MODELING TUMOR GROWTH AND ANTI-ANGIOGENIC DRUGS EFFICACY: FROM MULTISCALE TO MIXED-EFFECT MODELS
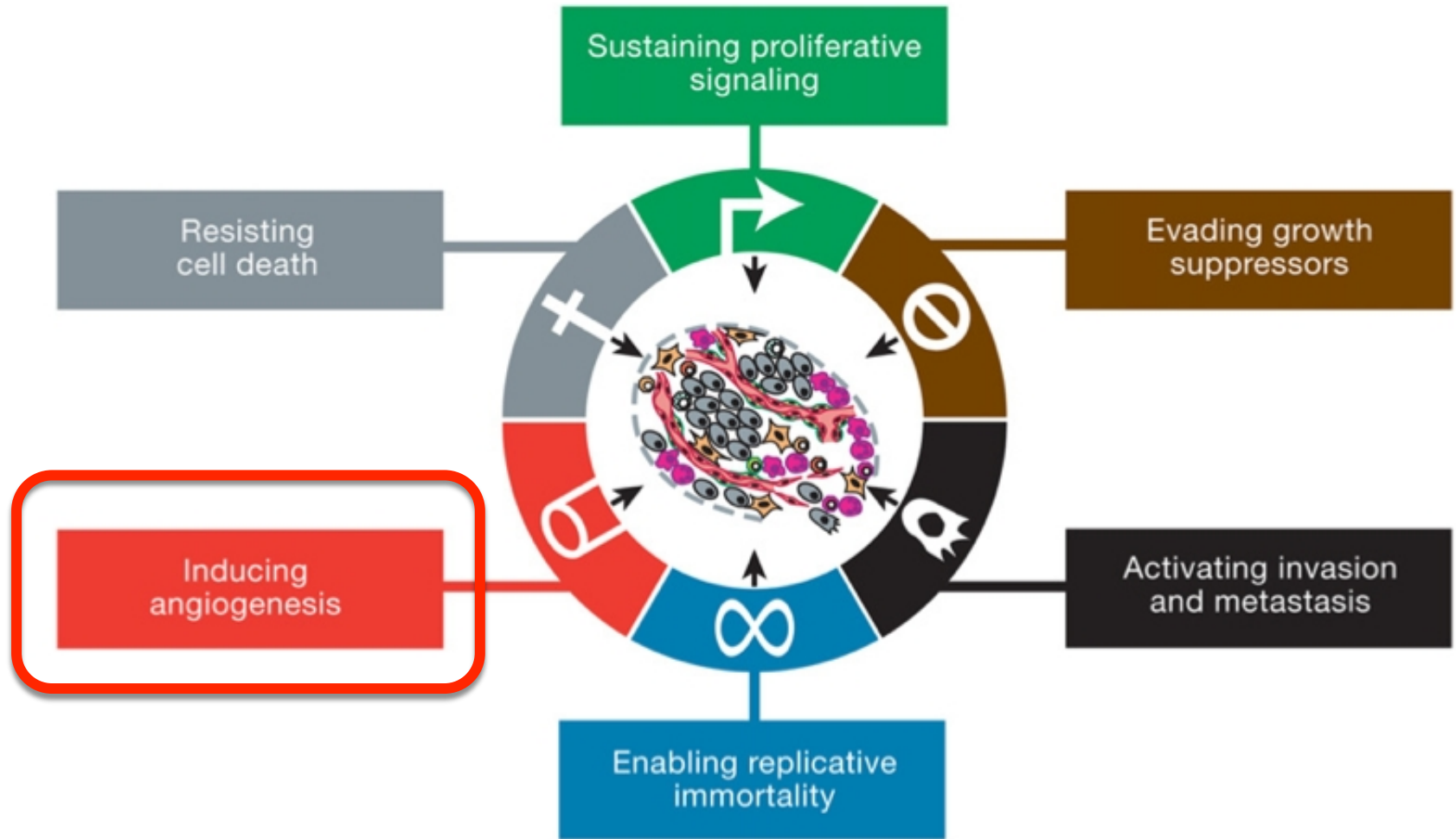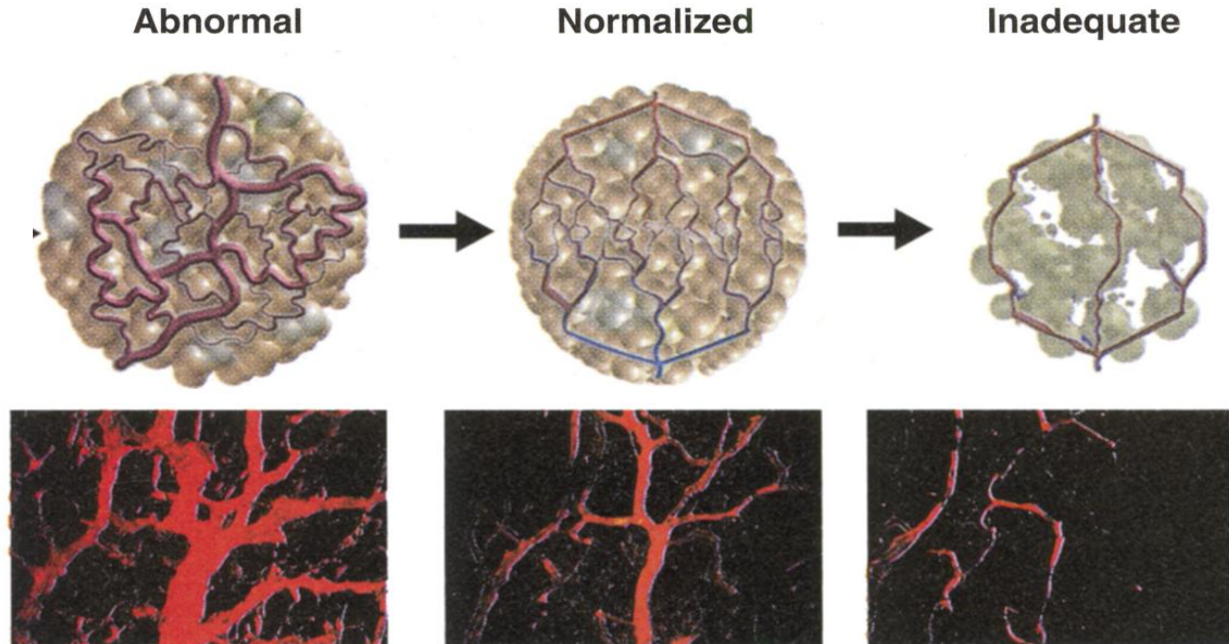
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MMSLS 2015

