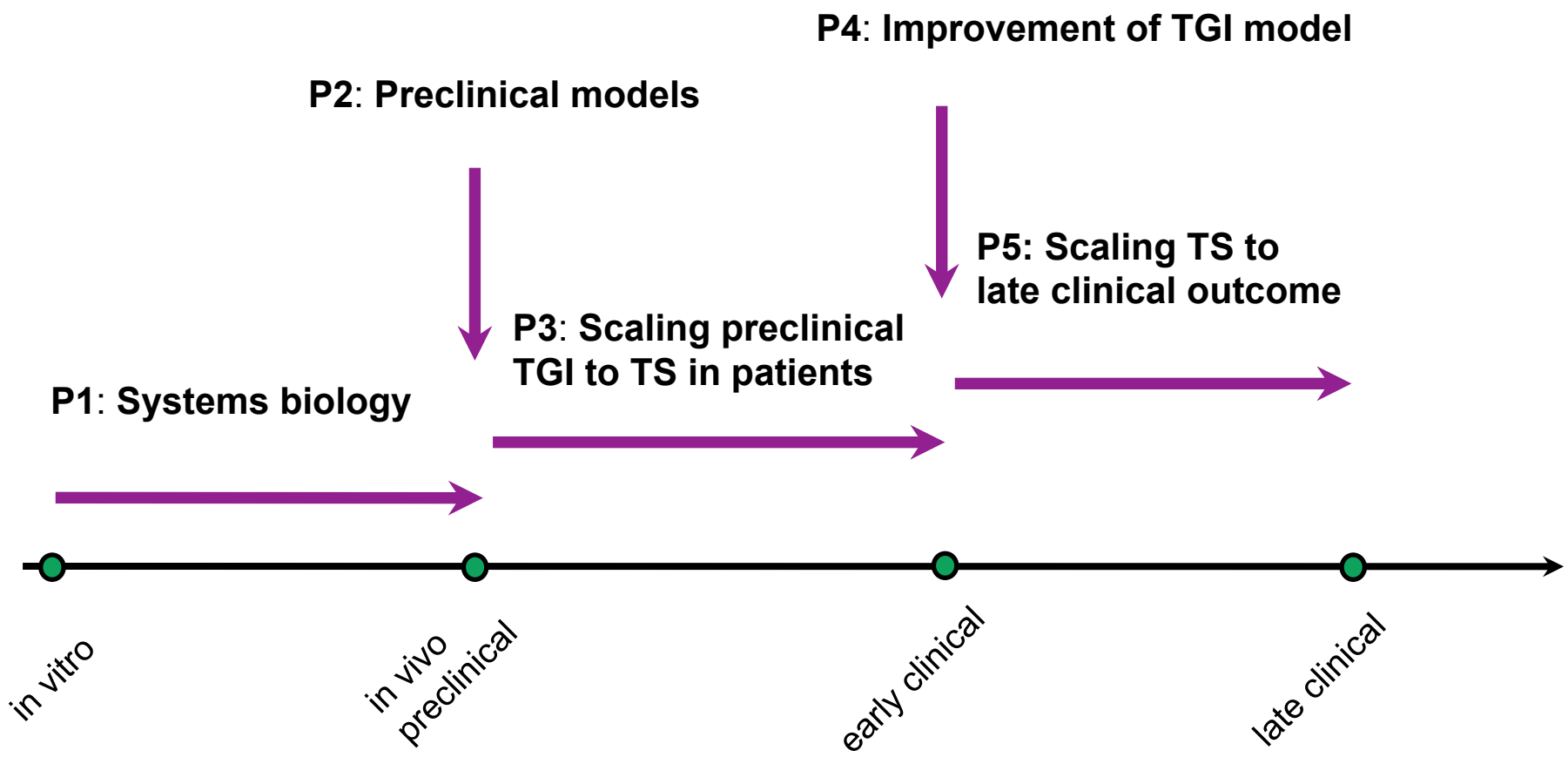
Modeling the synergism between the anti-angiogenic drug sunitinib and irinotecan in xenografted mice

S. Wilson, E. Grenier, M. Wei, V. Calvez, B. You, M. Tod, B. Ribba

INRIA Grenoble Rhône-Alpes

New Model Development In Oncology



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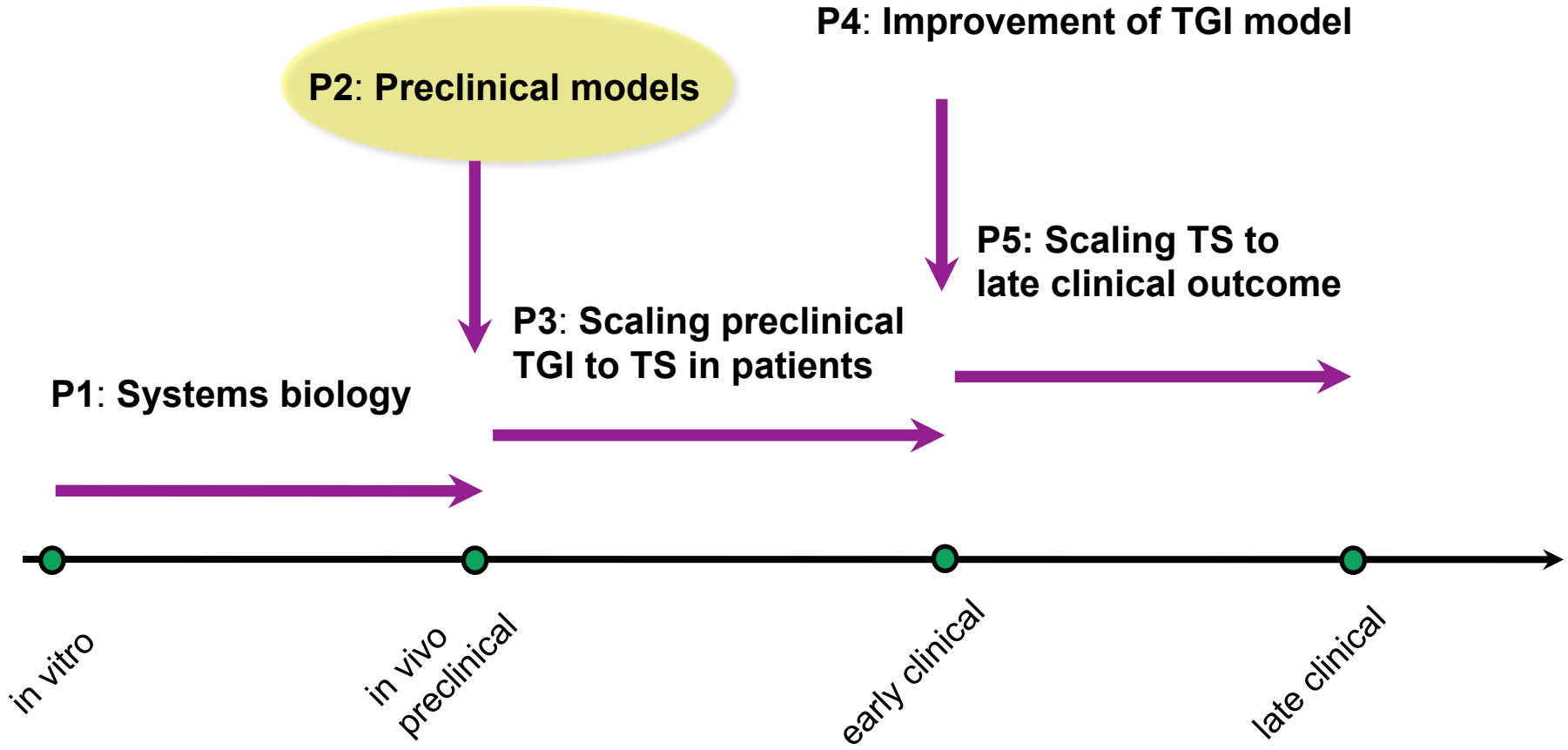

Angiogenesis Inhibitors

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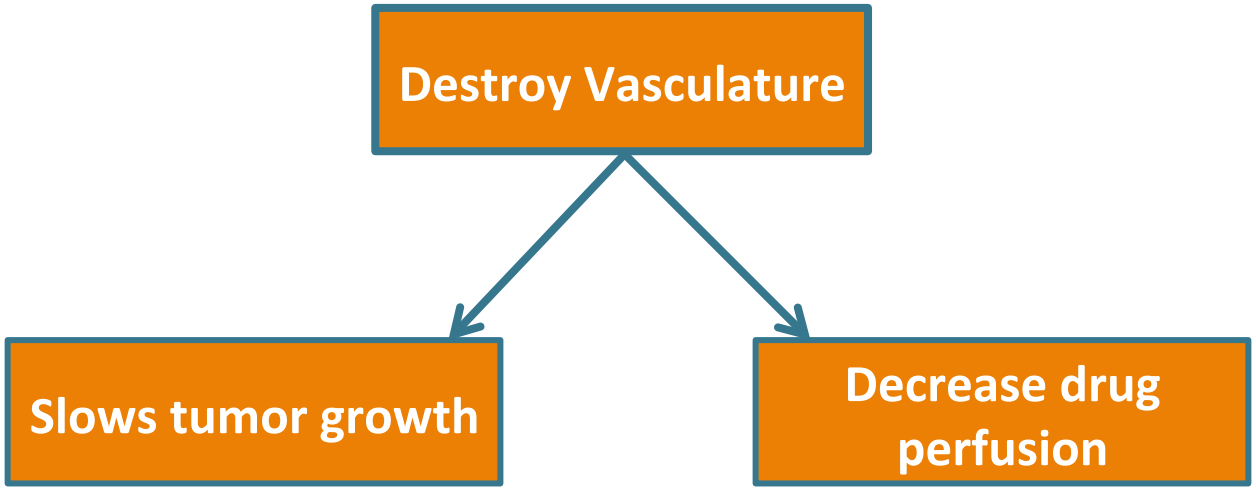

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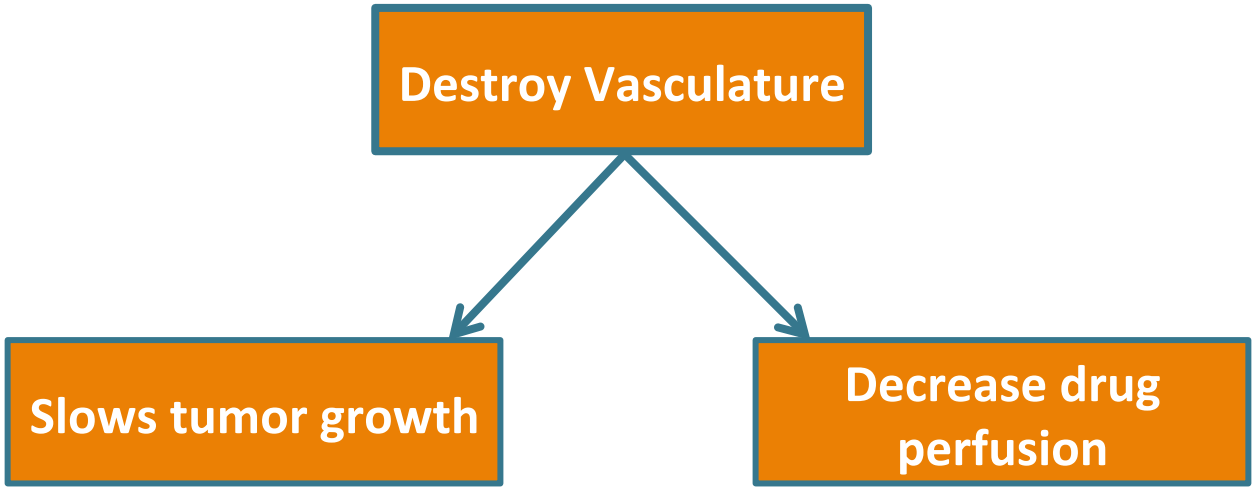

- Sunitinib
  - Oral small-molecule angiogenesis inhibitor
  - Multi-targeted RTKi (targets PDGF, VEGF, EGF receptors)

Objective

Evaluate a potential synergistic effect between sunitinib, an anti-angiogenic agent, when given in combination with irinotecan, a cytotoxic agent

Sunitinib Monotherapy Experimental Data

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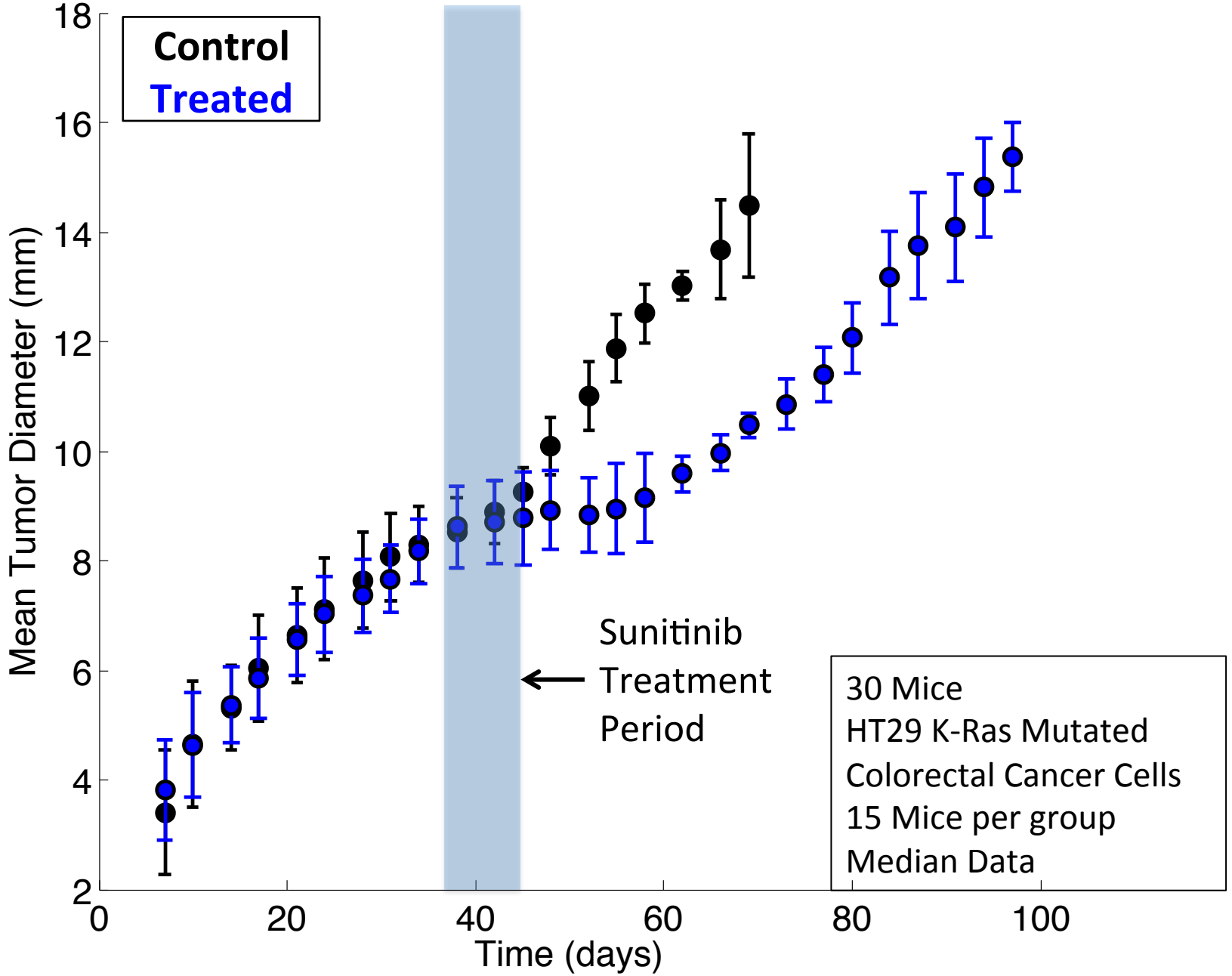
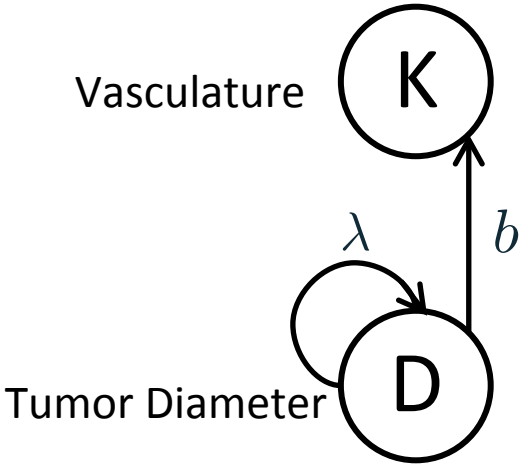


