Biophysical Monte Carlo modelling of irradiated cells

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Agenda

- Scope of work and collaboration
- Basics of the stochastic Monte Carlo modeling of irradiated cells
- Exemplary theoretical solutions
- Results
- Some other activities
  - Deterministic modeling of cancer cells creation and development
  - Bayesian methods in biodosimetry

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Low dose research in Poland

- National Centre for Nuclear Research (NCBJ)
  - Prof. Ludwik Dobrzyński et al.
- Military Institute of Hygiene and Epidemiology (WIHE)
  - Prof. Marek Janiak et al.

Scope of work and collaboration

- In the computational modeling of irradiated cells:
  - Prof. Ludwik Dobrzyński (NCBJ)
  - Ms. Joanna Reszczyńska, PhD student (NCBJ)
  - Dr. Yehoshua Socol (Falcon Analytics, Israel)
  - Dr. Krzysztof Fornalski (PGE)
    - Mr. Paweł Wysocki (WUT)
- In the biodosimetric Bayesian methods:
  - Dr. Maria Kowalska (CLOR)
  - Ms. Iwona Pacyniak, PhD student (CLOR, WUT)
    - Mr. Krzysztof Łukasik (WUT)
  - Dr. Krzysztof Fornalski (PGE)
    - Ms. Aleksandra Powojska (WUT)

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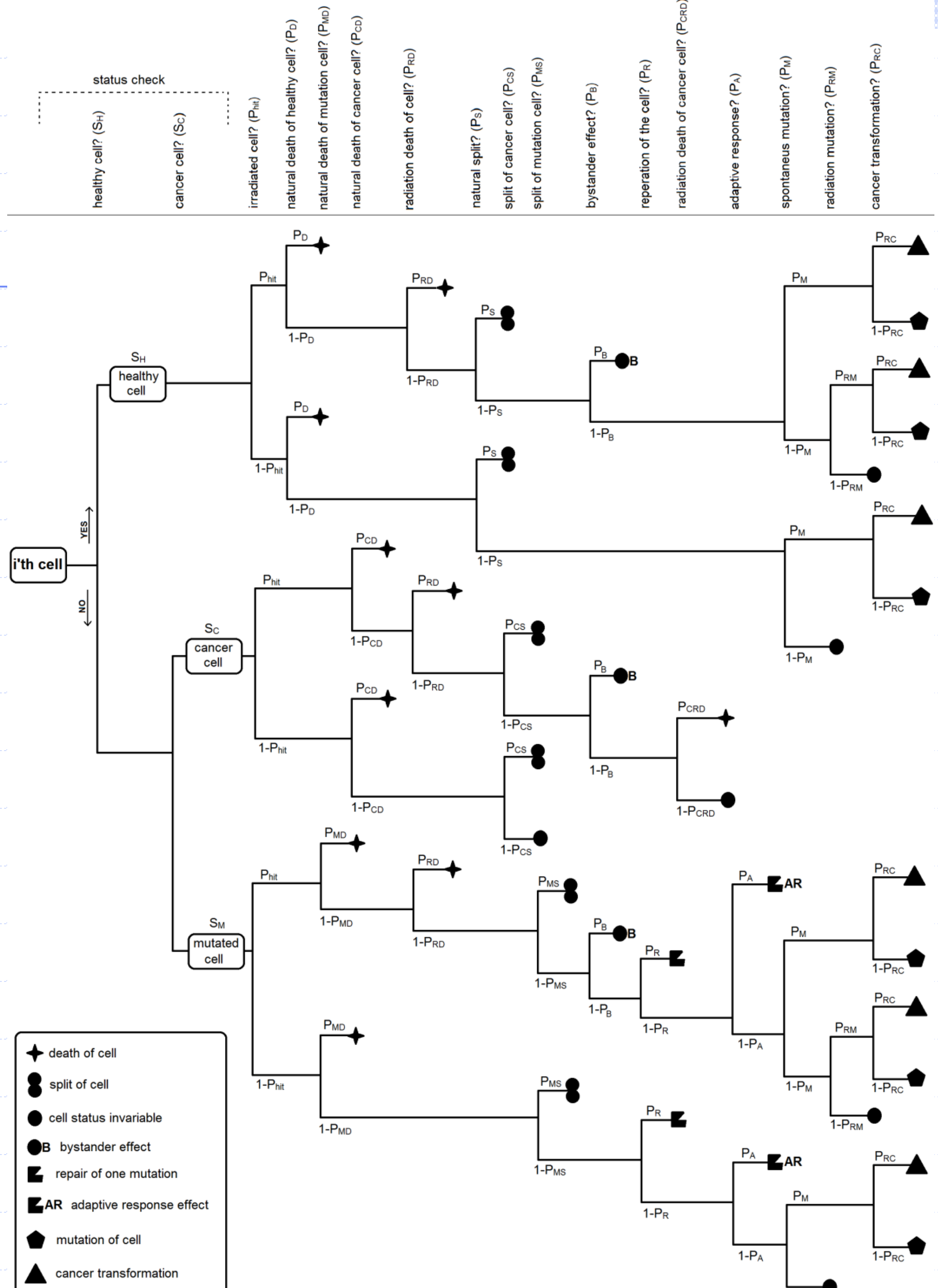
Main problems to solve

- 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 density function)
- Variables of PDFs: age, dose, no. of damages, status of the cell, other PDFs
- Method used in e.g. high energy particle and nucleus physics


status check
healthy cell? (SH)
cancer cell? (SC)
irradiated cell? (Phit)
natural death of healthy cell? (PD)
natural death of mutation cell? (PMD)
natural death of cancer cell? (PCD)
radiation death of cell? (PRD)
natural split? (PS)
split of cancer cell? (PCS)
split of mutation cell? (PMS)
bystander effect? (PB)
reperation of the cell? (PR)
radiation death of cancer cell? (PCRD)
adaptive response? (PA)
spontaneus mutation? (PM)
radiation mutation? (PRM)
cancer transformation? (PRC)
i'th cell
YES
NO
SH
healthy cell
SC
cancer cell
SM
mutated cell
B
AR
death of cell
split of cell
cell status invariable
B bystander effect
repair of one mutation
AR adaptive response effect
mutation of cell
cancer transformation

Advantages

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

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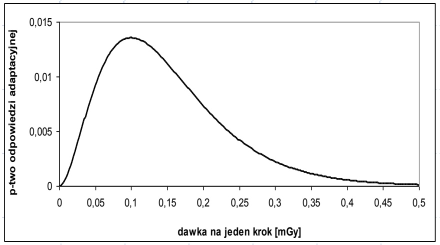
Exemplary probability functions used in the model

