The Monte Carlo simulation of the adaptive response effect in irradiated cells

Krzysztof Wojciech Fornalski, Paweł Wysocki

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Agenda

- The biophysical Monte Carlo model of the cell colony
- The novel mathematical description of the adaptive response effect
- How it works in practice?
- Conclusions

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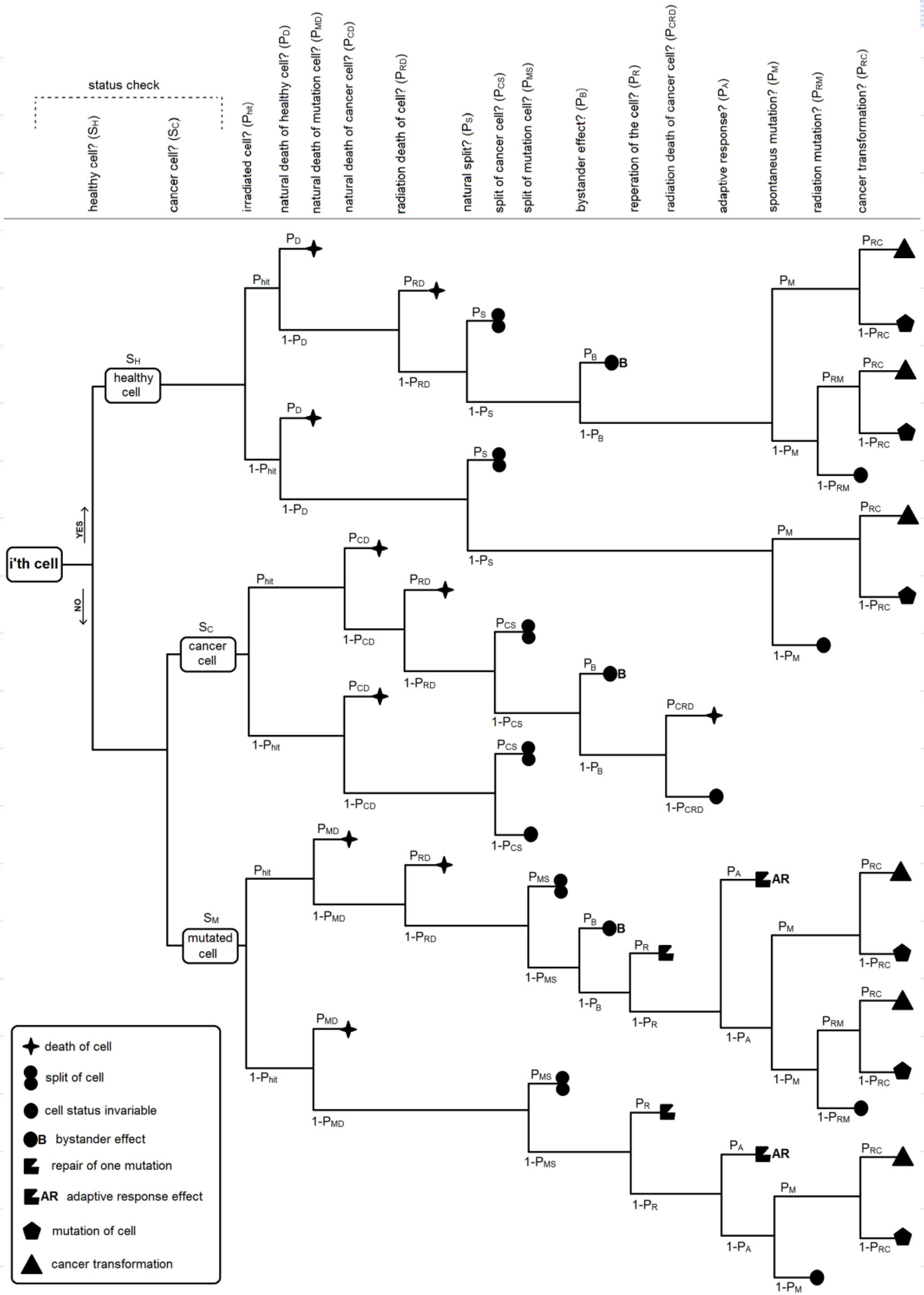
Main problems to solve

- To simulate the behaviour of a group of irradiated cells treated as a physical complex system
  - The group of cells = black box → to check the complex reaction to irradiation
- Implementation of the bystander effect and adaptive response phenomena
- Create a user-friendly software

Methods

- Monte Carlo simulation with a tree of probabilities (approx. 40 branches)
- Each branch represents a biophysics of the cell (probability function, PF)
- Variables of PFs: age, dose, no. of damages, status of the cell, other PFs
- Method used in e.g. high energy particle and nucleus physics

Tree of probabilities



Advantages

- Practical tool to „play” with data
- Each PF can be easily modified up to the recent knowledge or just if needed
- One can cut existing branches or add new ones (to obtain more detailed specific effect)
- No need of analytical solution
- Fully stochastic approach (Monte Carlo)

