

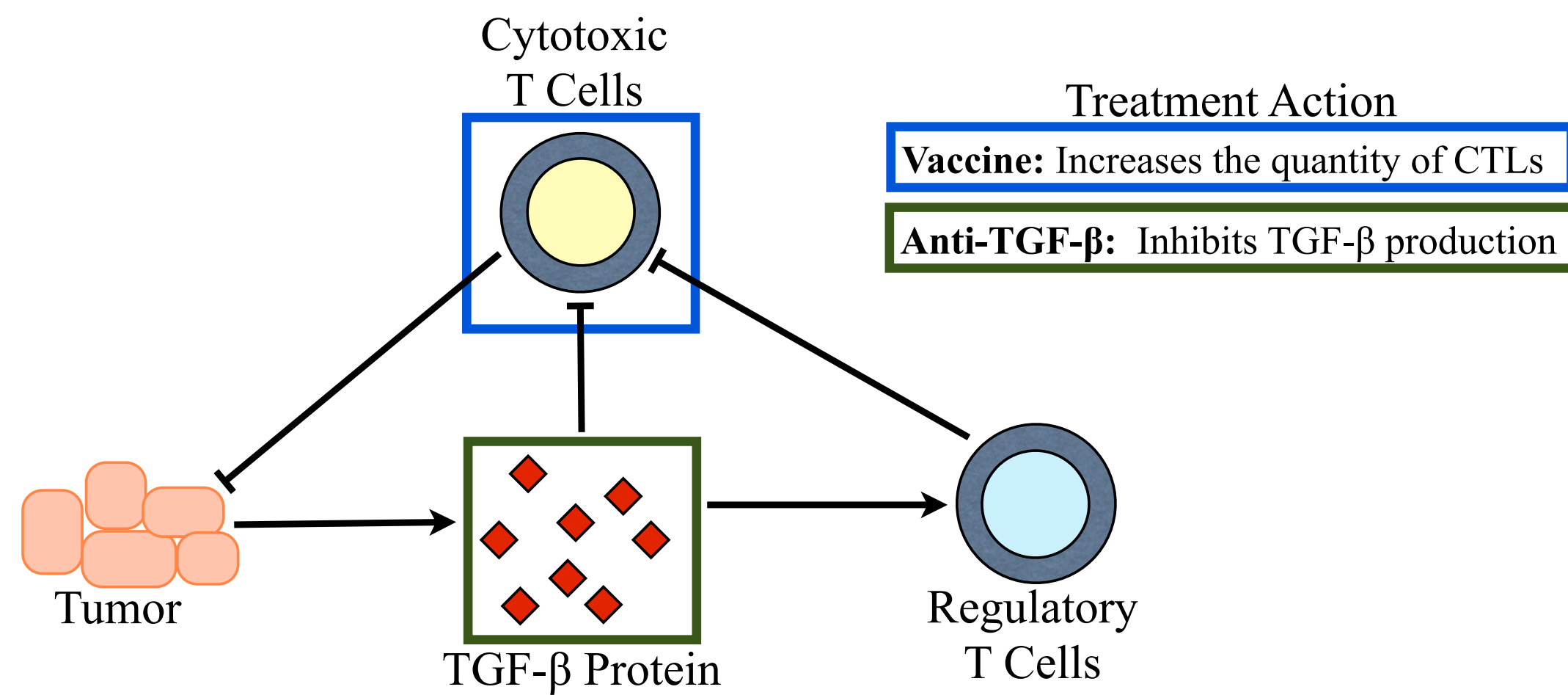
MODELING TUMOR GROWTH WITH VACCINE AND ANTI-TGF- β TREATMENT

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ABSTRACT

TGF- β is an immunoregulatory protein that contributes to inadequate anti-tumor immune responses in cancer patients. We develop a dynamical system to gain insight into recent data showing that anti-TGF- β treatment, given alone, provides no clinical benefits, yet can significantly amplify the anti-tumor immune response when combined with a vaccine. A hypothesis is put forth concerning the role that anti-TGF- β treatment plays in vaccine enhancement.

BIOLOGICAL SYSTEM



EXPERIMENTAL BACKGROUND

In [Terabe 2009], Terabe *et al.* examined whether TGF- β neutralization can potentiate immune responses caused by a CTL-inducing vaccine. Their goal was to determine the conditions under which this enhanced immune response inhibits and/or eliminates tumor growth in a mouse. Cancer cells were injected into the right flank of the mouse. Each mouse underwent one of four treatment options and tumor size was measured periodically over 30 days.

