# Optimal radiotherapy regimes for low grade gliomas: insights from a mathematical model

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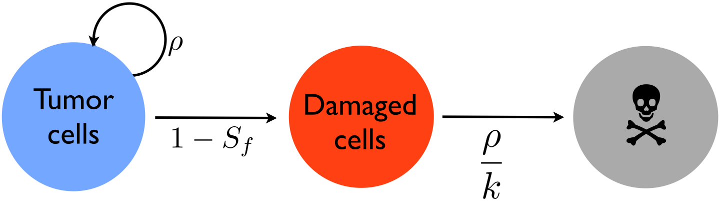
# Low grade gliomas

- Gliomas account for 50% of all primary brain tumors
- LGG: mostly incurable, median survival time $\sim$ 5 years
- Low evidence for currently used radiotherapy regimes

# Mathematical model

What could be obtained from mathematical model?

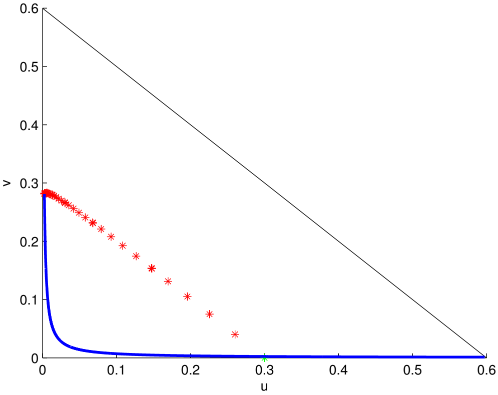
- Selecting LGGs patients that may benefit from radiotherapy
- Optimal fractionation schemes



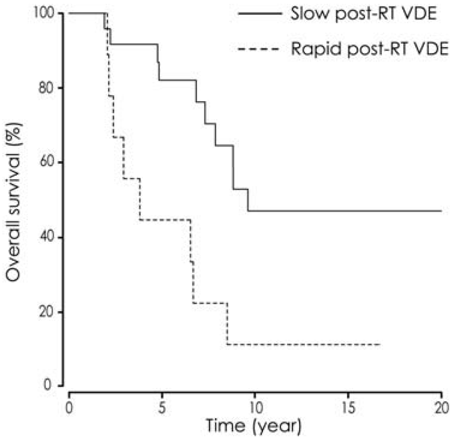

$$\frac{\partial u}{\partial t} = D\Delta u + \rho u(1-u-v),$$
$$\frac{\partial v}{\partial t} = D\Delta v - \frac{\rho}{k} v(1-u-v).$$

# Model dynamics

Standard radiotherapy scheme: 1.8 Gy every day during 30 days.



# Fast response — bad prognosis



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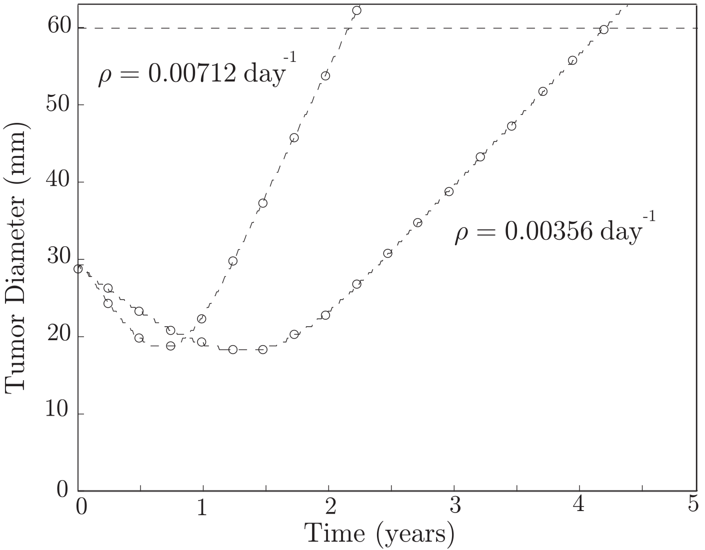
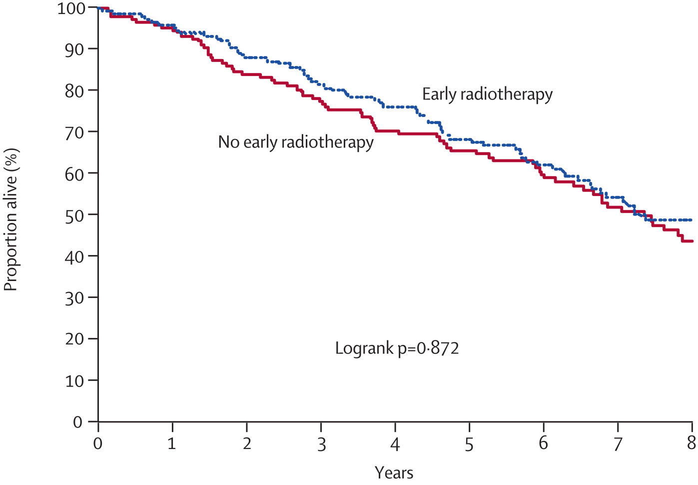


