Optimization of fractionated radiotherapy via mathematical modeling

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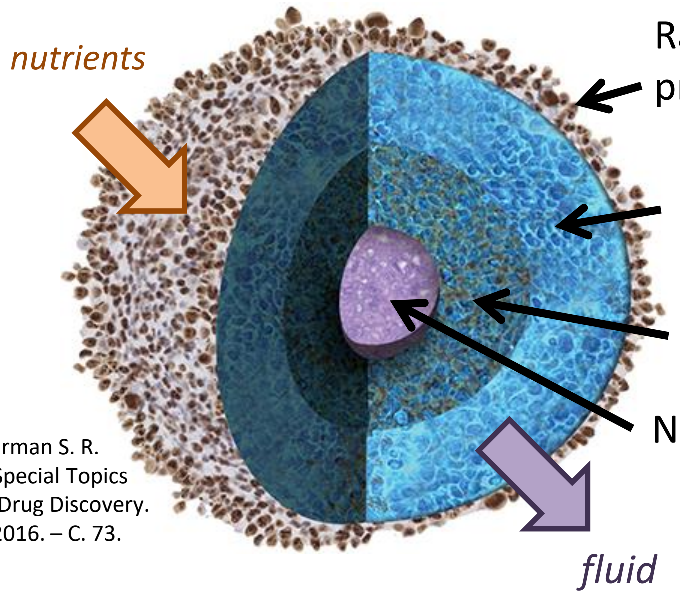
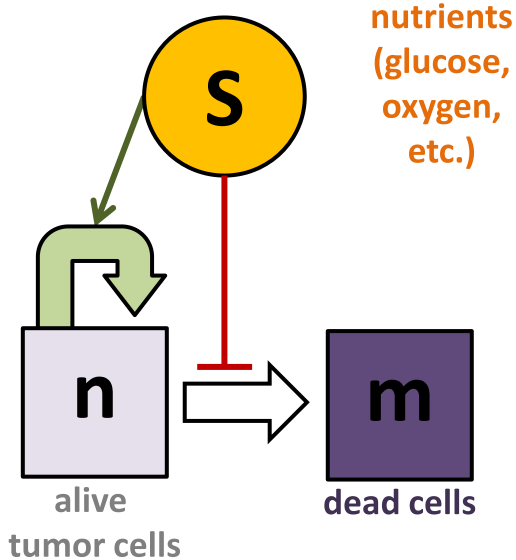
Basic approaches to modeling tumor growth

Tumor spheroid –
3D model of tumor in vitro

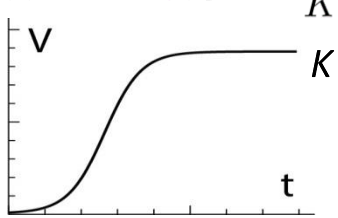


Horman S. R. //Special Topics in Drug Discovery. – 2016. – C. 73.



1) ODE, volume by time

$$V'(t) = BV(t)[1 - \frac{V(t)}{K}]$$



2) Reaction-diffusion for nutrients, ODE for spheroid

$$\frac{\partial S_i}{\partial t} = P_i + D_i \Delta S_i$$

$$\frac{\partial R}{\partial t} = f(\mathbf{S})$$

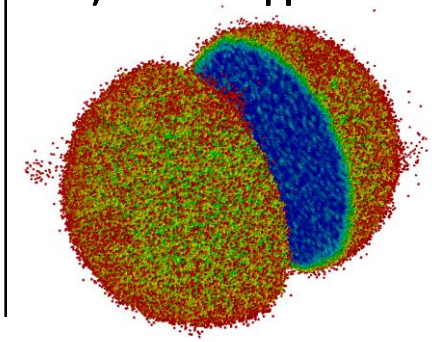
3) Continuity equation

$$\begin{cases} \frac{\partial n}{\partial t} + \nabla(\mathbf{I}n) = B(\mathbf{S})n - d(\mathbf{S})n \\ \frac{\partial m}{\partial t} + \nabla(\mathbf{I}m) = d(\mathbf{S})n \end{cases}$$

$n + m = 1$ **=>** $\nabla \mathbf{I} = B(\mathbf{S})n$

$$\mathbf{I}(x) = \int_0^x B(\mathbf{S})n$$

4) Discrete approach



Mathematical modeling in oncology: history, goals, difficulties

1930s
- 1932: 1st article with tumor growth curve

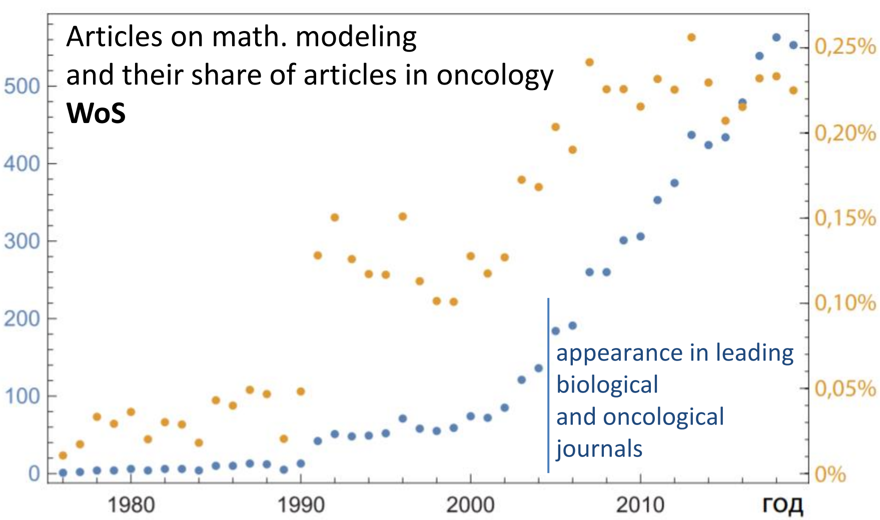
1950s
- other growth curves

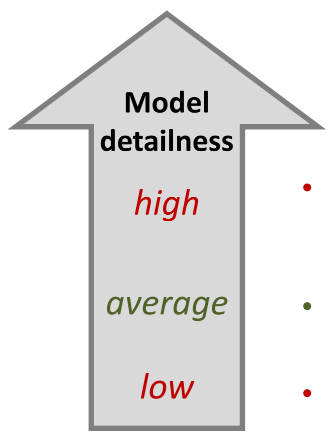
1970s
- spheroid growth modeling
- reaction-diffusion models (invasive tumors)
- optimal control
- mechanistic models
- account for immune system

1990s
- discrete models
- age-structured models, account for cell cycle
- account for angiogenesis
- complex molecular regulatory networks (systems biology)
- numerical optimization of radiotherapy

2010s
- phenotype-structured continuous models

Key practical goal:
optimization of anticancer therapy





Key problem:
choice of the level of detailness

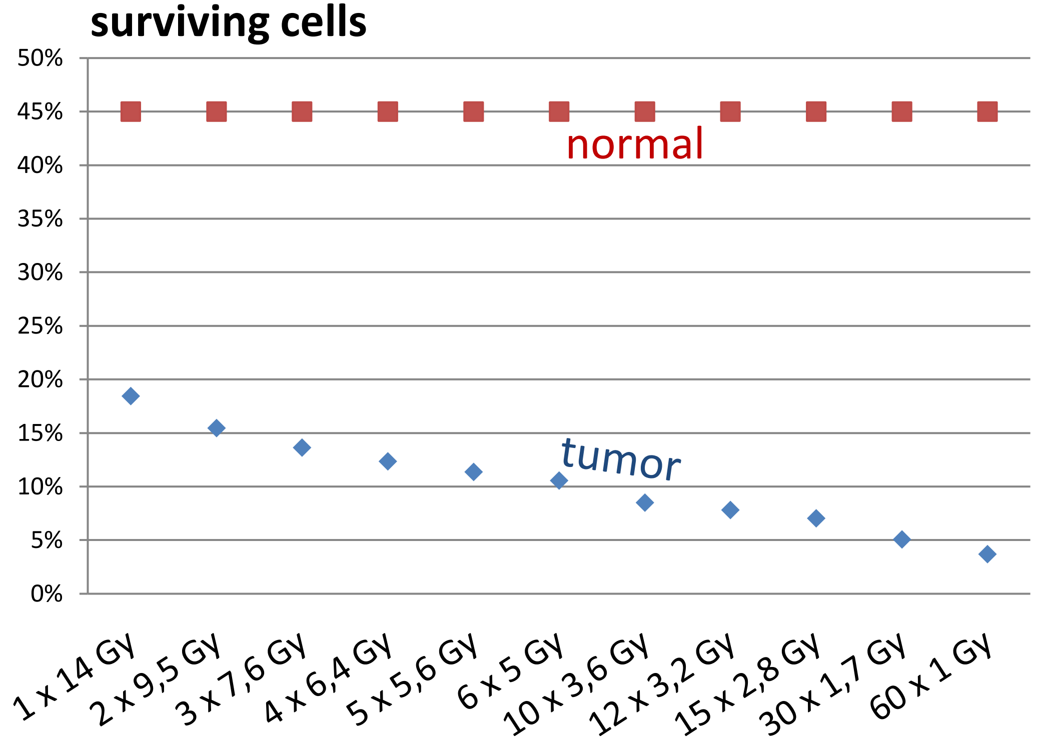
- **impossible to estimate all parameter values, enormous computational complexity**
- **amenable to analysis and gives an idea of the basic principles**
- **impossible to reproduce the key features of the object**

Fractionated radiotherapy

Fraction of cells, which survive after a single radiation dose D:

$$S(D) = e^{-\alpha D - \beta D^2}$$

Usually $\alpha_{tumor} > \alpha_{normal}$, but $(\alpha/\beta)_{tumor} > (\alpha/\beta)_{normal}$

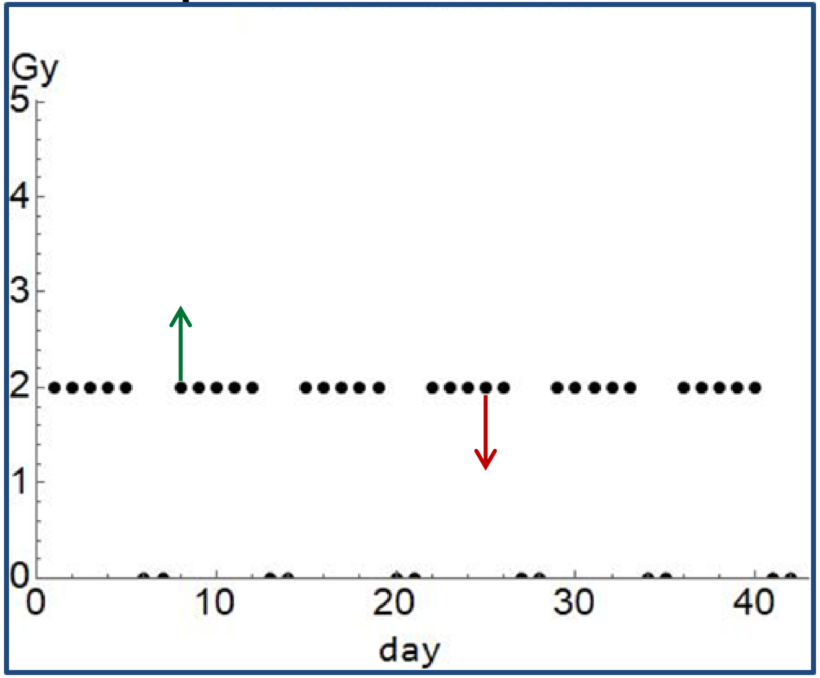


4 R's:

- **R**eoxygenation
- **R**edistribution of cell cycle
- **R**epopulation
- **R**epair of sublethal damage

Mathematical modeling for optimization of radiotherapy fractionation

Type of model	pros	cons
ODEs	• simple • analytical optimization methods	• analytical methods become unsolvable under complex non-linear terms and/or discontinuous treatments • cannot account for non-uniform cell radiosensitivity in space



Sketch of a simplest optimization algorithm:

1. Increase a random fractional dose
2. Decrease another random dose, maintaining overall tissue damage
3. If (profit), then repeat 1-3.

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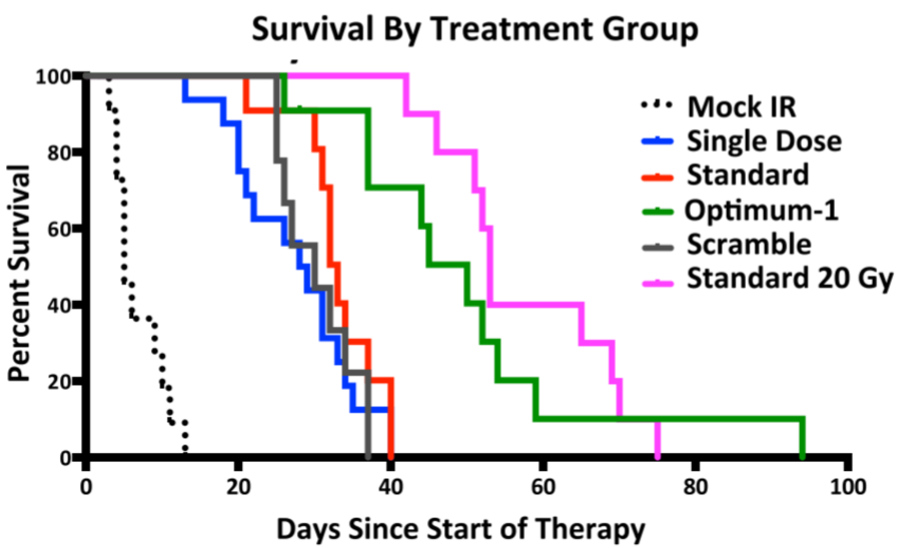
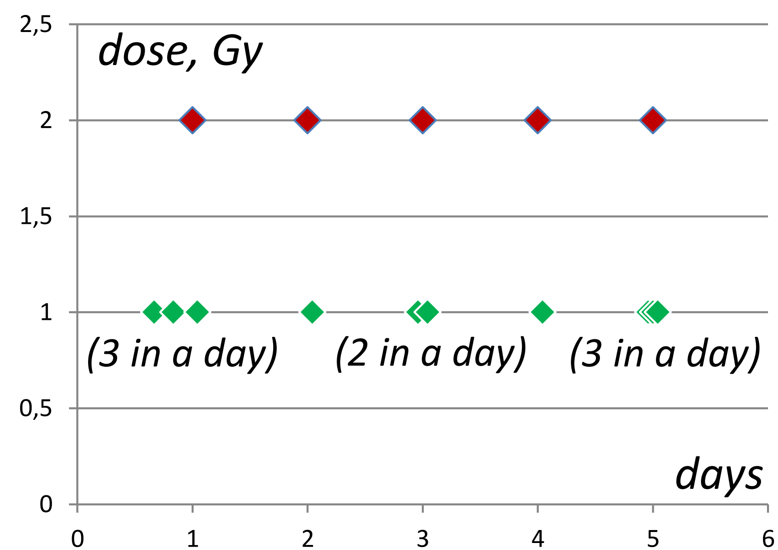
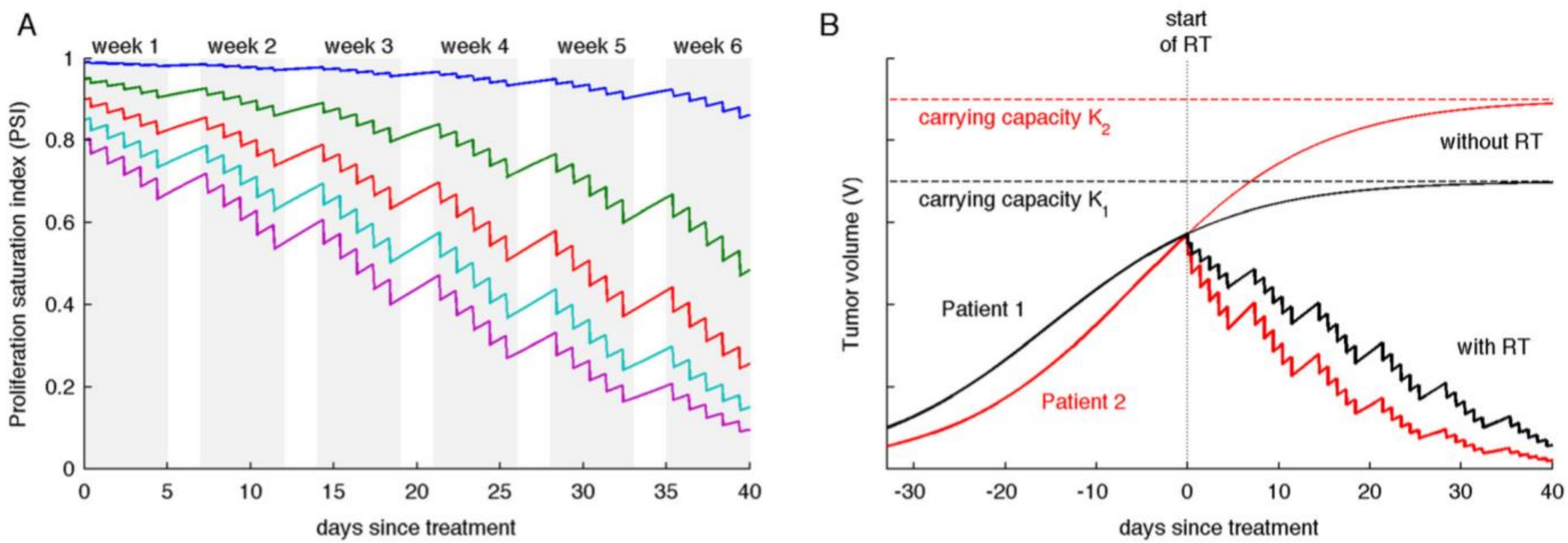


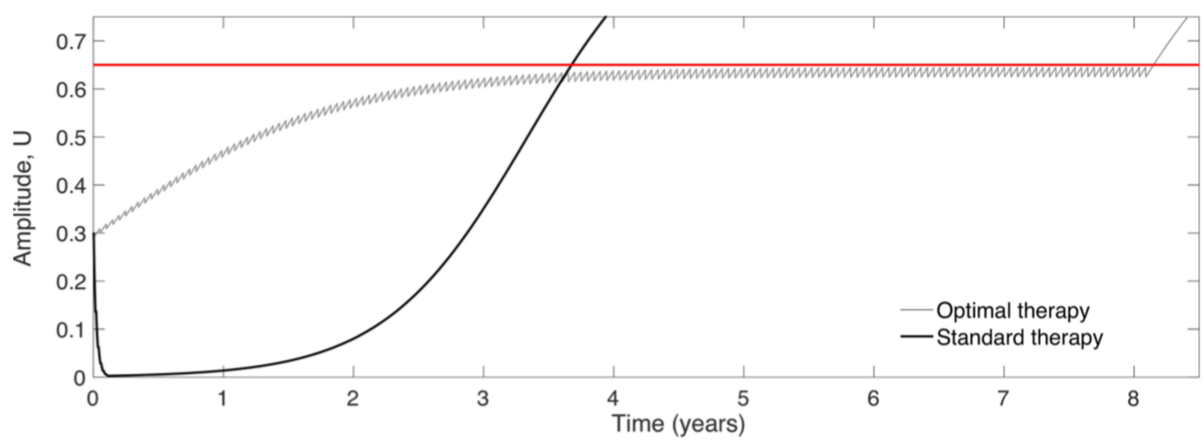


• Leder K. et al. Mathematical modeling of PDGF-driven glioblastoma reveals optimized radiation dosing schedules //Cell. – 2014. – T. 156. – №. 3. – C. 603-616.