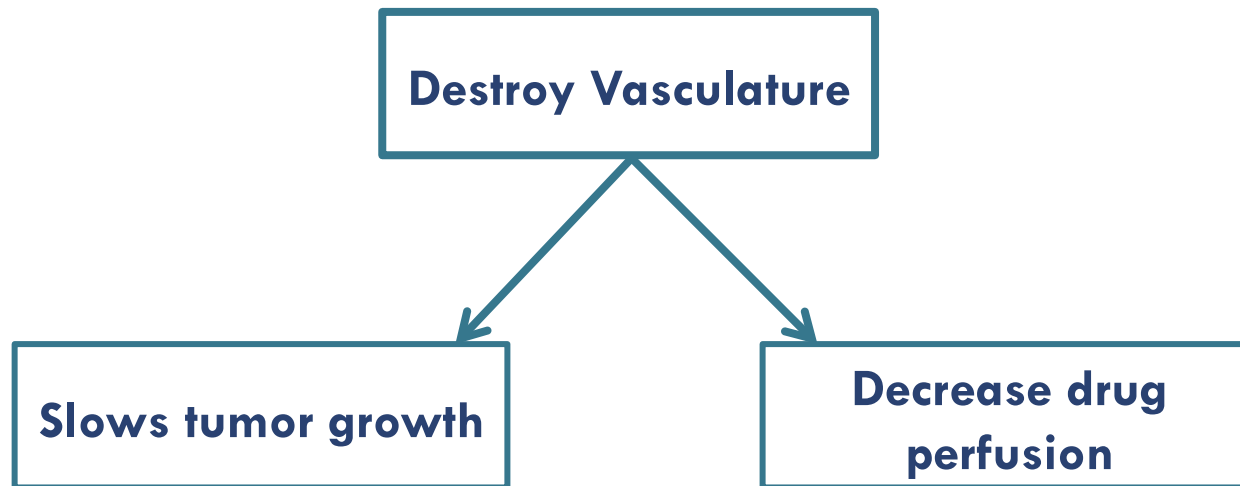# Hallmarks of Cancer

[Hanahan and Weinberg, Cell 2011]
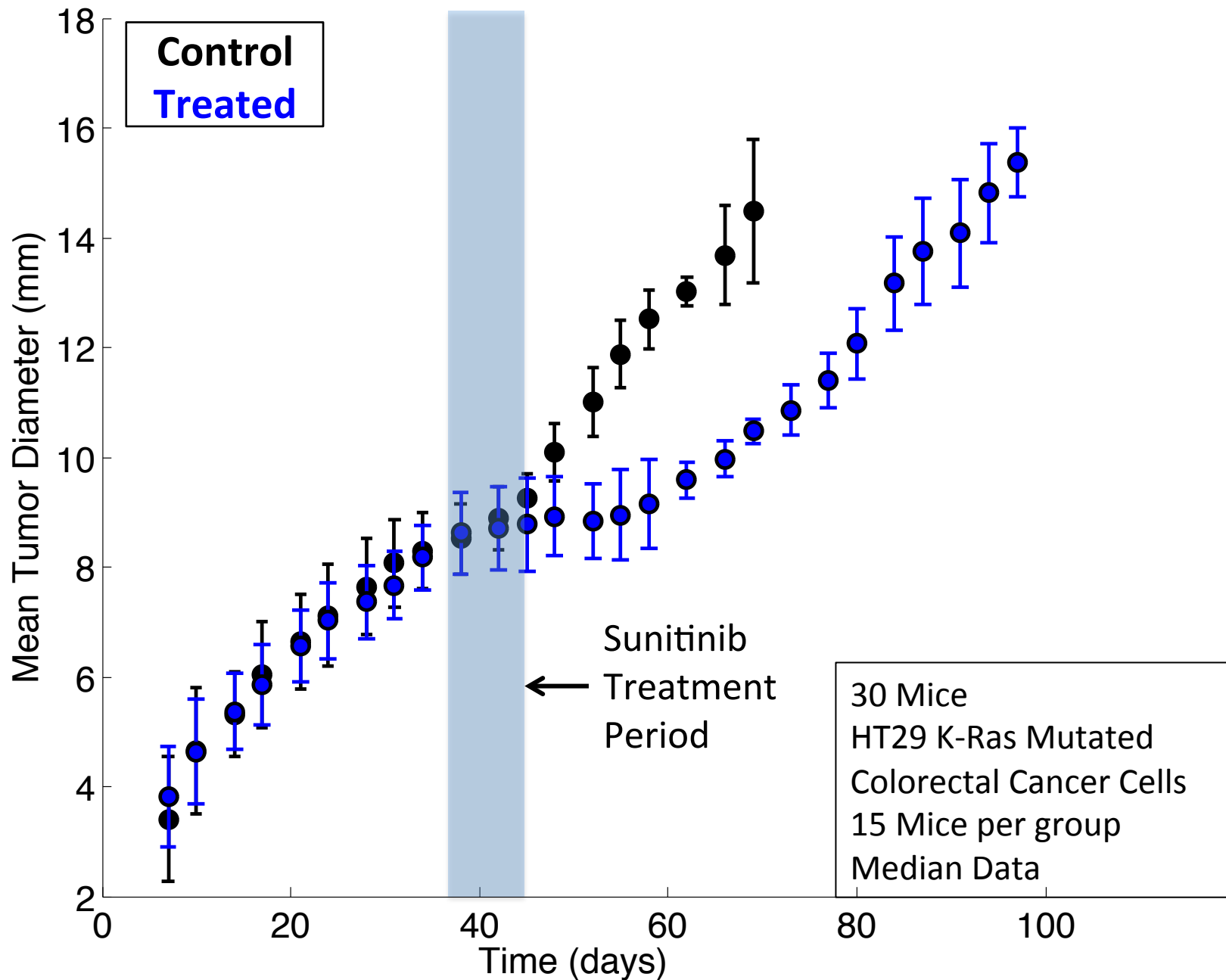
Targeting Angiogenesis

Abnormal → Normalized → Inadequate

[Jain 2006]

