Optimization of Dose Fractionation for Radiotherapy of a Solid Tumor with Account of Oxygen Effect and Proliferative Heterogeneity

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SECHENOV UNIVERSITY LIFE SCIENCES

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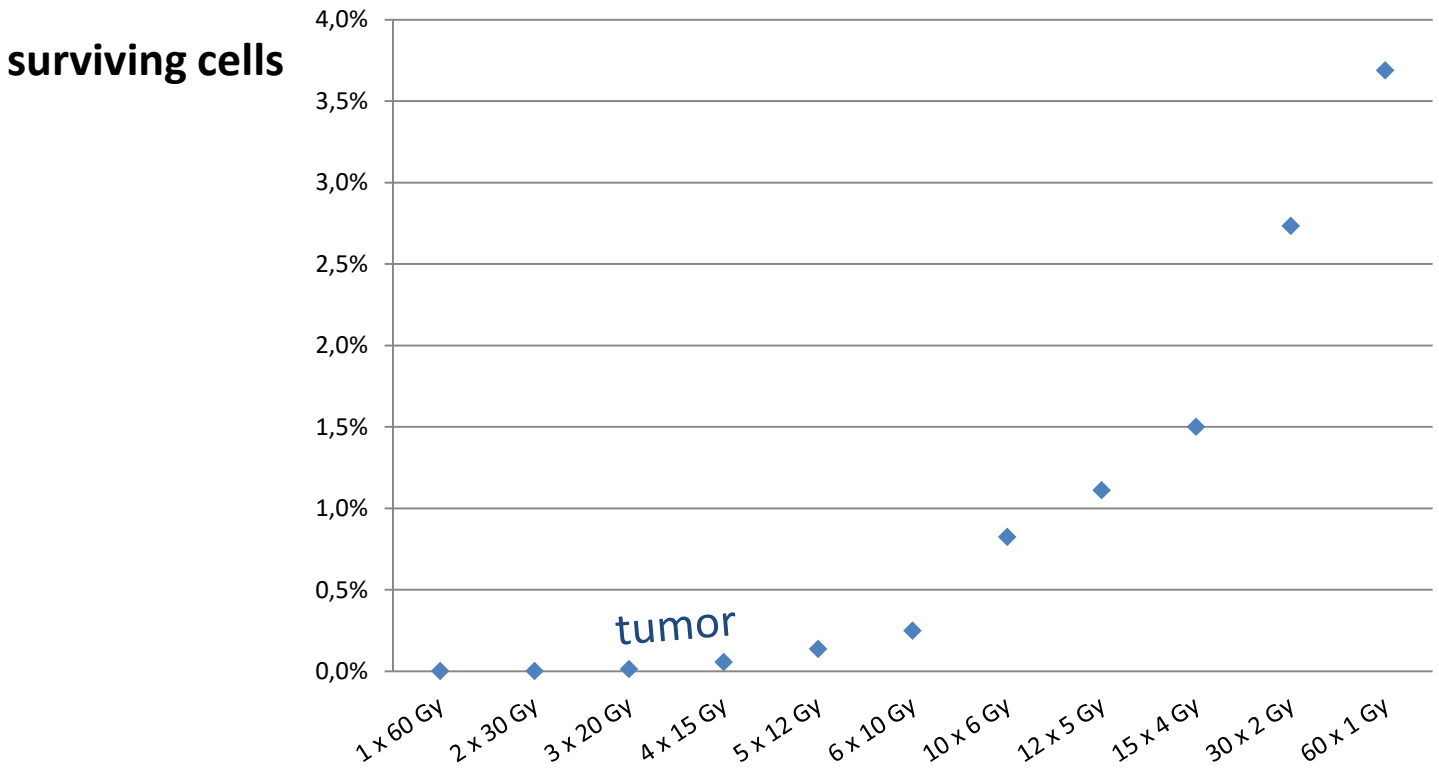
Why fractionate radiotherapy?

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

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



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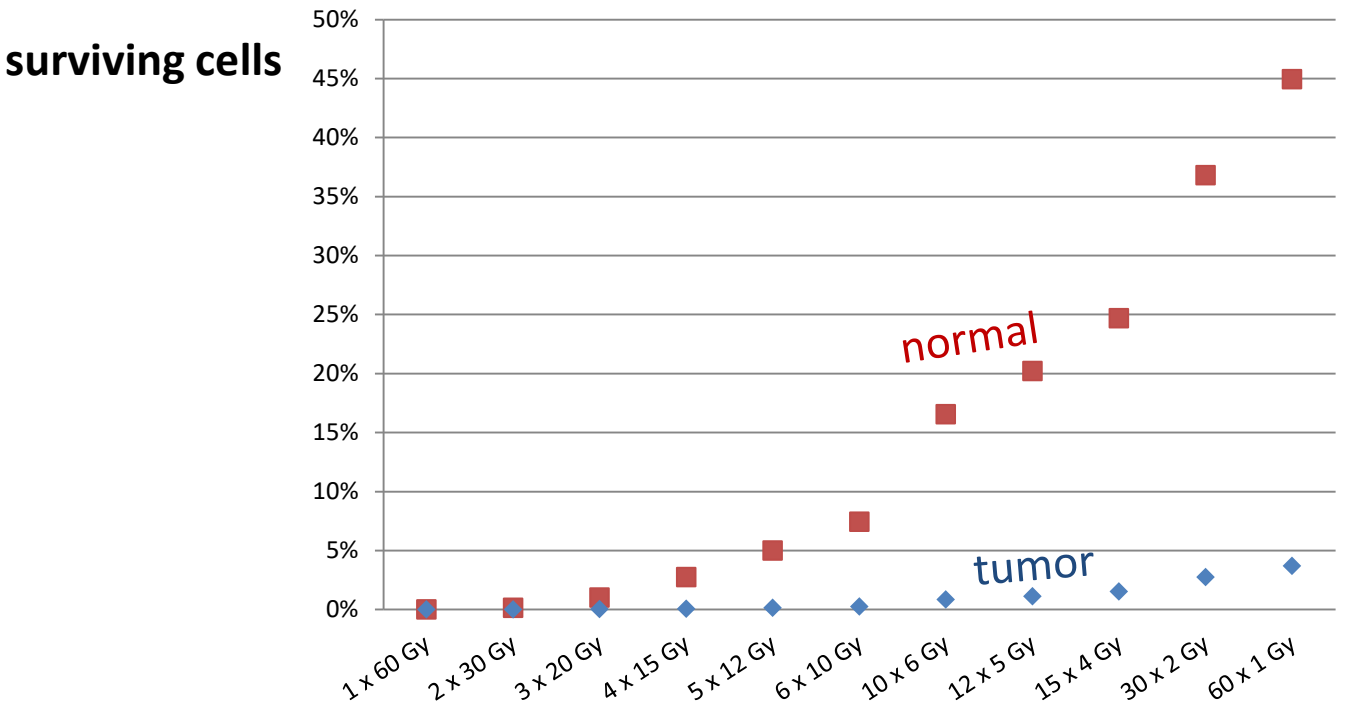

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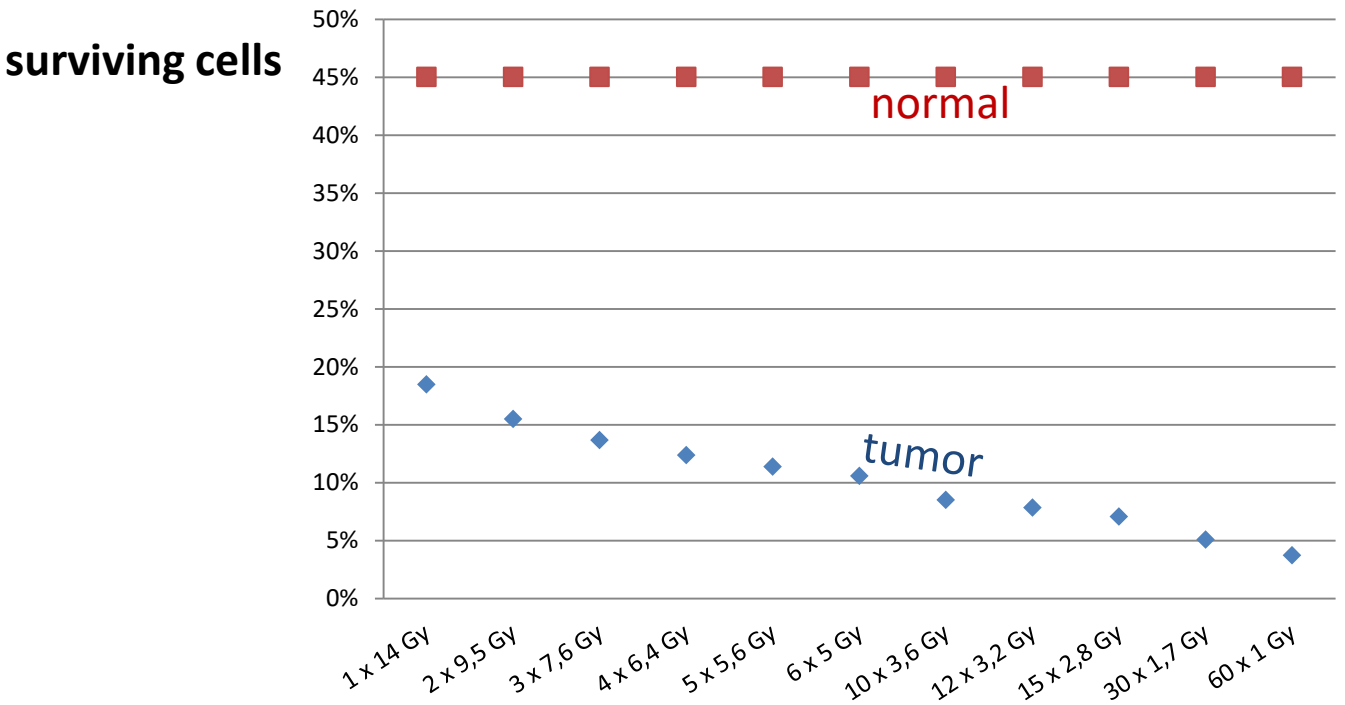

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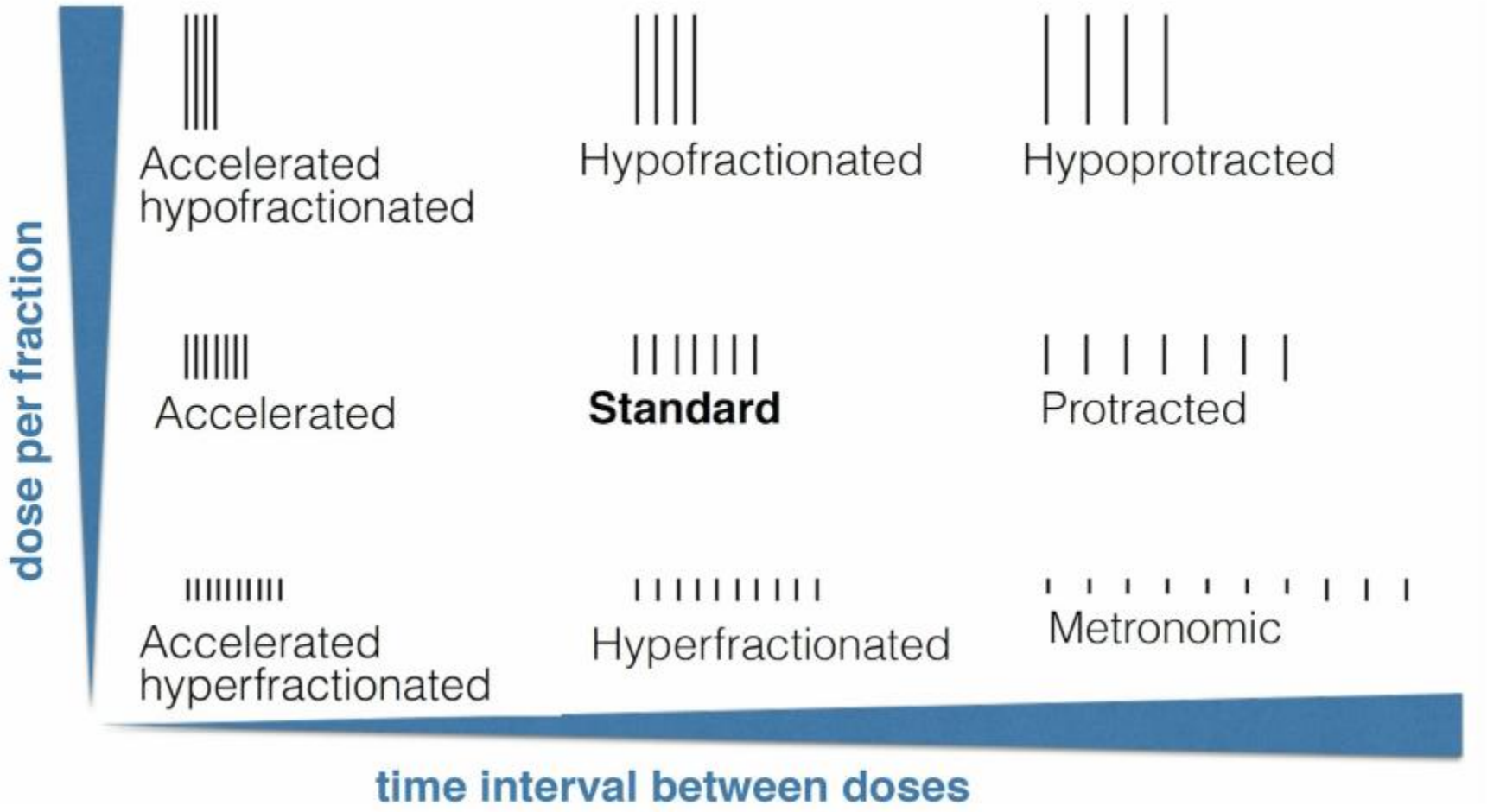
4 R's of radiotherapy:

- Reoxygenation (more O_2 – more cells die)
- Redistribution of cell cycle (proliferating cells die faster)
- Repopulation
- Repair of sublethal damage

Clinical fractionation schemes



- Henares-Molina A. et al. Non-standard radiotherapy fractionations delay the time to malignant transformation of low-grade gliomas //Plos one. – 2017. – Т. 12. – №. 6. – С. e0178552.