Mathematical modeling for optimization of radiotherapy fractionation



- Prokopiou S. et al. //Radiation Oncology. – 2015. – T. 10. – №. 1. – C. 1-8.



- Henares-Molina A. et al. //PLoS One. – 2017. – T. 12. – №. 6. – C. e0178552.

Mathematical modeling for optimization of radiotherapy fractionation

<table>
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<tr><td>ODEs</td><td>simple
analytical optimization methods</td><td>analytical methods become unsolvable under complex non-linear terms and/or discontinuous treatments
cannot account for non-uniform cell radiosensitivity in space</td></tr>
<tr><td>PDEs</td><td rowspan="2">can account for non-uniform cell radiosensitivity in space</td><td>need to develop optimization methods</td></tr>
<tr><td>Agent-based</td><td>numerical complexity does not allow to utilize optimization procedures
small number of cells is considered</td></tr>
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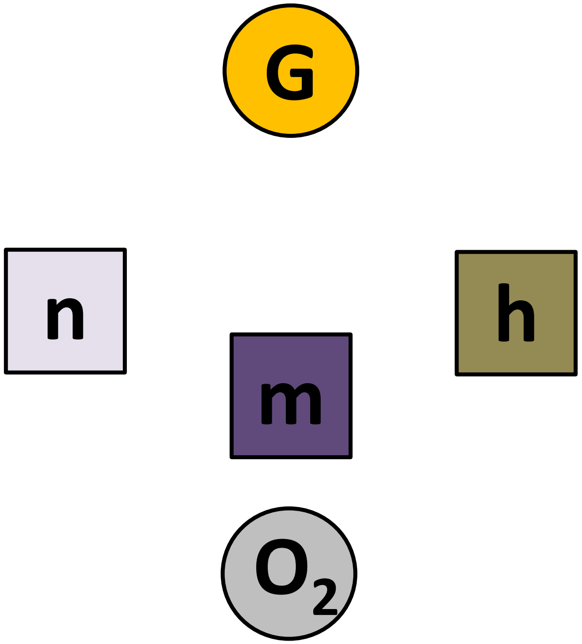
The model: variables



$n(x,t)$ – tumor cells

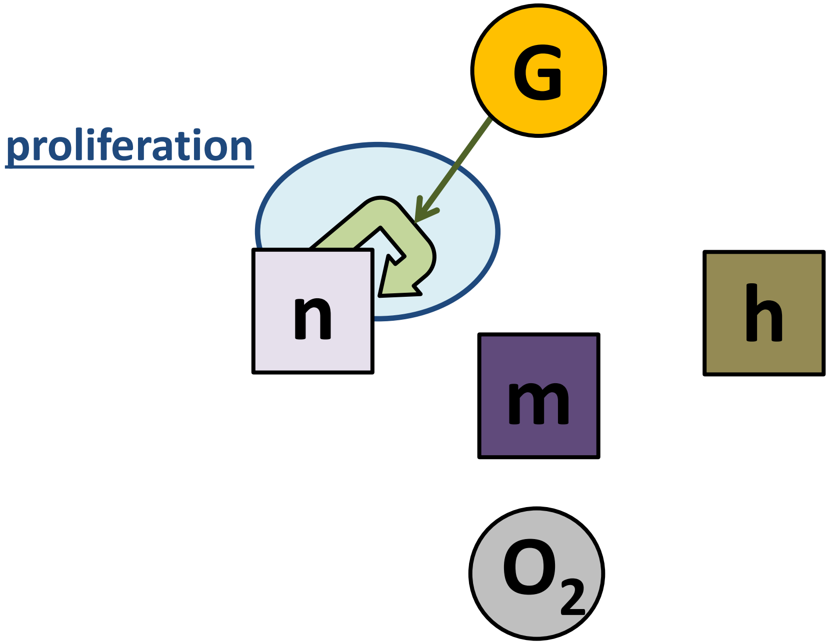
$m(x,t)$ – necrotic tissue

$h(x,t)$ – normal tissue

$G(x,t)$ – glucose

$O_2(x,t)$ – oxygen

The model: dynamics of cells and necrotic tissue



n(x,t)– tumor cells

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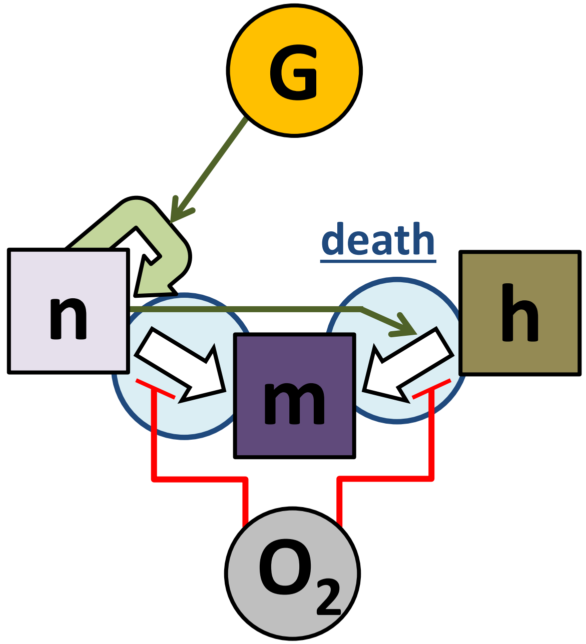
O_2**(x,t)** – oxygen

tumor cells: $$\frac{\partial n}{\partial t} = \overbrace{Bn\frac{g}{g+g^*}}^{\text{proliferation}}$$

The model: dynamics of cells and necrotic tissue



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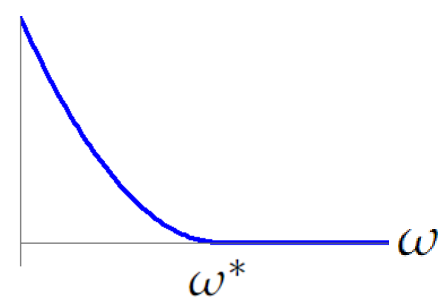
$$\text{tumor cells:} \quad \frac{\partial n}{\partial t} = \overbrace{Bn\frac{g}{g+g^*}}^{\text{proliferation}} \overbrace{-\epsilon M_h(\omega)n}^{\text{death}}$$

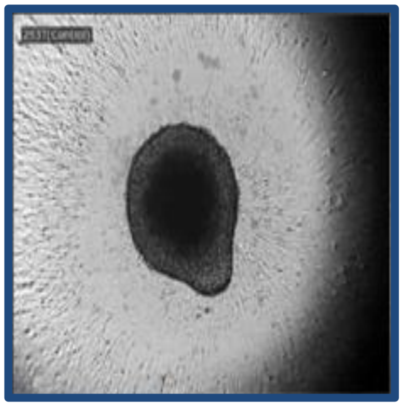
$$\text{normal cells:} \quad \frac{\partial h}{\partial t} = \overbrace{-[M_h(\omega) + Mn]h}^{\text{death}}$$

$$\text{necrotic tissue:} \quad \frac{\partial m}{\partial t} = \overbrace{\epsilon M_h(\omega)n + [M_h(\omega) + Mn]h}^{\text{cell death}}$$

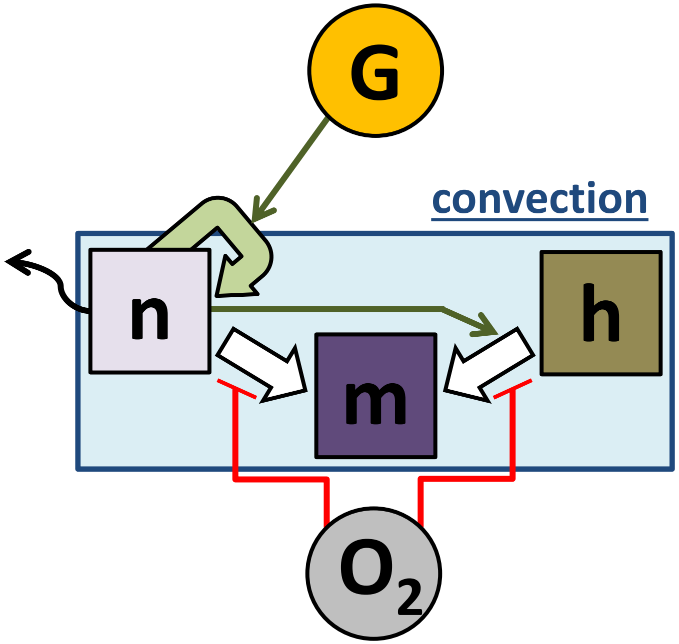
$$M_h(\omega) = \begin{cases} 0 \;\; if \;\; \omega \geq \omega^*; \\ M[\{\omega/\omega^*\}^2 - 2\{\omega/\omega^*\} + 1] \;\; if \;\; \omega < \omega^*; \end{cases}$$



The model: dynamics of cells and necrotic tissue



Baek, NamHuk, et al.
Drug design, development and therapy 10 (2016): 2155.



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$$\text{normal cells:} \quad \frac{\partial h}{\partial t} = \overbrace{-[M_h(\omega)+Mn]h}^{\text{death}} \overbrace{-\nabla(\mathbf{I}h)}^{\text{convection}};$$

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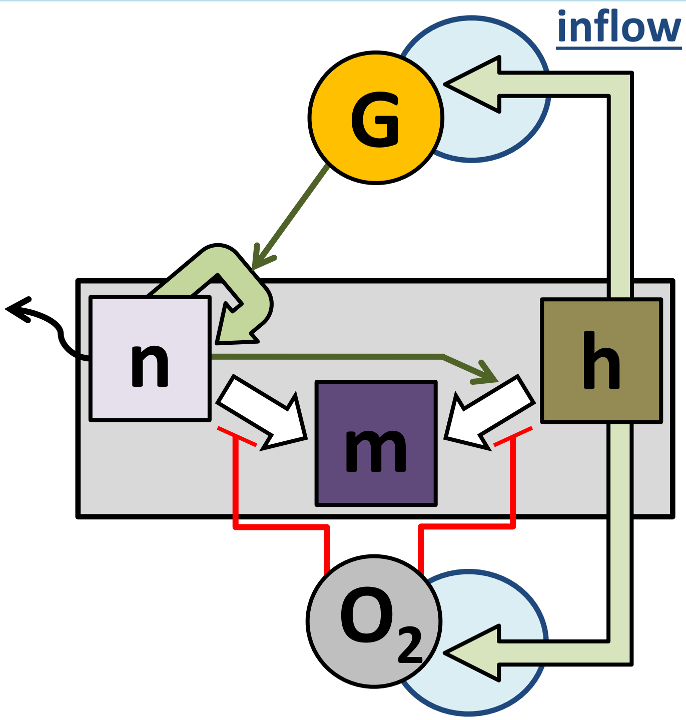
$$n+m+h=1;$$

$$\nabla\mathbf{I} = Bn\frac{g}{g+g^*}$$

The model: dynamics of nutrients



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h(x,t) – normal tissue

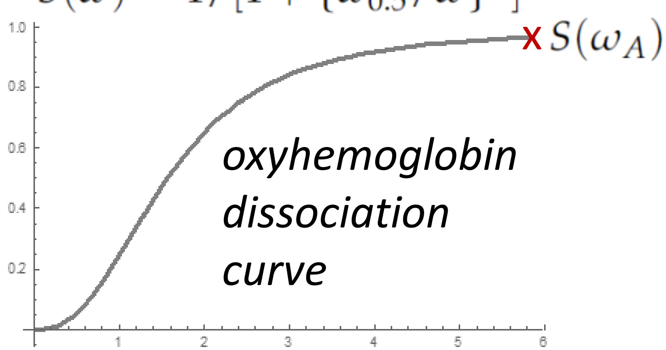
G(x,t) – glucose

O_2(x,t) – oxygen

$$\text{glucose:} \quad \frac{\partial g}{\partial t} = \overbrace{P_g h[1-g]}^{\text{inflow}}$$

$$\text{oxygen:} \quad \frac{\partial \omega}{\partial t} = \overbrace{P_\omega h[S(\omega_A) - S(\omega)]}^{\text{inflow}}$$

$$S(\omega) = 1/[1 + \{\omega_{0.5}/\omega\}^\chi]$$



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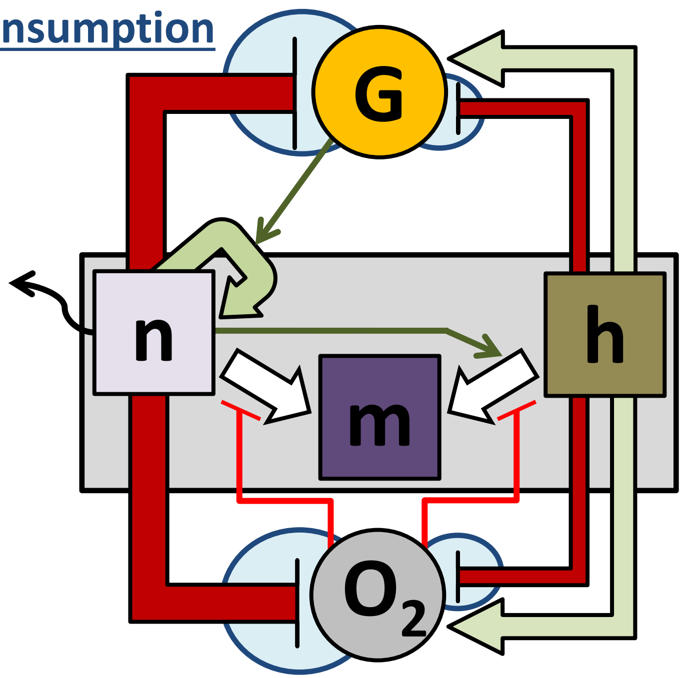

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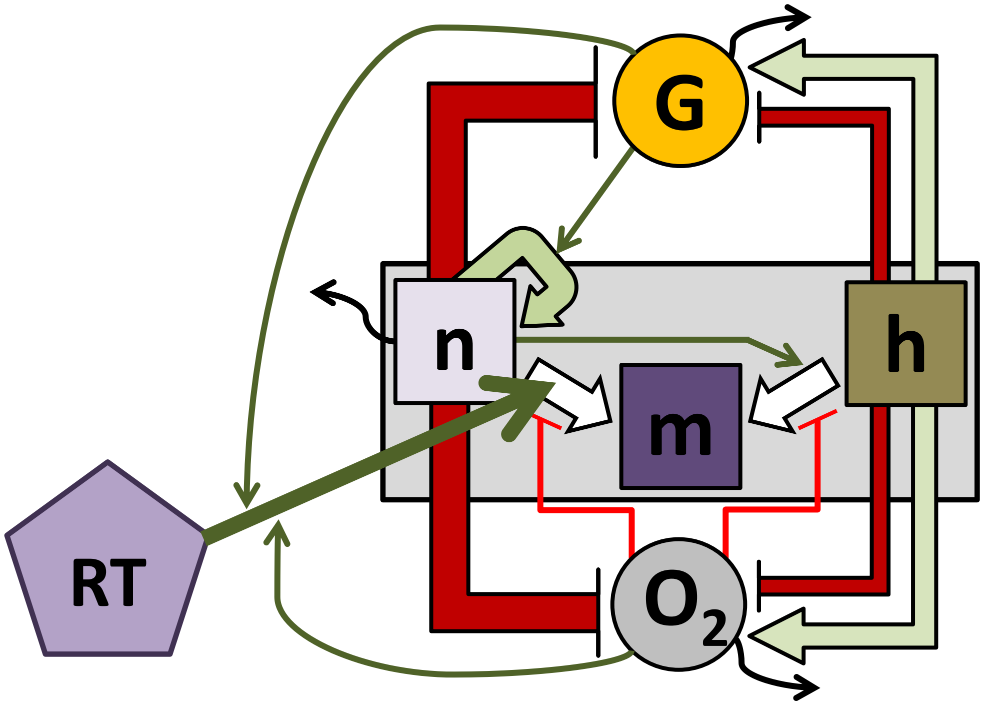
$$\overbrace{-[\{Q_n^\omega \frac{g}{g+g^*} + Q_h^\omega \frac{g^*}{g+g^*}\}n + Q_h^\omega h]\frac{\omega}{\omega+\omega^*}}^{\text{consumption}} \overbrace{+D_\omega \Delta \omega}^{\text{diffusion}};$$