Angiogenesis Inhibitors

◆ About 10 successfully developed compounds

◆ Often given in combination with chemotherapy

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┌─────────────────────┐
│  Destroy Vasculature │
└─────────────────────┘
        ↙        ↘
┌──────────────────┐   ┌──────────────────┐
│ Slows tumor growth│   │  Decrease drug    │
│                   │   │  perfusion        │
└──────────────────┘   └──────────────────┘
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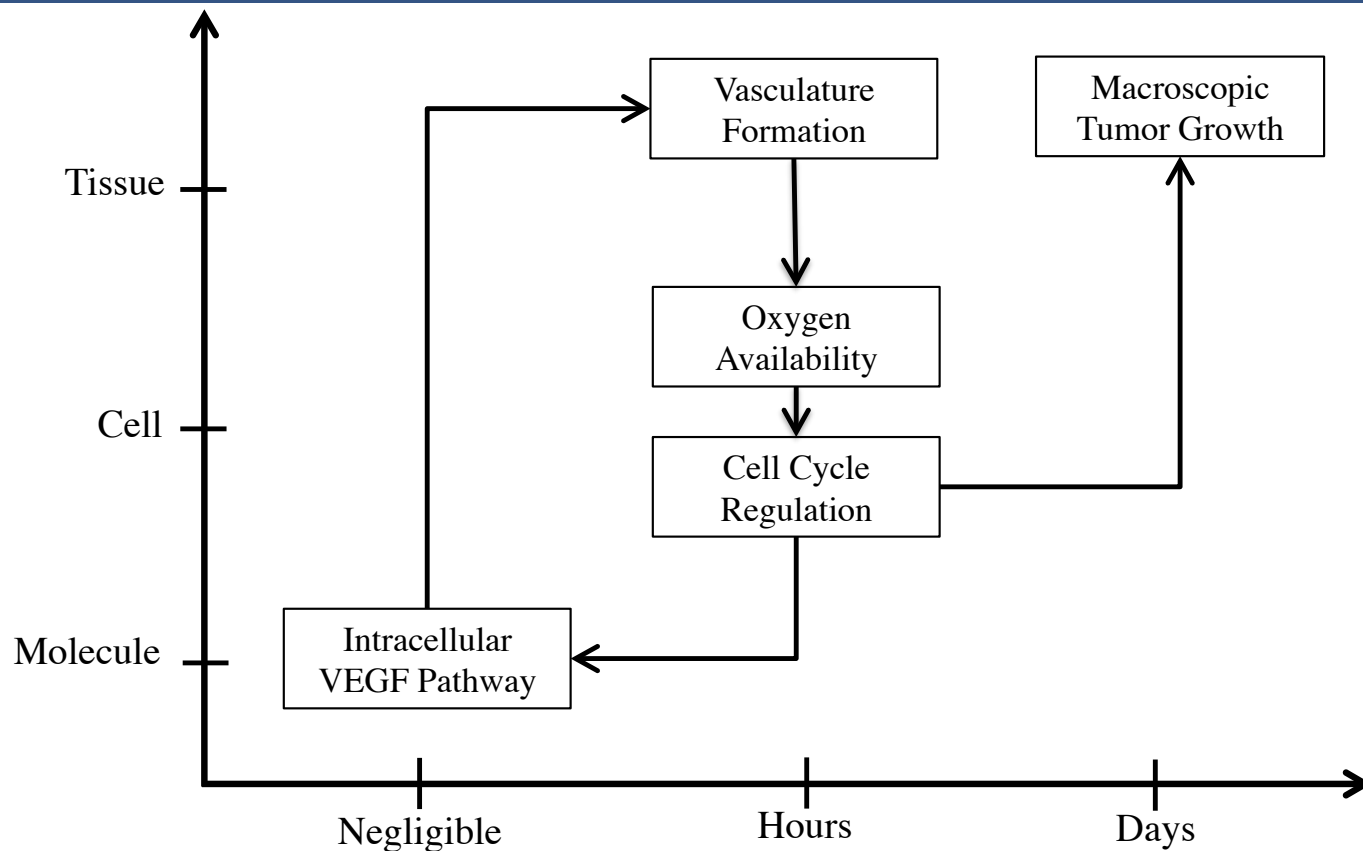
◆ Sunitinib

  ▫ Oral small-molecule angiogenesis inhibitor

  ▫ Multi-targeted RTKi (targets PDGF, VEGF, EGF receptors)

  ▫ Little to no cytotoxic effects on tumor cells with K-Ras Muataion

Sunitinib Monotherapy Experimental Data

Control
Treated

Mean Tumor Diameter (mm)

Time (days)

Sunitinib Treatment Period

30 Mice
HT29 K-Ras Mutated
Colorectal Cancer Cells
15 Mice per group
Median Data

A multiscale model of vascular tumor growth

- ◆ 64 Equations, 98 Parameters
- ◆ Coupled PDEs Describing :
  - ☐ Endothelial Cells, Tumor Cells, VEGF production, Cell Migration
- ◆ Parameter estimation is difficult, 2 hour simulation time

A simplified model

Concentration of Anti-angiogenic treatment $\longrightarrow$

$$\frac{dS}{dt} = -pS$$

Mean Tumor Diameter $\longrightarrow$

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

Tumor Capacity $\longrightarrow$

$$\frac{dK}{dt} = bD^2 - \beta pSK$$

A simplified model

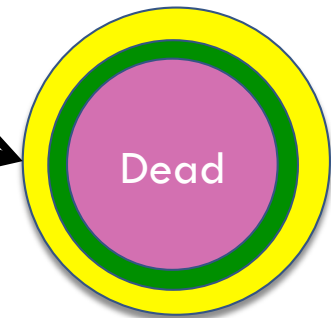Concentration of Anti-angiogenic treatment $\longrightarrow$ $\dfrac{dS}{dt} = -pS$

Mean Tumor Diameter $\longrightarrow$ $\dfrac{dD}{dt} = \lambda D \left(1 - \left(\dfrac{D}{K} \right)^{\alpha} \right)$

Tumor Capacity $\longrightarrow$ $\dfrac{dK}{dt} = bD^2 - \beta pSK$

Tumor Composition

Dead

"Healthy"

