Characterizing the Temporal Response of Glioma Cells to Single-Dose Radiation Therapy: Confrontation of a Mathematical Model to Experiments

Marianne Billoir[1,2], Stéphane Plaszczynski[1,2], Basile Grammaticos[1,2], Olivier Seksek[1,2], Delphine Crépin[1,2] and Mathilde Badoual[1,2]

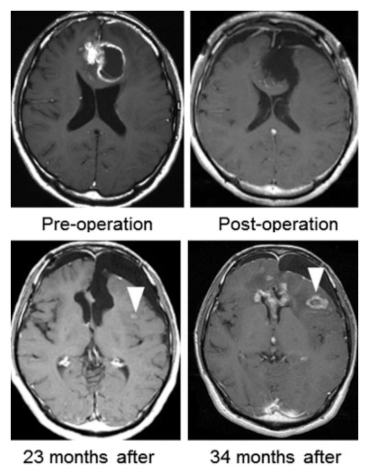
[1]Université Paris-Saclay, CNRS/IN2P3, IJCLab, 91405 Orsay, France
[2]Université Paris Cité, IJCLab, 91405 Orsay, France

Context

Gliomas are a type of brain tumor characterized by highly invasive cells, capable of migrating significant distances while remaining under the MRI detection threshold. This invasive behavior often leads to inevitable tumor recurrence following treatment [1,2].

Radiotherapy is a key component in this treatment, involving the administration of fractionated doses according to a precise schedule [1,2]. While fundamental aspects of radiotherapy treatment have been extensively studied, the current clinical model only predicts the survival fraction of cells after a given radiation dose without considering the timing of the response nor the collective effects [3].

By characterizing the temporal response of the tumor to irradiation, treatment schedules could be better tailored, resulting in improved outcomes of the disease.

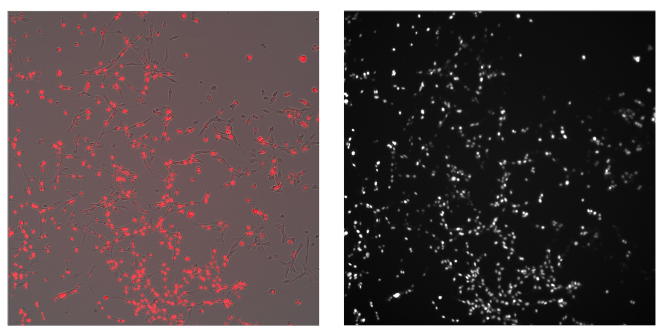


[4]

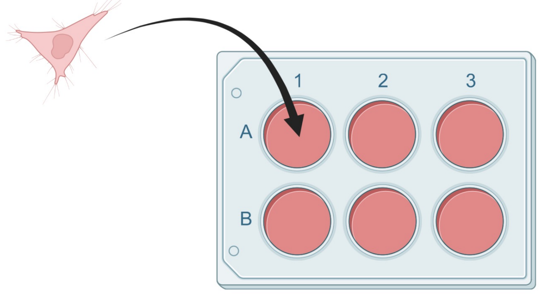
Material and Methods

Experiments:

1. Cell Transfection for a fluorescent nucleus [5]

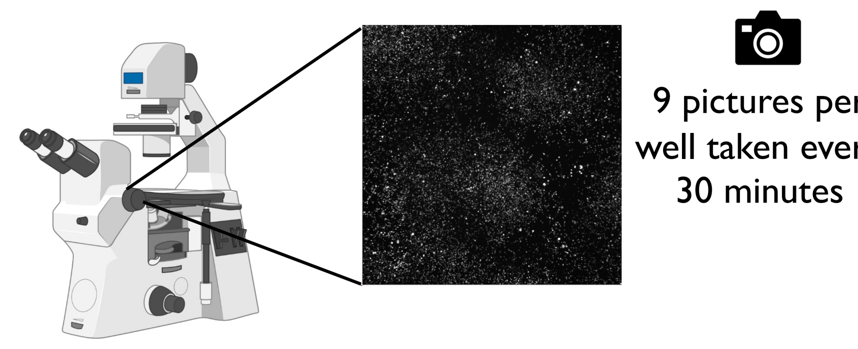


2. Cells seeded at 6 different concentrations



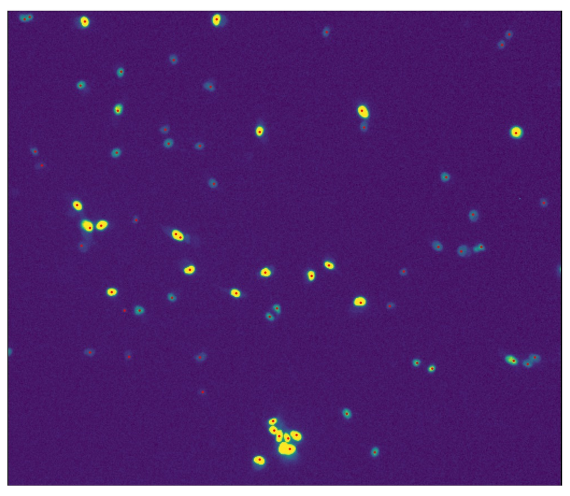
3. Radiation treatment at 0,10 and 20 Gy (X-Rays)

