UNIVERSITÄT SALZBURG

Nonlinear Dose-Response Mechanisms

Simulation with Bio-Mathematical Models

Helmut Schöllnberger
Ronald E.J. Mitchel

Institute of Physics and Biophysics

UNIVERSITÄT SALZBURG

Contents

- Introduction to the *State Vector Model*
- Detrimental bystander effects for chromosome aberrations
- Protective apoptosis-mediated BE for neoplastic transformation
- Update on studies with *Two-Stage Cancer* model

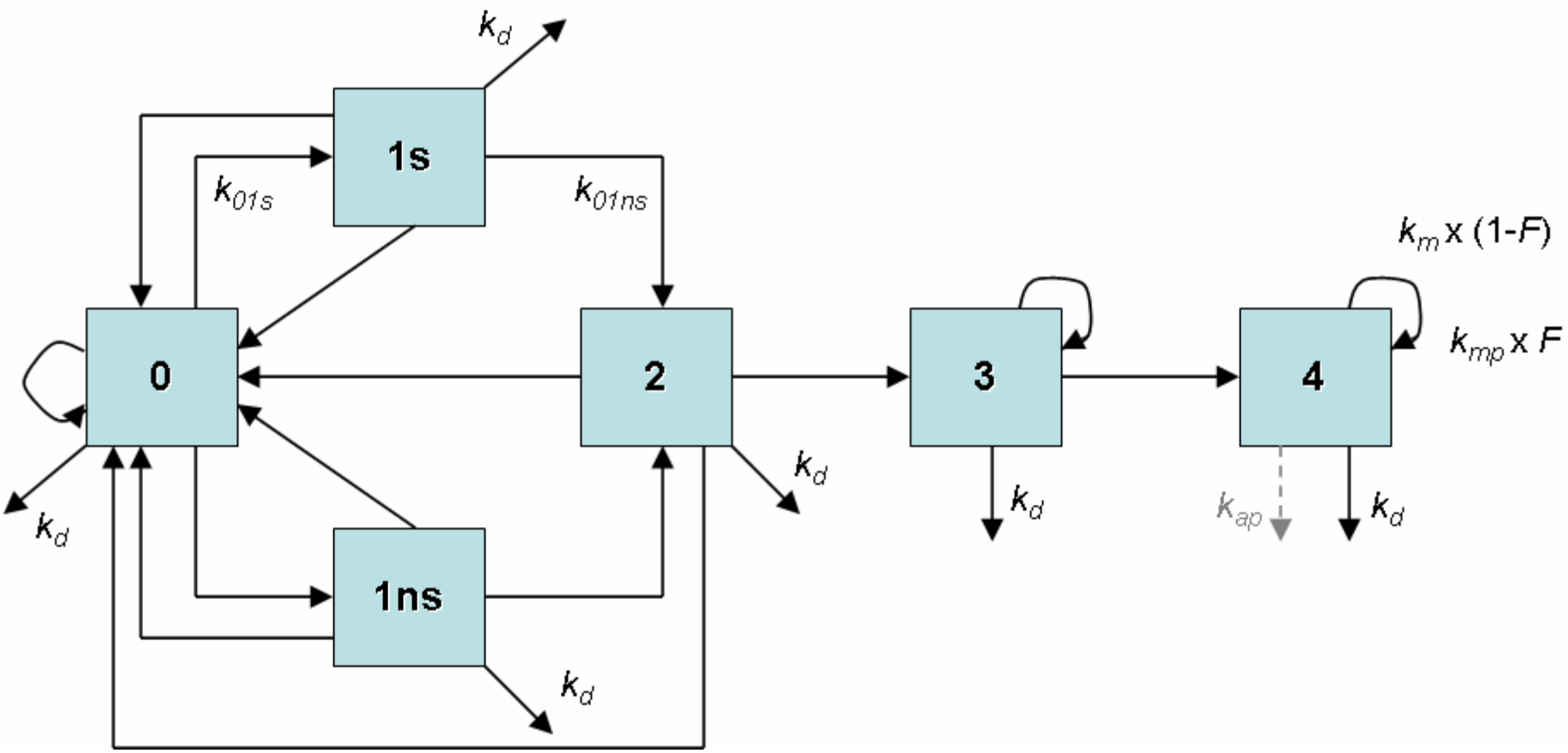
State Vector Model

For neoplastic transformation

- **initiation**
  via chromosome translocation
- **promotion**
  clonal expansion of I-cells
  loss of contact inhibition
- **DSB repair**
- **cell killing** – dose rate dependent

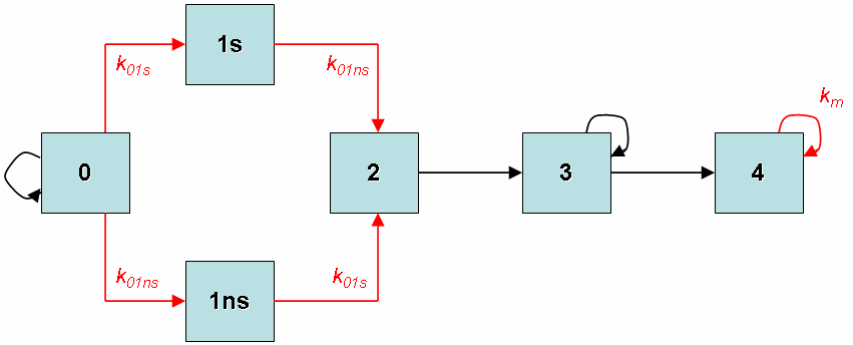
UNIVERSITÄT SALZBURG

State Vector Model



Detrimental bystander effects

- Included in a dose-dependent way – strongest effect at low doses



- New bystander rates:

1) $k_{01b\_by} \times \exp(-\lambda_{1by} \times D)$

2) $k_{01r\_by} \times DR \times \exp(-\lambda_{2by} \times D)$

3) $(1+k_{m\_by} \times \exp(-\lambda_{2by} \times D))$

- $k_{01b\_by} = k_{01r\_by} = k_{m\_by} = 0$ at $D = 0$

Data by Nagasawa and Little

Mutation Research 2002

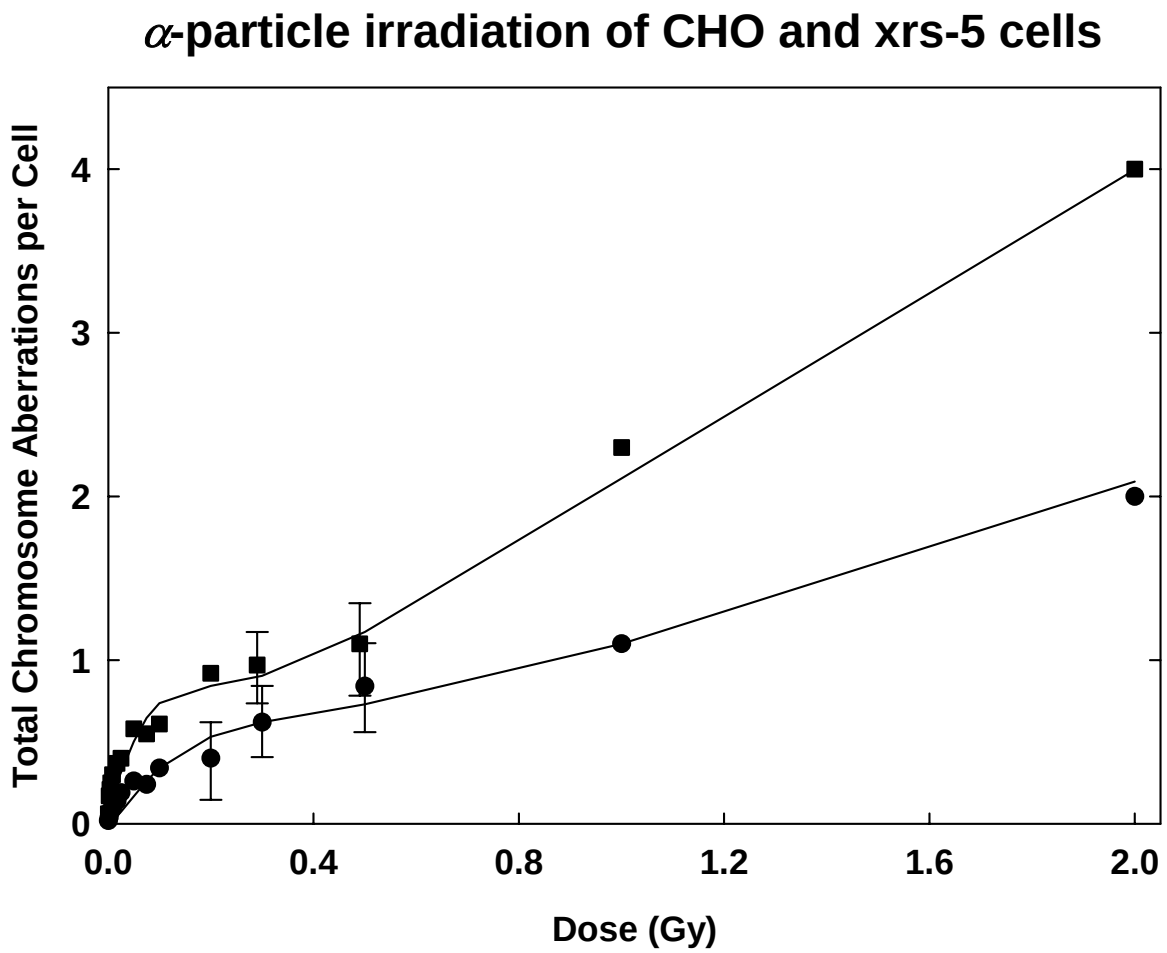
- CHO and xrs-5 cells, α-particles,

  total chromosome aberrations

- First, fit model without BE to control and high dose data

- Then, fit model with BE to all data

Data by Nagasawa and Little

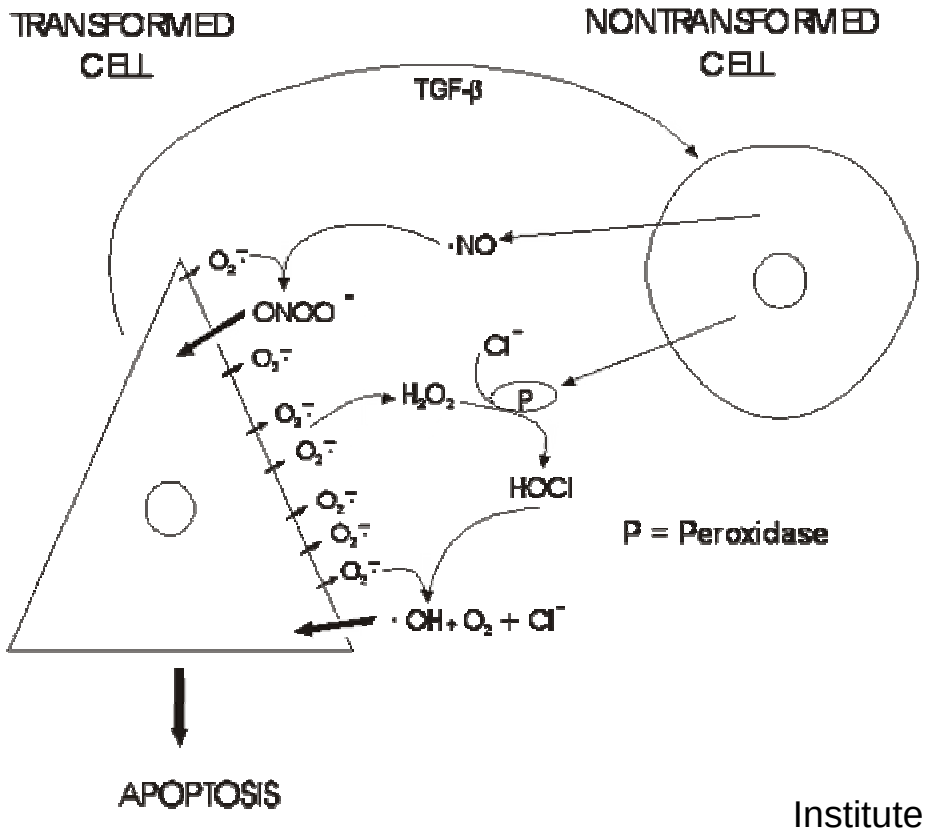


Fit results

- Approaches 1) and 3) worked equally well
- Approach 2) did not work → initiation due to BE is mostly post-exposure (as expected)
- To fit xrs-5 data apply reduction factor for DSB repair rates