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

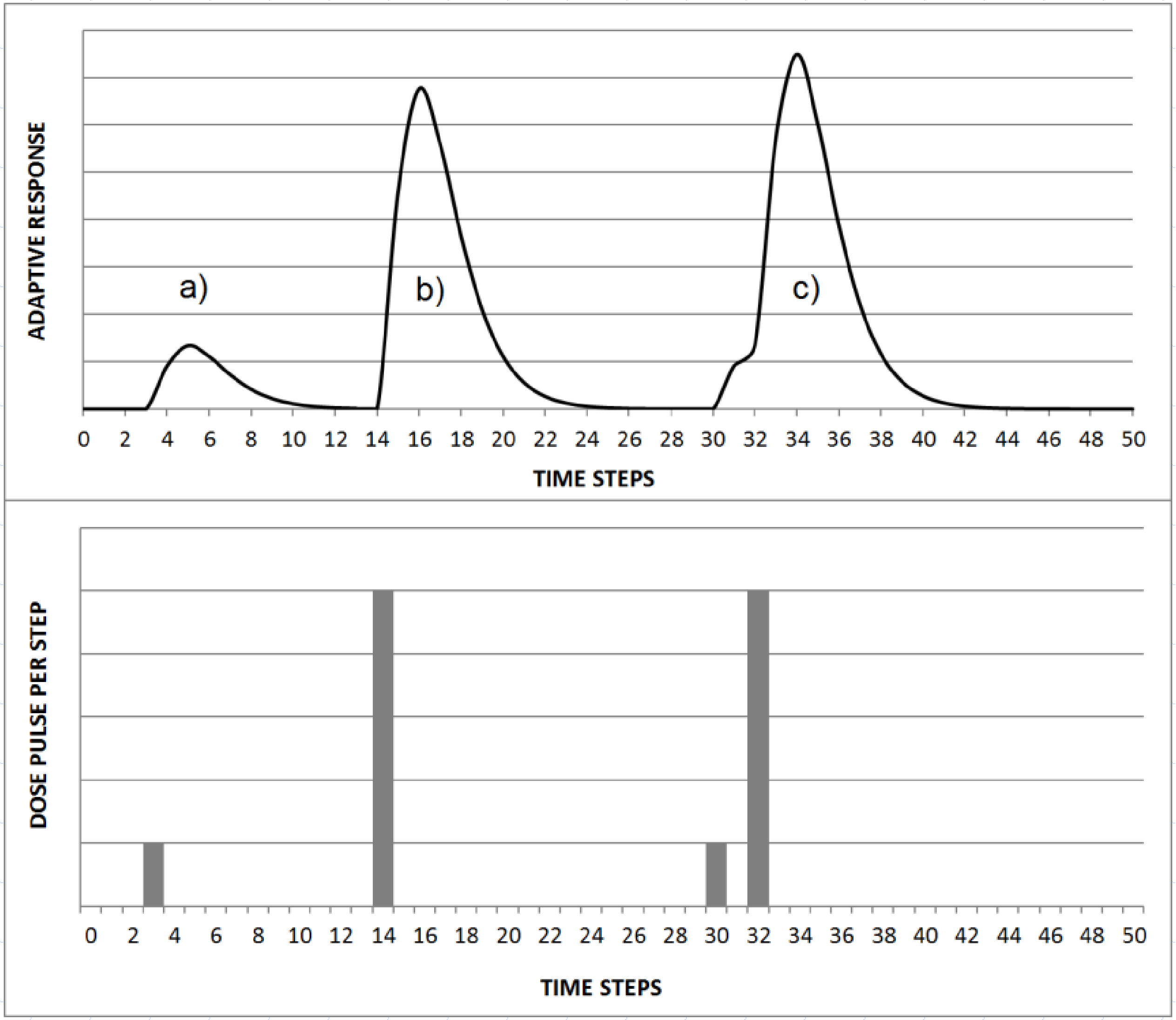
Some interesing findings: an adaptive response effect

- Usually the adaptive response effect is presented as a dose- or time-dependent functions:
  - p(D) = $\alpha_1 D^{\nu} e^{-\alpha_2 D}$
  - p(t) = $\alpha_4 t^{\delta} e^{-\alpha_3 t}$