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 • cannot account for reoxygenation & redistribution of cell cycle

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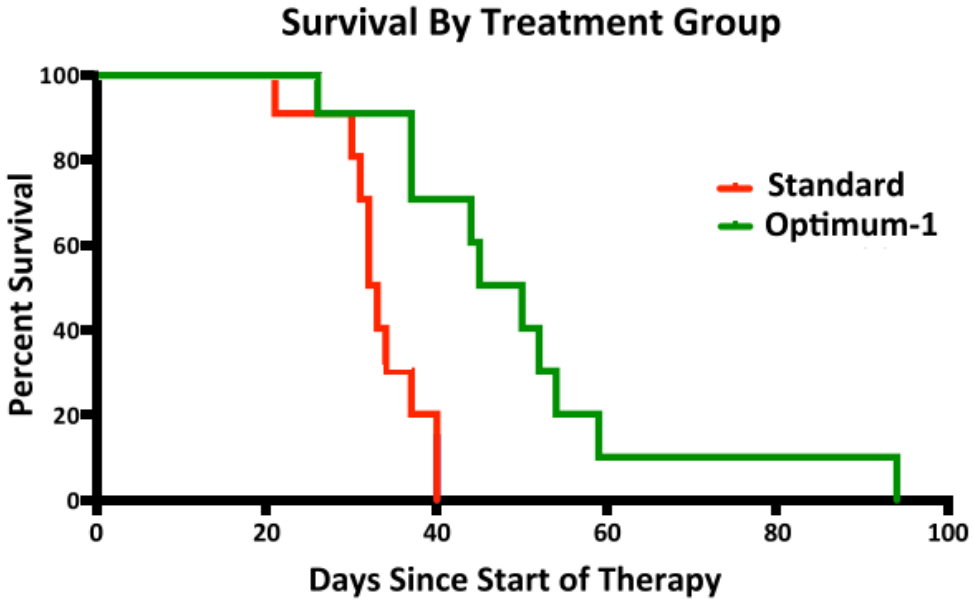

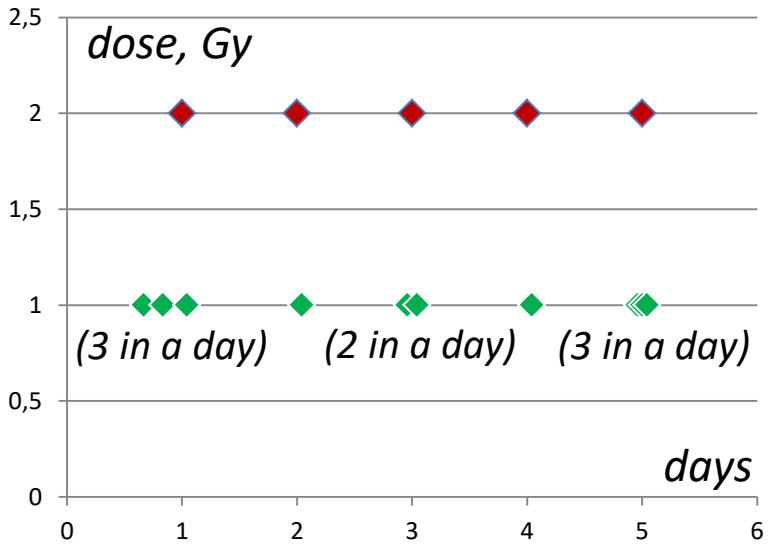

- Leder K. et al. Mathematical modeling of PDGF-driven glioblastoma reveals optimized radiation dosing schedules //Cell. – 2014. – Т. 156. – №. 3. – С. 603-616.

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But they don't

Such works consider homogeneous and constant radiosensivity:

our results support the optimality of current radiation fractionations

a constant-dose strategy seems to be the good choice

- Galochkina T., Bratus A., Pérez-García V. M. Optimal radiation fractionation for low-grade gliomas: Insights from a mathematical model //Mathematical biosciences. – 2015. – Т. 267. – С. 1-9.
- Fernández-Cara E., Prouvée L. Optimal control of mathematical models for the radiotherapy of gliomas: the scalar case //Computational and Applied Mathematics. – 2018. – Т. 37. – №. 1. – С. 745-762.

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PDEs	• can account for reoxygenation & redistribution of cell cycle	• need to develop optimization methods
Agent-based	• can account for reoxygenation & redistribution of cell cycle	• numerical complexity does not allow to utilize optimization procedures • small number of cells is considered

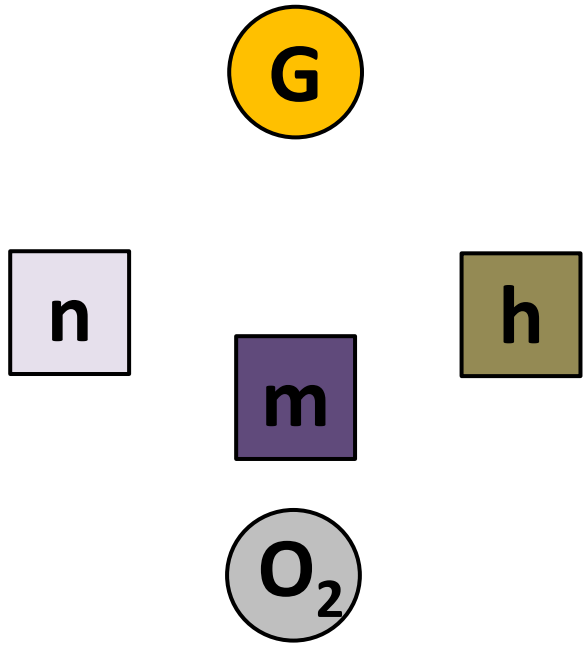
What we do:

- We present a PDE-governed **mathematical model** of solid tumor growth and treatment by fractionated RT that **explicitly accounts for tumor cell repopulation, reoxygenation and redistribution of proliferative states.**

- With the use of a **specially-developed algorithm**, we **find the optimized fractionation schemes** for varied radiosensitivity of tumor cells under the values of model parameters, that correspond to different degrees of tumor malignancy.

- The resulting schemes lead to **significant expansions in the curative ranges of** the values of tumor **radiosensitivity parameters**.

The model: variables



n(x,t)– tumor cells

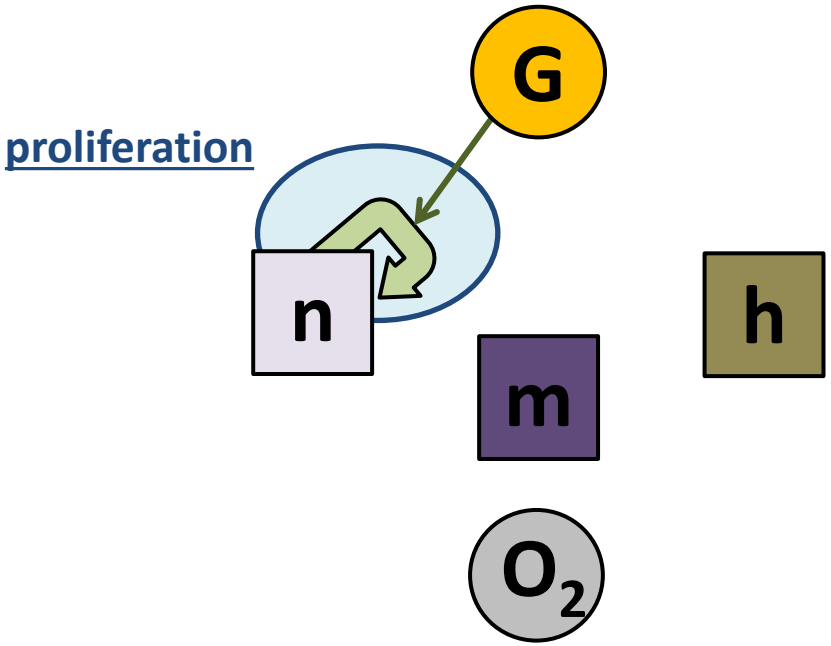
m(x,t) – necrotic tissue

h(x,t) – normal tissue

G(x,t) – glucose

O_2(x,t) – oxygen

The model: dynamics of cells and necrotic tissue



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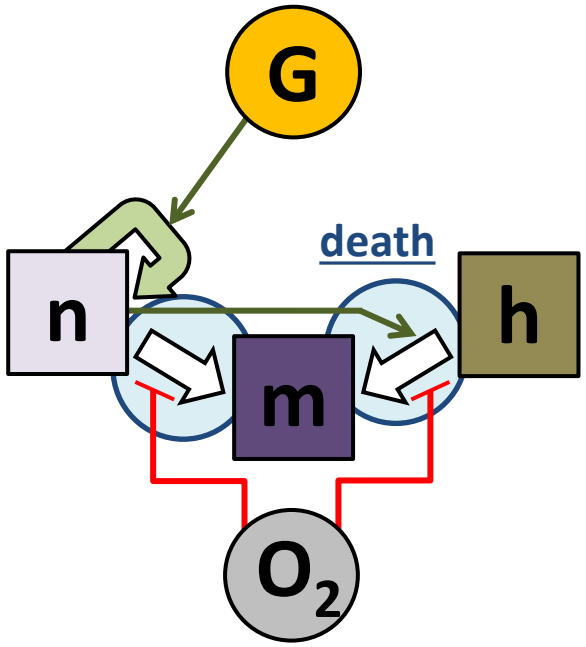

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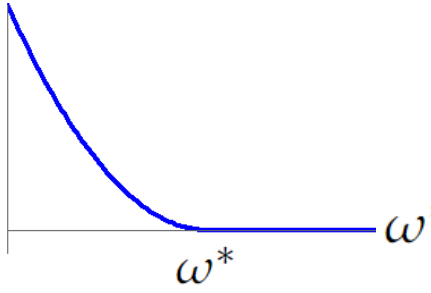
normal cells: $\frac{\partial h}{\partial t} = \overbrace{-[M_h(\omega)+Mn]h}^{\text{death}}$

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

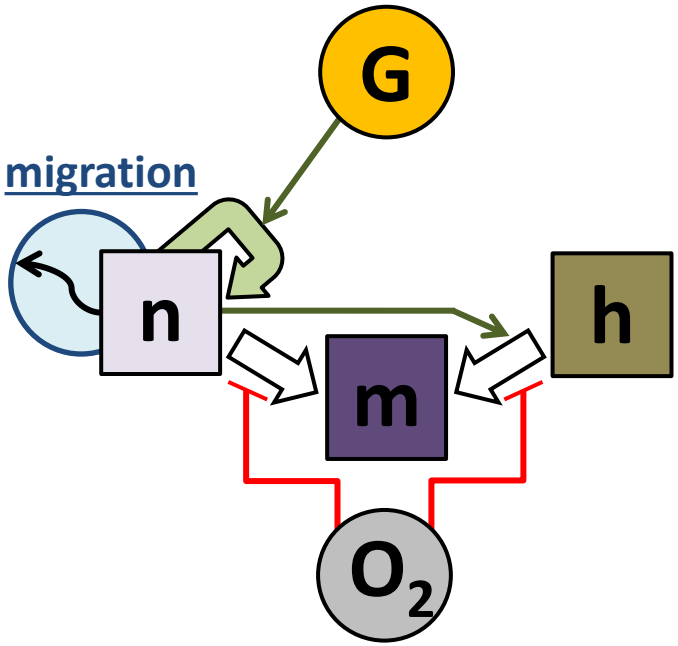
$$M_h(\omega) = \begin{cases} 0 \ \ if \ \ \omega \geq \omega^*; \\ M[\{\omega/\omega^*\}^2 - 2\{\omega/\omega^*\} + 1] \ \ if \ \ \omega < \omega^*; \end{cases}$$



The model: dynamics of cells and necrotic tissue

Two types of cell motion:
1) random migration

Van Roosmalen, Wies, et al.
The Journal of clinical investigation
125.4 (2015): 1648-1664.