The model: radiotherapy



n(x,t)– tumor cells

m(x,t) – necrotic tissue

h(x,t) – normal tissue

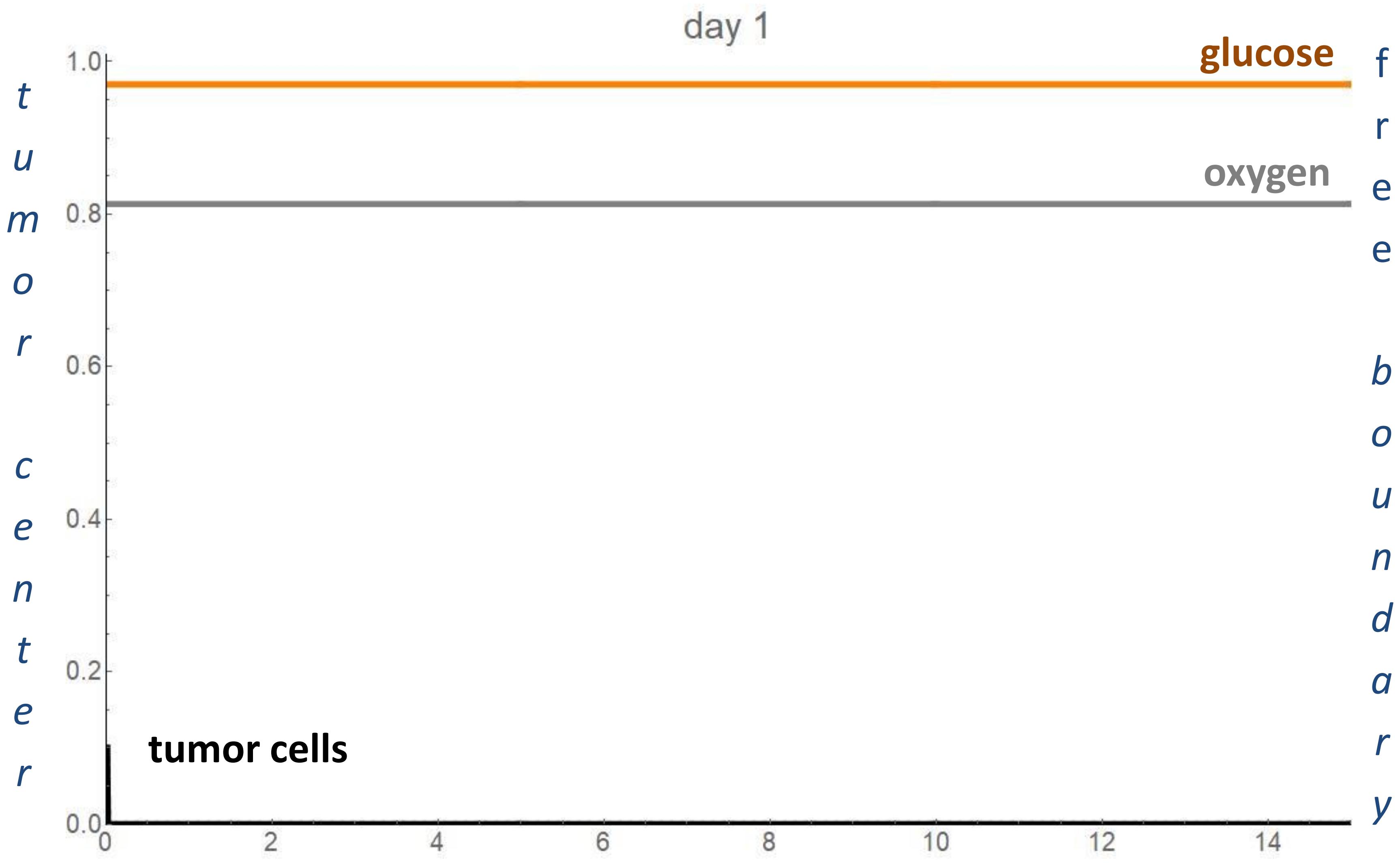
G(x,t) – glucose

O_2(x,t) – oxygen

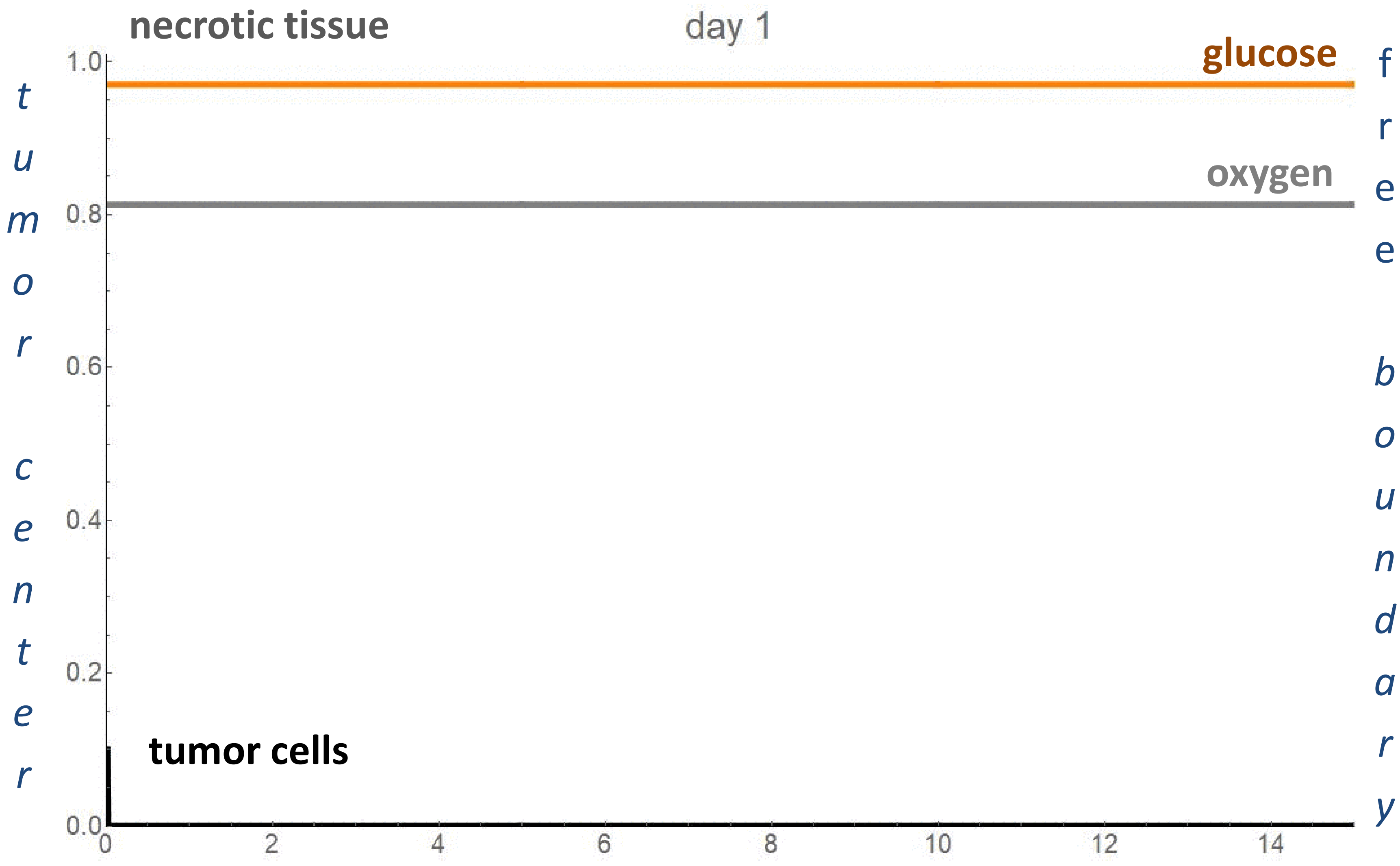
$$n|_{postRT} = n|_{preRT} \cdot exp(\{-\alpha\,[OER_\alpha(\omega)\cdot\gamma(g)\cdot D] - \beta\,[OER_\beta(\omega)\cdot\gamma(g)\cdot D]^2\}),$$
$$m|_{postRT} = m|_{preRT} + [n|_{preRT} - n|_{postRT}];$$

$$where\ OER_i(\omega) = \frac{\omega * OER_{i,m} + K_m}{\omega + K_m},\ i = \alpha, \beta;\ \ \gamma(g) = \frac{g + kg^*}{g + g^*}.$$

Simulation of tumor growth and radiotherapy



Simulation of tumor growth and radiotherapy



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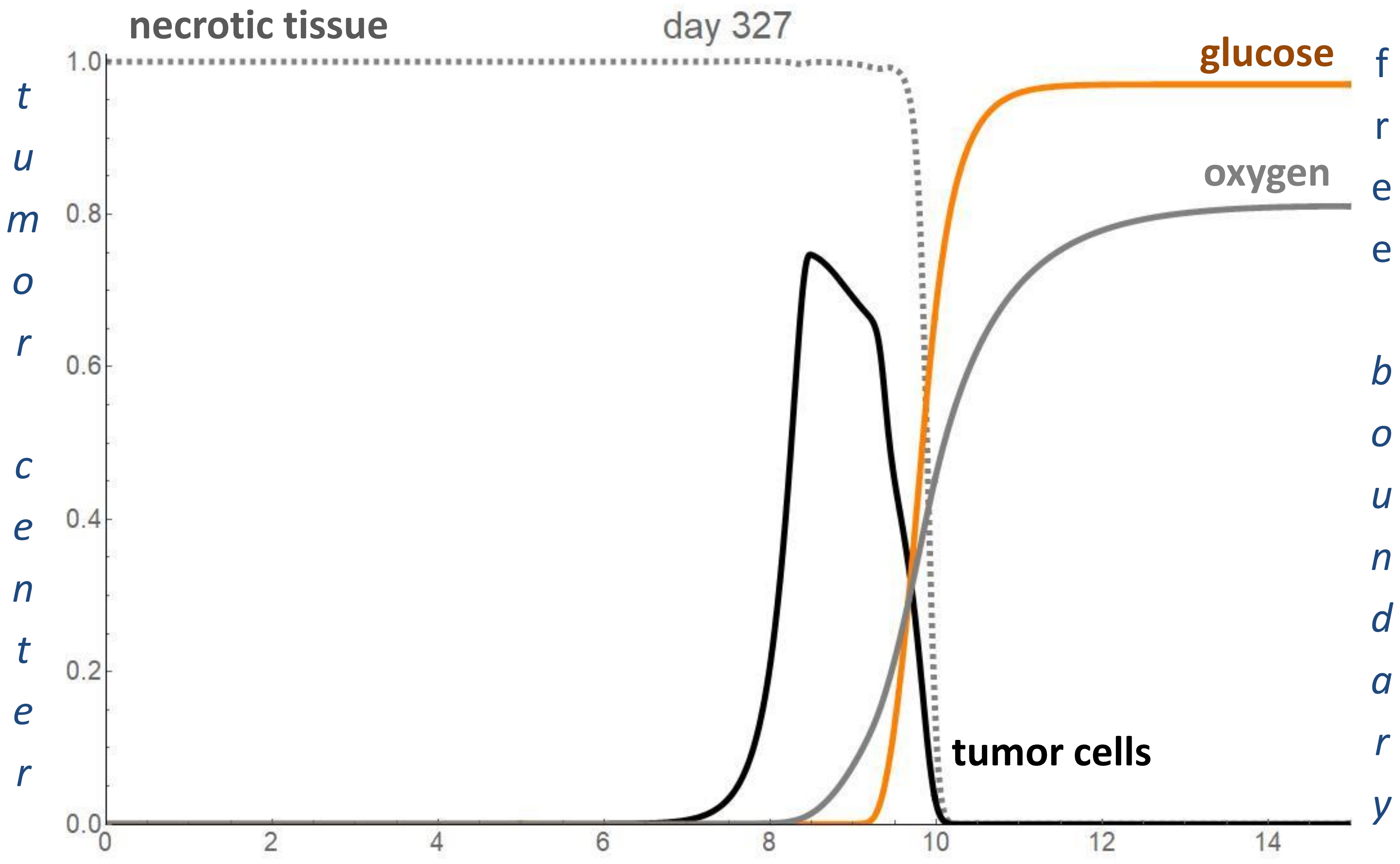

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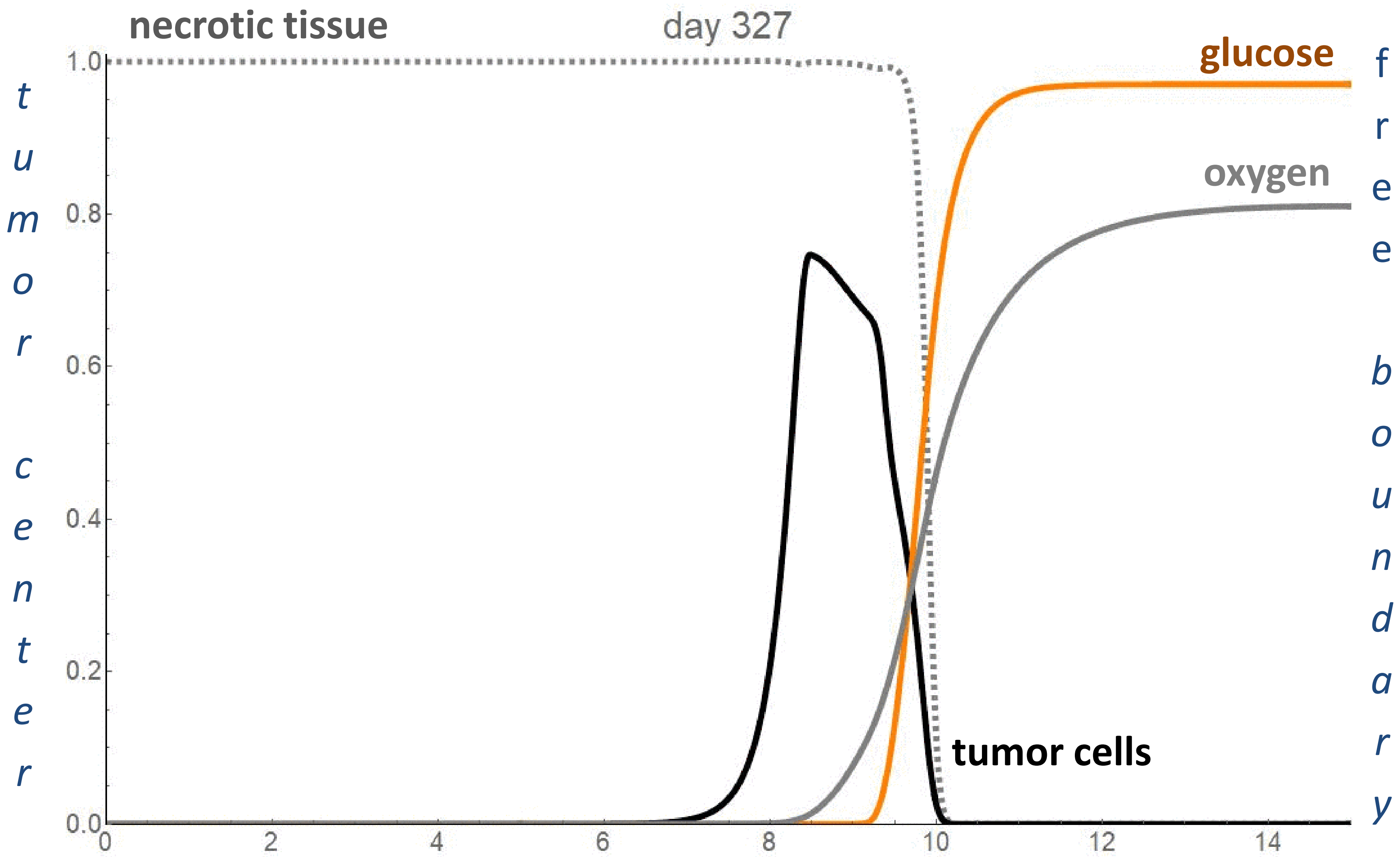

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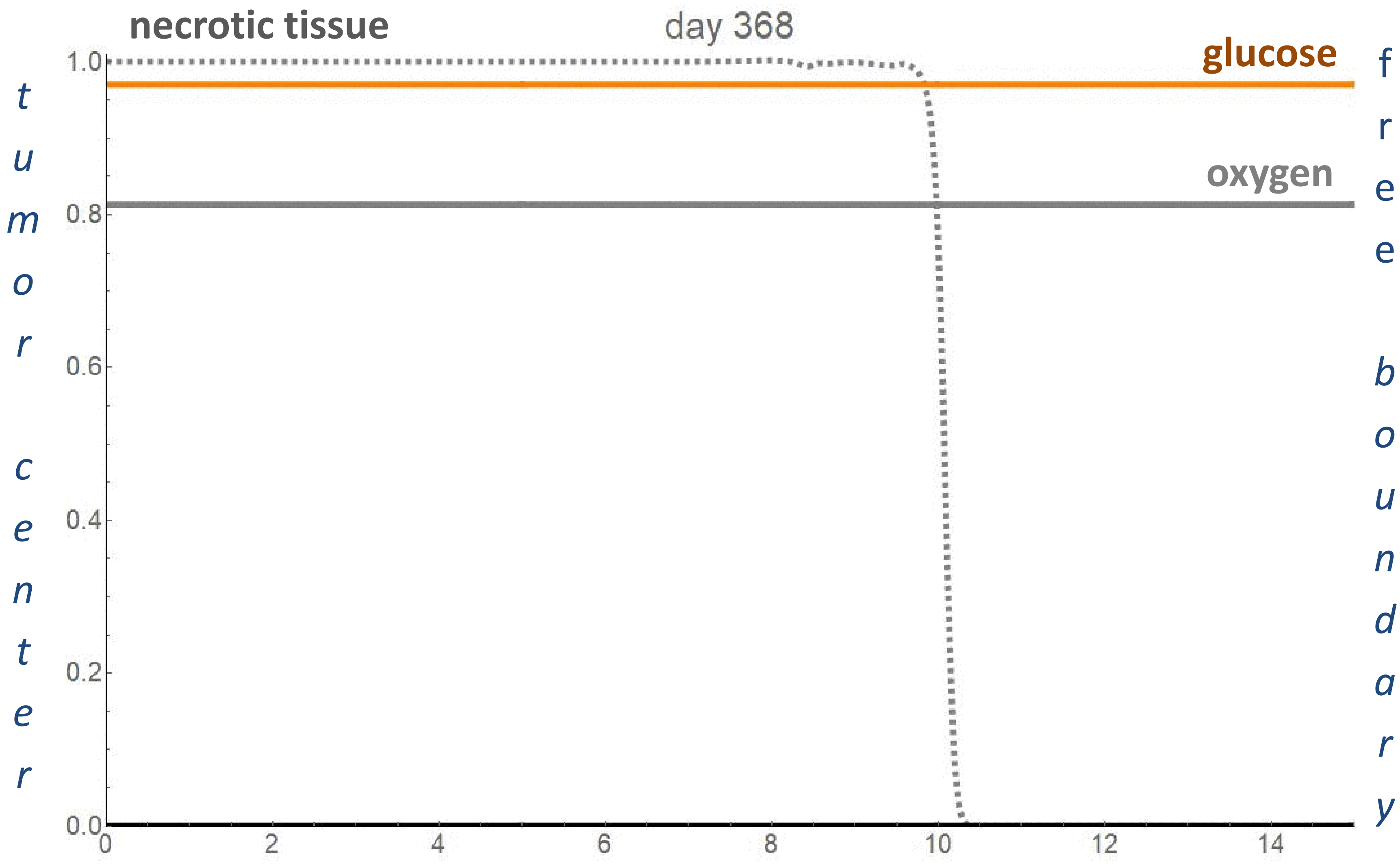


Optimization task

First irradiation was performed when **tumor radius reached 1 cm**.
Considered schemes consisted of **42 non-negative doses**,
administered successively **at 24 h interval**.