Bystander-induced apoptosis

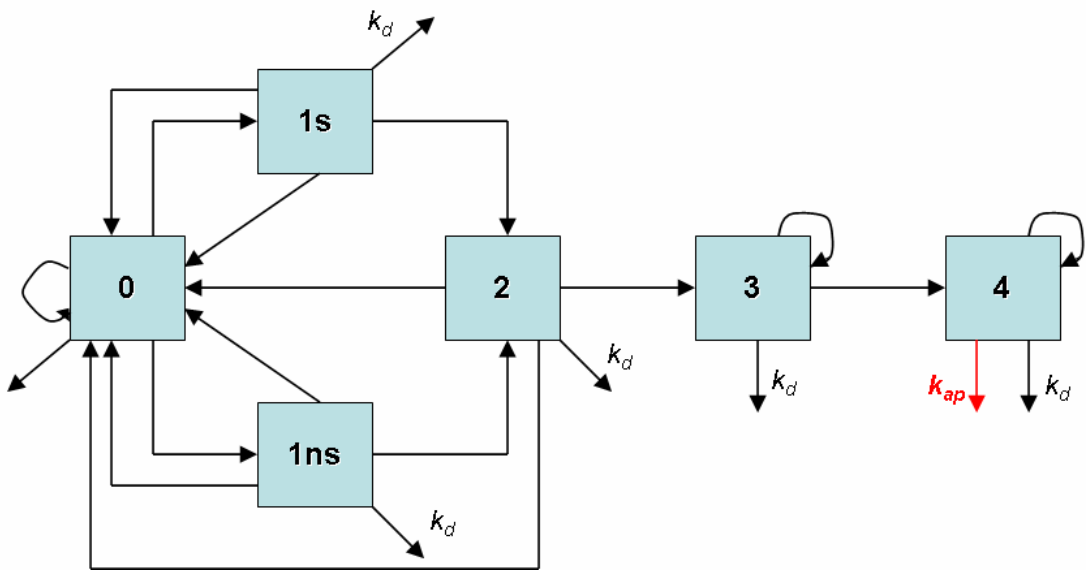
- Is a protective effect
- Dr. Georg Bauer (Anticancer Res 2000)



Bystander-induced apoptosis

For low-LET radiation

- **P**rotective **A**poptosis-**M**ediated process (PAM), B.R. Scott et al. (2003)
- PAM can eliminate cells in State 4



UNIVERSITÄT SALZBURG

Bystander-induced apoptosis

- PAM = 0 at $D = 0$
- PAM = 0 during irradiation
- PAM activated by 1 mGy low-LET radiation
- PAM activated for various times after irradiation
- PAM effective at low doses –

  no effect at $D > 200$ mGy

Data by Redpath et al.

Radiat. Res. 2001

- CGL1 cells, γ-rays, neoplastic transformation
- Irradiation period: 3.3 mGy/min for $D \leq 100$ mGy
  cell doubling time of 20 hrs
- 1 day holding period: 20 hrs
- 10 days exponential growth: 20 hrs
- Confluent growth until day 26: 38 days

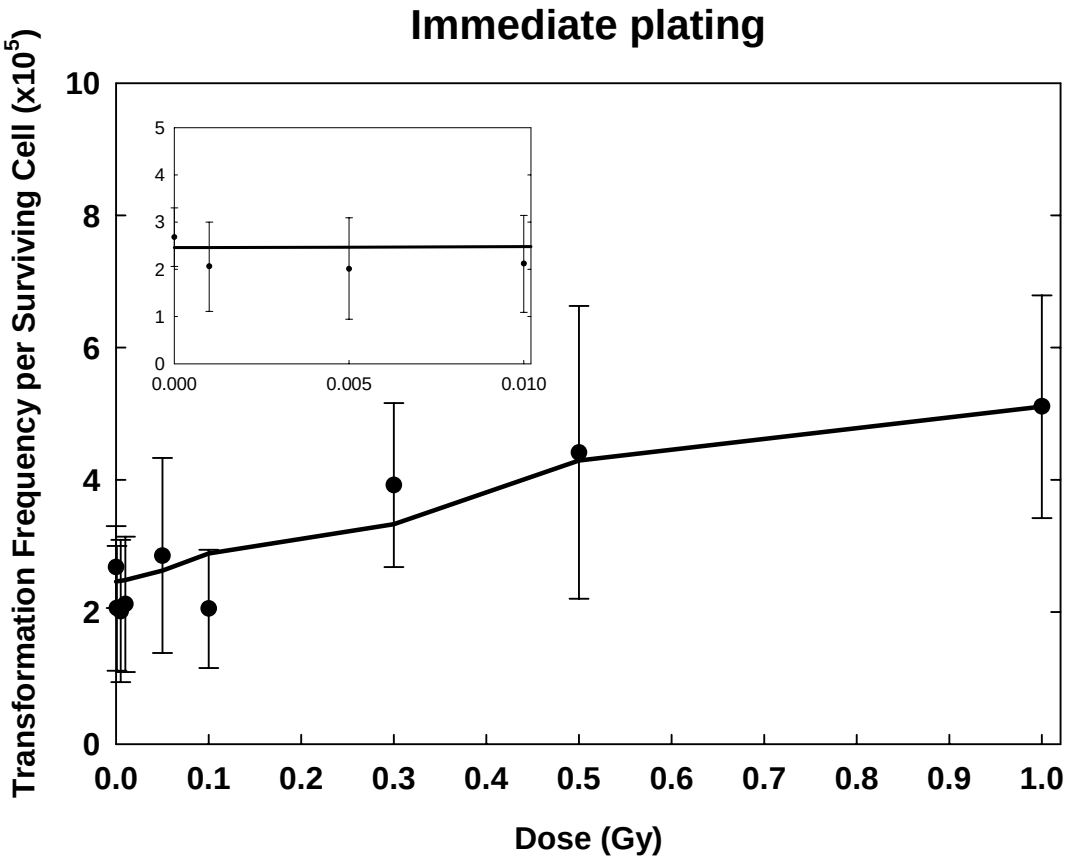
Fit approach

- TF/SC = $$\frac{N_4(t_{end})}{N_0(t_{end}) + N_{1s}(t_{end}) + N_{1ns}(t_{end}) + N_2(t_{end}) + N_3(t_{end}) + N_4(t_{end})}$$

- **Fit model without PAM** to control and high dose data for immediate and delayed plating simultaneously
- **Forward simulation without PAM** to all data points for immediate plating
- **Fit model with PAM** to all data points for delayed plating
  1 free parameter: k_{ap}
  2 free parameters: k_{ap} and t_{ap_off}

