XVIII PTBR National Meeting Satellite Symposium
Applications of low radiation doses in medical diagnosis and therapy

JERUSALEM COLLEGE OF TECHNOLOGY
LEV ACADEMIC CENTER

Irradiation of arbitrary time-dependence: *mathematical model of adaptive response and oscillatory behavior, and its consequences*

Yehoshua Socol, Yair Shaki
and Ludwik Dobrzyński

Kielce, September 18, 2019

Acknowledgements

- Prof. Ludwik Dobrzyński National Centre for Nuclear Research Świerk, Poland
- Dr. Yair Y. Shaki }
- Prof. Avi Caspi } Jerusalem College of Technology
- Dr. Jerry Cuttler Independent, Canada
- Prof. Ludwig Feinendegen Heinrich-Heine University, Dűsseldorf
- Prof. Kanokporn Rithidech Stony Brook Medical School
- Dr. Bobby R. Scott Lovelace Respiratory Research Institute
- Prof. James Welsh Loyola U. Chicago, Stritch School of Medicine
- Mr. Yaakov Socol Hebrew University Medical School, Jerusalem

In memoriam

Boris Dubrovin, mathematician 1950–2019

Moscow University

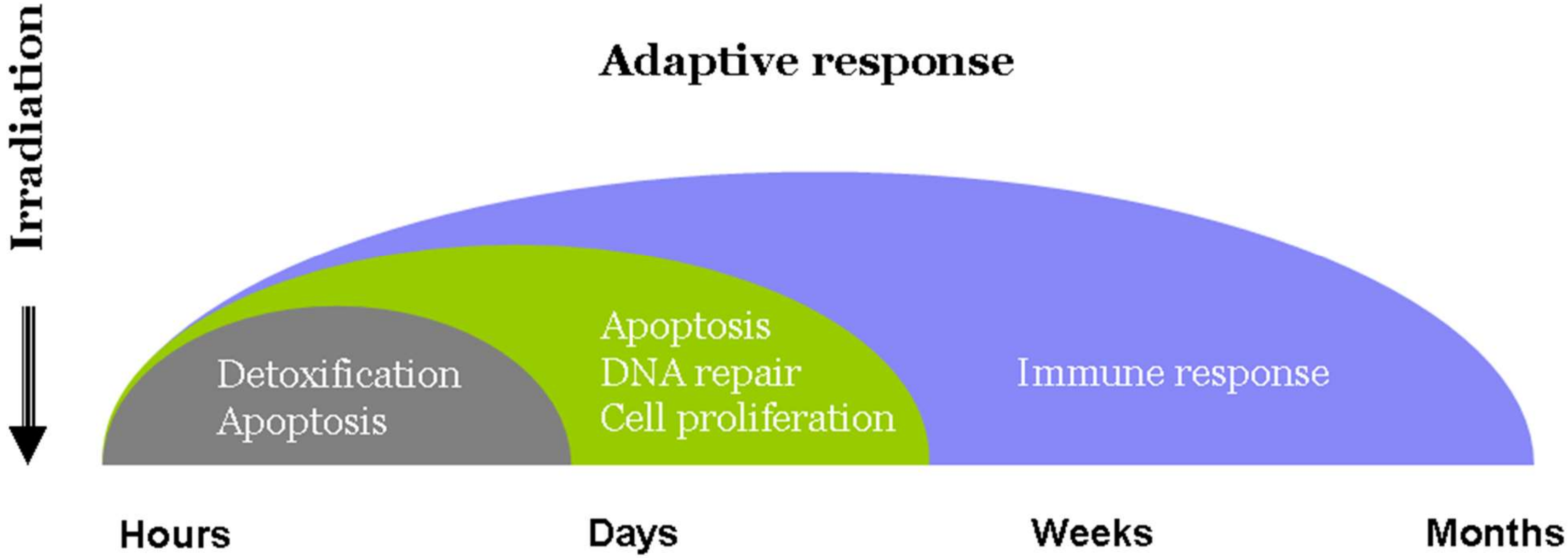
International School for Advanced Studies (SISSA) Italy

Cause of death: ALS

What we know

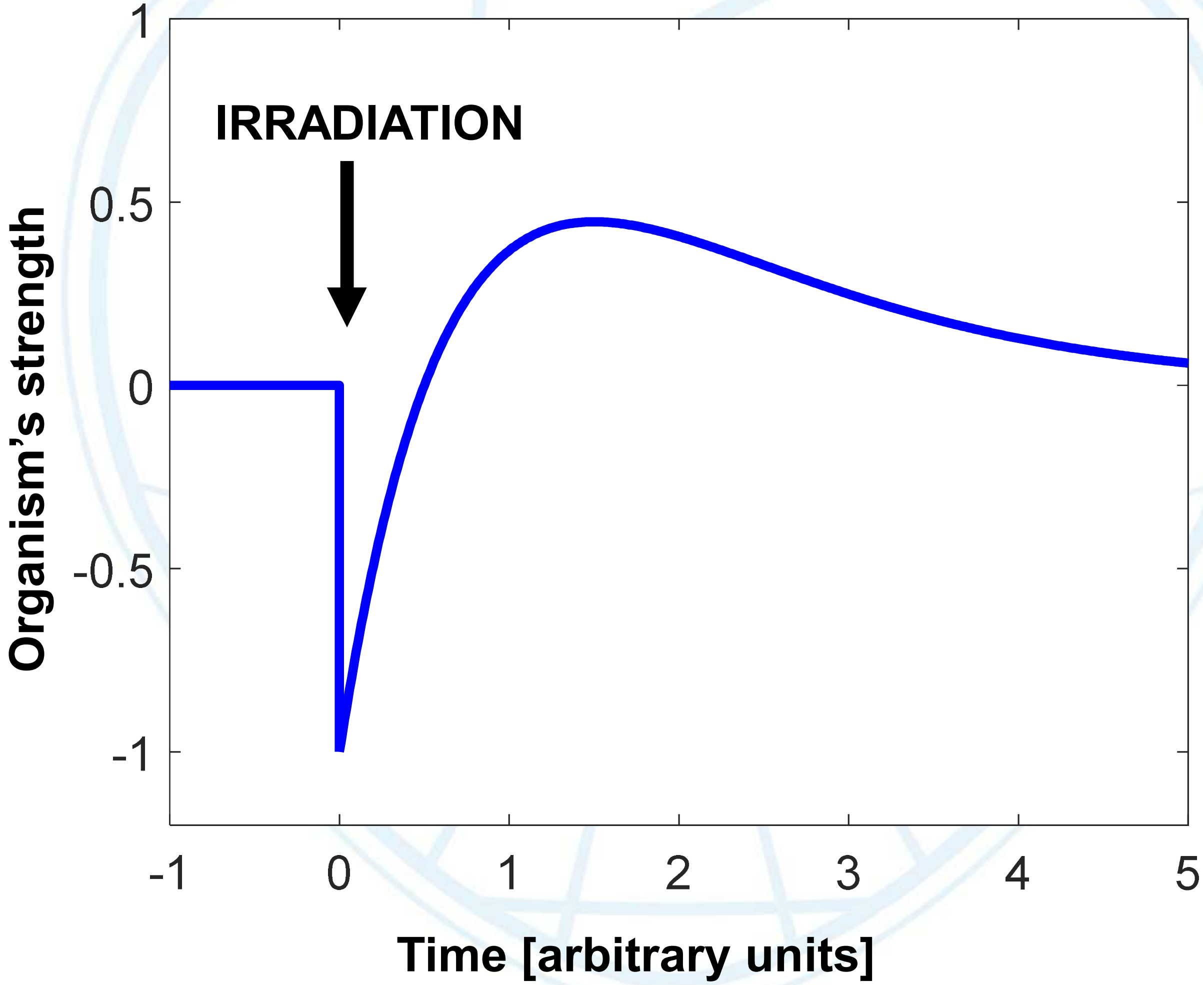
- High-dose radiation kills
- Low-dose: multiple adaptive response mechanisms
- Acute adverse health effects are fast (hours)
- Adaptive response (protection)
  - may switch on within hours or days
  - may last weeks and months

Adaptive response



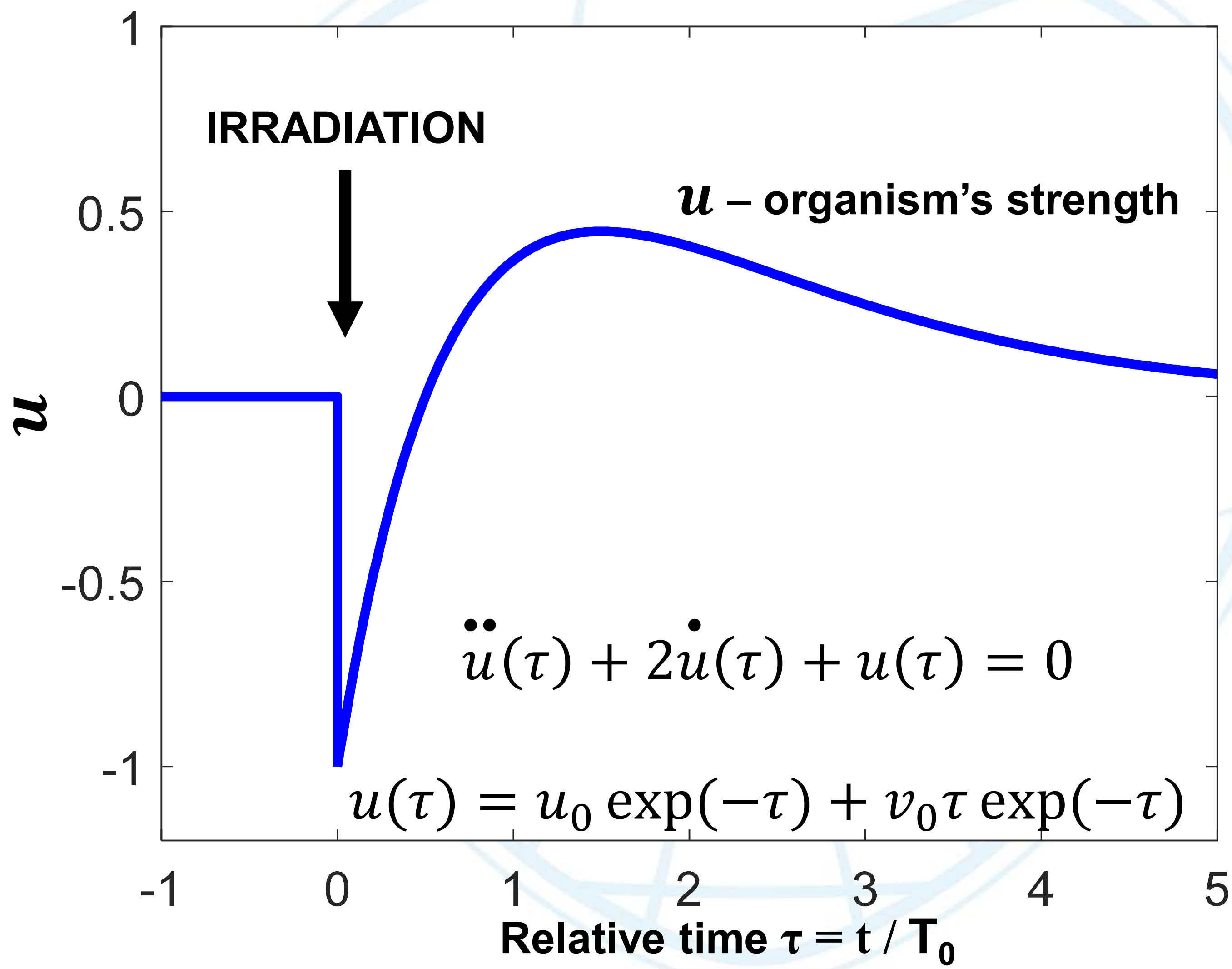
Adapted from:
Feinendegen *et al*. (2007)
Exp. Hematol. **35**, 37-46