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

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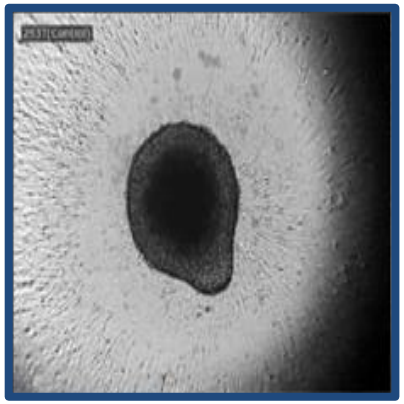
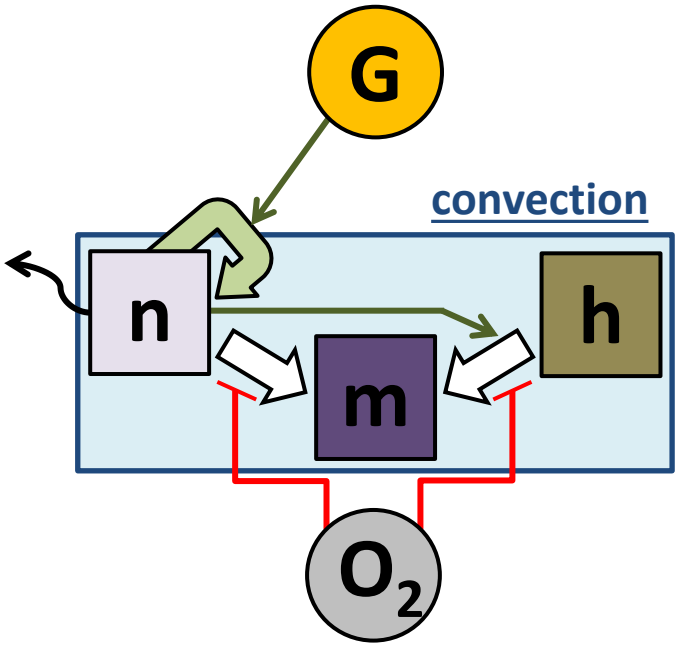
The model: dynamics of cells and necrotic tissue

Two types of cell motion:
2) convective movement



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



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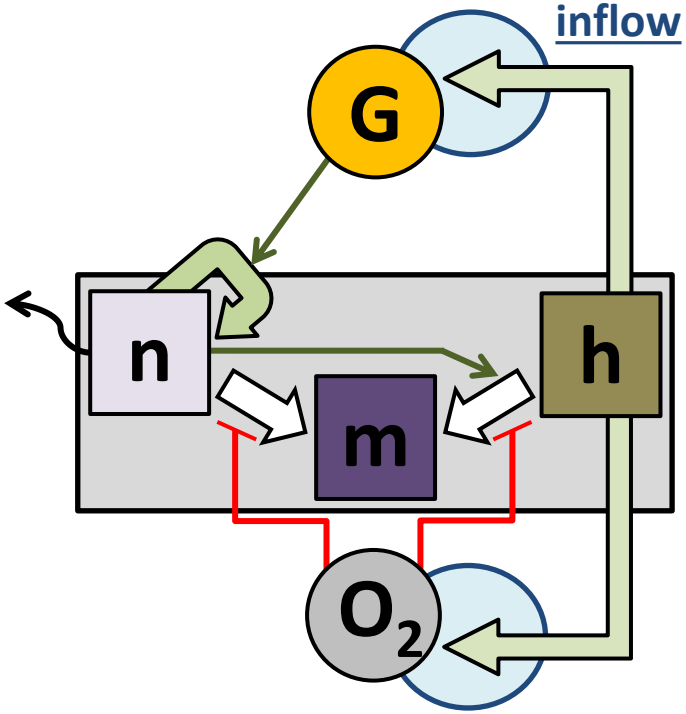
$$n+m+h=1;$$

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

The model: dynamics of nutrients



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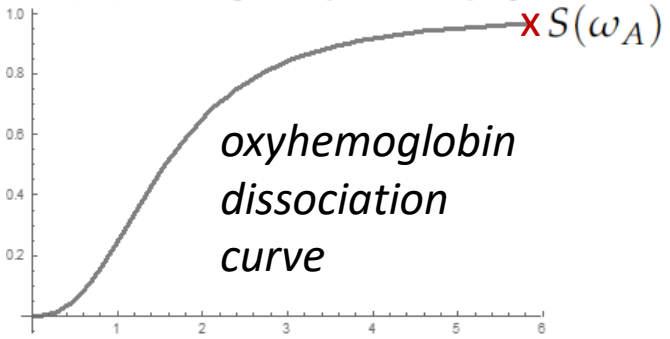
glucose: $\frac{\partial g}{\partial t} = \overbrace{P_g h[1-g]}^{\text{inflow}}$

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

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



oxyhemoglobin dissociation curve

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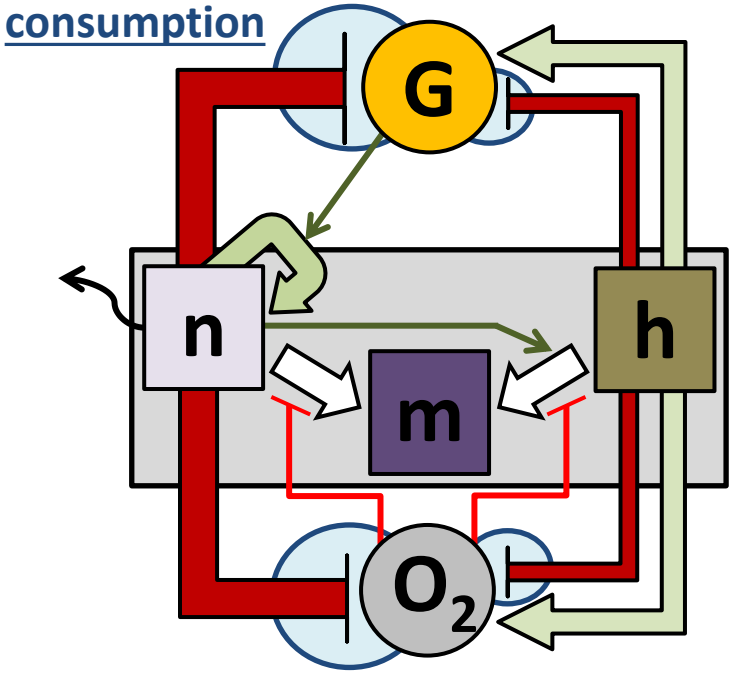

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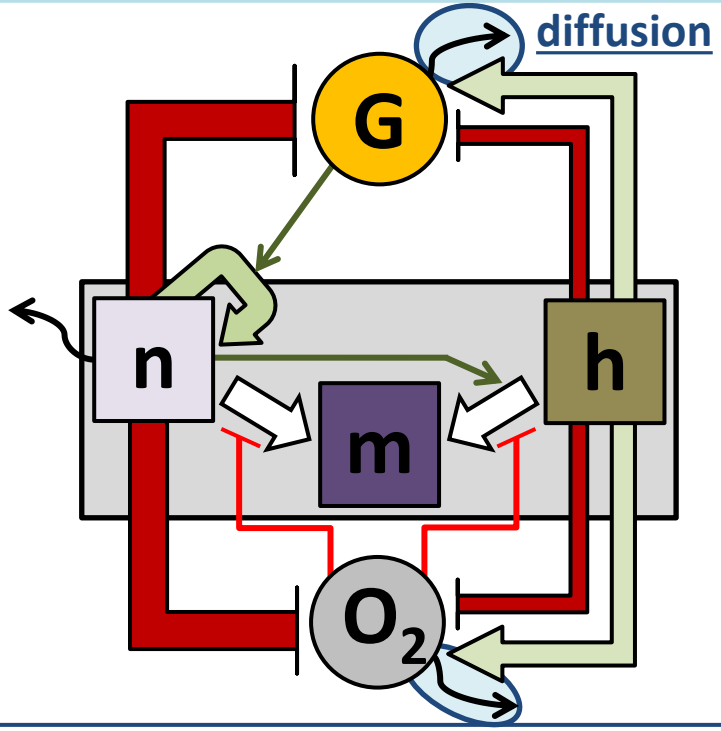

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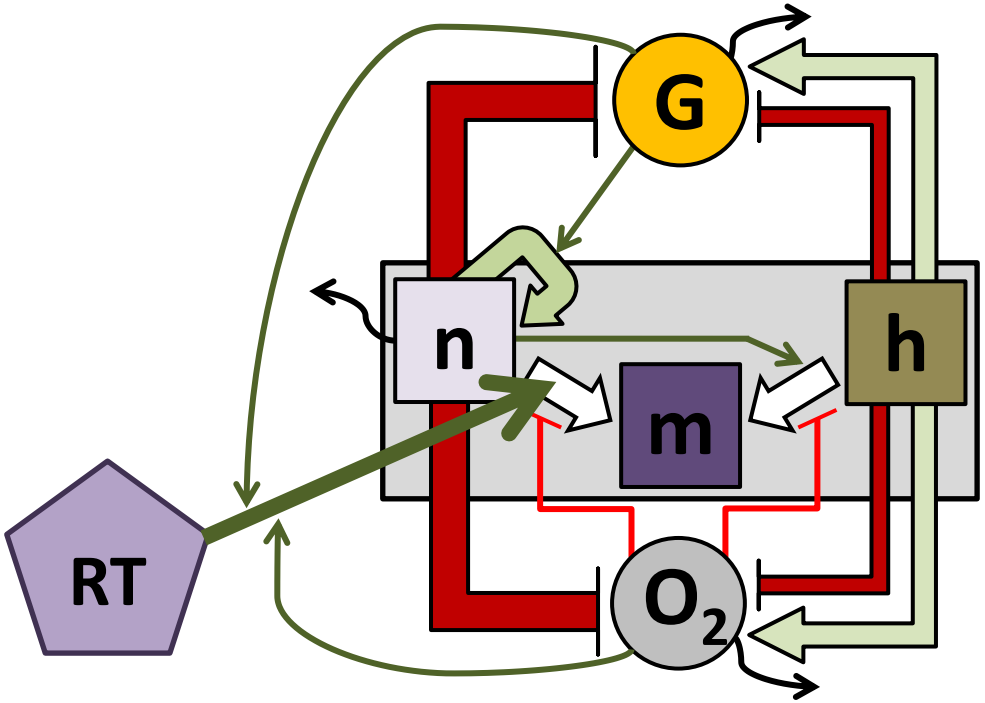
$$\overbrace{-[\{Q_n^\omega \frac{g}{g+g^*} + Q_h^\omega \frac{g^*}{g+g^*}\}n + Q_h^\omega h]\frac{\omega}{\omega+\omega^*}}^{\text{consumption}} \overbrace{+D_\omega \Delta \omega}^{\text{diffusion}};$$

The model: radiotherapy



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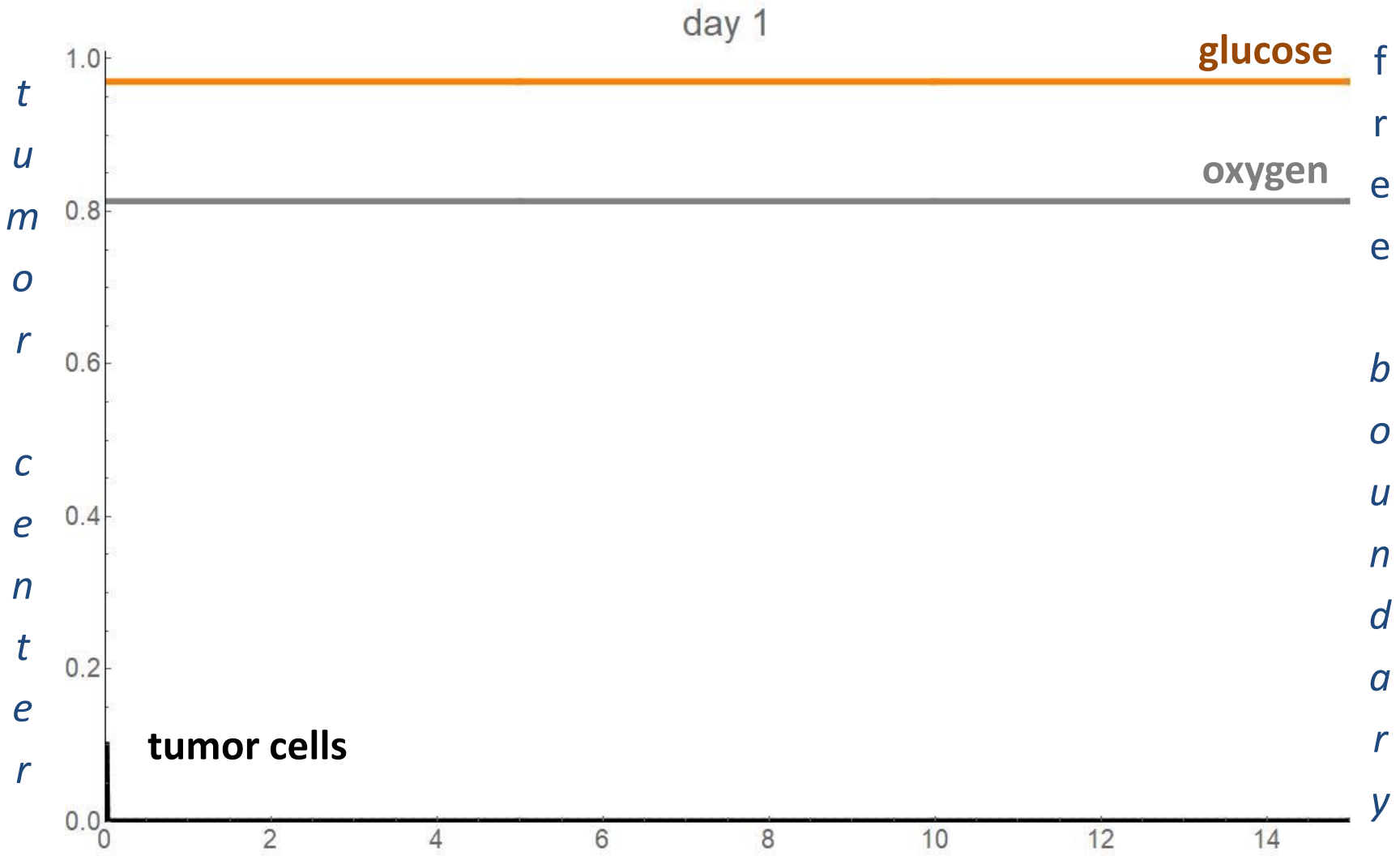
$$n|_{postRT} = n|_{preRT} \cdot exp(\{-\alpha\,[OER_\alpha(\omega)\cdot\gamma(g)\cdot D] - \beta\,[OER_\beta(\omega)\cdot\gamma(g)\cdot D]^2\}),$$
$$m|_{postRT} = m|_{preRT} + [n|_{preRT} - n|_{postRT}];$$