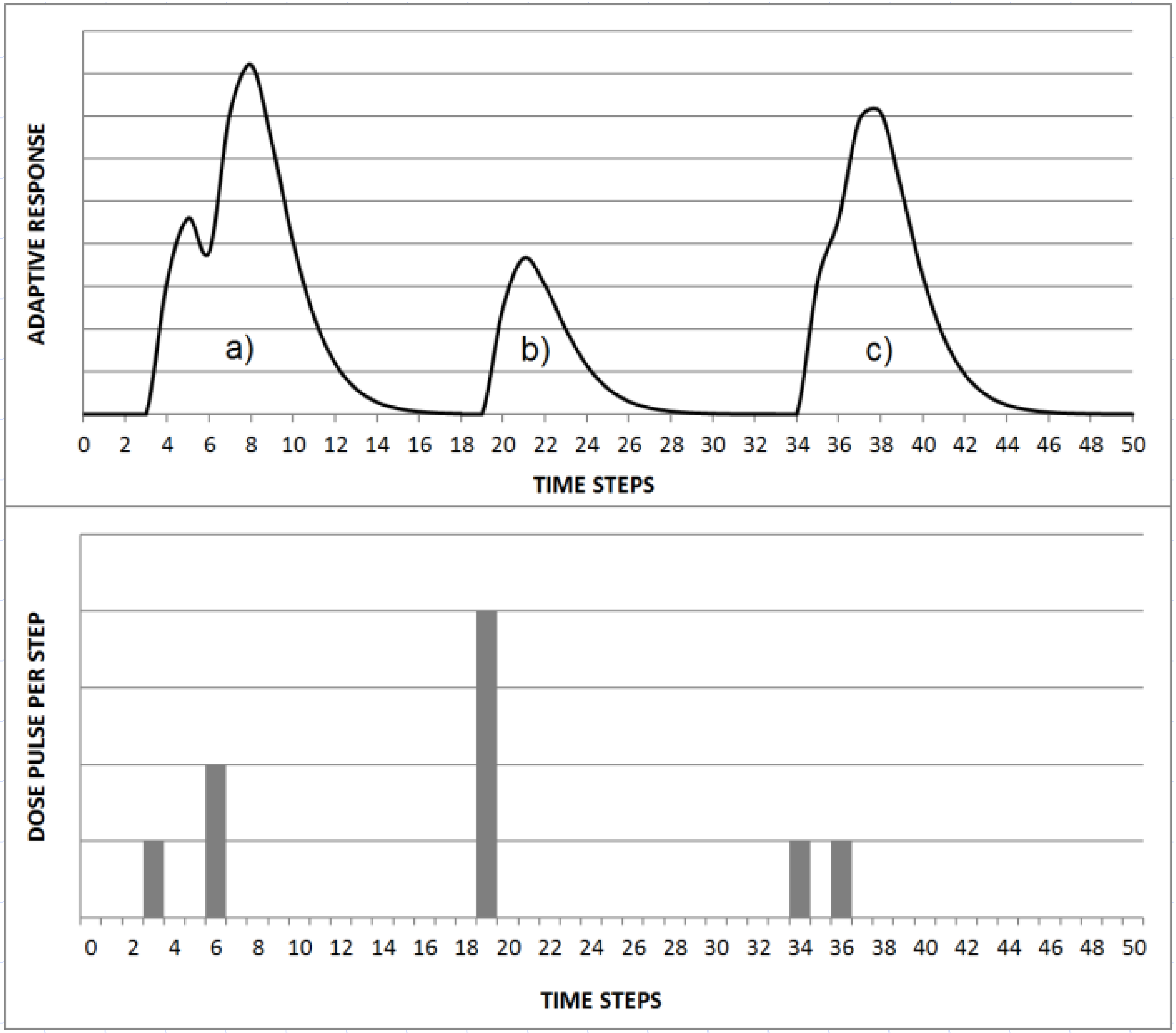


- Now, the dose- and time-dependent PDF can be presented as:
  - p(D,t) = $c D^{\nu} t^{\delta} e^{-\alpha_2 D - \alpha_3 t}$
  - $\mathrm{P(D,t)} = c \int_{t=0}^{T} \dot{D}^2(t)\ (T-t)^2\ e^{-\alpha_2 \dot{D}(t) - \alpha_3 (T-t)}\, dt$

