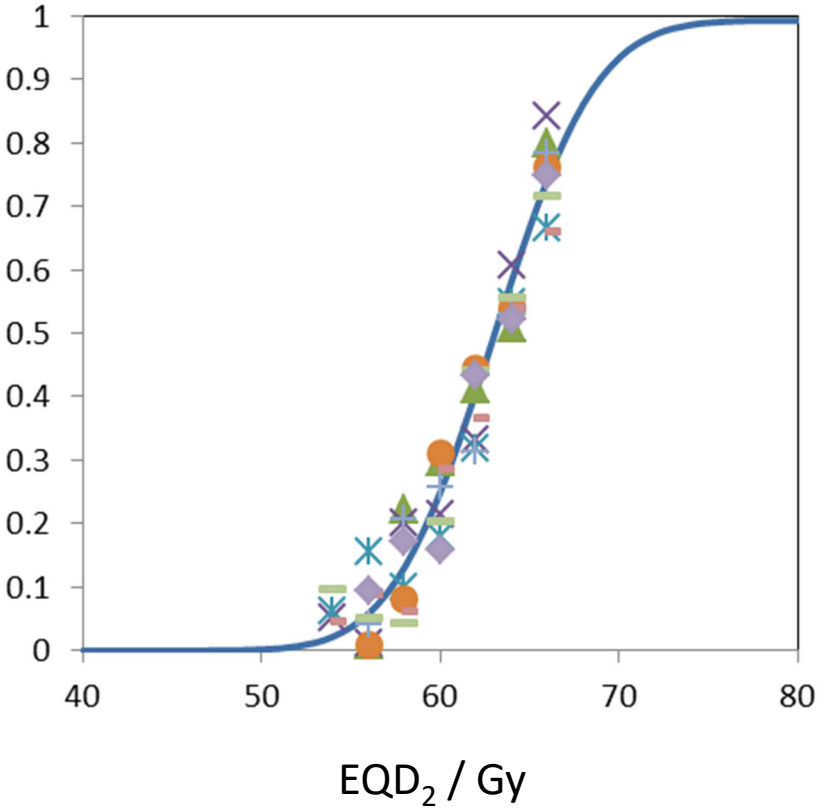
→ progress with an increasing number of studies on large patient samples with three-dimensional dosimetry.

→ Nevertheless, NTCP models are **not ideal**. Issues related to the grading of side effects, selection of appropriate statistical methods, testing of internal and external model validity, and quantification of predictive power and statistical uncertainty, → **limited usefulness** of much of the published literature!

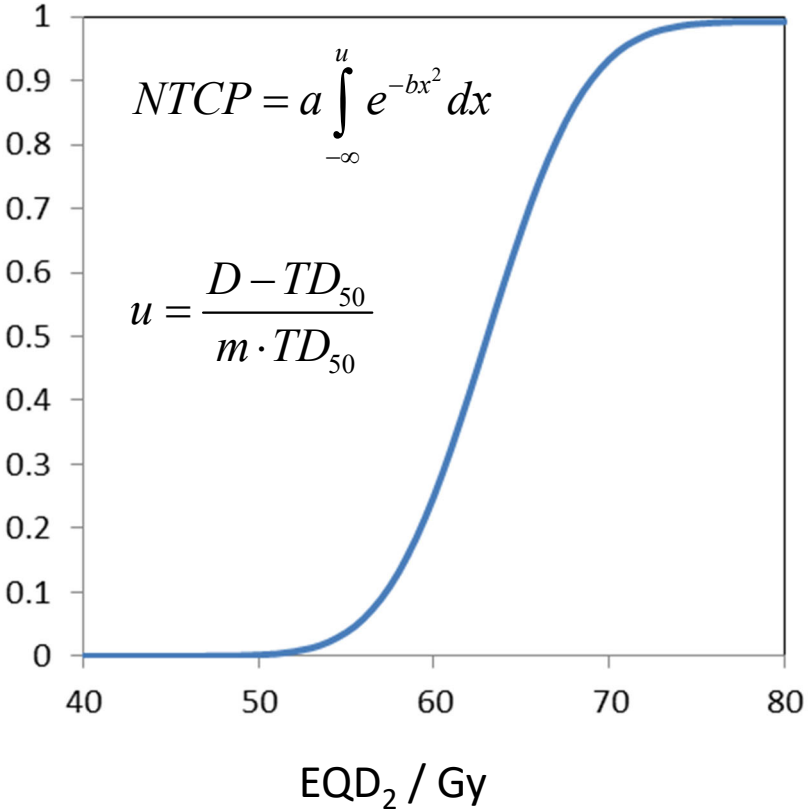
→ Synthesis (meta-analysis) of data from multiple studies is often impossible due to **suboptimal primary analysis**, **insufficient reporting** and **variations** in the **models** and predictors analyzed.