Model of Tumor Growth with Sunitinib Monotherapy



$$\frac{dD}{dt} = \lambda D\left(1 - \left(\frac{D}{K}\right)^{\alpha}\right)$$

$$\frac{dK}{dt} = bD^2$$

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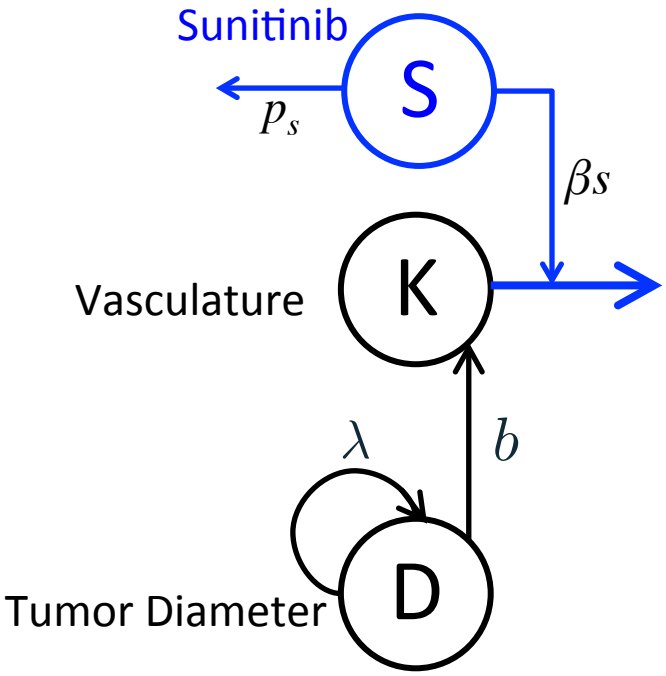
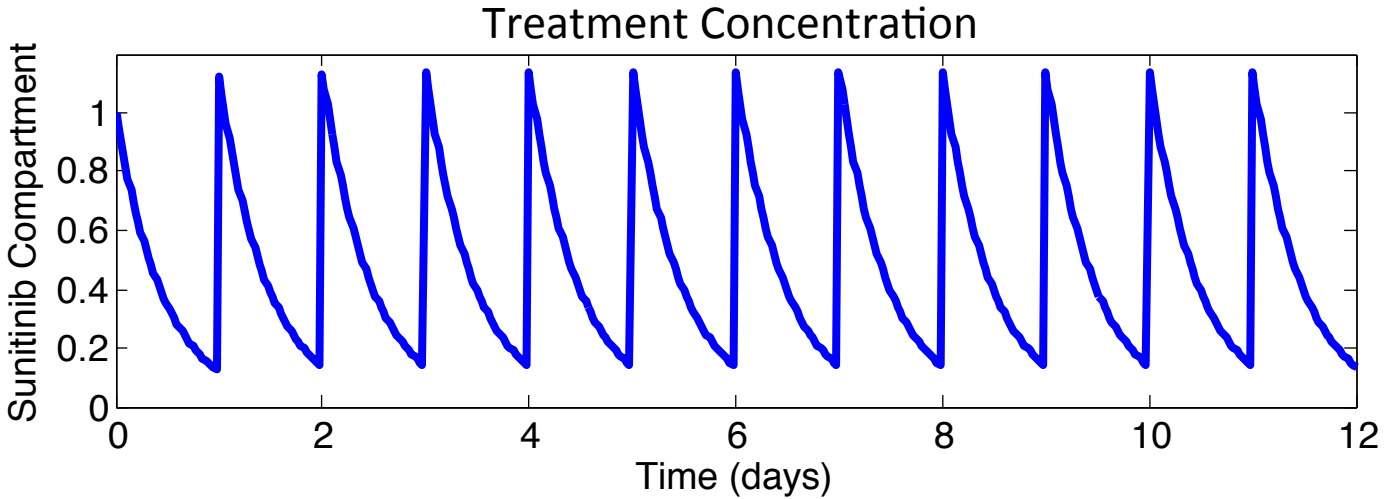


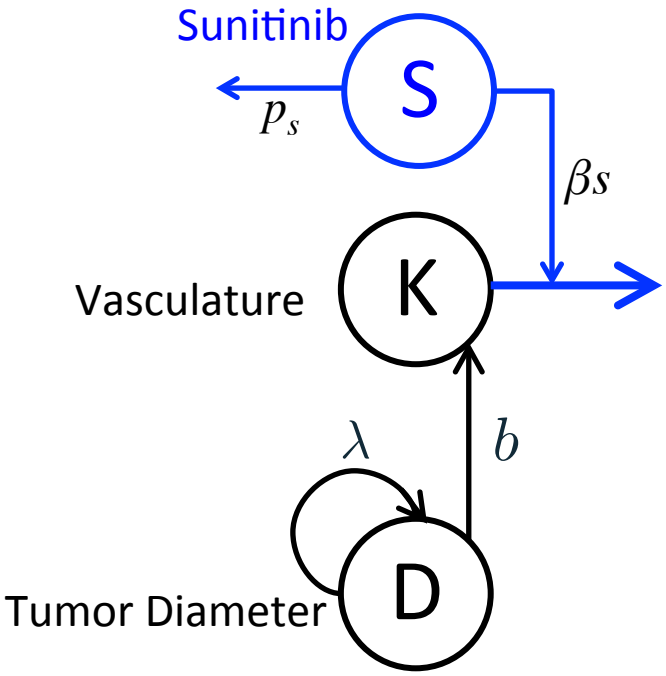
$$\frac{dS}{dt} = -p_s S$$

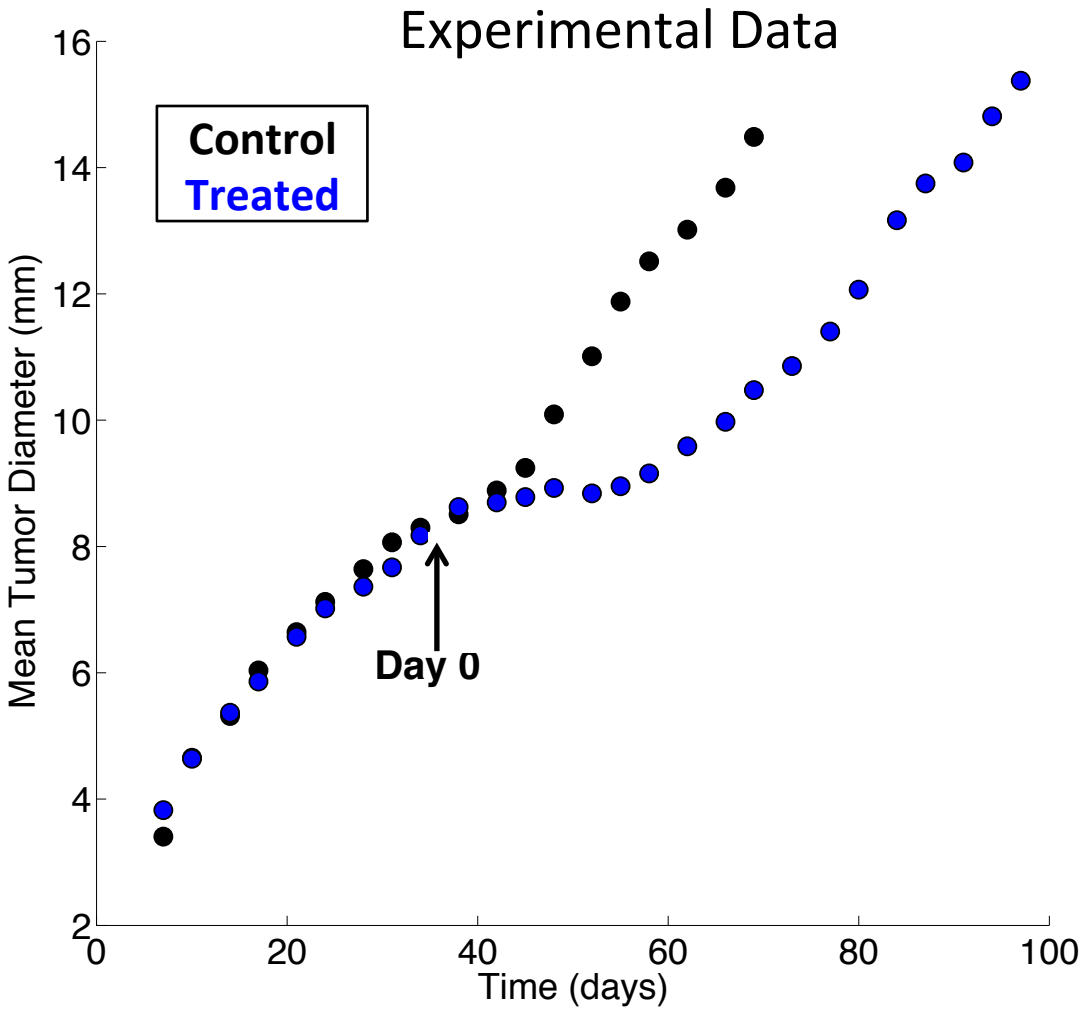
$$\frac{dD}{dt} = \lambda D\left(1 - \left(\frac{D}{K}\right)^{\alpha}\right)$$

$$\frac{dK}{dt} = bD^2 - \beta_S p_s S K$$



Parameter Fitting





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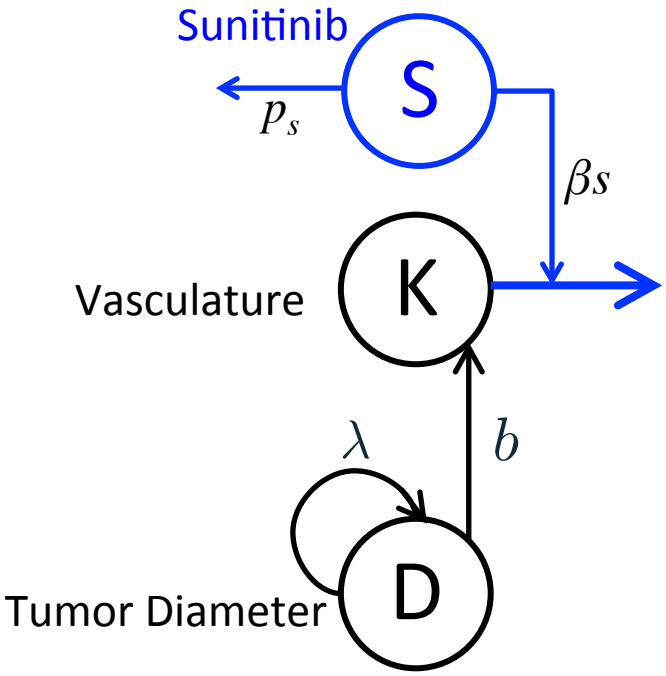

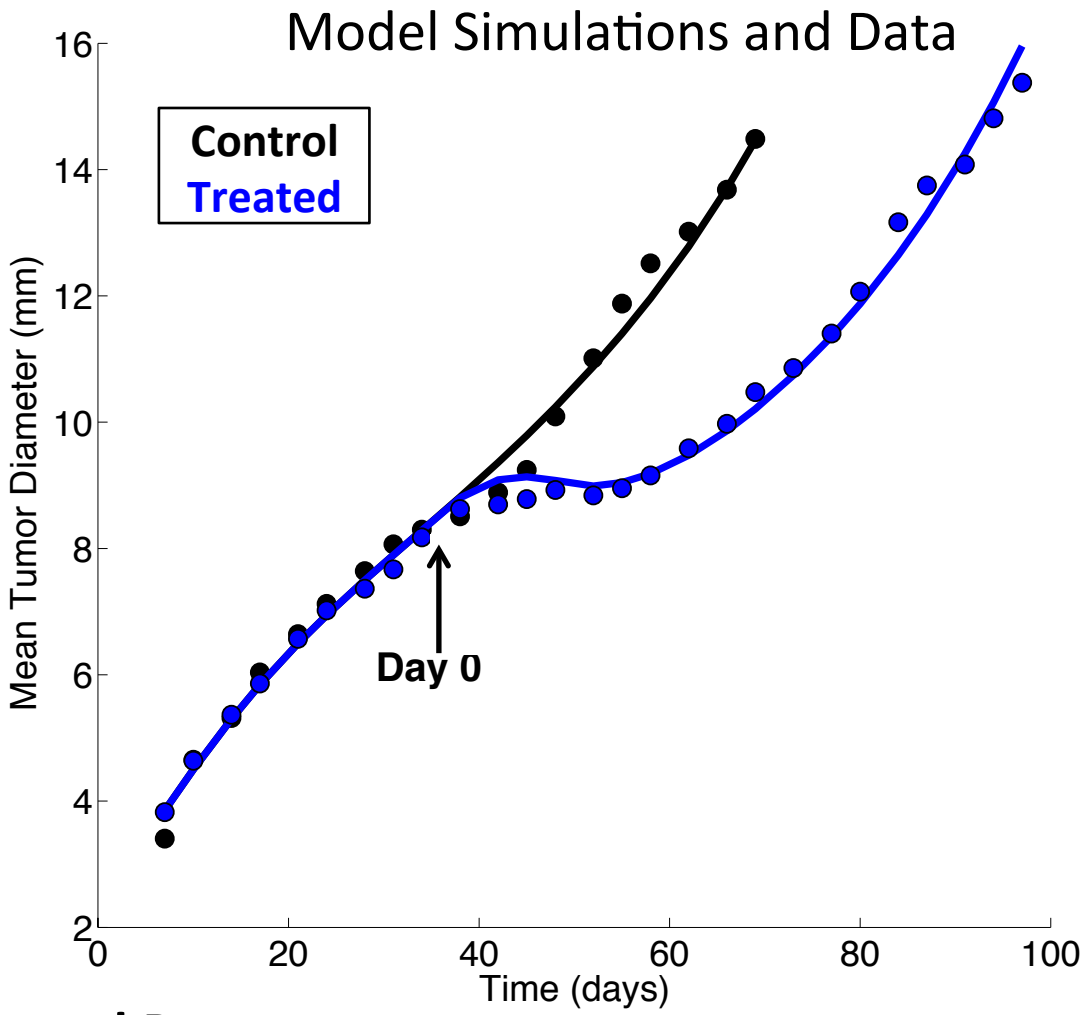

Estimated Parameters

Param	Value (error %)	Param	Value (error %)
D(t=0)	2.27 (26)	b	0.0019 (1)
K(t=0)	7.85 (22)	p_s	2.12 (fixed)
λ	0.82 (9)	β_s	0.032 (0.2)

Mixed Effect Parameter Estimation

Param	Mean (error %)	Var (error %)
D(t=0)	1.76 (7)	0.274 (10)
K(t=0)	7.43 (1)	0 (fixed)
λ	1.02 (4)	0.111 (20)
b	0.00168 (4)	0.142 (18)
p	2.12 (fixed)	0.5 (fixed)
β	0.0237(9)	0.08 (36)

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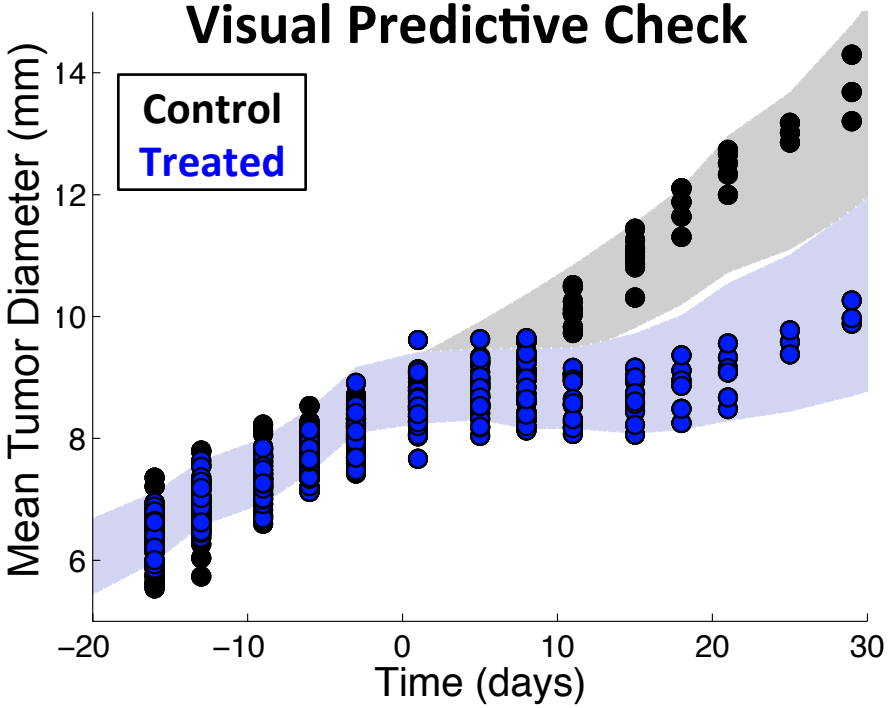
Visual Predictive Check