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

Simulation of tumor growth and radiotherapy



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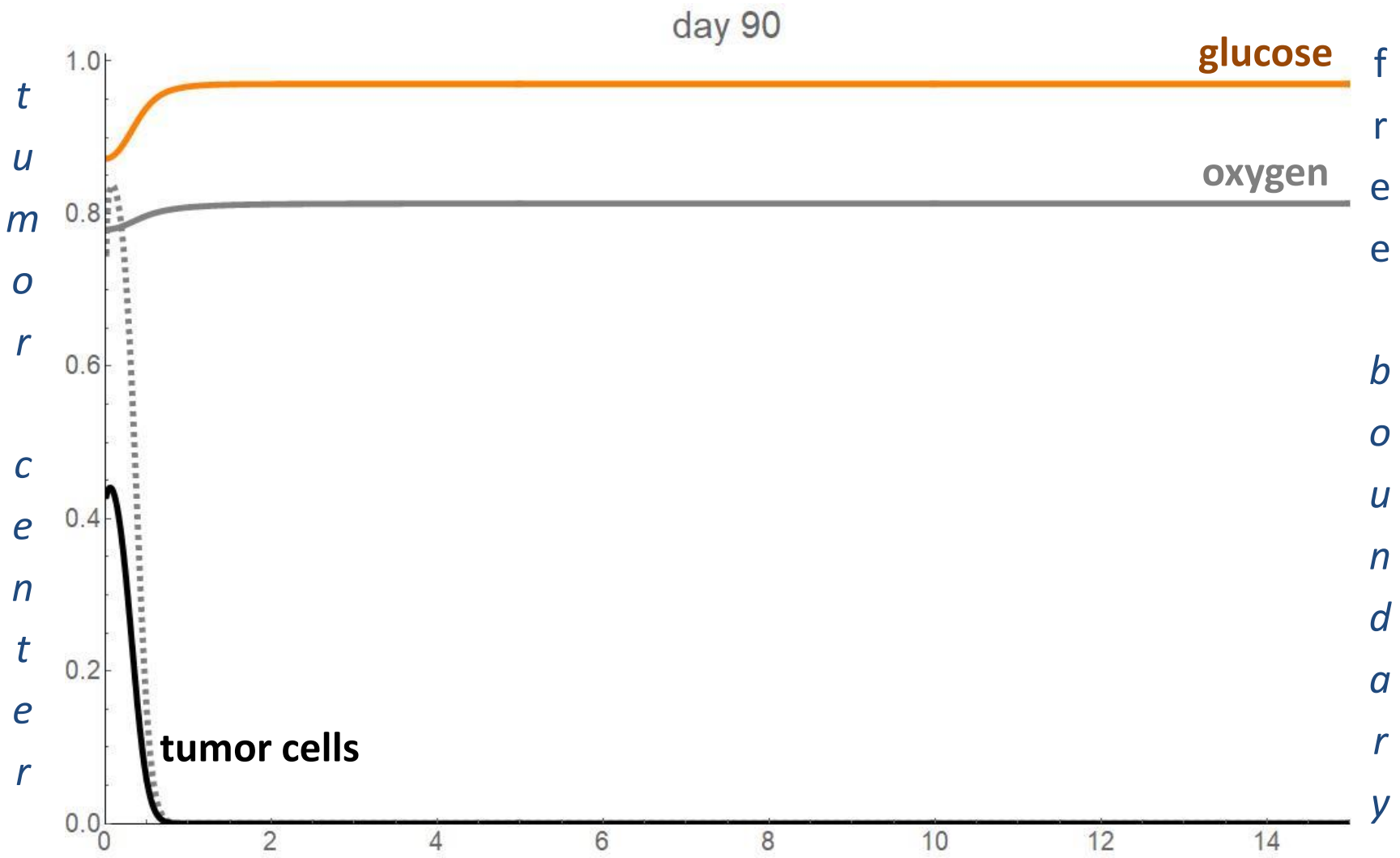

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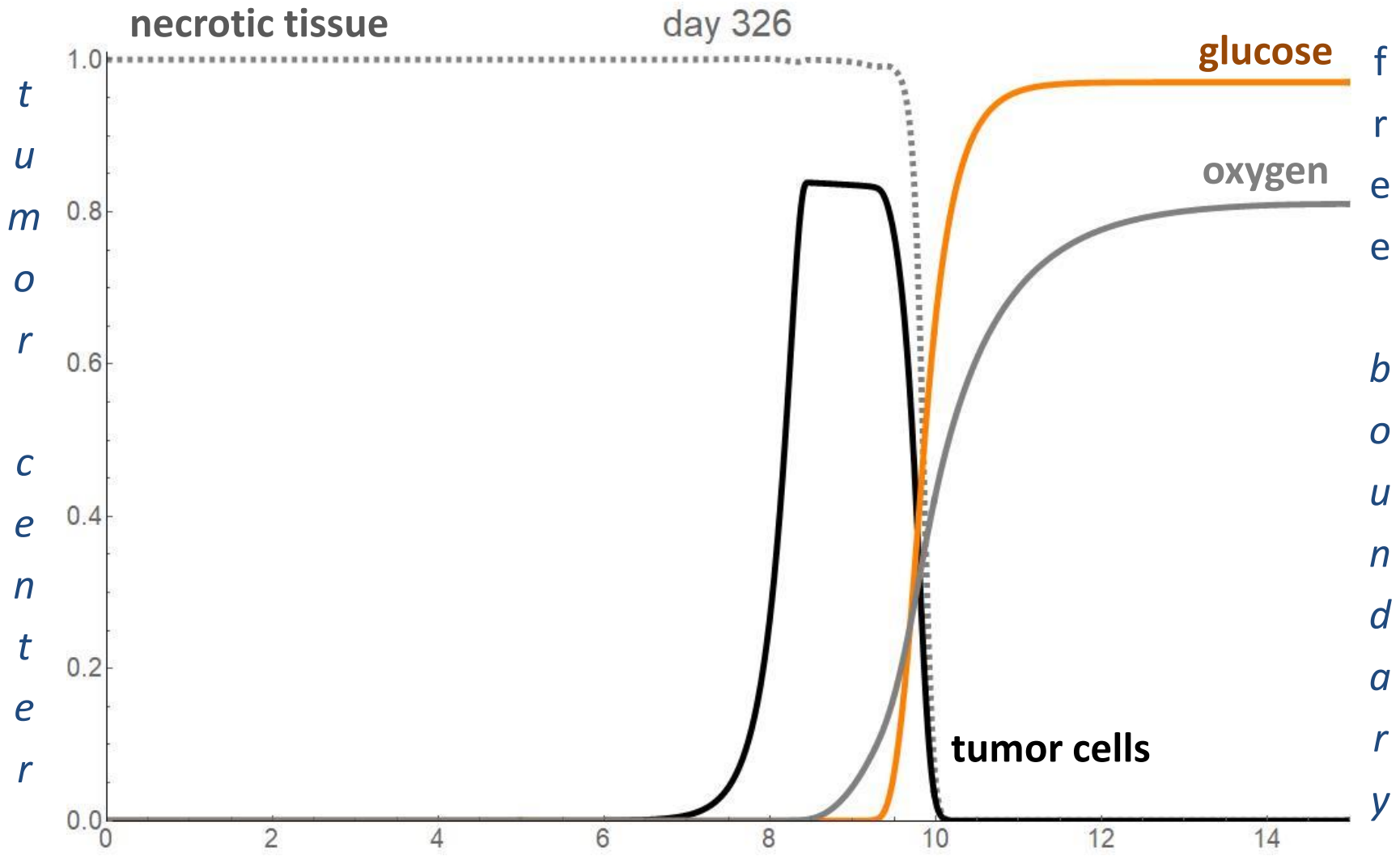

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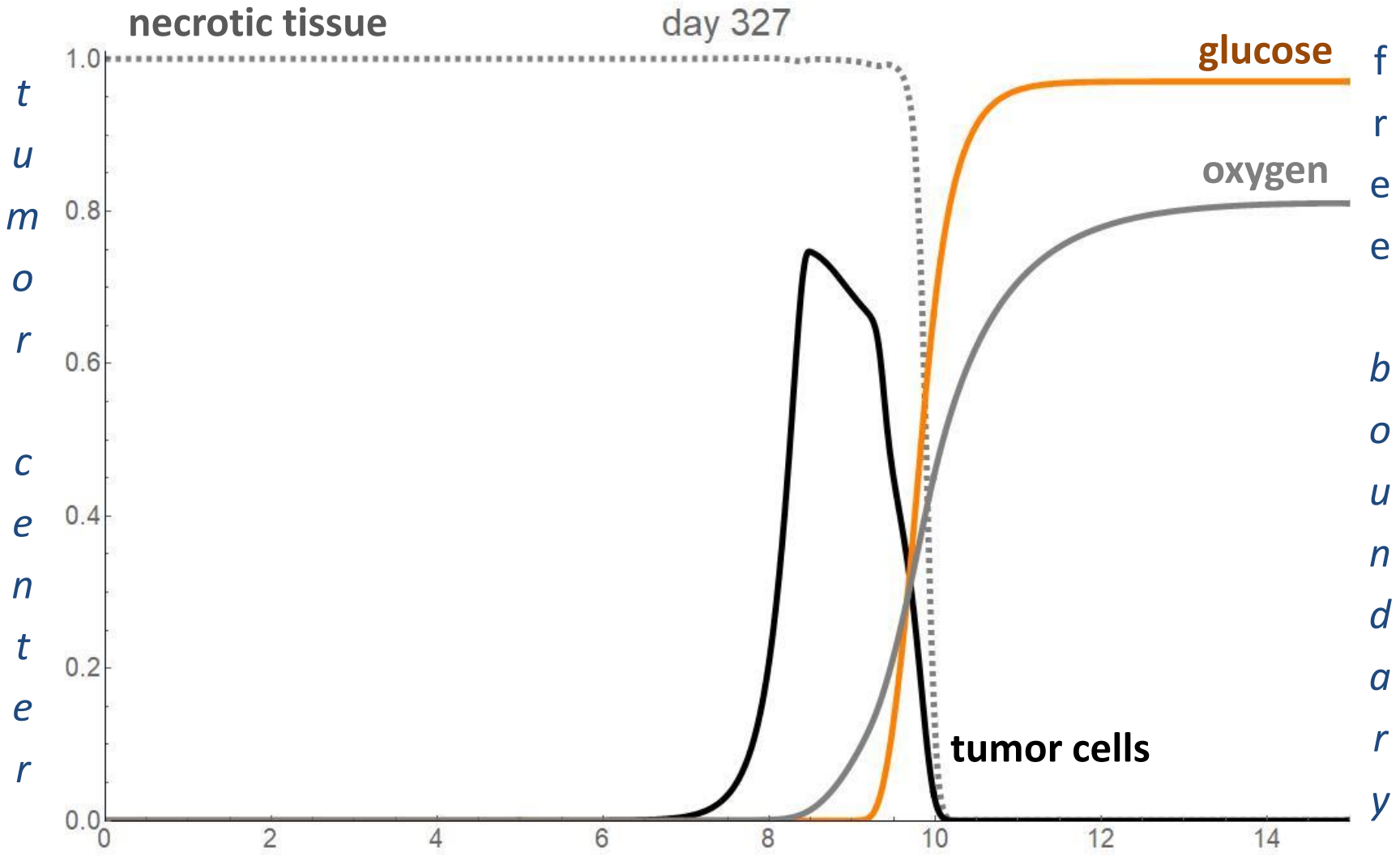

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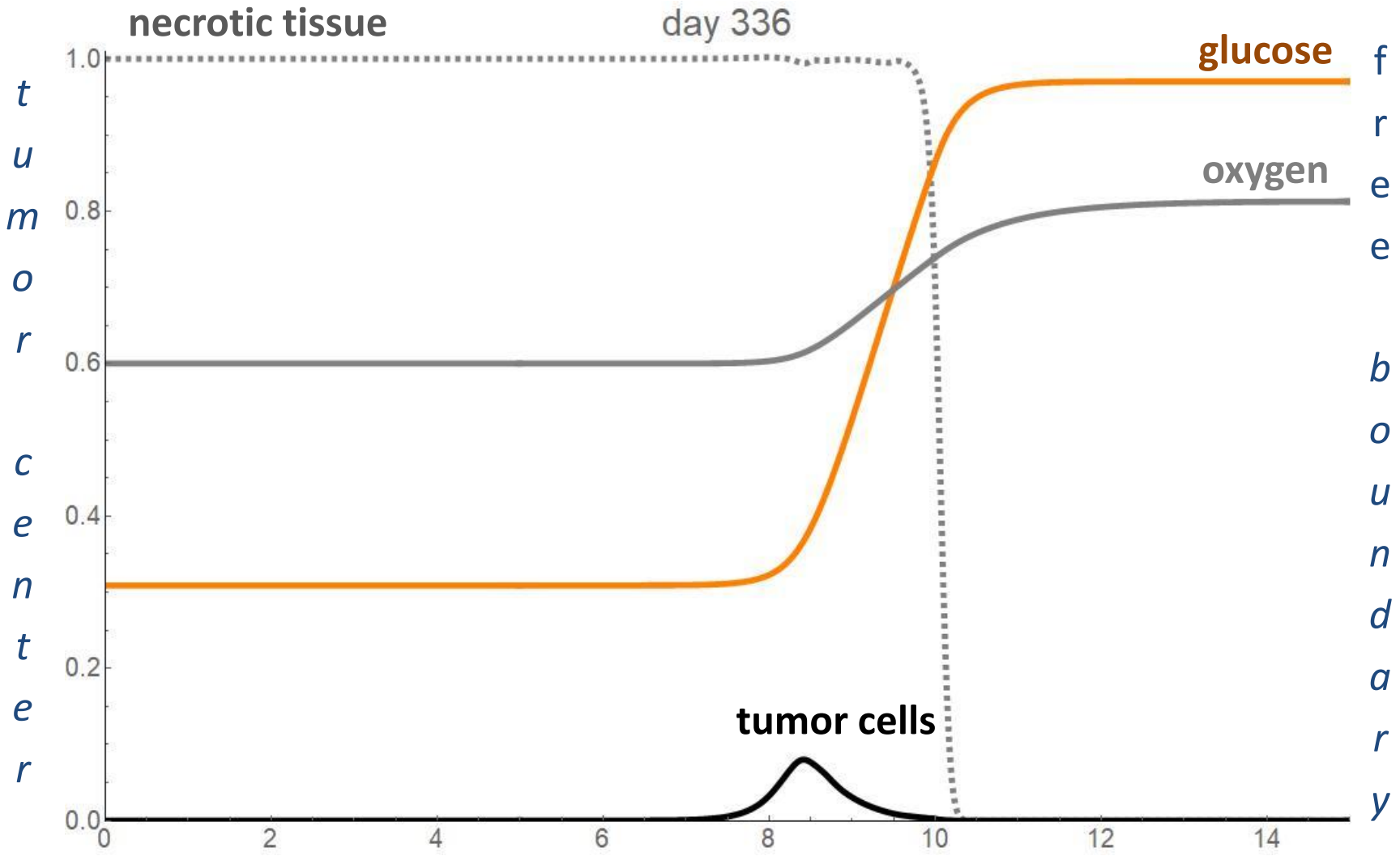