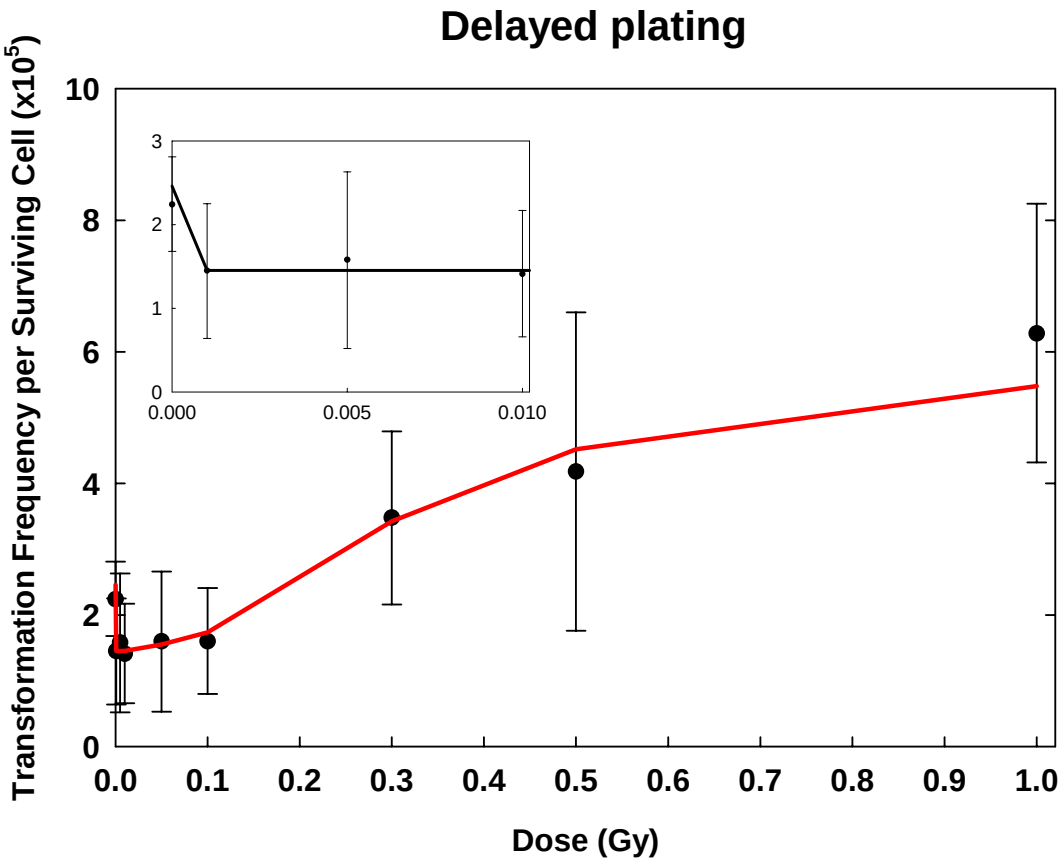
Data by Redpath et al.

Forward simulation



Data by Redpath et al.

Fit with two free parameters



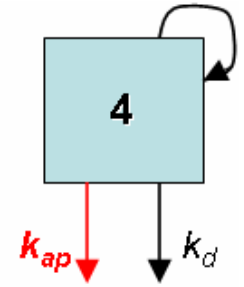
Fit results

- k_{ap} = 0.024/day → How many State 4 cells killed at day 26 after 100 mGy?

  Simulation performed starting with 1 cell:

  $N_4(26) - N_4(26;k_{ap}=0)$ = 9 cells

  $N_0(26) + N_{1s}(26) + \ldots + N_4(26) = 8 \cdot 10^5$

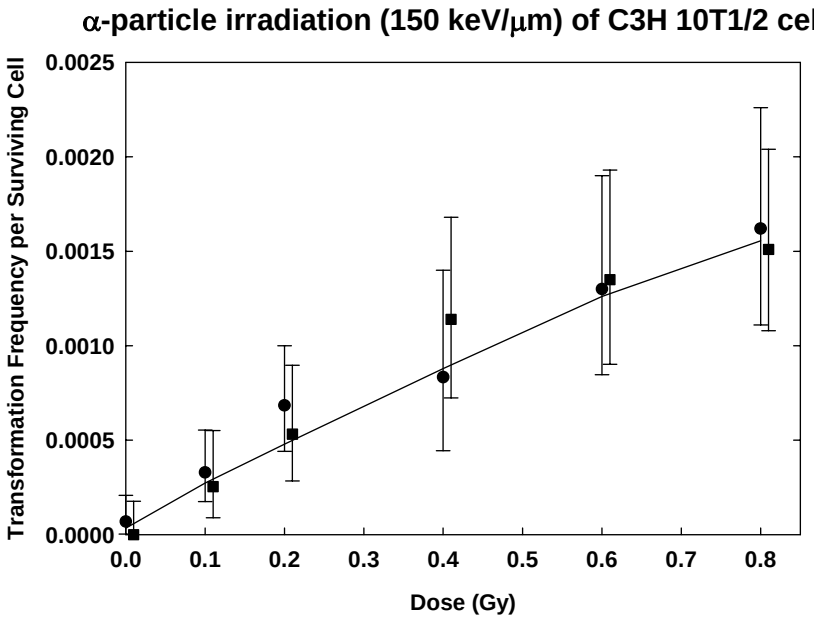


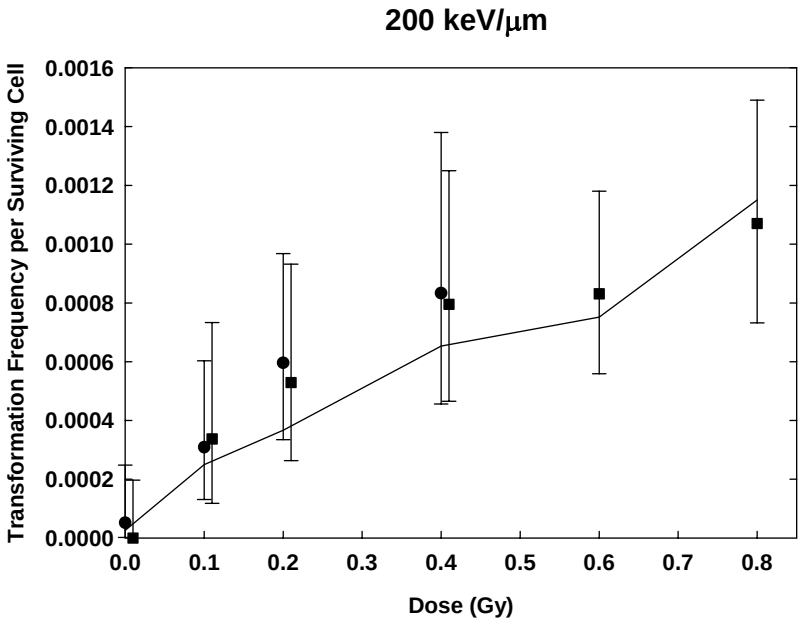
- t_{ap_off} = 22 days

  Jamali and Trott (1996): two week induction of apoptosis after 1 Gy X-irradiation

Data by Miller et al.