Standard scheme: 30 doses of 2 Gy, delivered every weekday over six weeks:

$$\mathbf{D^{st}} = (D_i^{st}),\ D_i^{st} = \begin{cases} 0 \ \ if\ i = 6 + 7[k-1] \ \vee \ i = 7k, \ \ k \in \mathbb{N}; \\ 2 \ \ otherwise; \end{cases} \qquad i \in [1, 42]$$

Two constraints on normal tissue damage:

$$NTD_h(\mathbf{D}) \equiv \sum_{i=1}^{42} [(\alpha/\beta)_h \cdot D_i + D_i^2] \leq NTD_{max} \equiv NTD_h(\mathbf{D^{st}});$$
$$D_i < D_{max} \ \ \forall i.$$

Aim: find the scheme to **decrease the number of tumor cells as much as possible**

$$F(\mathbf{D}) = \min_t(lgN(\mathbf{D},t)), \ \ where\ N(\mathbf{D},t) \equiv \hat{n}\hat{r}^3 \cdot 4\pi \int_0^X n(\mathbf{D},r,t) r^2 dr$$

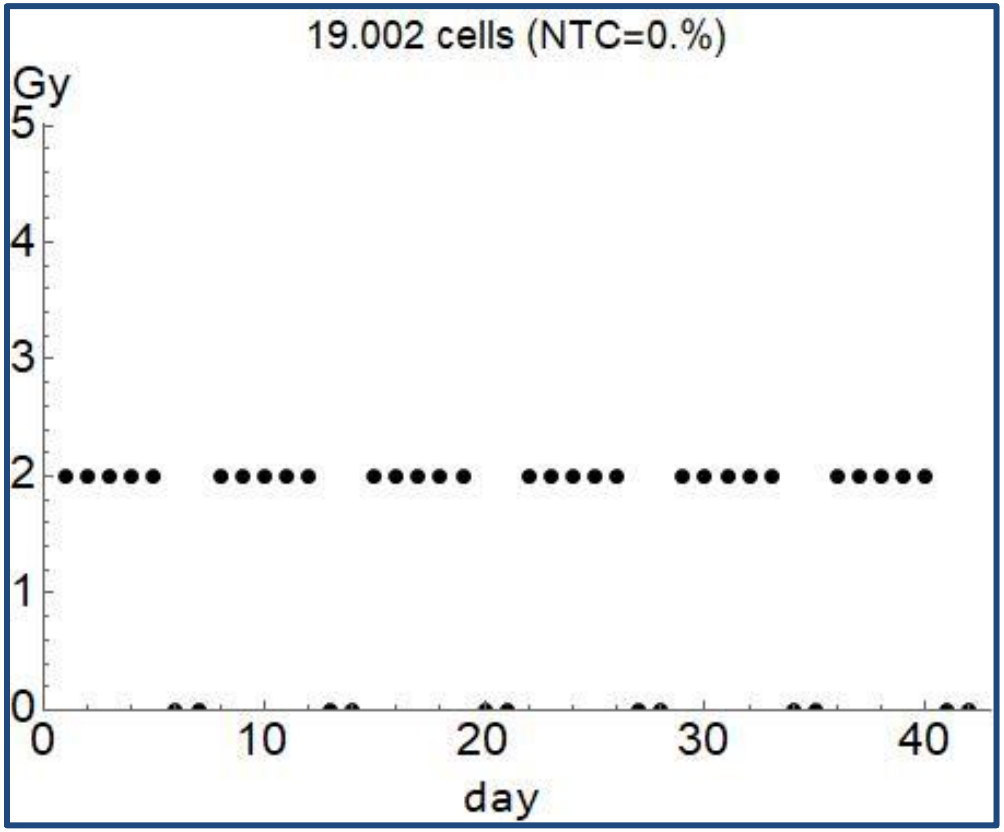
At that, the **Tumor Cure Probability increases**:

$$TCP(\mathbf{D}) = e^{-\min\limits_t(N(\mathbf{D},t))}$$

Optimization algorithm

Begin

Find optimal uniform fractionation scheme $\mathbf{D}_{actual}$



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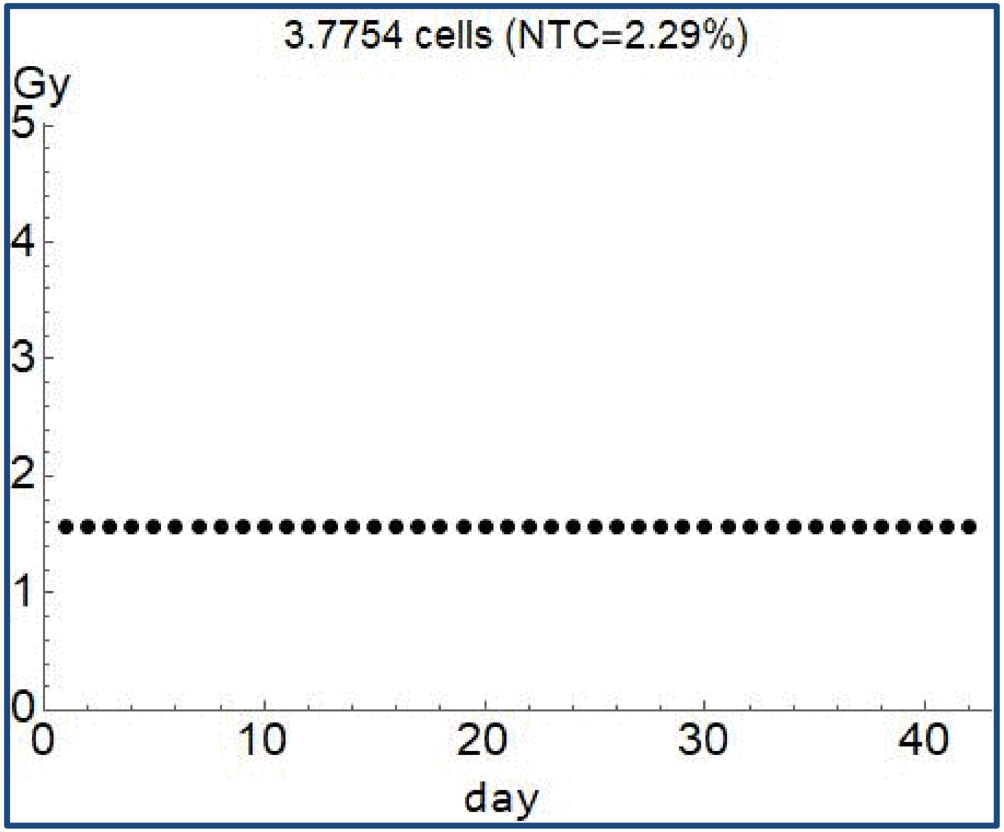

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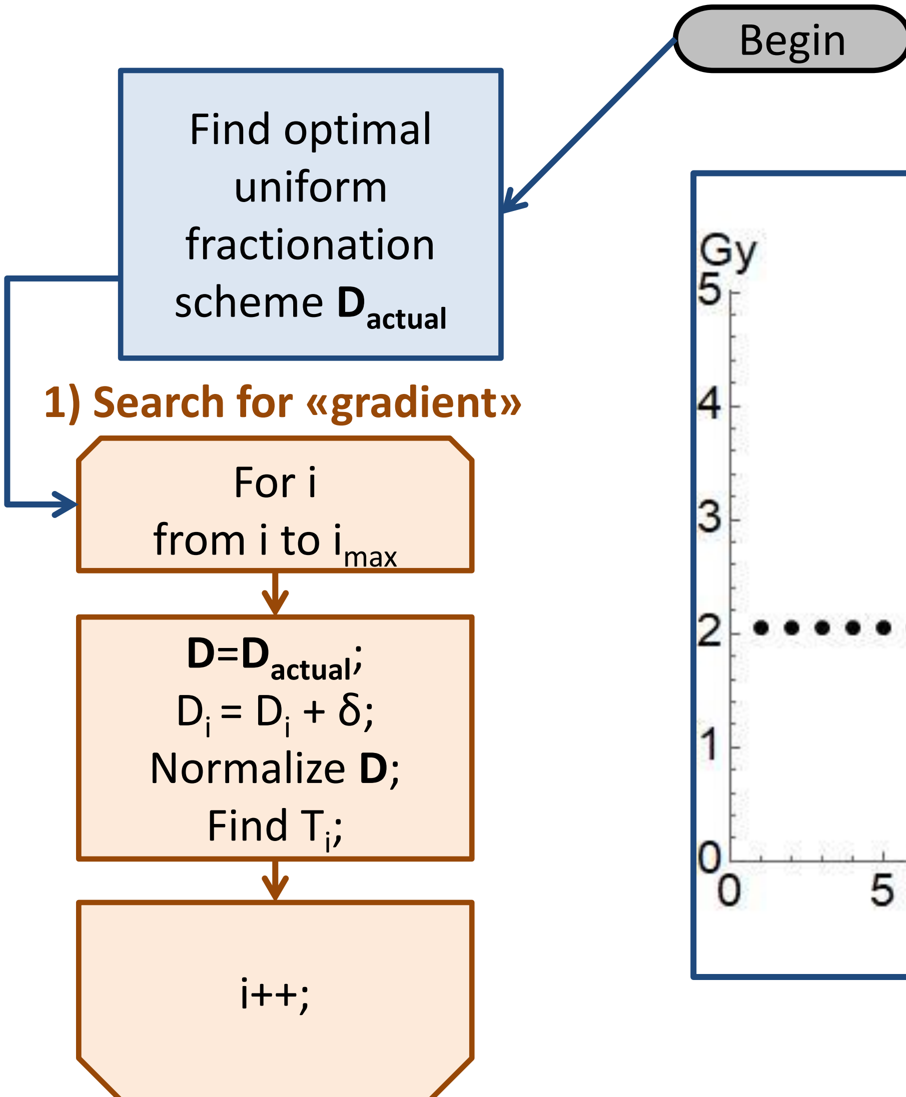

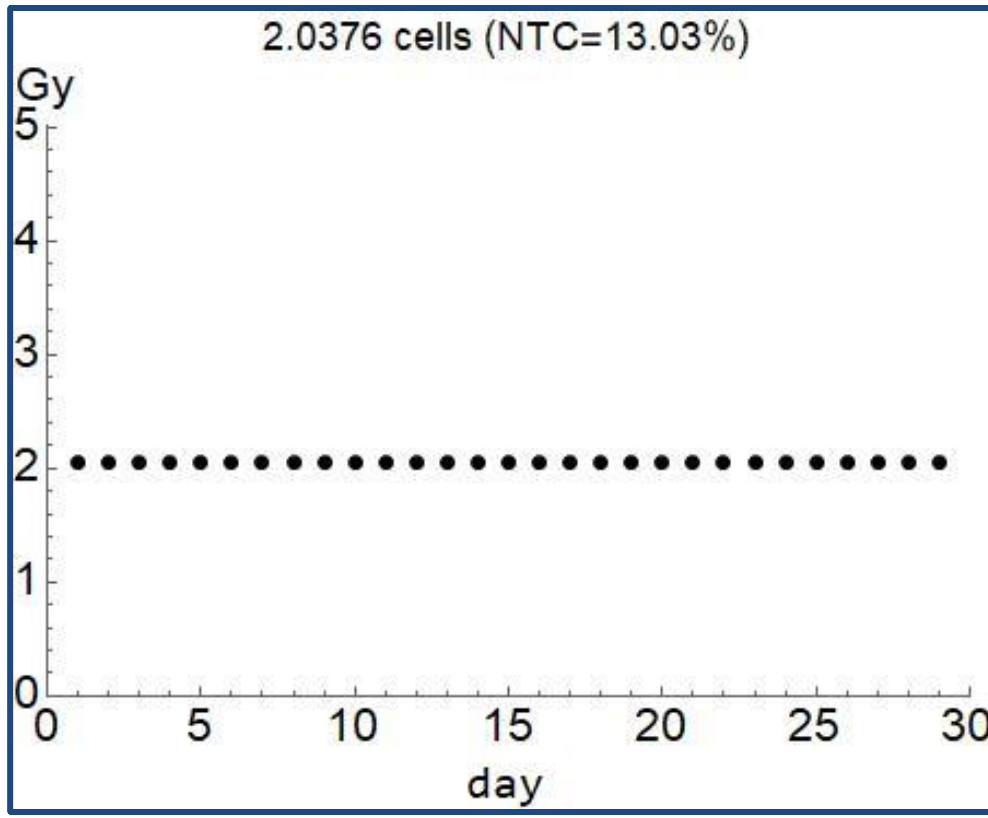

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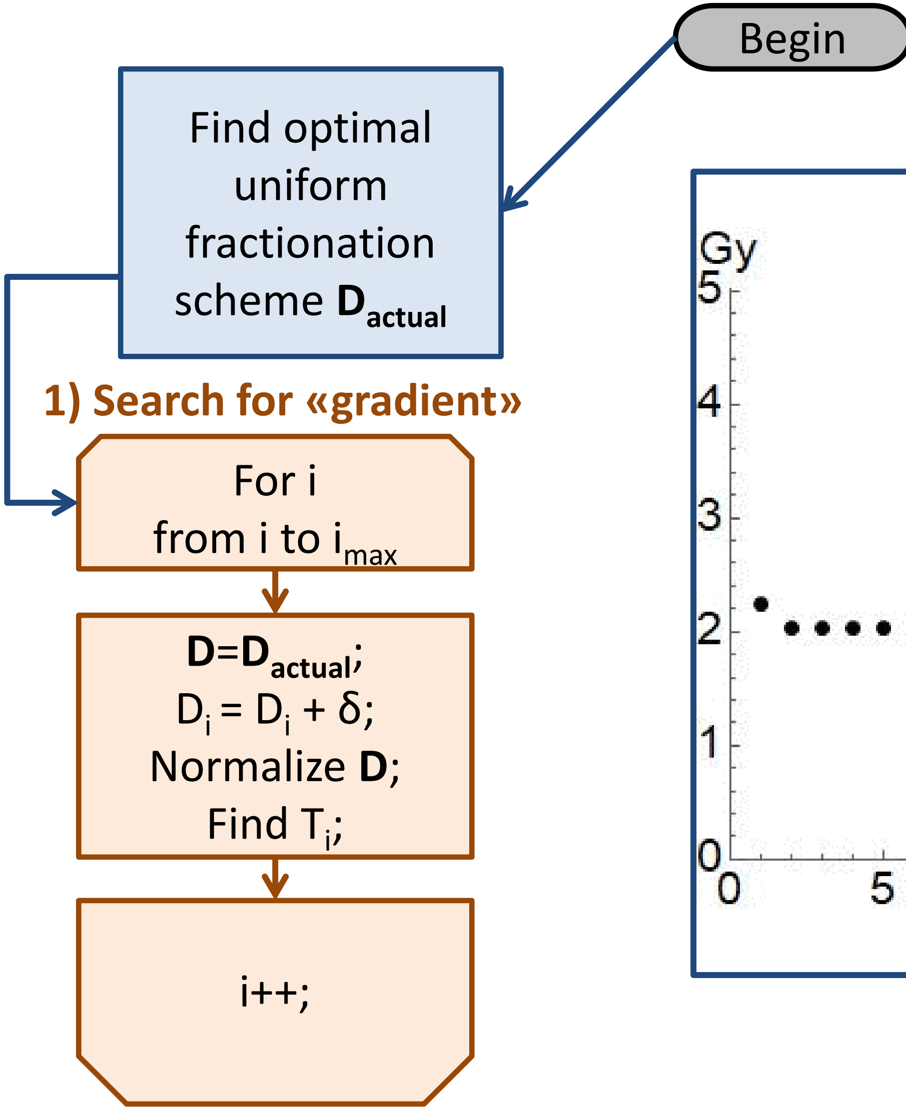

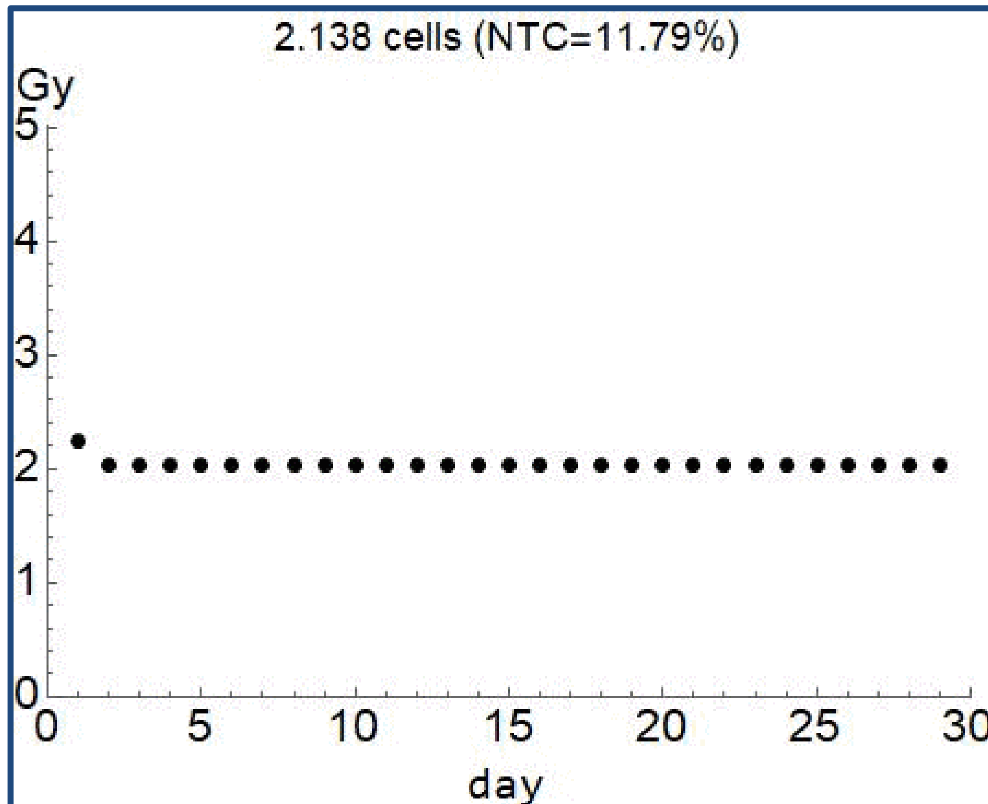

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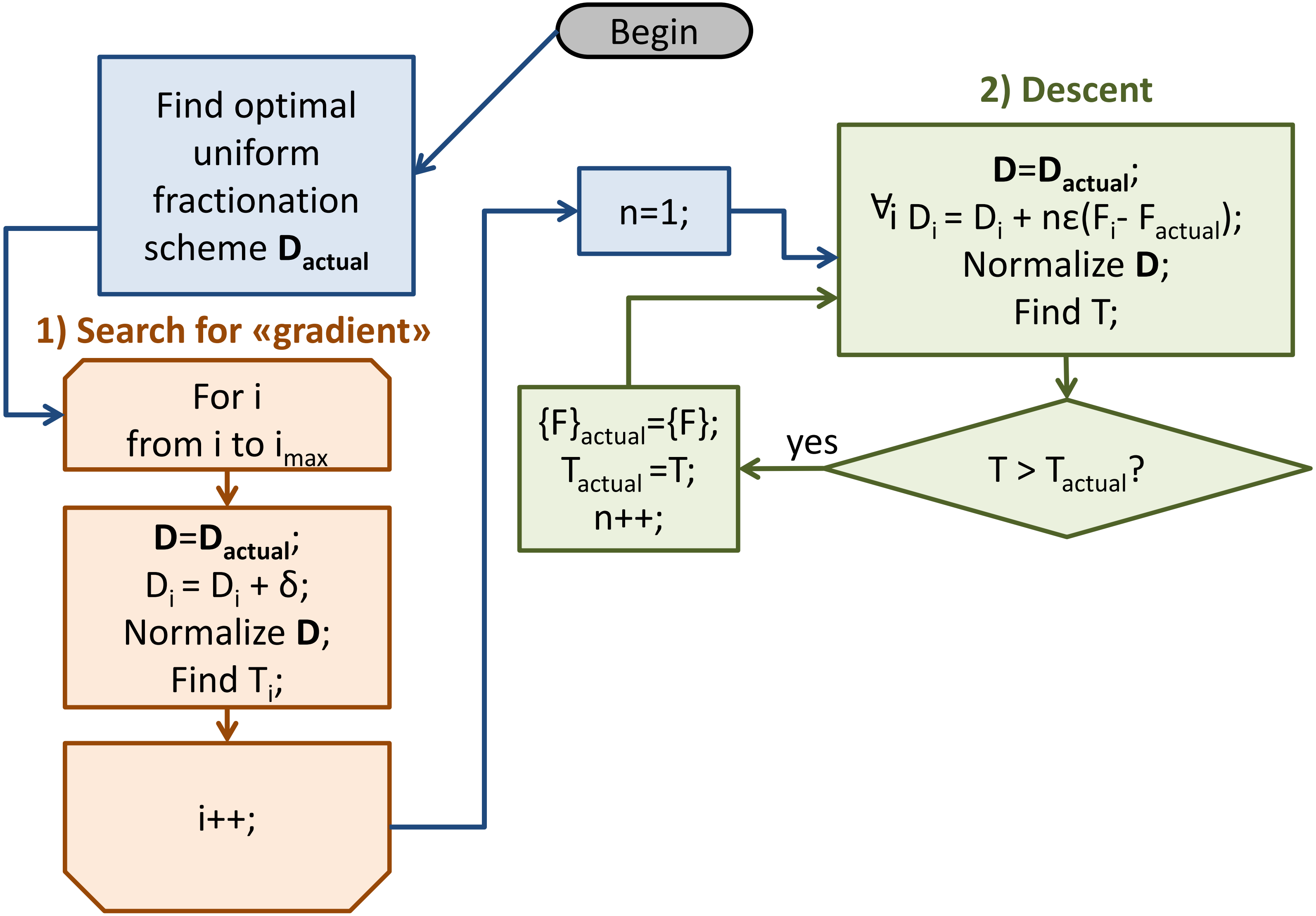