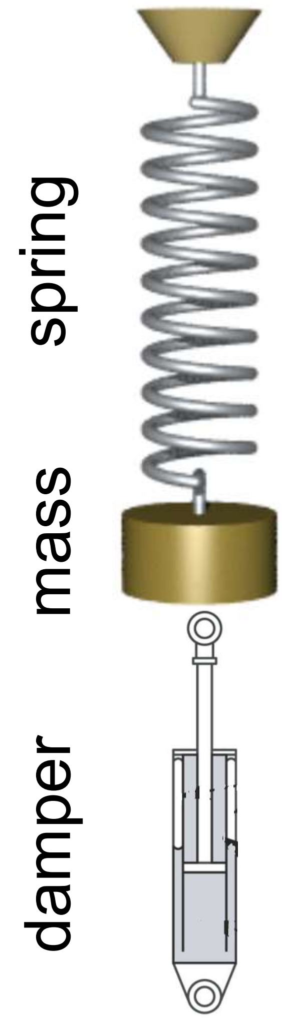
Hypothesis:



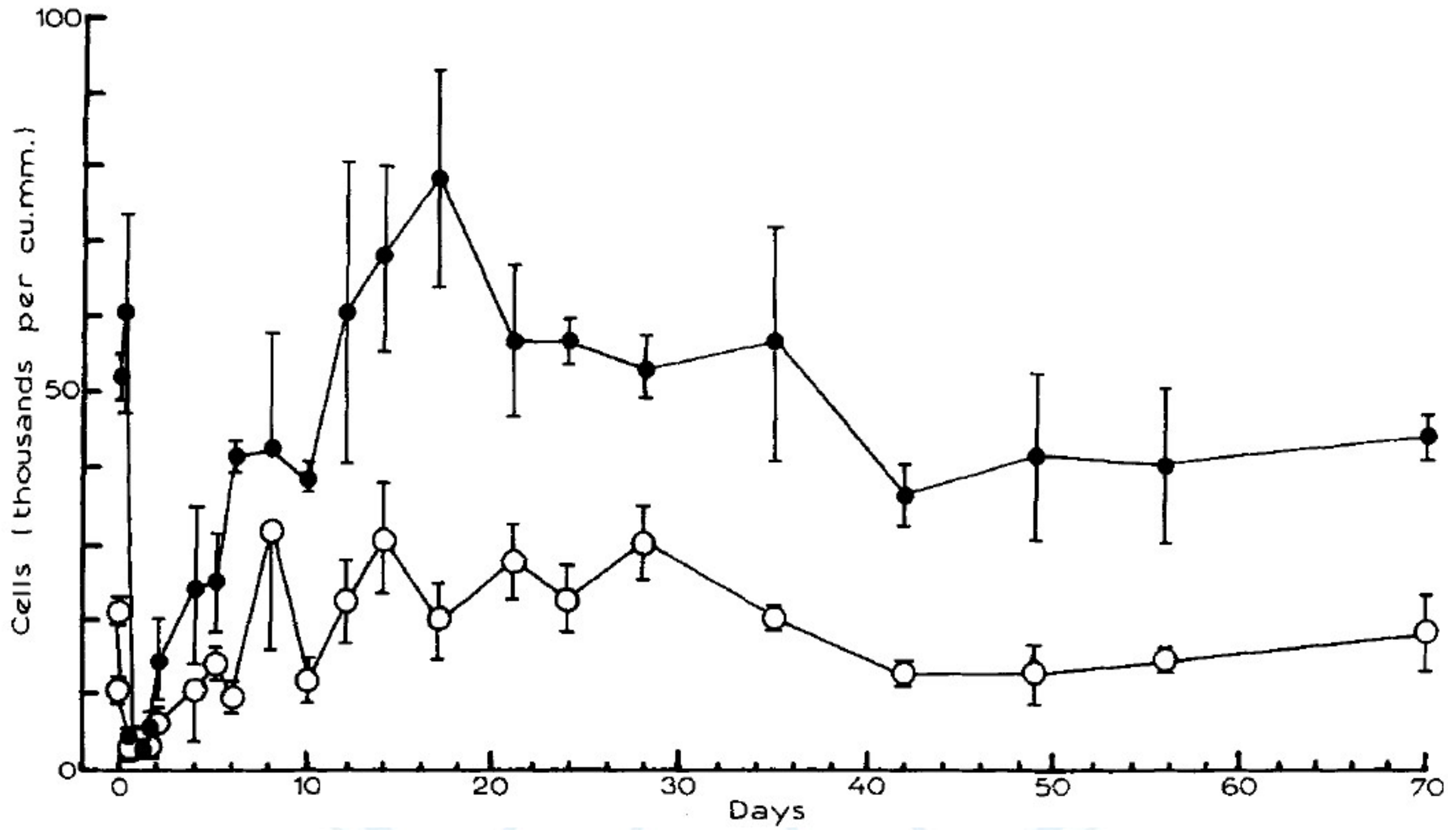
IRRADIATION
Organism's strength
1
0.5
0
-0.5
-1
-1
0
1
2
3
4
5
Time [arbitrary units]

Hypothesis: critical damping





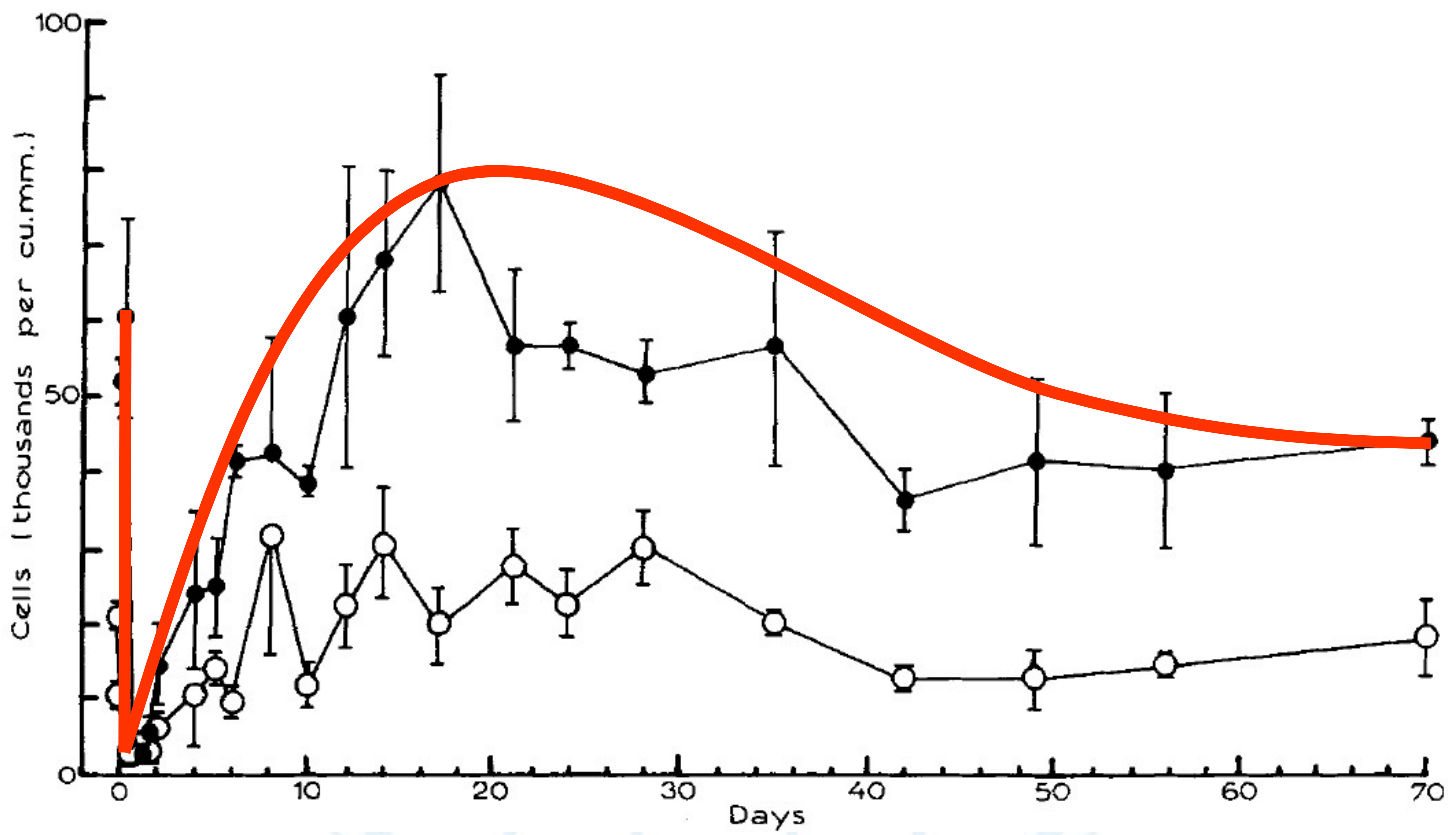
Data: rats, 400 R



Numbers of early normoblasts (●) and pronormoblsts (○), and their standard errors, in the marrow.

Hulse (1963) *Brit. J. Haemat*. **9**, 365-375

Data: rats, 400 R



Numbers of early normoblasts (●) and pronormoblsts (○), and their standard errors, in the marrow.

