Mathematical Modeling of PDGF-Driven Glioblastoma Reveals Optimized Radiation Dosing Schedules

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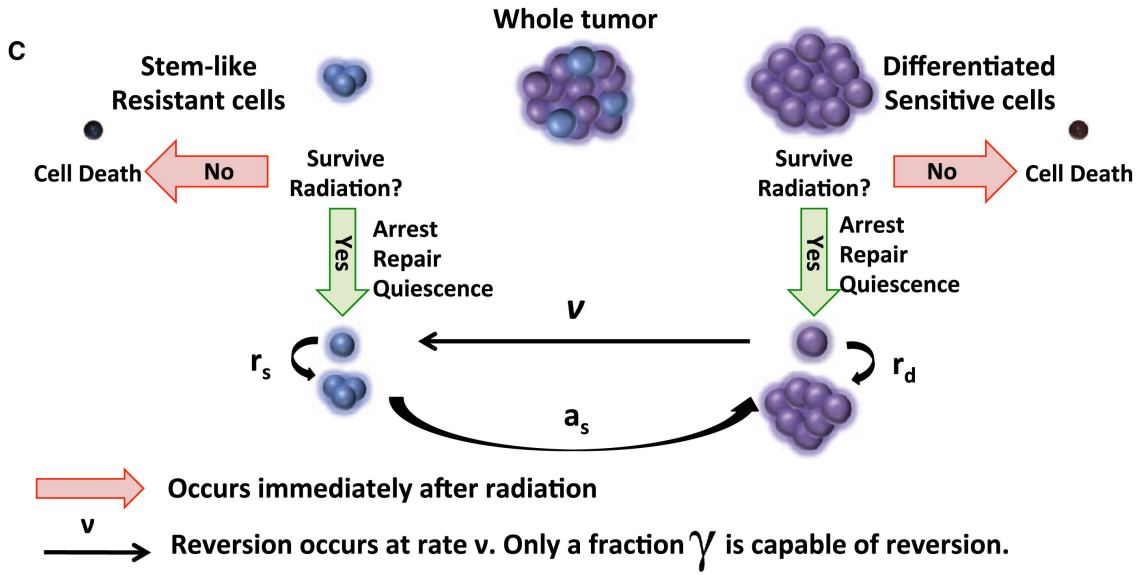
Overview

Glioblastoma Background

- Most common and malignant primary brain tumor
- Very poor survival rates
- Standard of care: surgery (if possible), radiation, chemotherapy
- Typical radiation dosing schedule: 2 Gy/day, 5 days/week, for 6 weeks

Glioblastoma Biology

- Three GBM subgroups related to signaling pathways:
  - **Abnormal platelet-derived growth factor (PDGF) signaling**
  - Epidermal growth factor receptor (EGFR) amplification
  - Loss of *NF1* function
- Subset of glioma cells have stem cell characteristics, are preferentially resistant to radiation



Mouse Model

- Generated PDGF-B-induced tumors in mice
- Model similar to human gliomas - mice transiently respond to radiation but then experience disease recurrence
- Dose response study lead to choice of 10 Gy dose for analysis

Initial Mathematical Model

- Consists of 2 cell subpopulations: stem-like/resistant cells (SLRCs) & differentiated/sensitive cells (DSCs)
- Bidirectional flow of cells between these states
- Only fraction of DSCs capable of reverting to SLRCs
- Includes radiation-induced cell-cycle arrest for certain time and minimum time for newly converted DSCs to begin reproducing
- Cell response to radiotherapy modeled with linear quadratic model
  - fraction of surviving cells after dose of d Gy $= \exp(-\alpha d - \beta d^2)$
  - parameters α and β cell-type specific