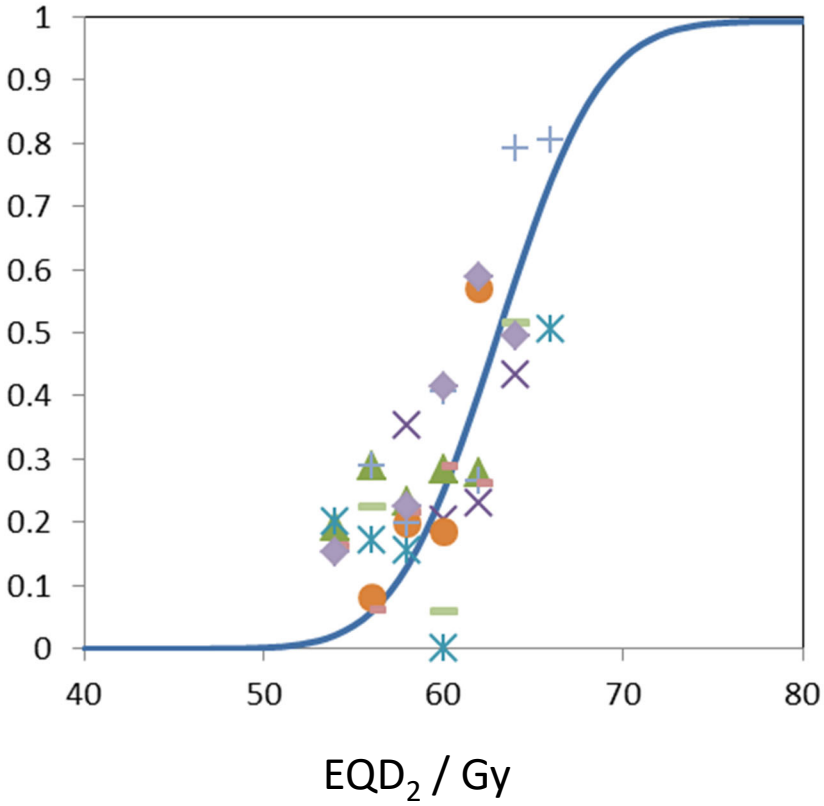
Modelling NTCP of Synthetic Data by Simplified Lyman Kutcher Burman (LKB) Model, Serial Structure / Organ (TD50/V^n with n=0)