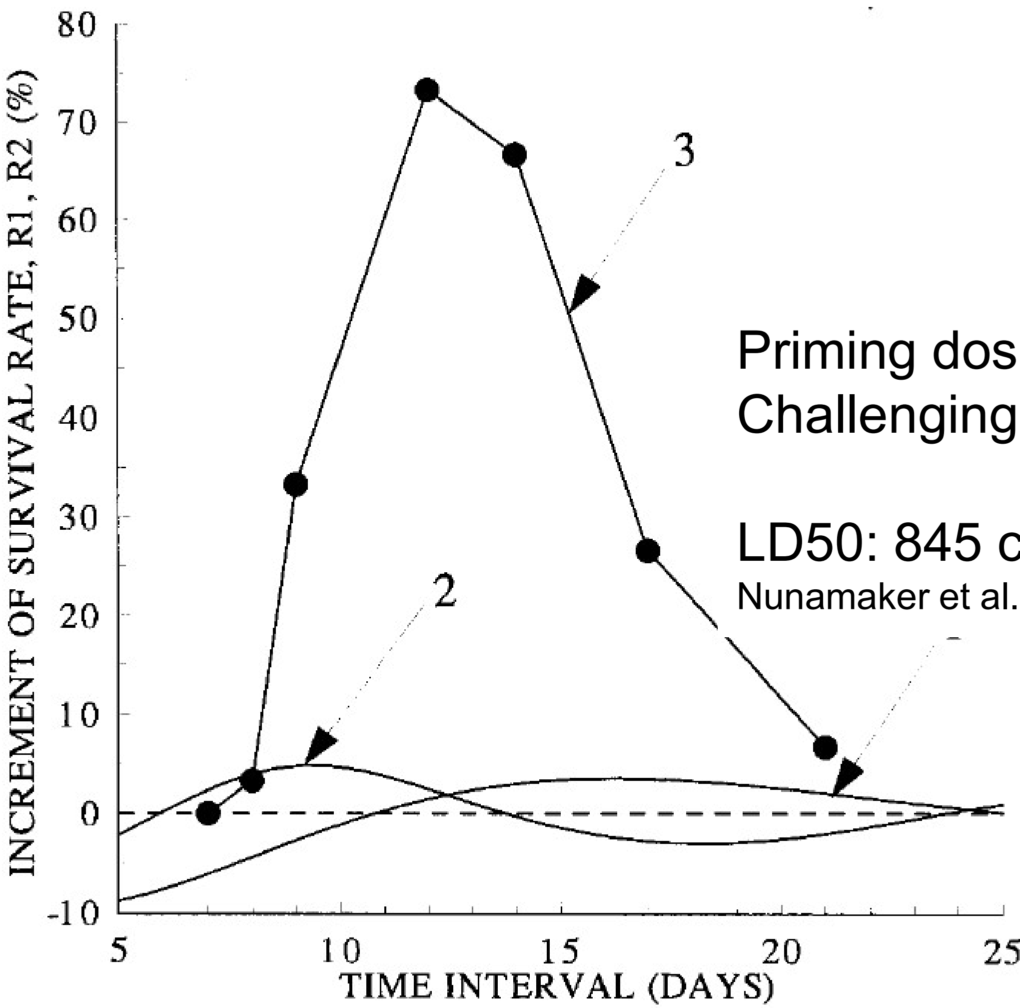
Hulse (1963) *Brit. J. Haemat*. **9**, 365-375

Data: mice
survival after pre-irradiation

Smirnova OA, Yonezawa M
Health Phys (2003) 85(2):150-158

Priming dose

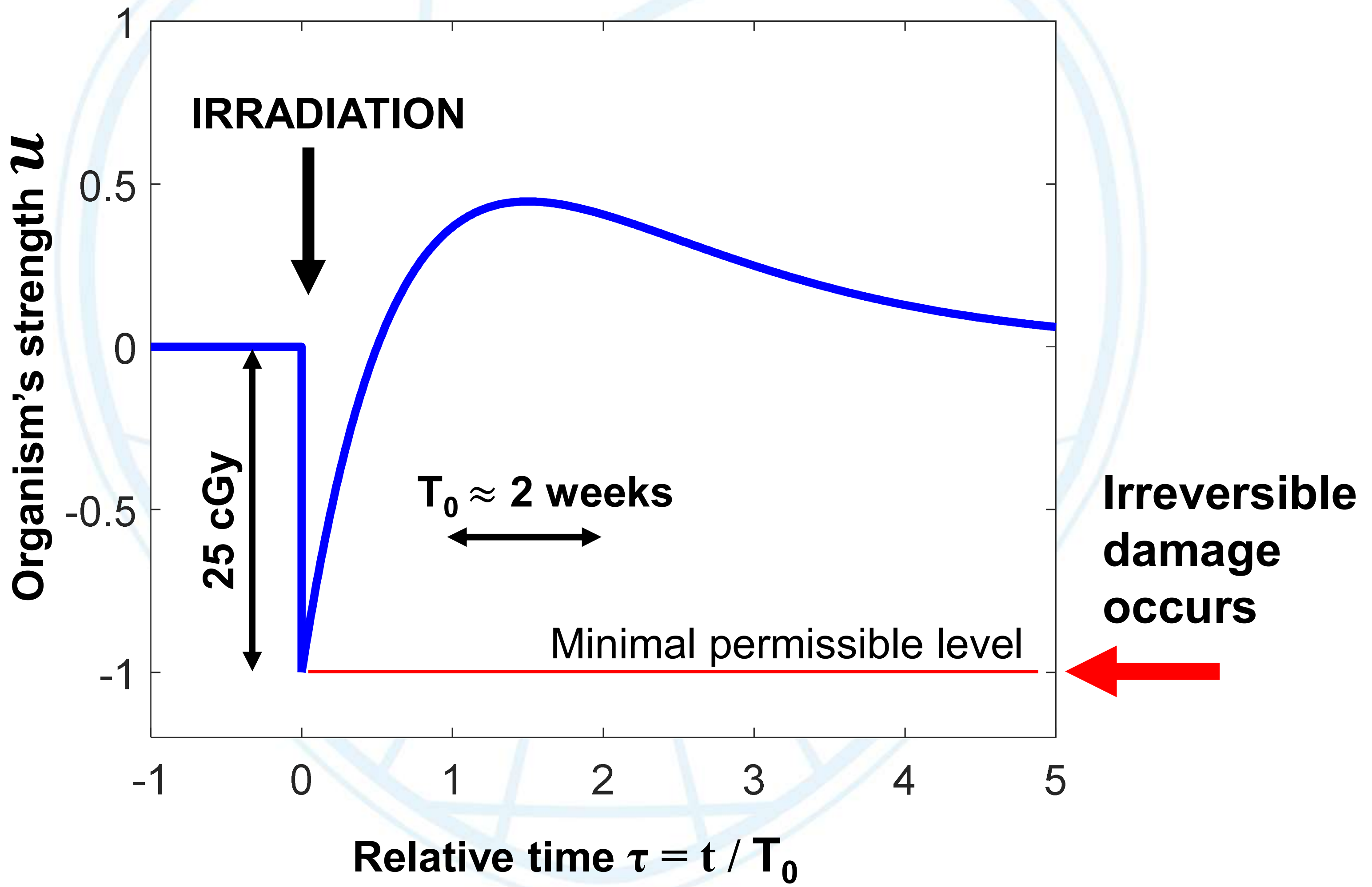
0



Priming dose: 45 cGy
Challenging dose: 675 cGy

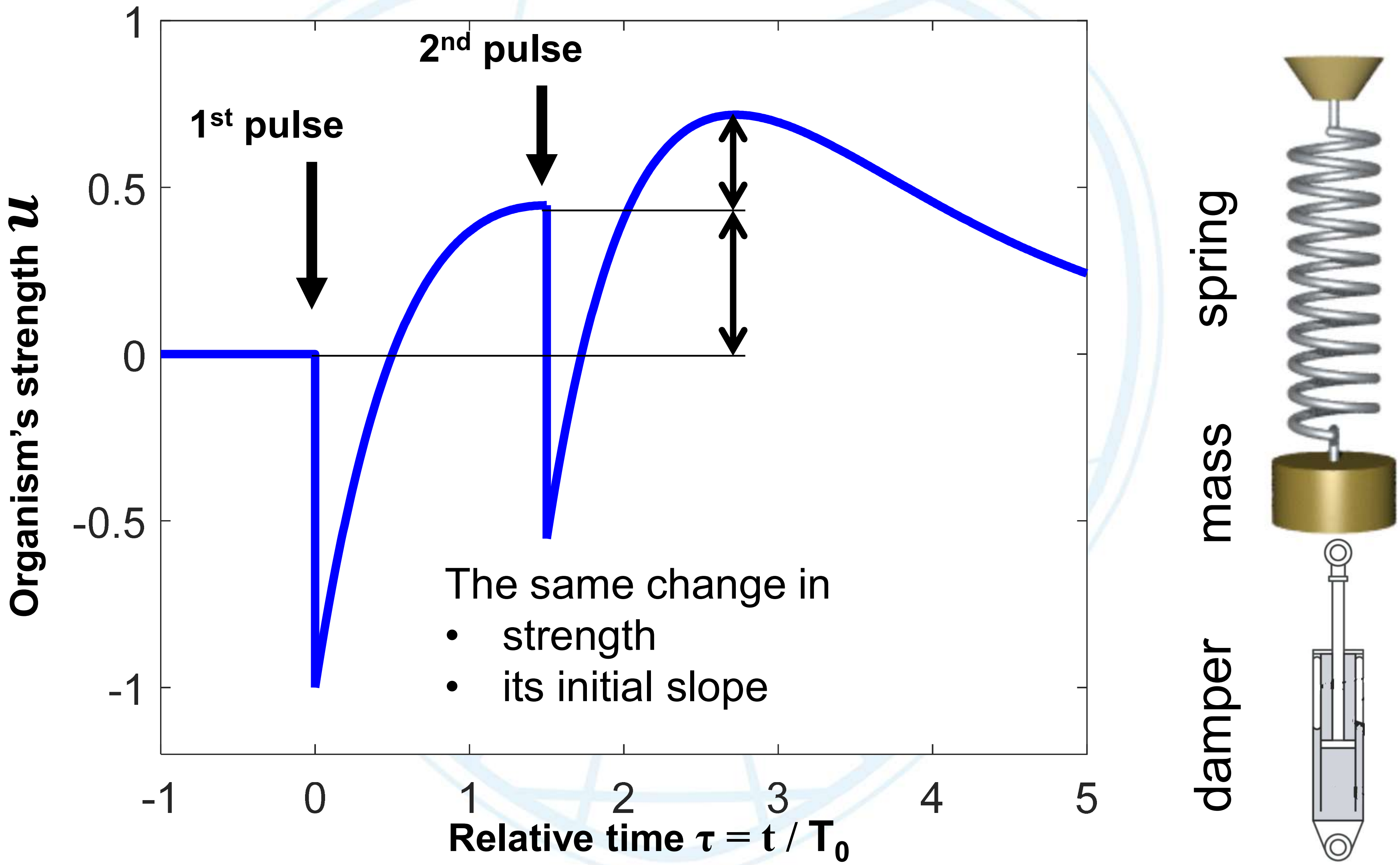
LD50: 845 cGy (C57BL/6)
Nunamaker et al., Comp Med 2013

Hypothesis:

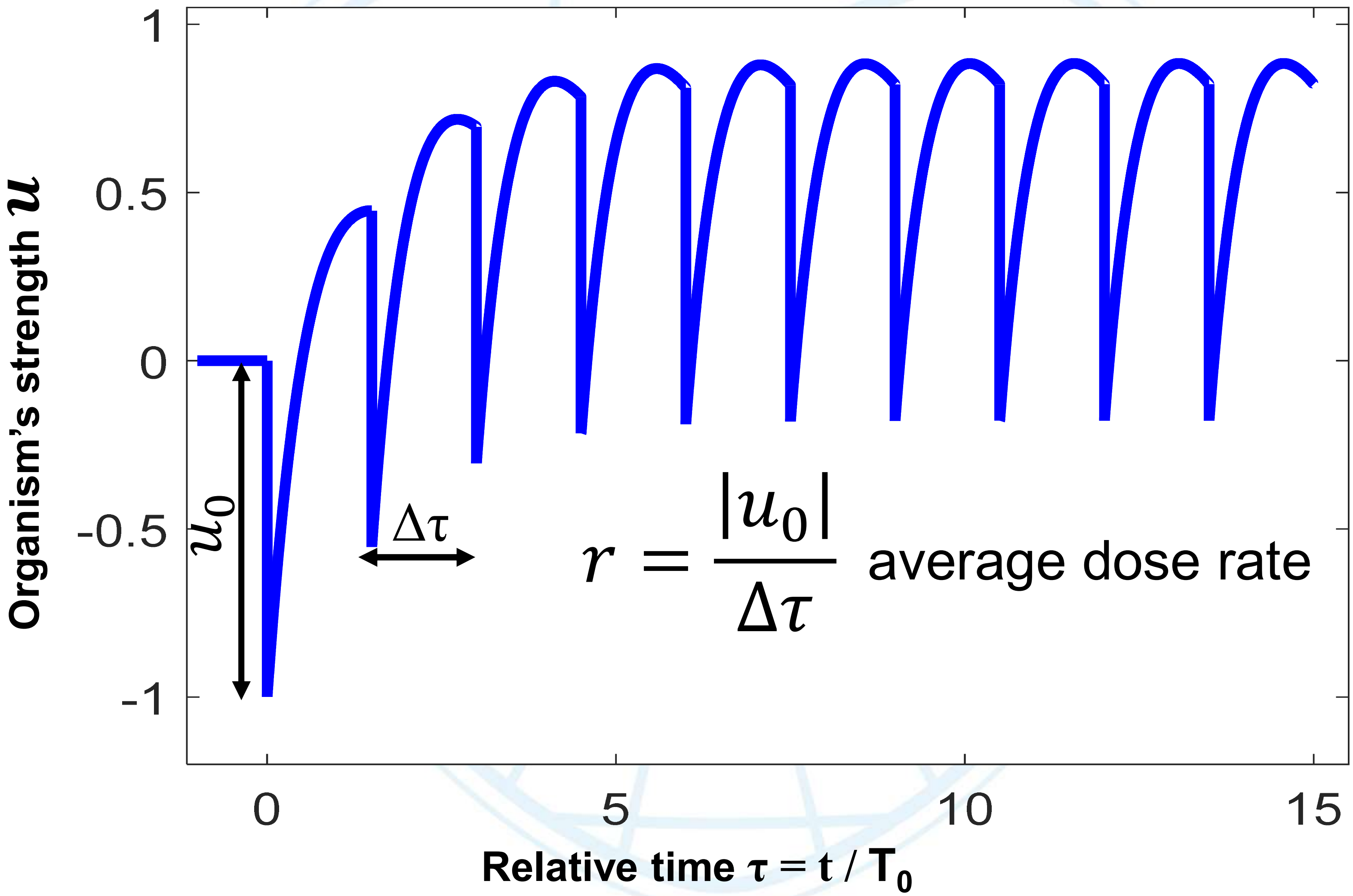


IRRADIATION
Organism's strength u
1
0.5
0
-0.5
-1
25 cGy
T0 ≈ 2 weeks
Minimal permissible level
-1
0
1
2
3
4
5
Relative time τ = t / T0
Irreversible damage occurs

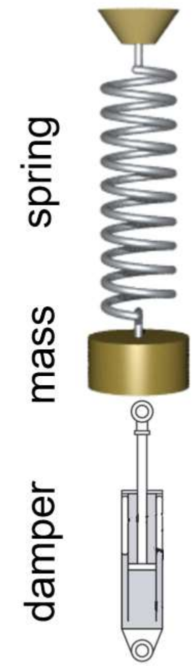
Assumption #2: second pulse



Pulse train

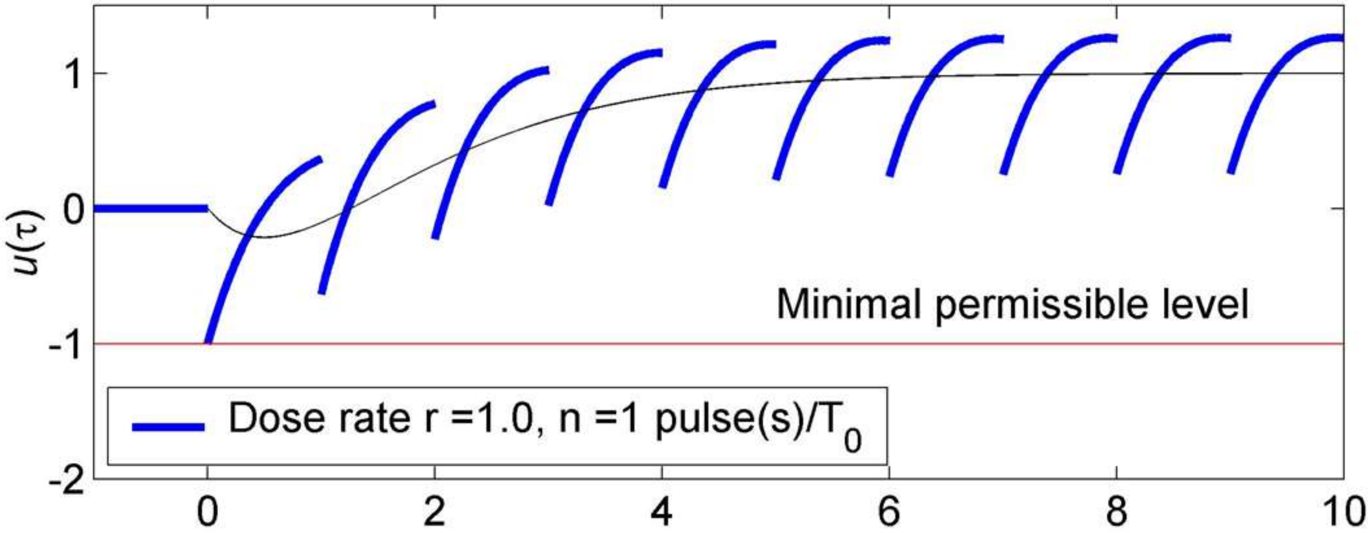


1
0.5
0
-0.5
-1
Organism's strength u
u_0
$\Delta\tau$
$r = \frac{|u_0|}{\Delta\tau}$ average dose rate
0
5
10
15
Relative time $\tau = t / T_0$



spring
mass
damper

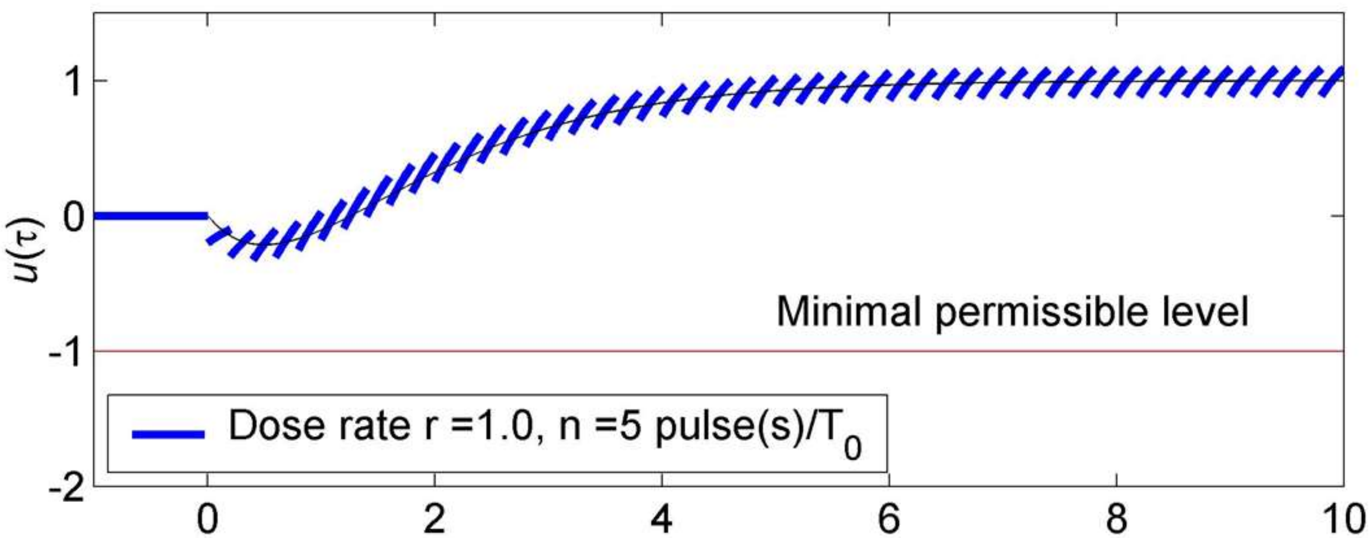
Effect of dose fractionation
hypothesized doses and times