Model 1: Number of DSCs

$$N_1^d = N_0^d e^{-\alpha_d d_i - \beta_d d_i^2} \Big[\underbrace{(1-\gamma)e^{r_d(t-L_d)^+}}_{(1)} + \underbrace{\gamma e^{-\nu t}}_{(2)} + \alpha_s \gamma \nu \int_0^t e^{r_d(t-s-M_d)^+} \times \underbrace{\int_0^{(s-L_S)^+} e^{-\nu y} e^{r_s(s-y-L_s)^+} dy ds}_{(3)} \Big] + \alpha_s N_0^s e^{-\alpha_s d - \beta_s d^2} \times \underbrace{\int_{L_s}^{\max(t_i, L_s)} e^{r_s(s-L_s)} e^{r_d(t-s-M_d)^+} ds}_{(4)},$$

(1) # DSCs survived radiation, can't revert to SLRC
(2) # DSCs that have started to revert
(3) Creation of new DSCs from new SLRC population
(4) Creation of DSC from original SLRC population

Model 1: Number of SLRCs

$$N_1^s = \underbrace{N_0^s e^{-\alpha_s d_i - \beta_s d_i^2} e^{r_s (t - L_s)^+}}_{(1)} + \underbrace{\gamma \nu N_0^d e^{-\alpha_d d_i - \beta_d d_i^2} \int_0^t e^{-\nu s} e^{r_s (t - s - L_s)^+} ds}_{(2)}$$

(1) # SLRCs survived radiation + growth
(2) # DSCs reverted to SLRC + growth

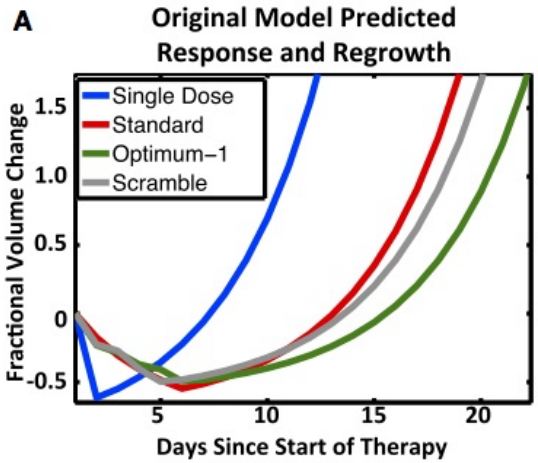
Model 2

- Model updated such that fraction of DSCs converting to SLRCs depends on time since previous radiation dose
- Two time-dependent parameters added
  - μ: time of maximal reversion after radiation
  - σ^2: width of window after radiation during which reversion can occur

Optimized Radiation Schedules

- For each model, generated optimized radiation schedule (optimum-1 and optimum-2)
- Schedule to minimize number of tumor cells 2 weeks after treatment conclusion under clinically motivated constraint set
- Done by Monte-Carlo based method (simulated annealing)

Model 1 Results



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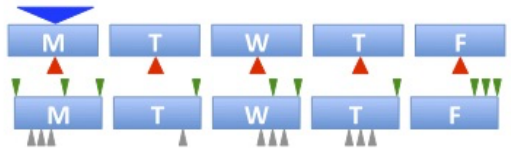
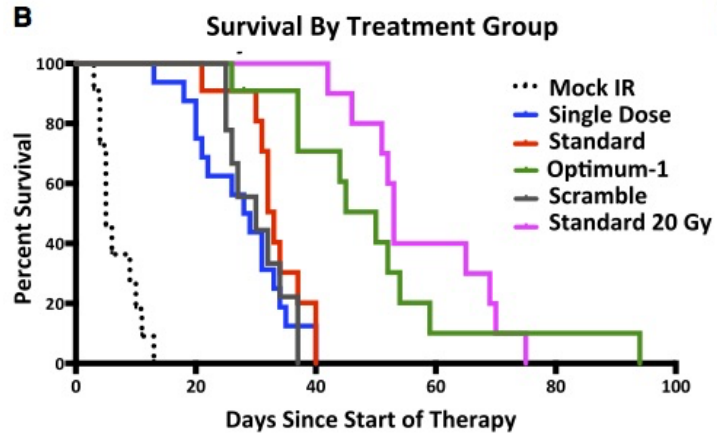
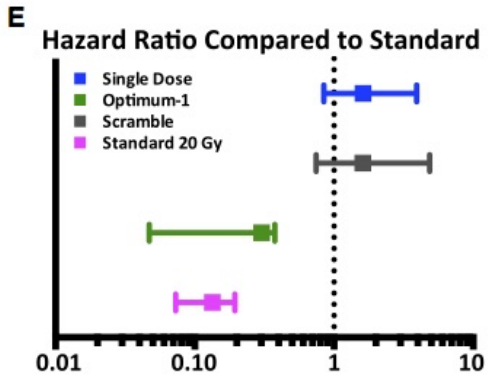