Dead

It is the **GREEN** cells that are driving angiogenesis

A simplified model

Concentration of Anti-angiogenic treatment $\longrightarrow$

$$\frac{dS}{dt} = -pS$$

Mean Tumor Diameter $\longrightarrow$

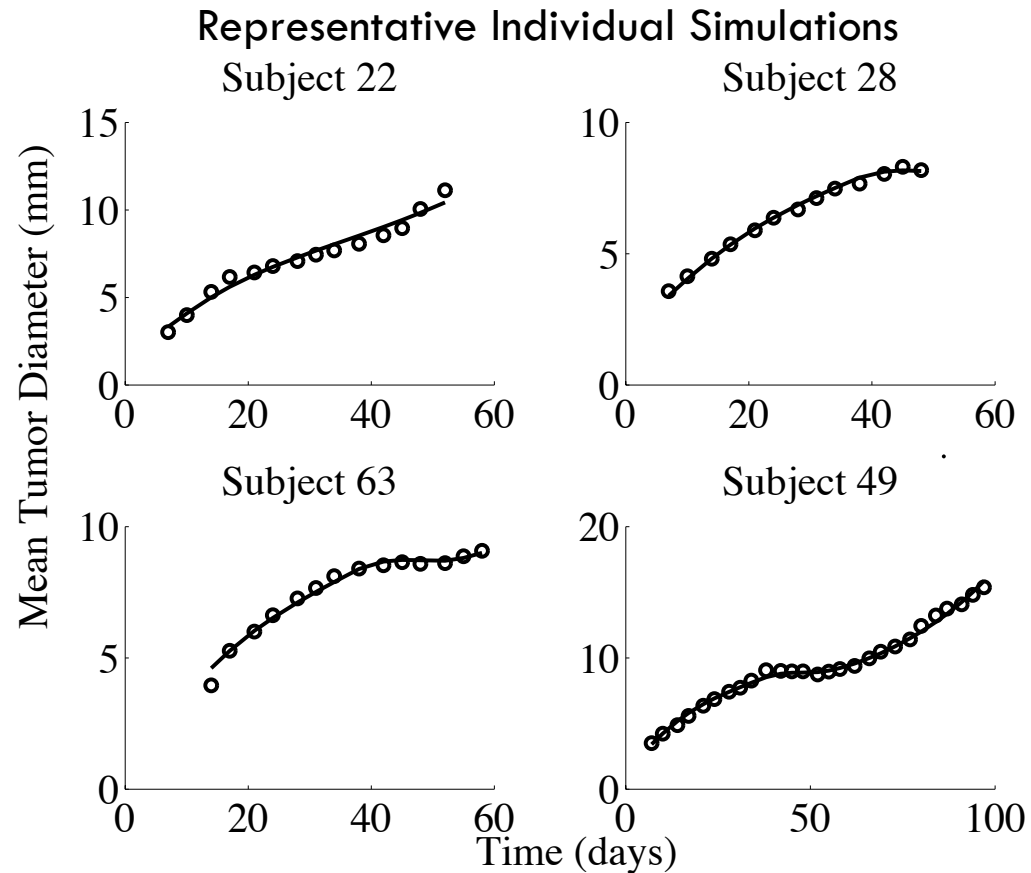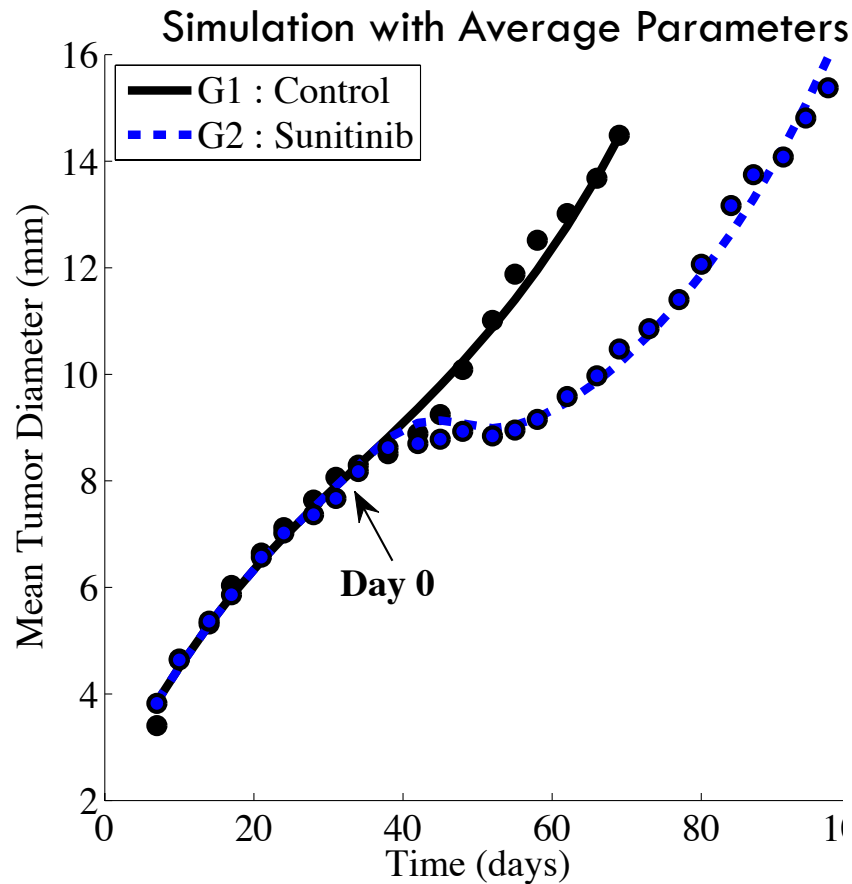$$\frac{dD}{dt} = \lambda D \left(1 - \left(\frac{D}{K} \right)^{\alpha} \right)$$