Adaptive response PDF



Adaptive response PDF



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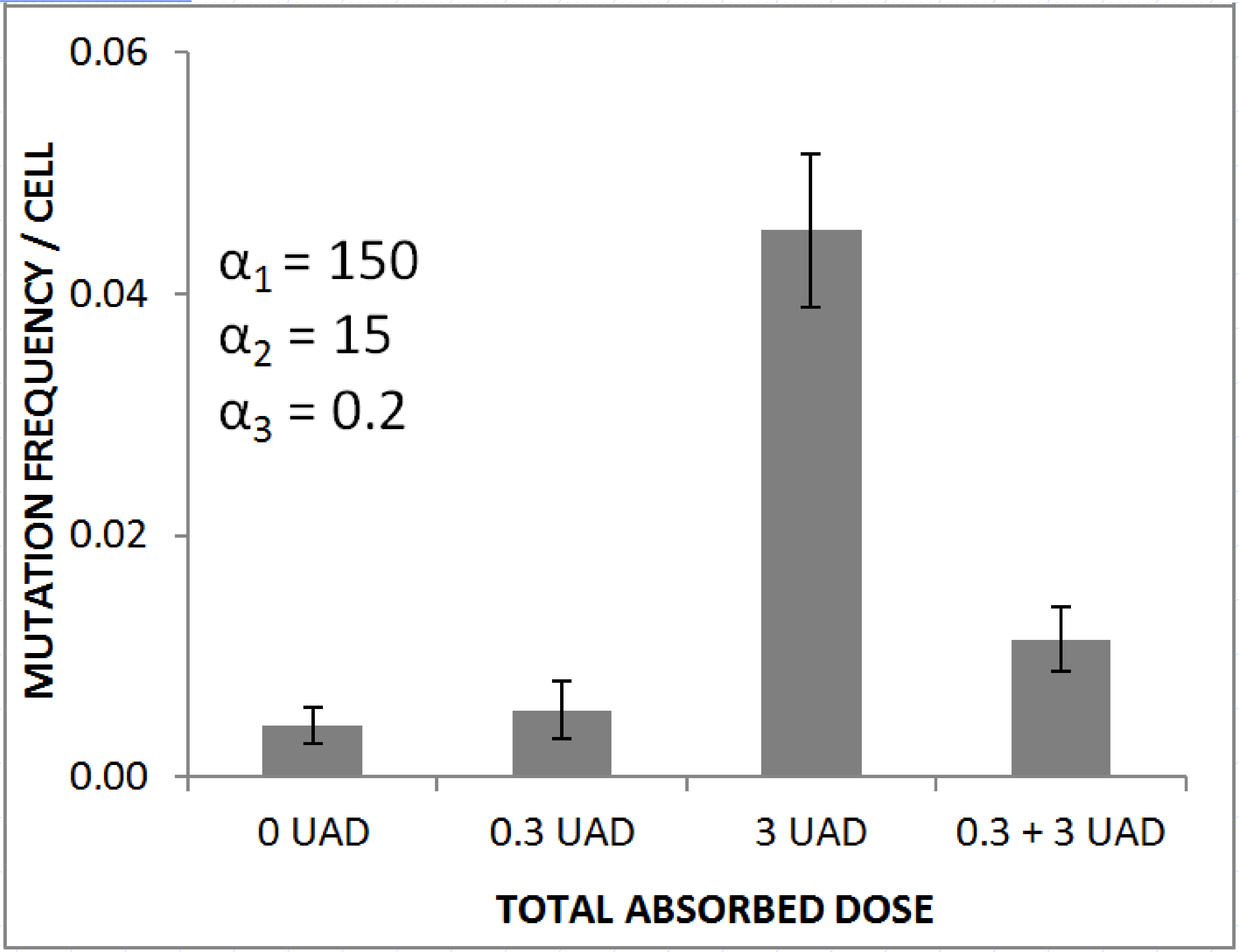
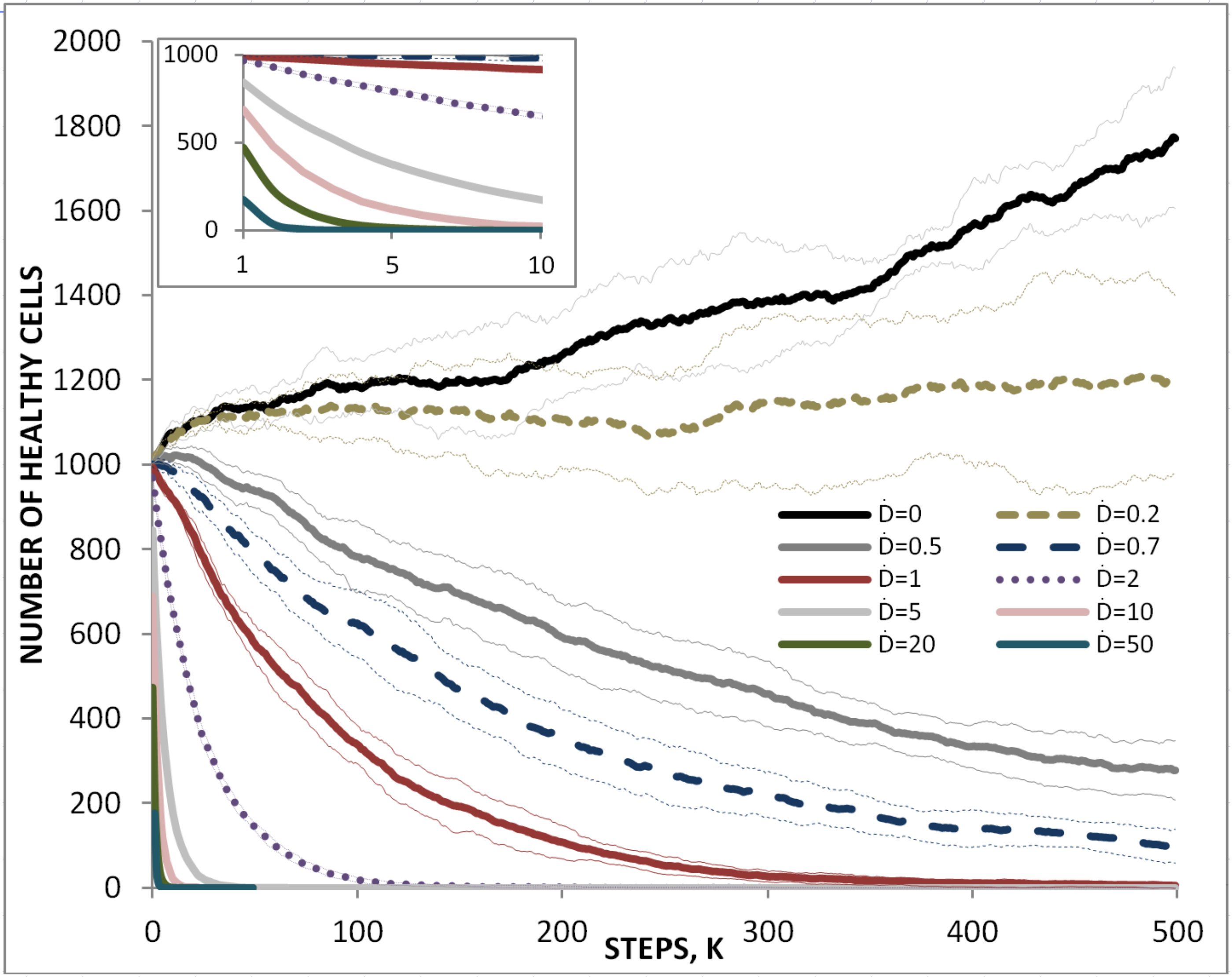
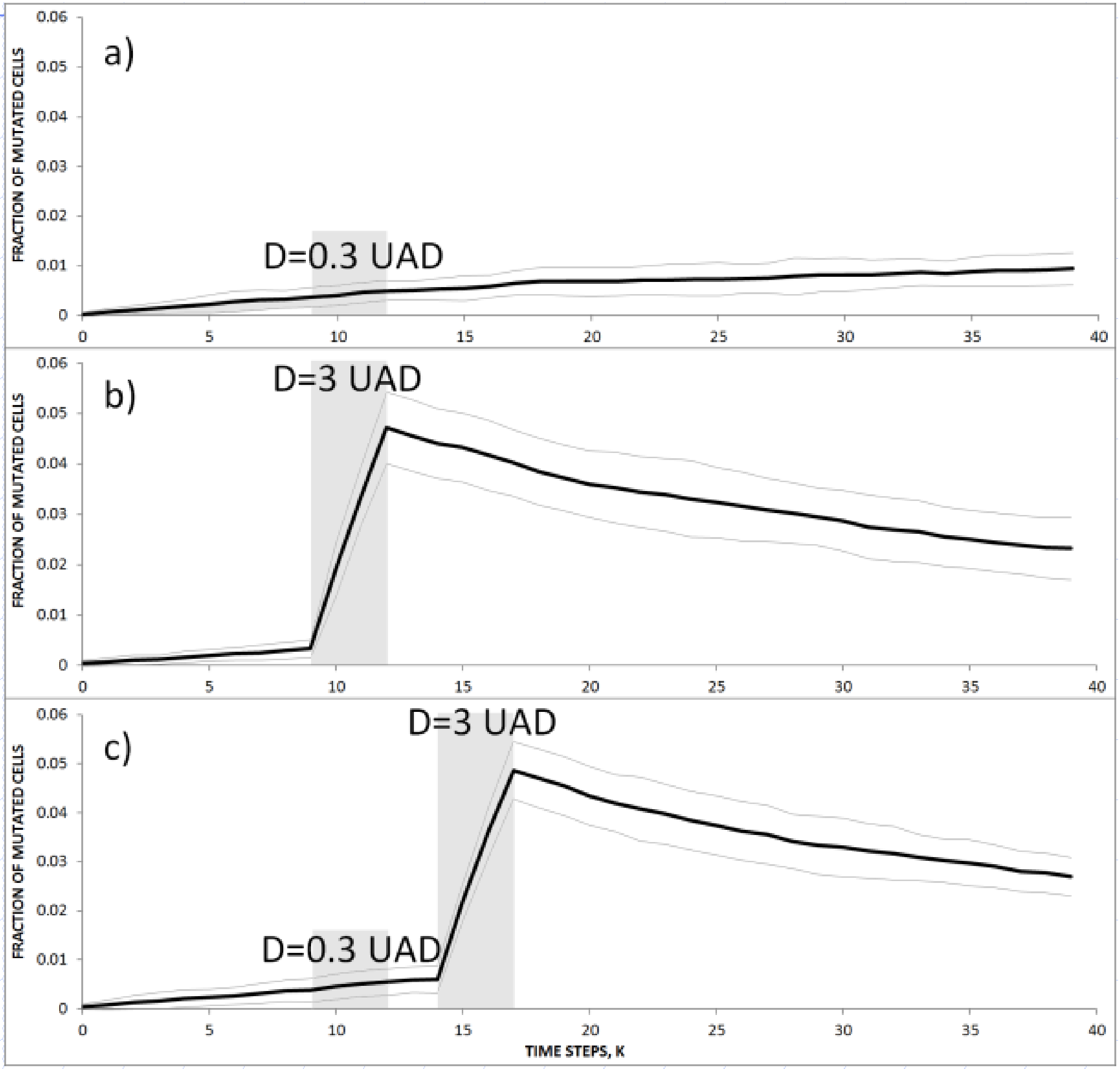
Results: the adaptive response creates a priming dose effect