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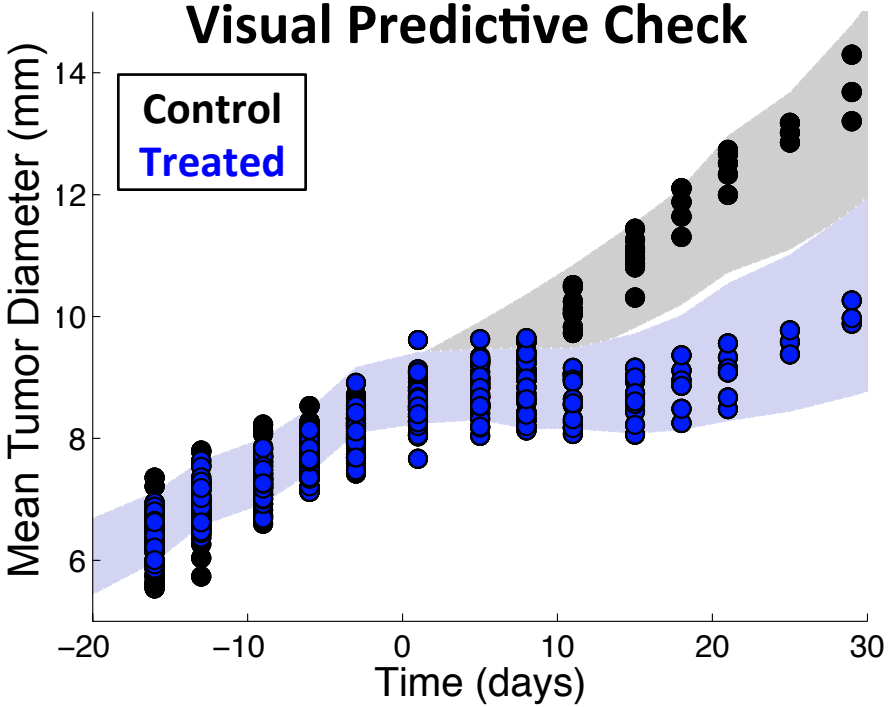
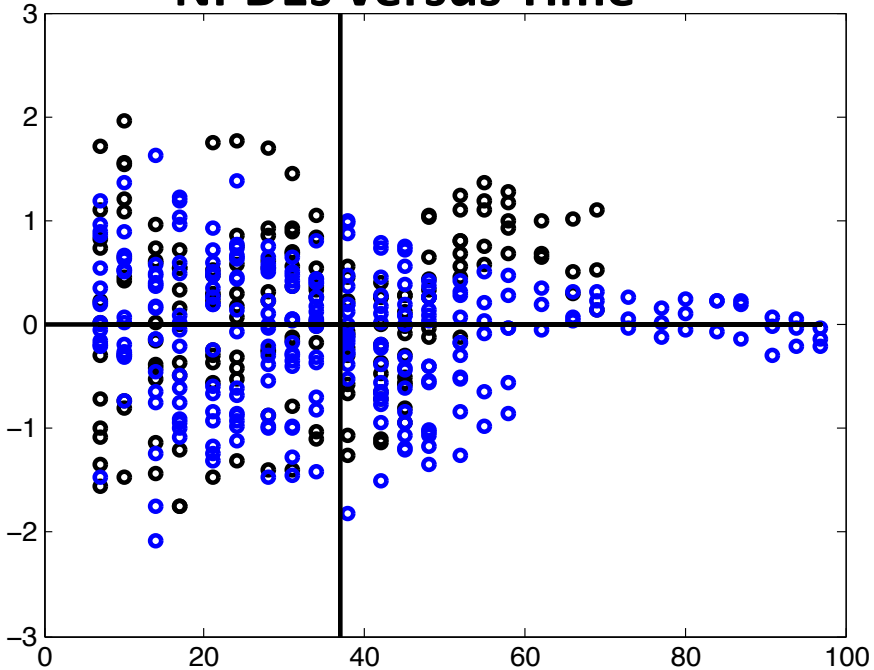
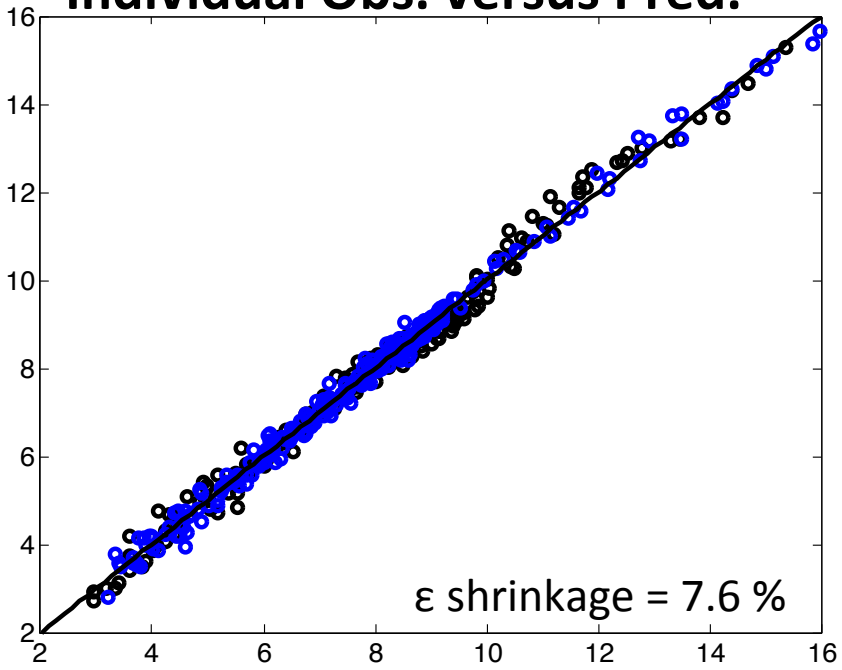


NPDEs versus Time



Individual Obs. versus Pred.

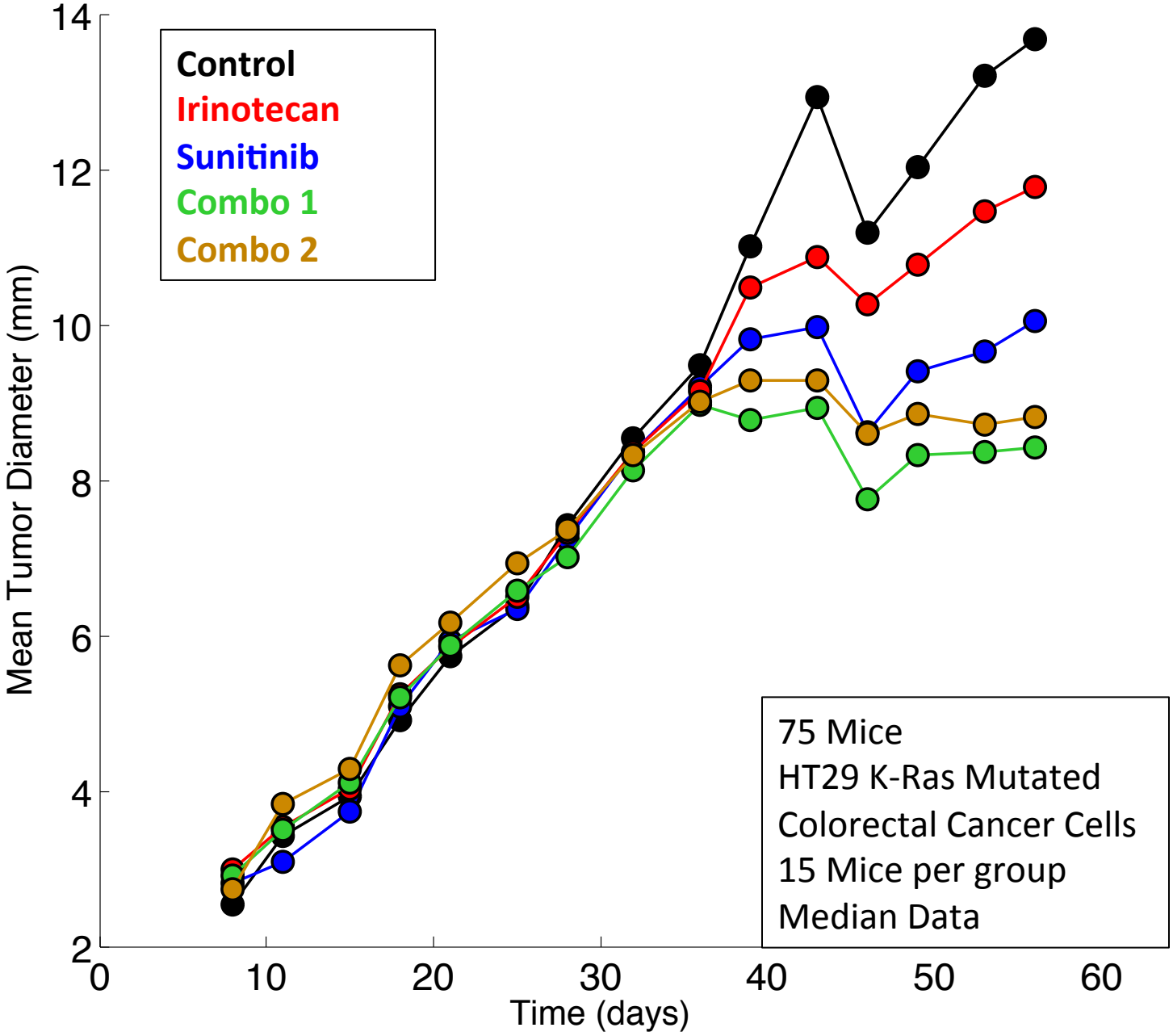


What next?

What next?

We continue by considering the combination of sunitinib with the chemotherapeutic agent irinotecan (CPT-11)

Combined Therapy Experimental Data



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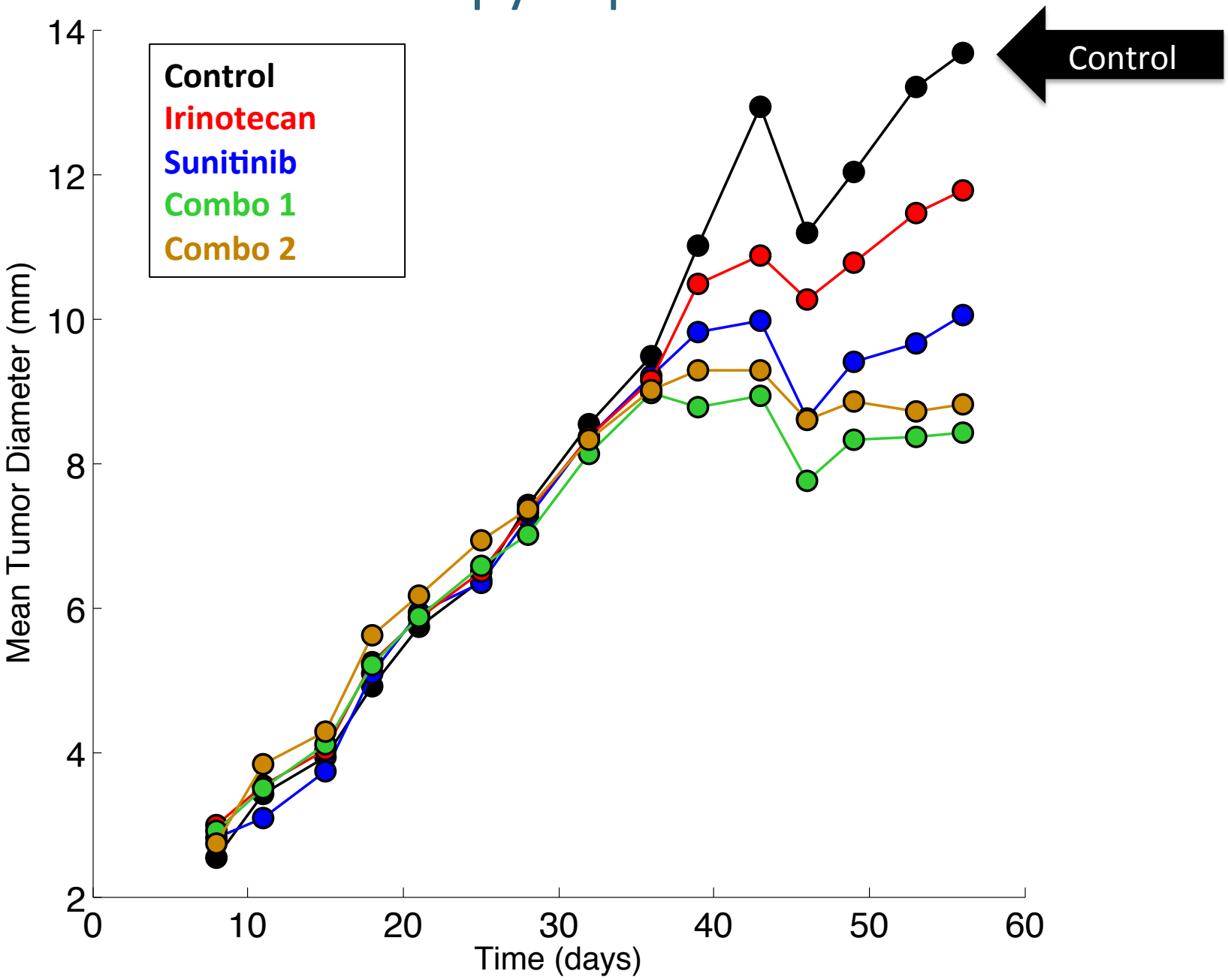

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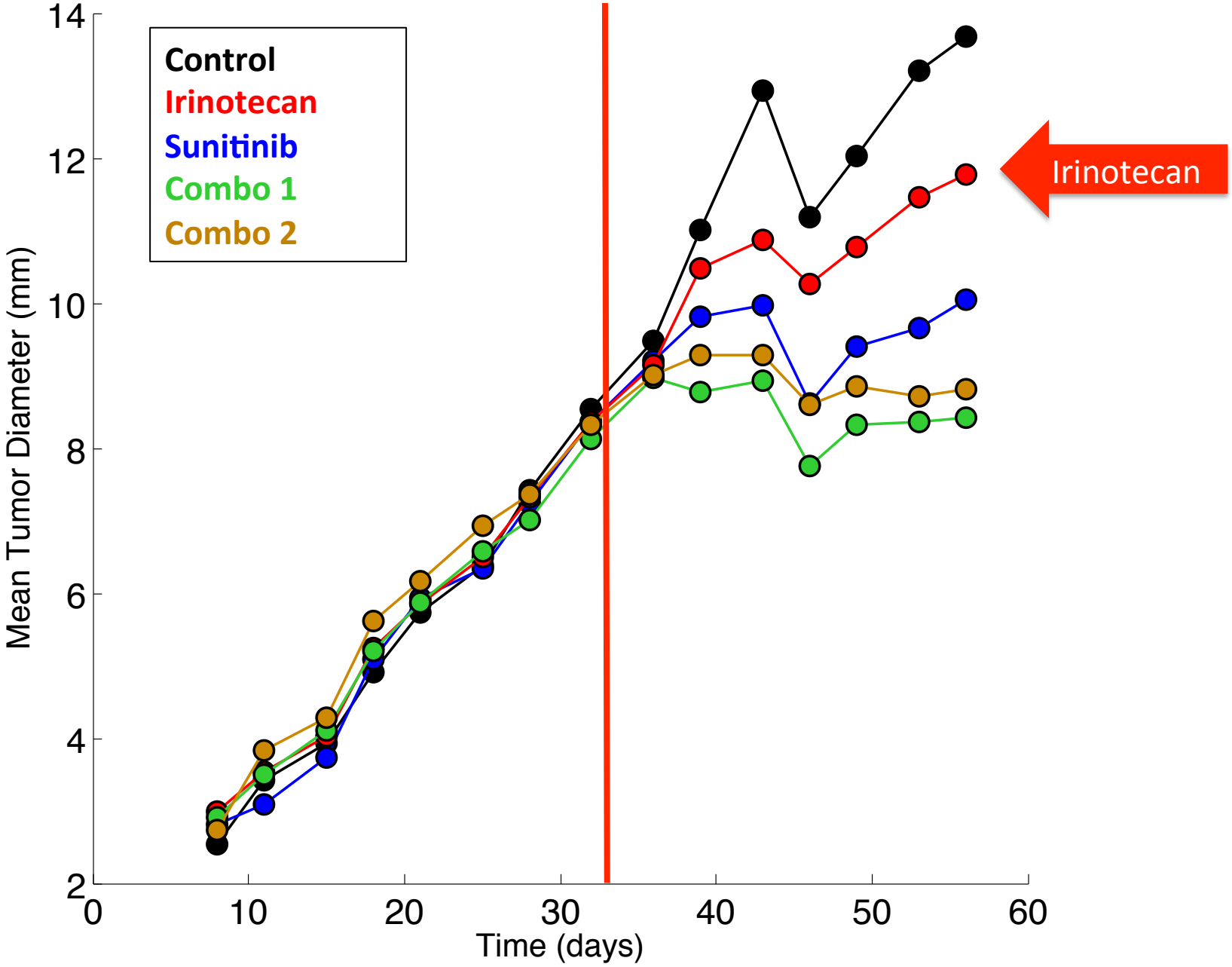

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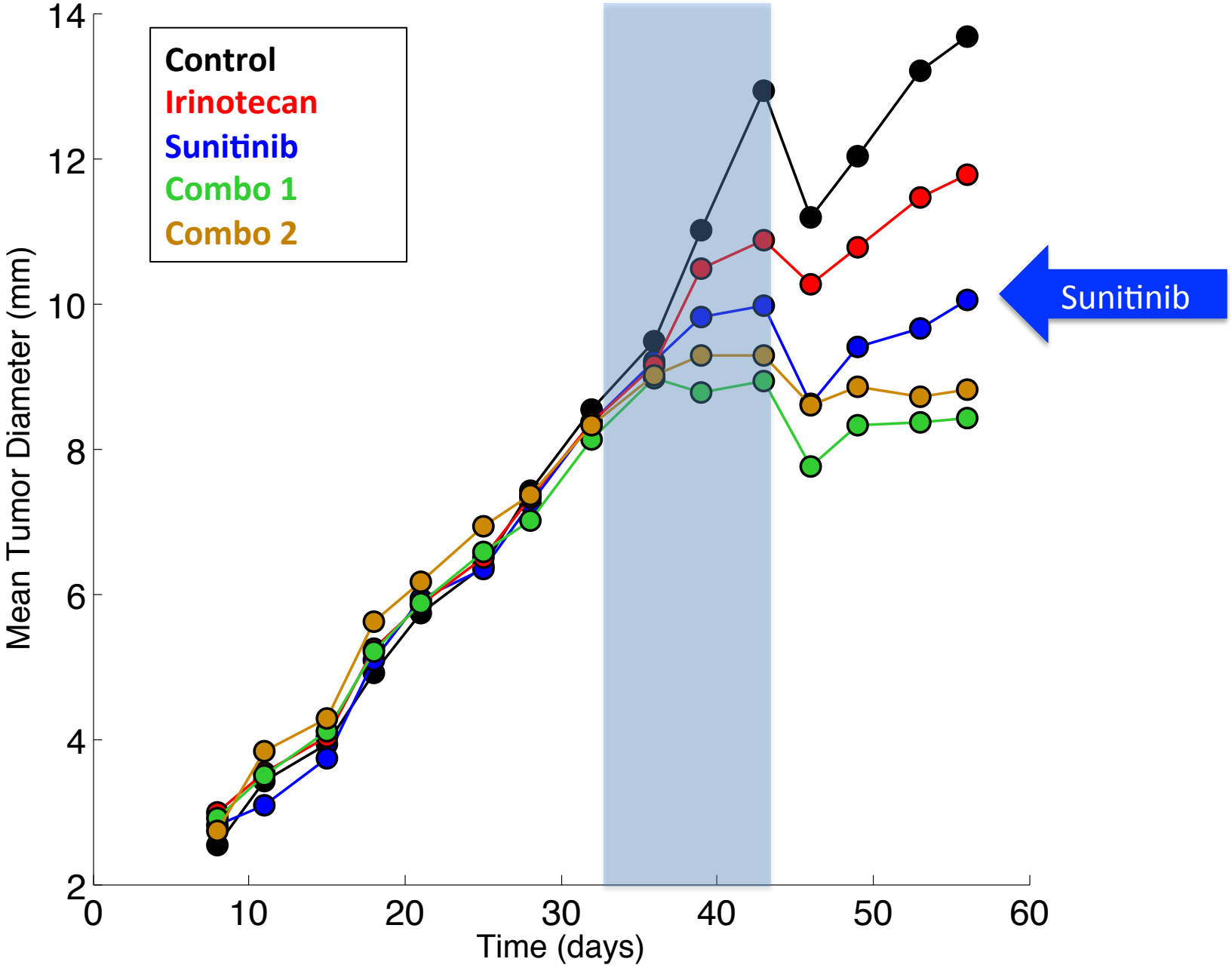