4. Monitoring with time-lapse fluorescence microscopy over 7 days

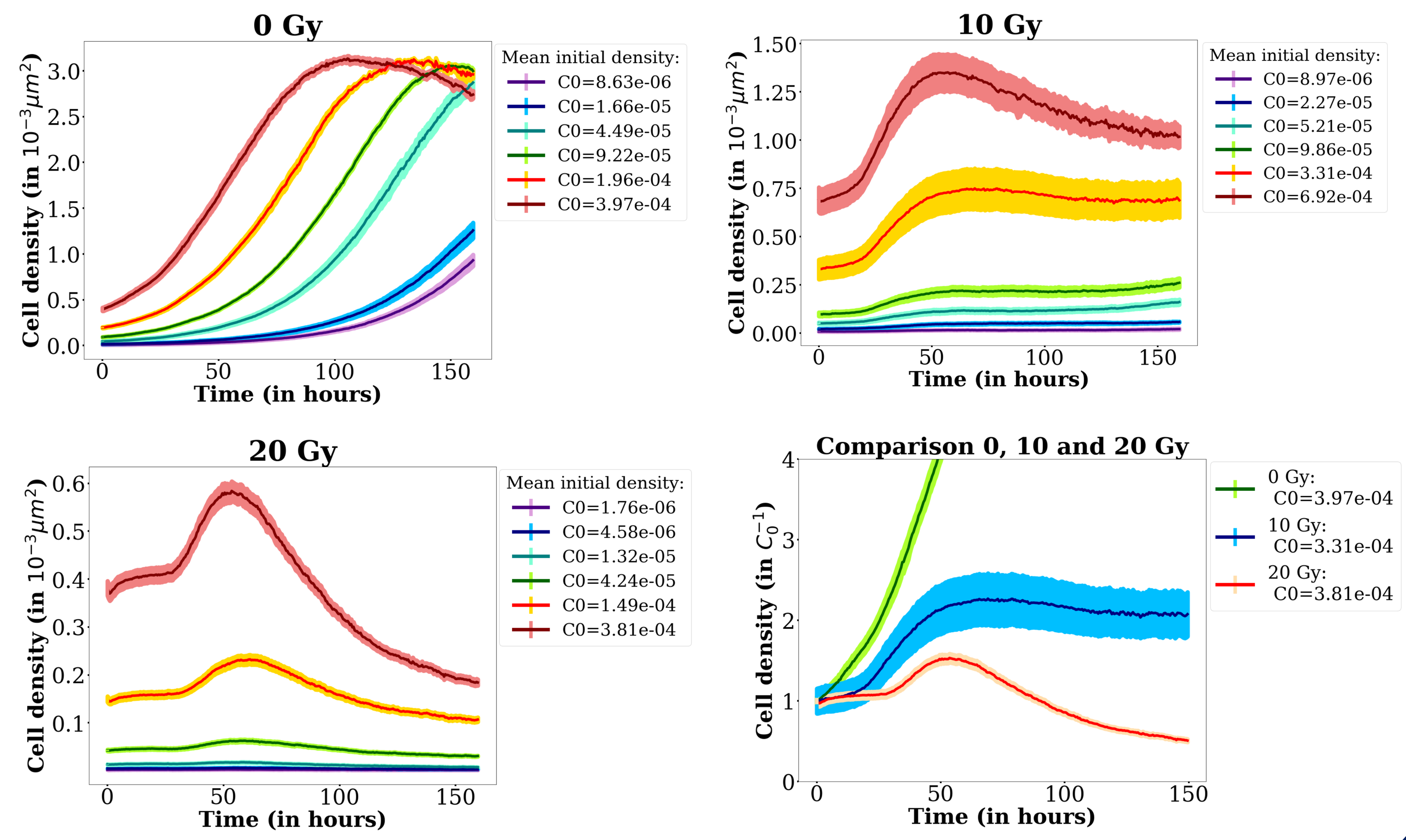


9 pictures per well taken every 30 minutes

Data Analysis: Homemade algorithm to detect and count the cells in each picture



Experimental Results



Models of Cell Growth

$C =$ cell density

Absence of Radiation:

We consider the space S as a function of C: $S = S_0 - s_{cell}C$

- **When cells have enough space:** Logistic growth with weak Allee effect [6]
- **Not enough space anymore:** Addition of an exponential term of death

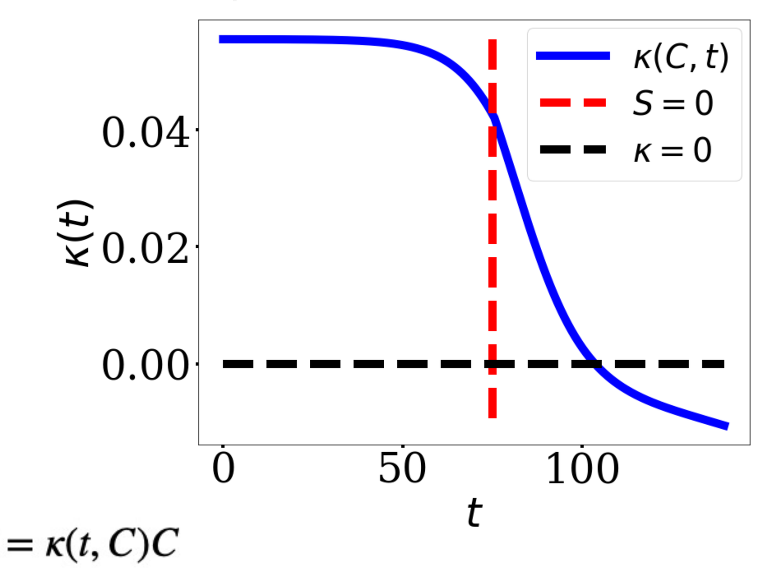
While $S > 0$:

$$\frac{dC}{dt} = (a - bC^2)C = \kappa(C)C$$

$$\frac{dS}{dt} = -s_{cell}\frac{dC}{dt}$$

When $S = 0$:

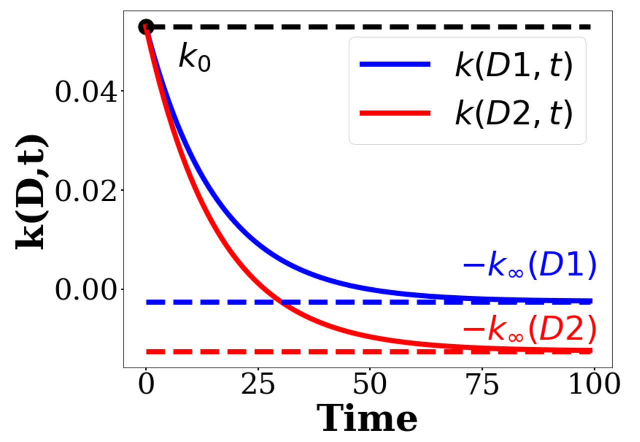
$$\frac{dC}{dt} = [a - bC^2 + A(e^{-d(t-t_0)} - 1)]C = \kappa(t, C)C$$



Response to Single-Dose Radiation Therapy:

$C =$ cell density

$$\frac{dC}{dt} = \underbrace{[(k_0 + k_\infty)e^{-\frac{t}{\tau}} - k_\infty]pC}_{\text{Damaged population}} + \underbrace{k_0(1-p)C}_{\text{Undamaged population}} = k(D,t)pC + k_0(1-p)C$$



- p : Fraction of damaged cells
- k_∞ : Death rate of the damaged population
- k_0 : Growth rate at null dose of irradiation
- τ : Characteristic time of the increase of damages

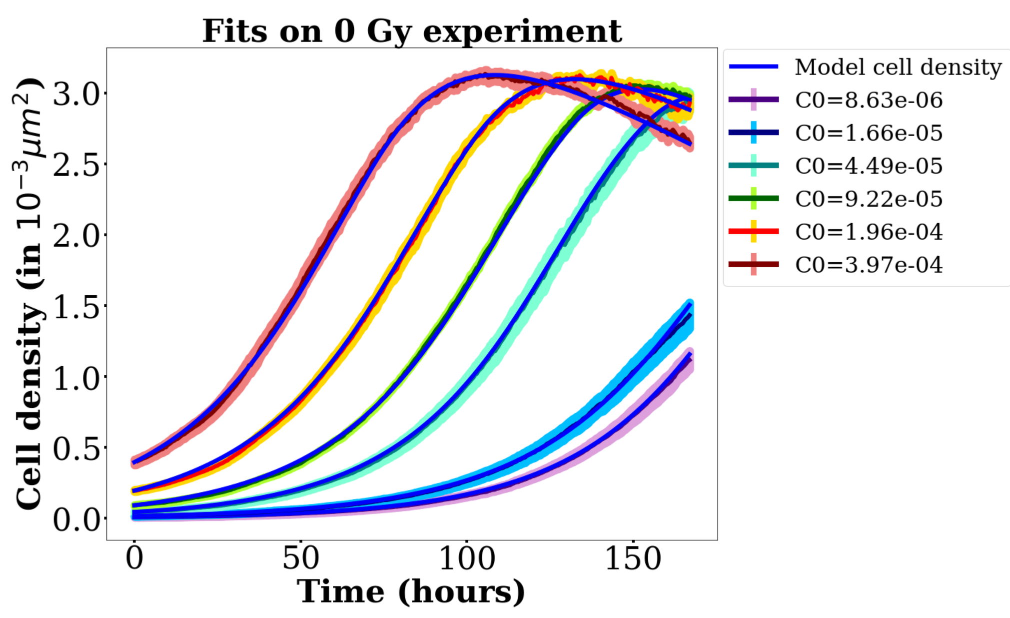
When integrated, gives:

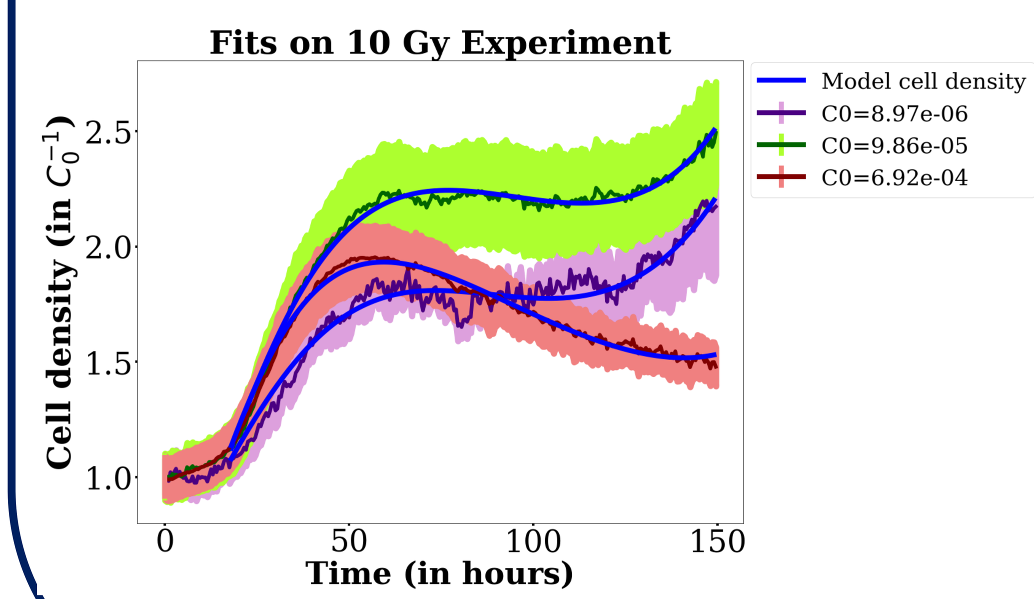
$$C(t,D) = pC_0e^{-k_\infty(t-T)}e^{(k_0+k_\infty)\tau(1-e^{-\frac{(t-T)}{\tau}})} + (1-p)C_0e^{k_0(t-T)}$$

