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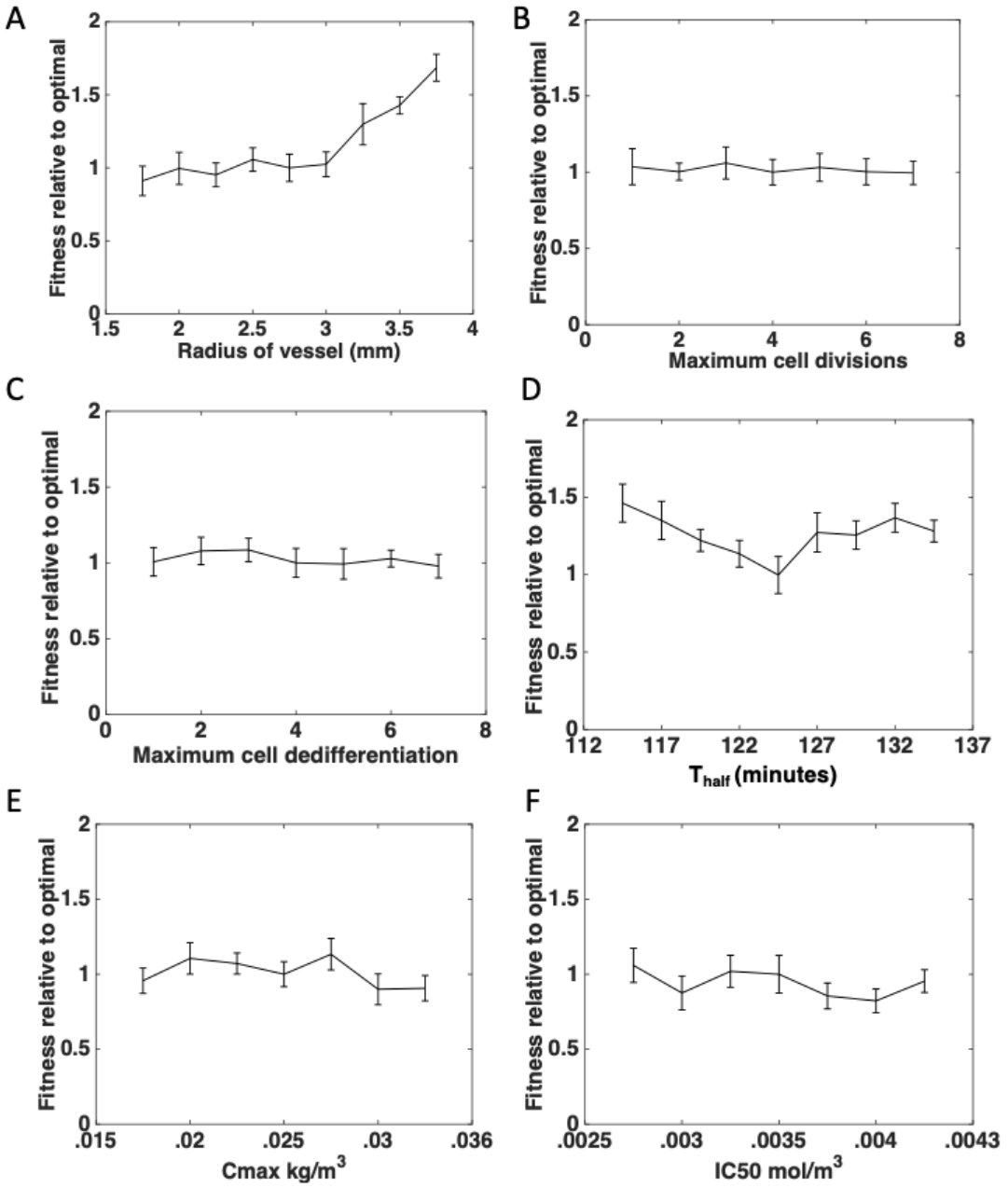
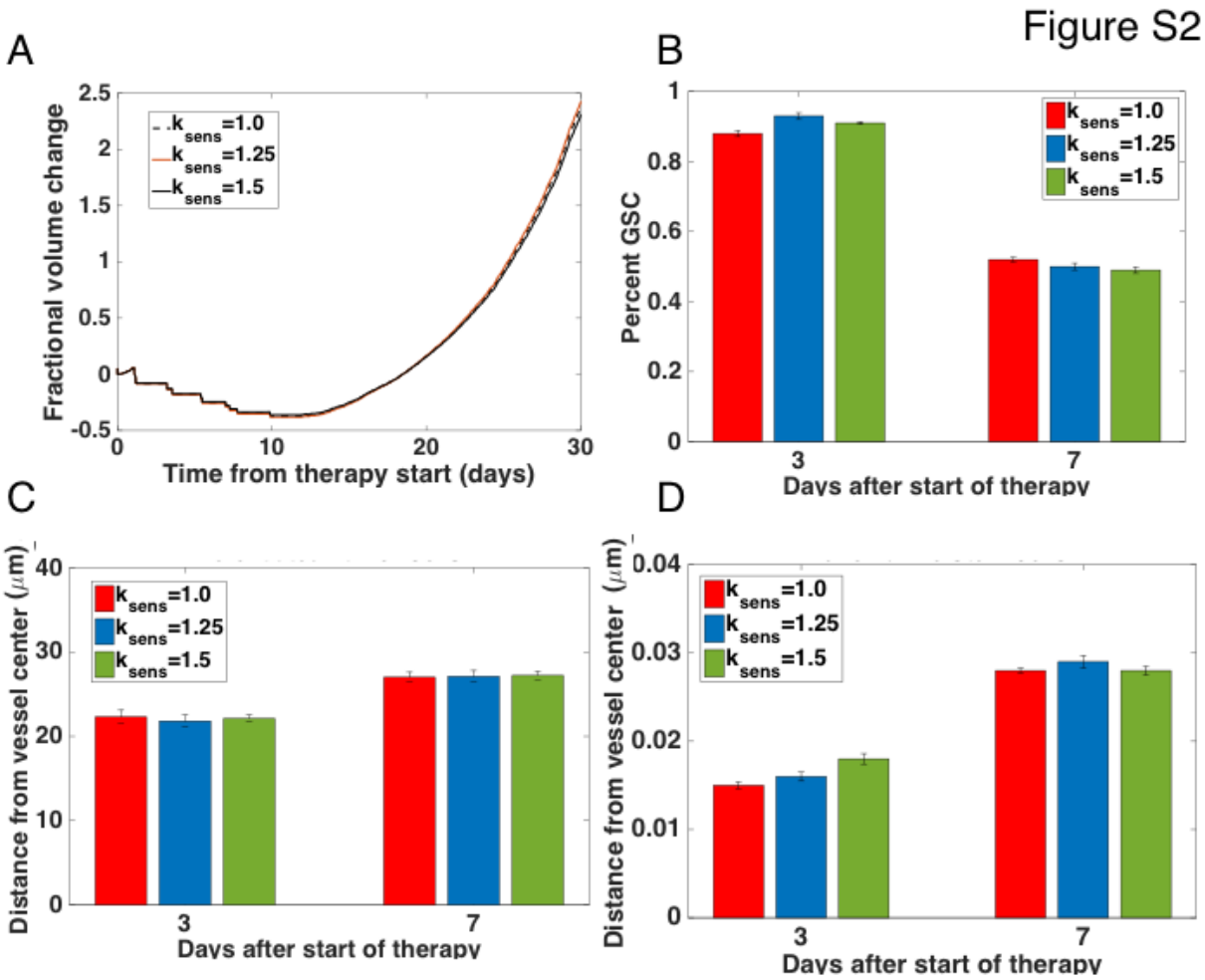
Figure S1