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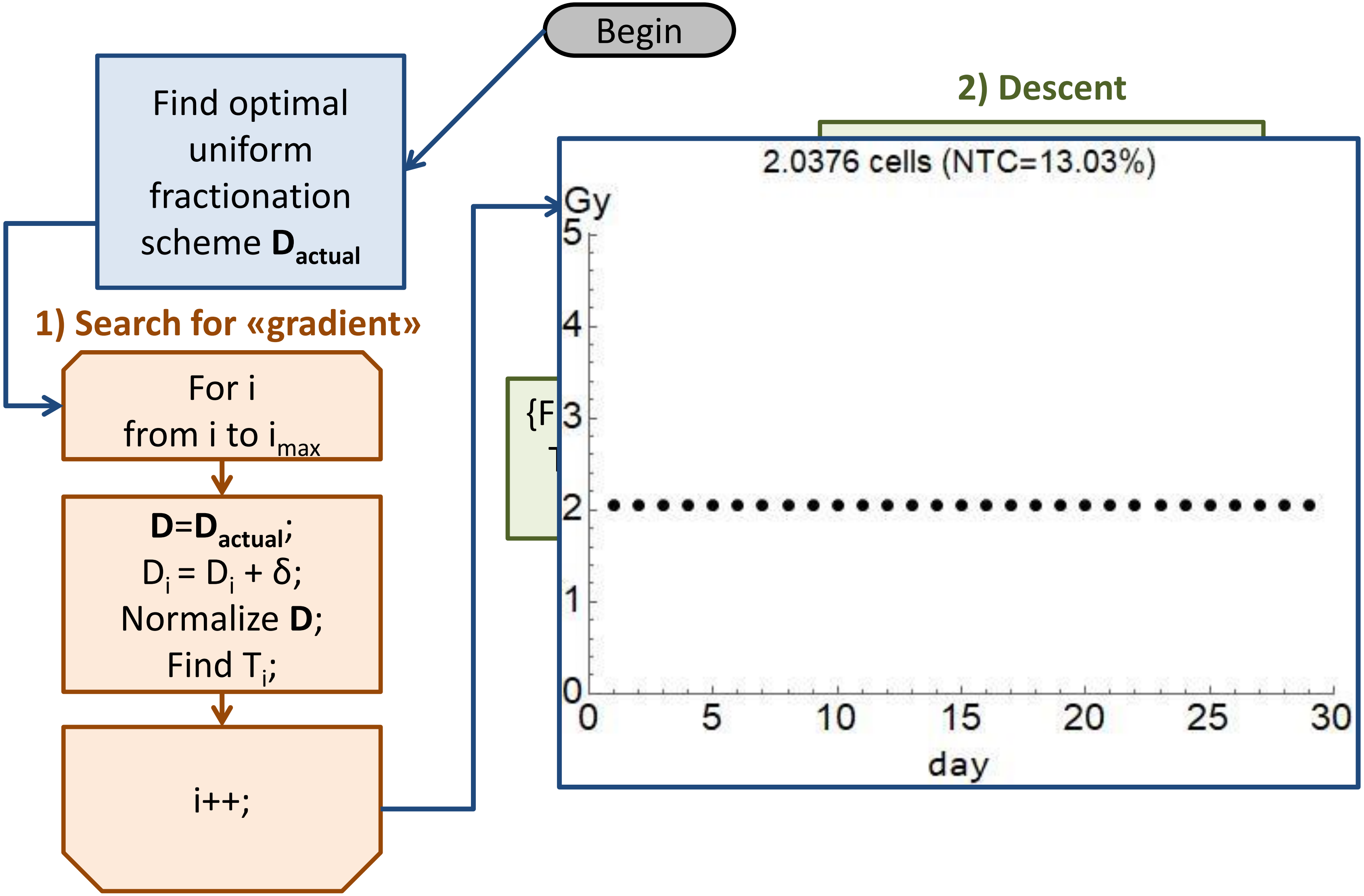

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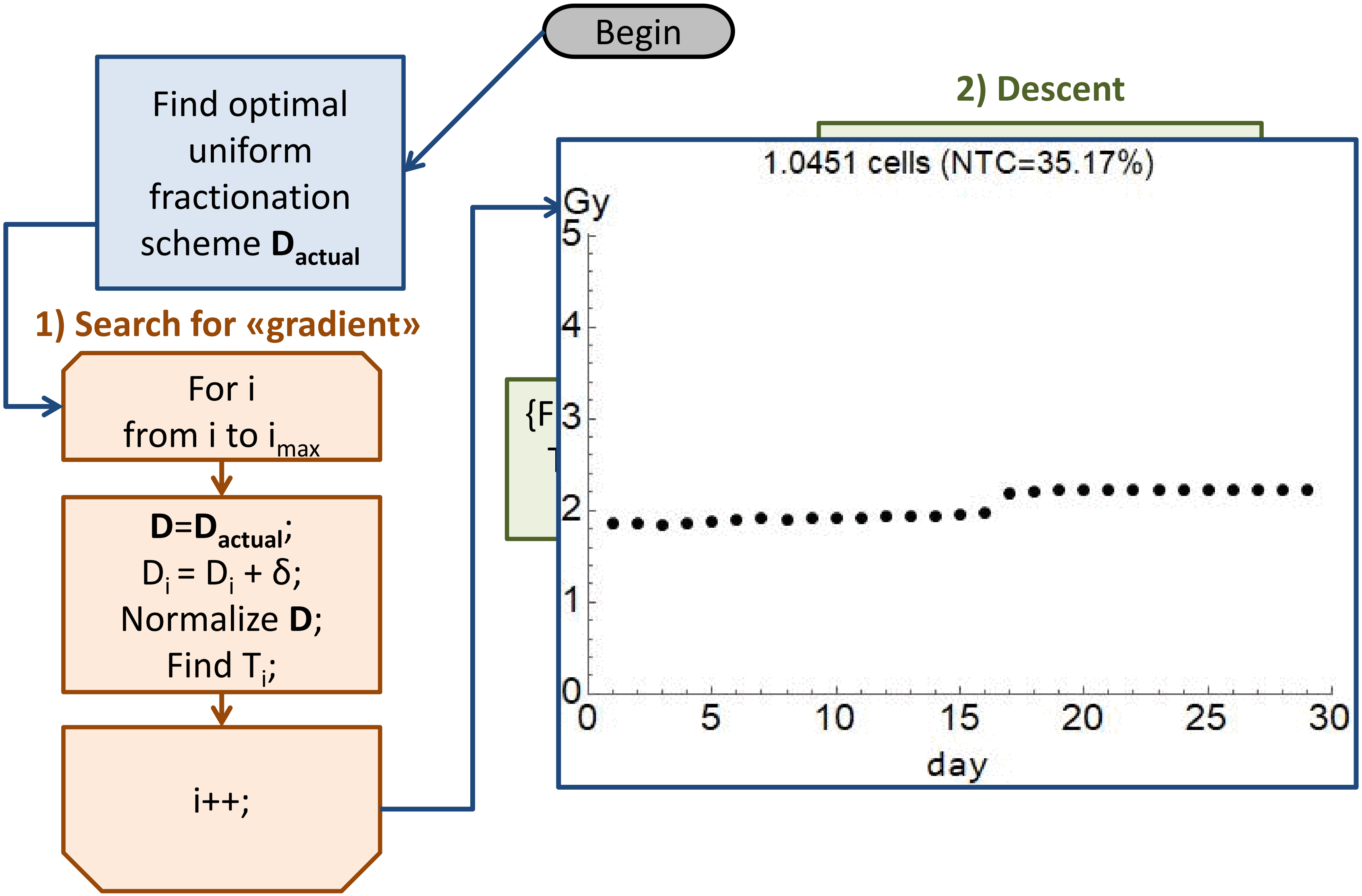

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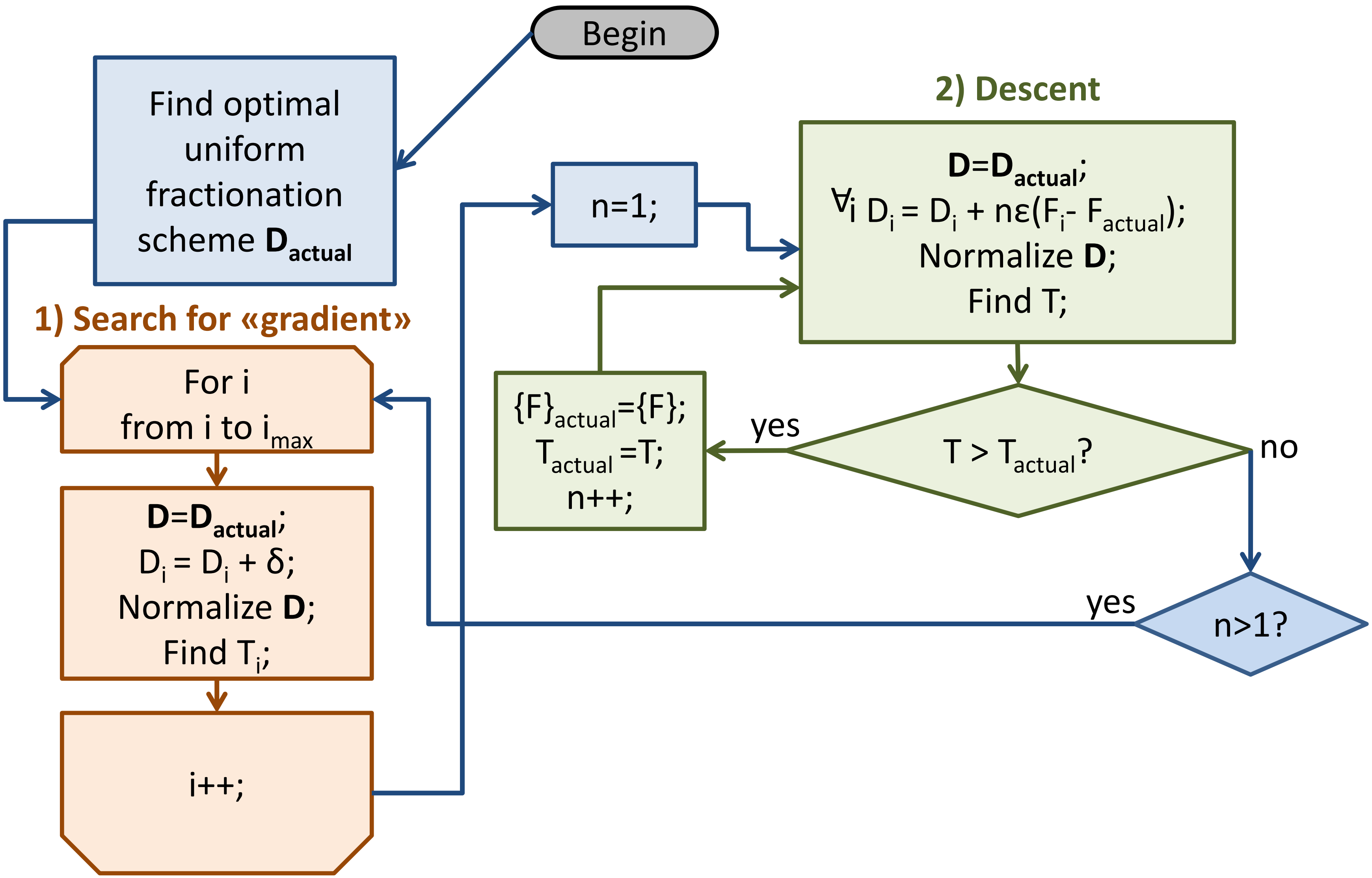

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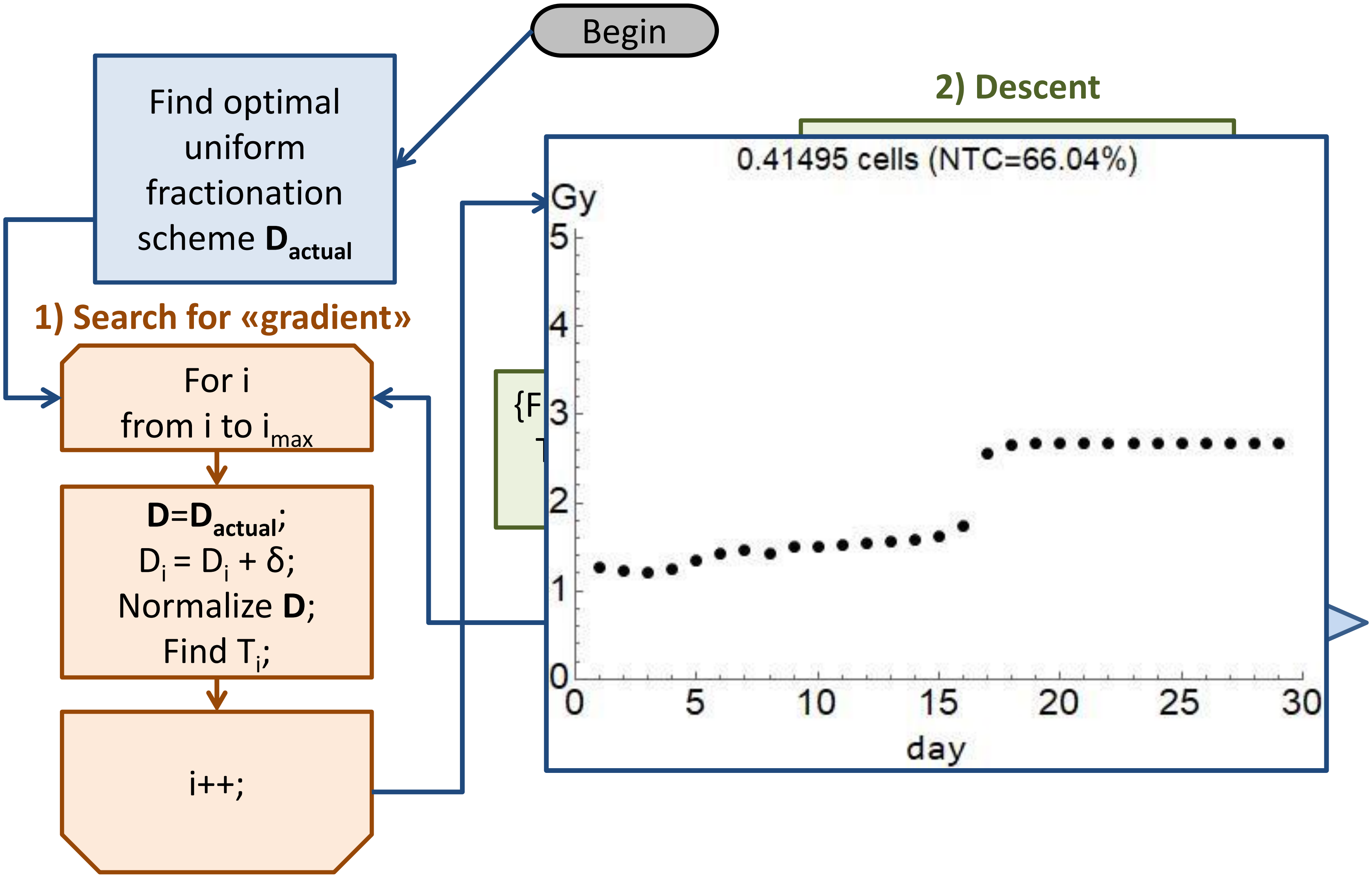