Tumor Capacity $\longrightarrow$

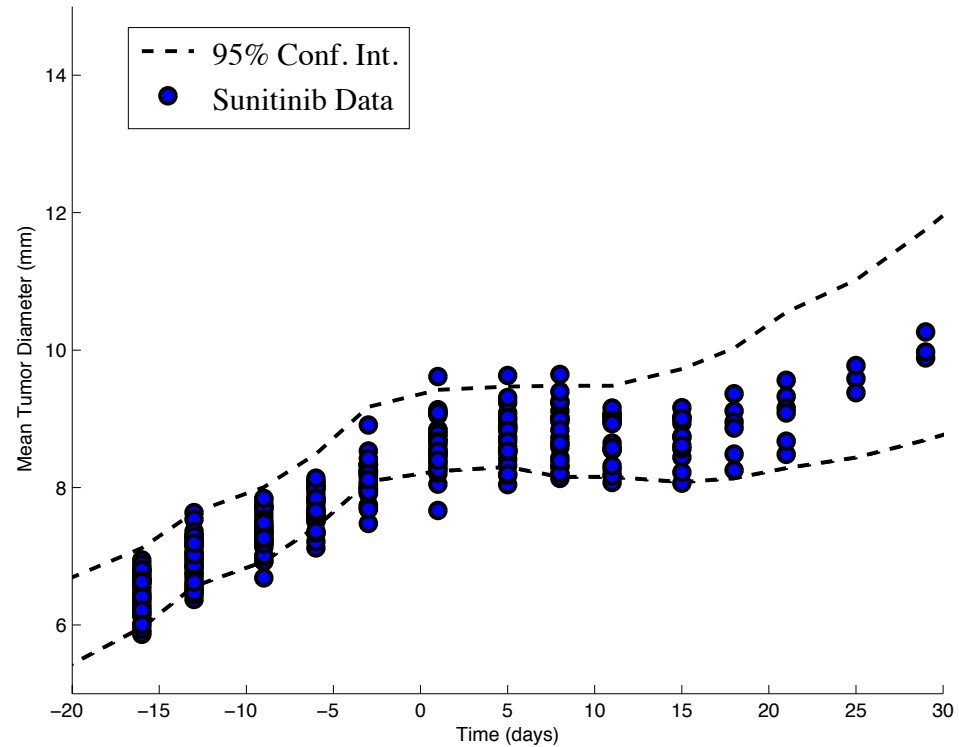$$\frac{dK}{dt} = bD^2 - \beta pSK$$
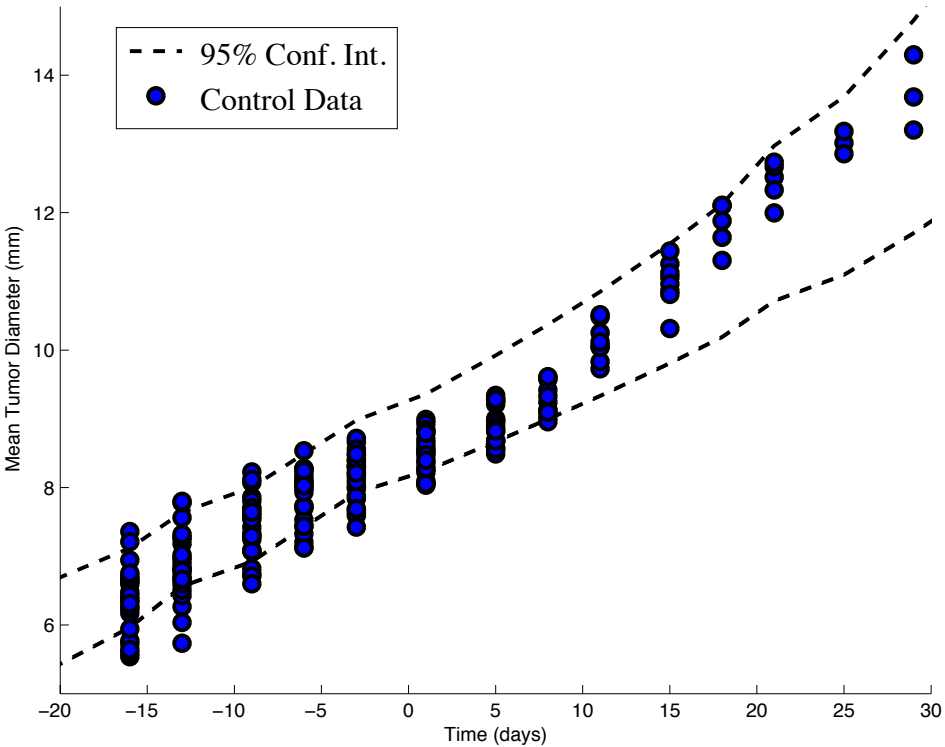
We have a SIMPLE model

Not so interesting on the dynamics side, but allows us to approach other interesting problems :
1. Parameter estimation
2. Optimizing treatment

Mixed-Effect Modeling Results

Mixed-Effect Modeling Results
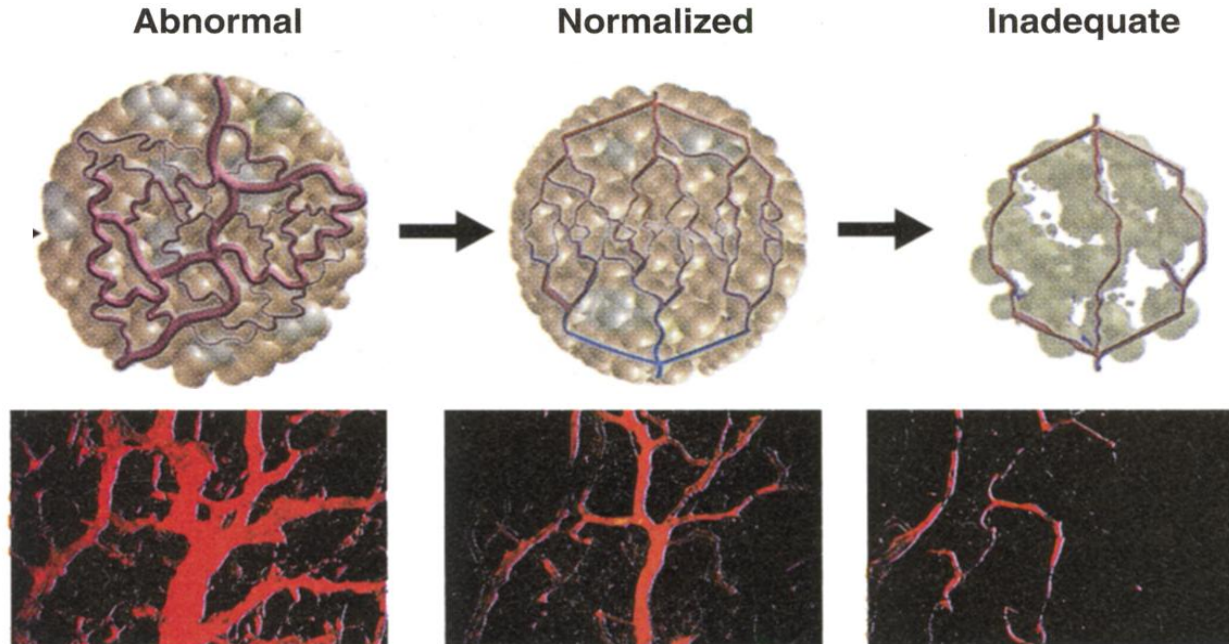
Developing a Combined Therapy Model

