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U-shaped Dose-Responses at Low Doses:

Explanation with a New Model for *in vitro* Neoplastic Transformation

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Contents

- Update on work with the State Vector Model
  - Calculation of uncertainties
- New model for *in vitro* neoplastic transformation
  - The model
  - Low dose HRS and IRR
  - Protective apoptosis-mediated bystander effect
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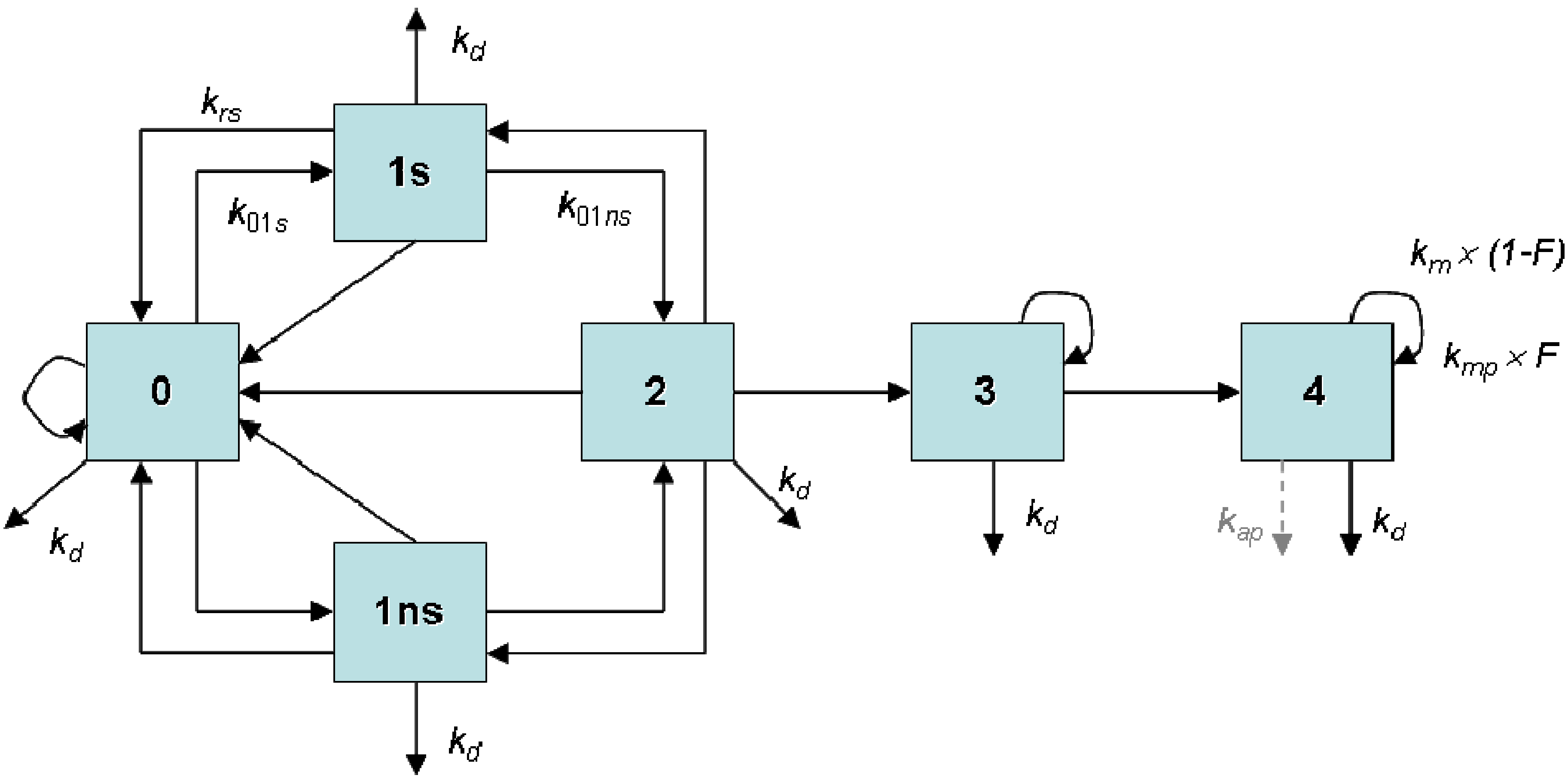
  - Monte Carlo simulations
  - Conclusions and Outlook

State Vector Model



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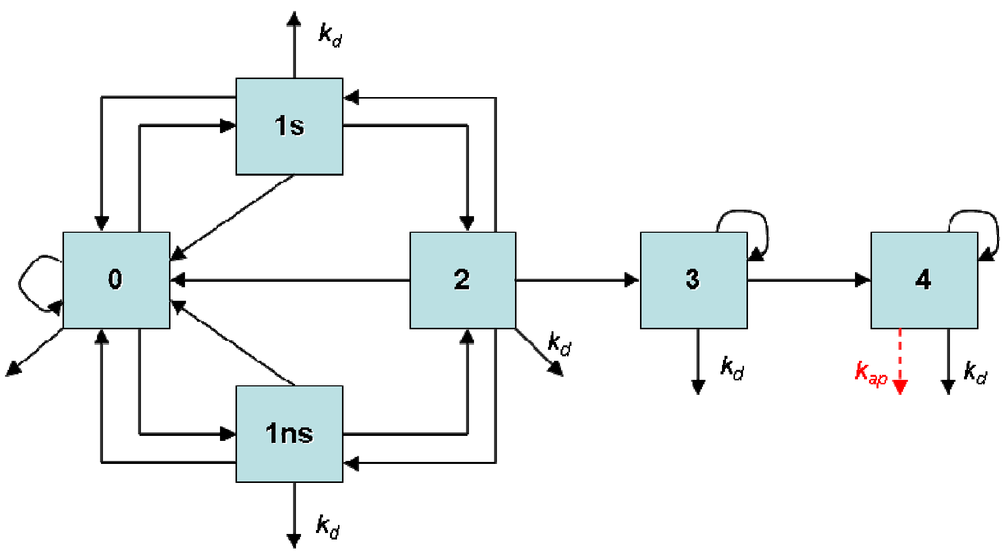
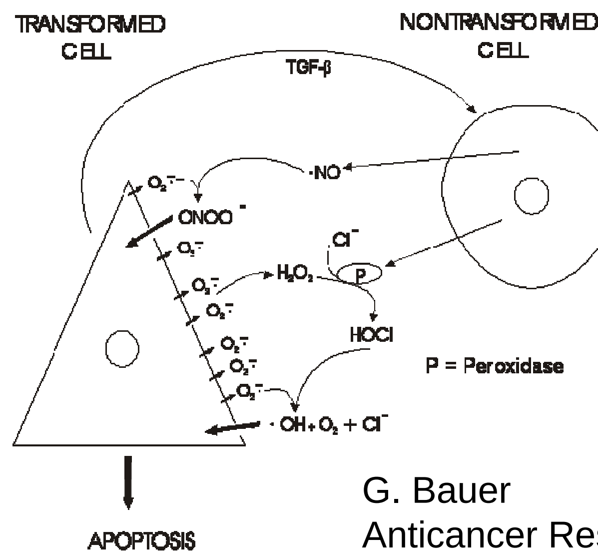
Bystander-induced apoptosis

For low-LET radiation

- **P**rotective **A**poptosis-**M**ediated process (PAM)
- PAM can eliminate cells in State 4