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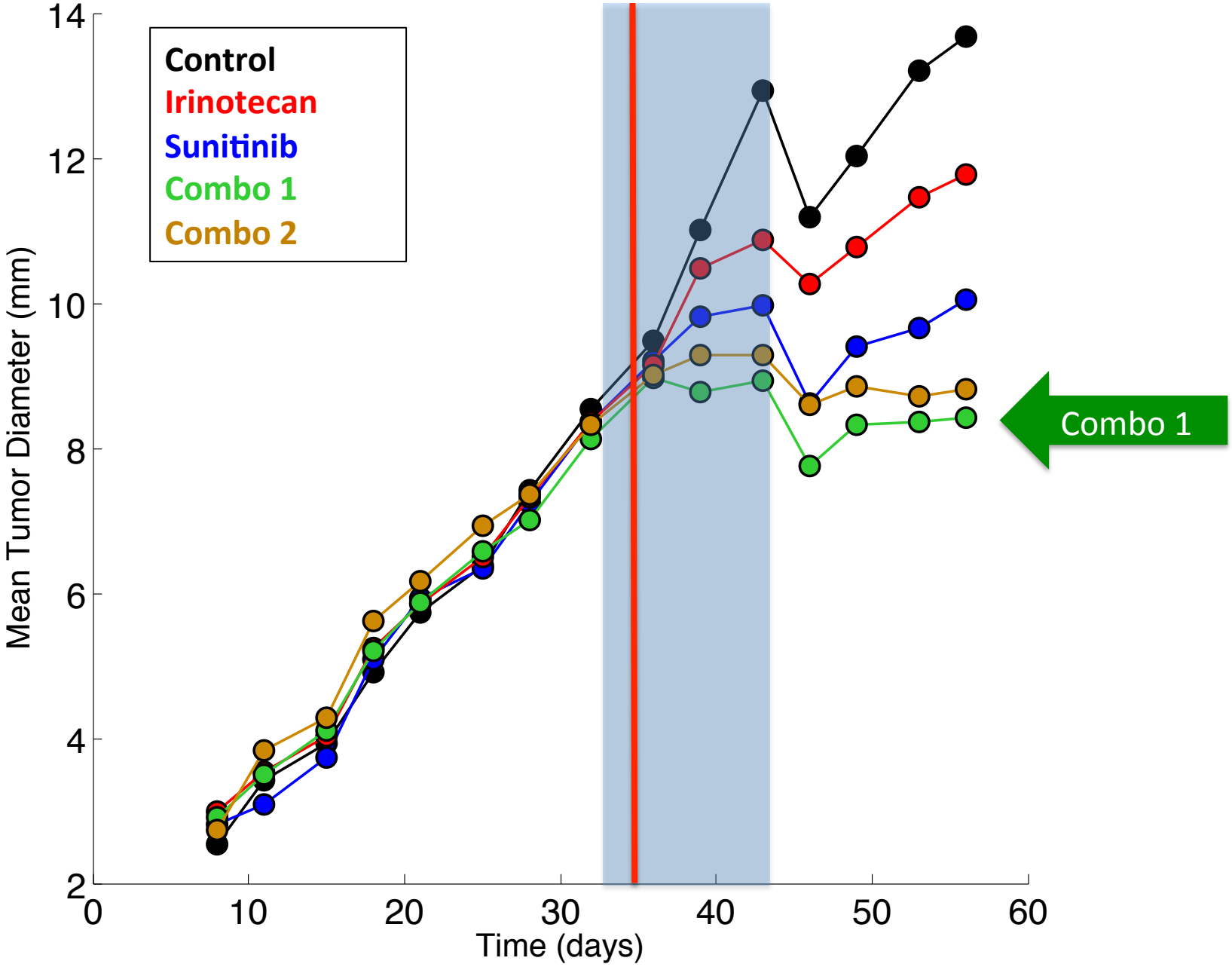

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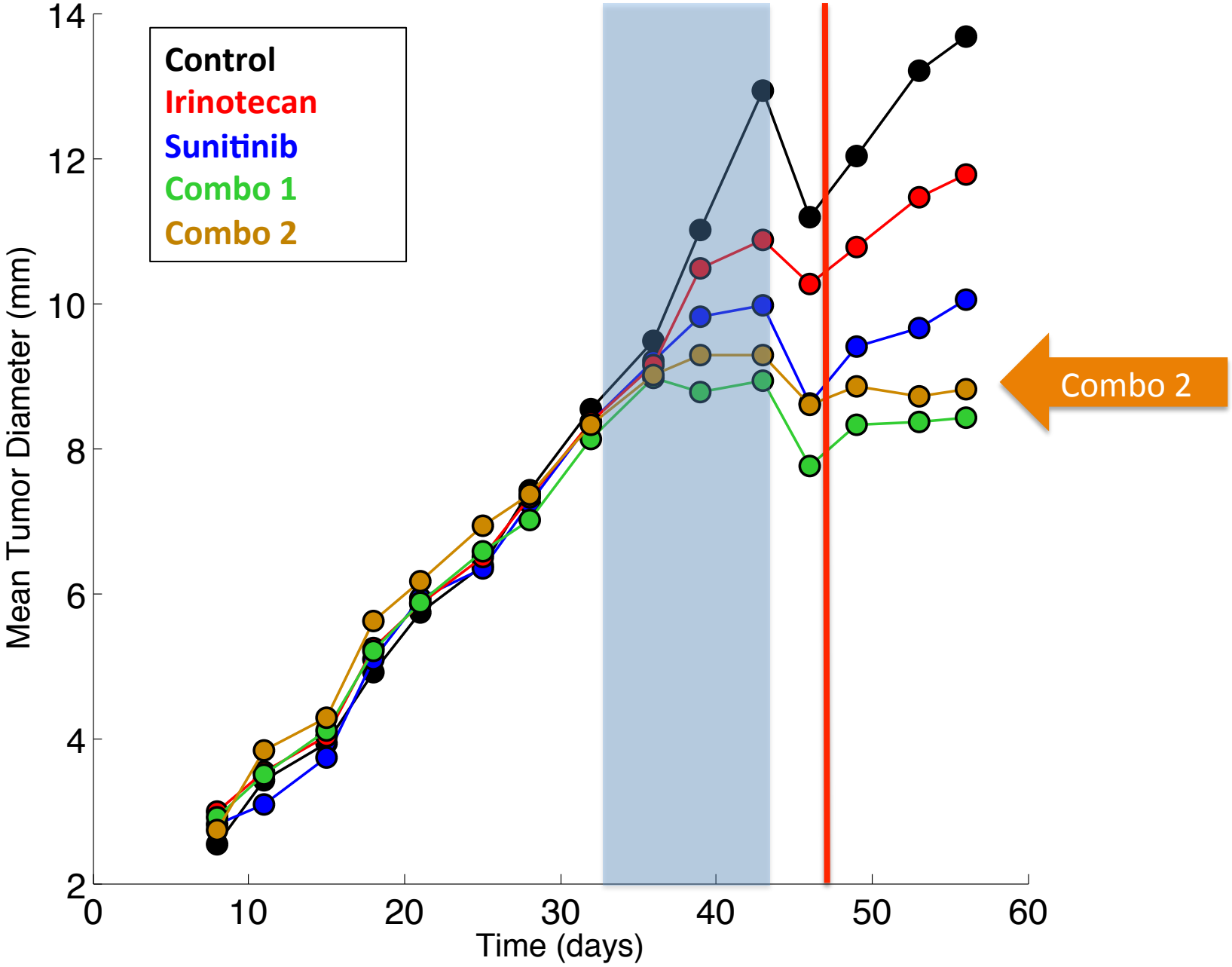
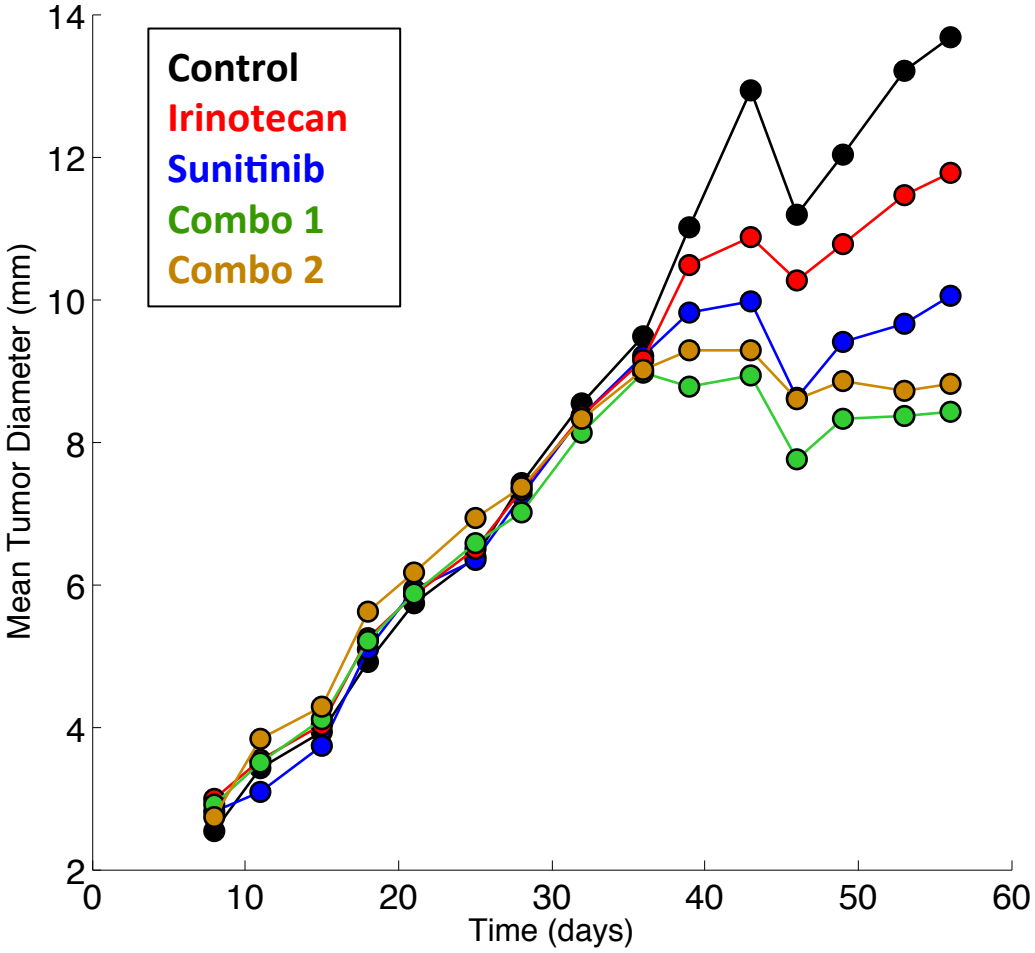


Motivations



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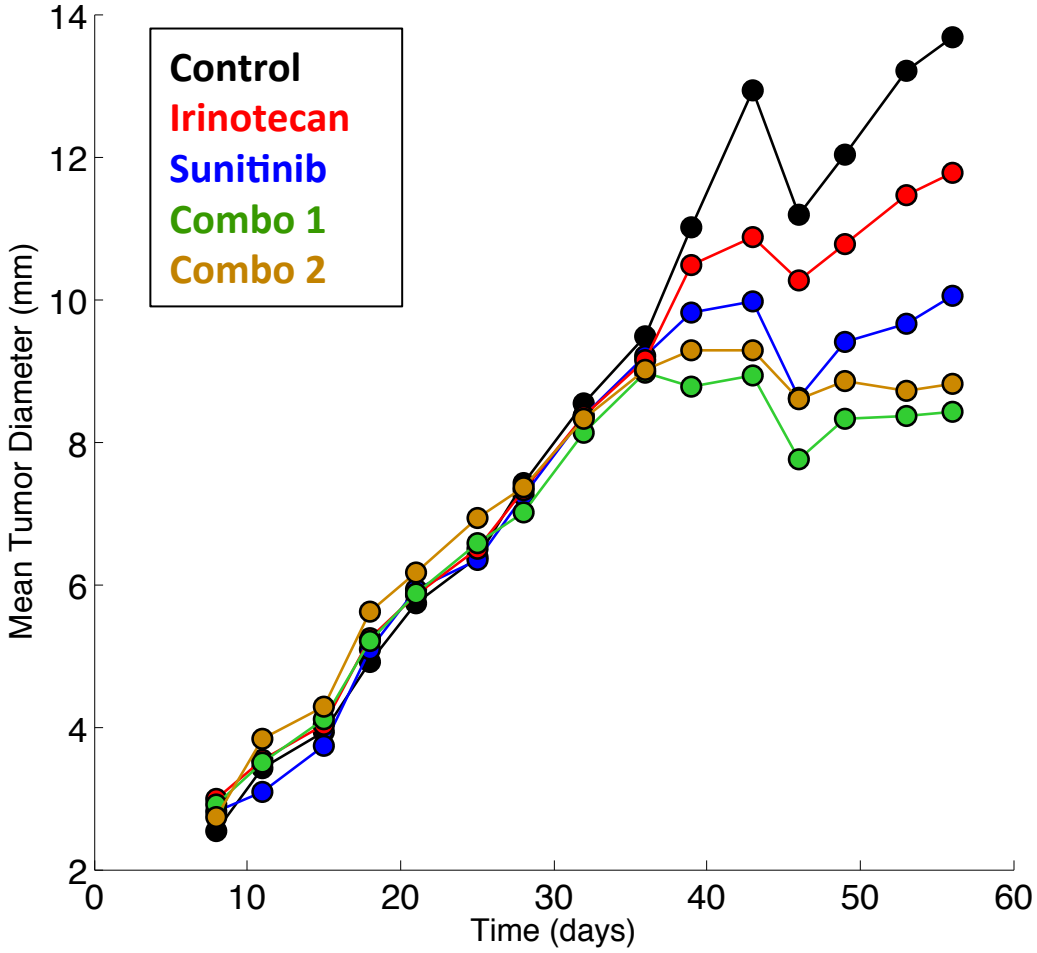
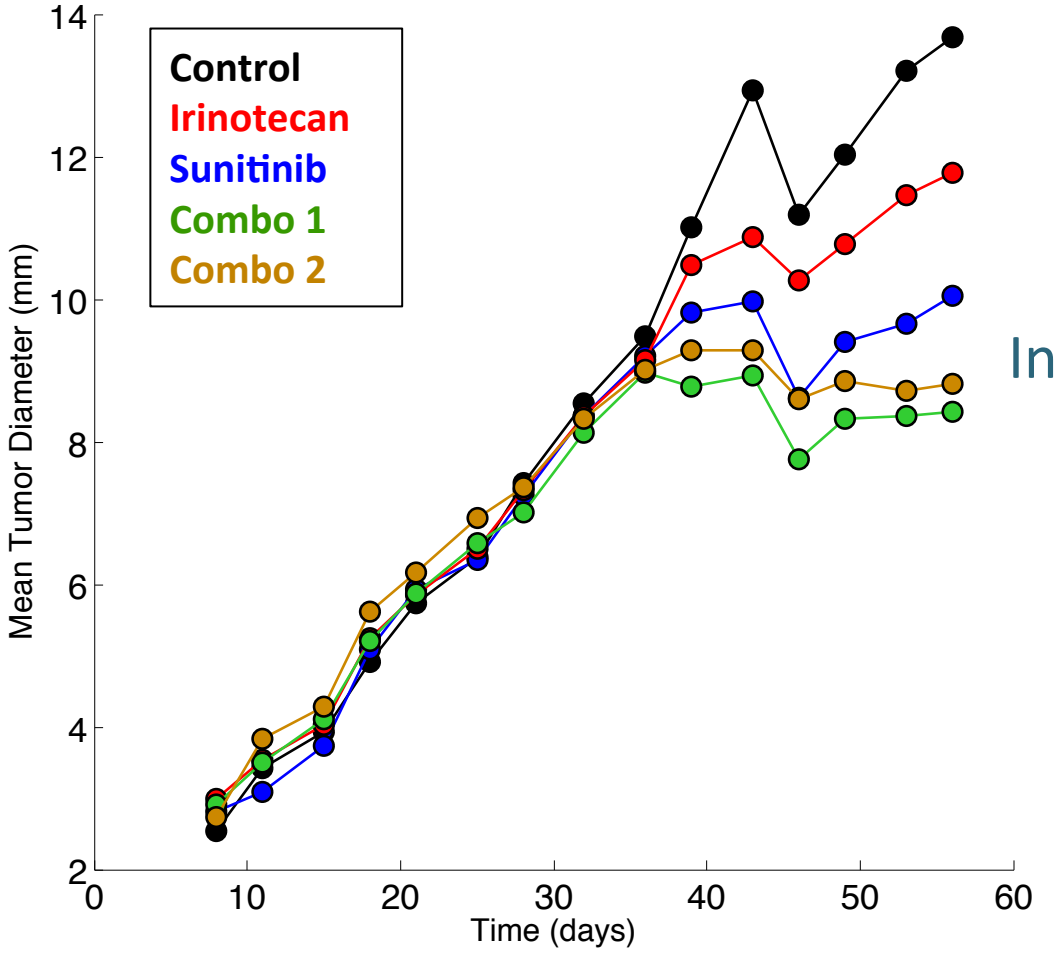