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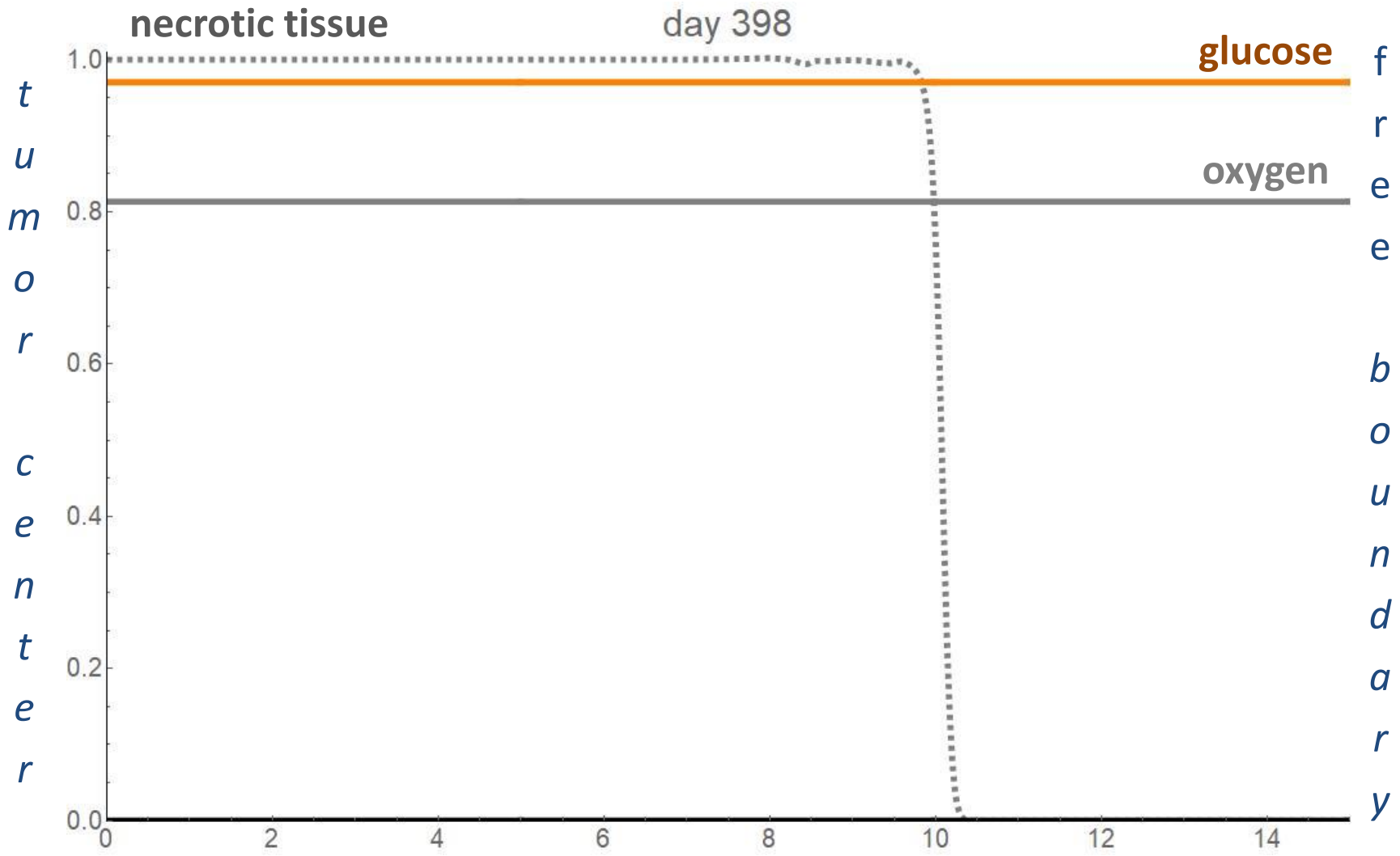


Optimization task

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:

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

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

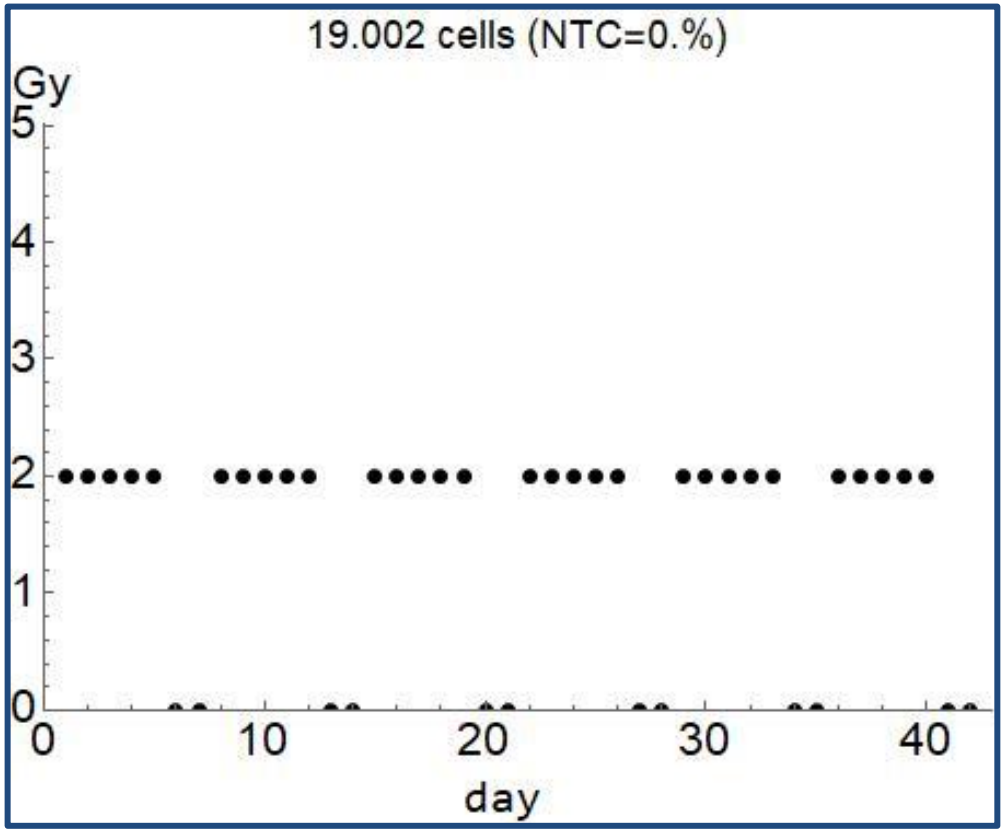
$$F(\mathbf{D}) = \min_t(lgN(\mathbf{D}, t)), \ \ where\ N(\mathbf{D}, t) \equiv \hat{n}\hat{r}^3 \cdot 4\pi \int_0^X n(\mathbf{D}, r, t) r^2 dr$$

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

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

Optimization algorithm

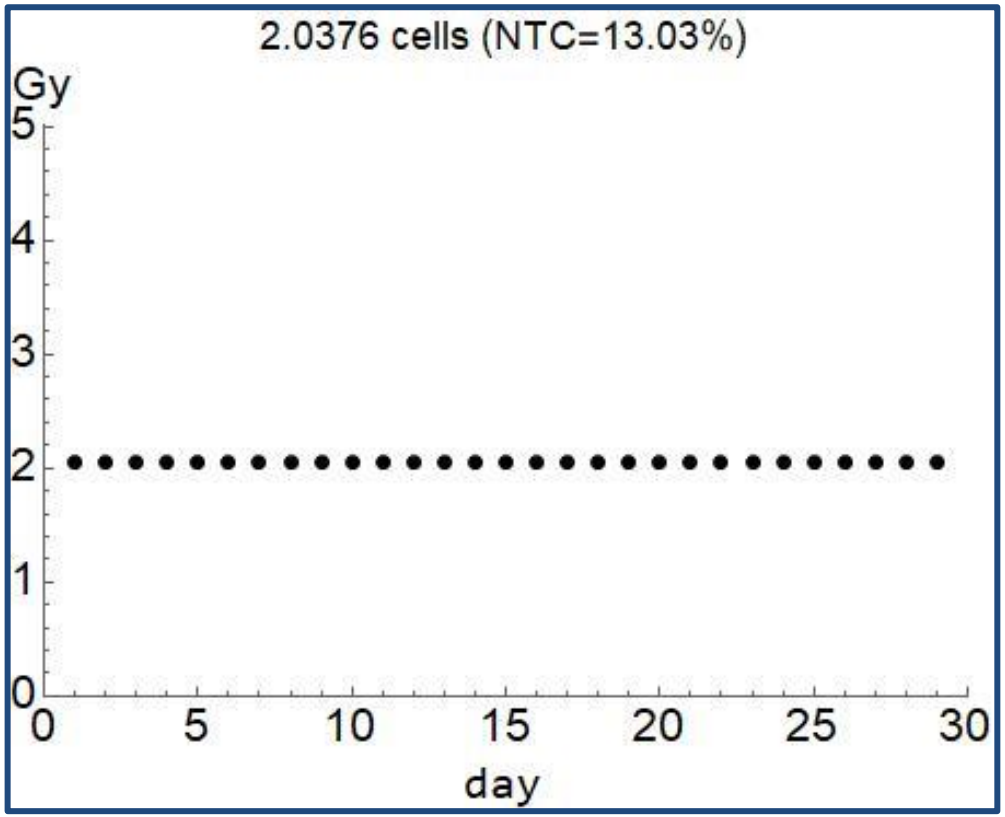
Begin



Optimization algorithm

Begin

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



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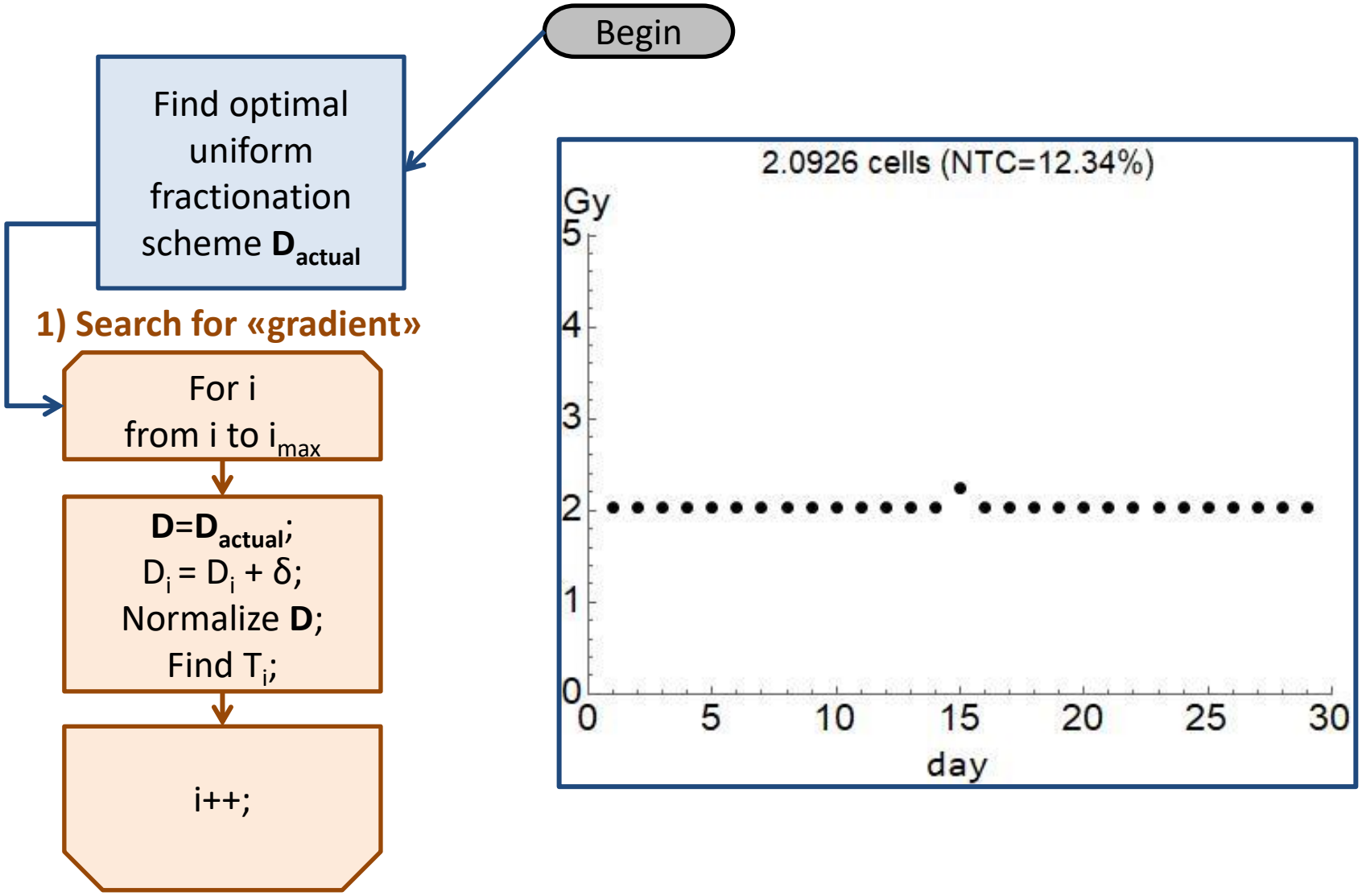