Exemplary probability functions used in the model

- Quasi-linear relationship instead of the linear one (e.g. to apply the concept of cross section from particle and nucleus physics)
  - $P(\xi)=1-e^{-const\cdot\xi}$
- The use of sigmoid function (Avrami equation from solid state physics)
  - $P(\xi)=1-e^{-a\xi^{n}}$

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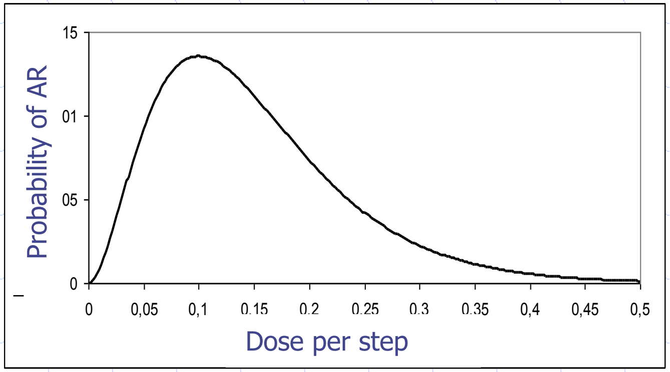
The subject-of-the-day: an adaptive response effect

- Usually, the adaptive response effect is presented as dose- <u>or</u> time-dependent functions:
  - p(D) = $\beta_1 D^{\nu} e^{-\alpha_1 D}$
  - p(t) = $\beta_2 t^{\delta} e^{-\alpha_2 t}$



- Now, the dose- <u>and</u> time-dependent PF can be presented as the joined formula:
  - p(D,t) = $cD^{\nu} t^{\delta} e^{-\alpha_1 D - \alpha_2 t}$

Adaptive response effect
- dose and time dependent function

- The **calculated PF** of the adaptive response:
  - $\mathrm{P(D,t)} = cD^2t^2e^{-\alpha_1 D-\alpha_2 t}$

    for single-pulse irradiation; t=time since irradiation

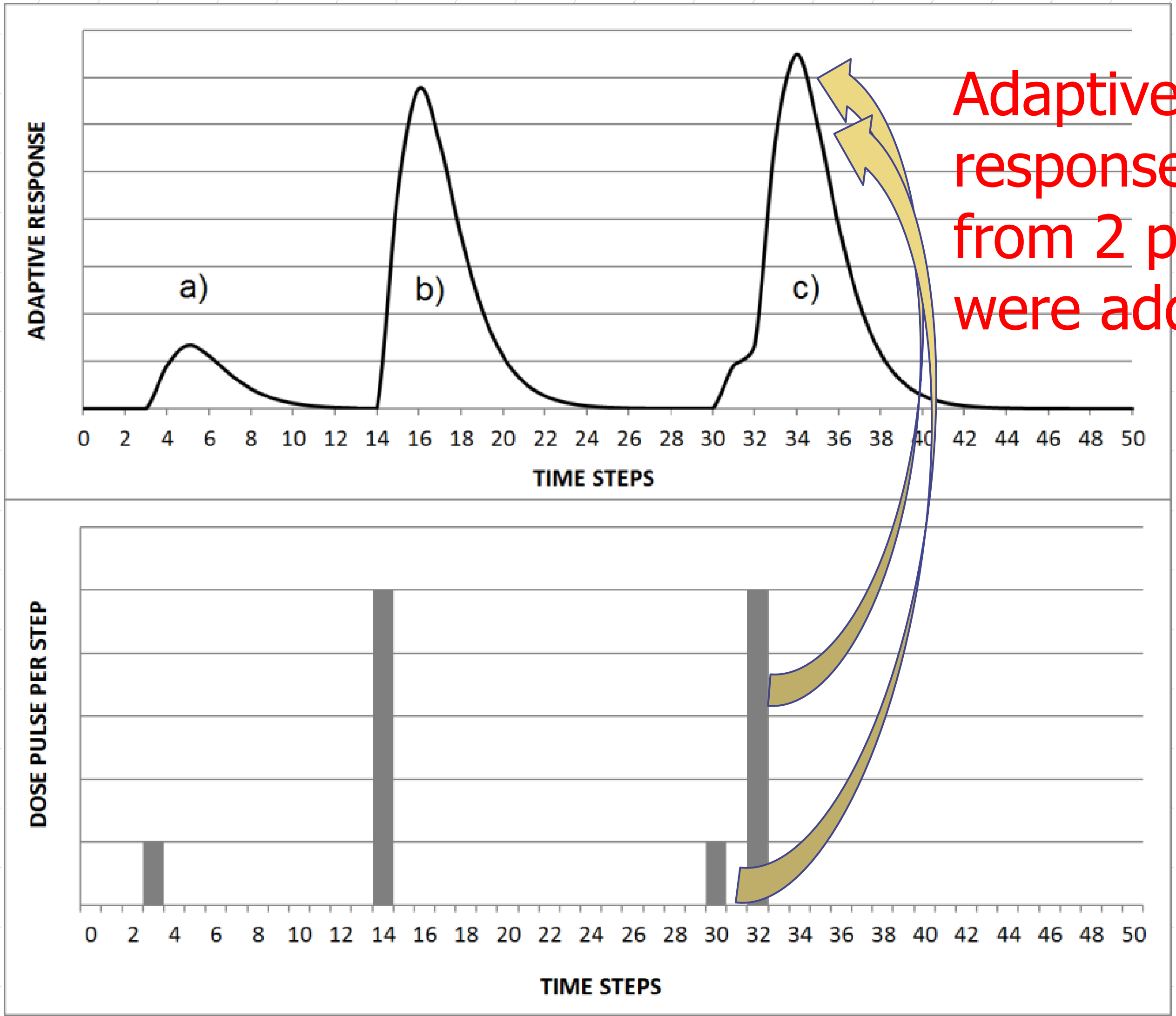
  - $\mathrm{P(D,K)} = c\sum_{k=0}^{K} D_k^2 (K-k)^2\ e^{-\alpha_1 D_k-\alpha_2 (K-k)}$