G. Bauer
Anticancer Res. 2000

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

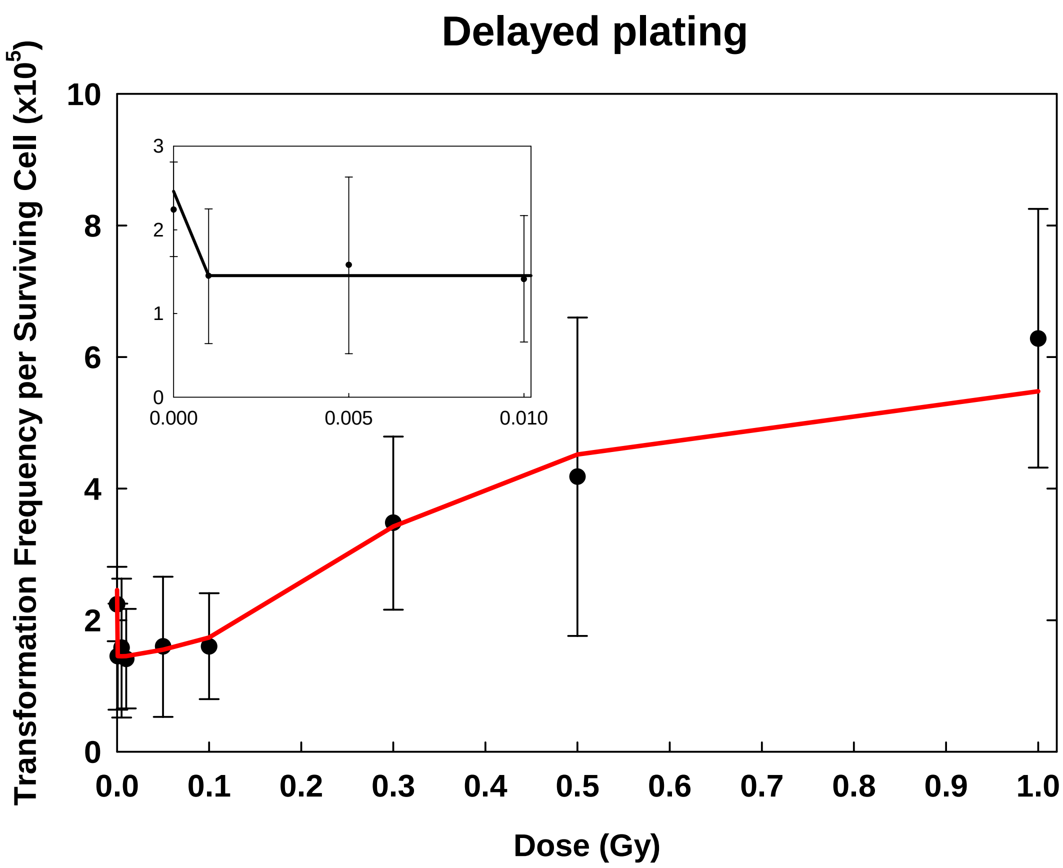
Fit approach

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

- **Fit model without PAM** to control and high dose data („direct contribution“)

- **Fit model with PAM** to all data points for delayed plating: 1 to 3 free parameters: k_{ap}, t_{ap_on}, t_{ap_off} („total contribution“)

Data by Redpath et al.



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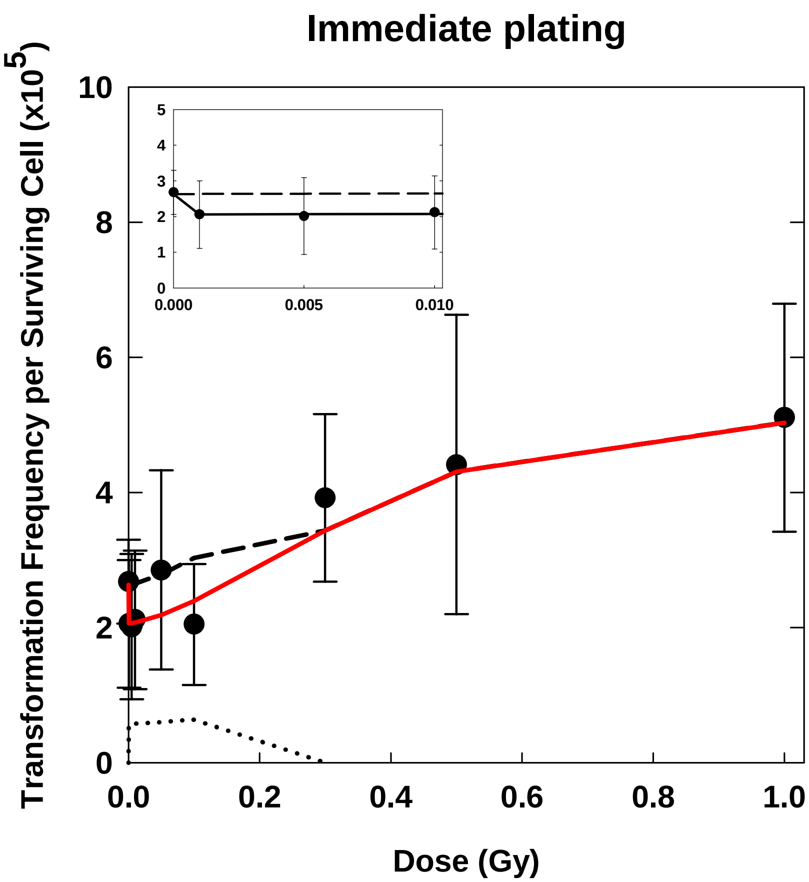
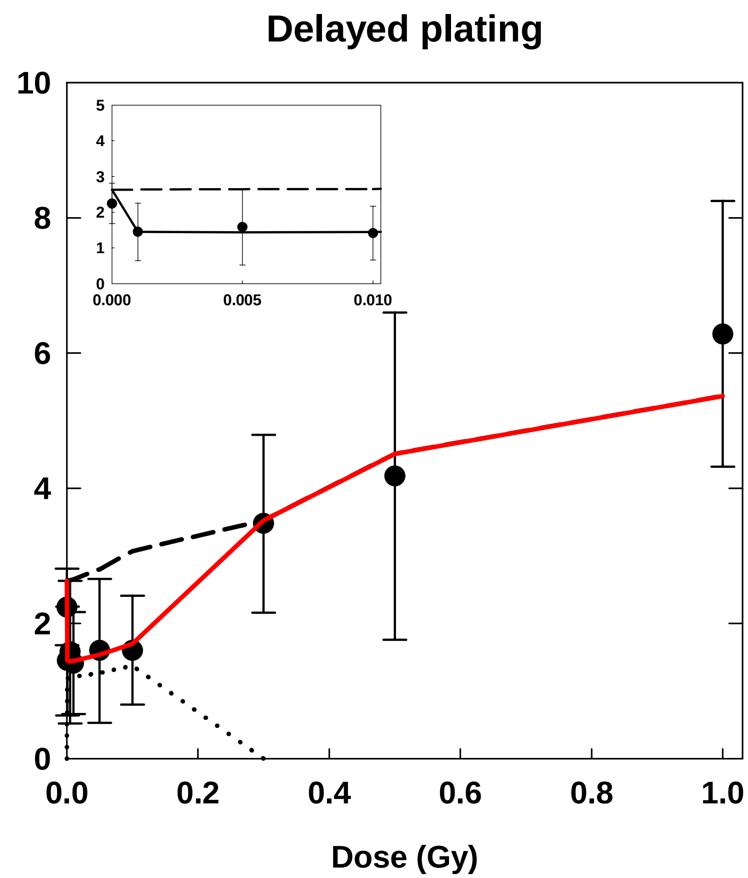