Modify model to include chemotherapy

Assess how the anti-angiogenic drug and chemotherapy interact
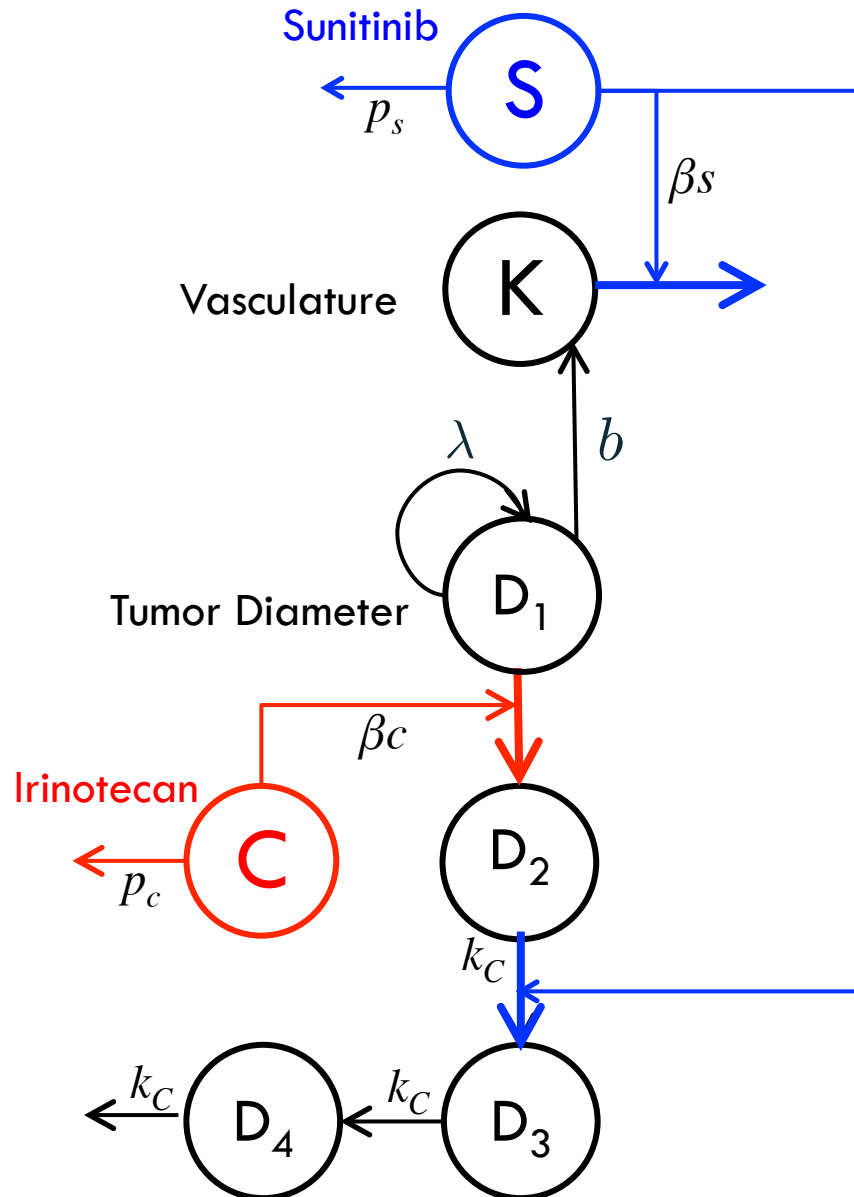
Make conclusions and predictions for future experiments
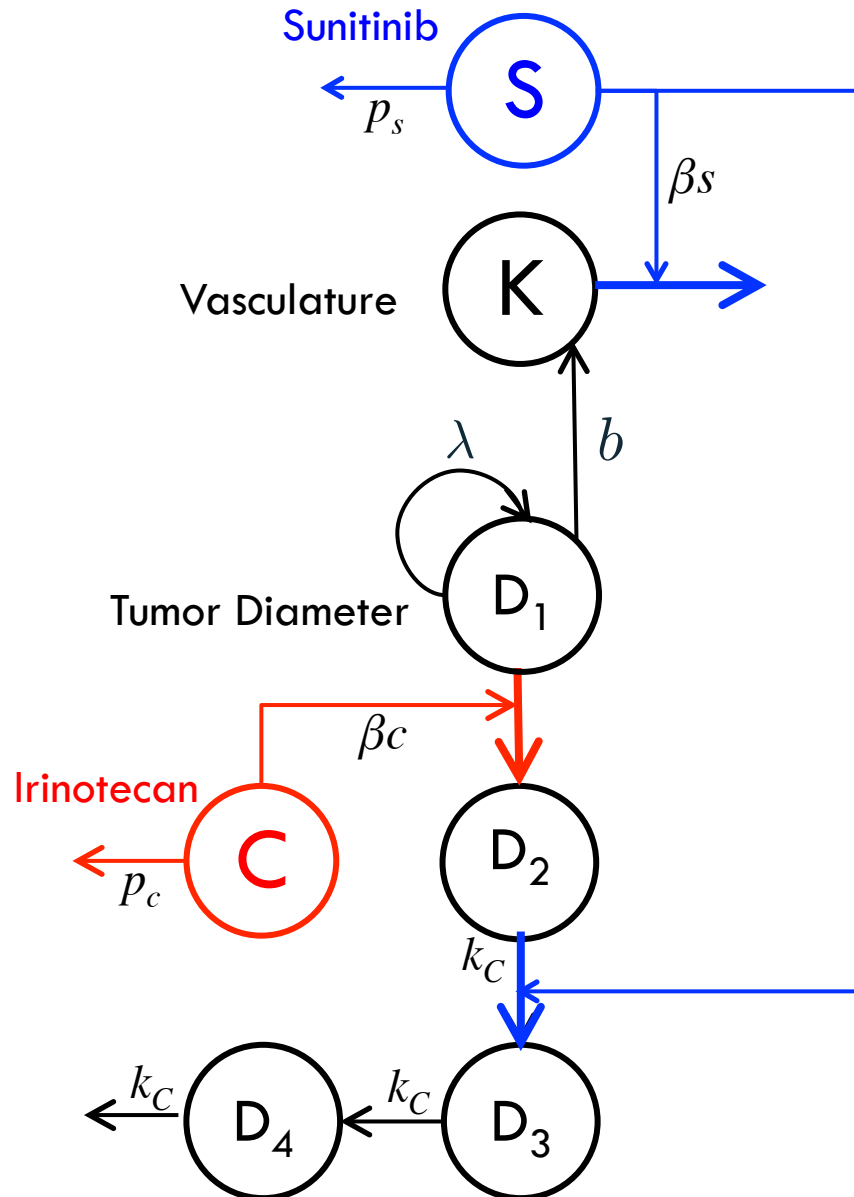
Do chemotherapy and anti-angiogenics interact?