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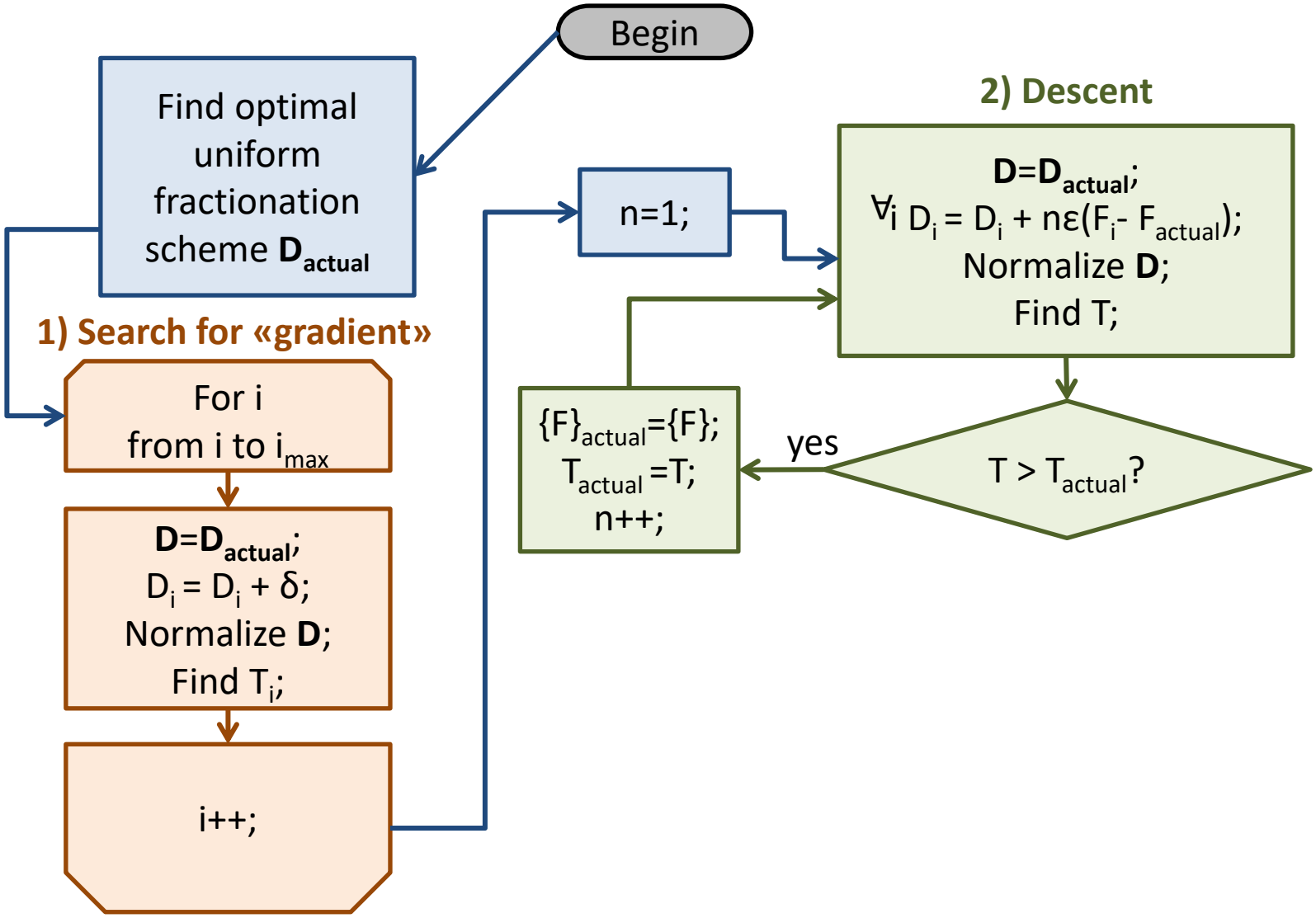

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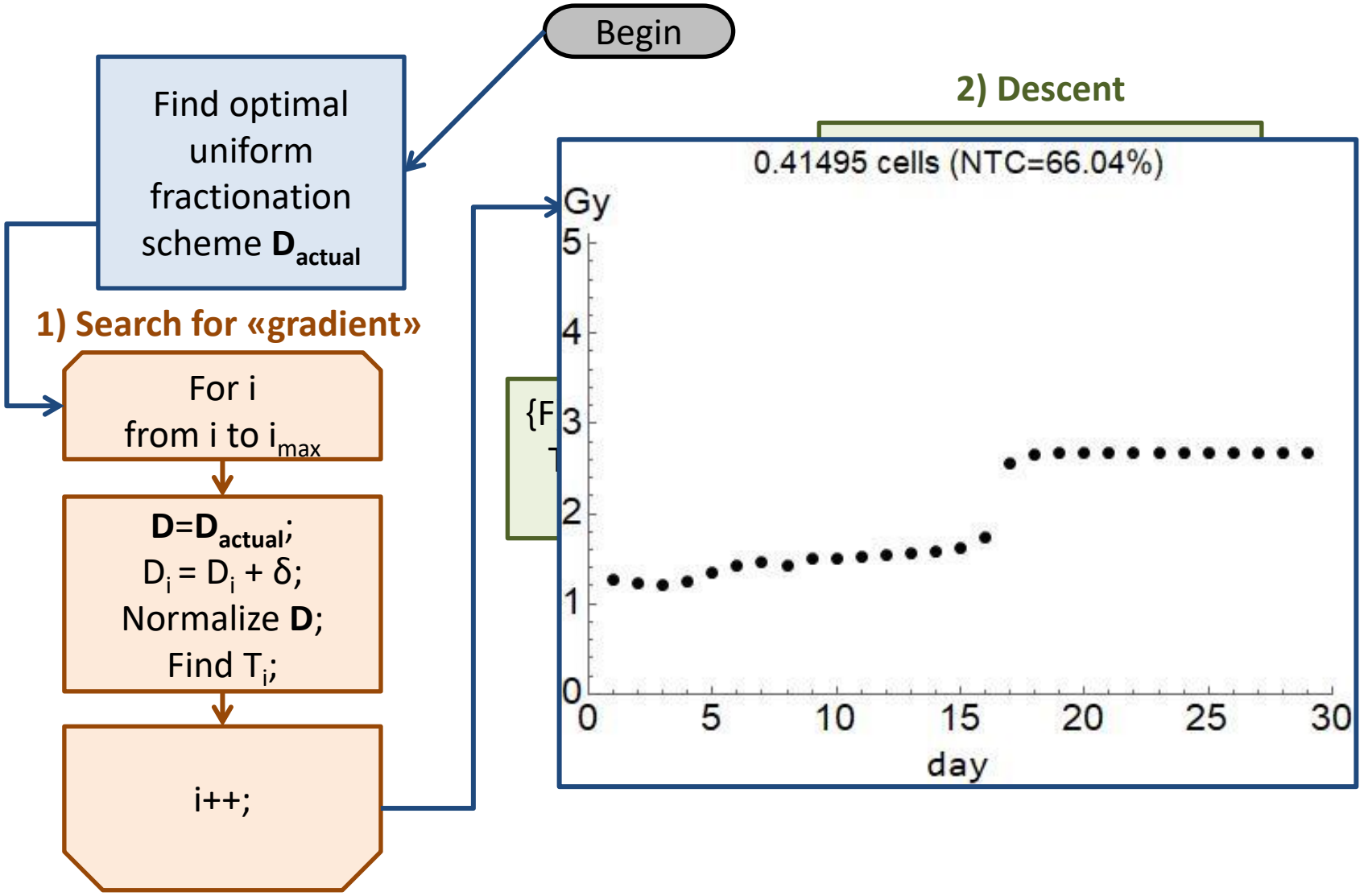

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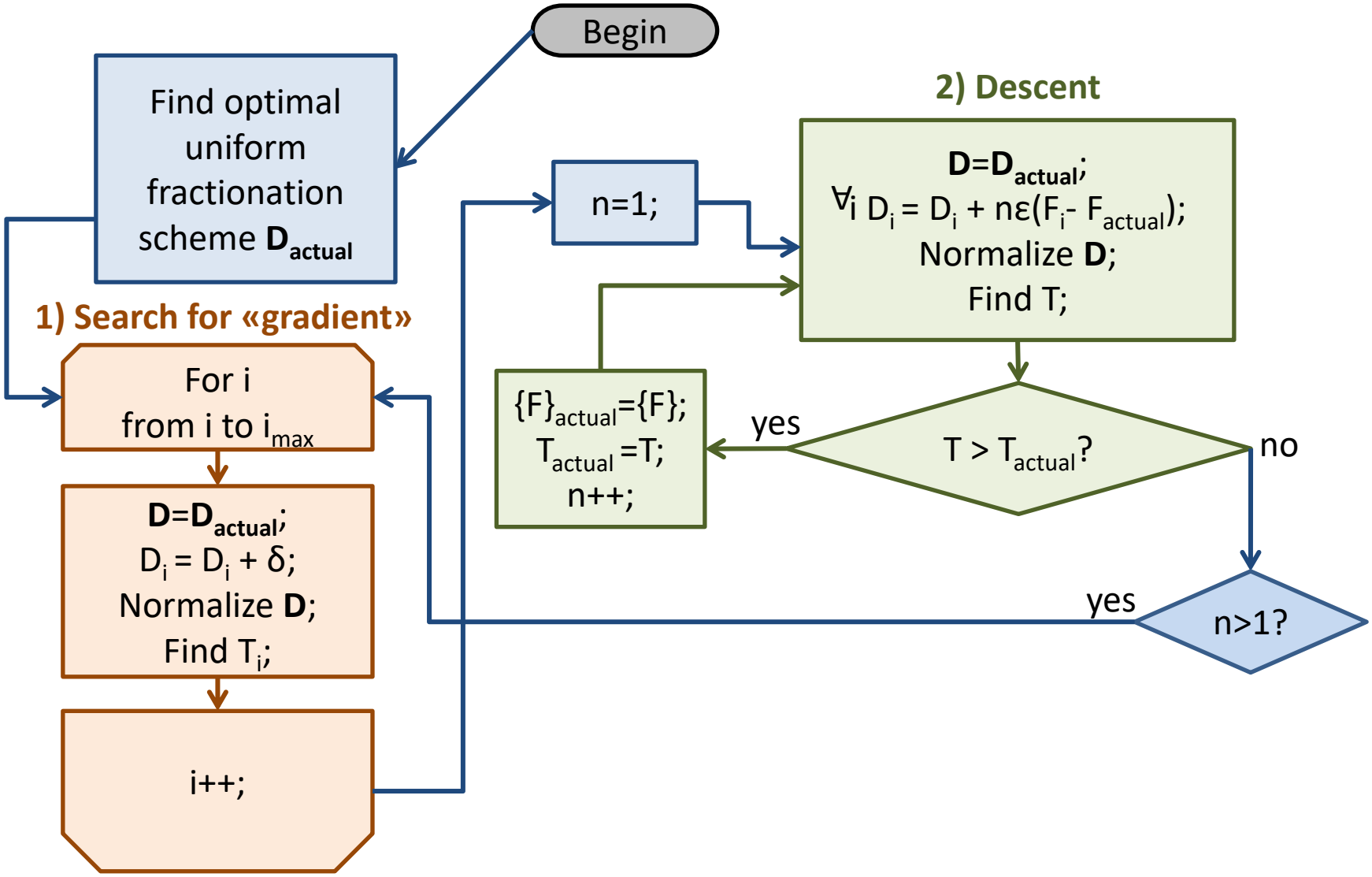

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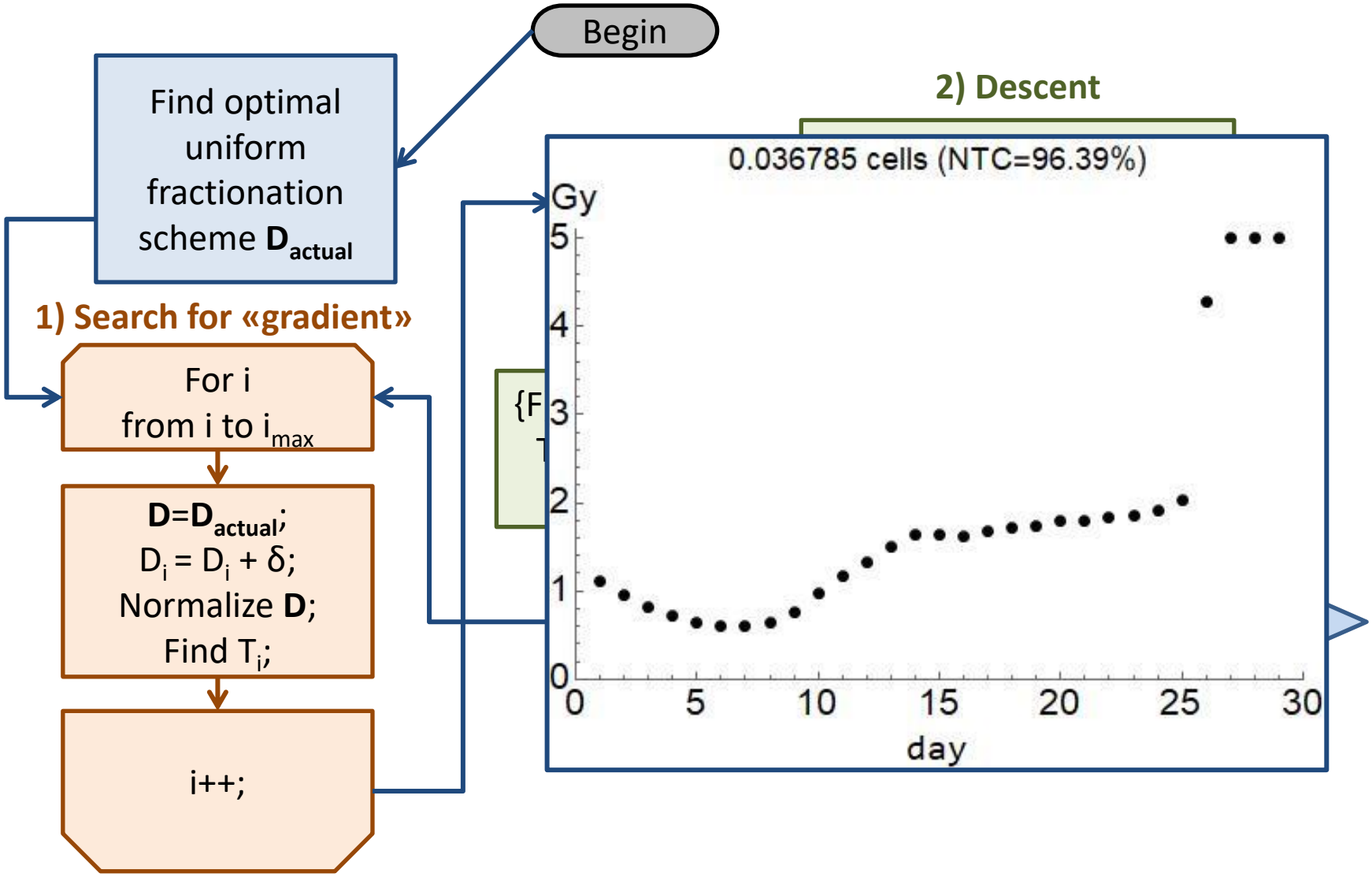