„Where is uncertainty?“

Perform local model fit → calculate the 95% CI for best estimated values with

- the Jacobian matrix, $J_f = \left(\frac{\partial f_i}{\partial \hat{\beta}_j} \right)_{i=1,\dots,m;\, j=1,\dots,n}$

  - numerical model solutions, f_i, (i.e. $TFSC_i$),
  - best estimated values, $\hat{\beta}_j$, of free model parameters

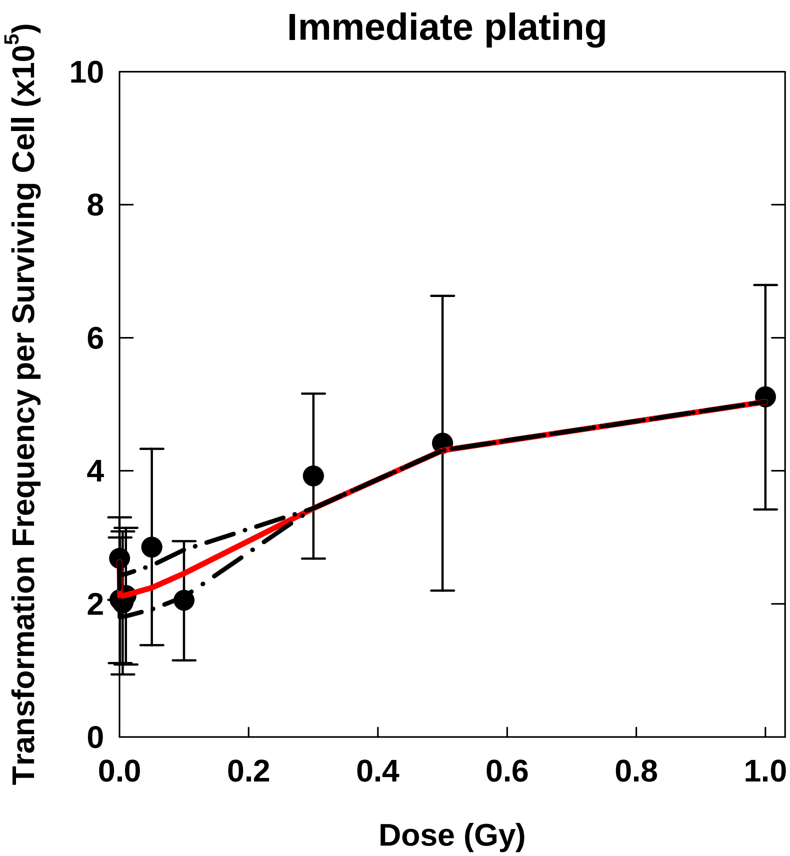
- the residuals (measured TFSC – model predicted TFSC)

i… # of data points (i.e. residuals), j… # of free parameters

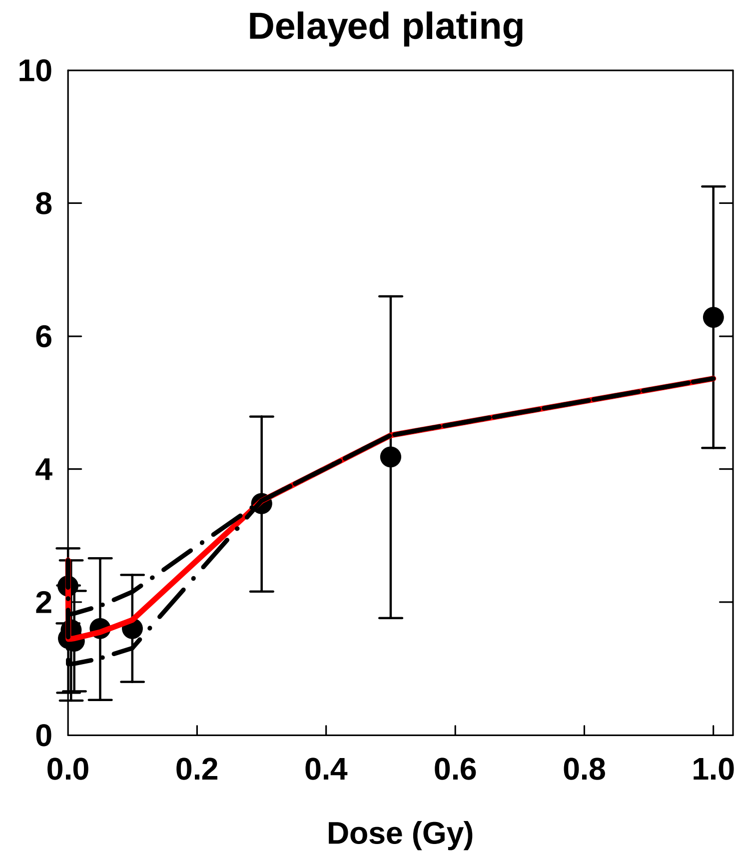
$\delta \propto$ 95%-tile of Student‘s t distribution with v degrees of freedom; v = # of residuals - # of free parameters.

95% CI = [$\hat{\beta}$ - δ; $\hat{\beta}$ - δ]

Data by Redpath et al.



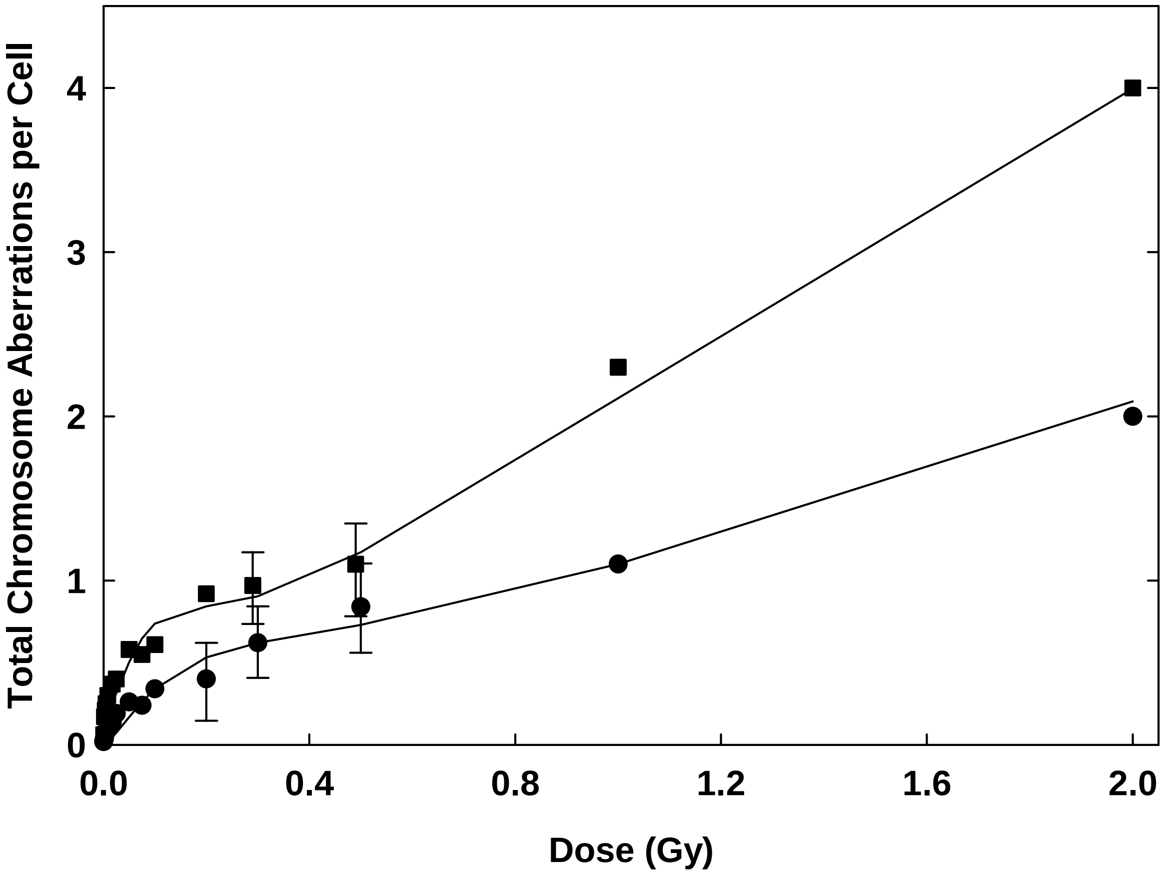
k_{ap} = 0.054/day (0.031–0.078)



k_{ap} = 0.022/day (0.007–0.036)