Radiat. Res. 1995



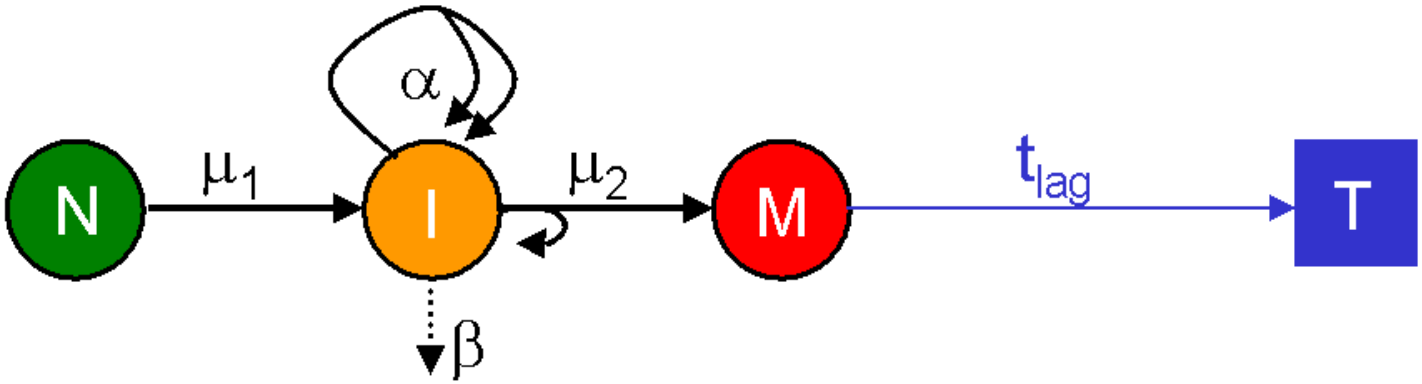


UNIVERSITÄT SALZBURG

Conclusions

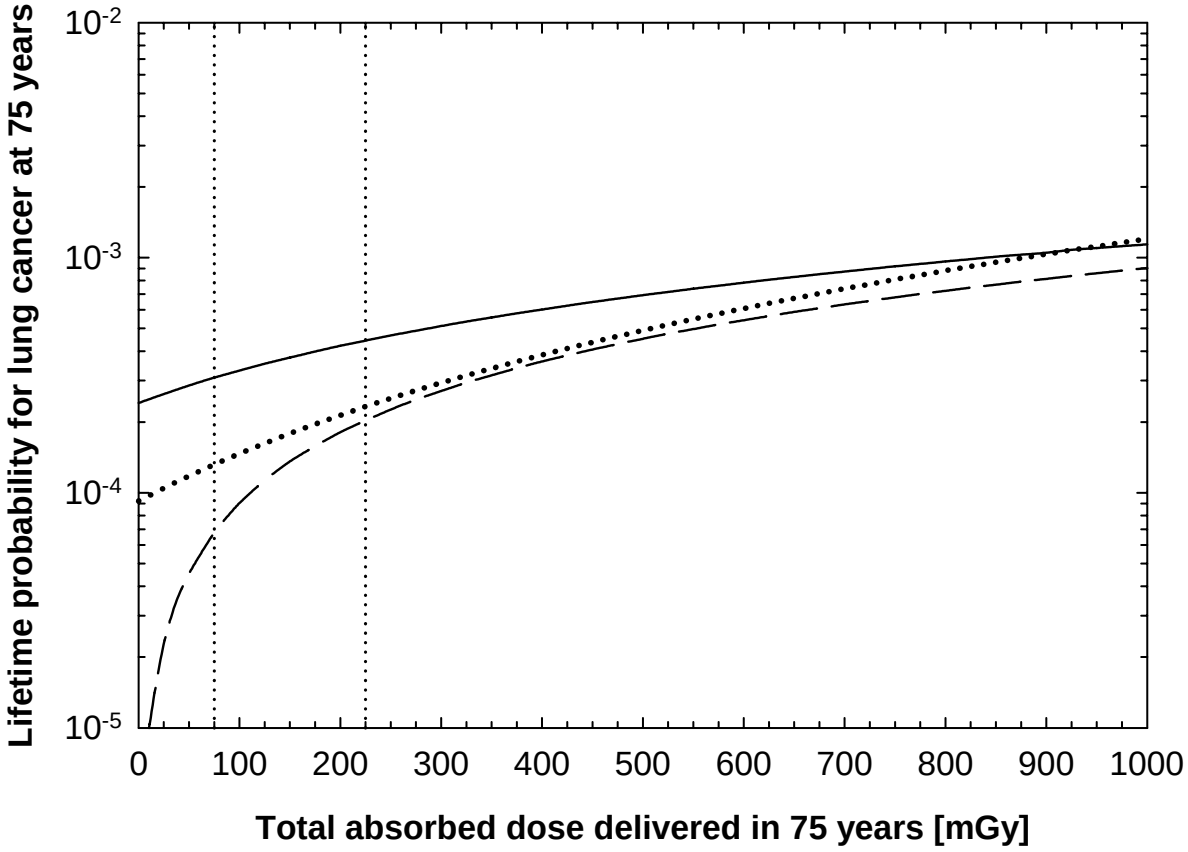
- SVM can describe detrimental and protective bystander effects
- The experimentally proven phenomenon of bystander-induced apoptosis can explain protective effects of low doses of low-LET radiation
- SVM can also explain LNT-shaped data sets
- Work towards a model than contains all essential mechanisms that work at low doses: inducible repair and radical scavenging, bystander effects …