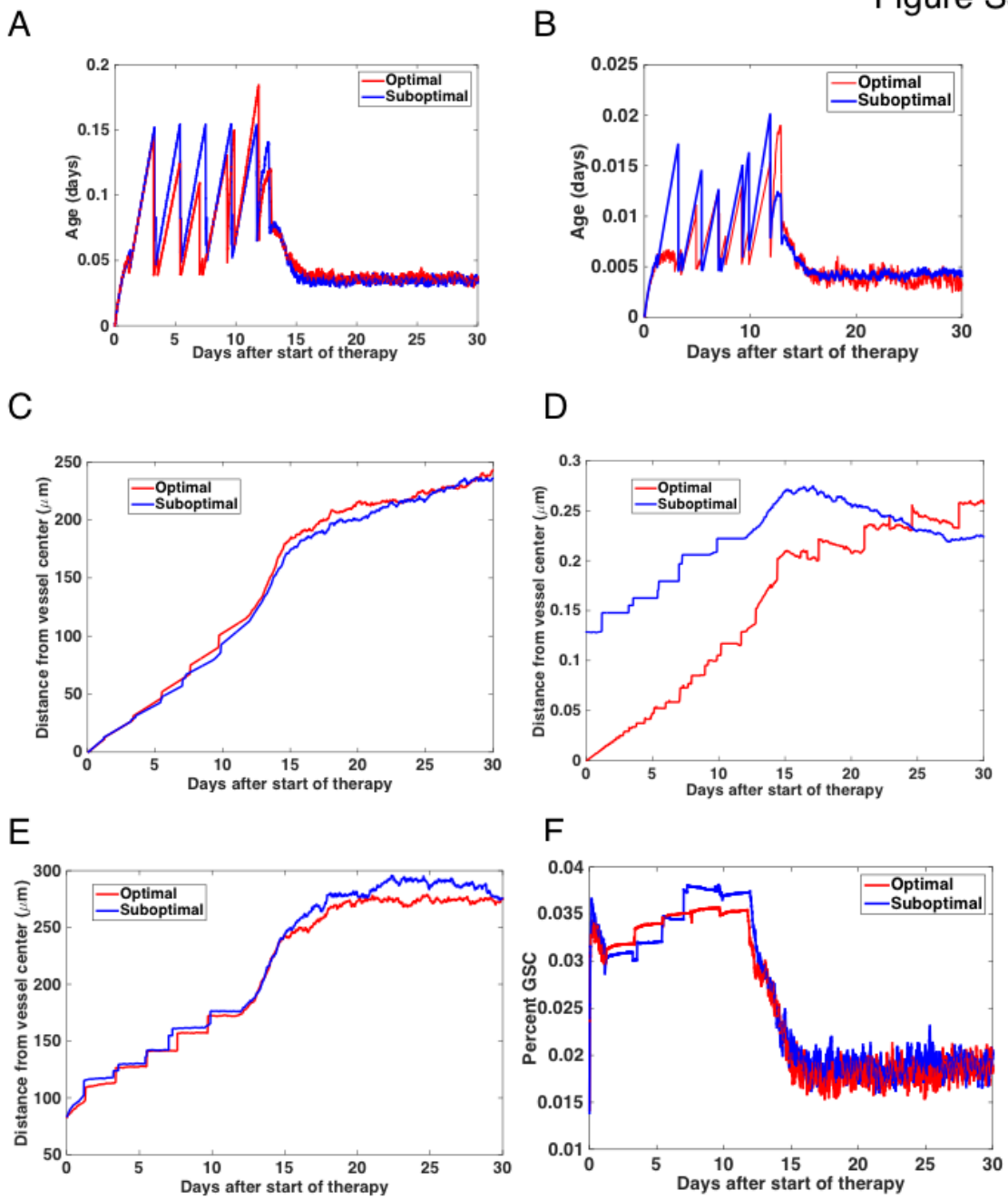


Supplementary Figure 1 | Sensitivity studies. The figure shows the relative efficacy of the fitness of the optimal schedule. To measure relative efficacy, we investigated the ratio of the tumor population under the given parameters to the tumor population under the nominal condition. This comparison was made 30 days after initiation of therapy. In panels **(A-F)** we varied parameters R_{vessel}, Z, Z_{revert}, T_{max}, T_{half}, C_{max}, and IC_{50}. To account for stochasticity in the model, each simulation was completed 128 times. Error bars, mean +/- s.d.