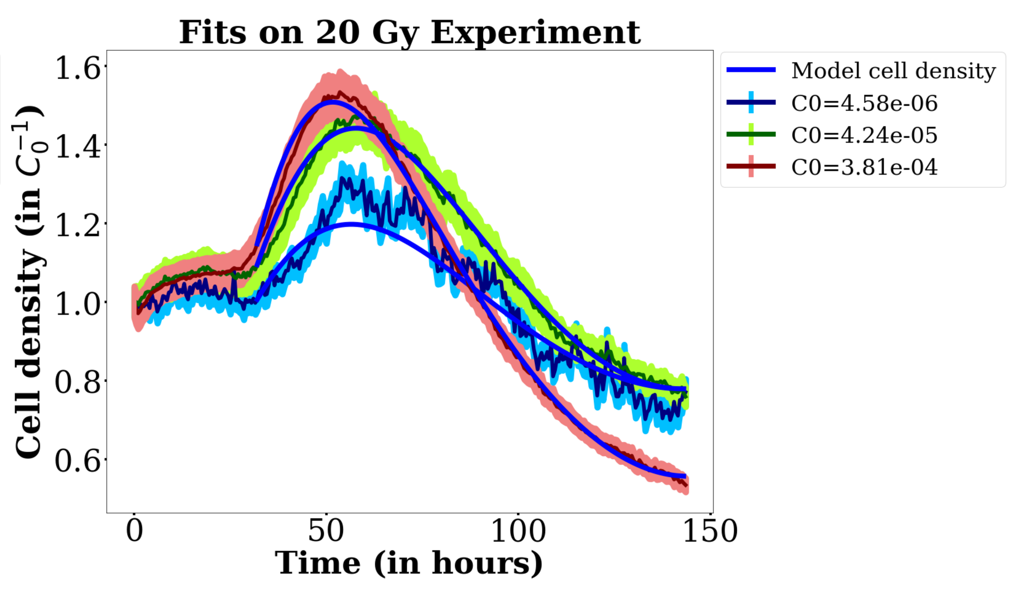
C_0 : Initial seeding density
T : Time of lag