TREATMENT SCENARIOS

- no treatment
- vaccine treatment
- anti-TGF- β treatment
- combined vaccine and anti-TGF- β treatment

MAIN RESULTS

- Blocking TGF- β enhances the effects of an anti-tumor peptide vaccine.
- Anti-TGF- β enhances vaccine-induced CD8+ CTL responses.
- The enhancement of the immune response was shown to be not due to suppression of regulatory T cells (Tregs).
- Dual treatment with both anti-TGF- β and vaccine had a positive impact on the quantity and the quality of the CD8+ T cell response. In the case where both treatments were given, the tumor burden was significantly lower than any other treatment option tested; and 40% of mice remained tumor free for at least 55 days after tumor challenge.

EQUATIONS & PARAMETERS

$$\frac{dT}{dt} = a_0 T(1 - c_0 T) - \delta_0 \frac{ET}{1 + c_1 B} - \delta_0 TV$$

$$\frac{dB}{dt} = a_1 \frac{T^2}{c_2 + T^2} - dB$$

$$\frac{dE}{dt} = \frac{fET}{1 + c_3 B} - rE - \delta_1(R + 1)E$$

$$\frac{dR}{dt} = rE - \delta_1 R$$

$$\frac{dV}{dt} = g(t) - \delta_1 V$$

$T(t)$: Tumor size.

$B(t)$: TGF- β concentration.

$E(t)$: Cytotoxic effector T cells.

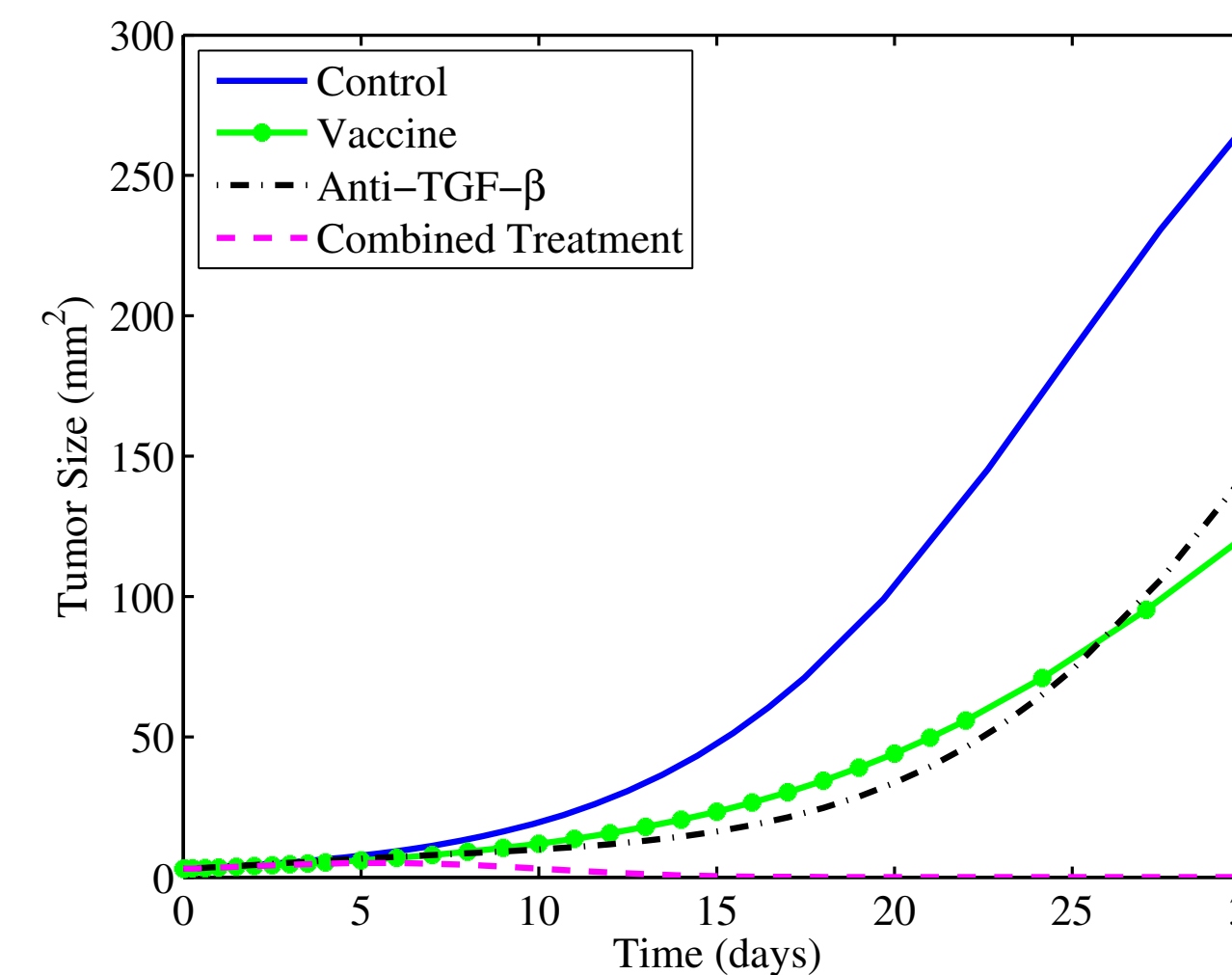
$R(t)$: Regulatory T cells.