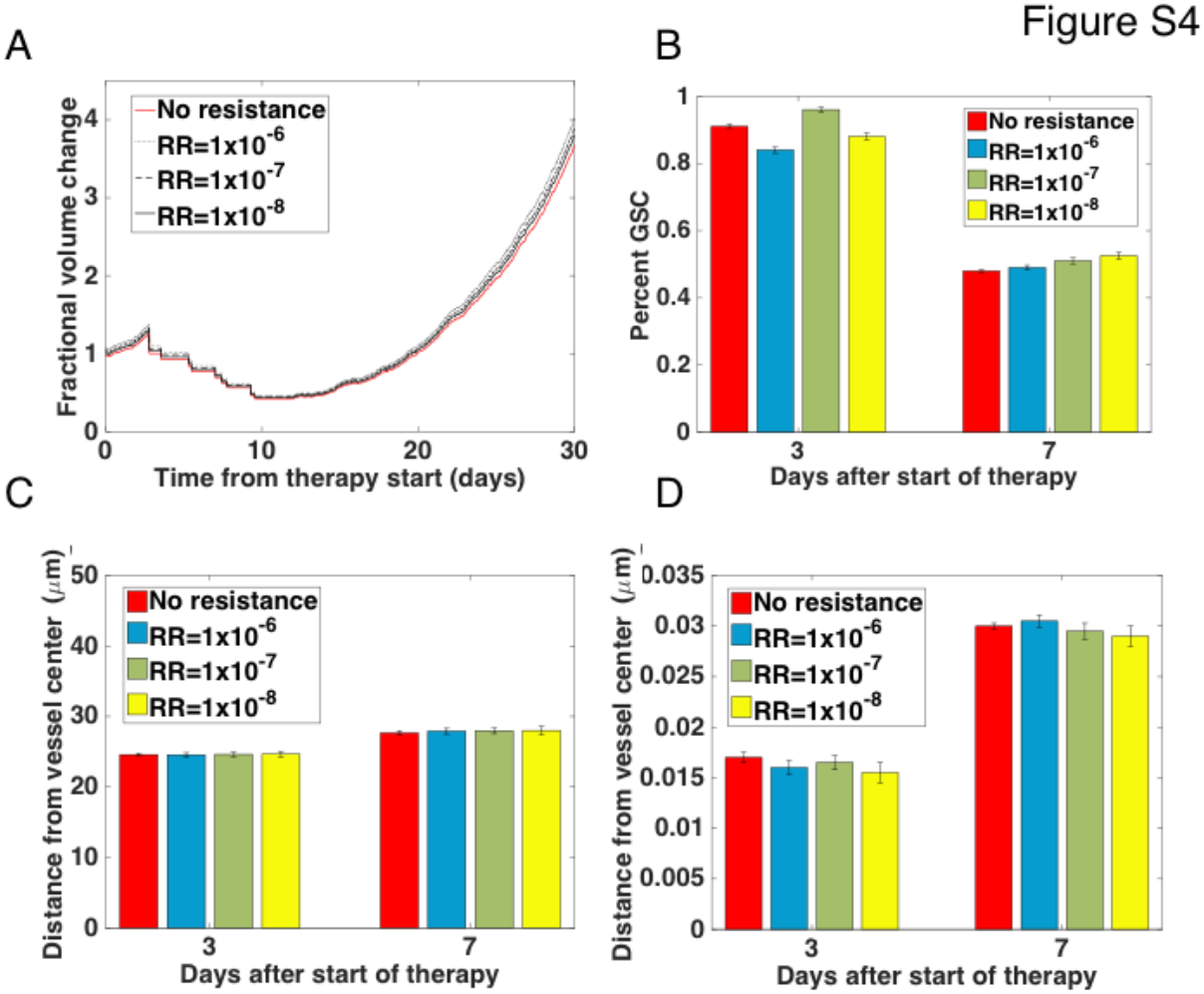
Supplementary Figure 2 | Radiosensitivity studies. The figure shows the relative effect on tumor fractional volume change for different time periods between administration of TMZ and radiation. To account for stochasticity in the model, each simulation was completed 128 times. **(A)** Fractional volume change under different settings for the k_{sens} parameter are depicted. **(B)** Further sensitivity studies are shown looking at the percent of glioma-like stem cells under each k_{sens} value at two key time points: one day and seven days after start of therapy. Error bars, mean +/- s.d. **(C-D)** Prediction plots showing the average distance from the vessel center 3 days and 7 days after treatment states for a model with a range of k_{sens} values. Error bars, mean +/- s.d. **(C)** shows the results for GSCs and **(D)** DTCs.