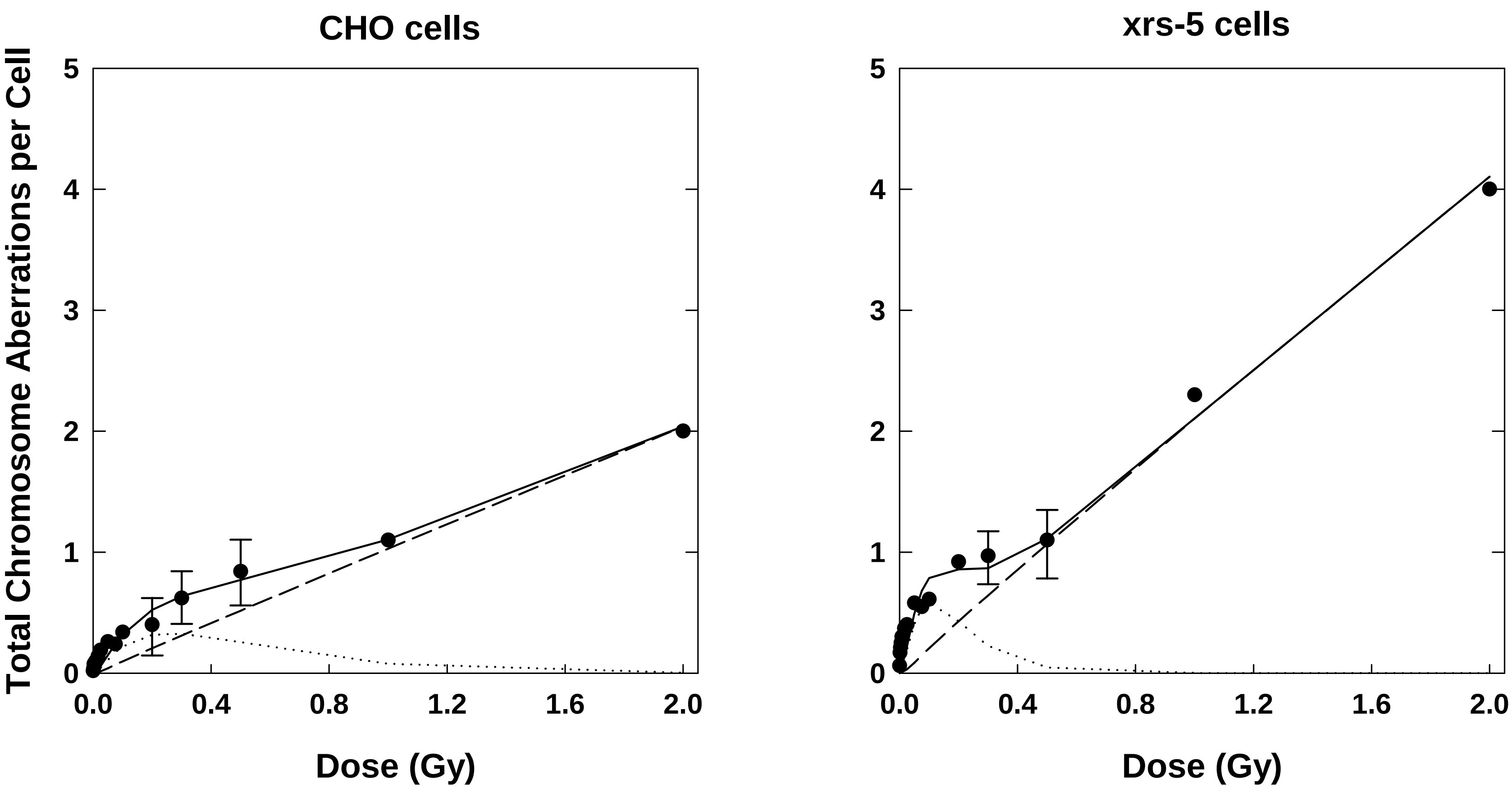
Data by Nagasawa and Little

Mutat Res. 2002, α-particles (112 keV/μm), CHO and xrs-5

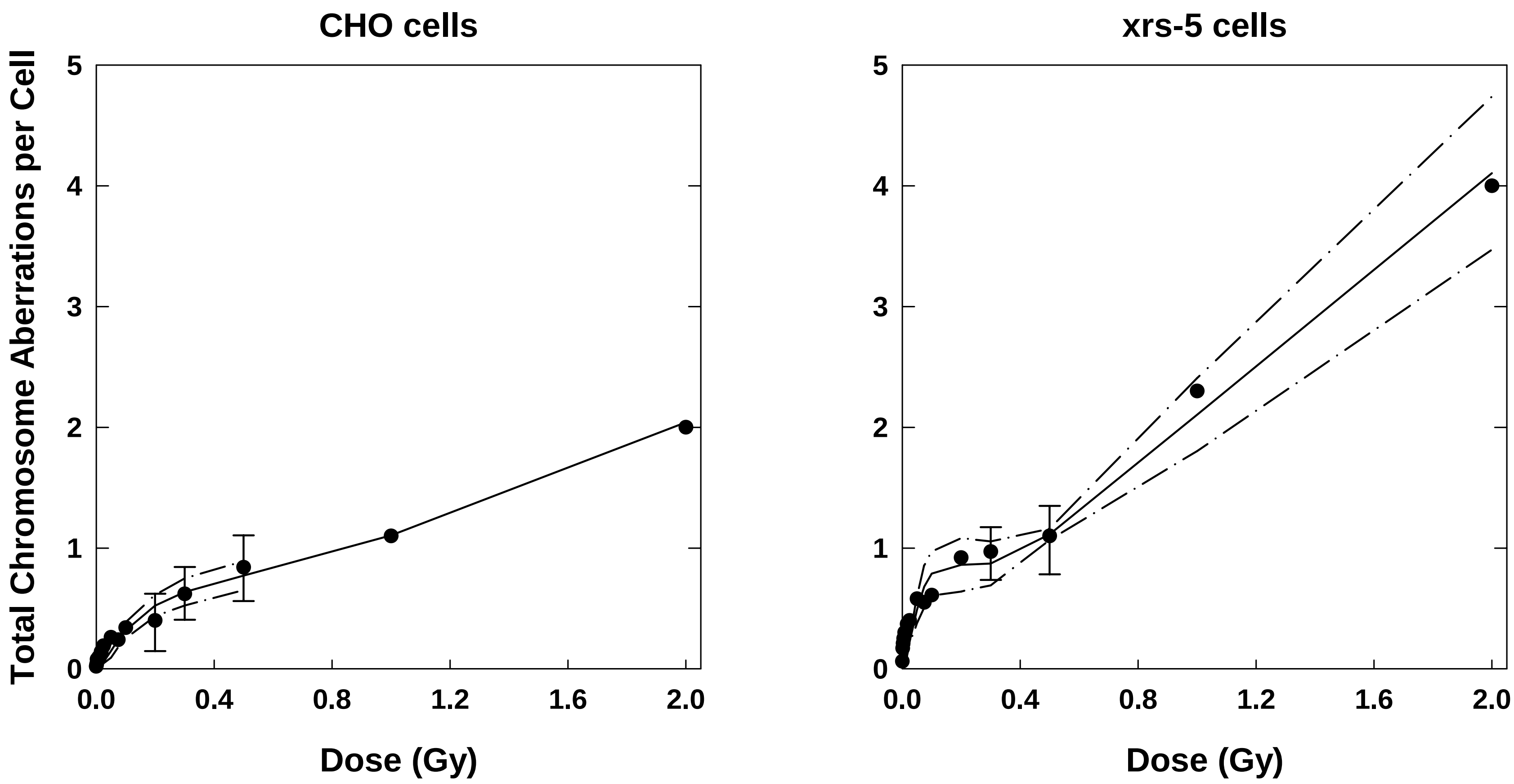