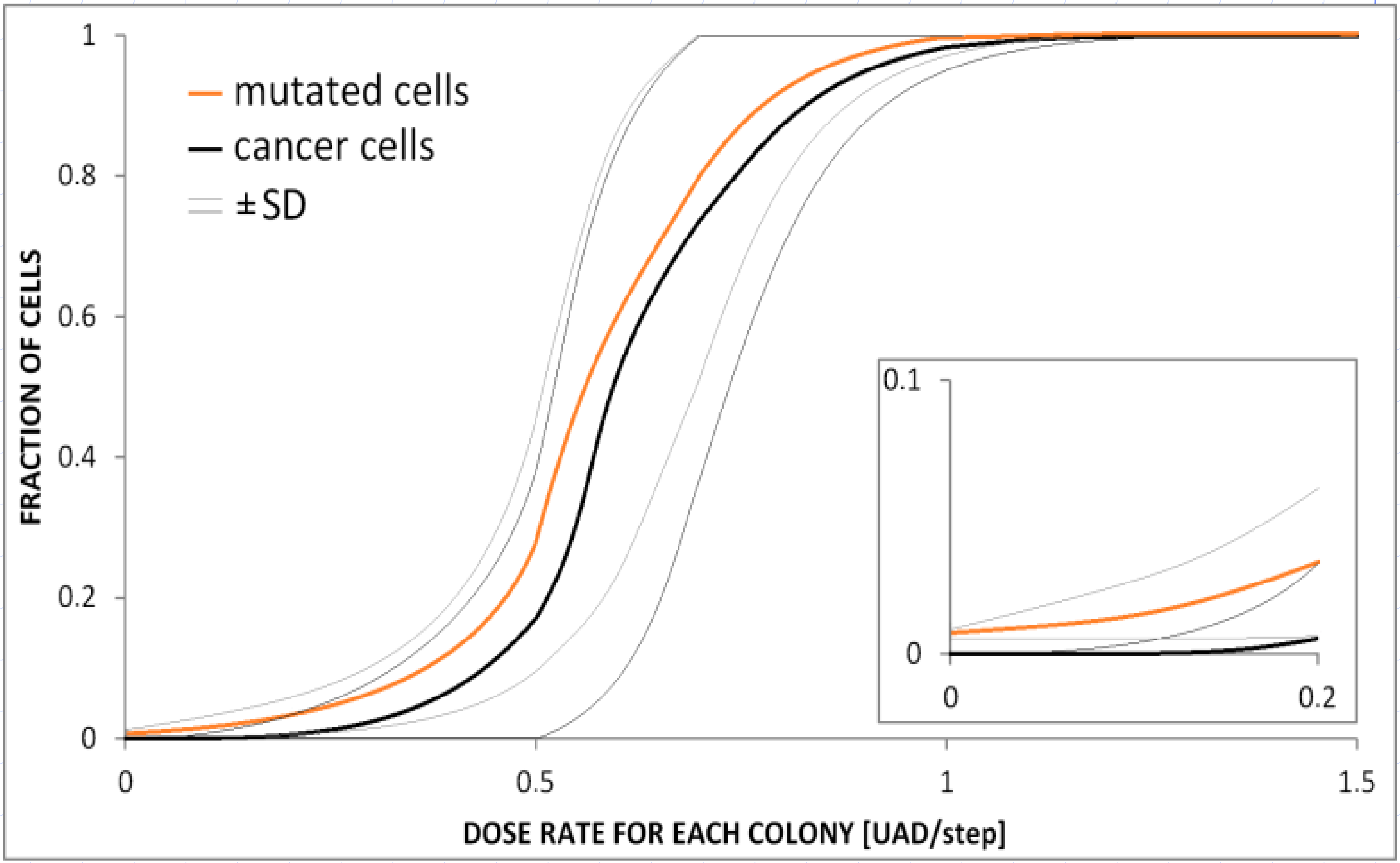
Results: the time evolution of healthy cells (with dose-rate)



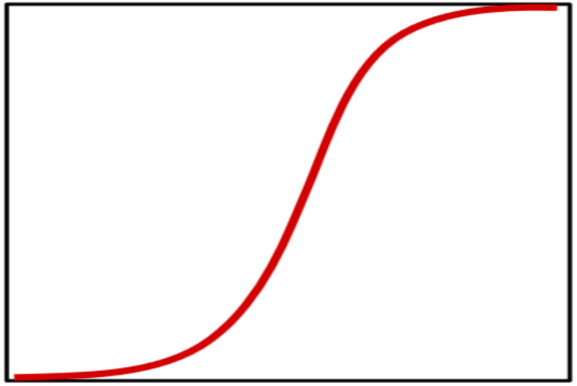
Results: mutation frequency after irradiation