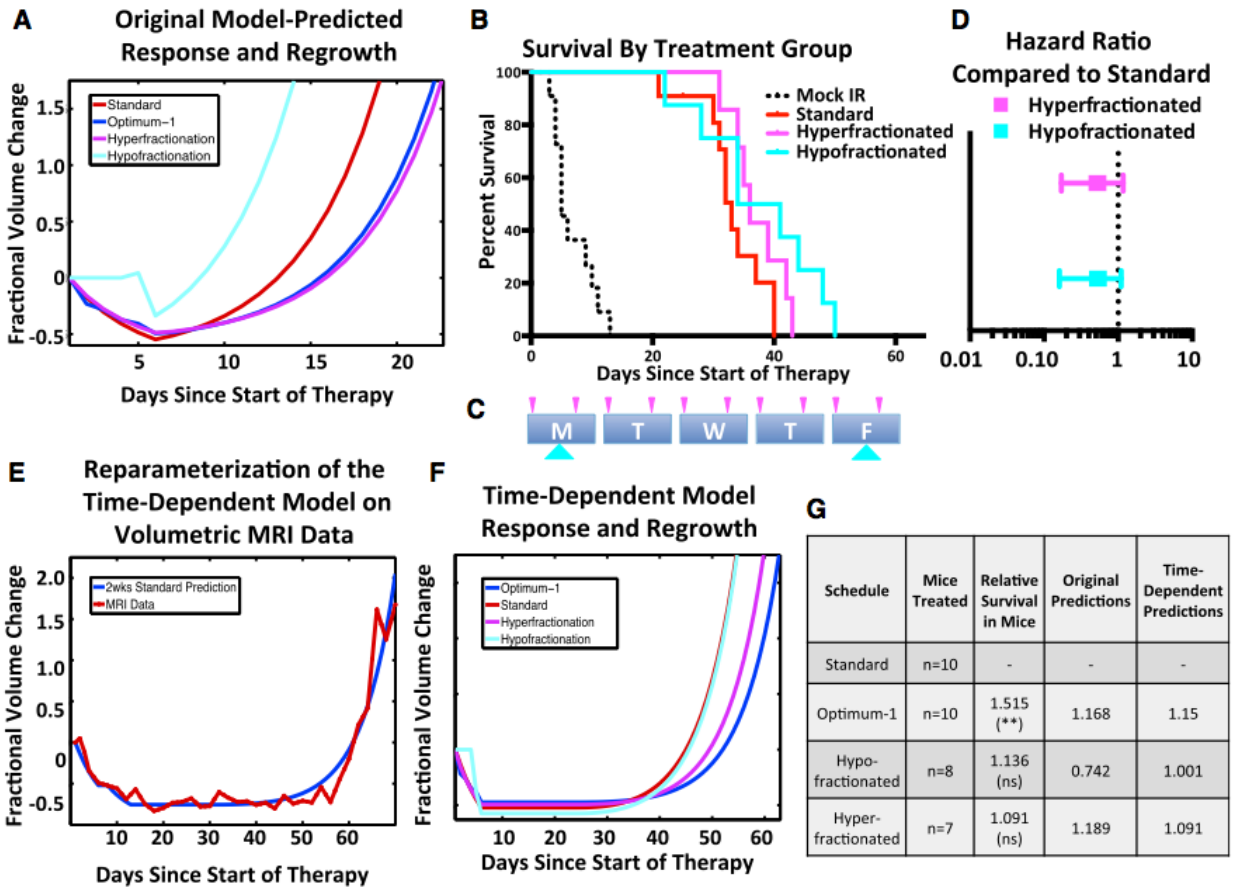
D

Schedule	Mice Treated	Experimental Relative Survival	Predicted Relative Survival	Δ Pred - Exp
Standard 10	n = 10	---	---	---
Single Dose	n = 16	0.864 (ns)	0.652	-0.212
Scramble	n = 9	0.909 (ns)	1.056	0.147
Optimum-1	n = 10	1.515 (**)	1.168	-0.347
Standard 20	n = 10	---	---	---





Model 1 Results: Failed Predictions

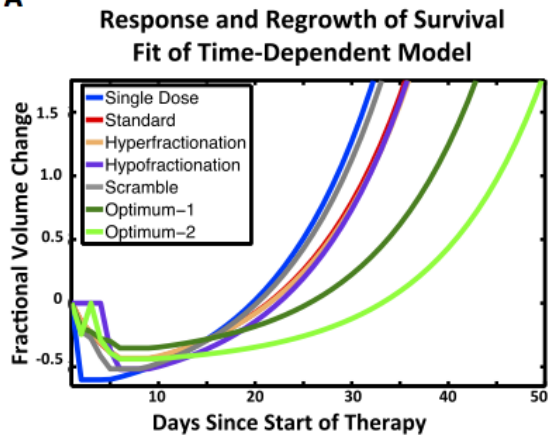


G

Schedule	Mice Treated	Relative Survival in Mice	Original Predictions	Time-Dependent Predictions
Standard	n=10	-	-	-
Optimum-1	n=10	1.515 (**)	1.168	1.15
Hypo-fractionated	n=8	1.136 (ns)	0.742	1.001