TSCE model with clonal expansion



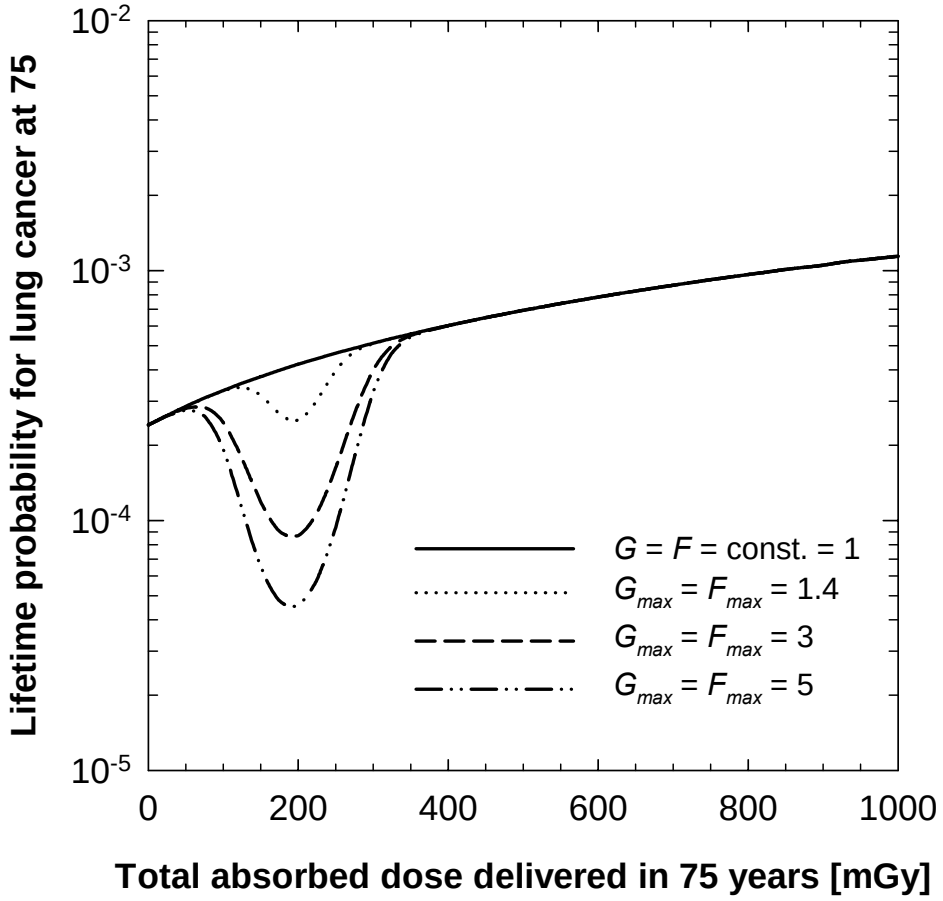
- Four age-independent stochastic rates (μ_1, μ_2, α, β)
- μ_1 a function of dose-rate - also included endogenous DNA damage

Lifetime probability for lung cancer
Low-LET radiation at low dose rates

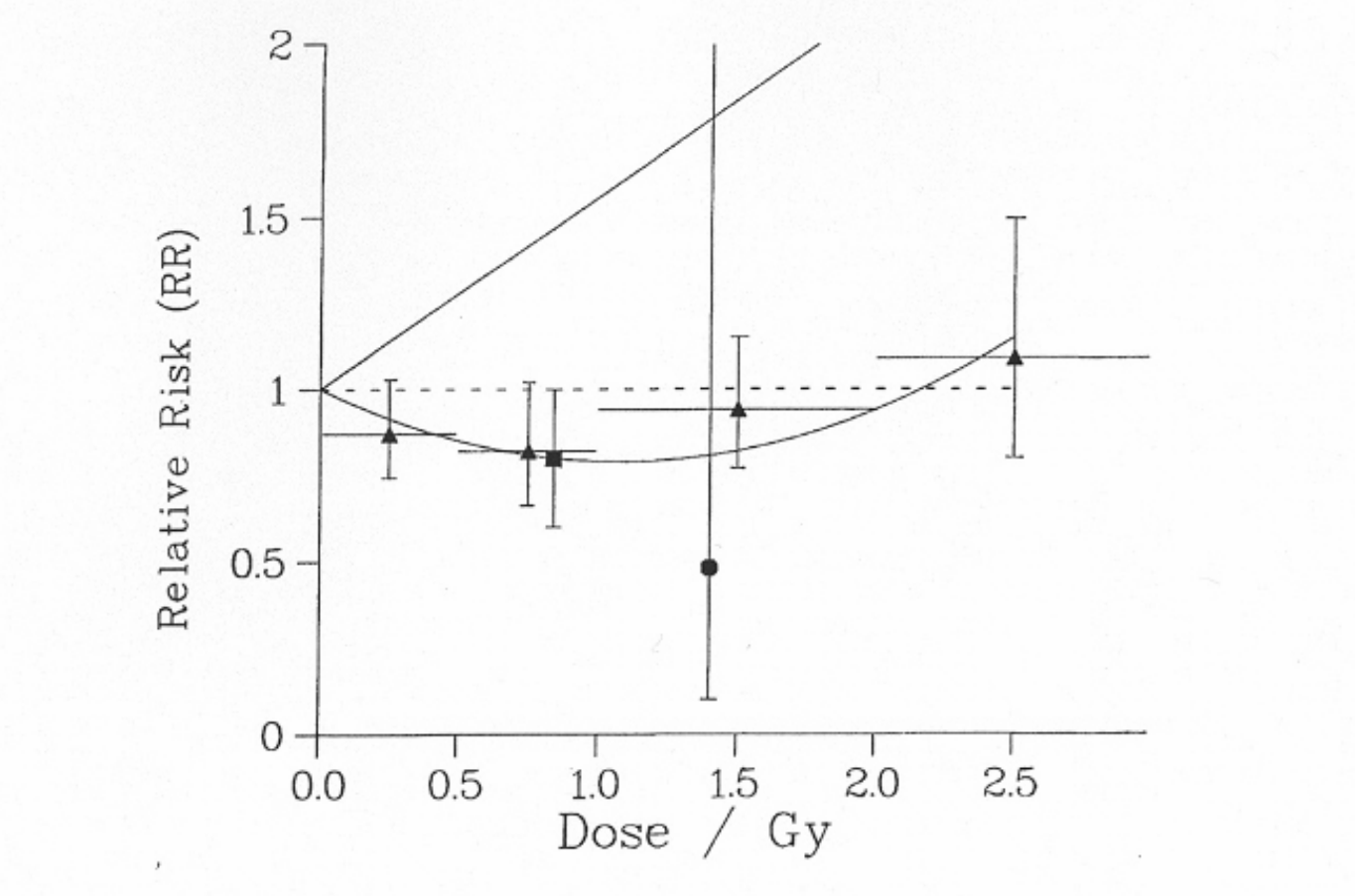


Lifetime probability for lung cancer

With repair and scavenger induction



Rossi and Zaider: "Radiogenic lung cancer: the effects of low doses of low LET radiation"
REB 1997