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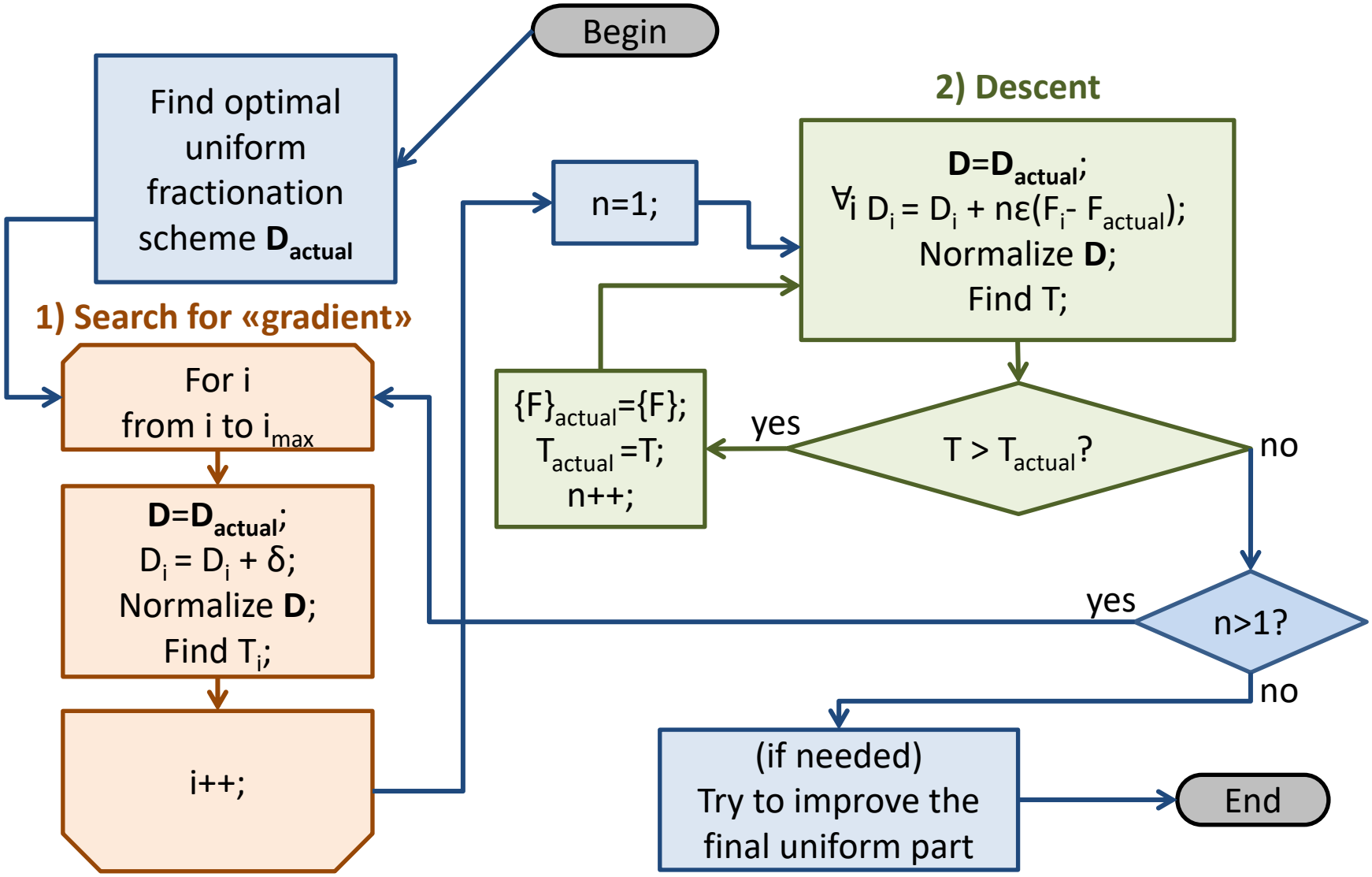


Model parameters

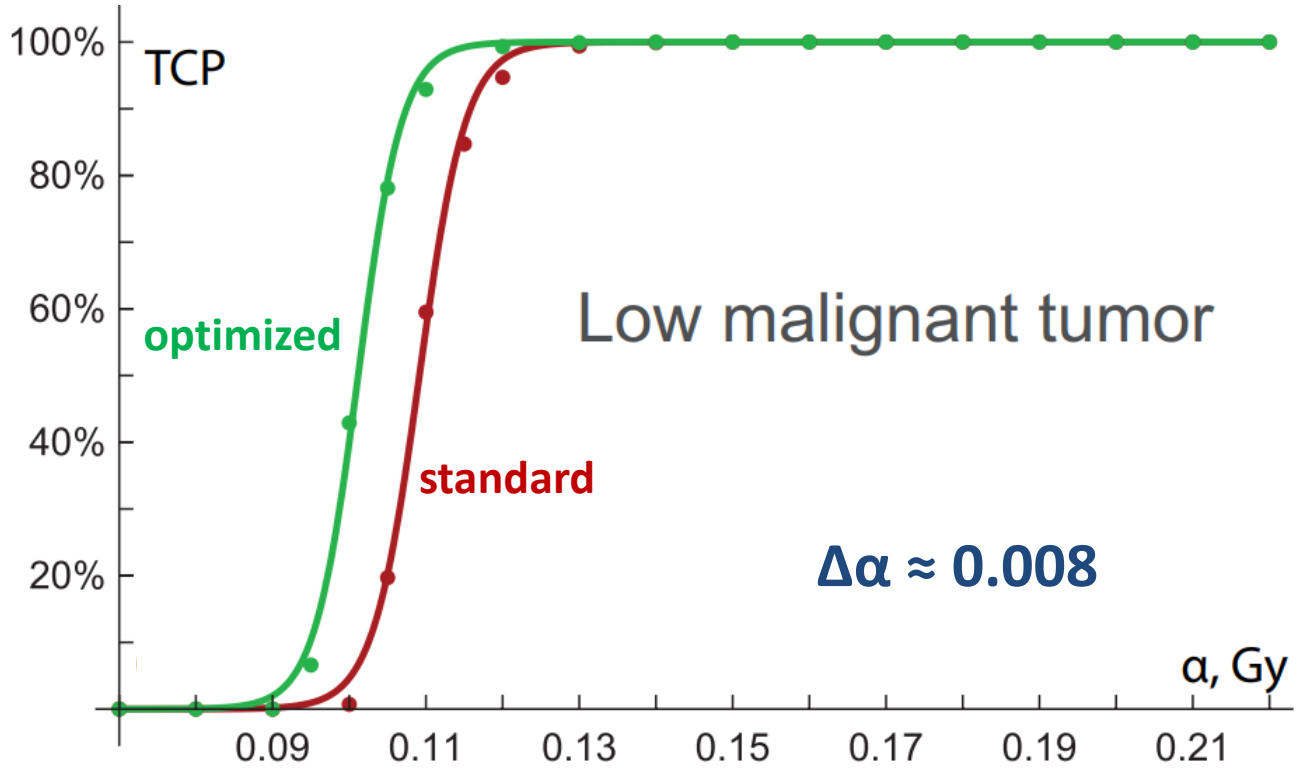
HM – high malignant tumor, *IM* – intermediate malignant tumor, *LM* – low malignant tumor.

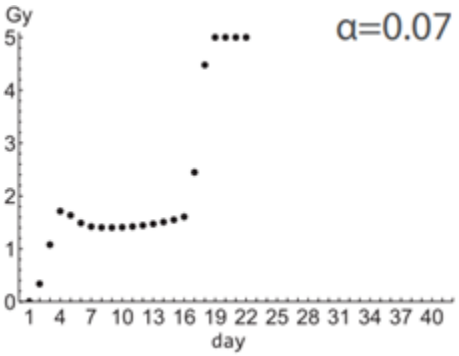
Parameter	Description	Model Value
B	tumor cells' proliferation rate	*HM:* 0.01 *IM:* 0.005 *LM:* 0.0025
ϵ	ratio of death rates of tumor and normal cells due to the lack of oxygen	*HM:* 0.3 *IM:* 0.7 *LM:* 1
D_n	tumor cells' motility	*HM:* 0.01 *IM:* 0.001 *LM:* 0
P_g	glucose inflow parameter	*HM:* 20 *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

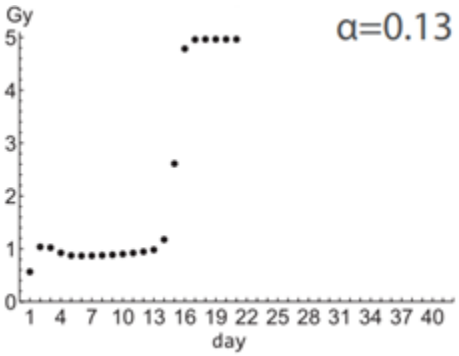
Malignant tumor cells:

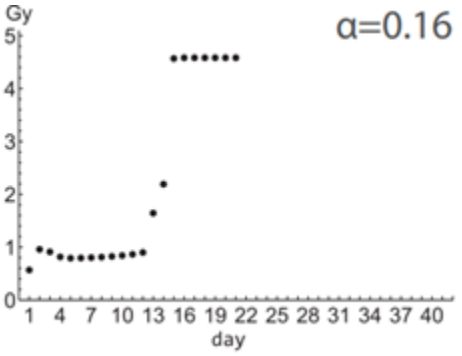
- **divide faster**
- die harder
- move faster
- induce angiogenesis
- consume more nutrients
- **become more radiosensitive in quiescent state (optional)**

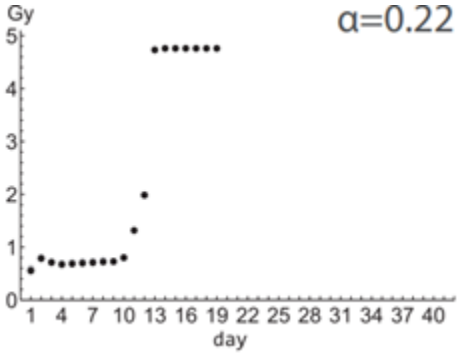
Standard vs. optimized fractionation schemes