# RT delay doesn't affect survival



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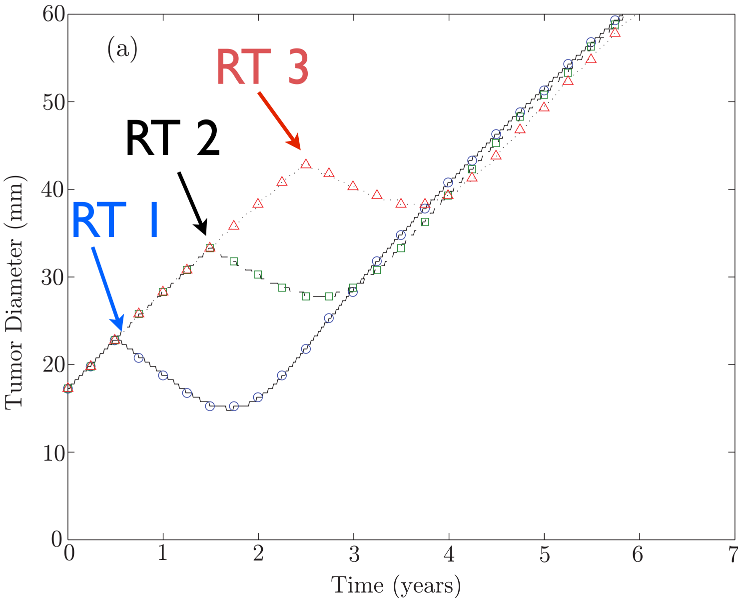


# Full mathematical problem

Tumor cell dynamics:

$$\begin{cases} \dfrac{\partial u}{\partial t} = D\Delta u + \rho u(1-u-v), \\ \dfrac{\partial u}{\partial t} = D\Delta v + \frac{\rho}{k} v(1-u-v), \\ u(0,x) = u_0(x),\ u_0(x) \in C^2(\bar{\Omega}),\ v(0,x) = 0, \\ \left.\dfrac{\partial u}{\partial \bar{n}}\right|_{\partial\Omega} = 0,\ \left.\dfrac{\partial v}{\partial \bar{n}}\right|_{\partial\Omega} = 0. \end{cases}$$

Response to RT:

$$\begin{cases} u_{n+1} = S_f u_n, \\ v_{n+1} = (1-S_f)u_n + v_n. \end{cases}$$

where: $S_f(d_k) = e^{-\alpha d_k - \beta d_k^2}$.

# Main restrictions

Restriction on normal tissue damage

$$E_h = \alpha_h \left( \sum_{j=1}^{N} d_j + \frac{1}{\alpha_h/\beta_h} \sum_{j=1}^{N} d_j^2 \right) \leq E_*, \ \frac{\alpha_h}{\beta_h} \approx 2$$

and on the maximal single dose irradiation value:

$$d_j \leq d_*, \ j = 1, \ldots, N$$

Maximization of survival time, tumor mass criterion:

$$\tau = \max\left\{t : \int_\Omega (u(t,x)+v(t,x))\,dx \le C\right\} \to \max_d,$$
$$\Omega \subset \mathbb{R}^2,\ d=(d_1,\ldots,d_N).$$

Maximization of survival time, maximal density criterion:

$$\tau = \max\{t : (u(t,x)+v(t,x))\} \le C \to \max_d,$$
$$\Omega \subset \mathbb{R}^2,\ d=(d_1,\ldots,d_N).$$

Results of optimization:

| $\tau$ | 1 week | 2 week | 3 week | 4 week | 5 week | 6 week |
|---|---|---|---|---|---|---|
| 6,15 years | 1.65 Gy | 1.76 Gy | 1.82 Gy | 1.84 Gy | 1.85 Gy | 1.86 Gy |
| 6,11 years | 1.8 Gy | 1.8 Gy | 1.8 Gy | 1.8 Gy | 1.8 Gy | 1.8 Gy |