Hyper-fractionated	n=7	1.091 (ns)	1.189	1.091

Model 2 Results

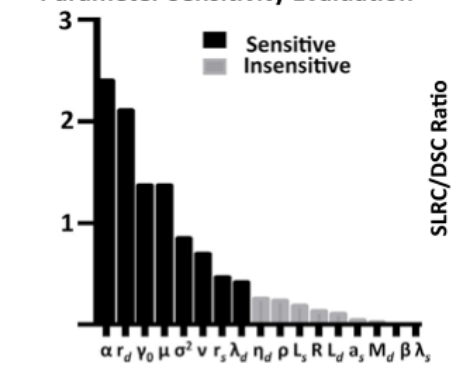
A



B

Schedule	Mice Treated	Exp. Relative Survival	Survival-Fit Predicted Survival	Δ Pred - Exp
Standard	n = 22	---	---	---
Single Dose	n = 16	0.864 (ns)	0.909	0.045
Hyper-fractionated	n = 7	1.091 (ns)	1.091	0
Hypo-fractionated	n = 8	1.136 (ns)	1.015	-0.121
Scramble	n = 9	0.909 (ns)	0.909	0
Optimum-1	n = 28	1.363 (****)	1.348	-0.015
Optimum-2	n =18	1.535 (****)	1.512	-0.023

C



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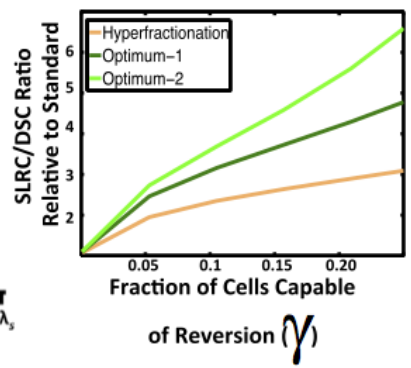