25 cGy
every 15 days

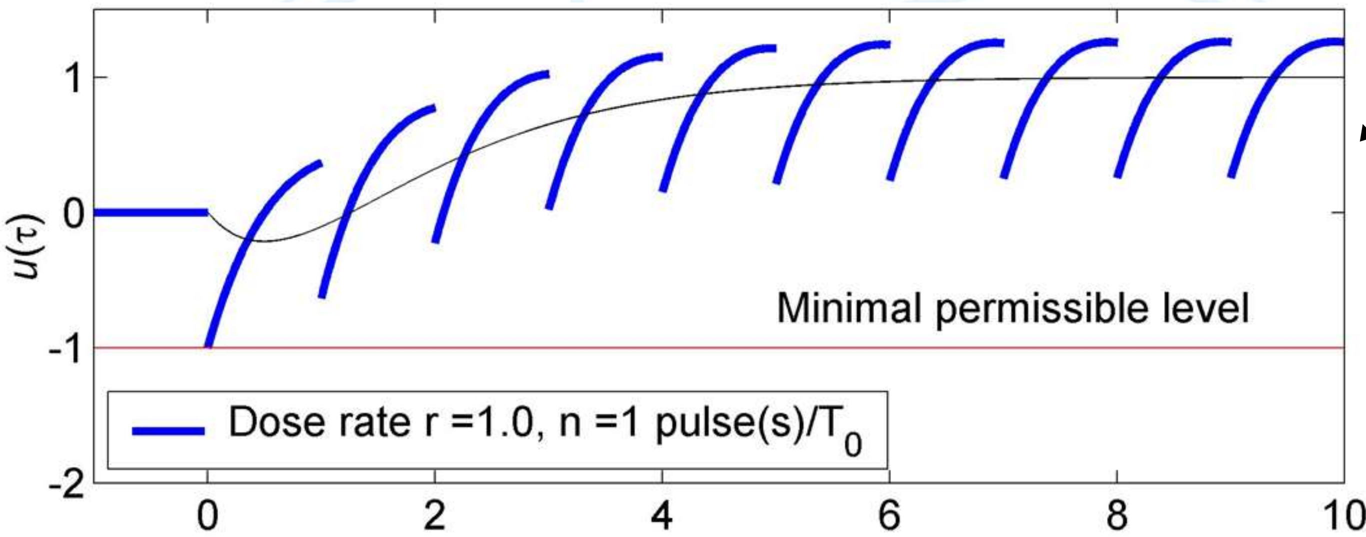
$$r = \frac{|u_0|}{\Delta\tau}$$

average
dose rate



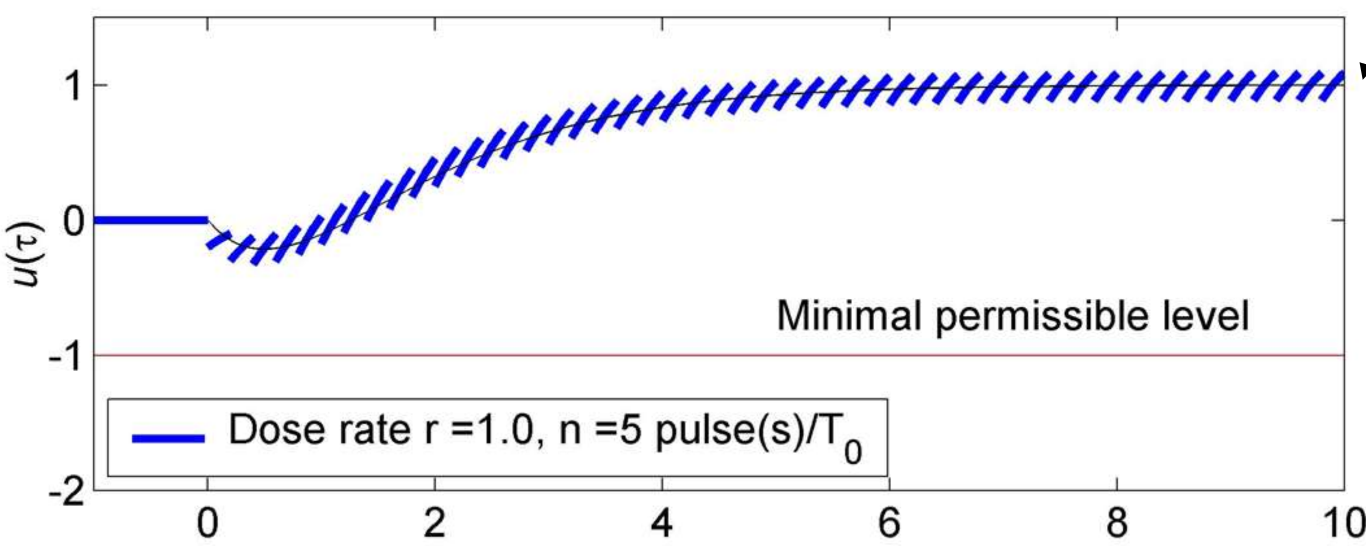
5 cGy
every 3 days

Effect of dose fractionation



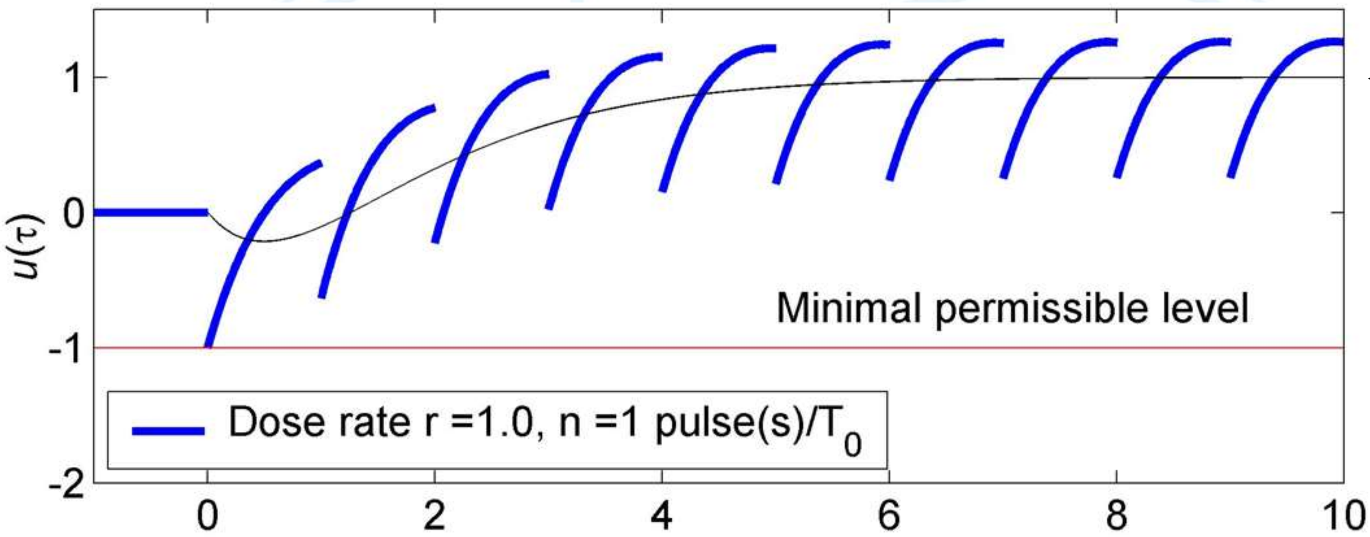
The same limit

$\tau \to \infty$



$u_\infty = r$?

Continuous irradiation limit



Continuous irradiation

Continuous irradiation:

$$\begin{cases} \dot{u}(\tau) = -r - u(\tau) + v(\tau) \\ \dot{v}(\tau) = \beta \times r - v(\tau) \end{cases}$$

Three parameters:

- Time scale $\mathbf{T_0}$
- Damage threshold
- Response β

Existing math model

$$\frac{dx_1}{dt} = Bx_1 - \gamma x_1 - \frac{N}{D_1}x_1\,, \quad (1)$$

$$\frac{dx_2}{dt} = \gamma x_1 - Fx_2 - \frac{N}{D_2}x_2\,, \quad (2)$$

$$\frac{dx_3}{dt} = Fx_2 - \psi x_3 - \frac{\mathrm{N}}{\mathrm{D}_3}x_3\,, \quad (3)$$

$$\frac{dx_4}{dt} = \psi x_3 - \kappa x_4 - \frac{\mathrm{N}}{\mathrm{D}_4}x_4\,, \quad (4)$$

$$\frac{dx_{di}}{dt} = \frac{\mathrm{N}}{D_i}\frac{1}{1+\rho_i}x_i - \nu_1 x_{\mathrm{di}}\,, \quad (5)$$

$$\frac{dx_{hdi}}{dt} = \frac{\mathrm{N}}{D_i}\frac{\rho_i}{1+\rho_i}x_i - \nu_2 x_{hdi},\ i = 1, \ldots, n\,, \quad (6)$$

× 4

$$\frac{dI}{dt} = G\sum_{i=1}^{m}[\theta_i(x_i + \Phi x_{di} + \Gamma x_{hdi})] - HI\,. \quad (7)$$