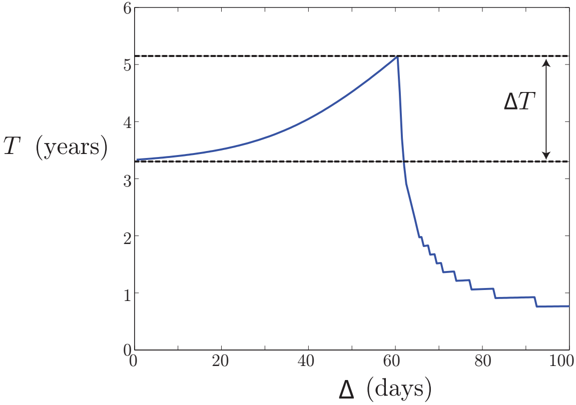
Standard dose values: $d = 1.8$ Gy.
Simpliest system dynamics:

$$\begin{cases} \dfrac{\partial u}{\partial t} = D\Delta u + \rho u(1-u), \\ u(0,x) = u_0(x),\ u_0(x) \in C^2(\bar{\Omega}), \\ \left.\dfrac{\partial u}{\partial \bar{n}}\right|_{\partial\Omega} = 0 \end{cases}$$

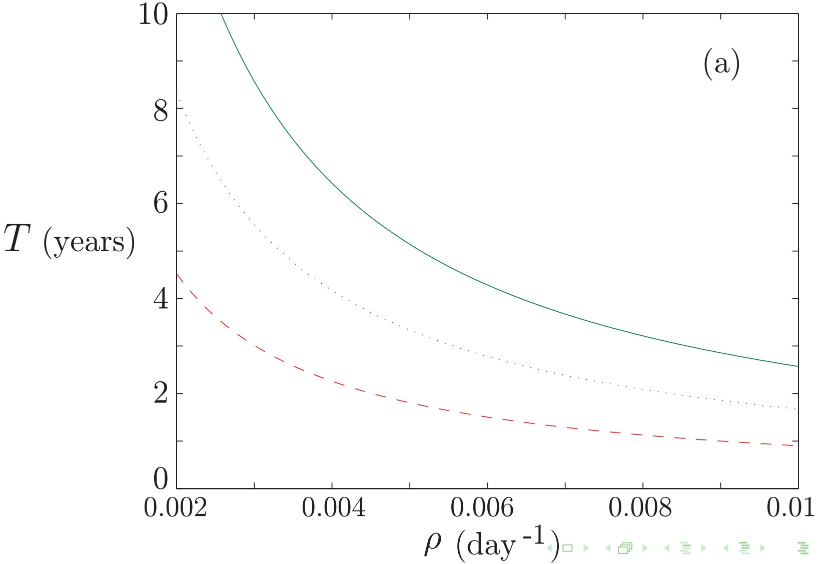
Radiotherapy: $u_{n+1} = S_f u_n$

# Optimization for time periods

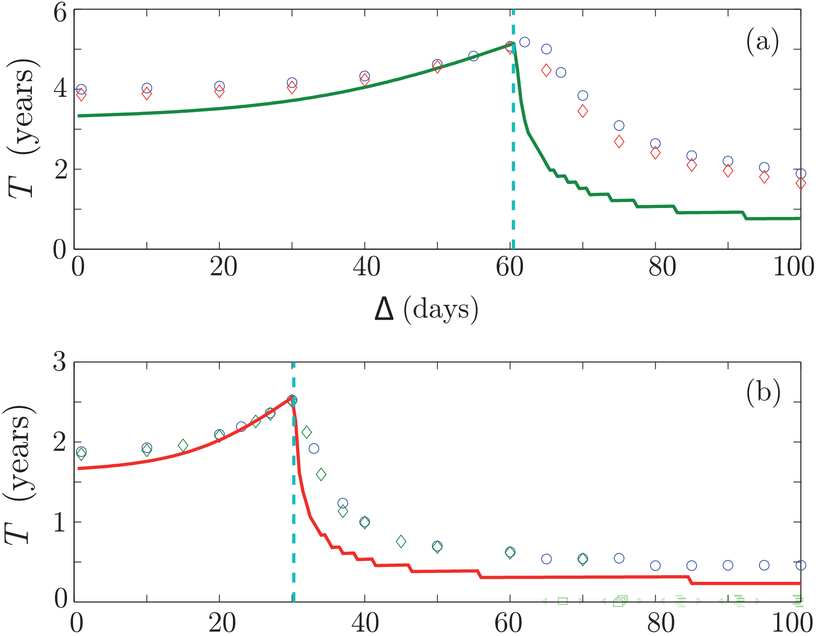
$$T:\ \max_{\Omega} u(t,x) \le U_* \to \max_{\Delta} \ \Rightarrow\ T(\Delta) = N\Delta + \frac{1}{\rho}\log\left[\frac{U_*(1-U_N)}{U_N(1-U_*)}\right]$$



# Gain in survival time



# 3d simulation



# What's next?

- Optimization of timing between doses for the full model
- Varying interval between doses independently
- Varying both dose values and scheduling: gain of metronomic therapy

Thank you for your attention!