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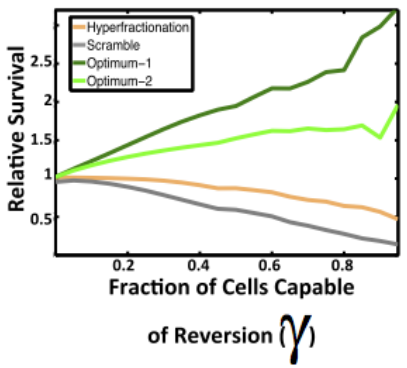
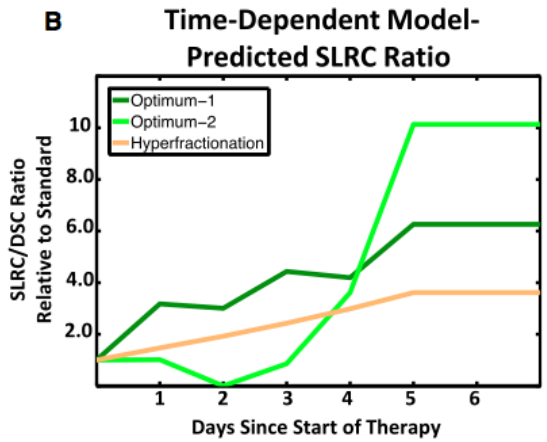
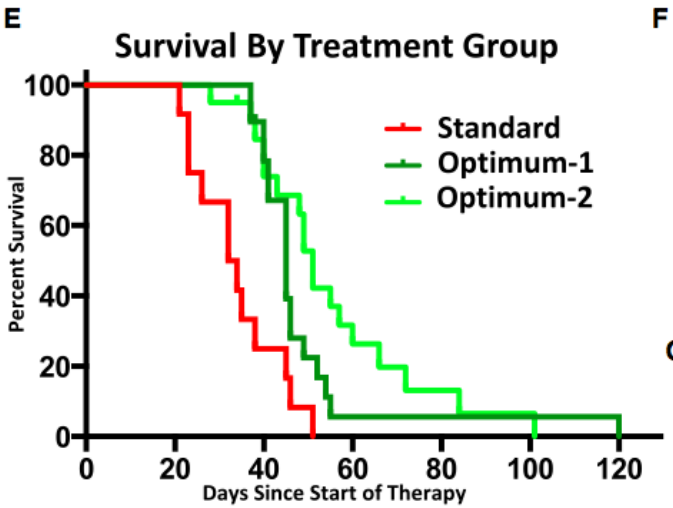
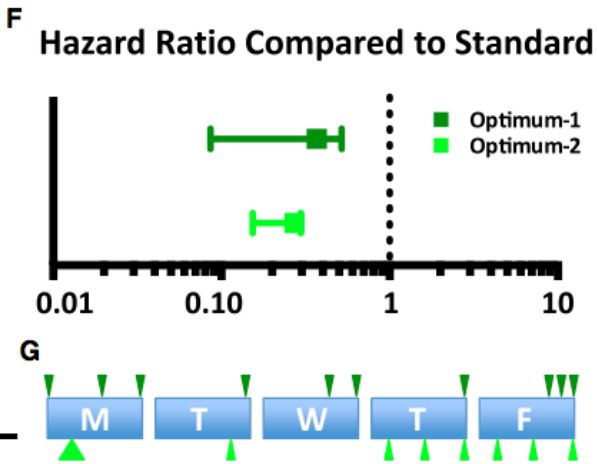


Model 2 Results







Conclusions

- Dosing schedule can have strong effect on overall survival times
- Optimum-1 and optimum-2 both lead to longer survival times through enriched number of SLRCs
- Suggests survival actually improved by higher SLRC (resistant) population - results in slower-growing tumor and longer time to recurrence
- Clearly not curative treatment
- Many challenges translating to human clinical setting

The End