Preliminary Results

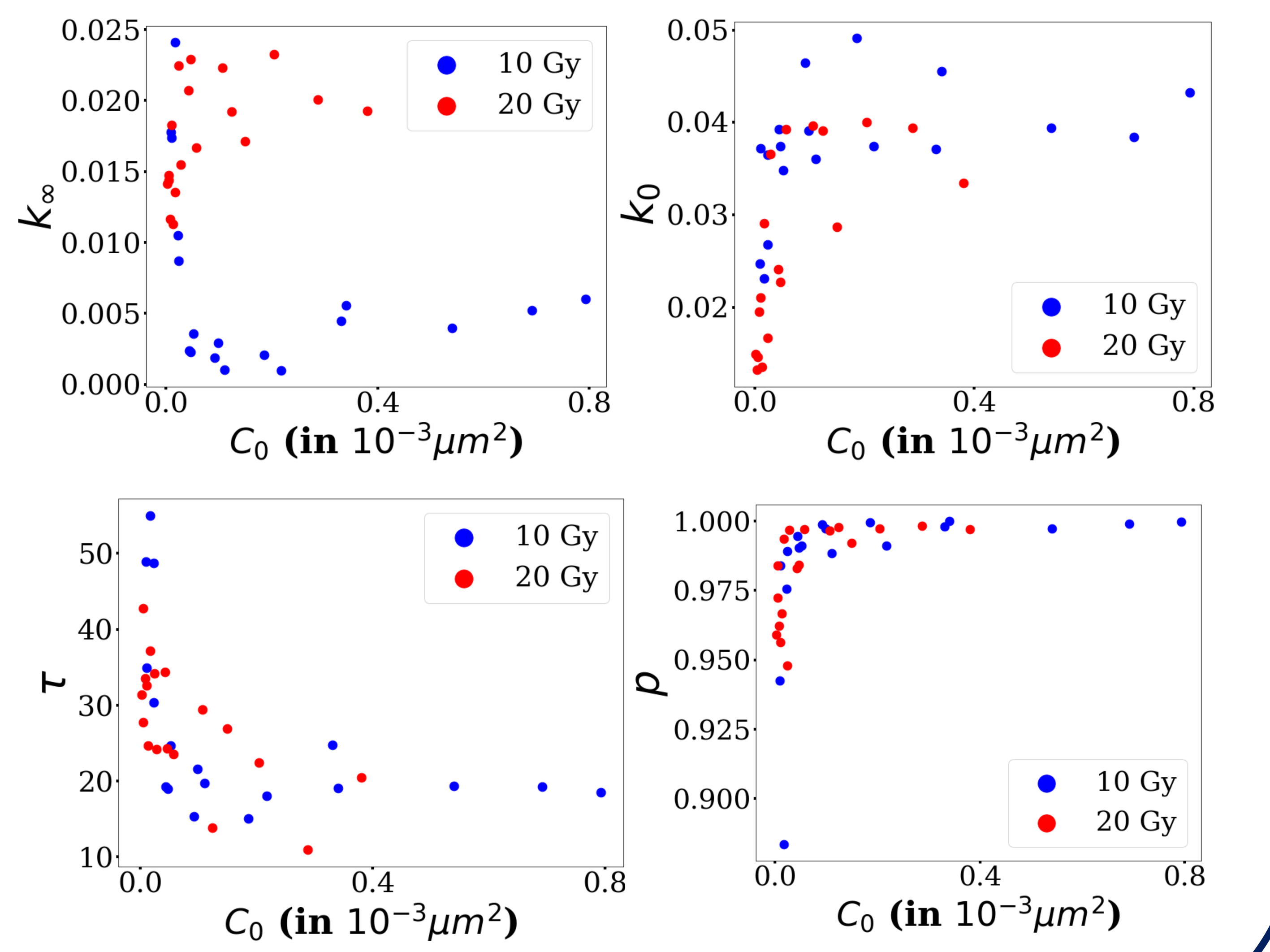
Models fitted on the experimental results







Parameters of the Response to Radiation as Function of the Dose D and Initial density C_0 :



Conclusion and Perspectives

- Dependance on D of k_∞: higher dose ⟹ higher death rate
- Dependance on C_0 of p and τ : at low density, less cells damaged and longer characteristic time of the damage effects ⟹ **Seems that a high density limits the regrowth of the population**
- New experiments at 5 and15 Gy
- Combination of both models
- Tracking of the cells
- Agent-based model

References:
[1] Fernandes, Catarina, et al. "Current standards of care in glioblastoma therapy", *Exon Publications* (2017): 197-241.
[2] Omuro, Antonio, and Lisa M. DeAngelis. "Glioblastoma and other malignant gliomas: a clinical review." *Jama* 310.17 (2013):1842-1850
[3] Jones, L., P. Hoban, and P. Metcalfe. "The use of the linear quadratic model in radiotherapy: a review." Australasian Physics & Engineering Sciences in Medicine 24 (2001): 132-146.
[4] Shibahara, Ichivo, et al. "Malignant clinical features of anaplastic gliomas without IDH mutation." *Neuro-oncology* 17.1 (2015):136-144.
[5] Chertkova, Anna O., et al. "Robust and bright genetically encoded fluorescent markers for highlighting structures and compartments in mammalian cells." *BioRxiv* (2017): 160374.
[6] Fadai, Nabil T., Stuart T., Johnston, and Matthew J. Simpson. "Unpacking the Allee effect: determining individual-level mechanisms that drive global population dynamics." *Proceedings of the Royal Society A* 476.2241 (2020): 20200350.