$V(t)$: Vaccine injected cytotoxic T cells.

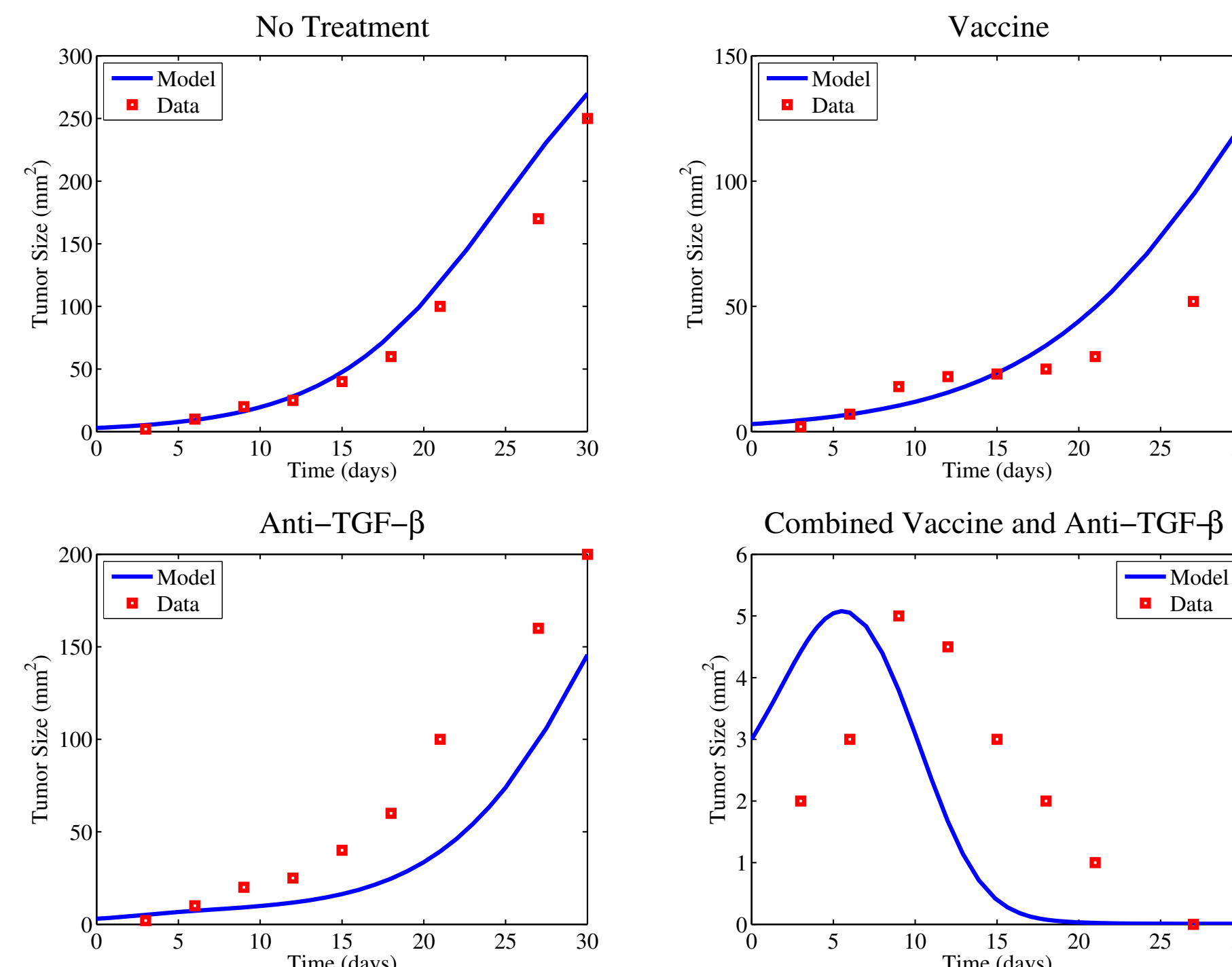
Parameter	Description	Estimate	Source
a_0	tumor growth rate	0.1946	[Terabe 2009]
$1/c_0$	tumor carrying capacity	369	[Terabe 2009]
δ_0	effector T-cell induced tumor death rate	1×10^{-5}	estimated
c_1	TGF- β inhibitory parameter for CTL induction of tumor death	$75 - 125$	estimated
a_1	maximal production rate of TGF- β	0.3	[Kirschner 2003]
c_2	steepness coefficient of TGF- β production	300 or 7,000	[Kirschner 2003]
d	degradation rate of TGF- β	$5 - 8 \times 10^{-4}$	[Kirschner 2003]
f	tumor antigenicity	0.62	estimated
c_3	TGF- β inhibitory parameter for tumor activation of CTLs	225 - 375	estimated
r	proportion of effector T cells that become regulatory T cells	0.01	[Kim 2010]
δ_1	natural death/removal rate of CTLs, Vaccine cells, and Tregs	1×10^{-5}	estimated