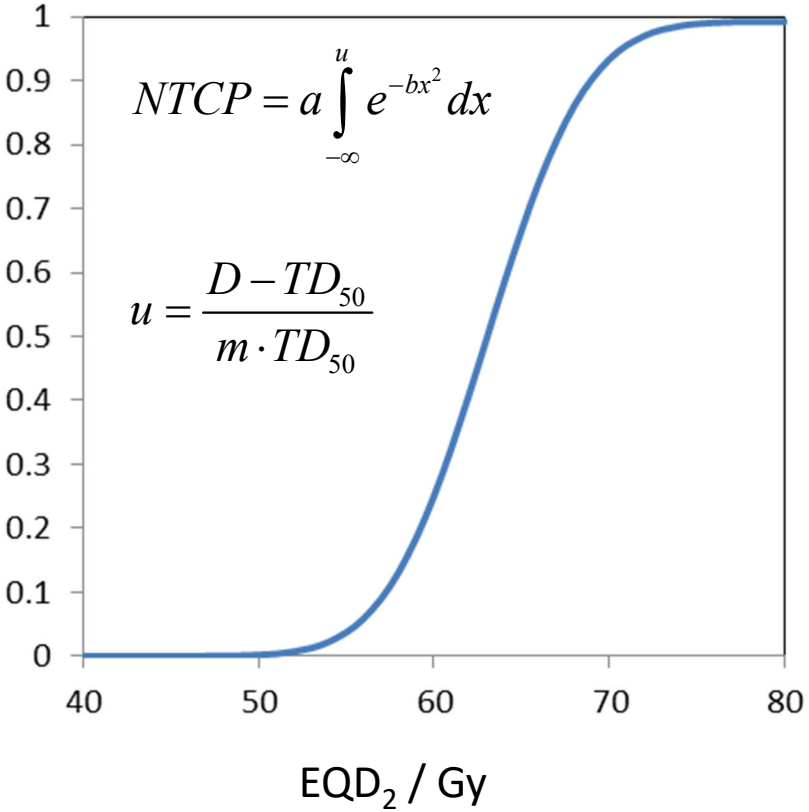


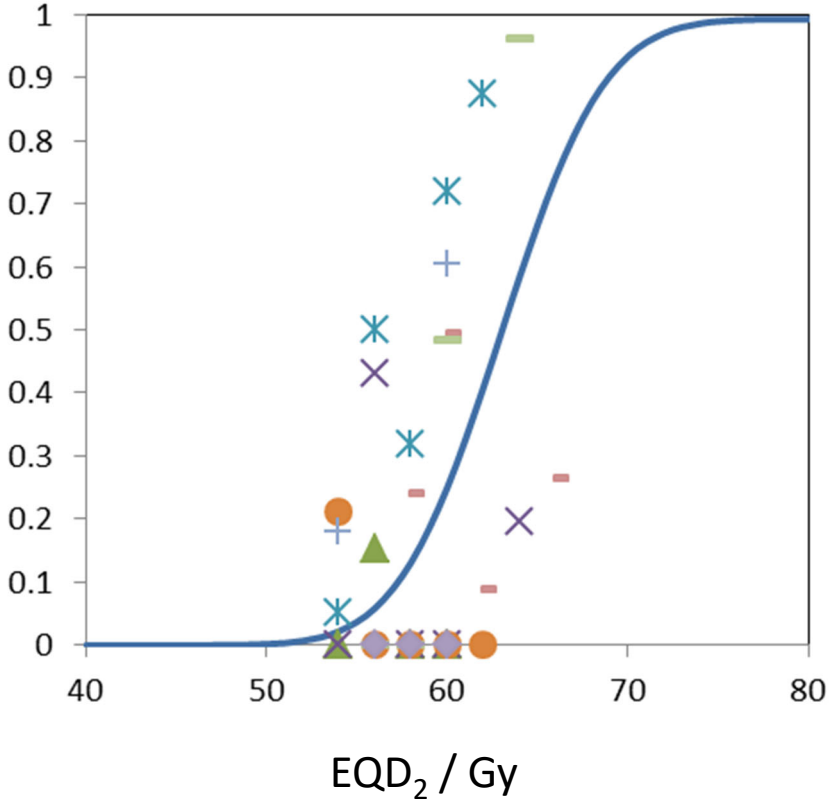
Modelling NTCP of Synthetic Data by Simplified Lyman Kutcher Burman (LKB) Model, Serial Structure / Organ (TD50/V^n with n=0)