$k_{01b\_by} \times e^{-\lambda_{1by} \times D}$

Data by Nagasawa and Little

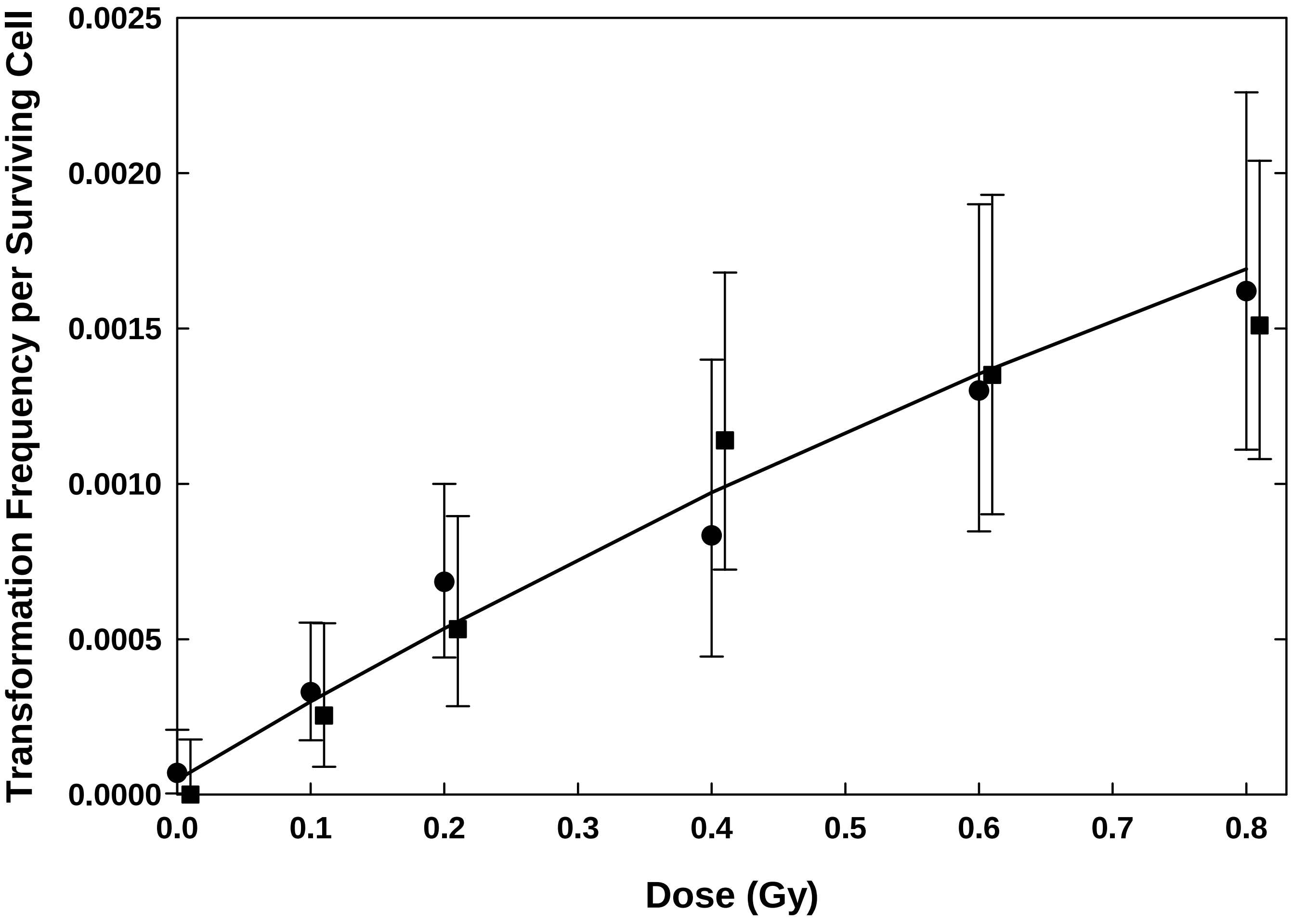


Data by Nagasawa and Little



Data by R.C. Miller et al.