[Jain 2006]

Combined chemo and anti-angiogenic therapy
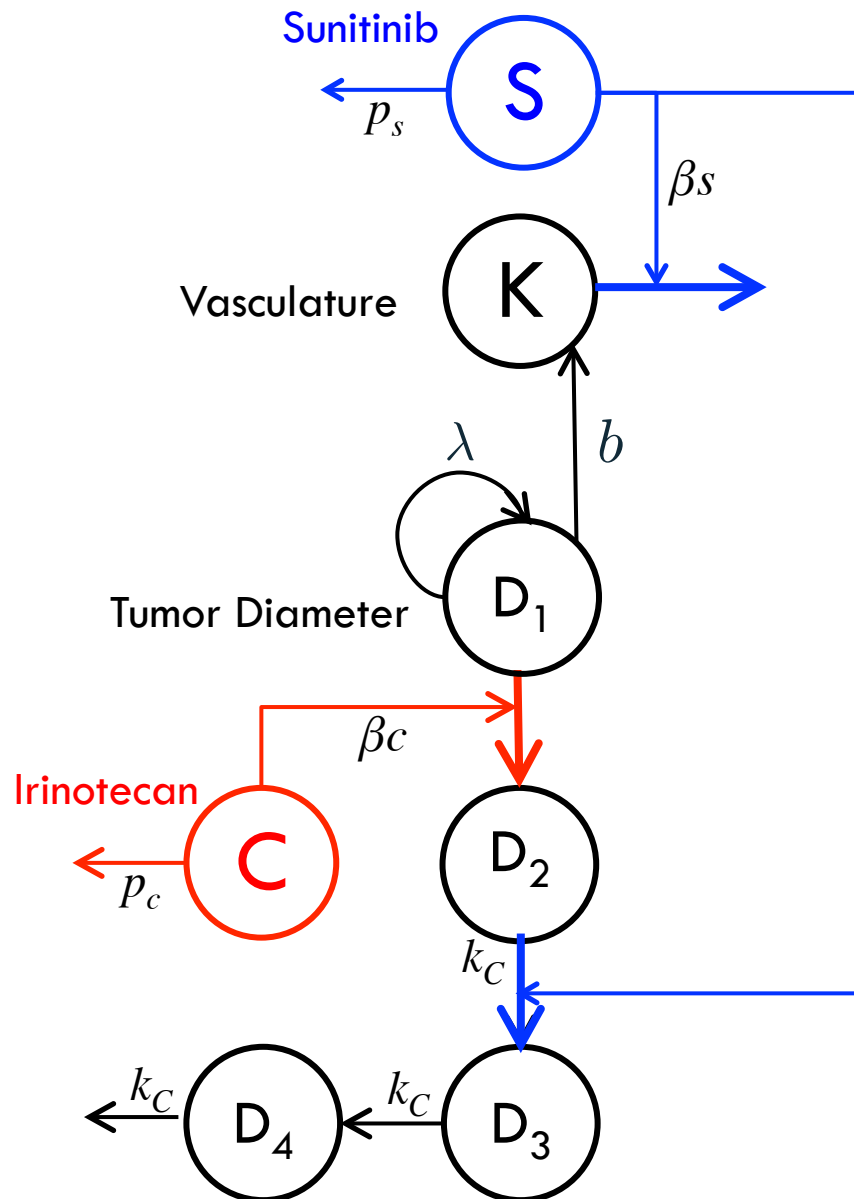
Combined chemo and anti-angiogenic therapy

Or more practically…

$$\frac{dD}{dt} = \lambda D \left(1 - \left(\frac{D}{K} \right)^{\alpha} \right) - f(C(t), S(t))D$$

$$\frac{dK}{dt} = bD^2 - \beta S(t)D$$

Combined chemo and anti-angiogenic therapy

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

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

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

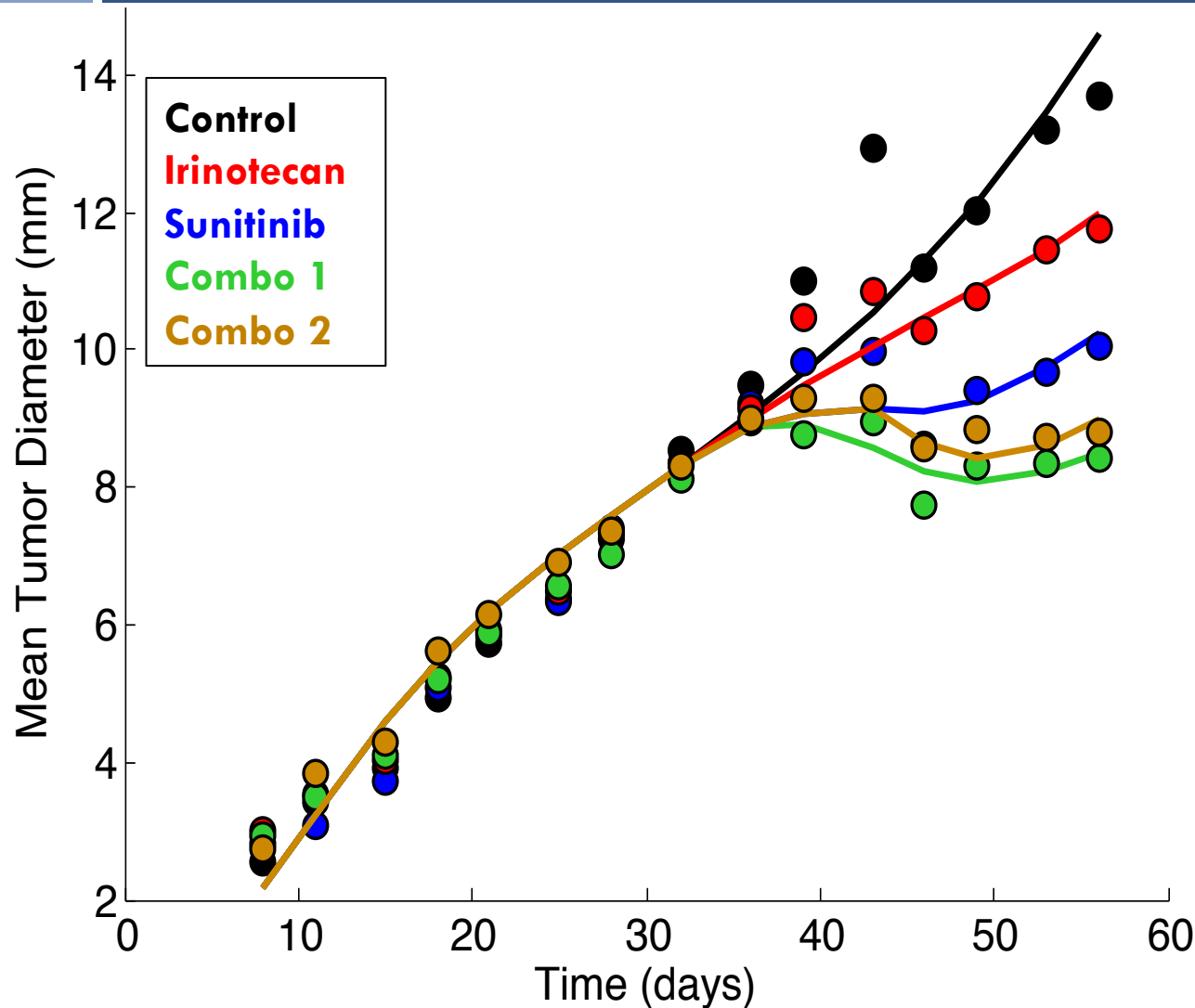$$\frac{dD_2}{dt} = \beta_C p_C C D_1 - k_C D_2$$