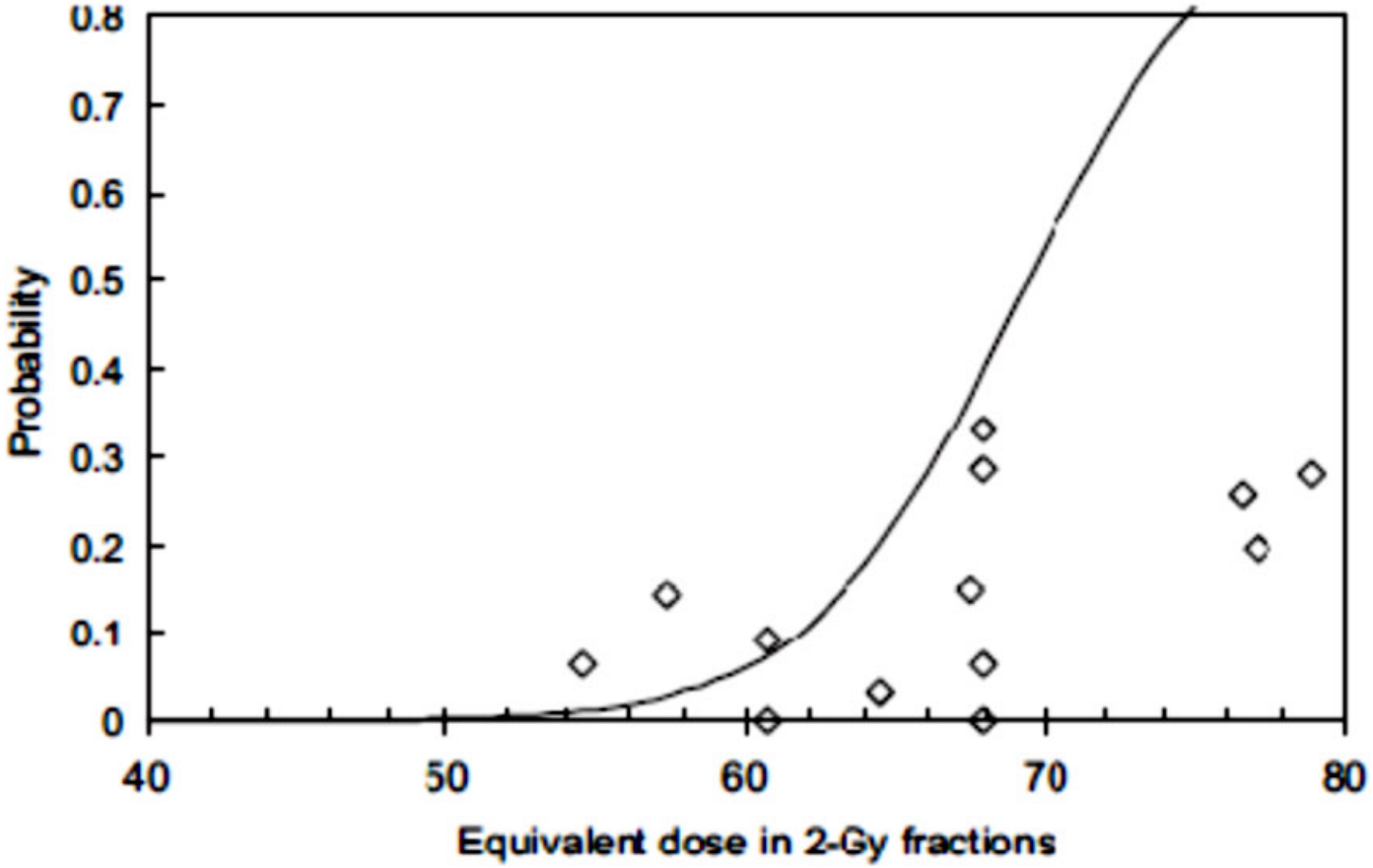


Modelling NTCP of Synthetic Data by Simplified Lyman Kutcher Burman (LKB) Model, Serial Structure / Organ (TD50/V^n with n=0)





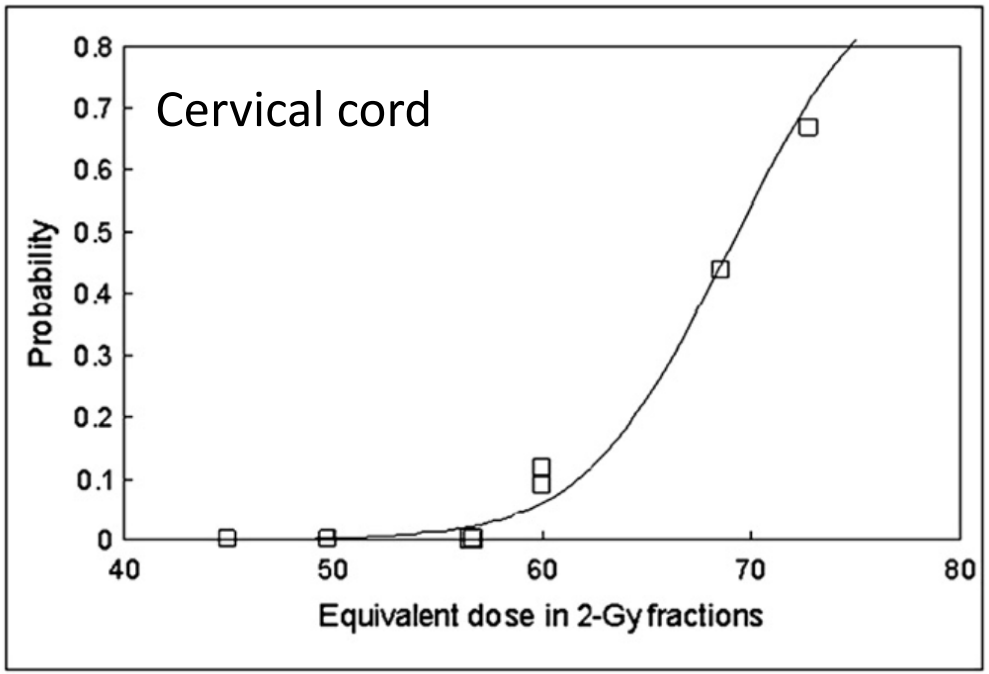
NTCP calculated from clinical data (spinal cord)