Results: creation of cancer cells

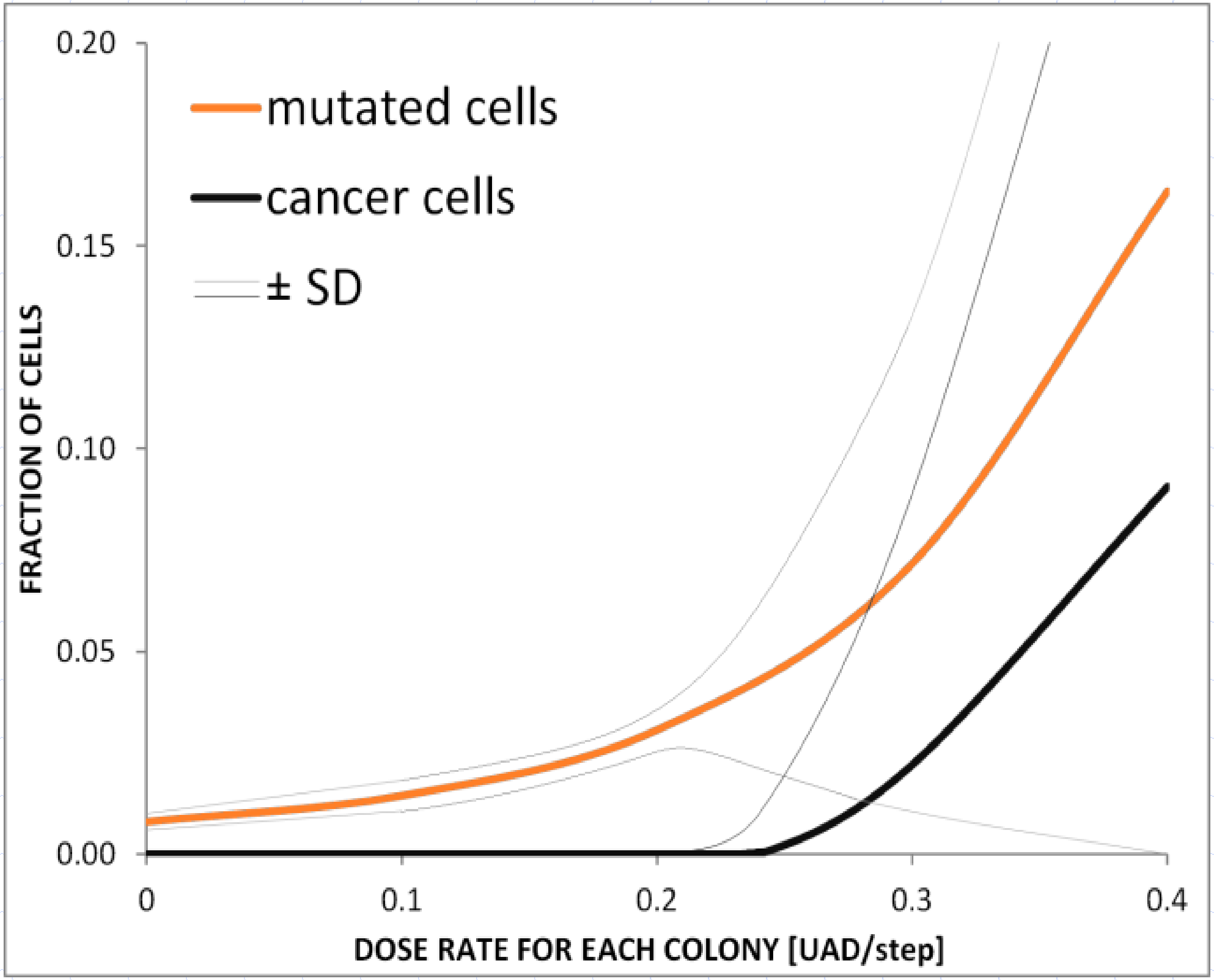


Sigmoid function

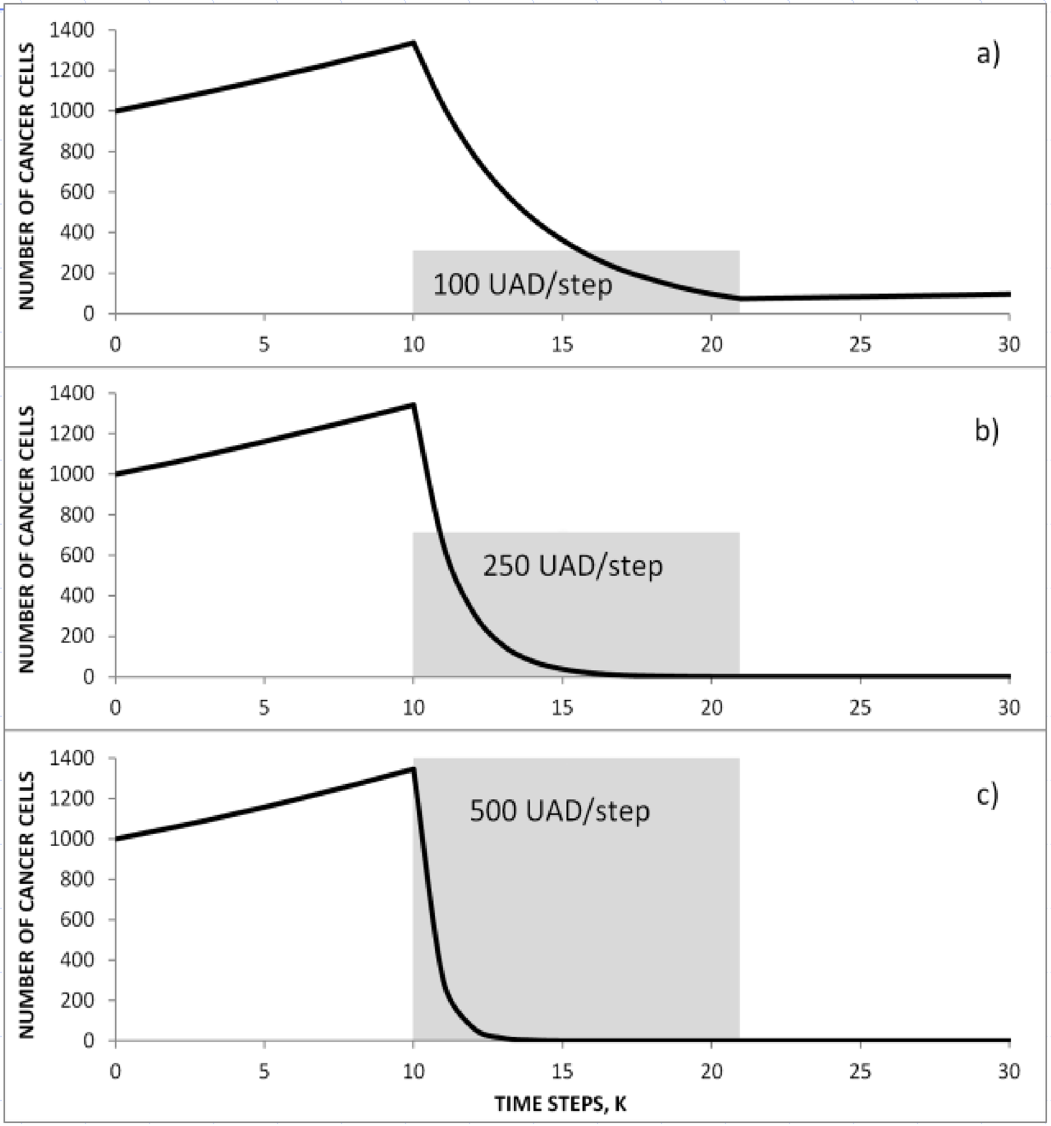


- Often used in theory of nucleation and growth, catastrophe theory or theory of self-organised criticality
- The common idea underlying these theories is a cumulative impact of some environmental stressors (here: radiation) on complex systems that may result in a rapid non-linear response when the stress exceeds some critical value
- Complex response to radiation???