Accurately model our data

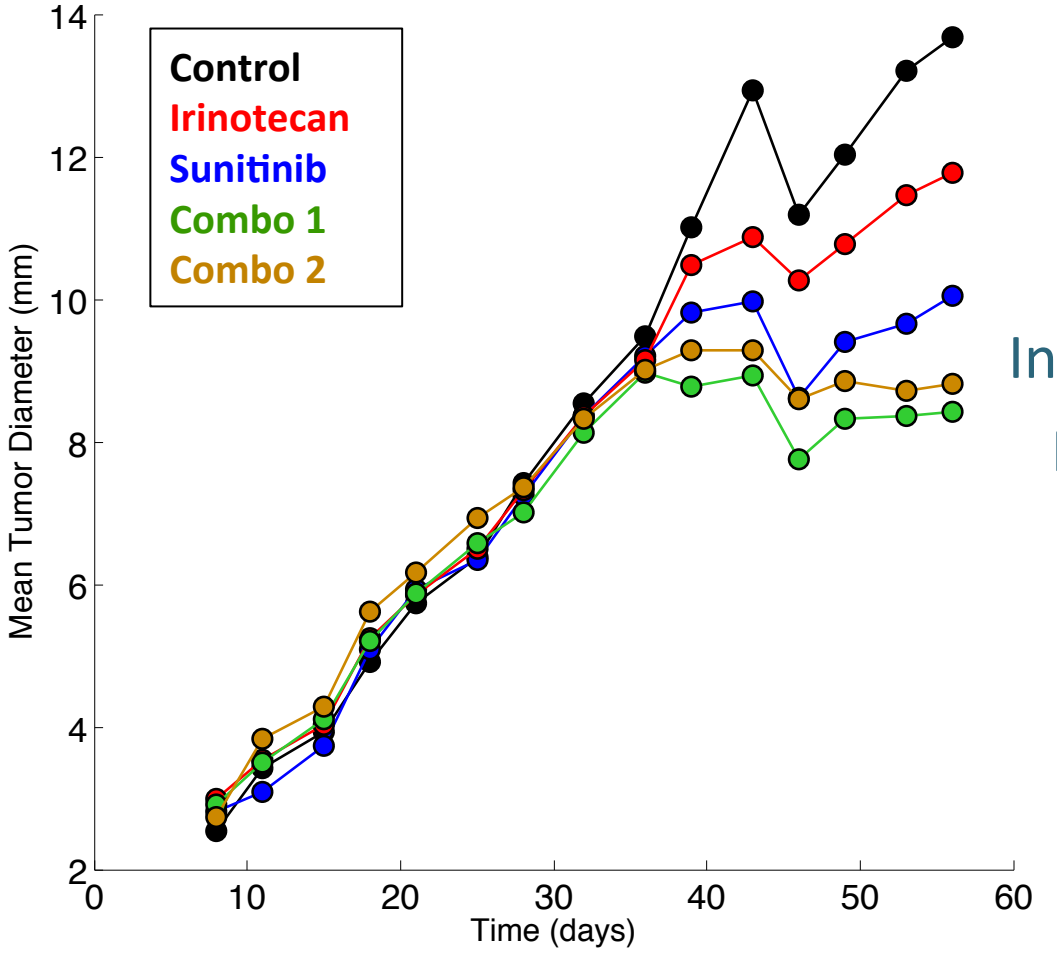
Motivations



Accurately model our data

Interaction versus NonInteraction

Motivations

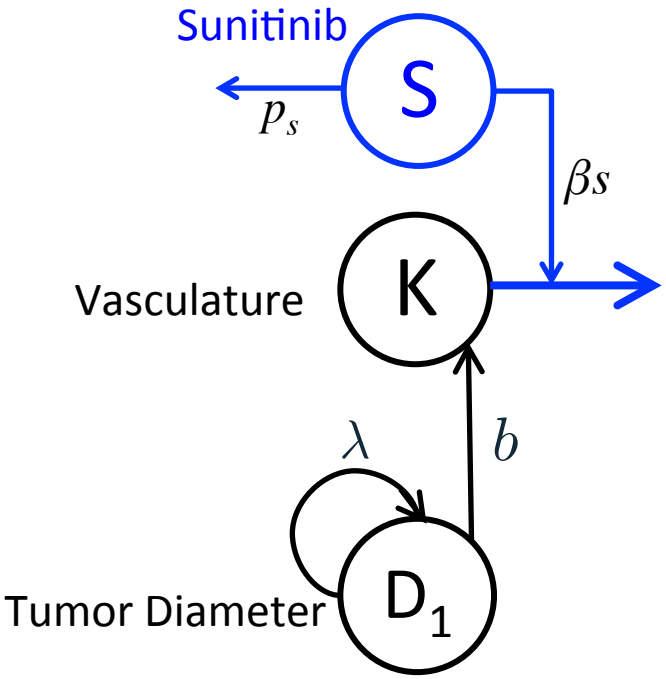


Accurately model our data

Interaction versus NonInteraction

Predict for future experiments

Adding Chemotherapy



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$$\frac{dD_1}{dt} = \lambda D_1 \left(1 - \left(\frac{D}{K}\right)^{\alpha}\right)$$

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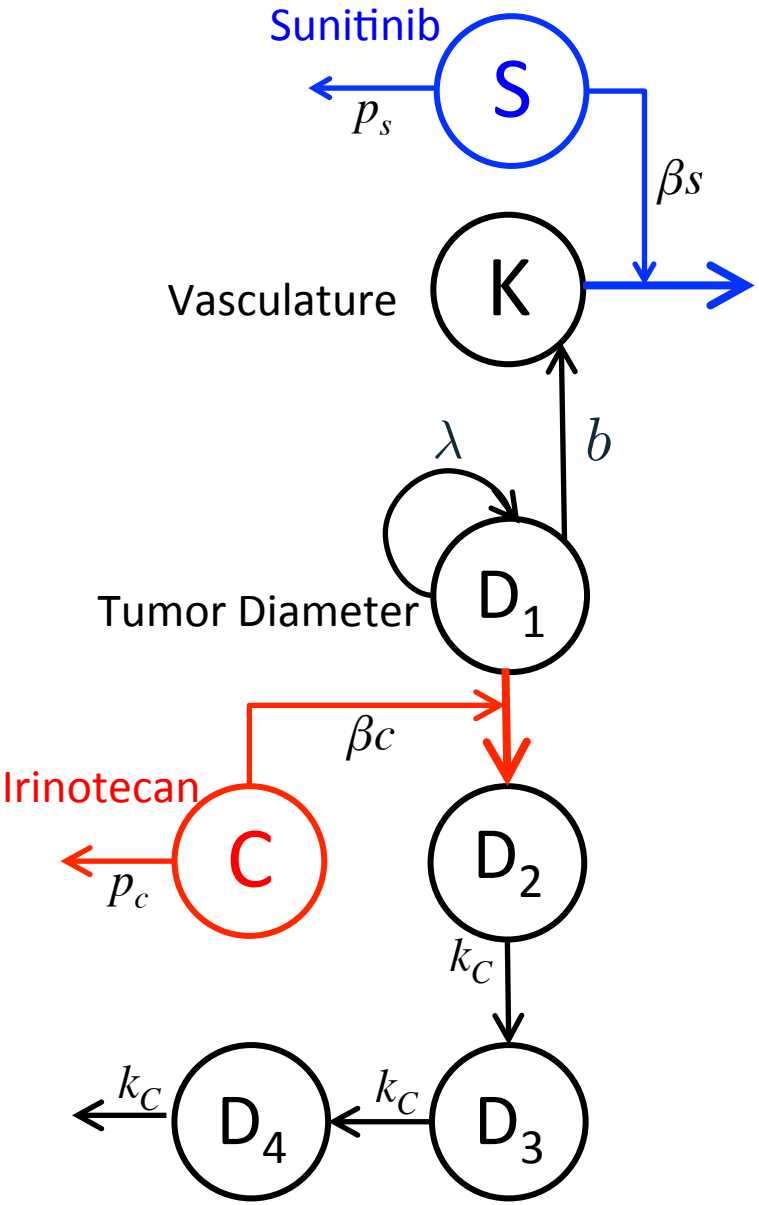

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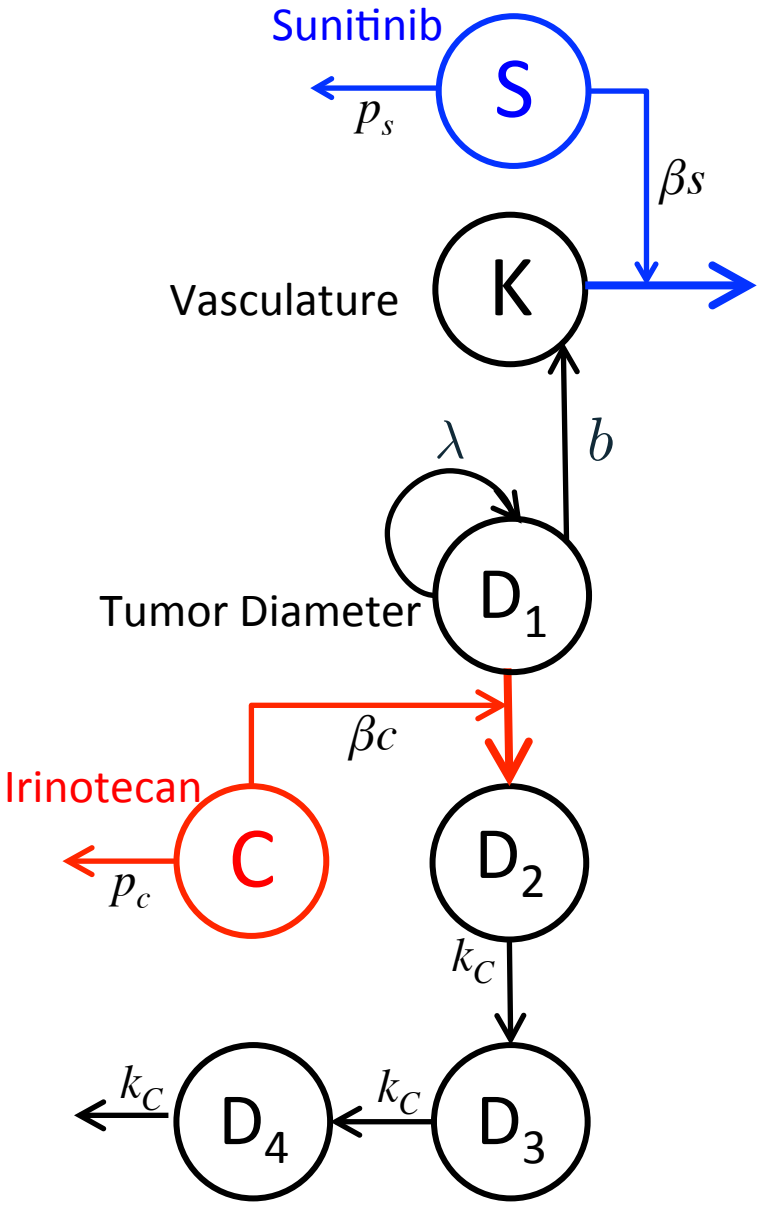


$$\frac{dC}{dt} = -p_c C$$

$$\frac{dS}{dt} = -p_s S$$

$$\frac{dD_1}{dt} = \lambda D_1 \left(1 - \left(\frac{D}{K}\right)^{\alpha}\right) - \beta_C p_C C D_1$$

$$\frac{dD_2}{dt} = \beta_C p_C C D_1 - k_C D_2$$

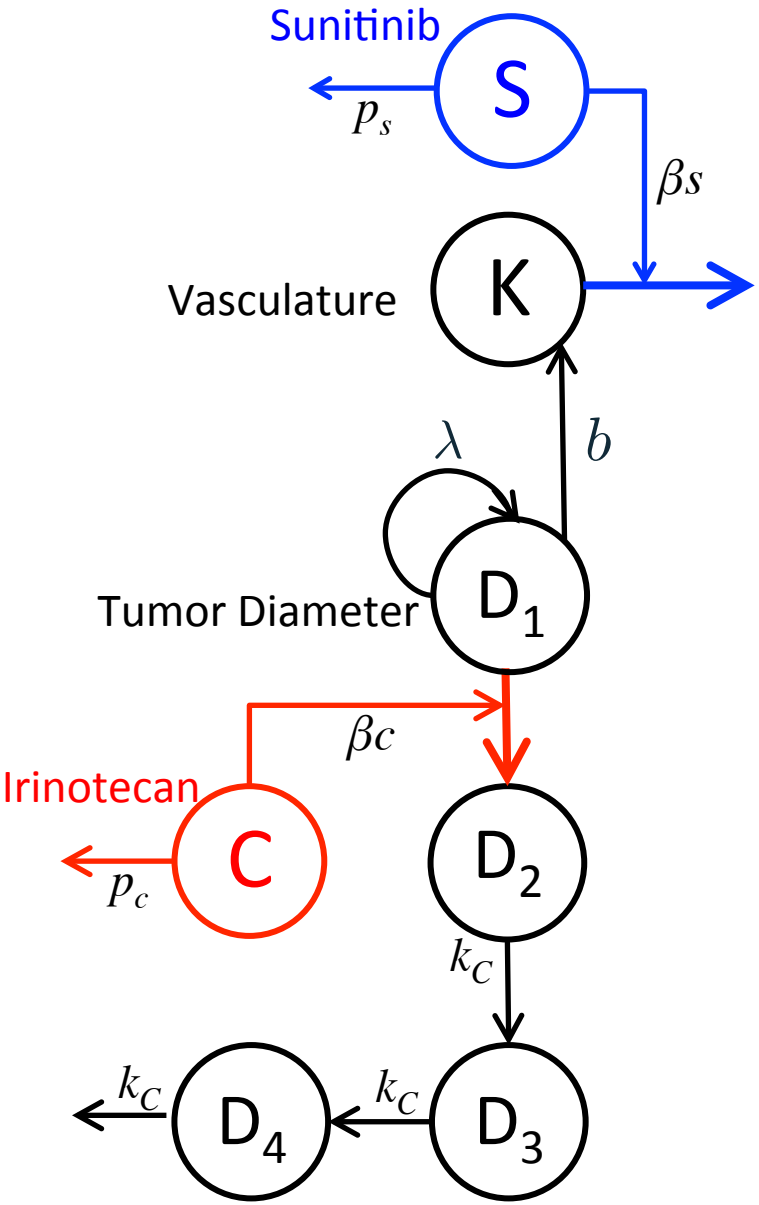
$$\frac{dD_3}{dt} = k_C D_2 - k_C D_3$$

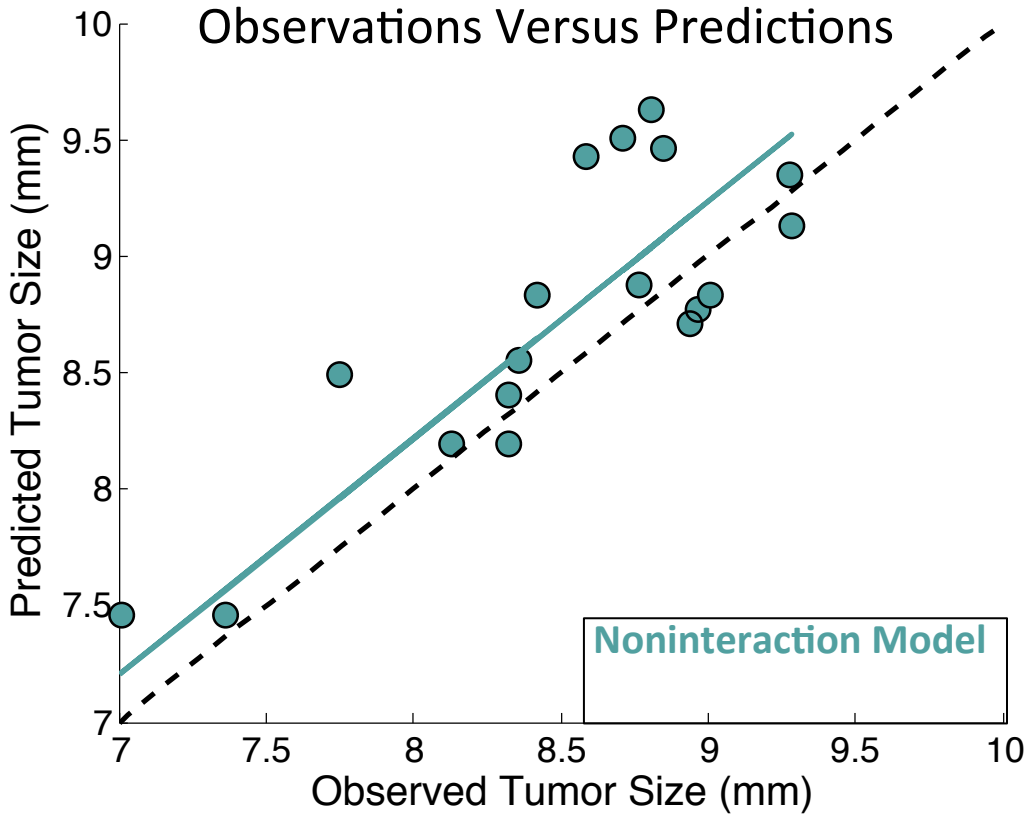
$$\frac{dD_4}{dt} = k_C D_3 - k_C D_4$$

$$\frac{dK}{dt} = bD_1^2 - \beta_S p_s S K$$

$$D = D_1 + D_2 + D_3 + D_4$$

Do Sunitinib and Irinotecan Interact Synergistically?