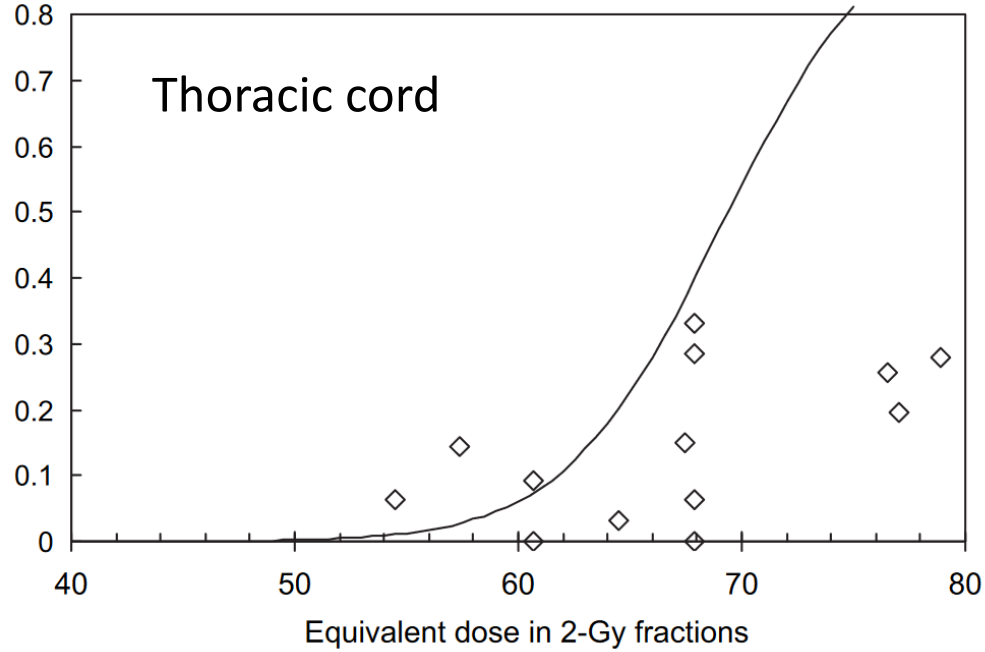


Spinal Cord

Table 1. Summary of published reports of cervical spinal cord myelopathy in patients receiving conventional radiotherapy (18)

Institution	Dose (Gy)	Dose/fraction (Gy)	Cases of myelopathy/ total number of patients	Probability of myelopathy*	2-Gy dose equivalent†
Wake Forest (19)	60	2	1/12	0.090	60.0
	65	1.63	0/24	0.000	56.6
Caen (5)	54	3	7/15	0.622	72.8
Brookhaven (20)	19	9.5	4/13	0.437	68.6
Florida (21)	47.5	1.9	0/211	0.000	45.0
	52.5	1.9	0/22	0.000	49.8
	60	2	2/19	0.118	60.0
Yugoslavia (22)	65	1.63	0/19	0.000	56.6