SIMULATIONS

TUMOR SIZE FOR EACH TREATMENT REGIME

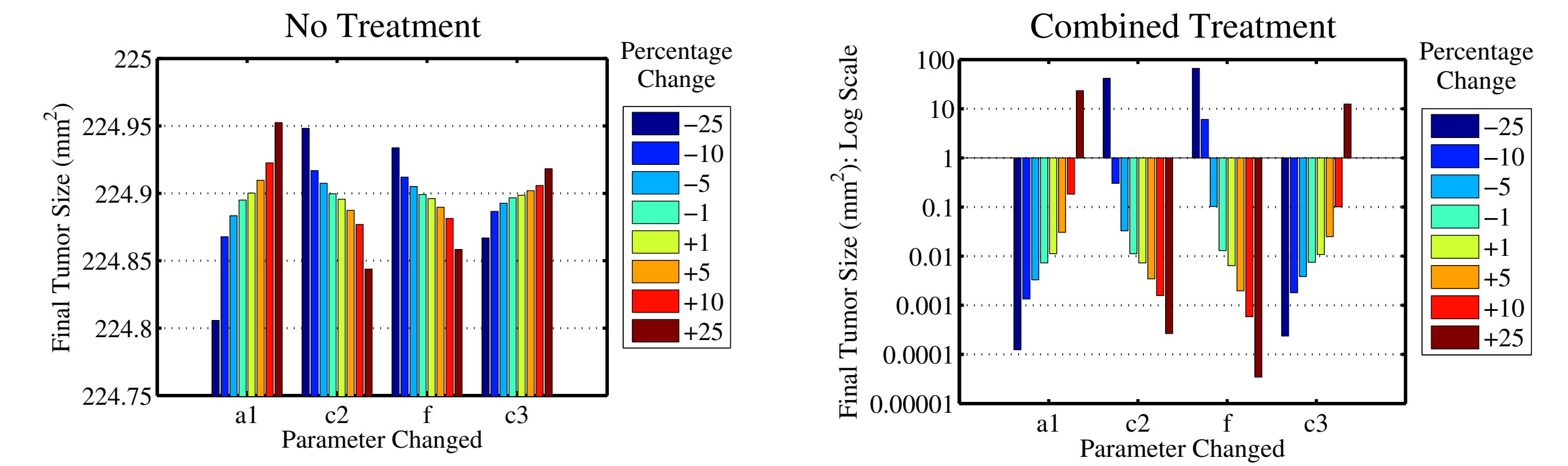


MODEL SIMULATION VS. EXPERIMENTAL DATA



MODEL SENSITIVITY

PARAMETER SENSITIVITY RESULTS FOR MOST SENSITIVE PARAMETERS



CONCLUSIONS & FUTURE DIRECTIONS

SIMULATIONS

- The qualitative characteristics of each of the four treatment cases has been captured by the present model.
- In the case of administering solely the vaccine or the TGF- β inhibitor, there is only a temporary delay in tumor growth.
- The vaccine provides a long-term immune response that is unaffected by the TGF- β that is present at later time points while the TGF- β inhibitor provides conditions that help the populations of immune cells to expand during the initial phases of tumor presentation.

PARAMETER SENSITIVITY

- Lack of treatment will lead to uncontrolled tumor growth.
- With combined treatment, the system is sensitive to a_1 , c_2 , f and c_3 .
- The system is most sensitive to the parameter f which aligns with the results concerning the corresponding parameters in [DePillis2005] and [Kirschner 2003].

FUTURE DIRECTIONS

- Modify the model to better capture the timing of tumor progression.
- Employ techniques of optimal control of nonlinear processes to determine treatment protocols for combined anti-TGF- β and vaccine treatments of tumors.

ACKNOWLEDGEMENTS

This work was supported in part by the joint NSF/NIGMS program under Grant Number DMS-0758374 and in part by Grant Number R01CA130817 from the National Cancer Institute.

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