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

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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:

![Graph showing the relationship between time and organism's strength after irradiation.](Image)
Hypothesis: critical damping

\[ \ddot{u}(\tau) + 2\dot{u}(\tau) + u(\tau) = 0 \]

\[ u(\tau) = u_0 \exp(-\tau) + v_0 \tau \exp(-\tau) \]
Data: rats, 400 R

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

Hulse (1963) Brit. J. Haemat. 9, 365-375
Numbers of early normoblasts (●) and pronormoblasts (○), and their standard errors, in the marrow.

Hulse (1963) *Brit. J. Haemat.* 9, 365-375
Data: mice survival after pre-irradiation

Priming dose: 45 cGy
Challenging dose: 675 cGy
LD50: 845 cGy (C57BL/6)

Nunamaker et al., Comp Med 2013

Hypothesis:

Organism’s strength $U$

Relative time $\tau = t / T_0$

IRRADIATION

$25 \text{ cGy}$

$T_0 \approx 2 \text{ weeks}$

Minimal permissible level

Irreversible damage occurs
Assumption #2: second pulse

The same change in
- strength
- its initial slope

Relative time $\tau = \frac{t}{T_0}$
Pulse train

Organism's strength $\mathcal{U}$

Relative time $\tau = t / T_0$

$\Delta \tau$

$u_0$

$r = \frac{|u_0|}{\Delta \tau}$ average dose rate

$\mathcal{U}$

mass

damper

spring

$\mathcal{L}$

Low-dose PTBR symposium, Kielce
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

Dose rate $r = 1.0$, $n = 1$ pulse(s)/$T_0$

Dose rate $r = 1.0$, $n = 5$ pulse(s)/$T_0$
Effect of dose fractionation

The same limit \( \tau \rightarrow \infty \)

\( u_\infty = r \)?
Continuous irradiation limit

Continuous irradiation:
\[
\begin{align*}
    u(\tau) &= -r - u(\tau) + v(\tau) \\
    v(\tau) &= \beta \times r - v(\tau)
\end{align*}
\]

Three parameters:
- Time scale $T_0$
- Damage threshold
- Response $\beta$
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

\[ u_\infty = r \]

- For \( r = 1.0 \):
  - 5 cGy every 3 days
- For \( r = 6.0 \):
  - 30 cGy every 3 days
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?

Organism's strength $U$

Relative time $\tau = \frac{t}{T_0}$

Minimal permissible level

Irreversible damage
– to increase radiation rate $r$ while $u = -1$!
$u_{\text{max}}$ vs. irradiation duration $\tau_{\text{rad}}$
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

\[ r \approx 5 \]
\[ 5 \times 25 = 125 \text{ cGy} \]
\[ 125 / 14 \approx 9 \text{ cGy/day} \]
Tolerance dose-rate: dogs’ mortality

Dose rate [cGy / day]

0.75 cGy / day: statistically significant life shortening

LD50:
Dog 250 cGy
Man 400 cGy

9 cGy/day – too high

Fritz (2002)
Brit J Radiol suppl
Nonlinear response

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

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

![Graph showing cumulative radiation dose vs. adaptive response.](image)

- Adaptive Response
- Cumulative Radiation Dose
- $D_M$
- $V_{max}$
- $\frac{1}{2}V_{max}$
Approximation:

![Graph showing cumulative radiation dose and adaptive response.](image)
Analytical result

\[
\begin{align*}
\dot{u}(\tau) &= -r(\tau) - u(\tau) + v(\tau) \\
\dot{v}(\tau) &= \begin{cases} 
\beta \times r(\tau) - v(\tau), & \tau \leq D_M \\
-r(\tau) - v(\tau), & \tau > D_M
\end{cases}
\end{align*}
\]

$D_M = 600 \text{ cGy}$

$r = 25 \text{ cGy/week}$

Organism’s strength $u$

Relative time $\tau = t / T_0$

24 weeks
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!