Mutation models for high dose rates

Rate of change in the expected number of simple or complex lesions per cell at time *t*

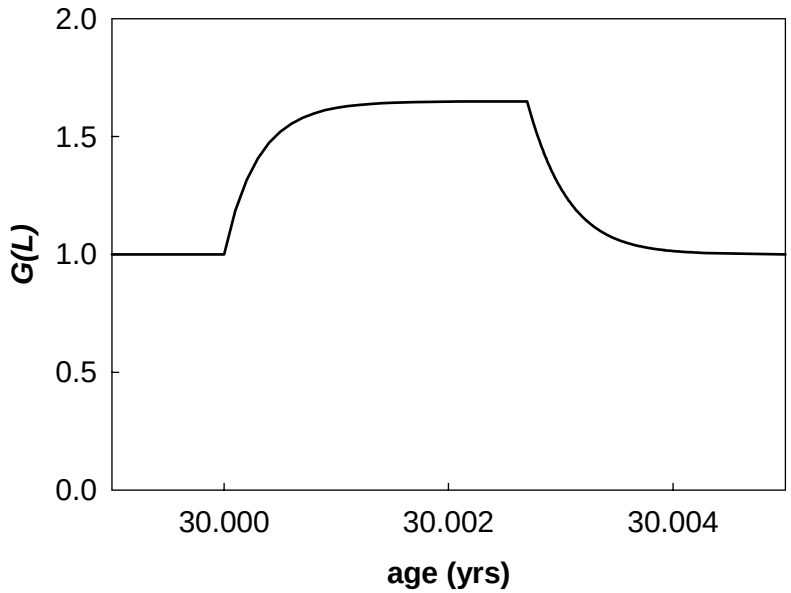
$$\frac{dL_i(t)}{dt} = \Sigma_i^{endo} + \Sigma_i^{rad}\,\dot{D} - \lambda_i L_i(t)$$

$$\mu_1(t) \propto \frac{\varphi_{sl}}{G(L_{sl})}\lambda_{sl}L_{sl}(t) + \frac{\varphi_{cl}}{G(L_{cl})}\lambda_{cl}L_{cl}(t)$$

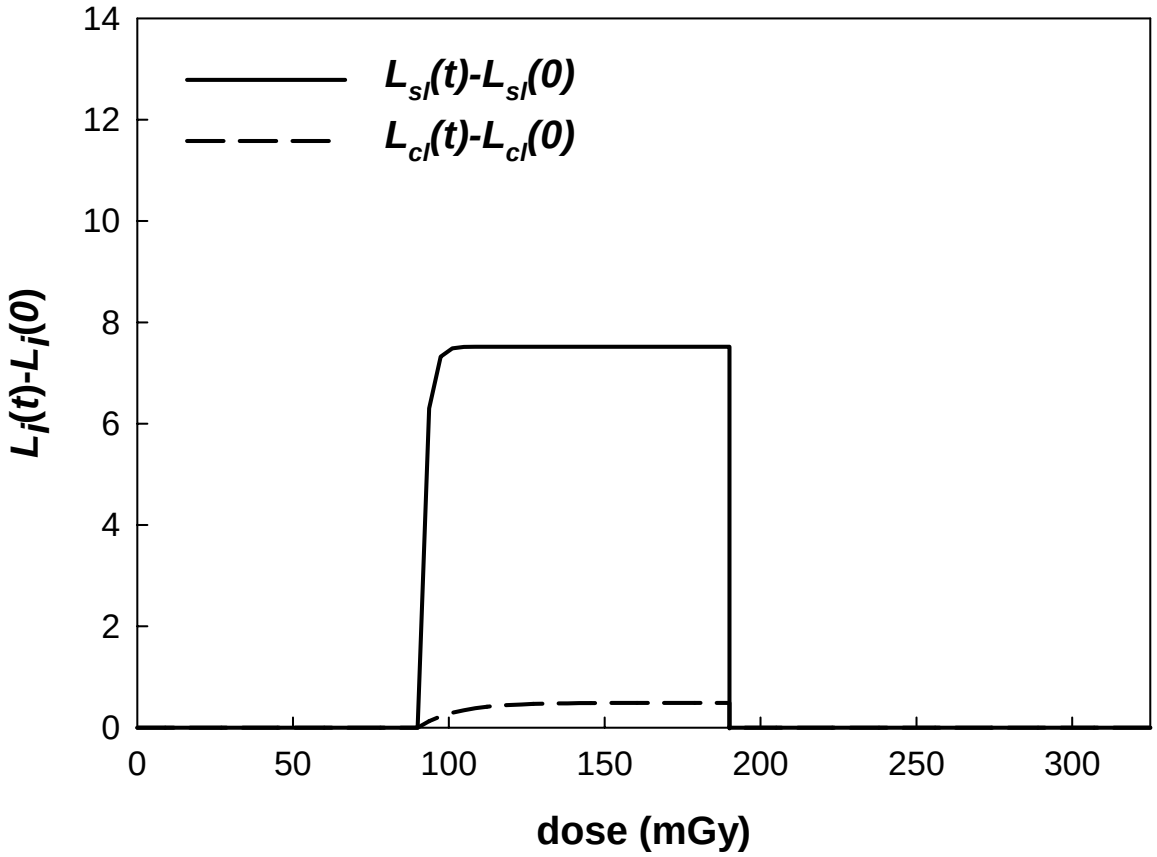
φ_i probability *i*th type (simple or complex) of lesion is misrepaired

Misrepair probability modified with..