    for multi-irradiation (discrete formula); K=time step

  - $\mathrm{P(D,T)} = c\int_{t=0}^{T} \dot{D}^2(T)\ (T-t)^2\ e^{-\alpha_1 \dot{D}(T)-\alpha_2 (T-t)}\ dT$

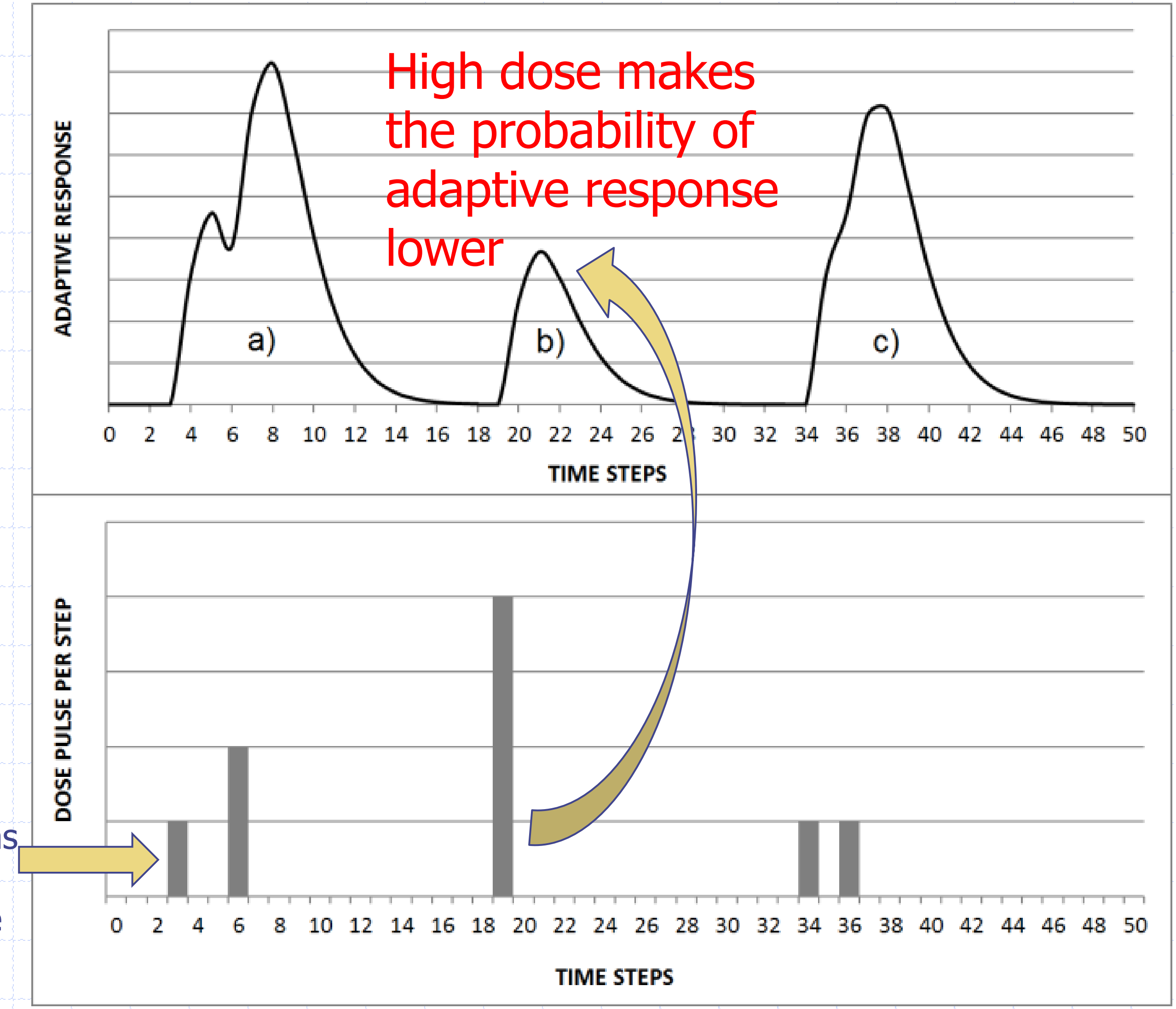
    for multi-irradiation (continuous formula); T=time (age)