Radiat Res. 1995, α-particles (150 keV/μm), C3H 10T1/2



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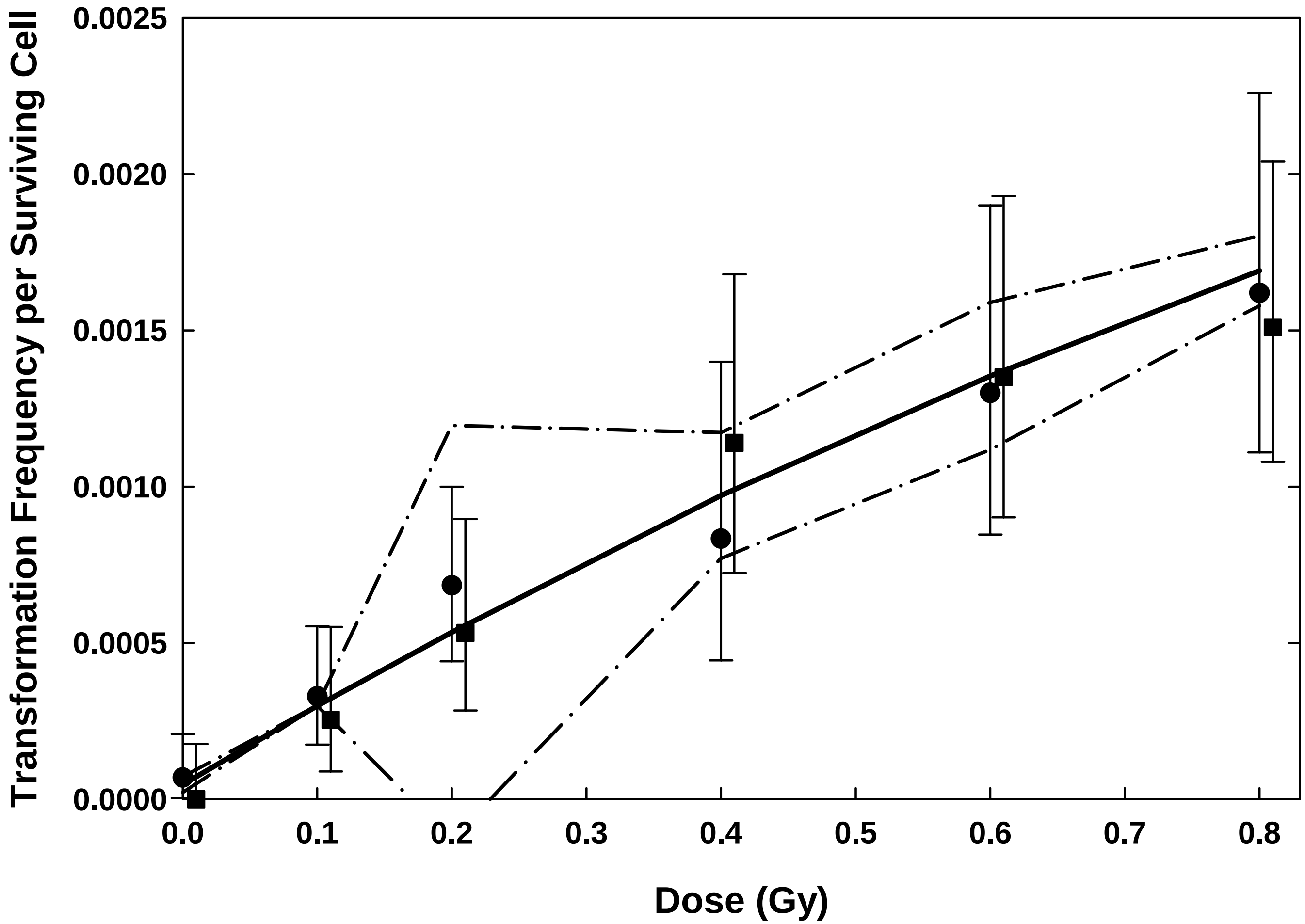
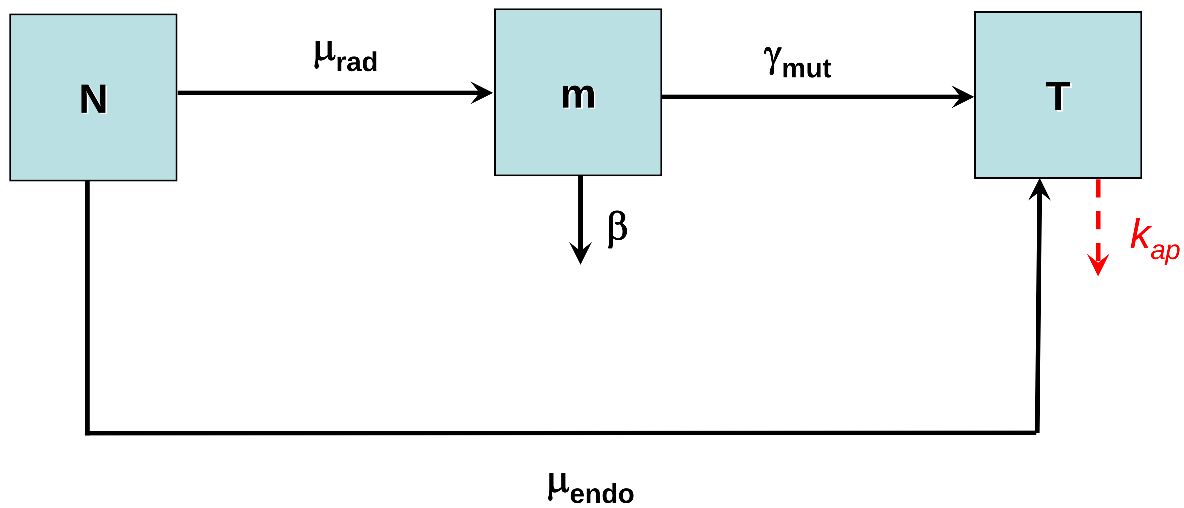


New model for neopl. transformation

Cellular level



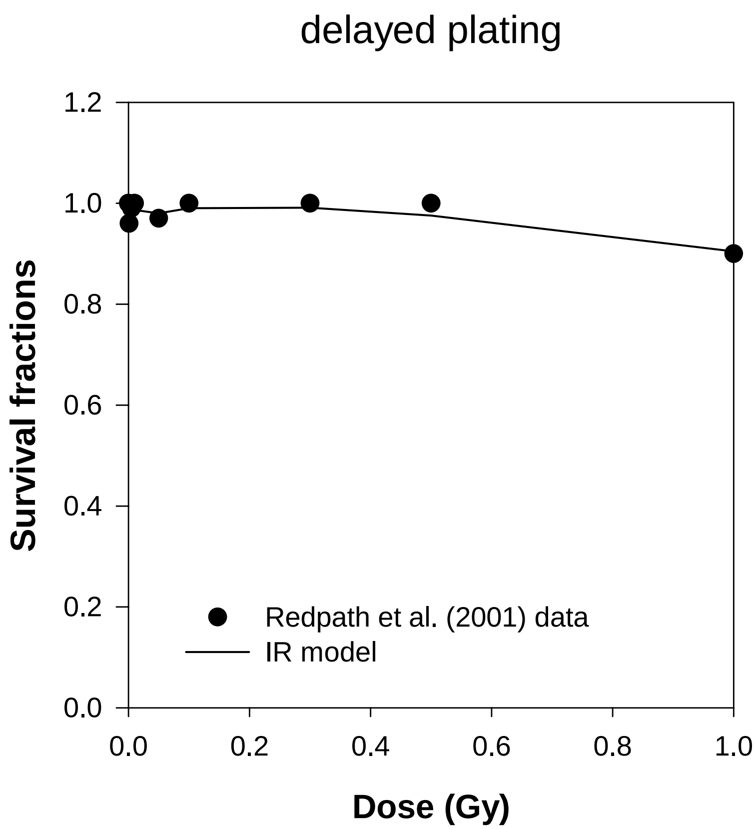
Molecular level

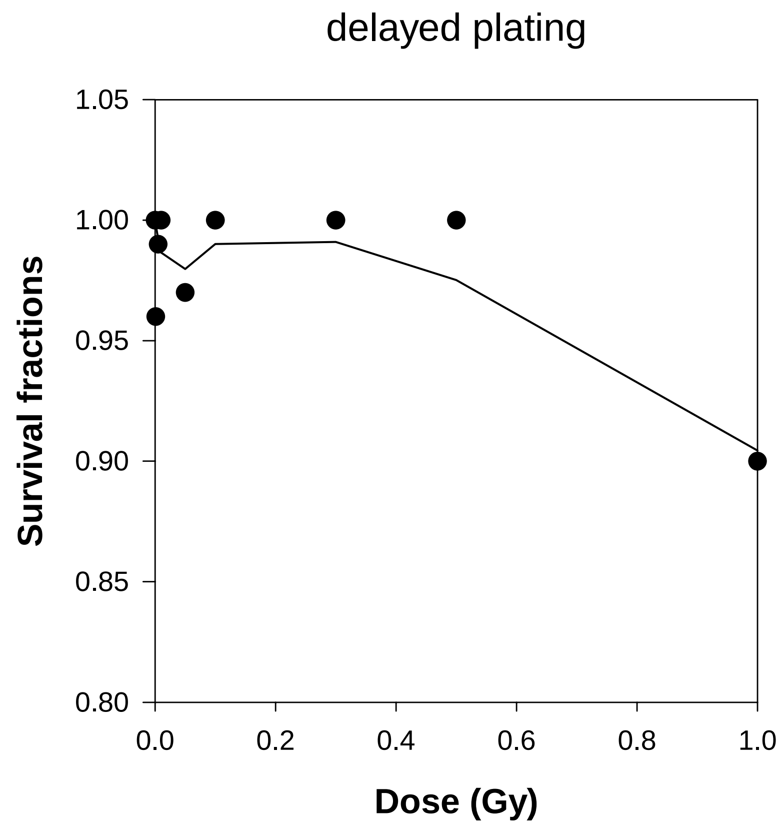
DNA damage production: $\Sigma_{sl}^{endo}, \Sigma_{cl}^{endo}, \Sigma_{sl}^{rad}, \Sigma_{cl}^{rad}$