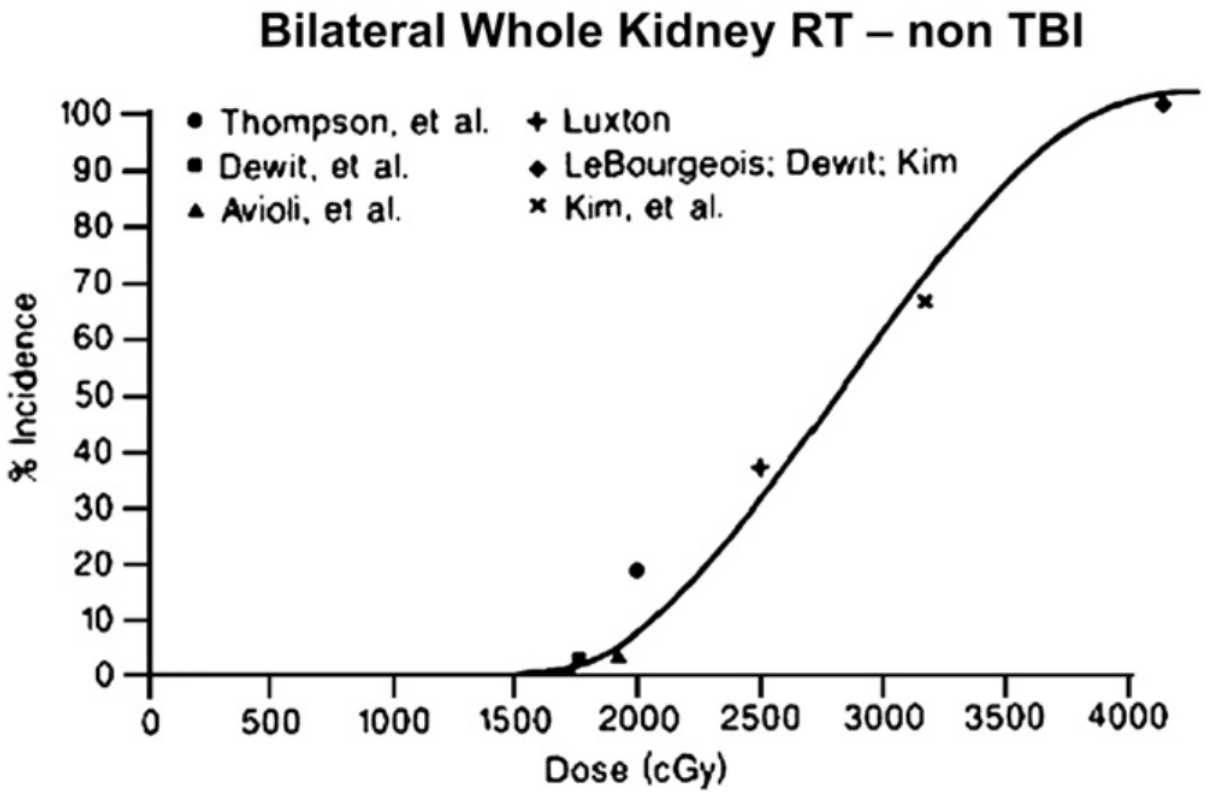




Kirkpatrick, JP., et al. (2010): Radiation dose–volume effects in the spinal cord. *Int J Radiat Oncol Biol Phys.* **76**(3 Suppl): : S42-S49.