Adaptive response PF



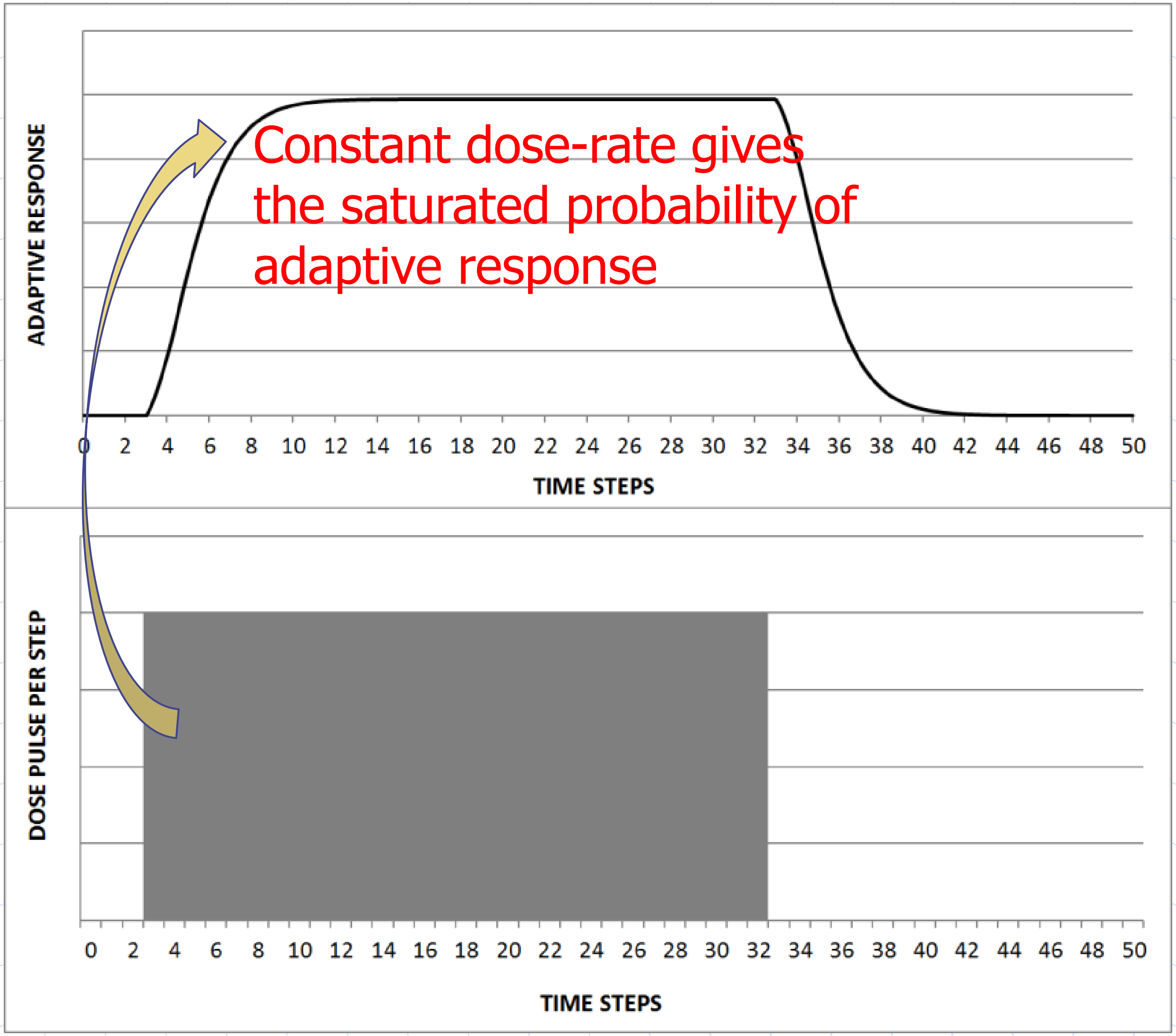
Adaptive response signals from 2 pulses were added up