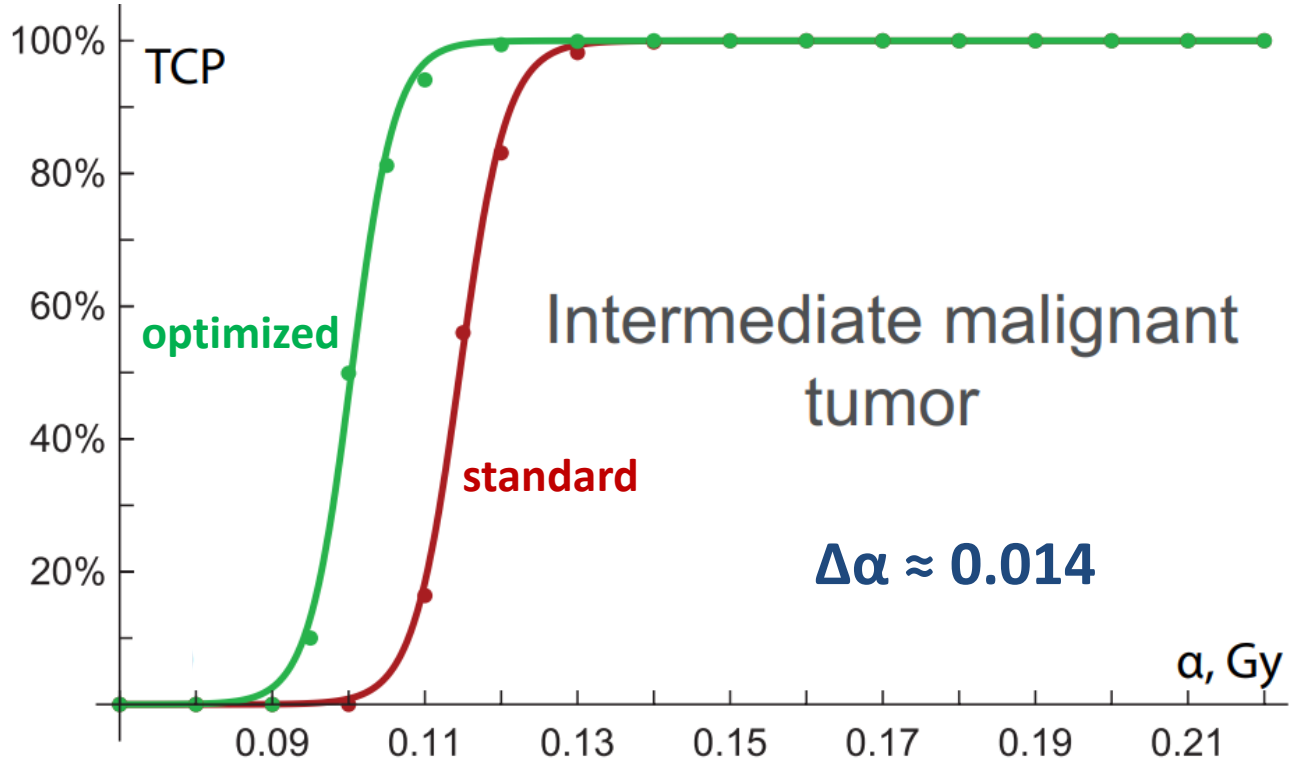


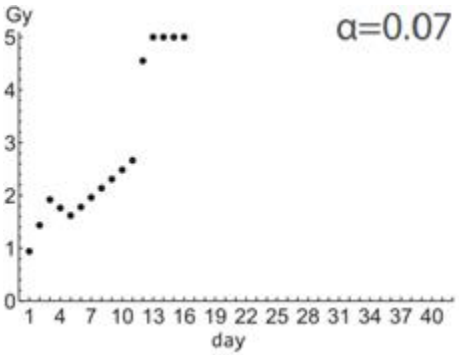


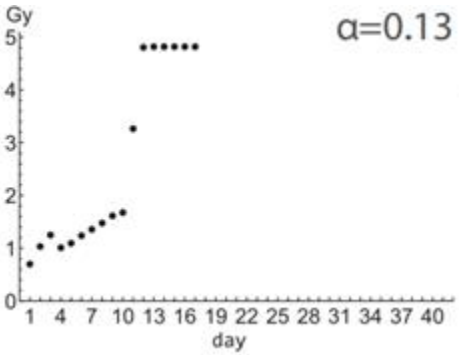


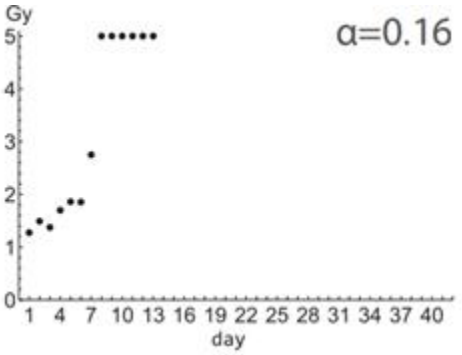


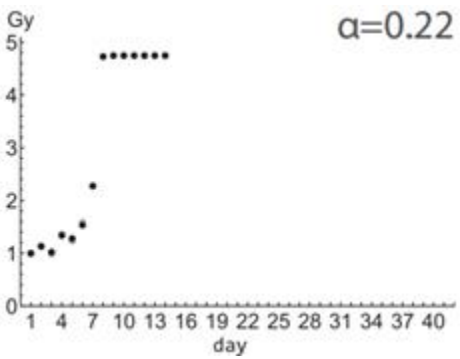
Standard vs. optimized fractionation schemes



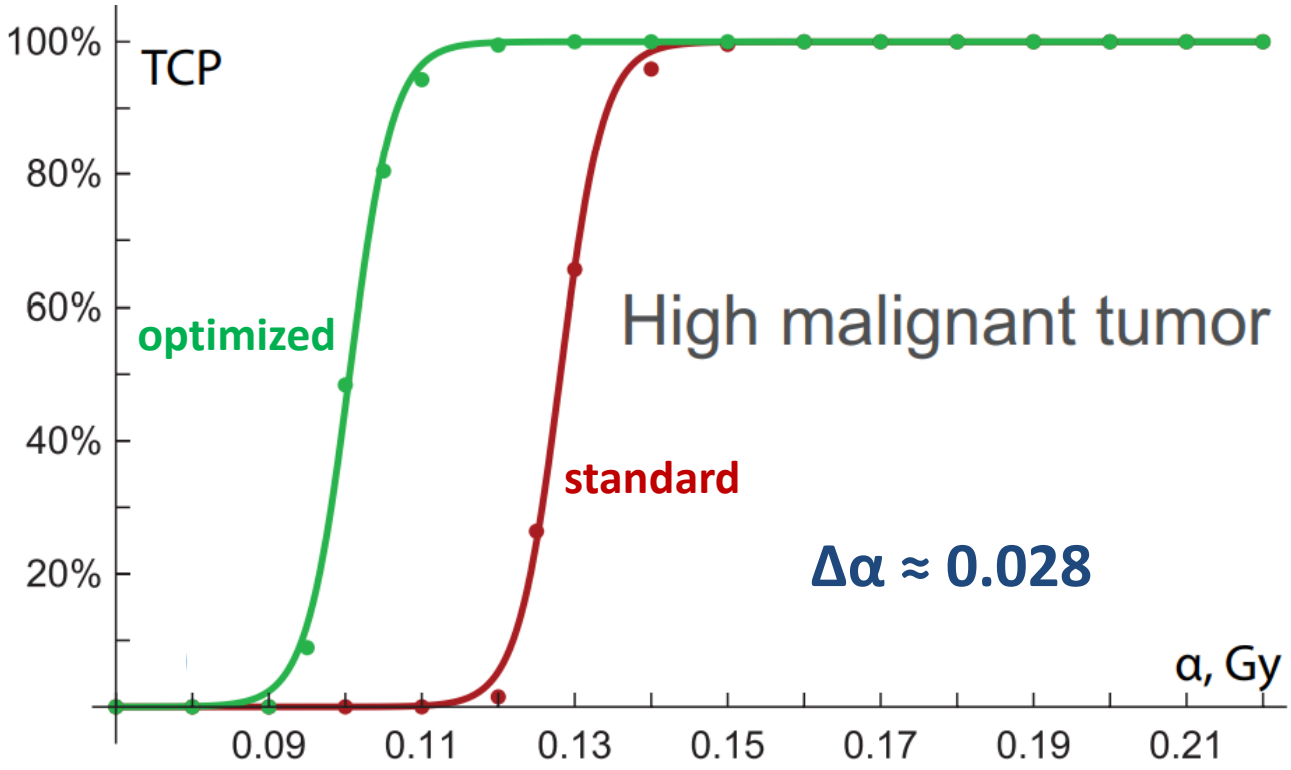


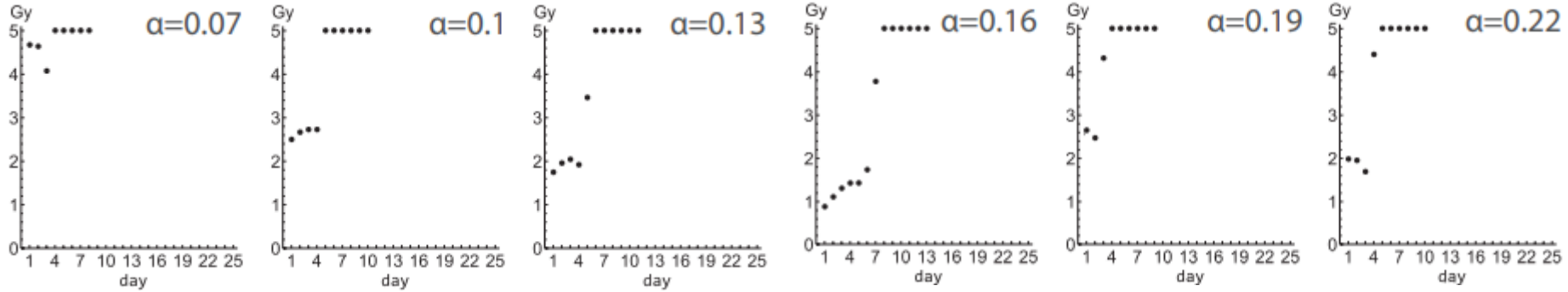




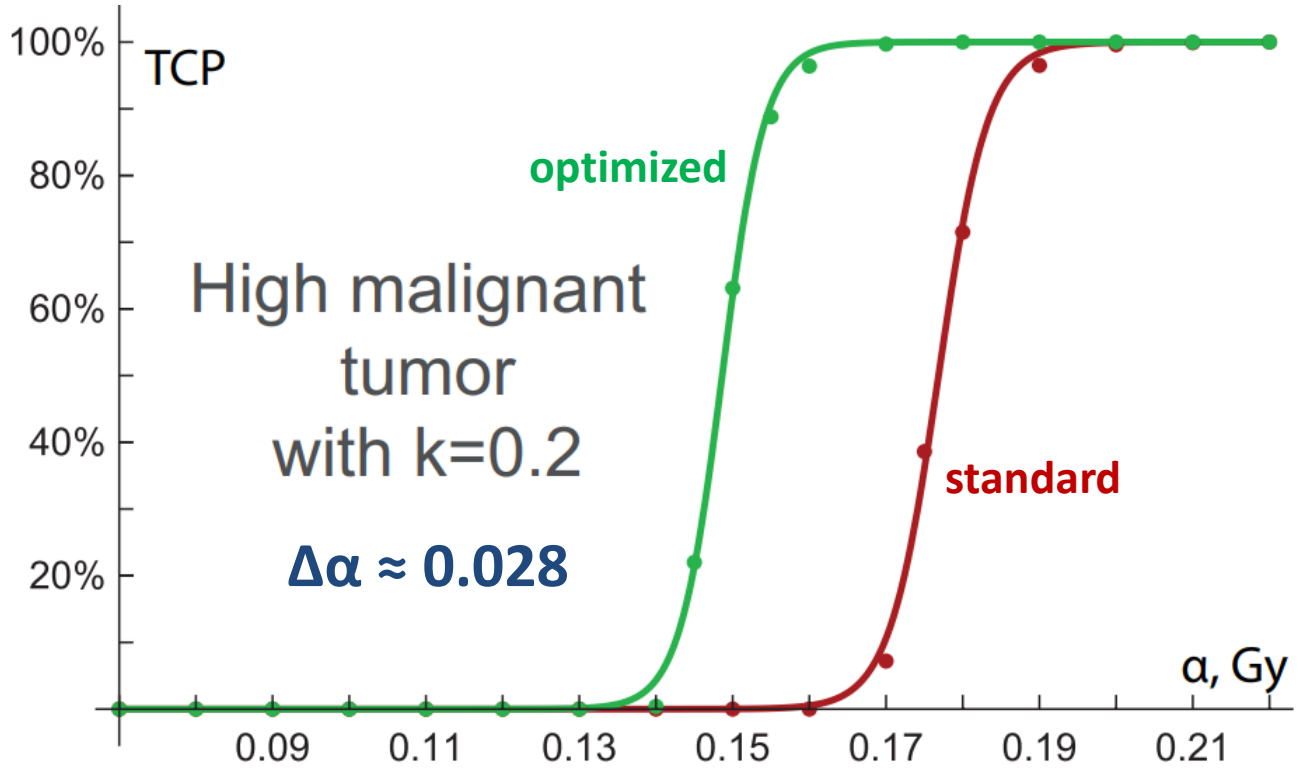


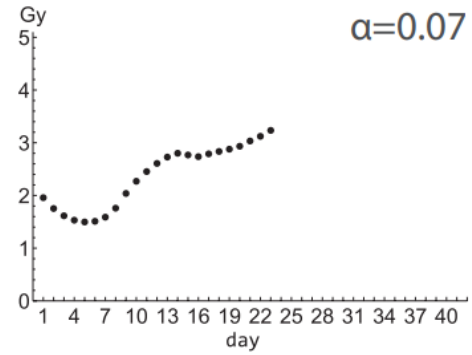
Standard vs. optimized fractionation schemes

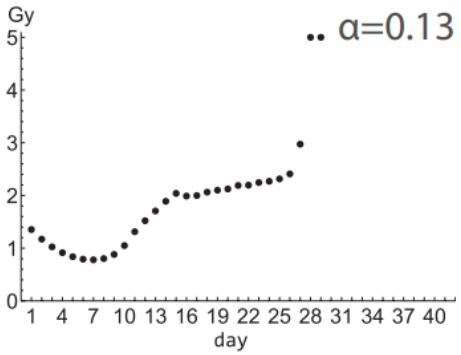


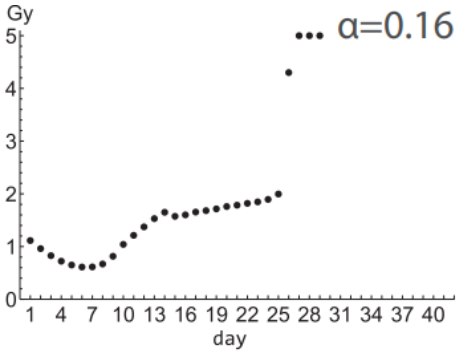


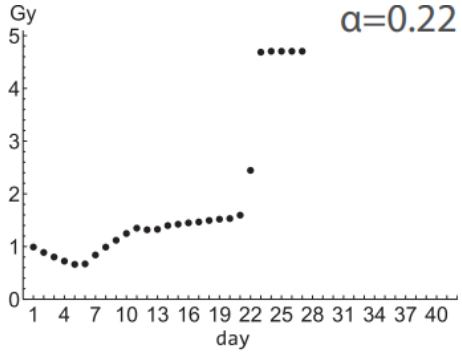
Standard vs. optimized fractionation schemes











Conclusions

- **A special algorithm is developed, aimed at finding the fractionation schemes that provide increased tumor cure probability**
  under the constraints of maximum normal tissue damage and maximum fractional dose.

- **The resulting optimized schemes consist of two stages.**
  The first stages are aimed to increase the radiosensitivity of the tumor cells, remaining after their end, sparing the caused normal tissue damage.
  This allows to increase the doses during the second stages and thus to **take advantage of the obtained increased radiosensitivity.**

- This study represent the theoretical proof of concept that **non-uniform radiotherapy fractionation schemes may be considerably more effective than the uniform ones**,
  due to the time and space-dependent effects.

Thank you for your attention!

Results are published:

Kuznetsov Maxim and Kolobov Andrey.
"Optimization of Dose Fractionation for Radiotherapy of a Solid Tumor with Account of Oxygen Effect and Proliferative Heterogeneity."
Mathematics 8.8 (2020): 1204.