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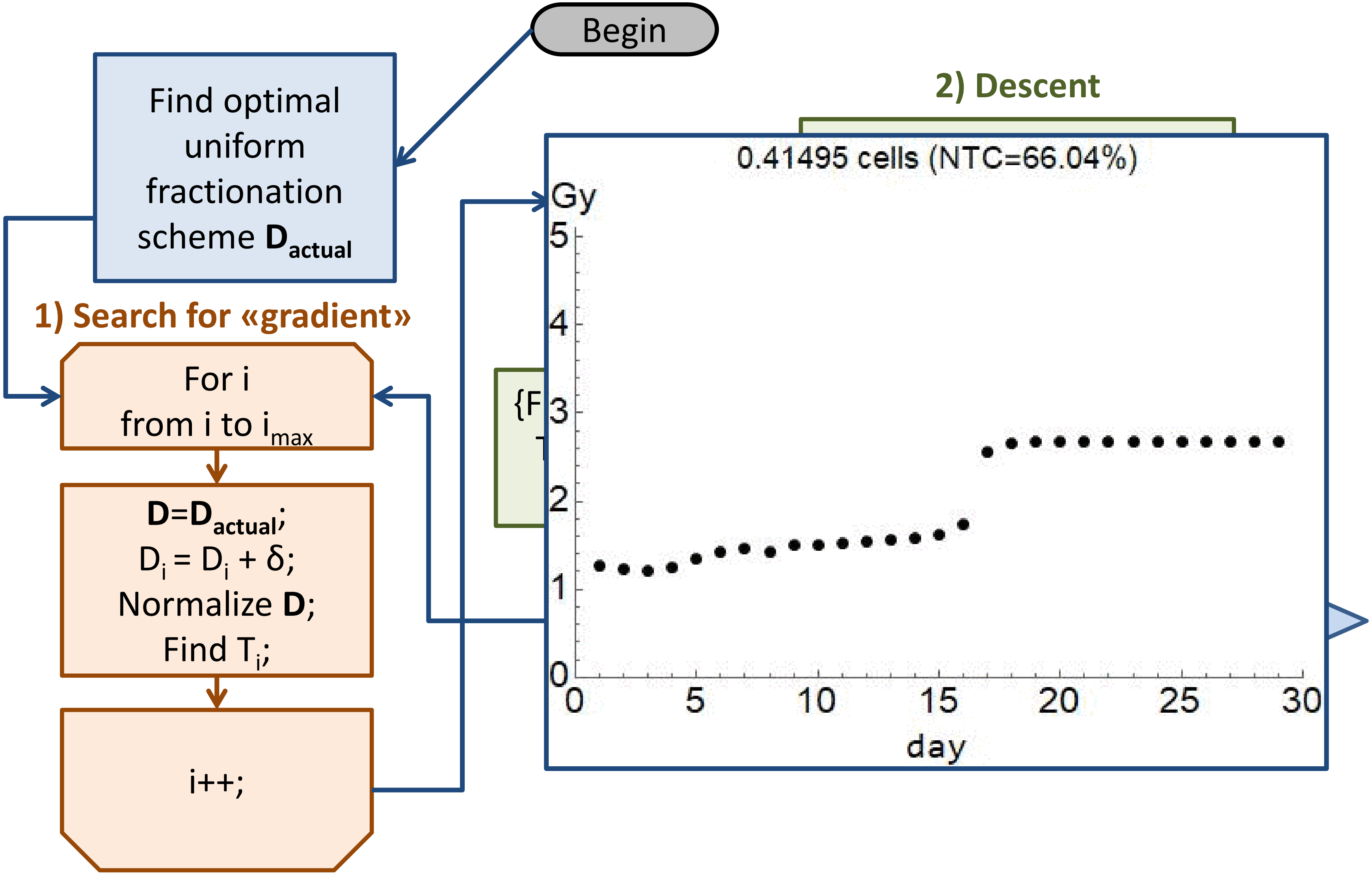


Model parameters

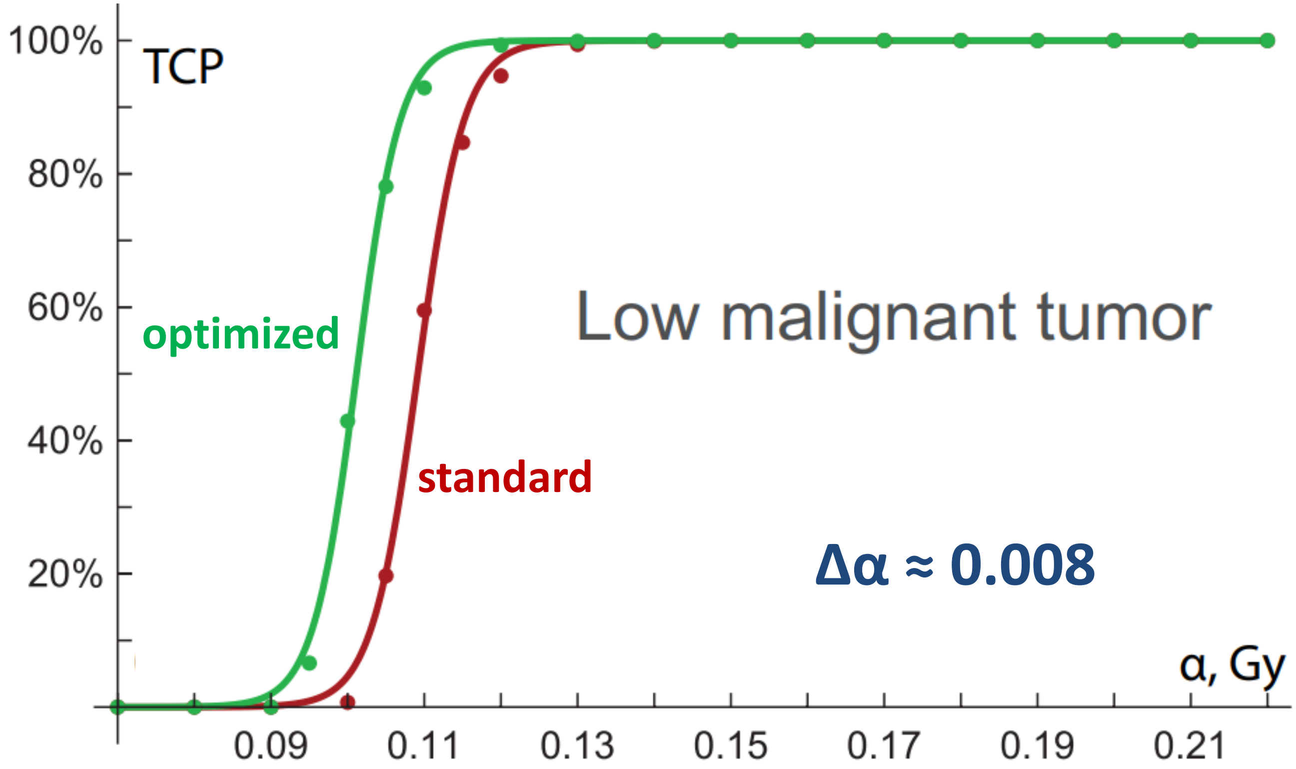
HM – high malignant tumor, *IM* – intermediate malignant tumor, *LM* – low malignant tumor.

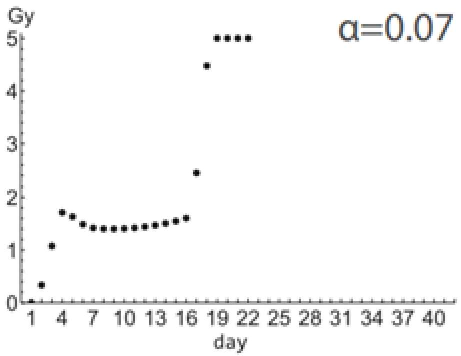
Parameter	Description	Model Value
B	tumor cells' proliferation rate	*HM*: 0.01 *IM*: 0.005 *LM*: 0.0025
ϵ	ratio of death rates of tumor and normal cells due to the lack of oxygen	*HM*: 0.3 *IM*: 0.7 *LM*: 1
D_n	tumor cells' motility	*HM*: 0.01 *IM*: 0.001 *LM*: 0
P_g	glucose inflow parameter	*HM*: 20 *IM*: 10 *LM*: 4
P_ω	oxygen inflow parameter	*HM*: 50.8 *IM*: 35.8 *LM*: 25.4
Q_n^g	tumor cells' glucose consumption rate	*HM*: 12 *IM*: 6 *LM*: 3
Q_n^ω	tumor cells' oxygen consumption rate	*HM*: 63 *IM*: 31.5 *LM*: 15.75
k	ratio of radiosensitivity of quiescent and proliferating tumor cells	*HM*: 1 *IM*: 0.5 *LM*: 0.2

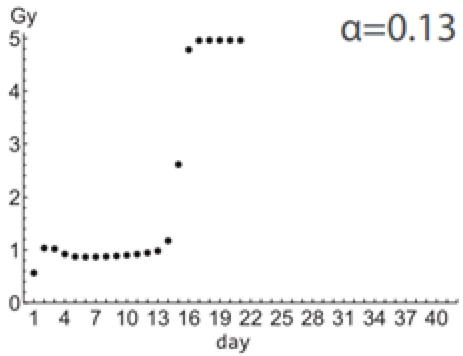
Malignant tumor cells:

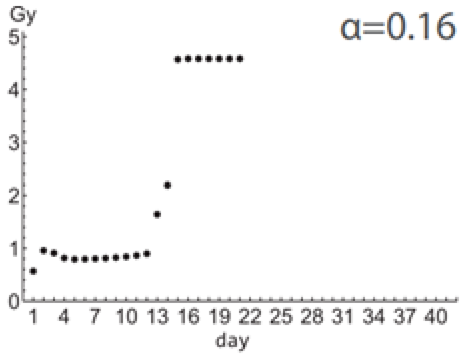
- **divide faster**
- die harder
- move faster
- induce angiogenesis
- consume more nutrients
- **become more radiosensitive in quiescent state (optional)**

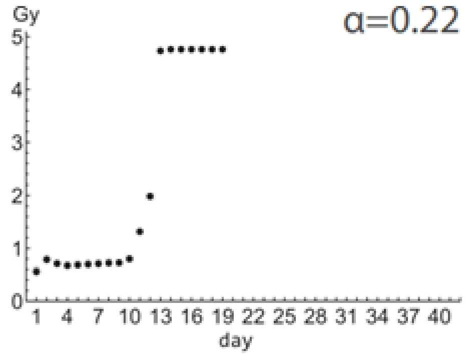
Standard vs. optimized fractionation schemes



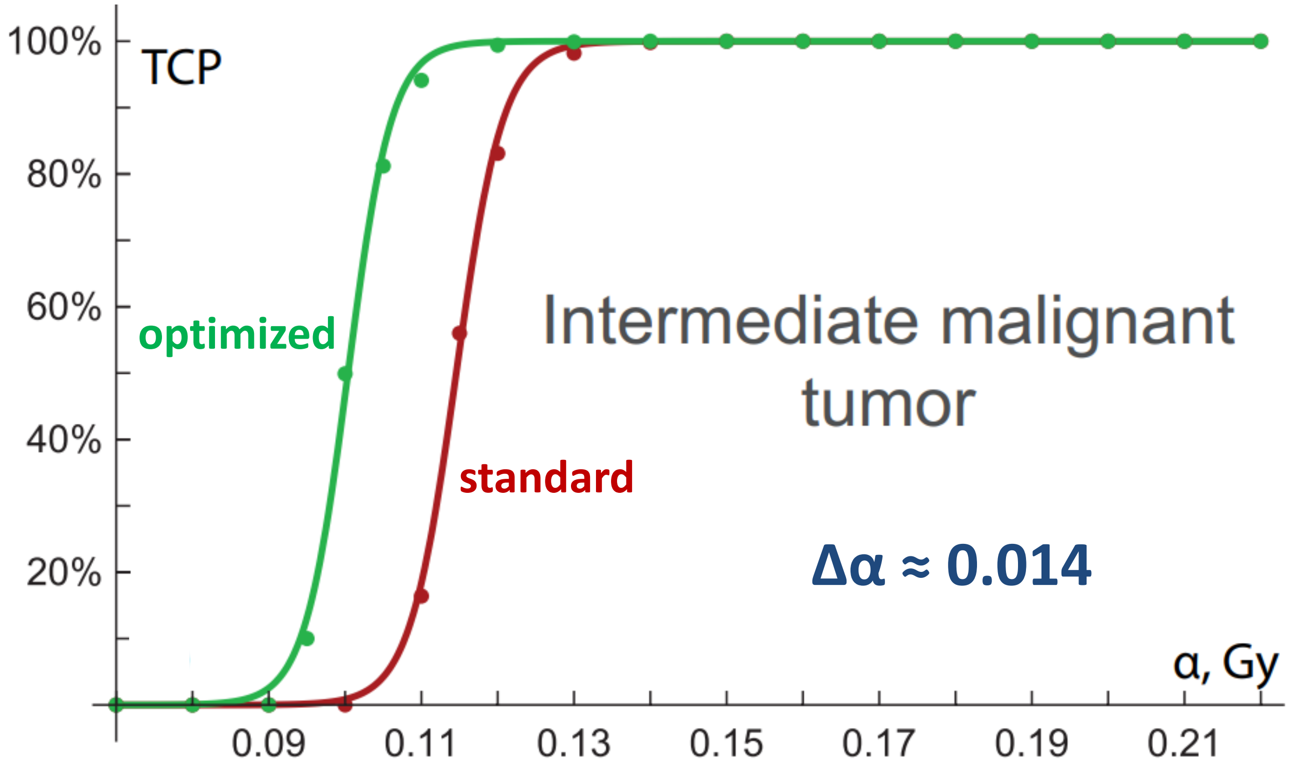


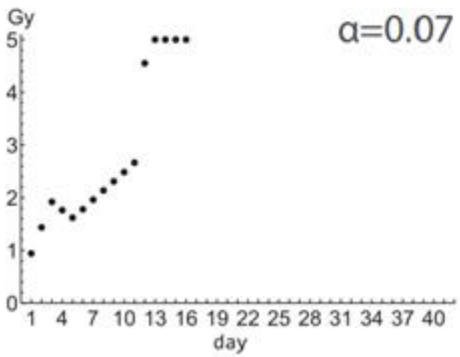


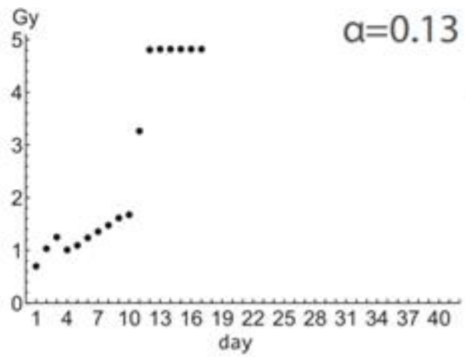


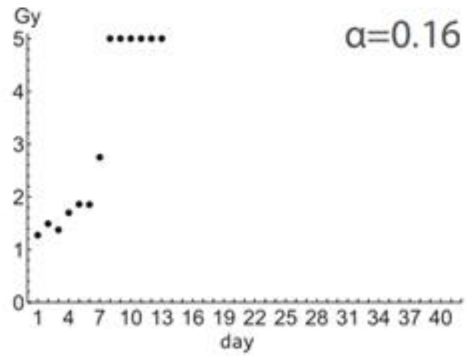


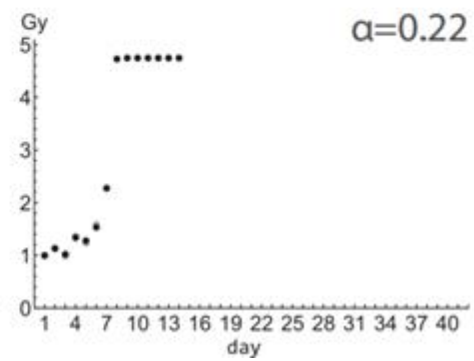
Standard vs. optimized fractionation schemes