Adaptive response PF

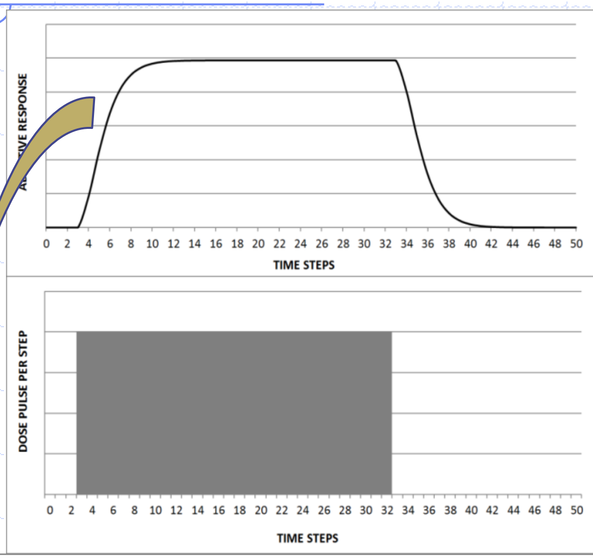


This small dose-pile is the same as the big one from the previous slide

Adaptive response PF



Constant dose-rate

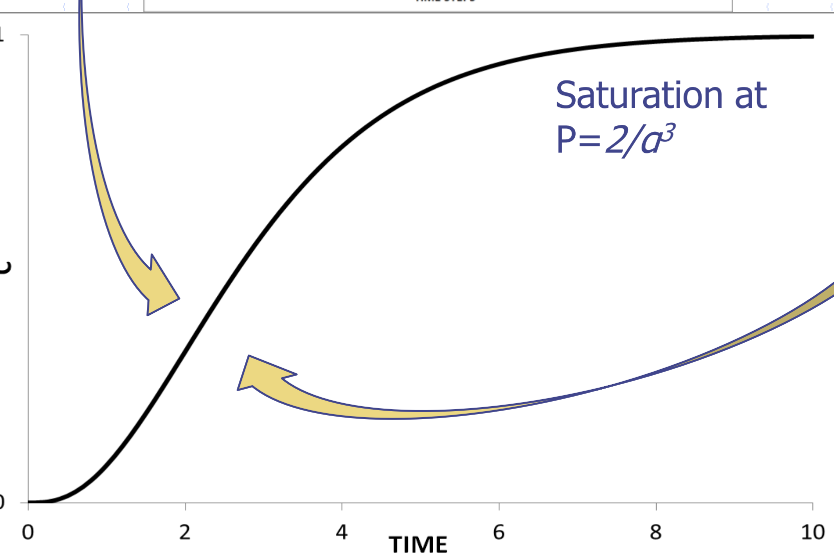


This finding can be also obtained analytically from the continuous PF of adaptive response when one assumes the constant dose-rate, which results in the simplification:

$$\mathrm{P(D,T)}=\tilde{c}\int_{t=0}^{T} (T-t)^2\ e^{-\alpha(T-t)}\,dT$$

Thus, the analytical solution can be presented as:

$$P(T)=\frac{2}{\alpha^3}\left[1-e^{-\alpha T}-(0.5\alpha^2T^2+\alpha T)e^{-\alpha T}\right]$$



see: *Dobrzyński L., Fornalski K.W., Socol Y., Reszczyńska J.M. 'Modeling of irradiated cell transformation: dose- and time-dependent effects'. Radiation Research, Vol. 186, 2016*

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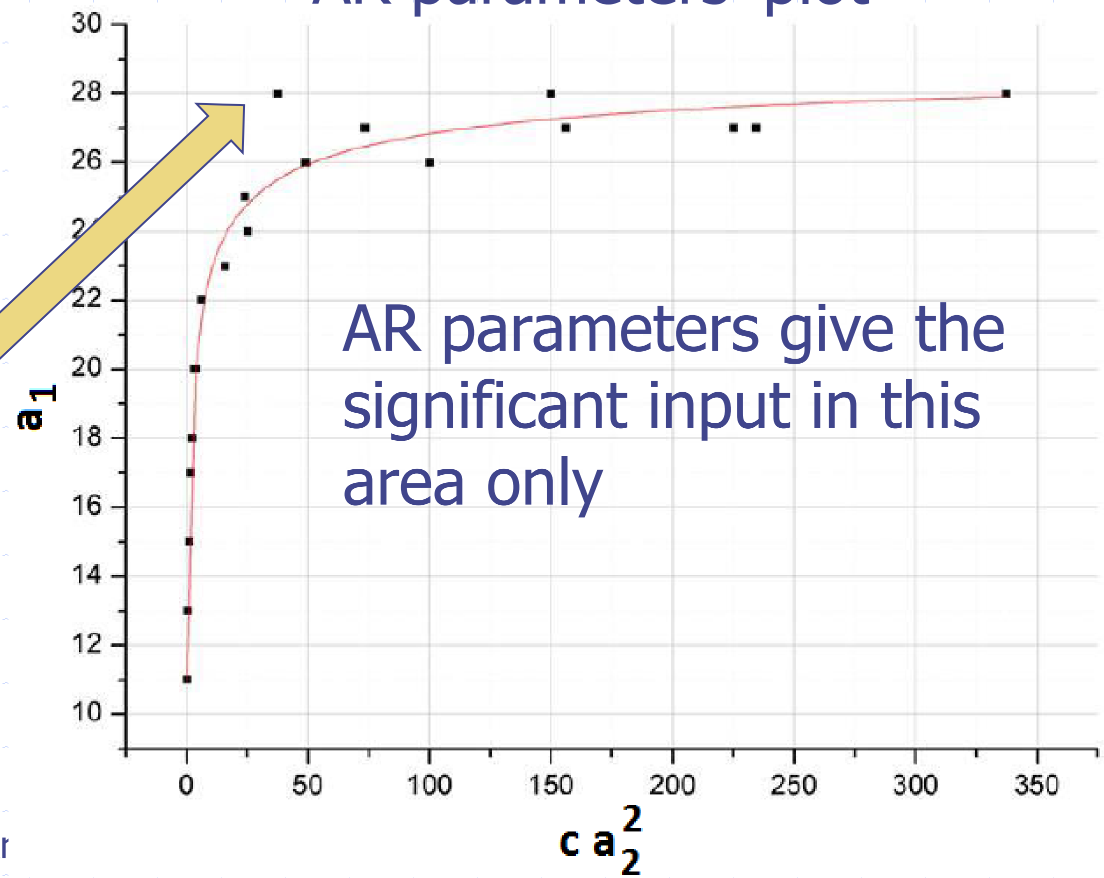
How to use the adaptive response probability function?