DNA repair: $\lambda_{sl}, \lambda_{HR}, \lambda_{NHEJ}$

DNA misrepair: $\varphi_{sl}^{endo}, \varphi_{cl}^{endo}, \Phi_{HR}, \Phi_{NHEJ}$

Low Dose HRS and IRR





IR model: $SF = \exp\{-\alpha_r[1+((\alpha_S/\alpha_r) - 1)\exp(-D/D_c)]D - \beta_1 D^2\}$

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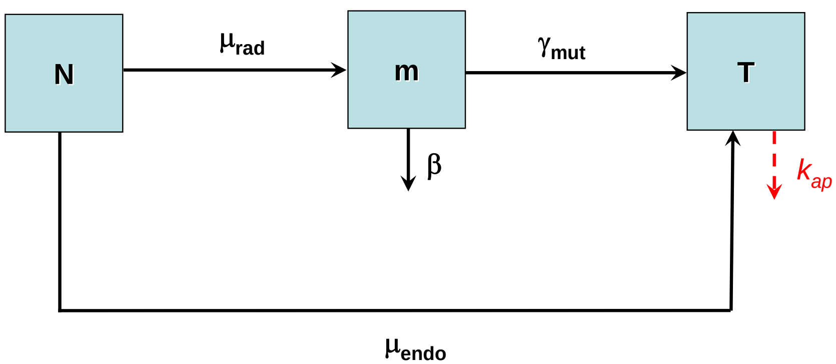
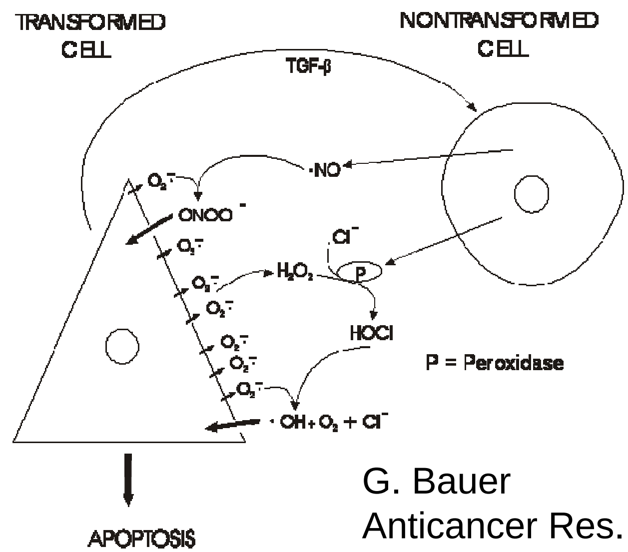
Bystander-induced apoptosis

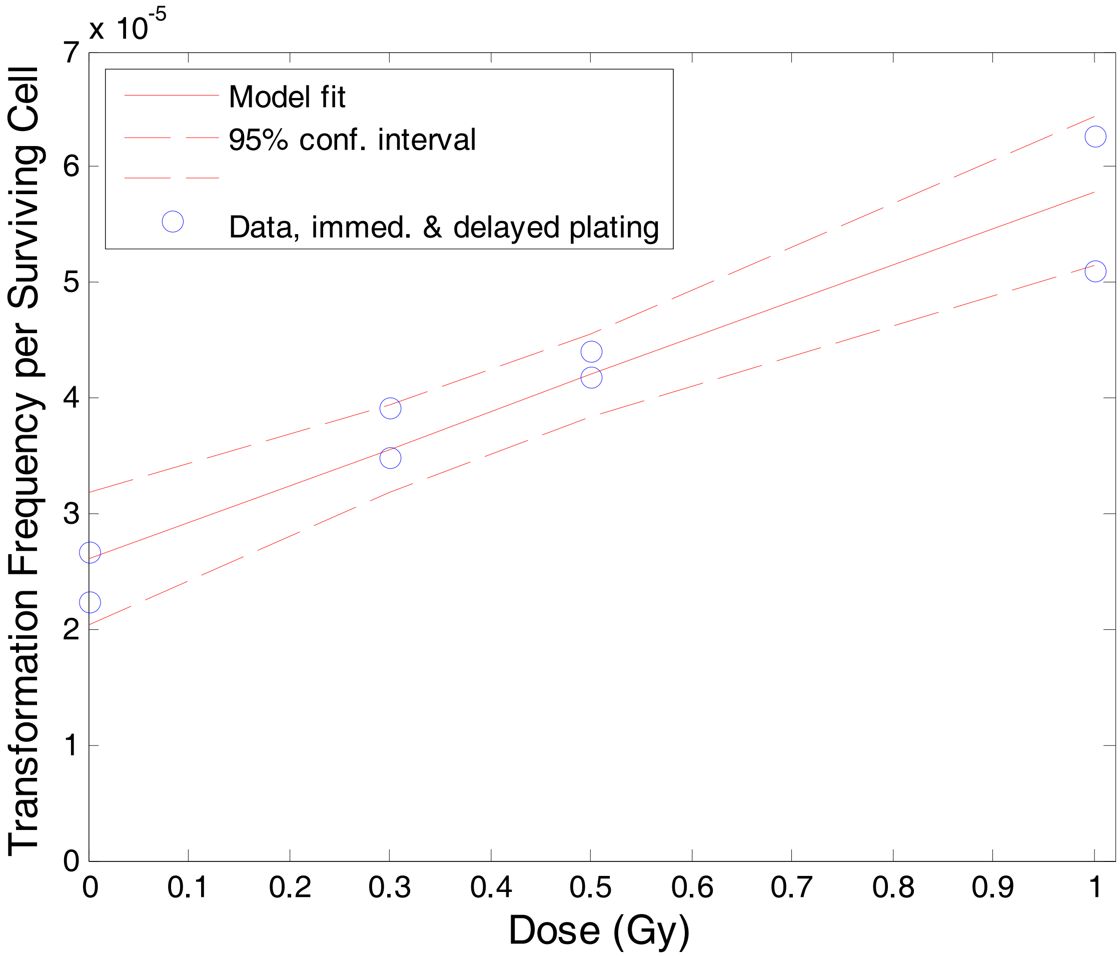
- **P**rotective **A**poptosis-**M**ediated process (PAM)
- PAM can eliminate transformed cells