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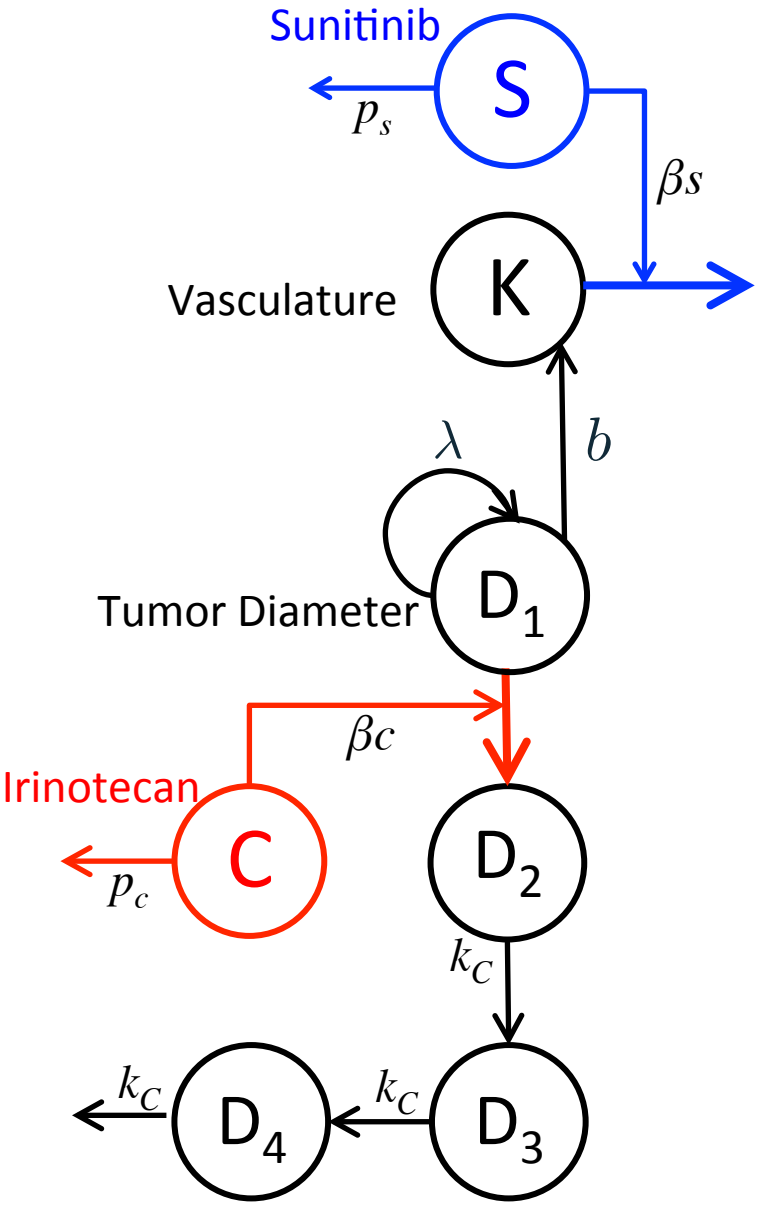

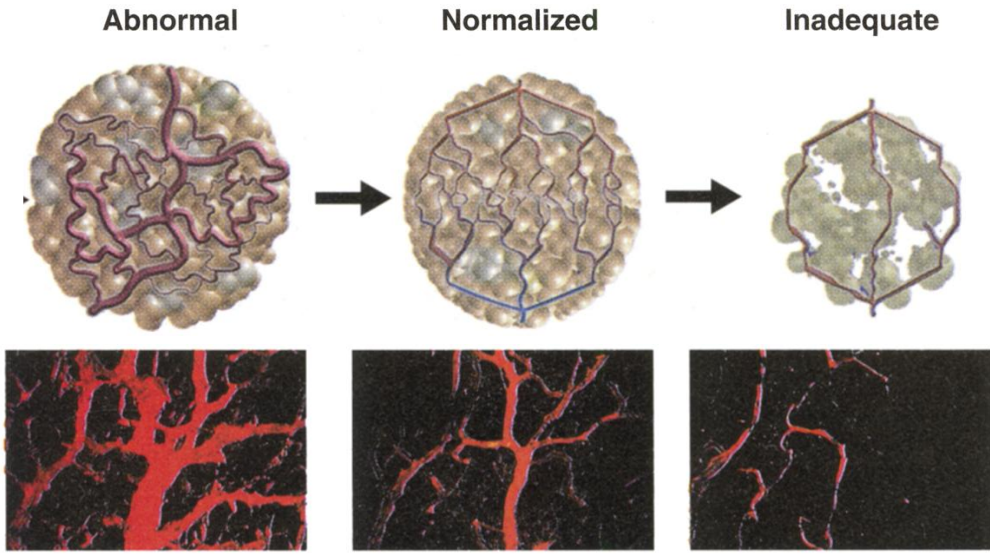

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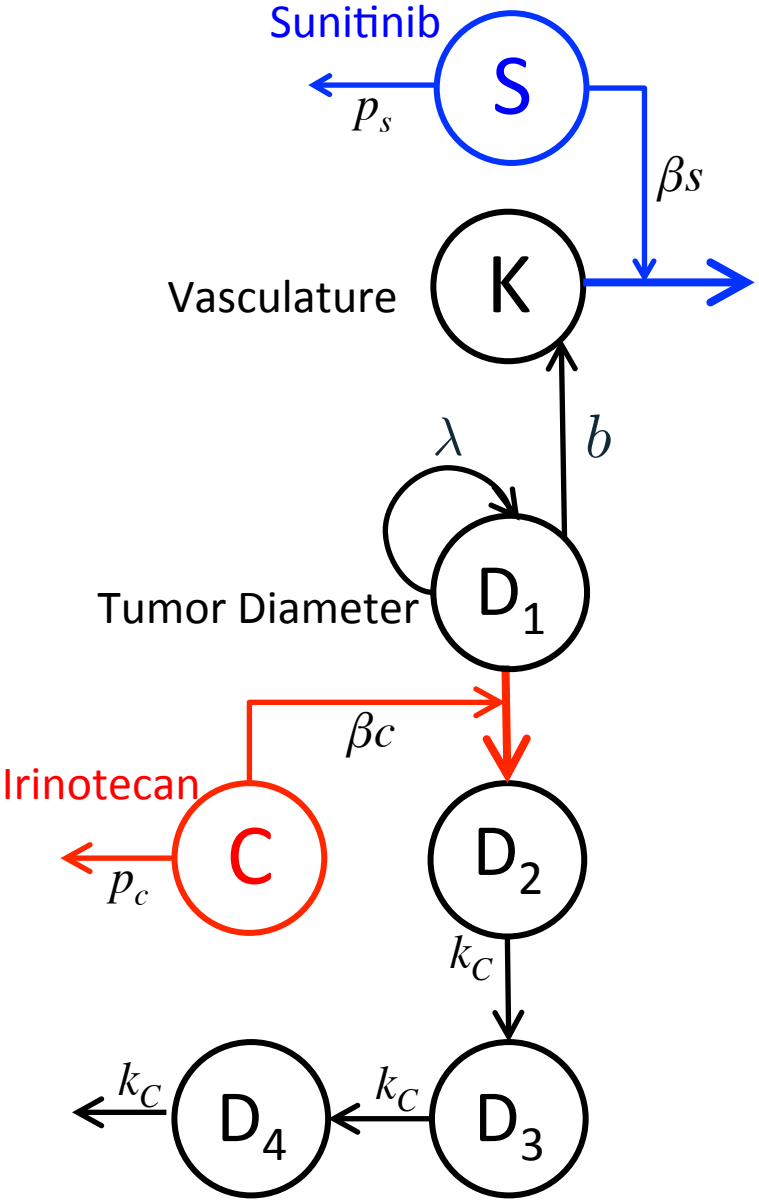

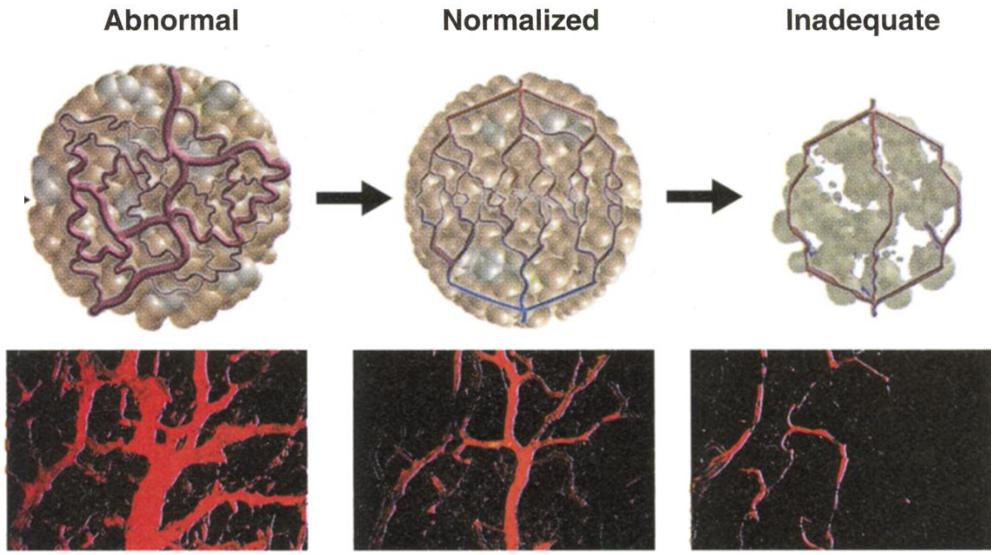

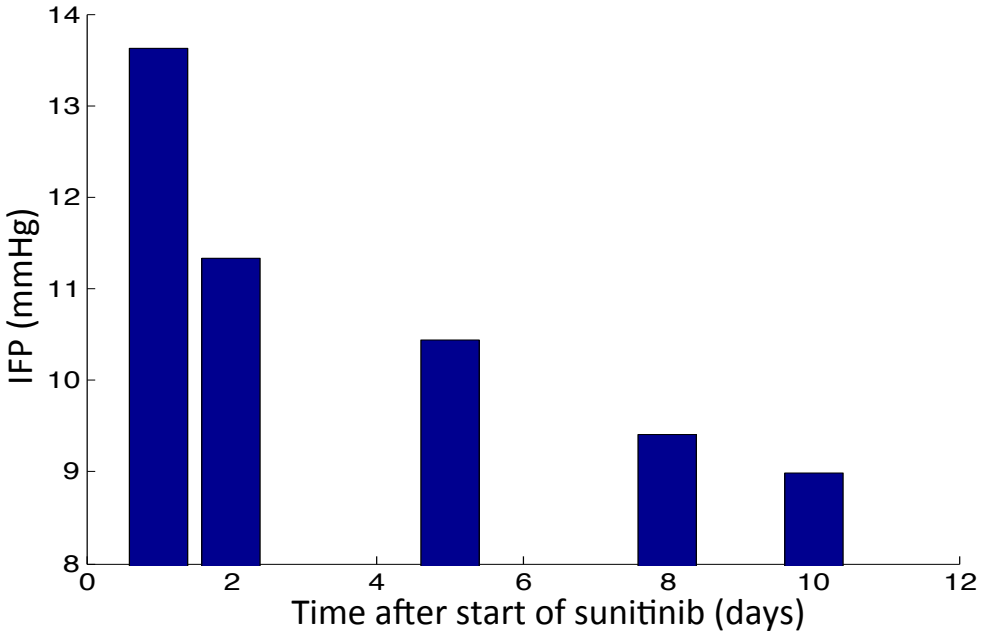

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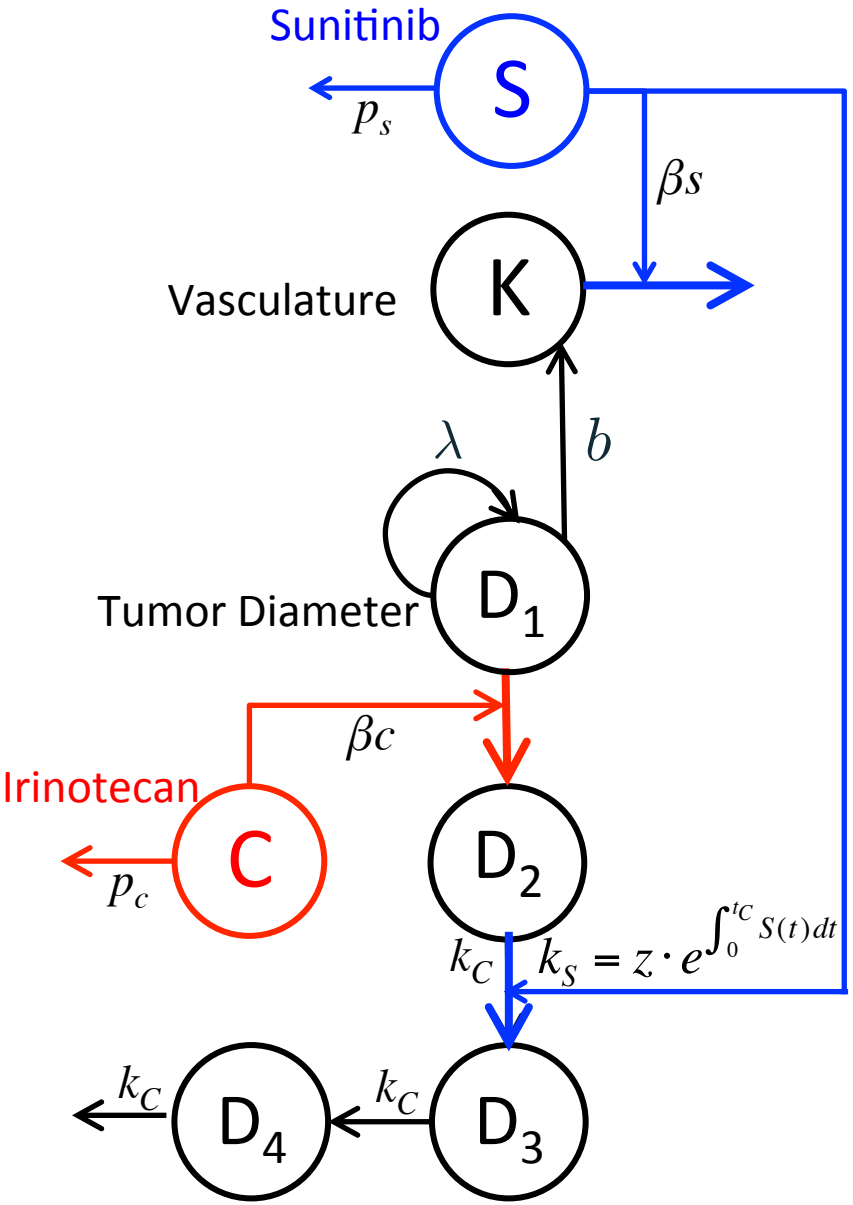