- Check for which parameters the adaptive response (AR) signal gives a significant reply

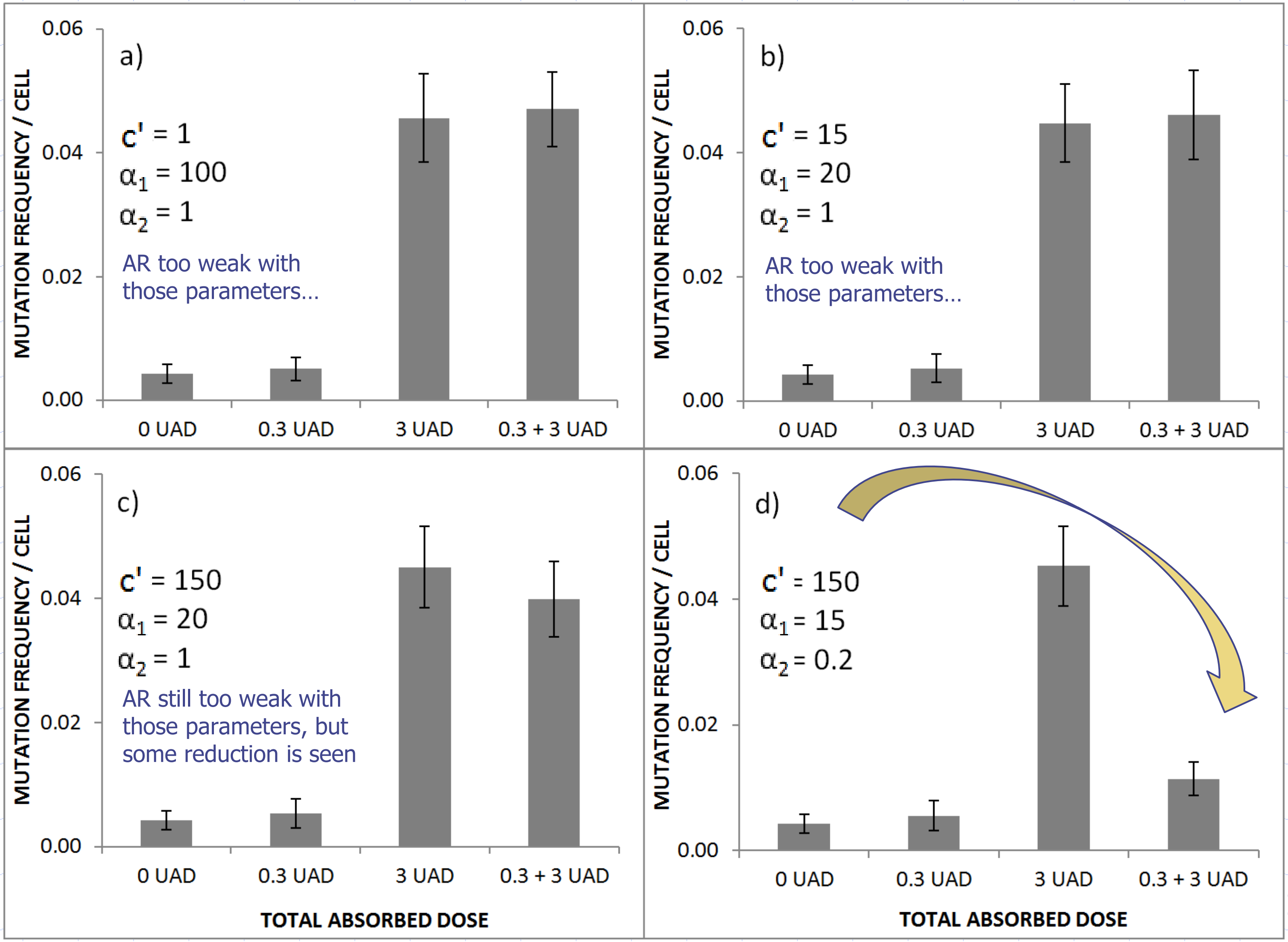
AR parameters' plot



AR parameters give the significant input in this area only