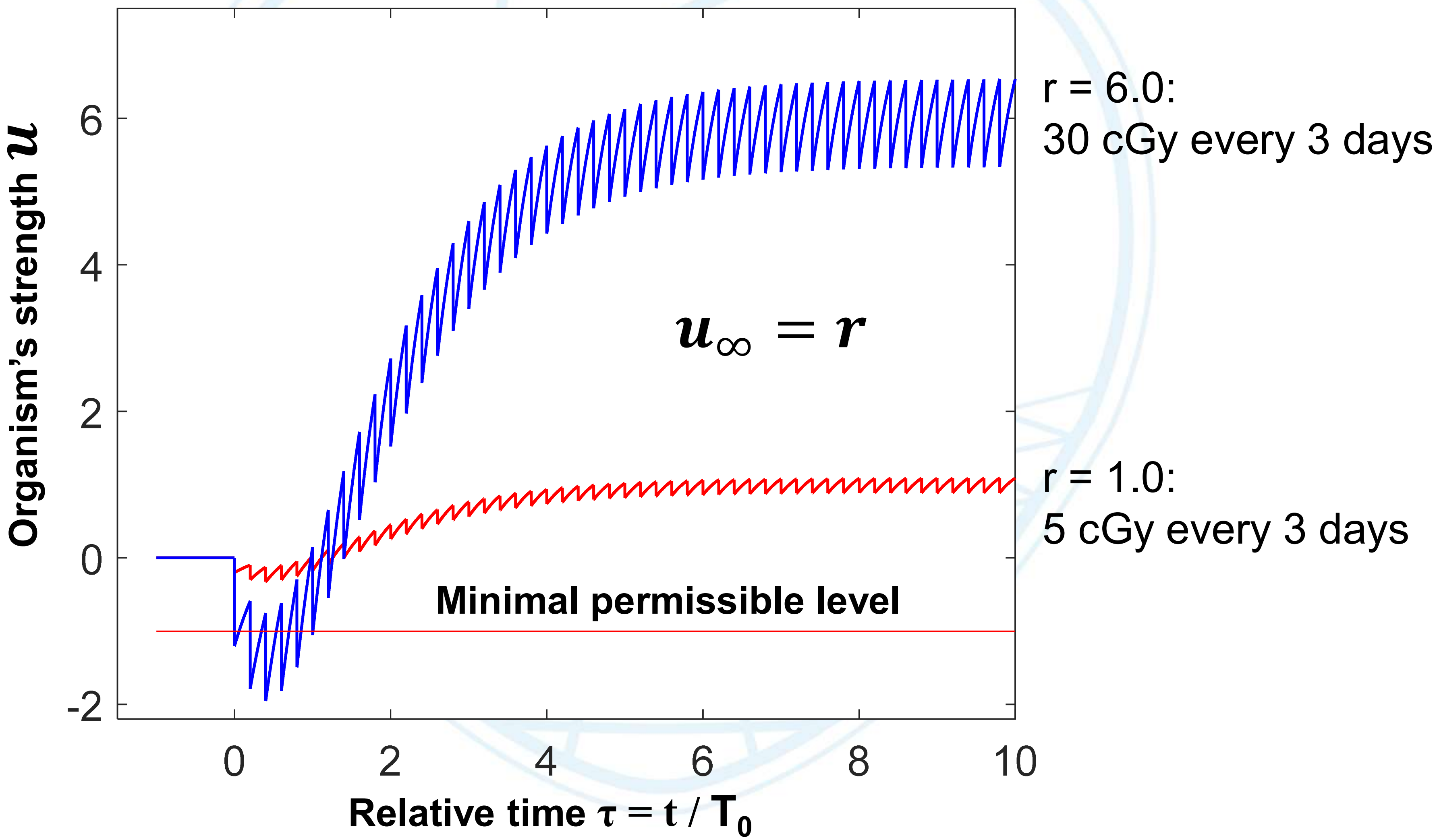
Smirnova OA, Yonezawa M

RADIOPROTECTION EFFECT OF LOW LEVEL PREIRRADIATION ON MAMMALS: MODELING AND EXPERIMENTAL INVESTIGATIONS

Health Phys. 85(2):150–158; 2003

13 differential equations
about 50 parameters

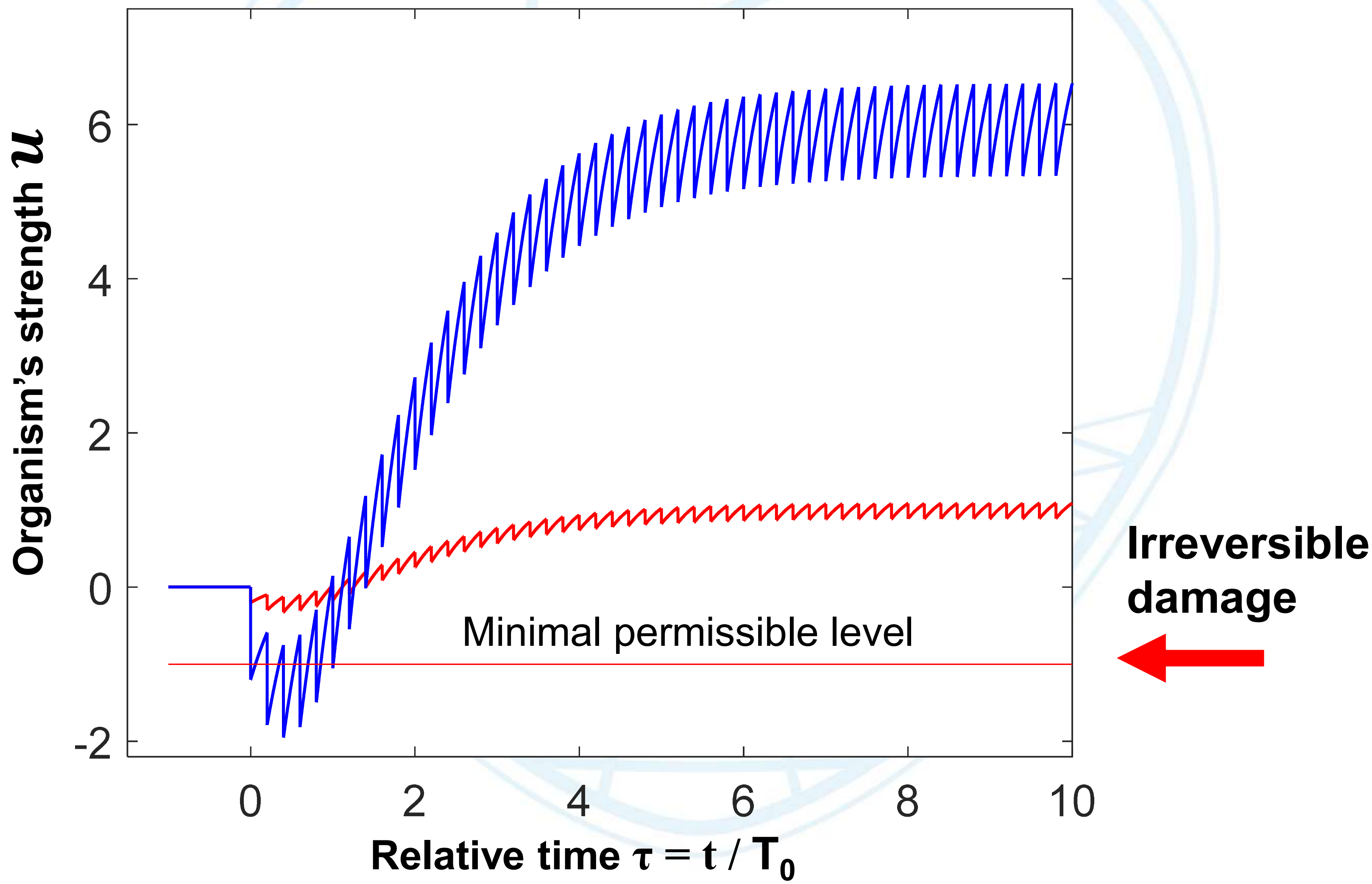
Effect of dose rate
hypothesized doses and times



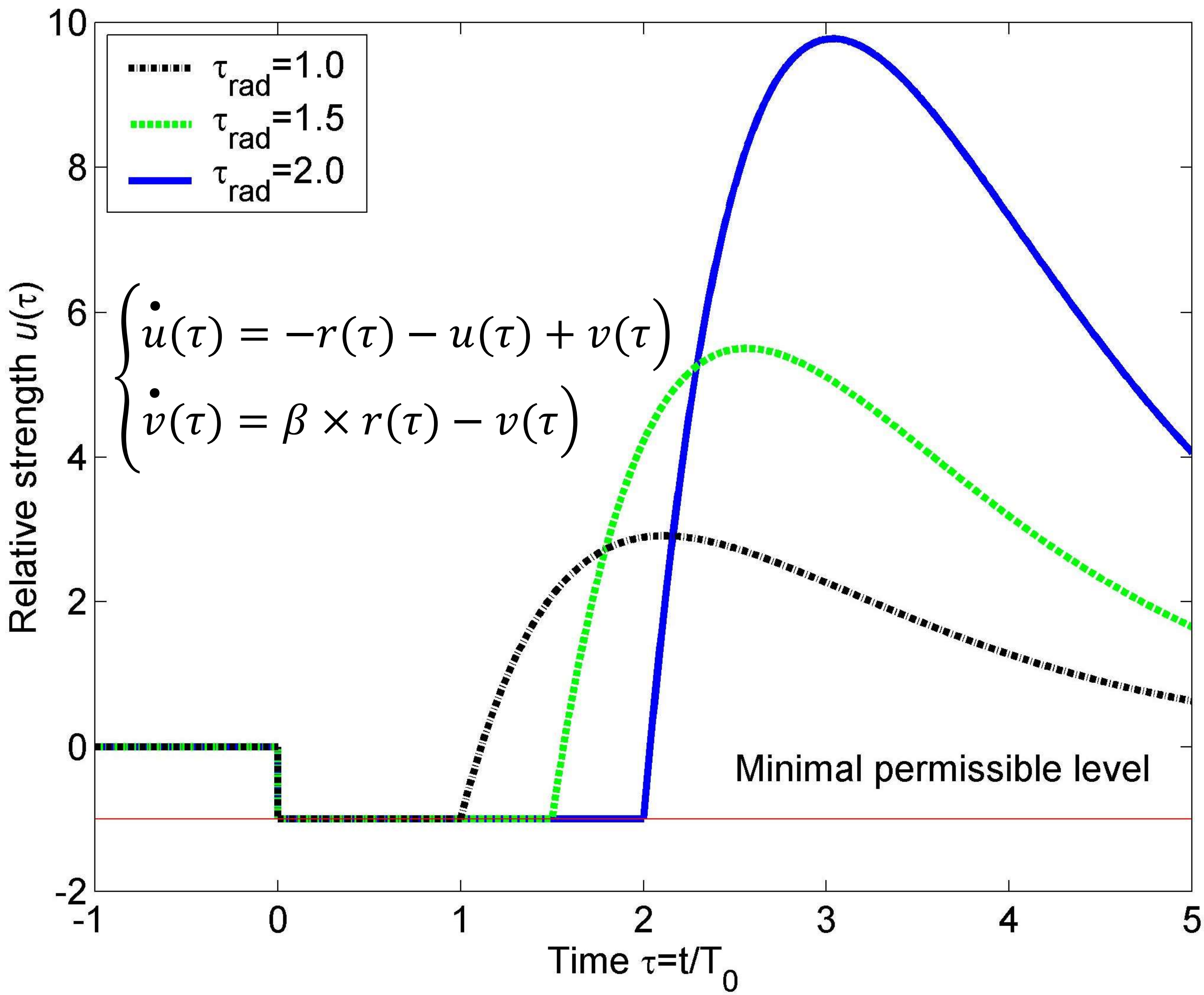
Adaptive response and radiation therapy (RT)

- RT side effects are important
- Dose fractionation is commonly used to mitigate the side effects; however, no kind of training has been reported
- By whole-body irradiation we hope to increase radiation resistance of the body, but NOT of the tumor

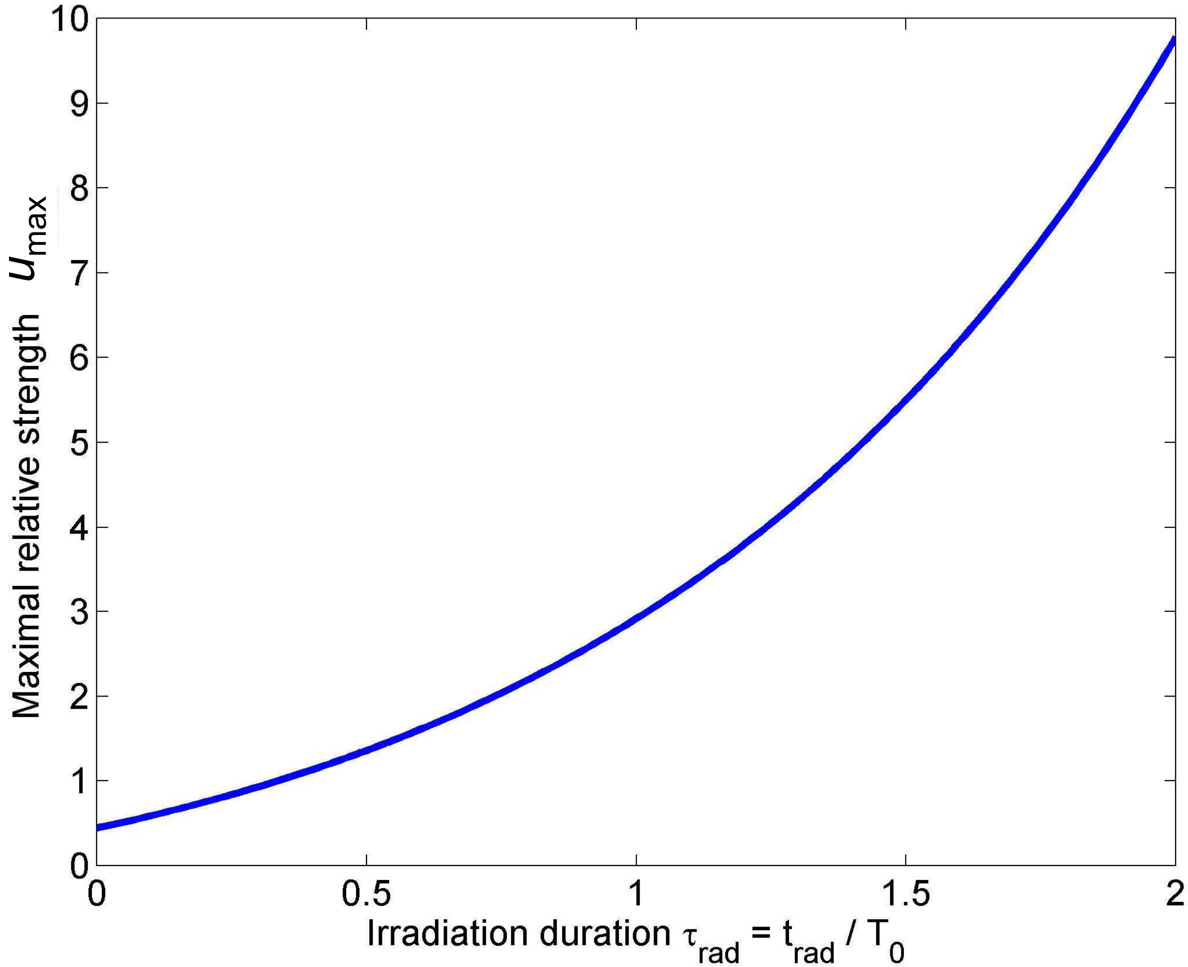
How to achieve high value of *u* **without crossing** the "red line" of irreversible damage?