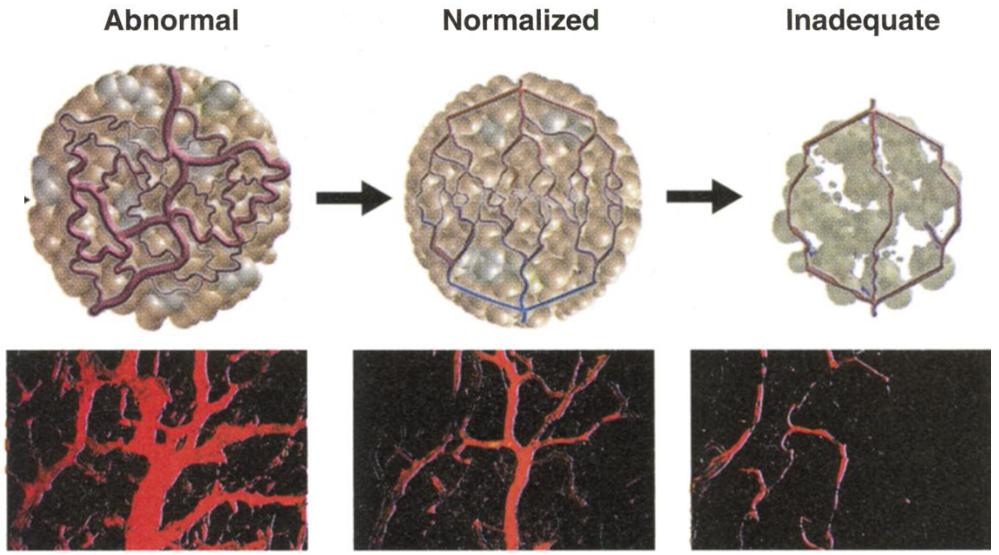

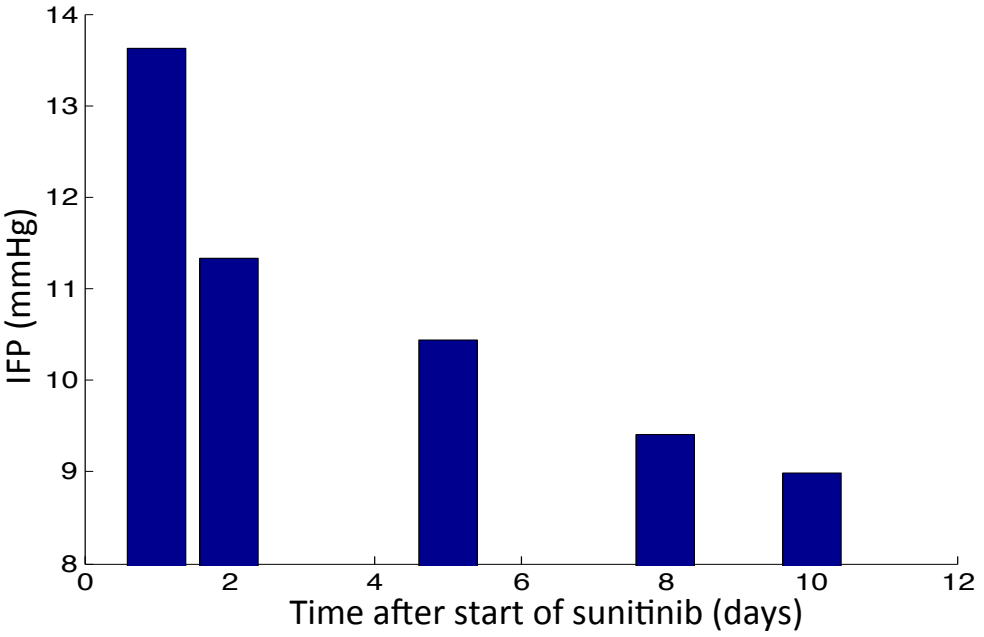

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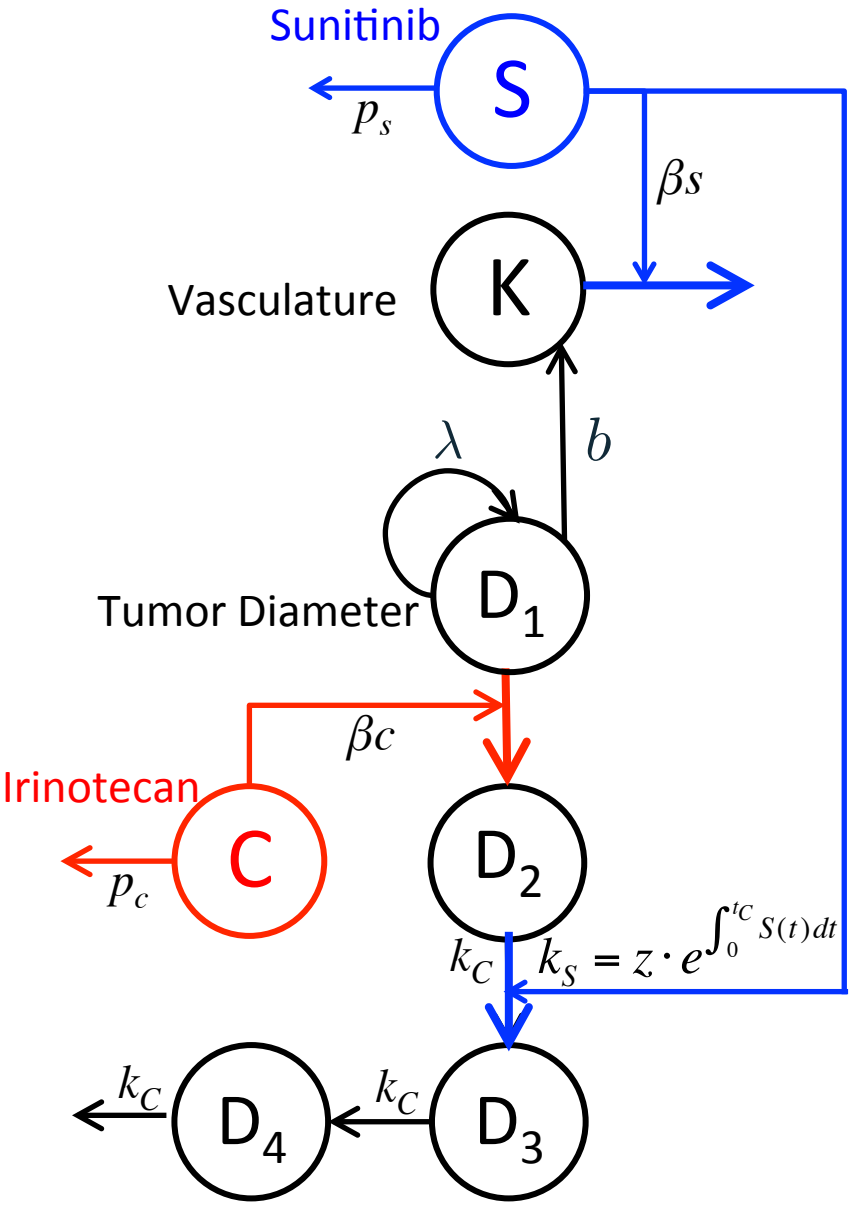

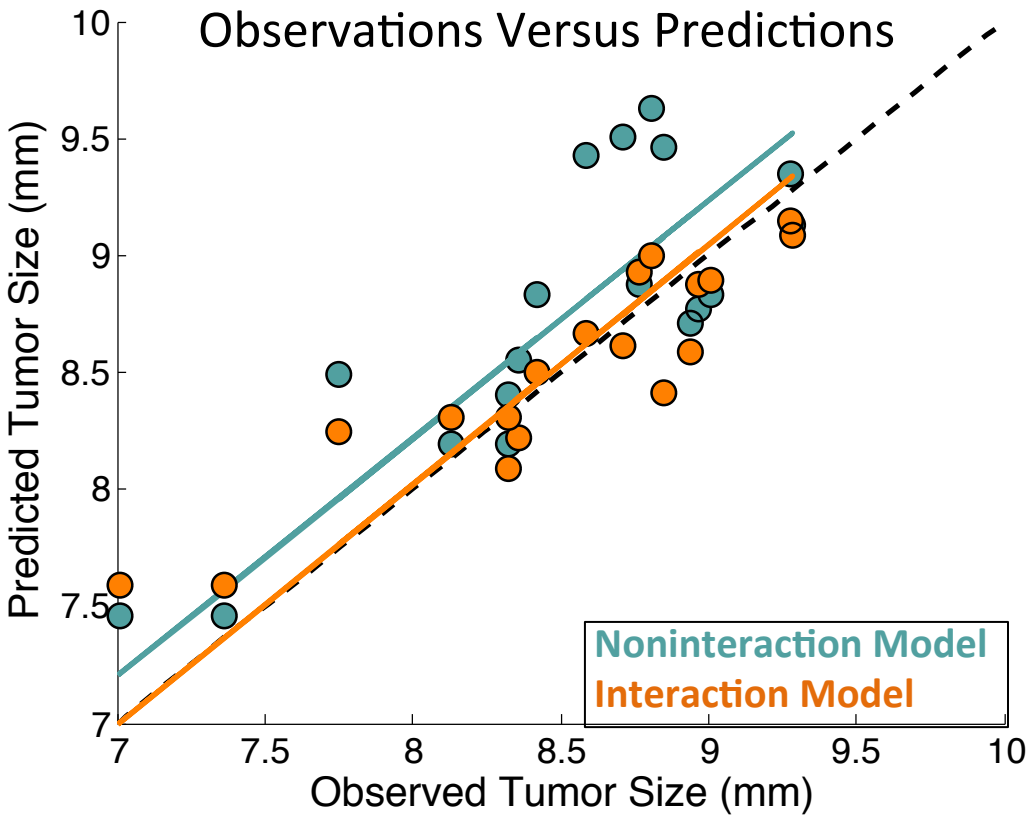

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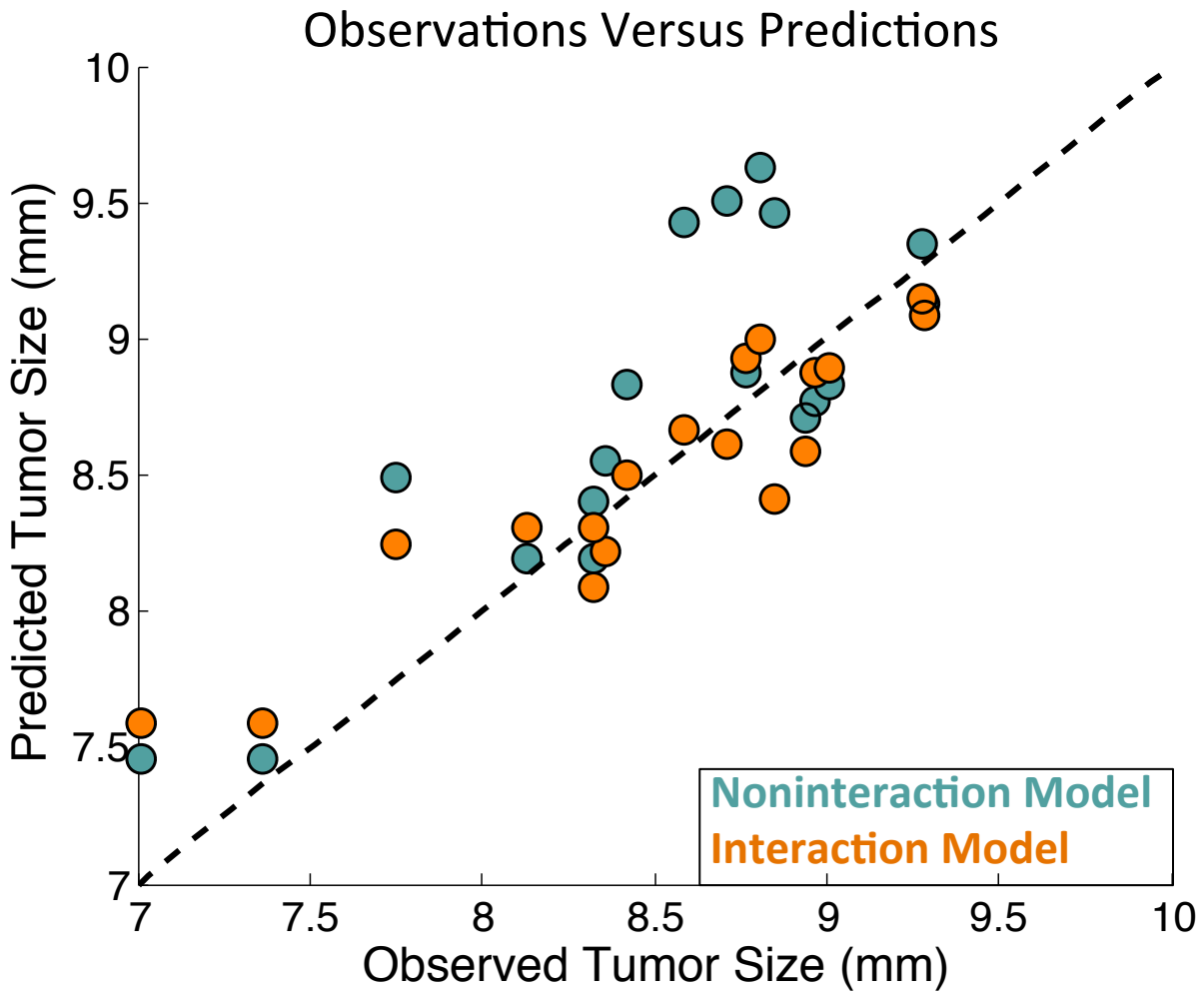

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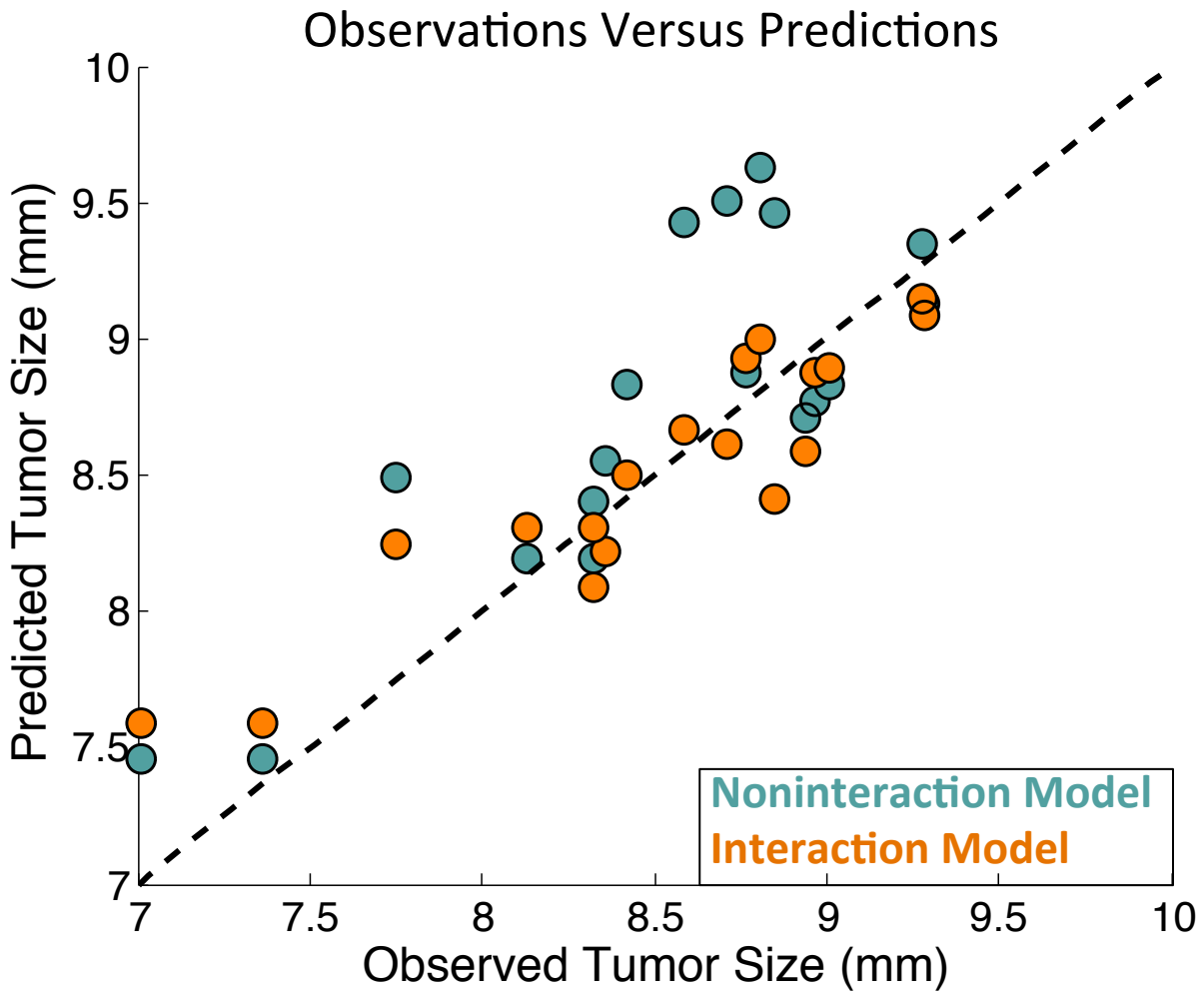

Log likelihood ratio test $\Delta L = -5.9955$ ($p<0.01$)