G. Bauer
Anticancer Res. 2000

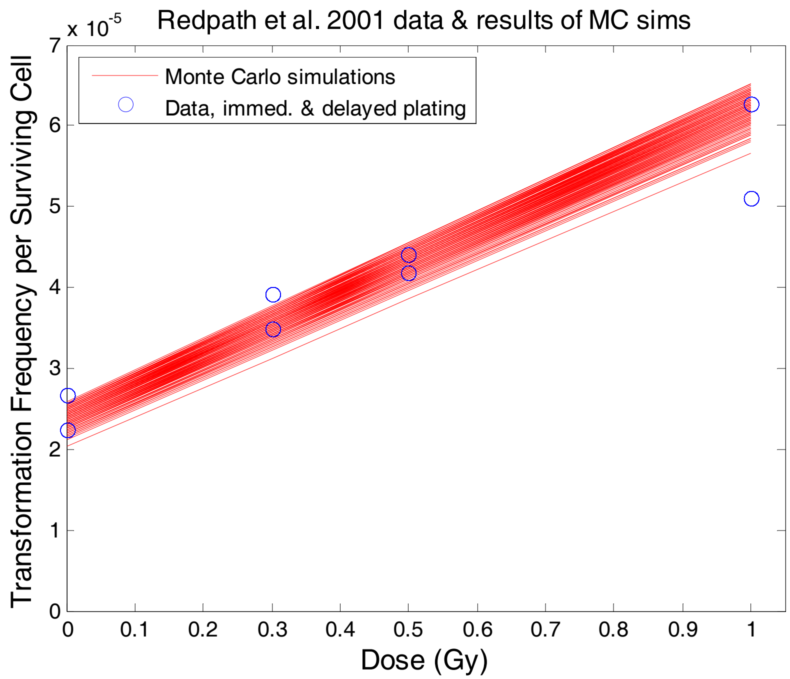
Model fits

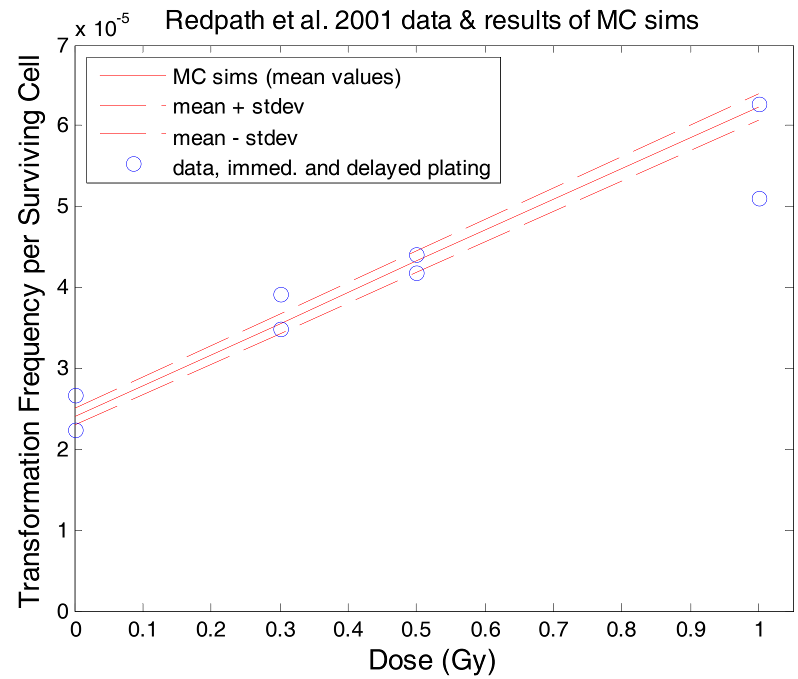


$\Omega = 1.2 \times 10^{-5}$ (9.3×10^{-6} - 1.4×10^{-5})

$\gamma_{mut} = 1.4 \times 10^{-3}$/day ($7.2 \times 10^{-4}$ – 2.2×10^{-3})

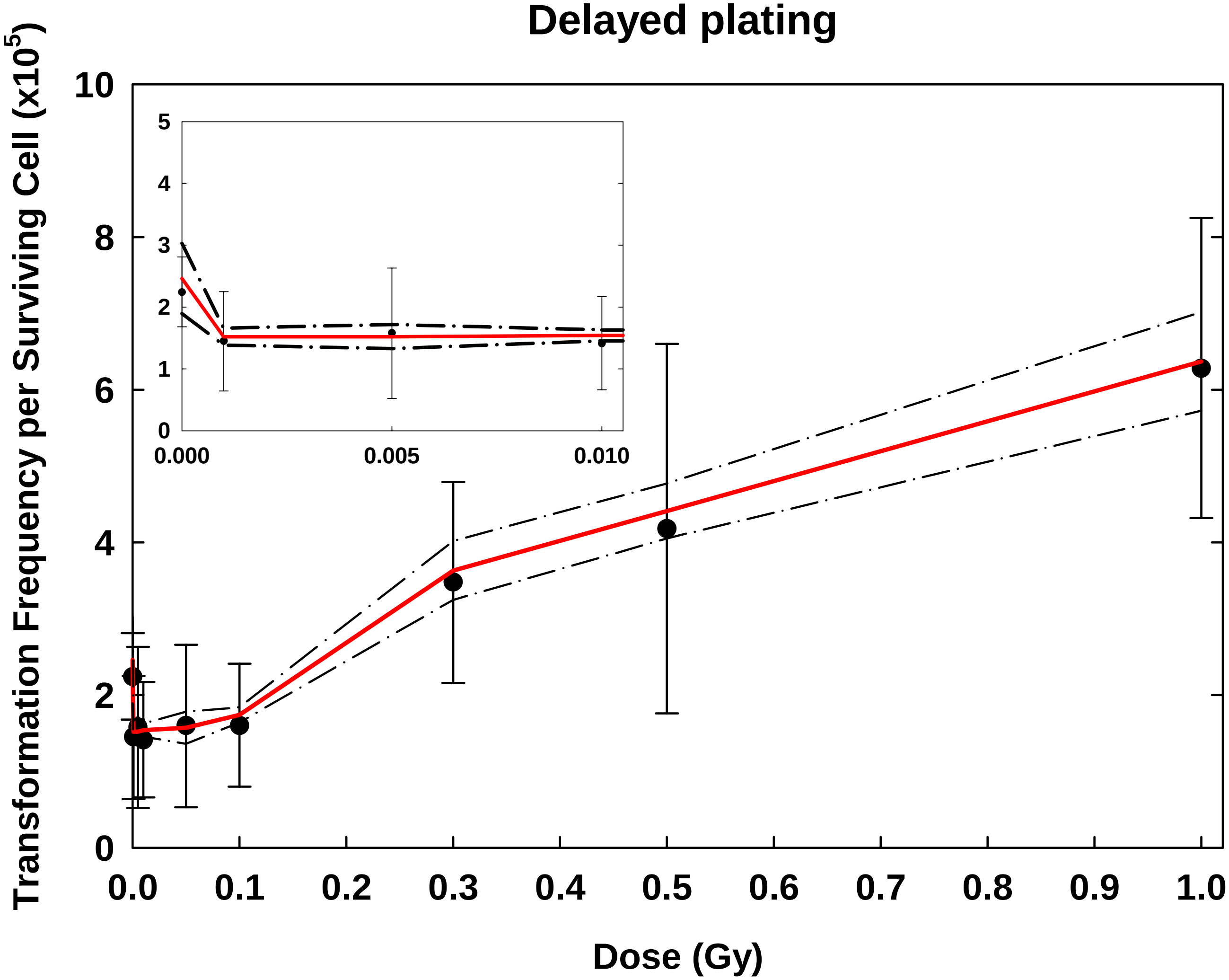
Monte Carlo simulations





200 forward simulations with allowed uncertainties in λ_{HR}, λ_{NHEJ}, and λ_{sl}.

Delayed plating



k_{ap} = 2.0/day (-1.7 – 5.7)

Conclusions

- SVM successfully equipped with algorithms that allow to calculate 95% CI for model predictions and best estimated values
- New compartment model for *in vitro* neoplastic transformation
- Model has system-biological aspects and contains
  - endogenous and radiation-induced lesions
  - DSB repair via HR and NHEJ
  - misrepair

Conclusions

- low dose HRS/IRR
- bystander-induced apoptosis

- Model successfully equipped with algorithms that allow to calculate 95% CI for model predictions and best estimated values
- Model made stochastic via Monte Carlo methods

Outlook

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- Work towards model that contains all mechanisms that are rate-limiting and essential at low doses:
  - Low dose HRS/IRR ✓
  - Genomic Instability
  - endogenous DNA lesions ✓
  - inducible repair
  - radical scavenging
  - protective bystander effects ✓
  - detrimental bystander effects
  - Stochasticity ✓
  - Uncertainty ranges ✓

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