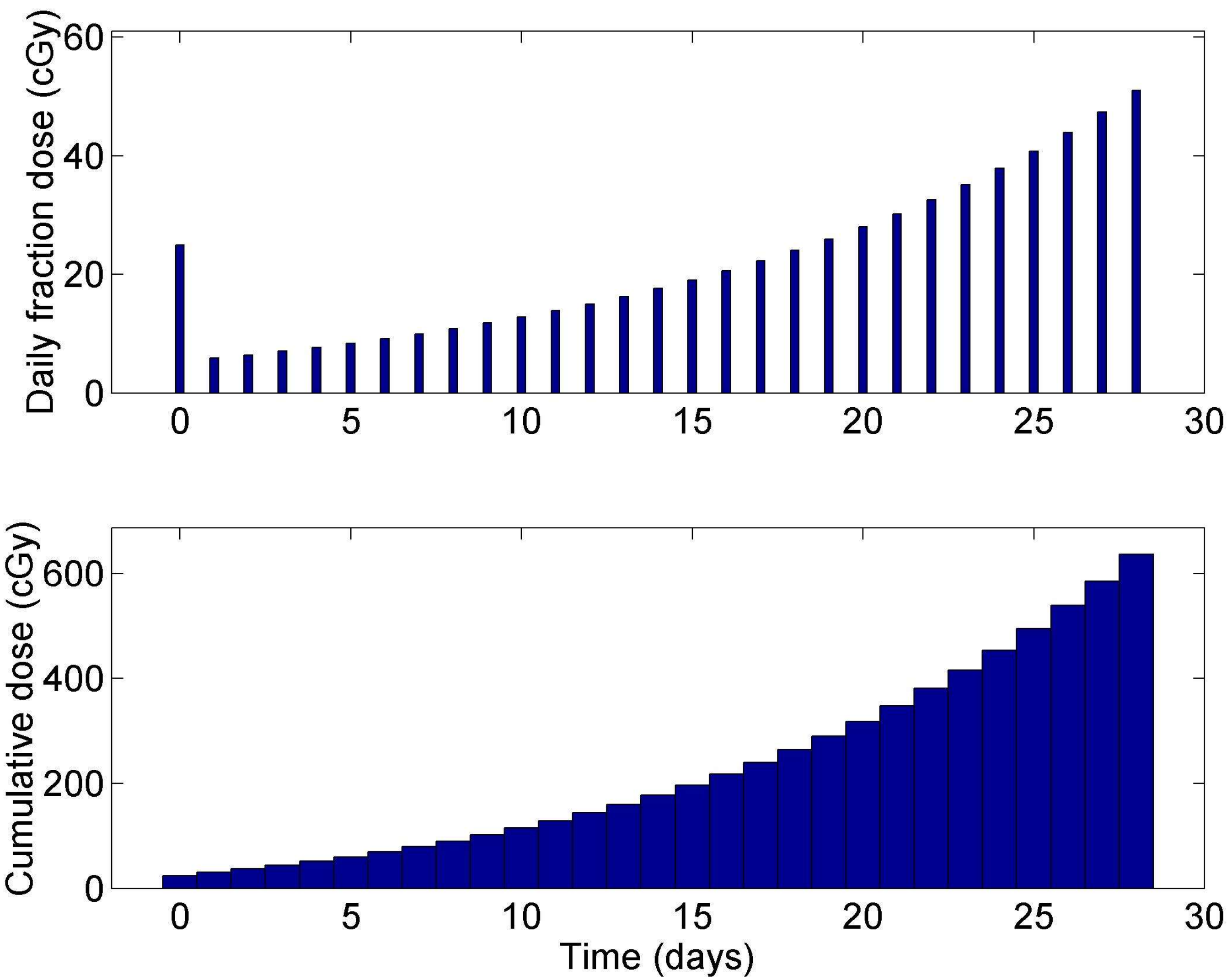
– to increase radiation rate *r* while *u* = –1!