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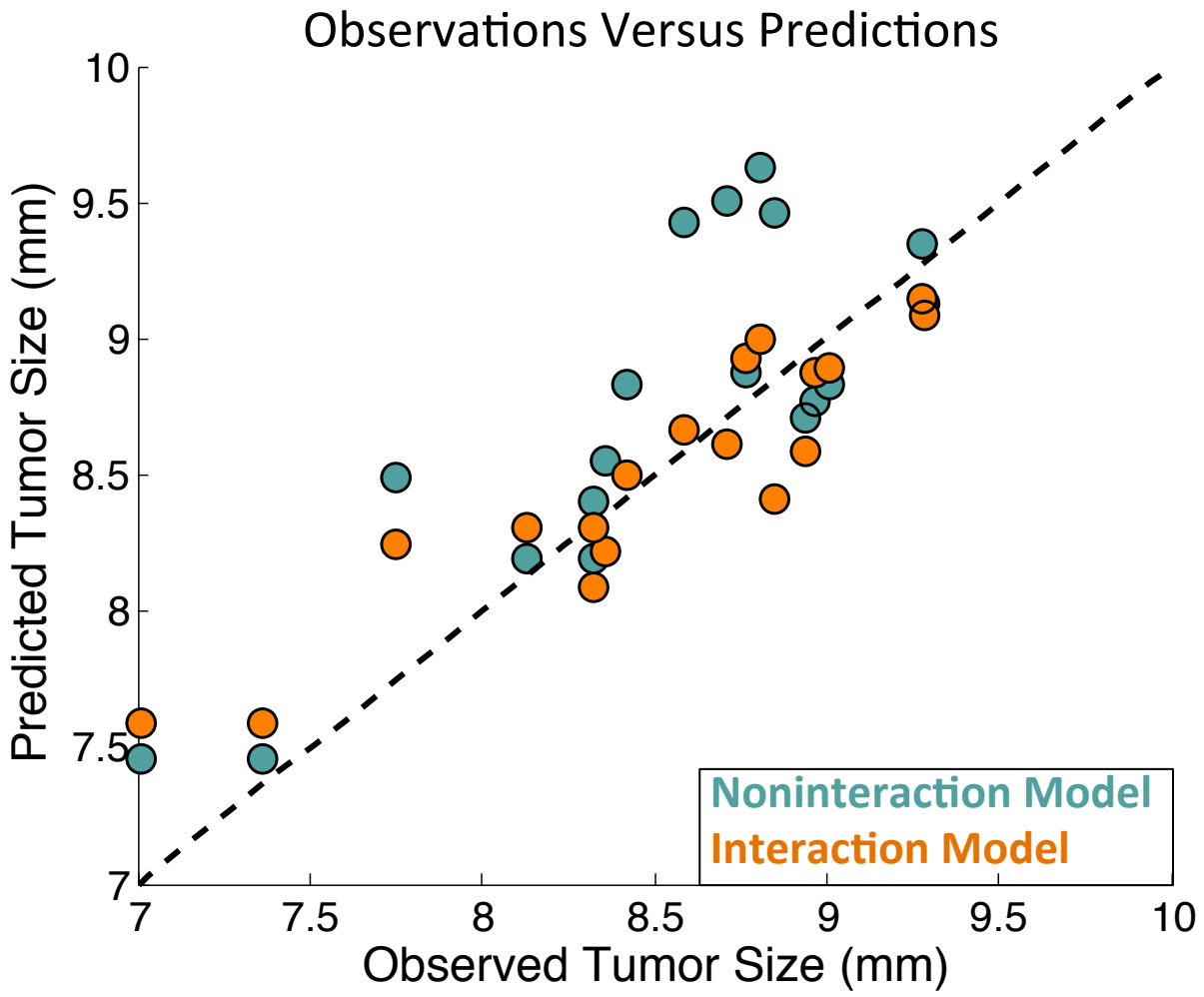

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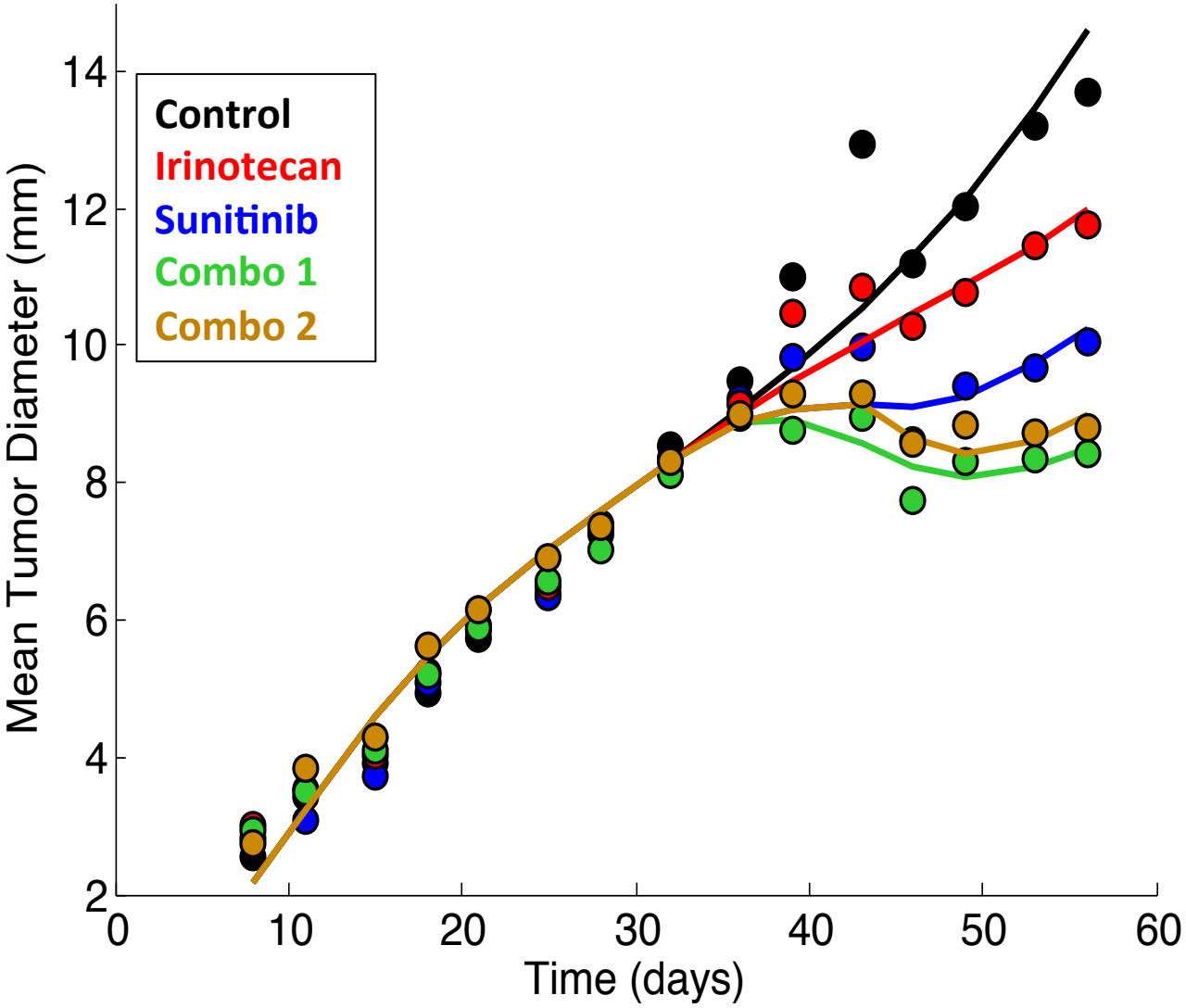
Hence, we have significant improvement of the model under the hypothesis that sunitinib and irinotecan interact synergistically.

Model Simulations



Param	Value (error %)
V_0	0.802 (--)
K_0	7.43 (--)
λ	1.1037 (10)
b	0.003 (0.04)
Ps	2.12 (--)
βs	0.036 (0.31)
Pc	2.00 (--)
βc	0.2419 (5)
kc	0.1032 (6)
z	0.2238 (11)

Implications of a Synergistic Interaction

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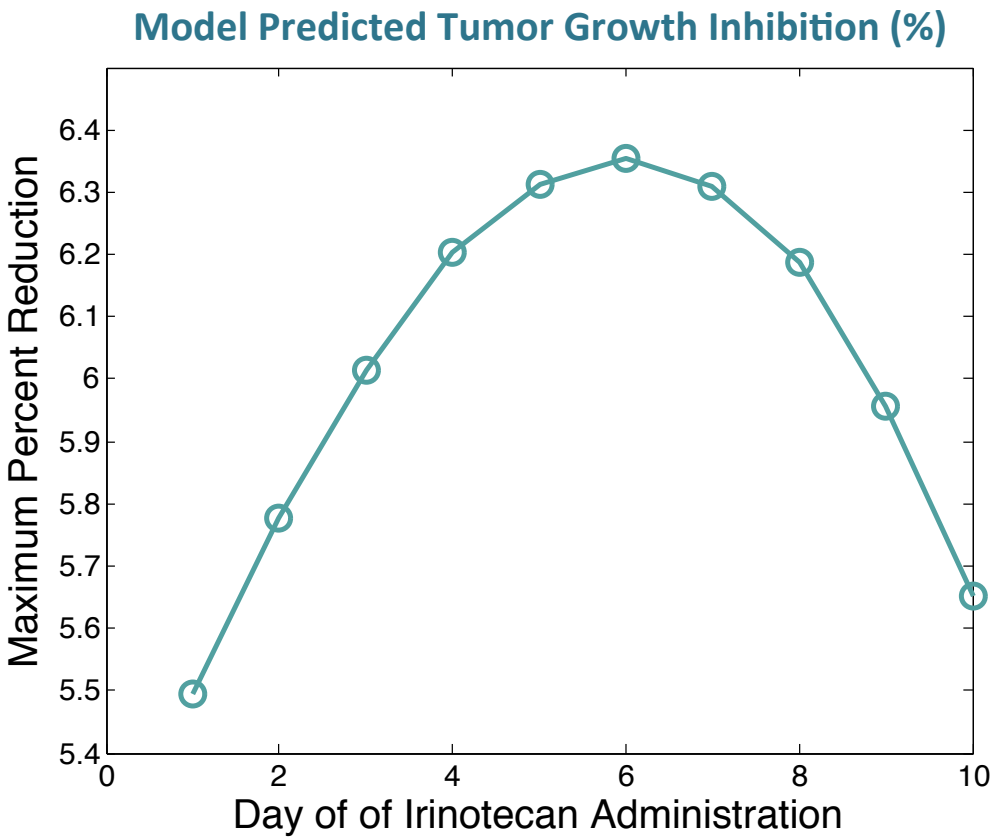

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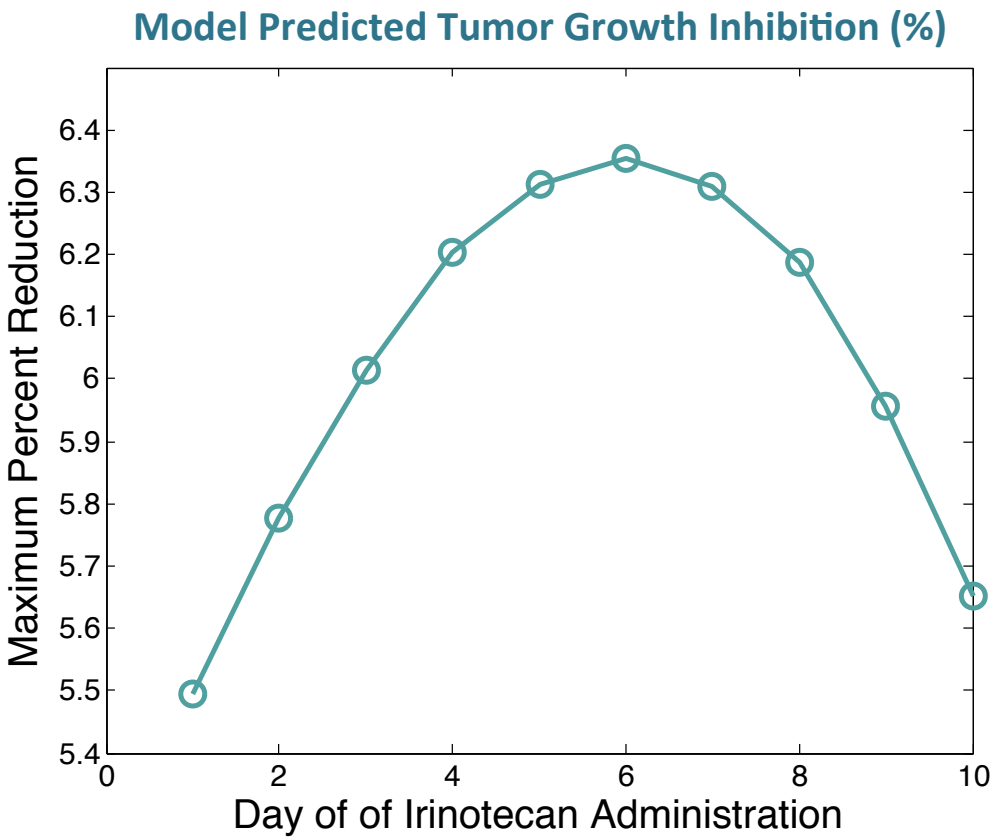
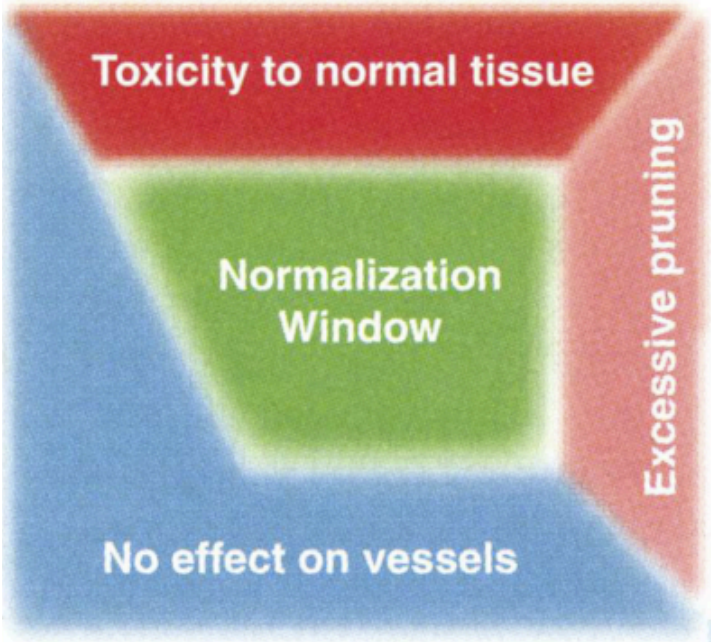
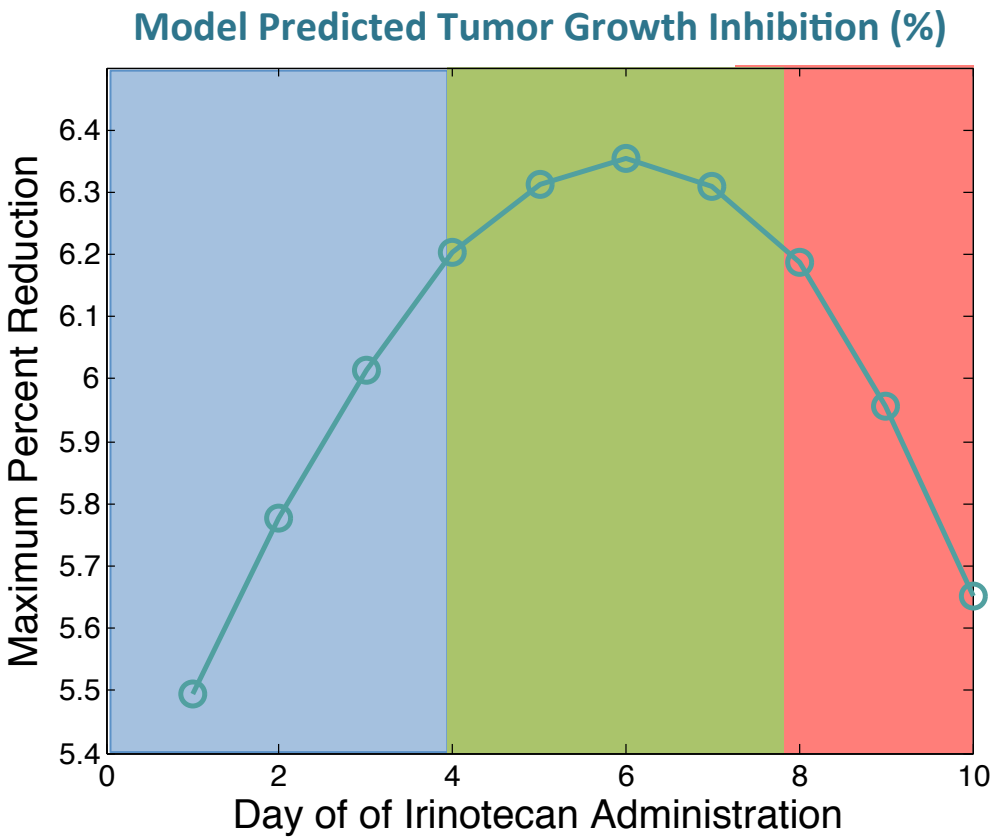


Normalization Window

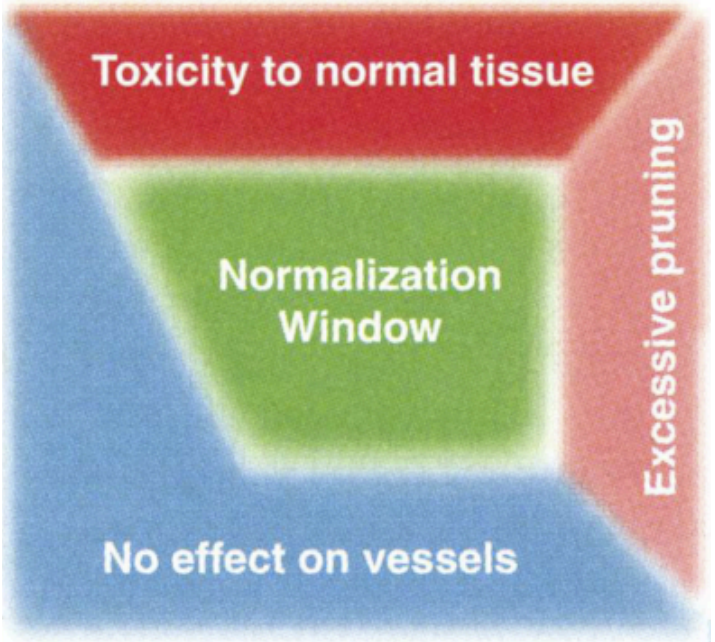


[Jain Science 2005]

Implications of a Synergistic Interaction



Normalization Window



[Jain Science 2005]

Conclusions

- Model of sunitinib and its combination w/ irinotecan in preclinical colorectal cancer

- Model supports that there is a synergistic interaction between the drugs
  - Interaction between irinotecan and sunitinib is proportional to amount of sunitinib given prior to irinotecan administration
  - Model exhibits evidence of a normalization window, consistent with *[JAIN SCIENCE 2005] & [ARJAANS CR 2013]*

Acknowledgements

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We have open PhD and Postdoc positions.
If interested, please contact Benjamin Ribba
Benjamin.ribba@inria.fr