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

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

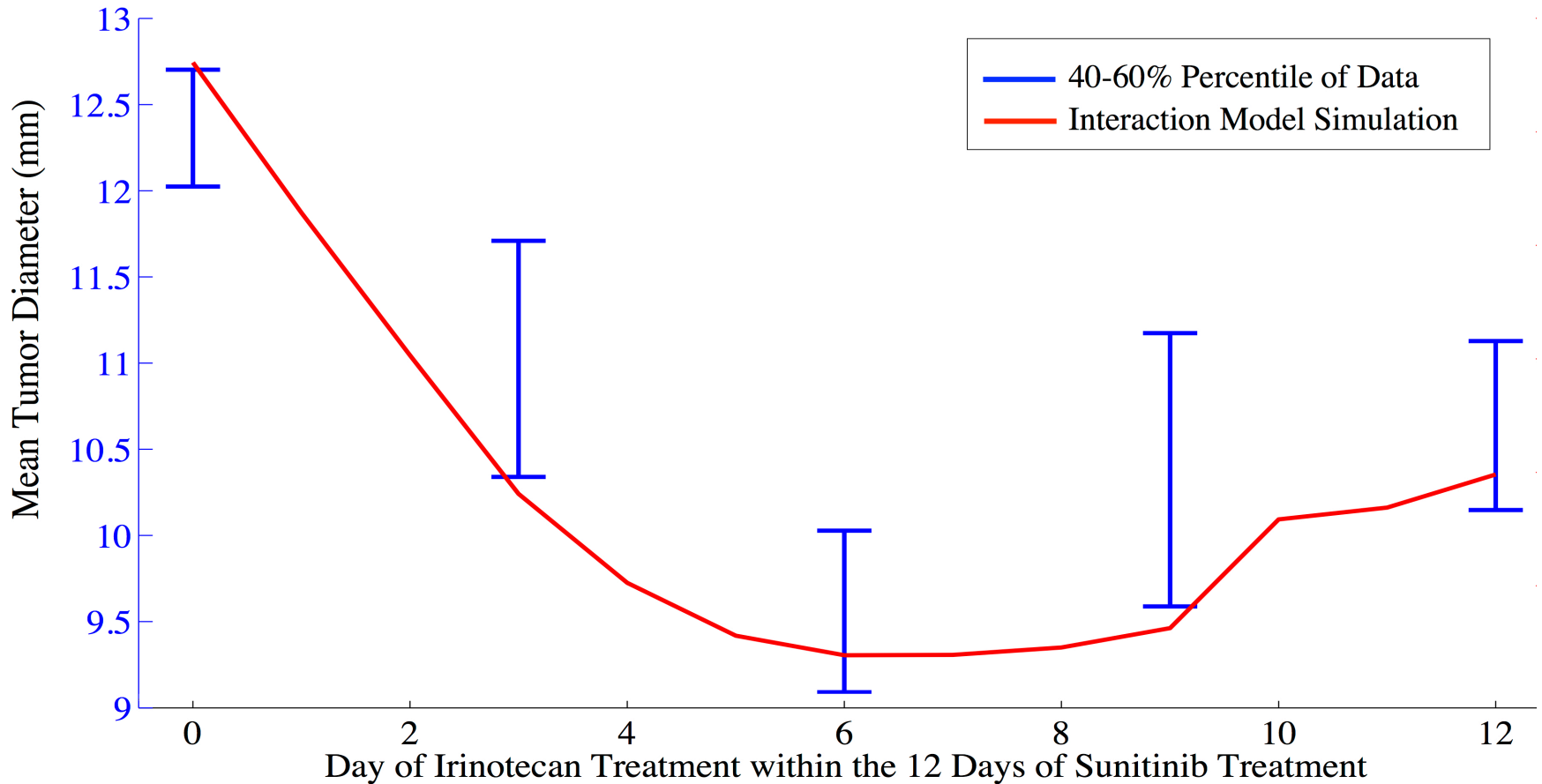$$\frac{dK}{dt} = b D_1^2 - \beta_S p_s S K$$

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

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)

Predictions for a Follow Up Experiment

Conclusions / Future Work

◆ Model has reasonable predictive capability

◆ There is a (weak) synergistic interaction between the drugs

◆ Evidence of a vascular normalization window, consistent with *[Jain Science 2005] & [Arjaans CR 2013]*

◆ Future Mathematics
  ◻ Optimal Control, Parameter Sensitivity
  ◻ Compare simulations, analytical, experimental results

Thank you!