Parameters taken from this region give the insignificant AR effect

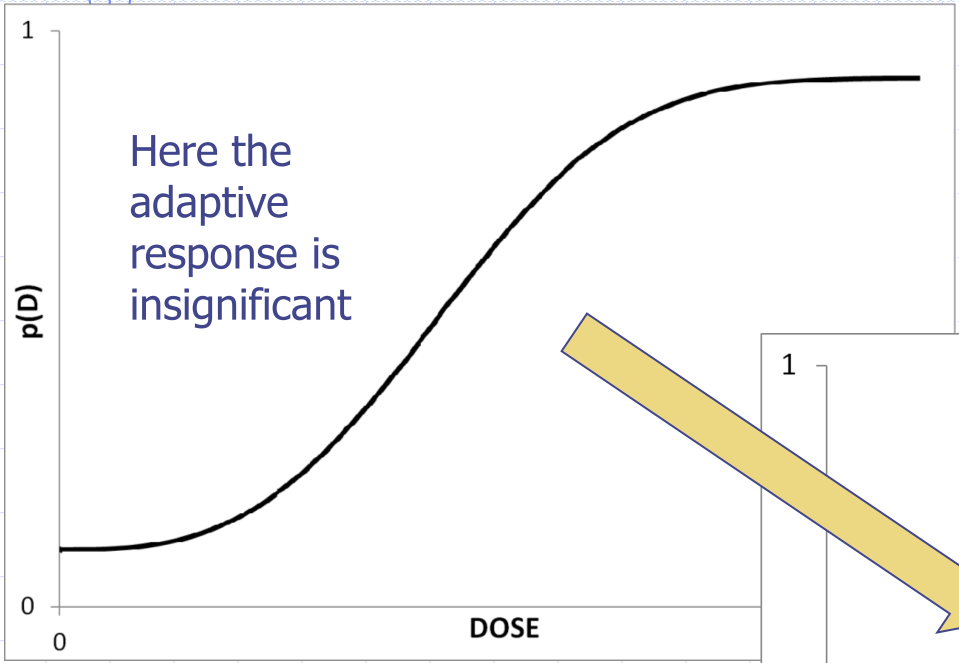
Priming dose effect



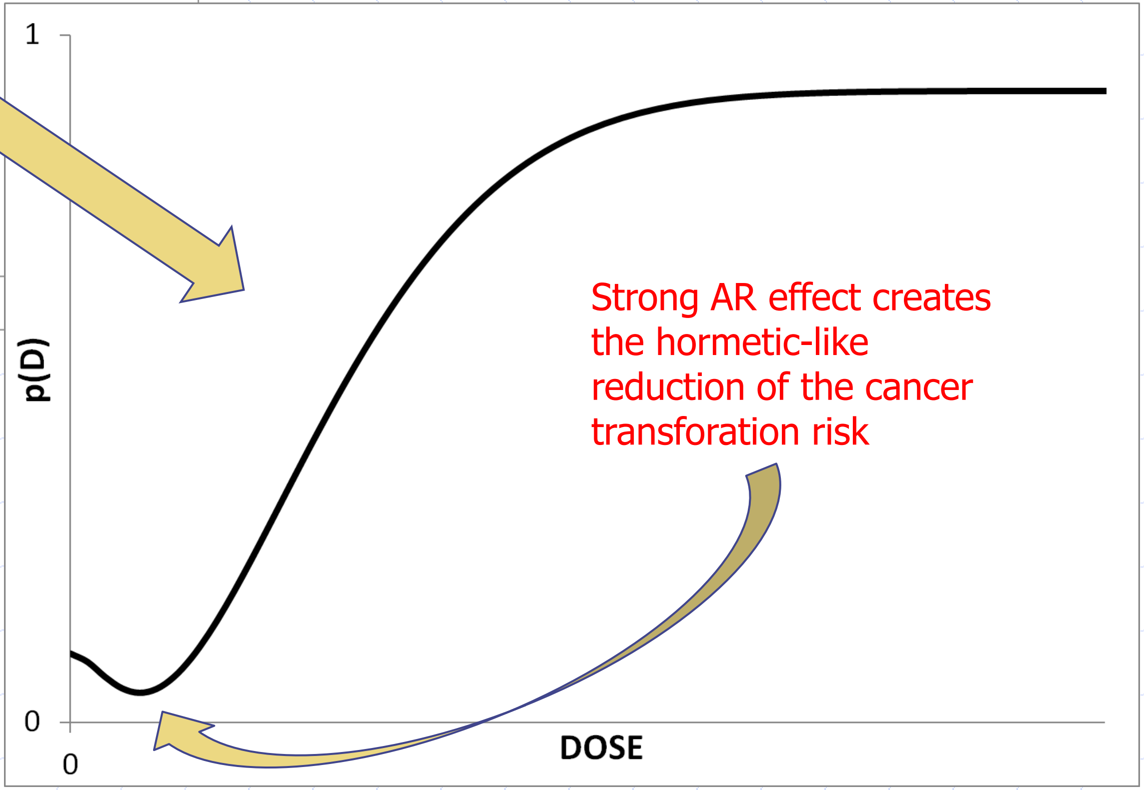
Significant adaptive response causes significant priming dose effect