u_{max} vs. irradiation duration τ_{rad}



Radiation training



Assumptions:
T_0 = 2 weeks
u= –1: 25 cGy

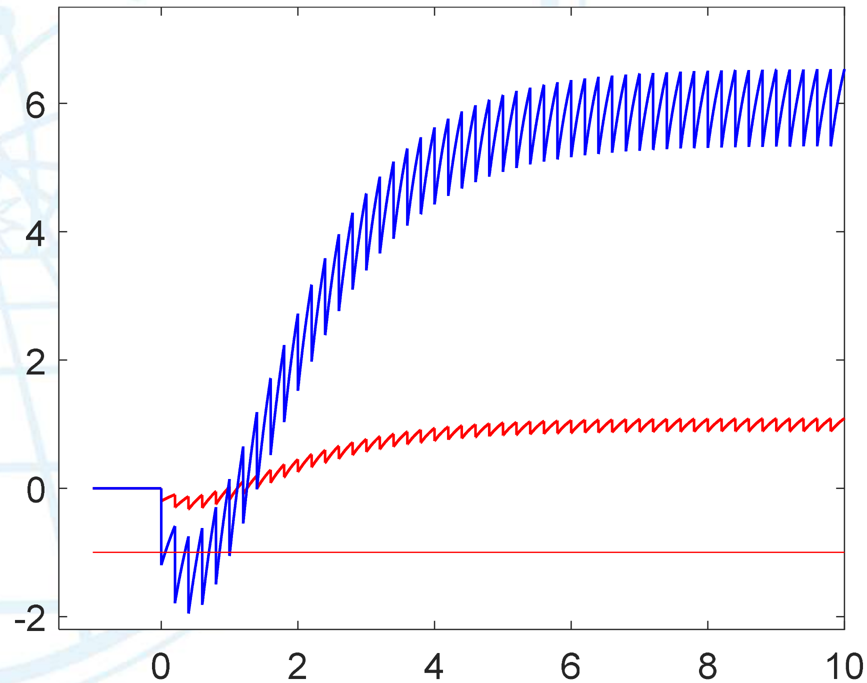
Problems with the model

- No limit for maximal achievable effect
- Too high value of tolerance dose rate

$r \approx 5$

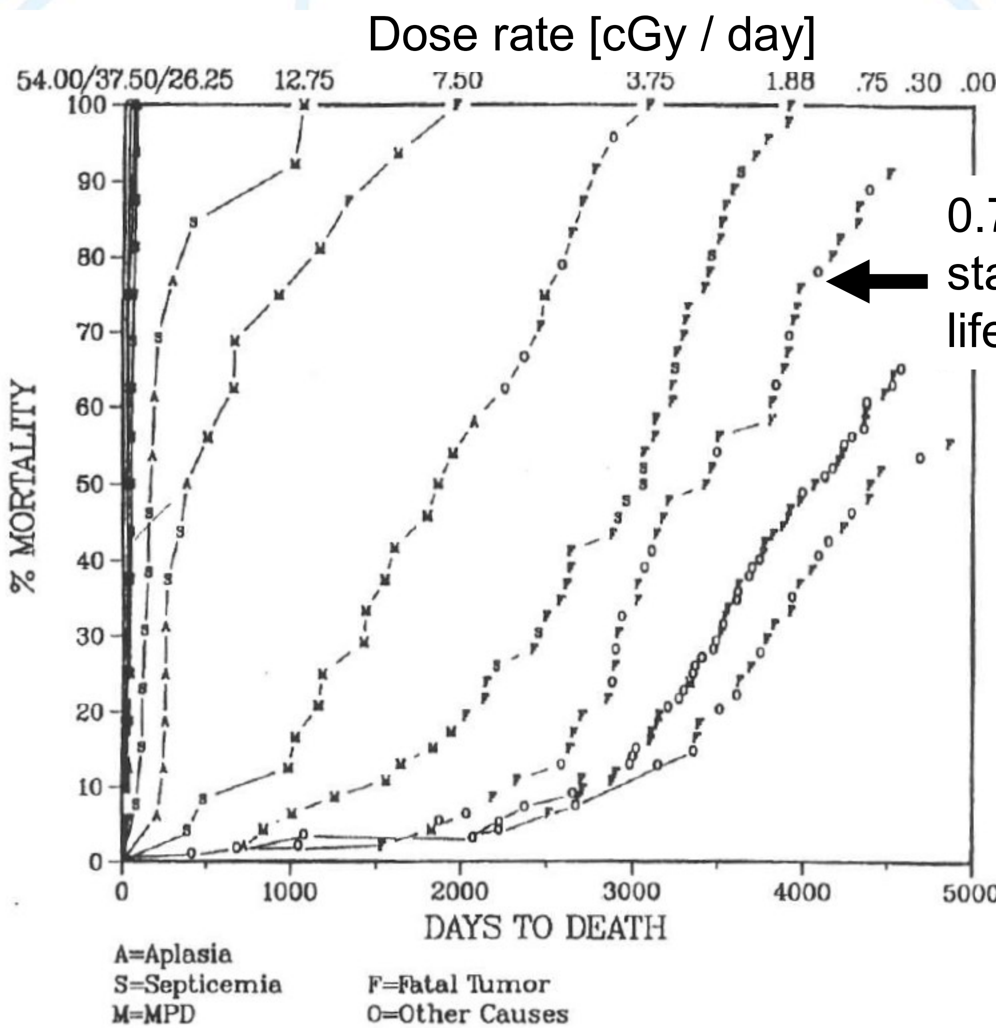
$5 \times 25 = 125$ cGy

$125 / 14 \approx 9$ cGy/day



Tolerance dose-rate: dogs' mortality

Fritz (2002)
Brit J Radiol suppl



0.75 cGy / day: statistically significant life shortening

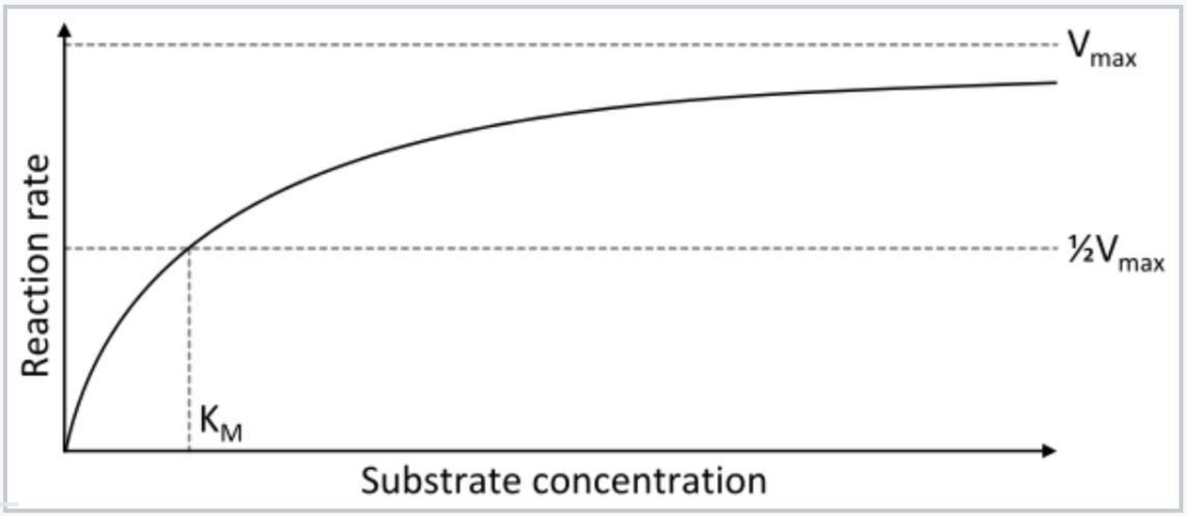
LD50:
Dog 250 cGy
Man 400 cGy

9 cGy/day – too high

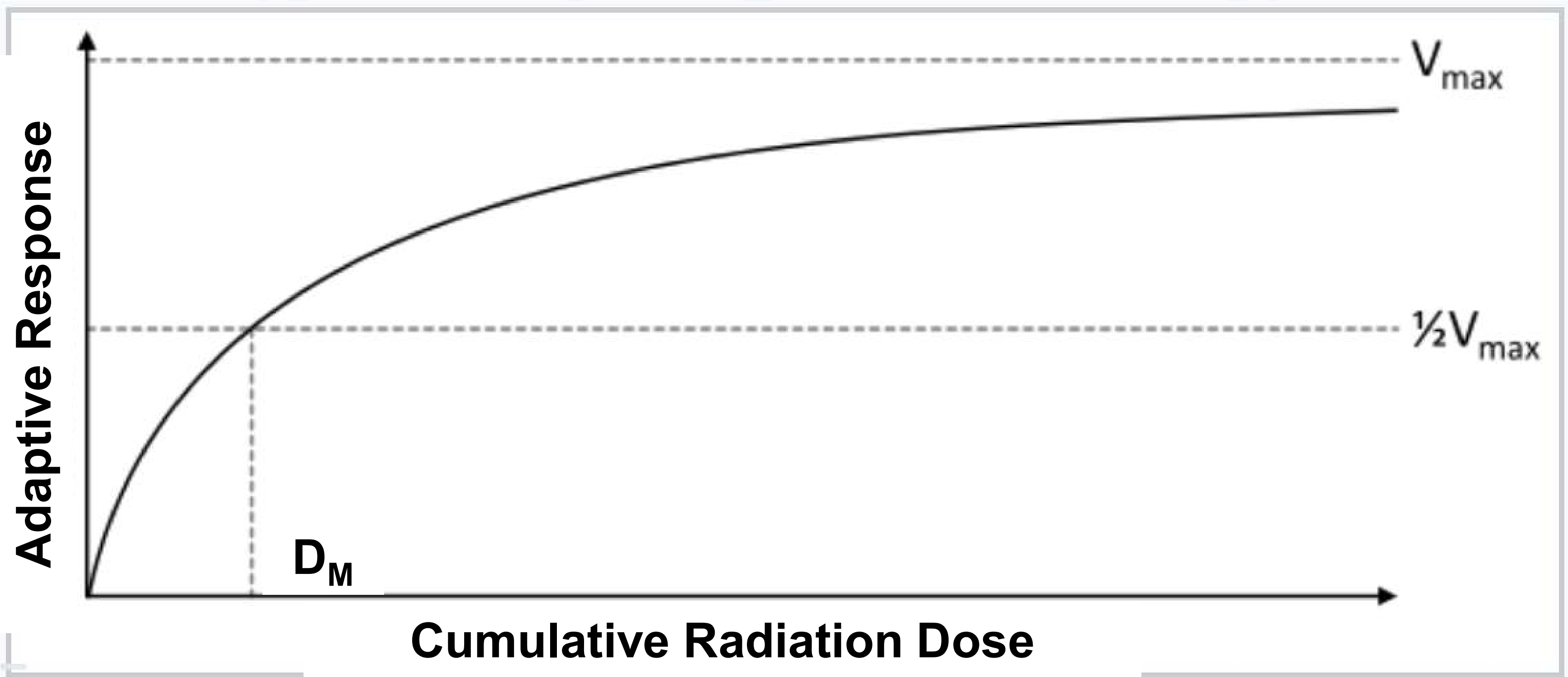
Nonlinear response

- Monod equation: microbial growth
- Michaelis–Menten equation:
  enzyme kinetics

$$v = \frac{d[P]}{dt} = \frac{V_{max}[S]}{K_M + [S]}$$

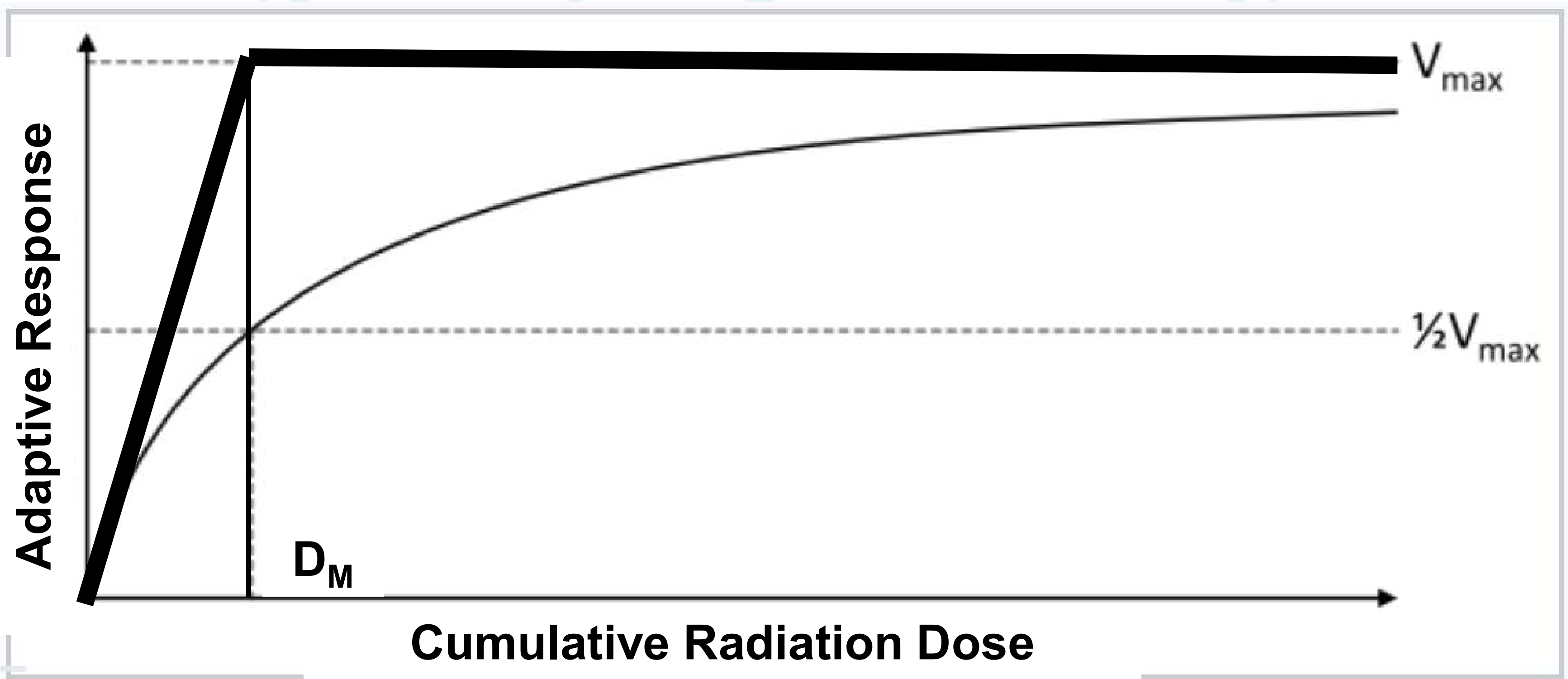


Hypothesis:



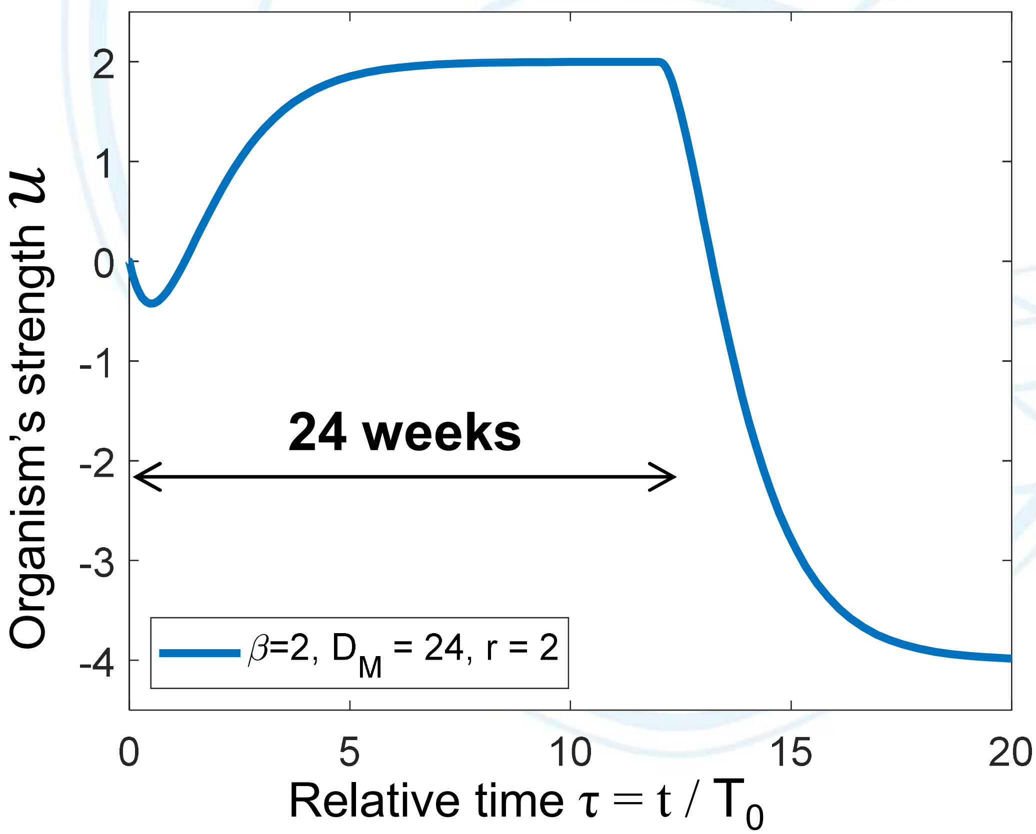
Adaptive Response
Vmax
½Vmax
DM
Cumulative Radiation Dose

Approximation:



Analytical result

$$\begin{cases} \dot{u}(\tau) = -r(\tau) - u(\tau) + v(\tau) \\ \dot{v}(\tau) = \begin{cases} \beta \times r(\tau) - v(\tau), & \tau \le \mathrm{D_M} \\ -r(\tau) - v(\tau), & \tau > \mathrm{D_M} \end{cases} \end{cases}$$



D_M = 600 cGy
***r* = 25 cGy/week**

Pro and contra

- Pro
  - analytical tool, one parameter added (D_M)
  - logical result for radiation training efficiency limit
  - no change for results with total dose below D_M
- Contra
  - crude biological model
  - crude math approximation
  - no explanation for tolerance dose rate

Future directions

- Introduce smooth Monod-like response
- Add parameter to connect tolerance dose (acute) with tolerance dose rate

- Tune the model based on future data

  Experimentalists, please!!!

Conclusions

- Rather simple math model for adaptive response developed
- Practical ideas for “radiation training” in radiation therapy
- Experimental data are urgently needed!

Thank you!