After a strong adaptive response



Results: killing of cancer cells in high dose irradiation



Next problems

- Create a user-friendly software, which will allow to modify the model
- PDFs' parameters should be based more on experimental data
- Development of the model for more detail effects
- The latest approved version of the model: ***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***

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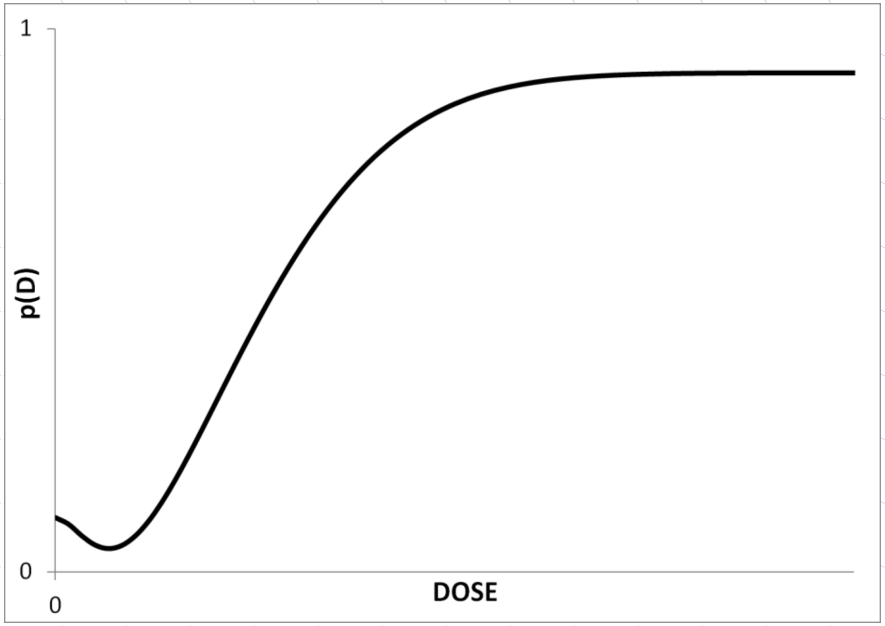
Deterministic modeling of cancer cells creation and development

- To find an analytical solution of the complex response of irradiated cells
- Two items to include:
  - The probability function of single cell's cancer transformation
  - The dynamics (dose, time and dose-rate evolution) of existing cancer cells

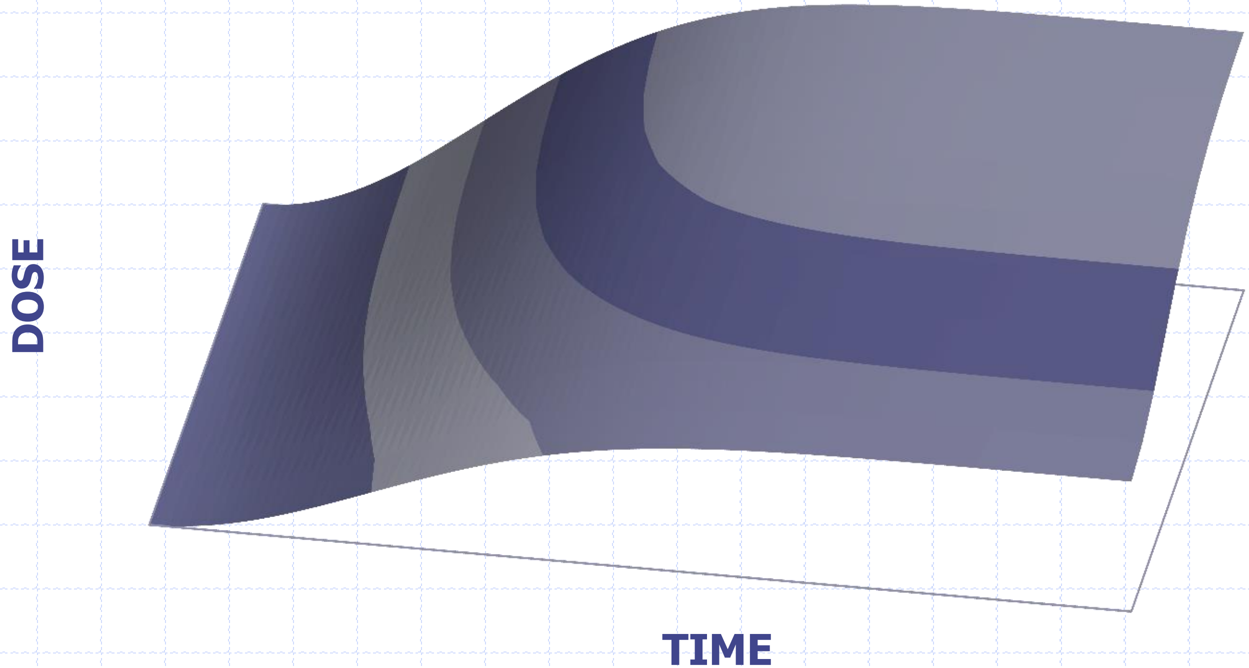
Deterministic approach – an exemplary result

- Dose- and time-dependent probability function of cancer transformation
  - $p(D,t) = P_{CT} \propto \left[1 - e^{-\sum_{i=1}^{R} \beta_i D^i}\right]\left(1 + be^{-\lambda\, t}\right) - \; cD^2 t^2 e^{-\alpha_2 D - \alpha_3 t}$
  - Taking time as a constant value:



Deterministic approach – an exemplary result #2

- Dose- and time-dependent evolution of existing cancer cells
  - $P_N(D,t) \propto \left[N_0\left(1-e^{-\sum \theta_i D^{n_i+1}}\right)+N_0^0 e^{-\sum \theta_i D^{n_i+1}}\right]\left(1-e^{-a\,\mathrm{t}^n}\right)$



Reference

- L. Dobrzyński, K.W. Fornalski, Y. Socol, "Modeling of irradiated cells' transformation: the dose and time-dependent effects"
- Just submitted ☺