Kidney

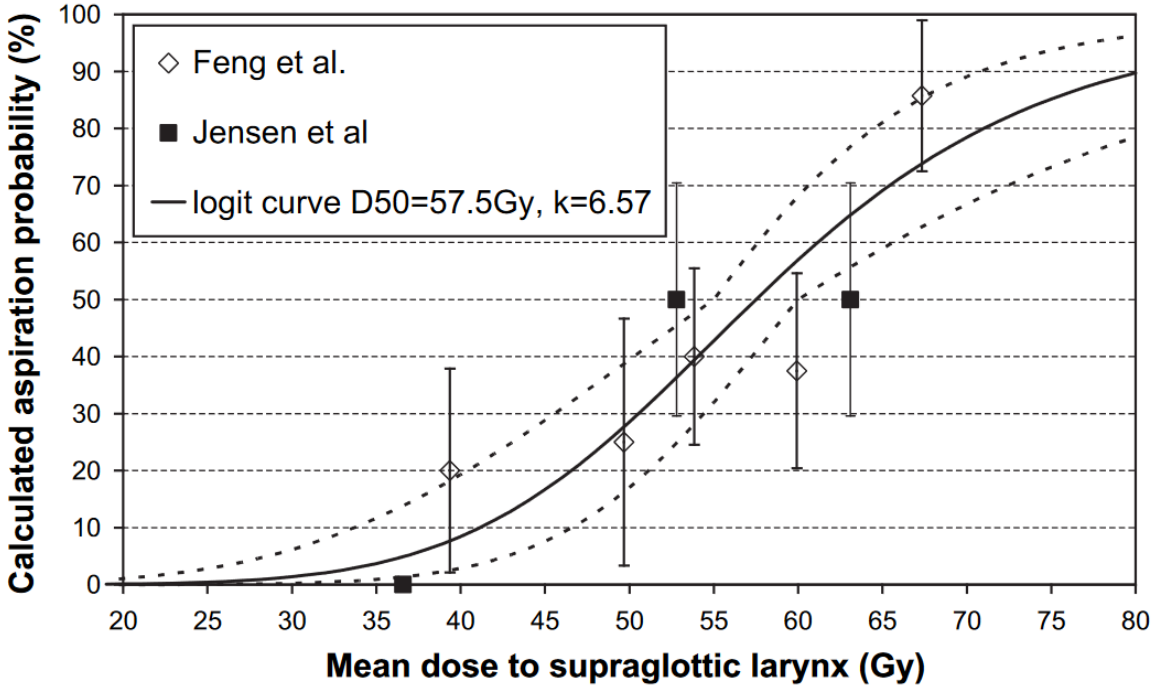
Kidney	Bilateral whole kidney[‡]	Bilateral whole organ or 3D-CRT	Clinically relevant renal dysfunction	Mean dose <15–18	<5
	Bilateral whole kidney[‡]	Bilateral whole organ	Clinically relevant renal dysfunction	Mean dose <28	<50



Dawson, LA., et al. (2010): Radiation-associated kidney injury. *Int J Radiat Oncol Biol Phys.* **76**(3 Suppl): : S108-S115.

Larynx

Larynx	Whole organ	3D-CRT	Vocal dysfunction	Dmax <66	<20	With chemotherapy, based on single study (see Section A4.2 in paper)
	Whole organ	3D-CRT	Aspiration	Mean dose <50	<30	With chemotherapy, based on single study (see Fig. 1 in paper)
	Whole organ	3D-CRT	Edema	Mean dose <44	<20	Without chemotherapy, based on single study in patients without larynx cancer**
	Whole organ	3D-CRT	Edema	V50 <27%	<20	



Rancati, T., et al. (2010): Radiation dose-volume effects in the larynx and pharynx. *Int J Radiat Oncol Biol Phys.* **76**(3 Suppl): : S64-S69.

Dynamic NTCP Models

Lopez Alfonso et al. (2018): Med Phys 45(7), 3466-3474

N: Recovery of normal tissue

→ Model is a mix of a dynamic (logistic growth) model with a data descriptive (LQ) model

$$\frac{dN}{dt} = \mu N \cdot (1 - N) - \delta(t - t_i) \cdot (1 - S) \cdot N \cdot (1 - N)$$

$$S = e^{-(\alpha d + \beta d^2)} \qquad \delta(t - t_i) = 1 \text{ for } t = t_i \text{ and} = 0 \text{ for } t \neq t_i$$