UAD = Unit of Absorbed Dose

Probability of cancer transformation of a single cell

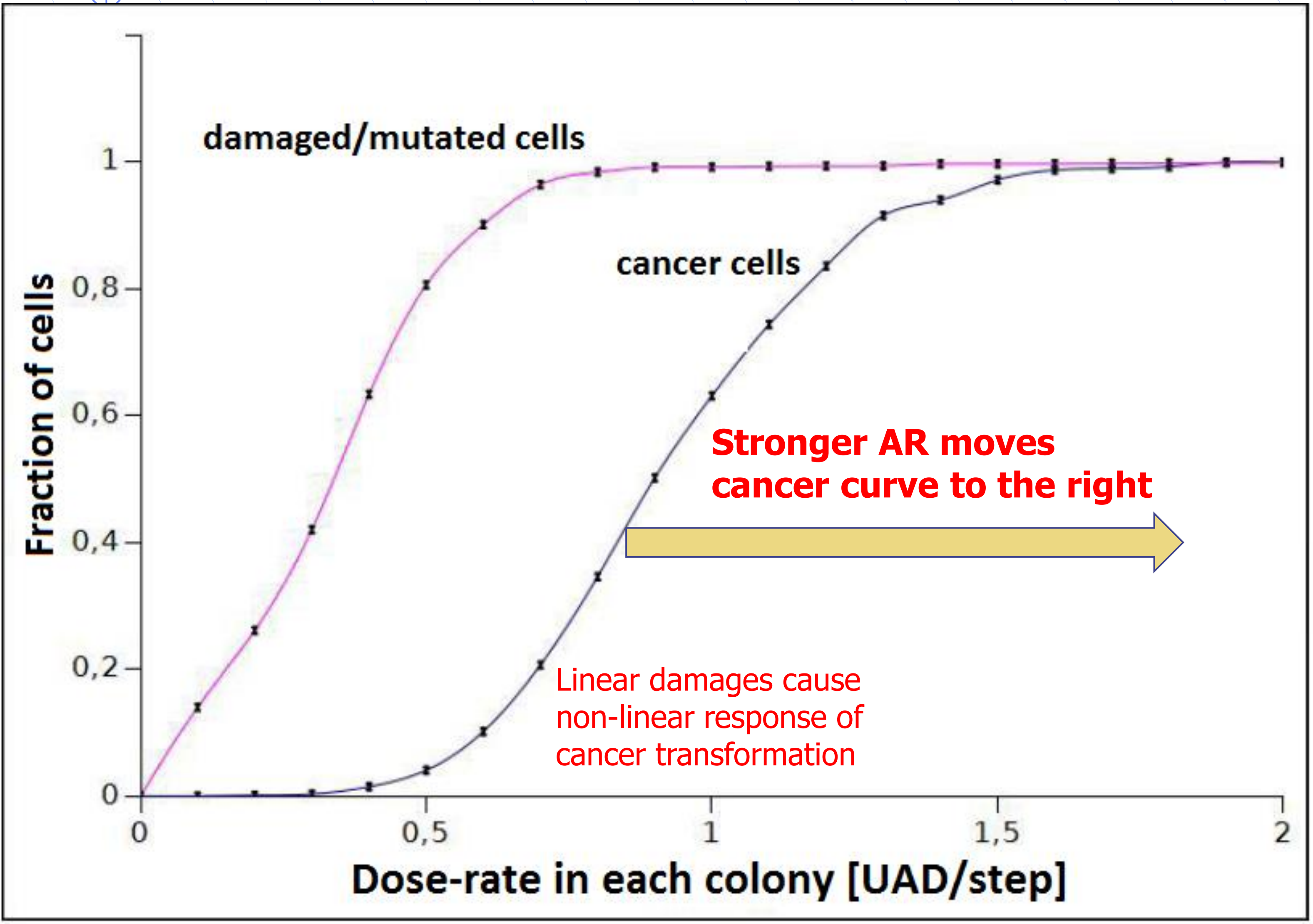


The model allows to present the risk curve of the cancer transformation of a single cell



The sigmoidal shape changes when adaptive response is strong enough

The fraction of damaged and cancer cells



Each point represents the independent simulation of 700 healthy cells during 300 time steps in constant dose-rate per step (horizontal axis)

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Conclusions

- The presented Monte Carlo stochastic model is the useful tool to simulate the irradiation of cells colony
- The new concept of the dose- and time-dependent probability function of adaptive response gives many interesting findings and works well
- The future development of the model is needed - the actual studies are focused on:
  - AR parameters calibration on the experimental data,
  - implementation of more advanced bystander effect,
  - creation of the user-friendly software,
  - development of the analytical approach to all biophysical solutions used in this model (see today presentation of Reszczyńska et al.)

References

- Fornalski K.W. 'Mechanistic model of the cells irradiation using the stochastic biophysical input'. International Journal of Low Radiation, vol. 9, no. 5/6, 2014, pp. 370-395.
- Dobrzyński L., Fornalski K.W., Socol Y., Reszczyńska J.M. 'Modeling of irradiated cell transformation: dose- and time-dependent effects'. Radiation Research, Vol. 186, 2016, pp. 396–406.
- Fornalski K.W., Dobrzyński L., Reszczyńska J.M. 'Modelling of the radiation carcinogenesis - the analytic and stochastic approaches'. Research Perspectives CRM Barcelona (Springer), in-press, 2016. Proceedings of the LD-RadStats: DoReMi Workshop for Statisticians Interested in Contributing to EU Low Dose Radiation Research. 26-28.10.2015; Barcelona, Spain.
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THANK YOU

krzysztof.fornalski@gmail.com