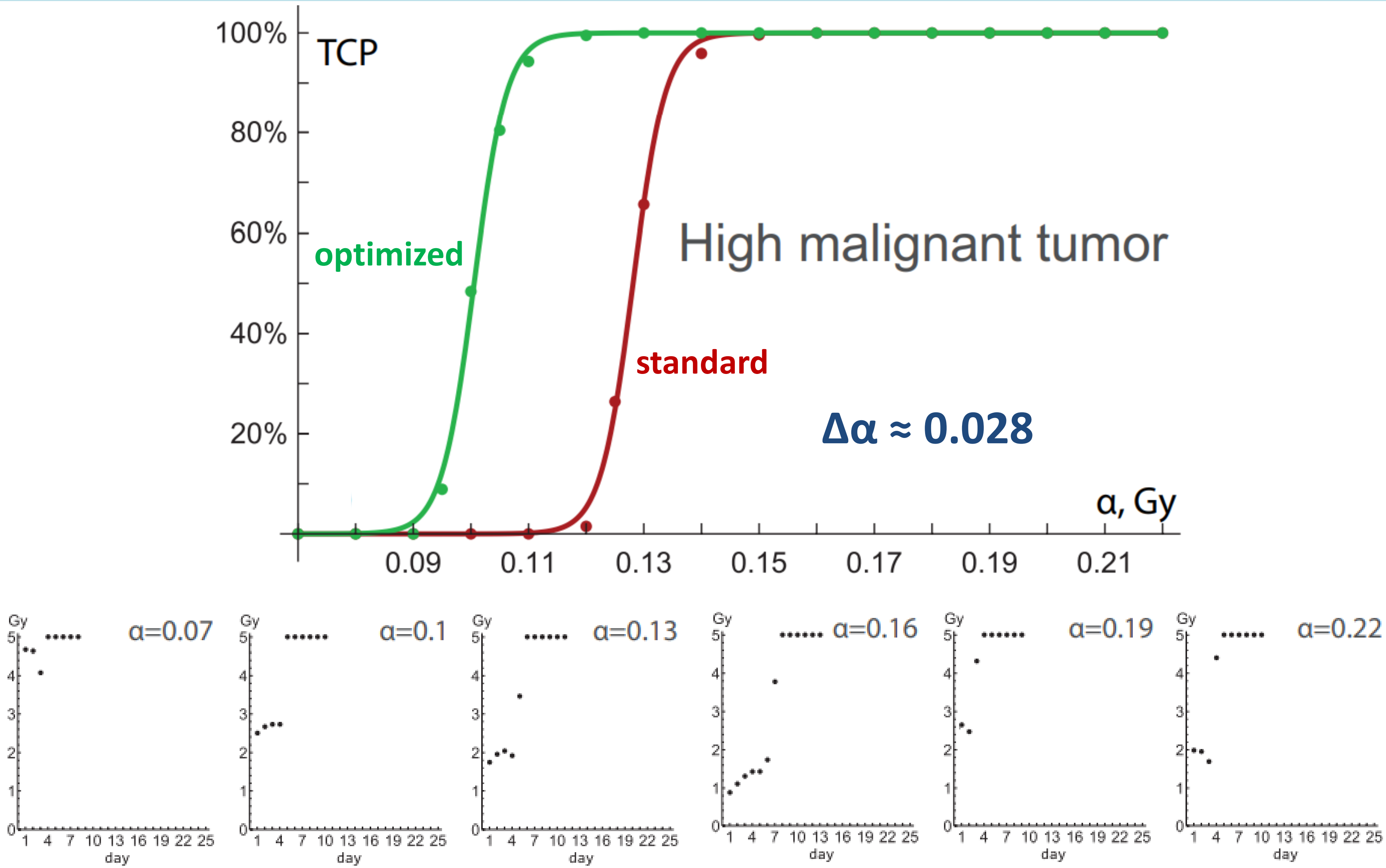




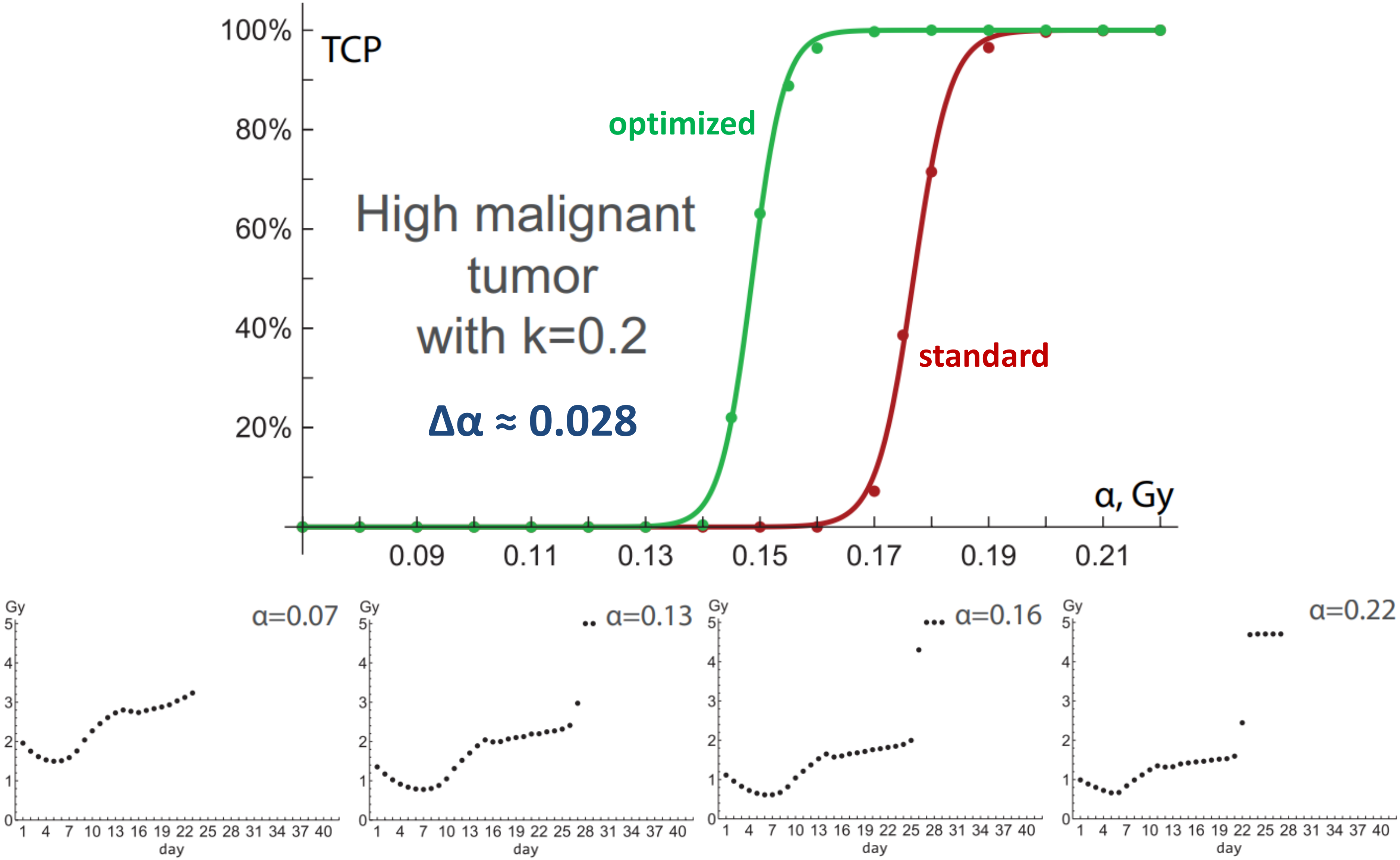




Standard vs. optimized fractionation schemes



Standard vs. optimized fractionation schemes



Optimization of spatial distribution of irradiation – what happens now

Imaging-based **dose painting** – first suggested in 2000 *(Ling et al. 2000)*

What can be accounted for:

- **hypoxia profile**
- **cell proliferation profile**
- **cell density profile**
- stem cells positioning

How it can be accounted for:

- **PET imaging**
- **FDG-PET, FLT-PET**
- **DW-MRI**

→ **dose painting by volume**

→ **dose painting by number**

Main problems:

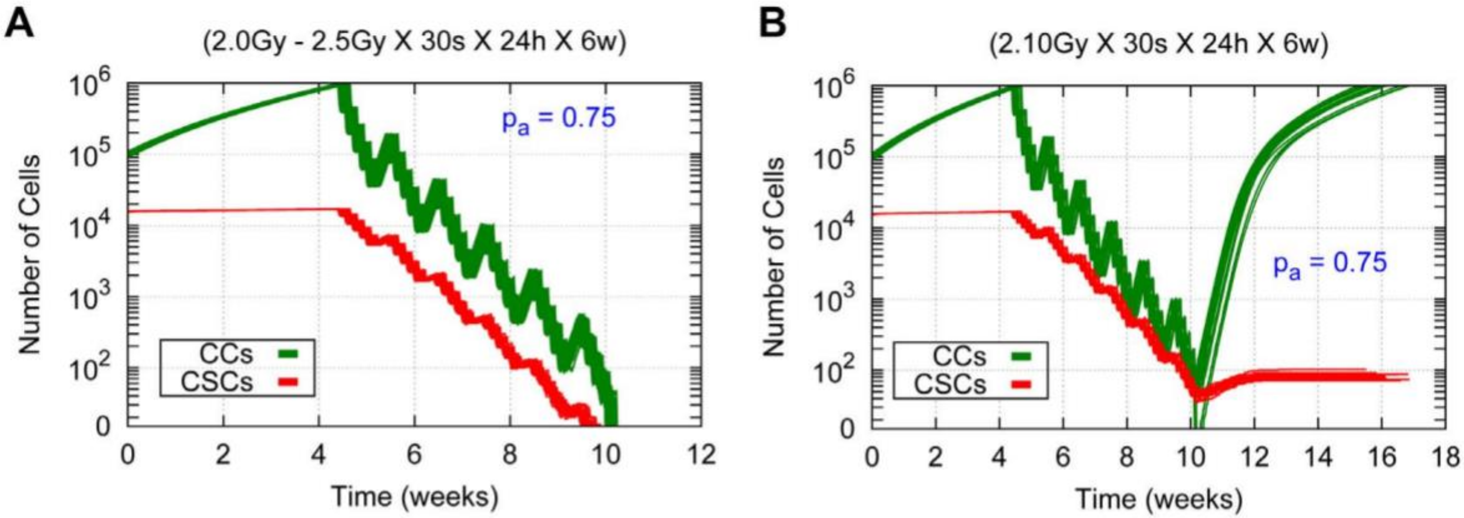
heterogeneity in time & lack of resolution

Results:

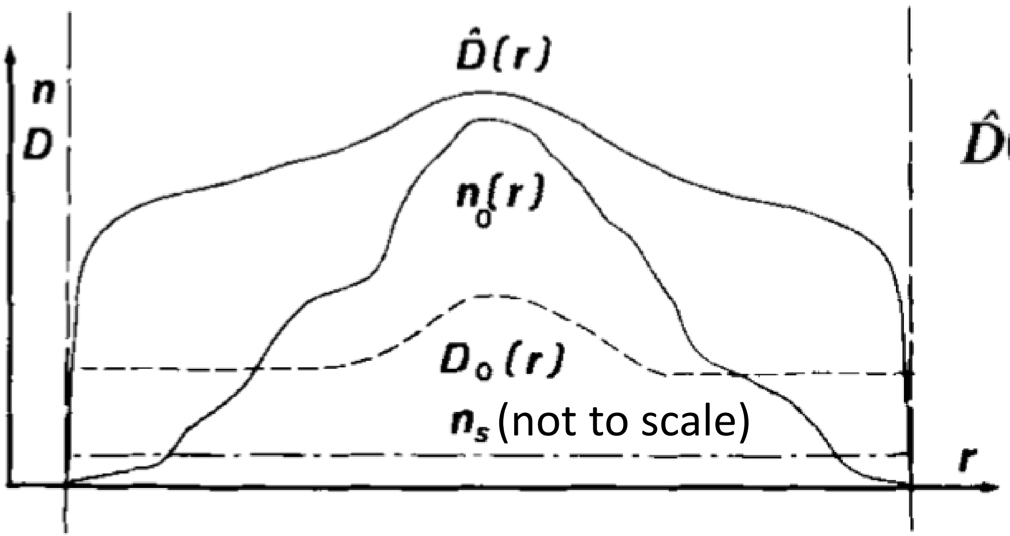
- **hypoxia dose painting is feasible** ***(Lee et al. 2008, Servagi-Vernat et al. 2015)*** **but does not improve tumor response** ***(Vera et al. 2017)***
- **FDG-PET dose painting is feasible but only phase I trial has been conducted** ***(Madani et al. 2011)***
- **No clinical dose painting studies for DW-MRI**

Joiner M. C., van der Kogel A. J. (ed.) Basic clinical radiobiology, 2018.

Optimization of spatial distribution of irradiation – what works exist



López Alfonso J. C. et al. //PloS one. – 2014. – T. 9. – №. 2. – C. e89380.



$$\hat{D}(\mathbf{r}) = D_0(\mathbf{r}) \ln \left\{ \frac{n_0(\mathbf{r})}{\bar{n}_s} \right\} = D_0(\mathbf{r}) \ln \left\{ \frac{n_0(\mathbf{r}) V_t}{-\ln P_e} \right\}$$

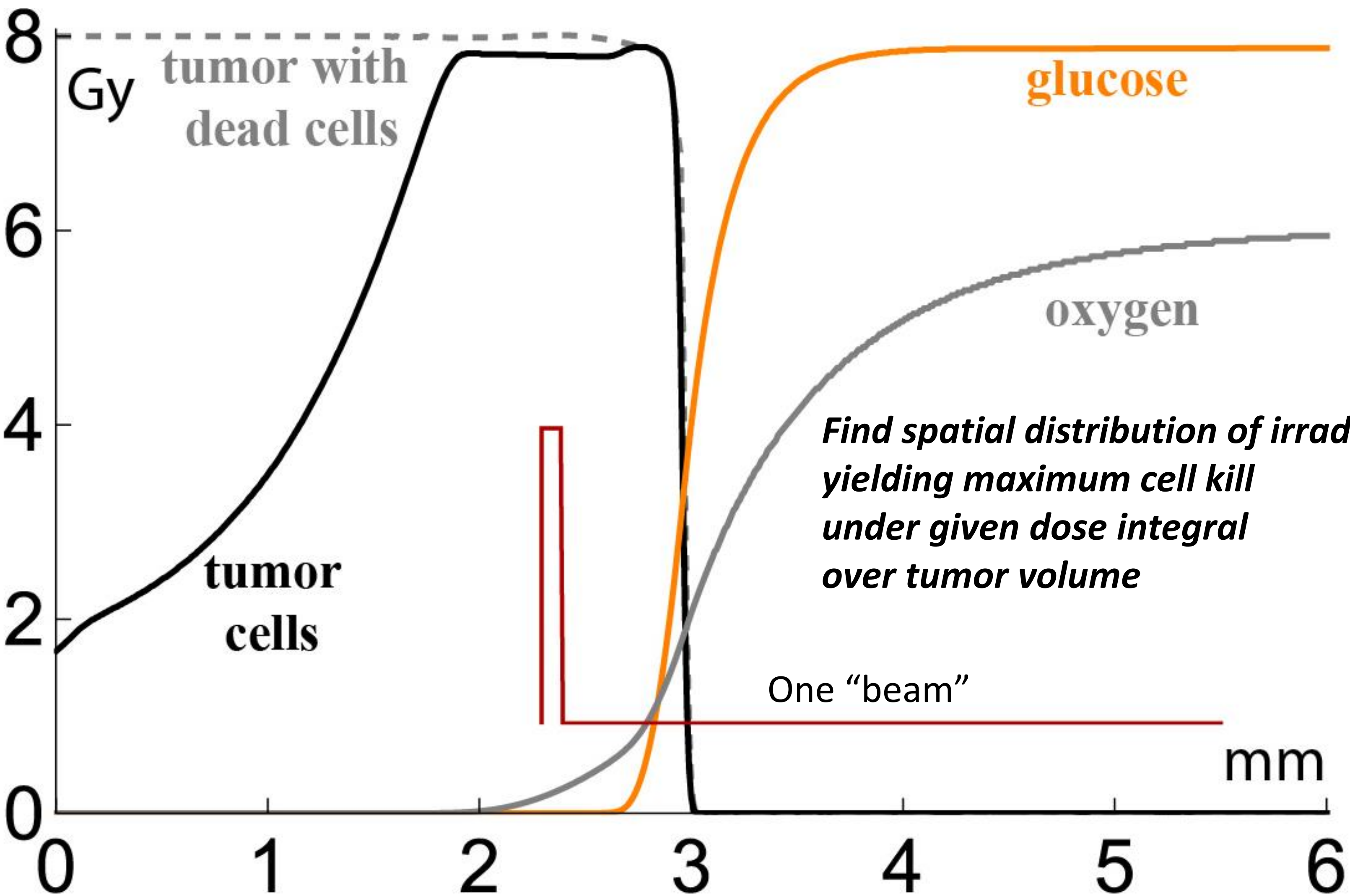
tumor volume

radioresistance (1/α)

desired probability of tumor eradication

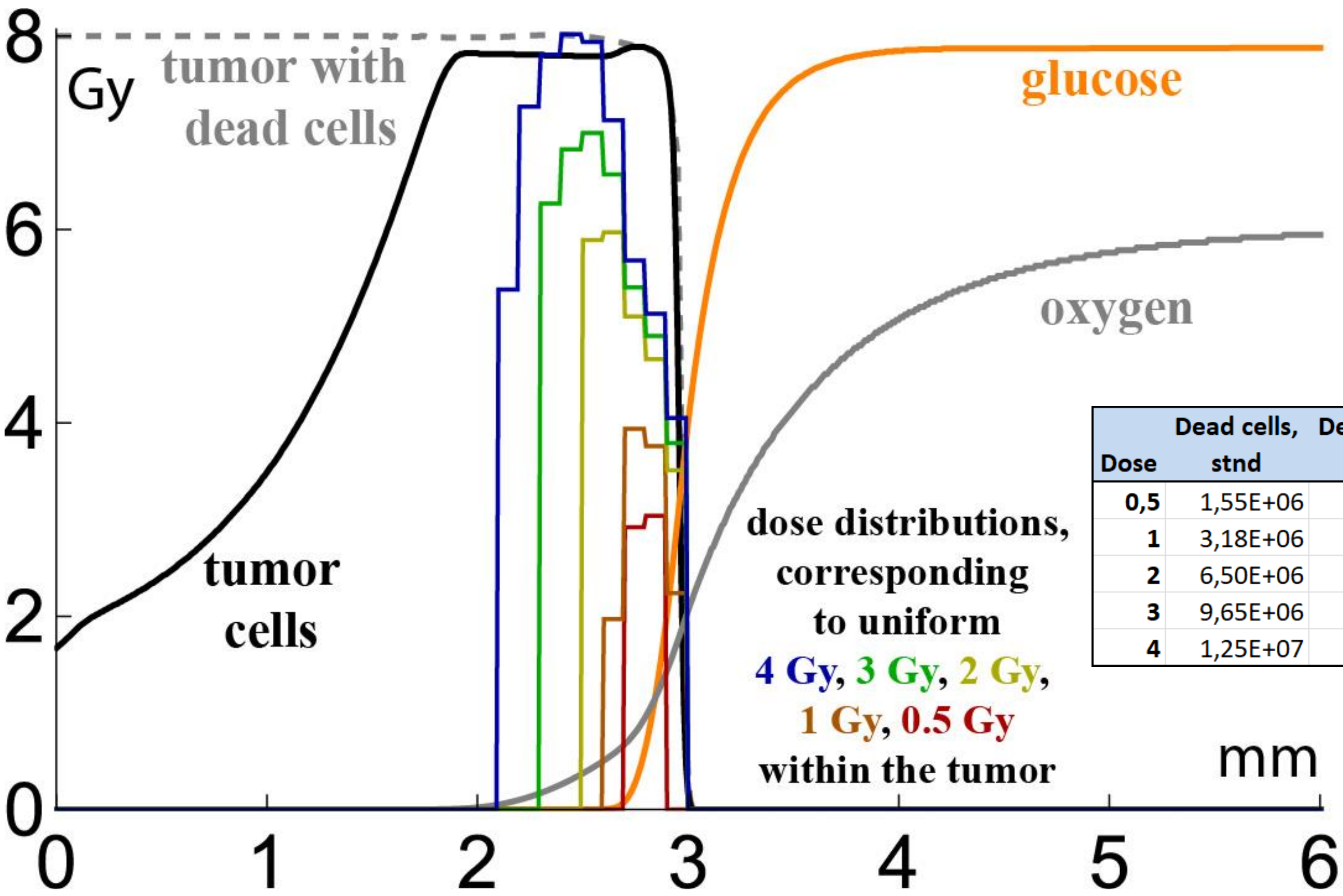
Brahme A., Argren A. K. //Acta Oncologica. – 1987. – T. 26. – №. 5. – C. 377-385.