$$NTCP = 1 - N$$

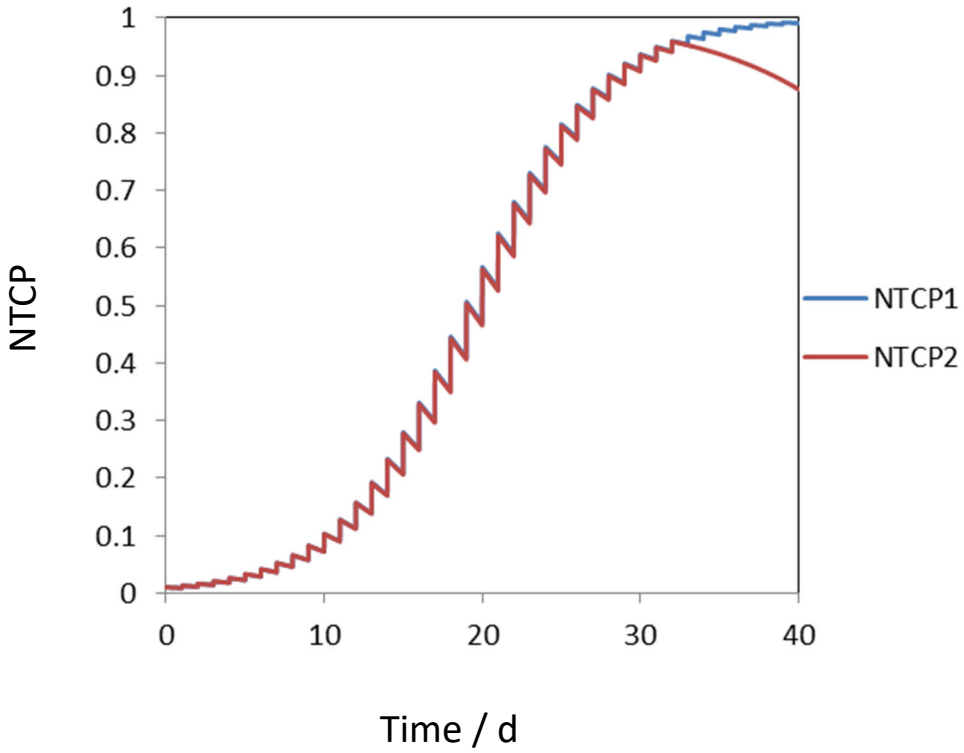
Dynamic NTCP Models

This NTCP model can be combined with the Γ-LQ model to get a fully dynamic and more flexible model:

$$\frac{dN}{dt} = \mu N \cdot (1 - N) - (\alpha + 2\beta\Gamma) \cdot R(t) \cdot N \cdot (1 - N)$$

$$\frac{d\Gamma}{dt} = R - f(\Gamma)$$

Dynamic NTCP Models



Using LQ models for NT recovery

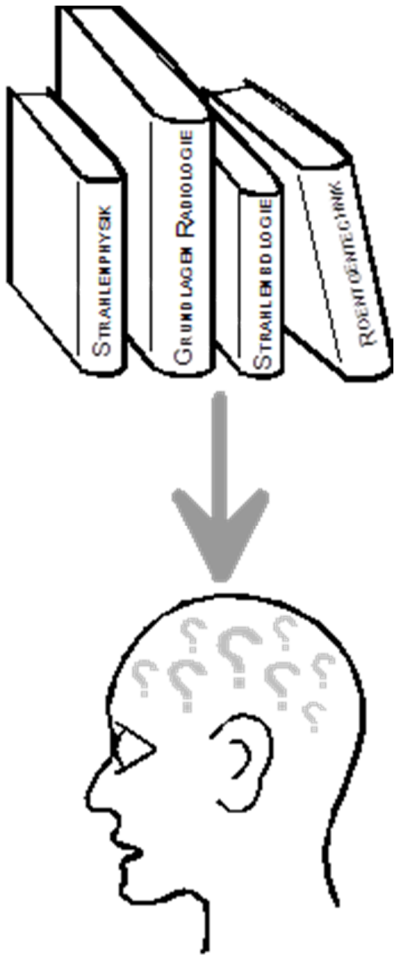
→ For 2 Gy fractions, LQ formula and G-LQ models produce similar results

→ Very simplistic approaches

→ NTCP for serial vs. parallel organs?

→ α/β-ration for late responding tissues (3 Gy), but $\mu = 0.15\ d^{-1}$ corresponds more to fast reacting tissues (10 Gy)!

Conclusions – Take Home Messages



- → Calibration of radiobiological models should include data from different scales under different conditions (e.g. comet vs. survival; dose rates, etc.)
- → Interpretation of dynamic models is difficult (semantic mapping of model components to biology, exceptions are chemical reaction models on molecular level, but even for small signalling pathways, a large number of parameters hinder a proper calibration)
- → Interpretation for data-descriptive models often impossible (e.g. LQ-parameters!)
- → Caution: The use of models for biological treatment planning requires validated models. Actual models (e.g. LQ-based models) can only be applied as a rough approximation in a small range of conditions!
- → In contrast to data-descriptive models, dynamic models allow a deeper insight into the biological processes → generation of understanding