Figure S3



Supplementary Figure 3 | Prediction of GBM growth and treatment response with chemoradiation resistance. (A-B) Plots showing the average age of the cells at up to 30 days after the treatment started. **(A)** shows the results for GSCs and **(B)** DTCs. **(C-D)** Prediction plots showing the average distance from the vessel center up to 30 days after treatment commences. **(C)** shows the results for GSCs and **(D)** for DTCs. **(E)** Maximum distance from the vessel that any of the cells travel up to 30 days after treatment commences. **(F)** Percent of cells that are GSC up to 30 days after treatment initiation.

Figure S4



Supplementary Figure 4 | The emergence of chemoradiation resistance. The figure shows the effects of the emergence of therapy-resistant cells. **(A)** Plot showing the expected fractional volume change over time for the optimized schedule from **Table 1A** without the inclusion of resistant cells versus models with the resistance rate set to a range of values. **(B)** Percent of cells that are GSC at 3 and 7 day after treatment starts. Error bars, mean +/- s.d. **(C-D)** Prediction plots showing the average distance from the vessel center 3 days after treatment starts and 7 days after treatment starts for a model with a range of resistance rate settings. Error bars, mean +/- s.d. **(C)** shows the results for DTCs and **(D)** for GSCs.

Supplementary Table S1 | Description and values of the mathematical model parameters. Note that no single source was available to quantify all parameters and their variability; to address this limitation we performed sensitivity analyses of the parameters as outlined in the methods. Note also that the values of α_d and α_s might represent a lower bound.

Biological Process	Symbol	Value	Method	Citation
Per Gy production of lethal DNA lesions from single radiation track in DSC and SLRC	α_d / α_s	0.0987/0.00987	inferred	[18]
Per Gy^2 production of lethal DNA lesions from two radiation tracks in DSC and SLRC	β_d / β_s	1.14×10^{-7} / 1.14×10^{-8}	inferred	[18]
Rate at which newly converted DSC leads to clonal expansion (hr)	η_d	0.054	inferred	
Minimum time for newly converted DSC to begin clonal expansion (hr)	M_d	24	inferred	[18]
Minimum time DSC and SLRC are in quiescence (hr)	L_d / L_s	24/36	inferred	[18]
Rate at which DSC and SLRC exit quiescence	λ_d / λ_s	0.1/.0328	inferred	[18]
Proliferation rate of DSC and SLRC after exiting quiescence	r_d / r_s	0.0038/0.008	inferred	[18]
Initial ratio of DSC to SLRC	R	20	inferred	[18]
Rate at which SLRC convert to DSC	a_s	0.0019	inferred	[18]
Rate of reversion of DSC to SLRC	v	0.45	inferred	[18]
Fraction of DSC capable of reverting to SLRC	γ	0.4	inferred	[18]
Time to peak reversion after irradiation	μ	3.25	inferred	[18]
Width of window of reversion	σ^2	1.46	inferred	[18]
Half-life of chemotherapy	$T_{1/2}$	1.25	PK value	[47]
Maximum concentration of chemotherapeutic in the blood	C_{max}	36	PK value	[14]
Timepoint of maximum chemotherapeutic concentration (hrs)	T_{max}	0.5	PK value	[14]
Number of times a cell can dedifferentiate	z_{revert}	7	Sensitivity analysis	this work
Molecular weight of TMZ	MW	194.12	PK value	[42]
EC50 for TMZ (mol/m^3)	$EC50$	0.004268	PK vlaue	[42]