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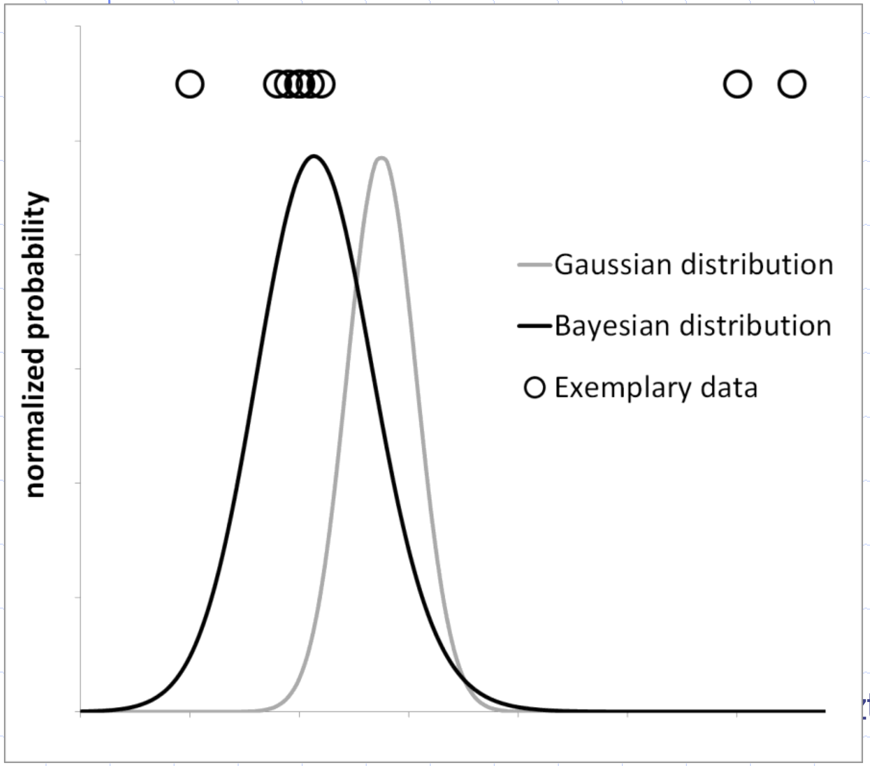
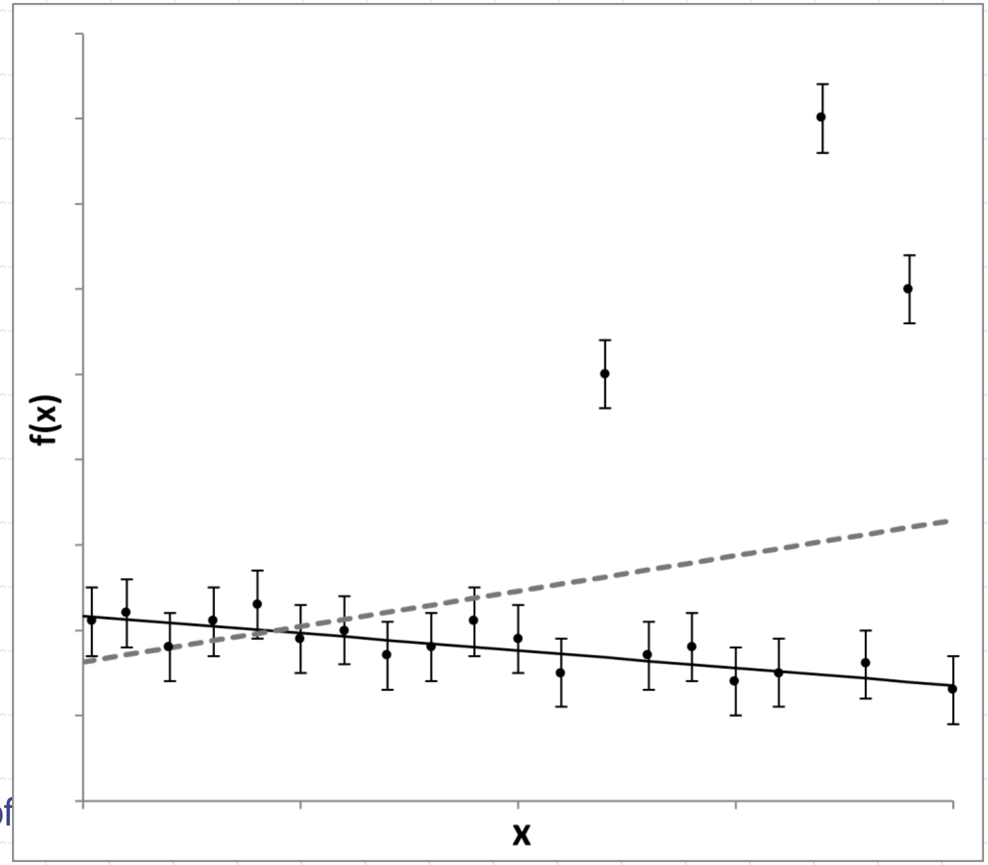
Bayesian methods in biodosimetry #1

- The robust Bayesian regression method
- Outliers omission





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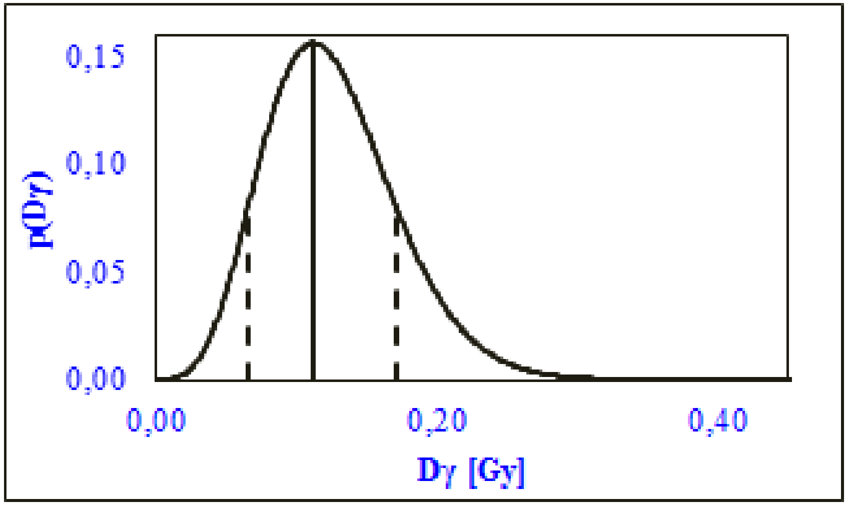
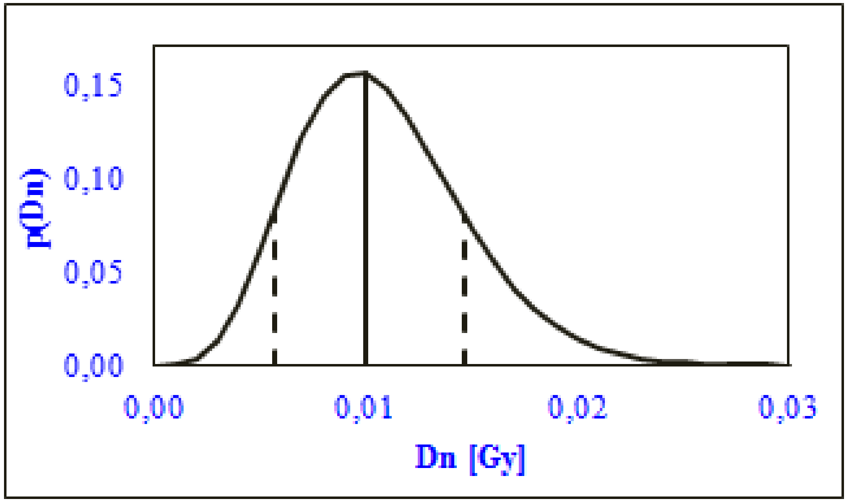
Bayesian methods in biodosimetry #2

- The dose assessment after incidential n+γ irradiation
- Neutron to gamma ratio unknown – given by a proper prior function (informative or non-informative)





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THANK YOU

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