Task formulation



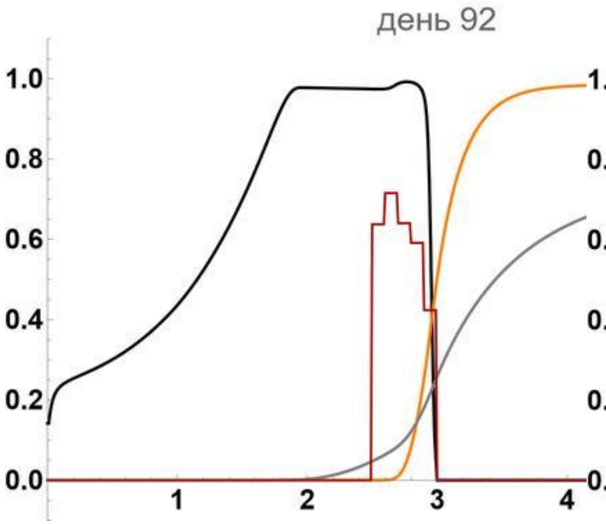
Find spatial distribution of irradiation, yielding maximum cell kill under given dose integral over tumor volume

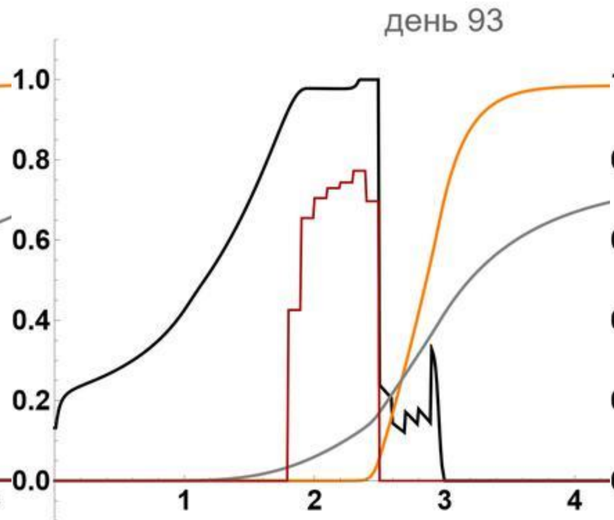
Spatial optimization of one irradiation

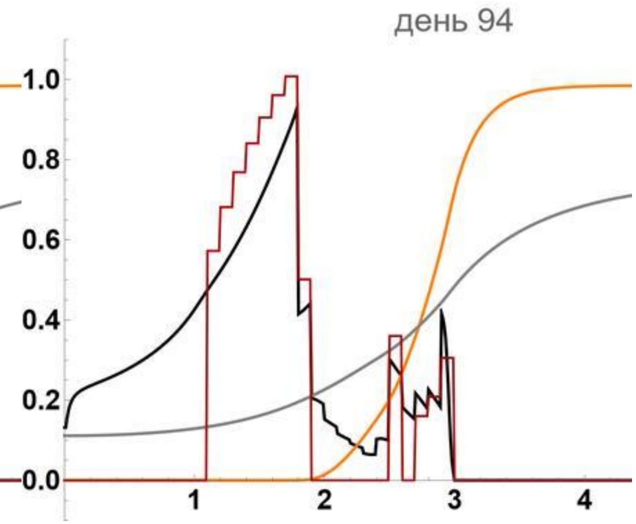


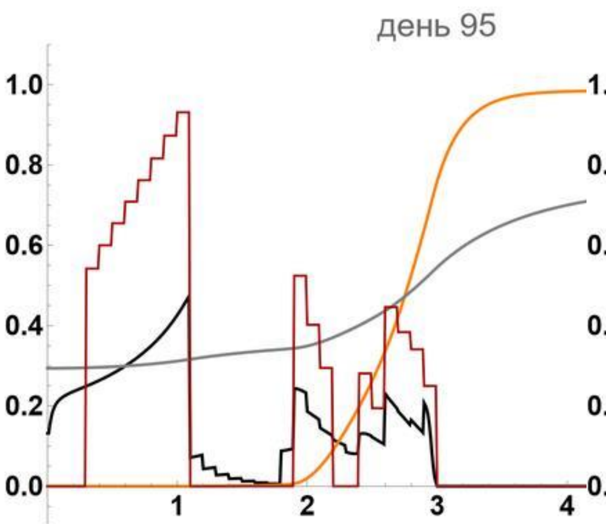
Dose	Dead cells, stnd	Dead cells, opt	Ratio
0,5	1,55E+06	3,36E+06	**217%**
1	3,18E+06	5,67E+06	**179%**
2	6,50E+06	9,19E+06	**141%**
3	9,65E+06	1,20E+07	**124%**
4	1,25E+07	1,43E+07	**115%**

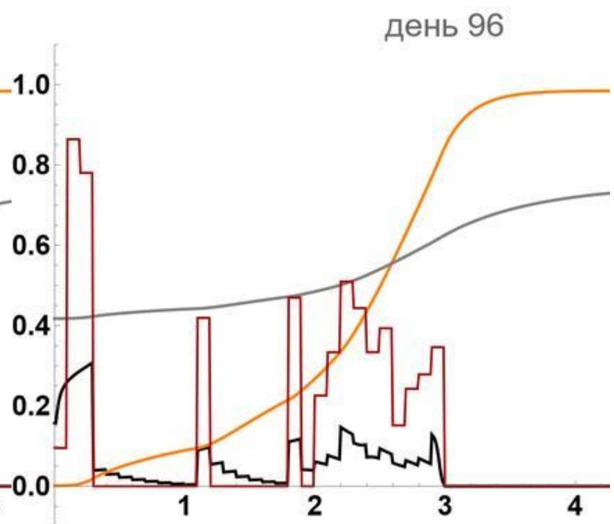
Spatial optimization of 5 irradiations





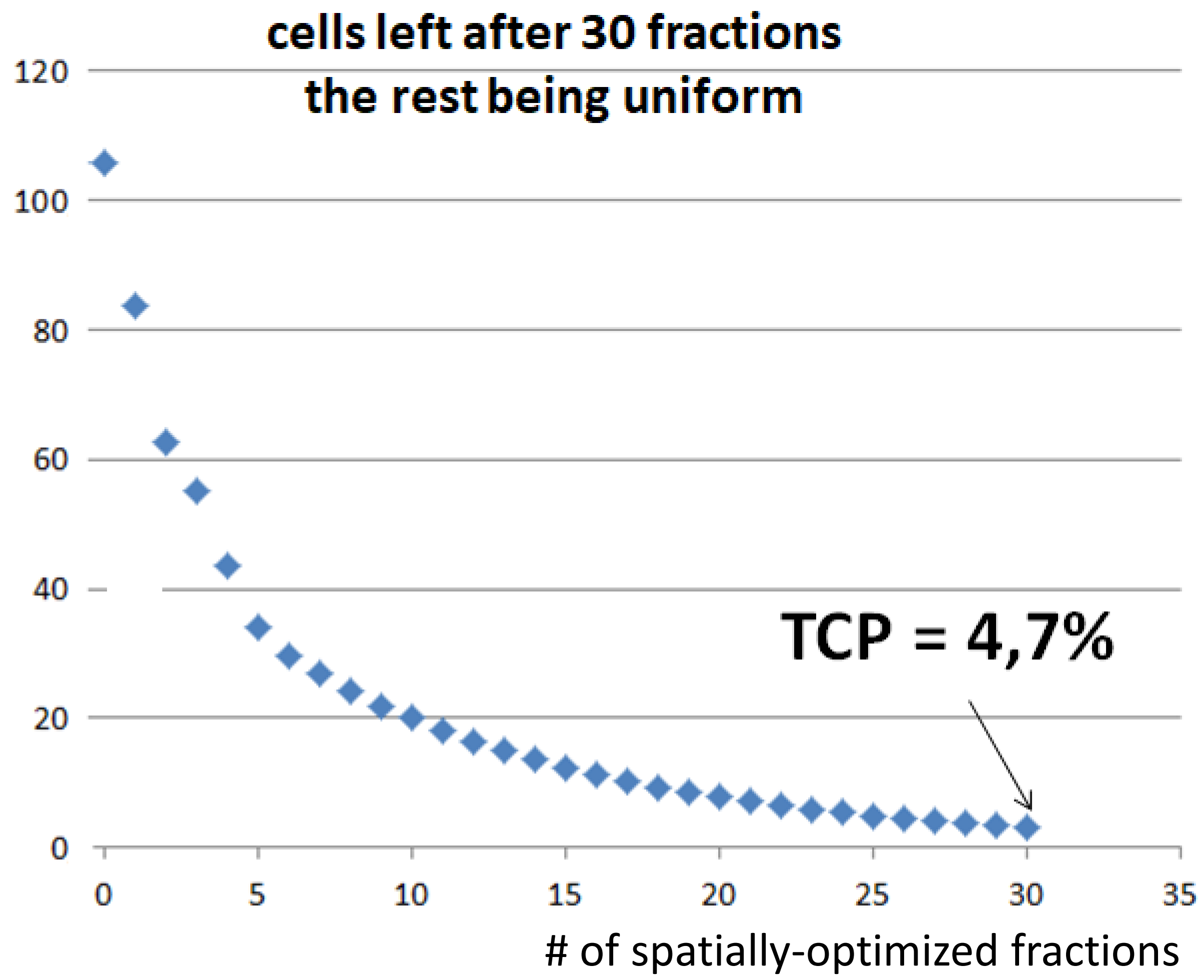




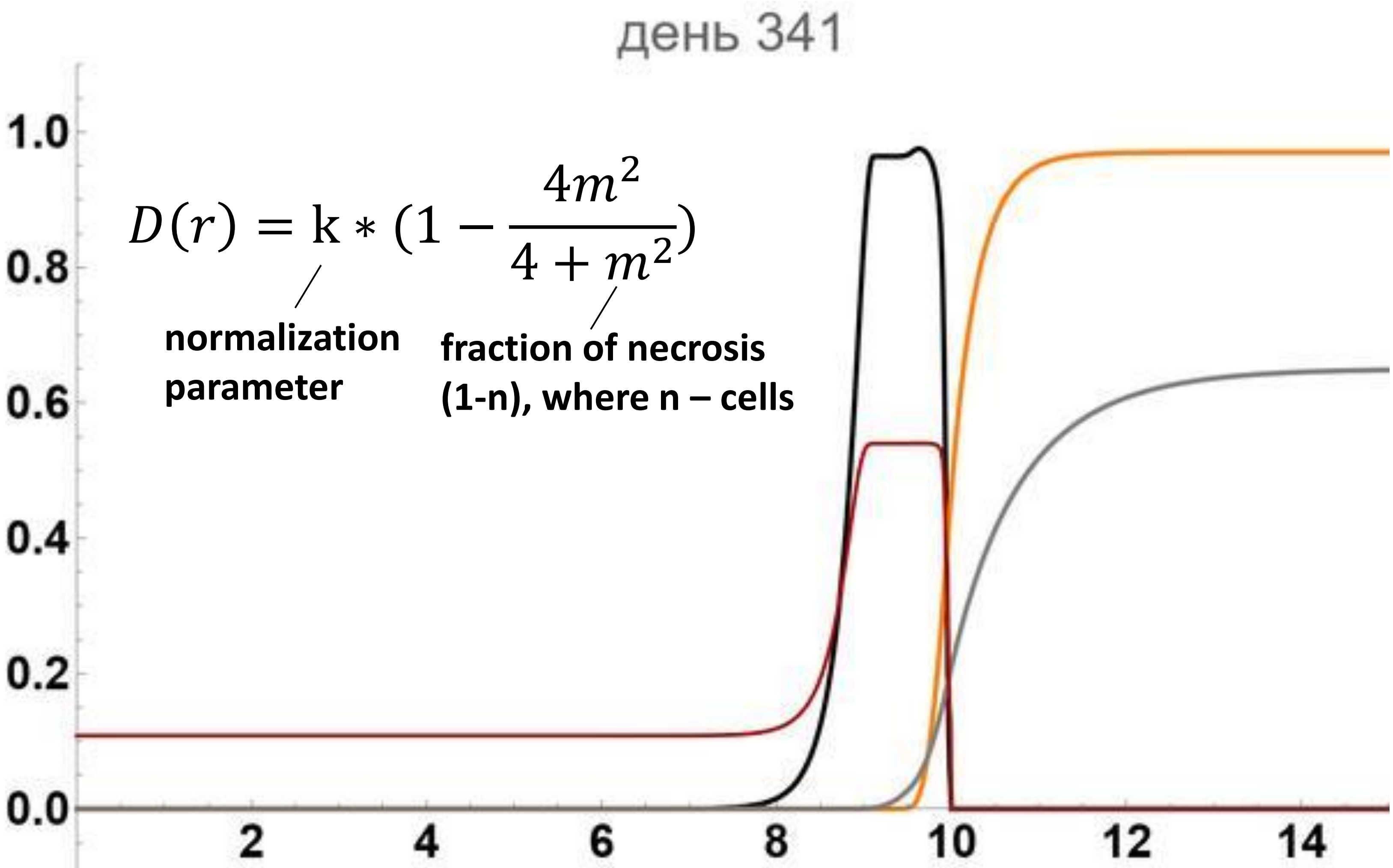


#	relative efficiency compared to uniform	cells left after 30 fractions the rest being uniform
0	141%	106
1	162%	84
2	141%	63
3	128%	55
4	121%	44
5	112%	34

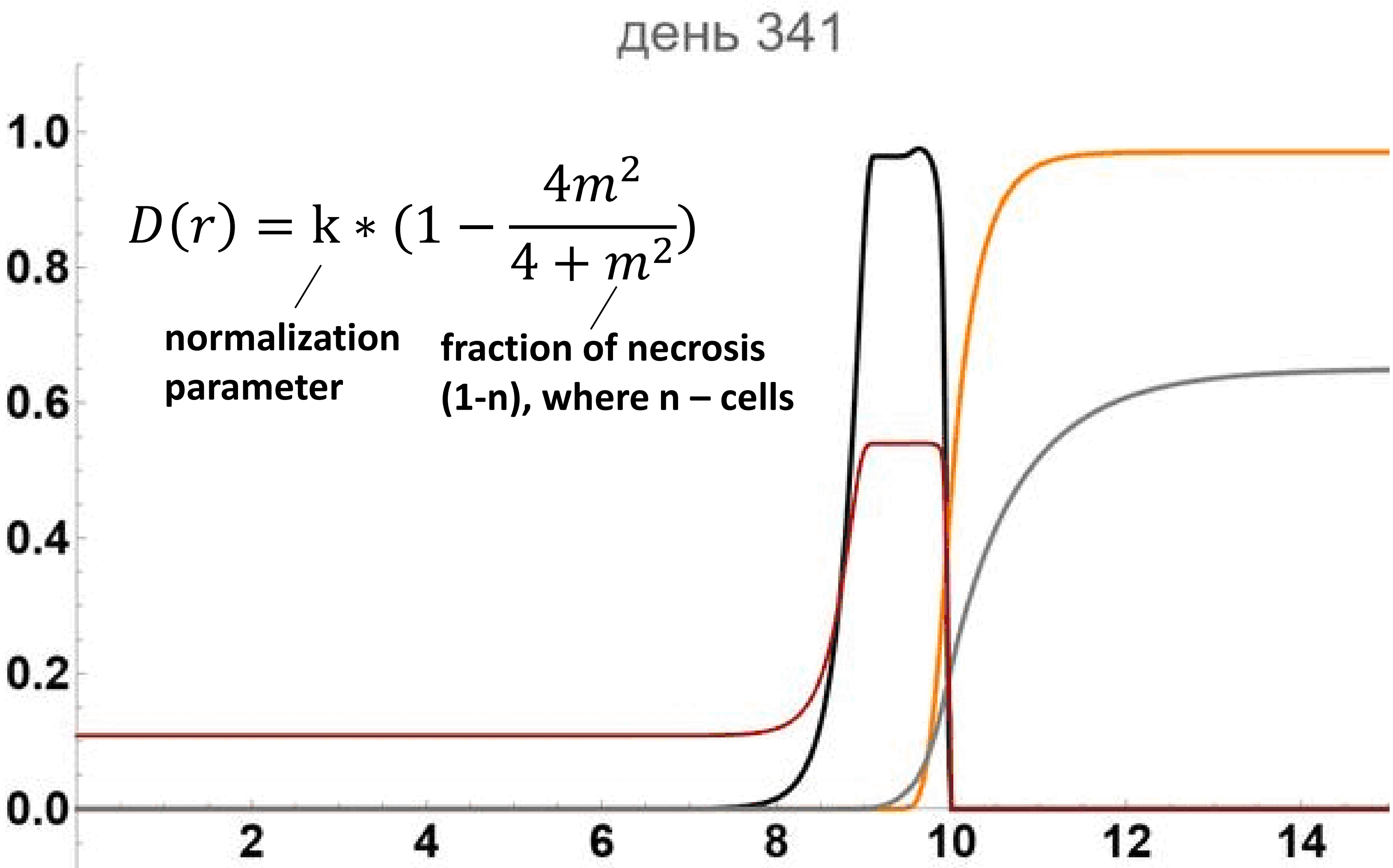
Spatial optimization of each of 30 irradiations



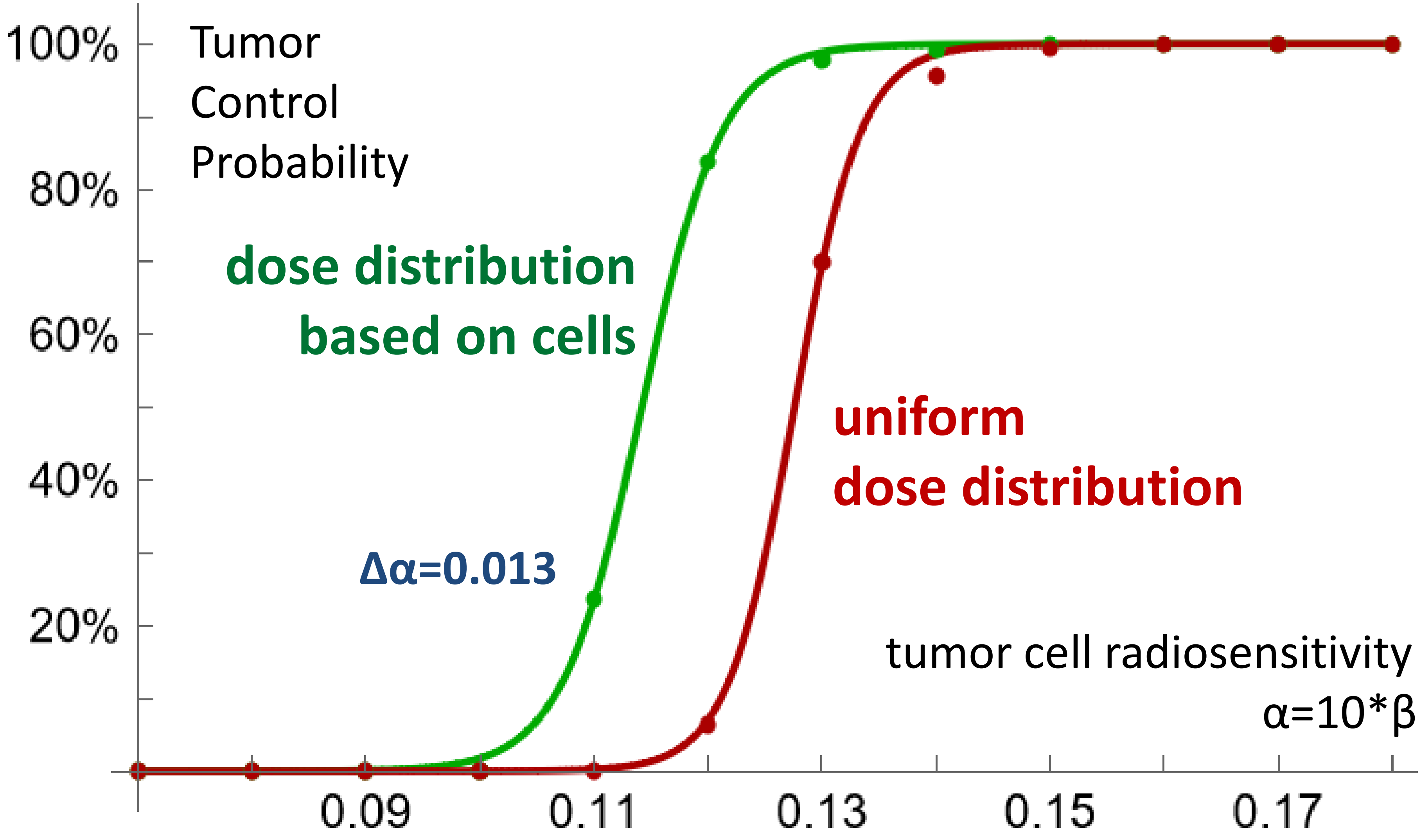
Spatial optimization based on cell distribution



Spatial optimization based on cell distribution



Spatial optimization based on cell distribution



Discussion

Conclusions:

- **non-uniform radiotherapy fractionation schemes** may be more effective that uniform ones,
  due to the time and space-dependent effects;
- **spatial distribution of irradiation can be optimized**
  yielding increased tumor cure probability
  under preserved tissue damage level;
- **dose painting based on necrosis level**
  may by itself be efficient
  for tumors with well pronounced necrotic cores.

Further work:

- account for non-instant cell death and fluid outflow;
- spatio-temporal optimization.

Thank you for your attention!

- Kuznetsov M., Clairambault J., Volpert V. Improving cancer treatments via dynamical biophysical models //Physics of Life Reviews. – 2021.

- Kuznetsov M., Kolobov A. Optimization of dose fractionation for radiotherapy of a solid tumor with account of oxygen effect and proliferative heterogeneity //Mathematics. – 2020. – T. 8. – №. 8. – C. 1204.