$$G(L) = 1 + \delta\left[1 - e^{-\gamma \Delta L(t)}\right]$$



$$G(L) = 1 + \delta\left[1 - e^{-\gamma \Delta L(t)}\right]$$

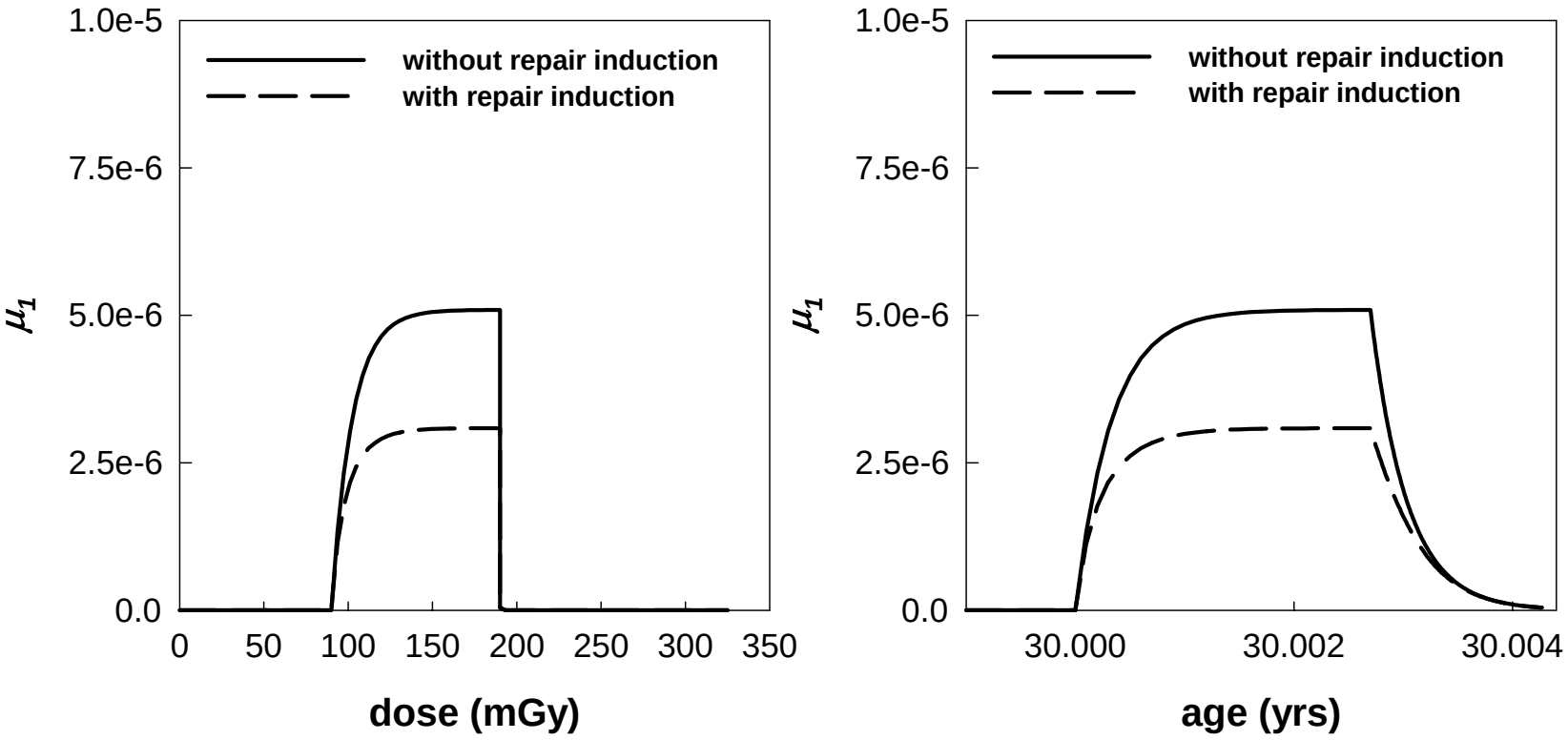


D_x = 100 mGy

Δt = 1 day

$\dot{D}_b$ = 3 mGy/yr

$$\mu_1(t) \propto \frac{\varphi_{sl}}{G(L_{sl})}\lambda_{sl}L_{sl}(t) + \frac{\varphi_{cl}}{G(L_{cl})}\lambda_{cl}L_{cl}(t)$$



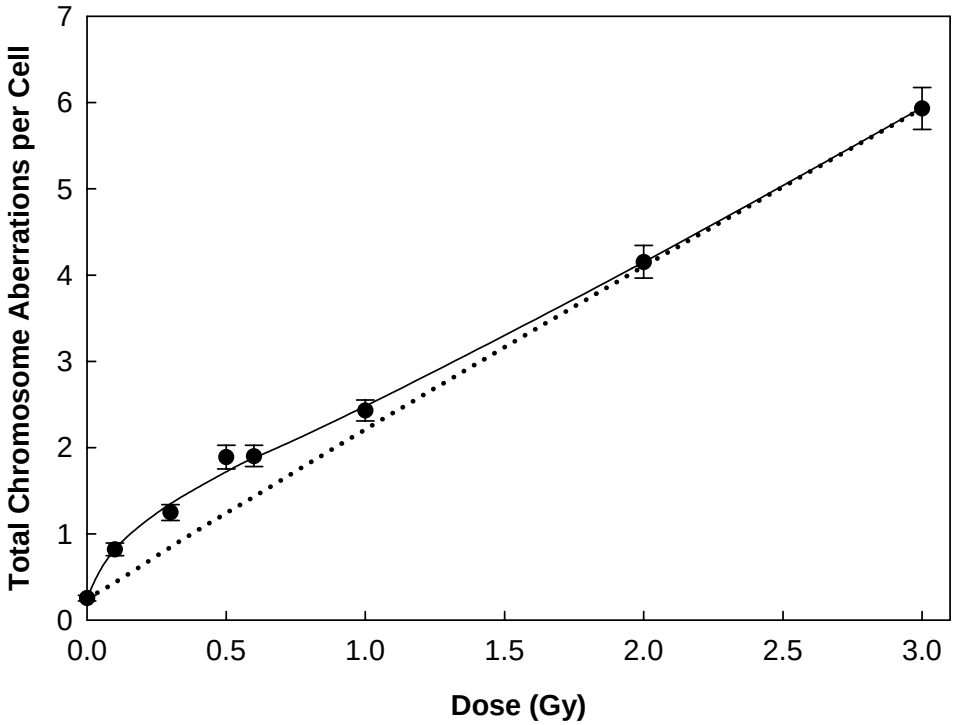
UNIVERSITÄT SALZBURG

Acknowledgements

- **Collaborator: Dr. Robert D. Stewart**
- **Austrian Science Foundation FWF** (project P18055-N02)
- **RISC-RAD project**, EC Contract No. FI6R-CT-2003-508842
- **EU Marie Curie Individual Fellowship**, EC Contract No. FIGH-CT-2002-50513
- **Marie Curie European Reintegration Grant**, EC Contract No. MERG-CT-2004-006610
- **Atomic Energy of Canada Limited**
- **US Department of Energy**, Grant Nos. DE-FG02-03ER63541 and DE-FG02-03ER63665

Data by Durante et al.
IJRB 1992

- Supralinearity assumed to be HRS
- SVM repair rates divided by $1+\lambda_{red}\times\exp(-\lambda_{decr}\times D)$



Data by Redpath et al.

Fit of control and high dose data for immediate and delayed plating simultaneously