A dynamical study of concomitant tumor resistance

S. Benzekry[1,2], C. Lamont[2], L. Hlatky[2] and P. Hahnfeldt[2]

MMLS, Bedlewo, Poland, June 2015

[1]INRIA, Bordeaux
[2]Center of Cancer and Systems Biology, Boston

What is concomitant tumor resistance?

- **Inhibition** of secondary **growth** by the primary mass
- Evidenced more than **100 years ago** *Ehrlich, 1906*
- Primary hypothesis: athrepsia (deprivation of **nutrients**)
- Other hypothesis: immune enhancement from the primary. "**Concomitant immunity**"
- 1980's: it happens in immune-deprived mice *Gorelik,, Cancer Res 1983*
- 1990's: Folkman's work on **systemic inhibition of angiogenesis (SIA)**
  O'Reilly, Folkman et al., Cell, 1994
- Others also proposed direct distant inhibition of proliferation

Post-surgery metastatic acceleration

- **Clinically** evidenced from:
  - Patients cases reports *Coffey et al., Excisional surgery for cancer cure: therapy at a cost, Lancet Oncology, 2003*
  - Bimodal relapse hazard (breast) *Retsky et al., Surgery triggers outgrowth of latent distant disease in breast cancer: an inconvenient truth?, Cancers 2010*
- Reported in numerous **animal experiments** since more than 100 years *Marie and Clunet, 1910*
- Could be due to the **surgical trauma** itself
- Experiments suggested other hypothesis, linked with **metastatic dormancy**
- **Concomitant resistance**

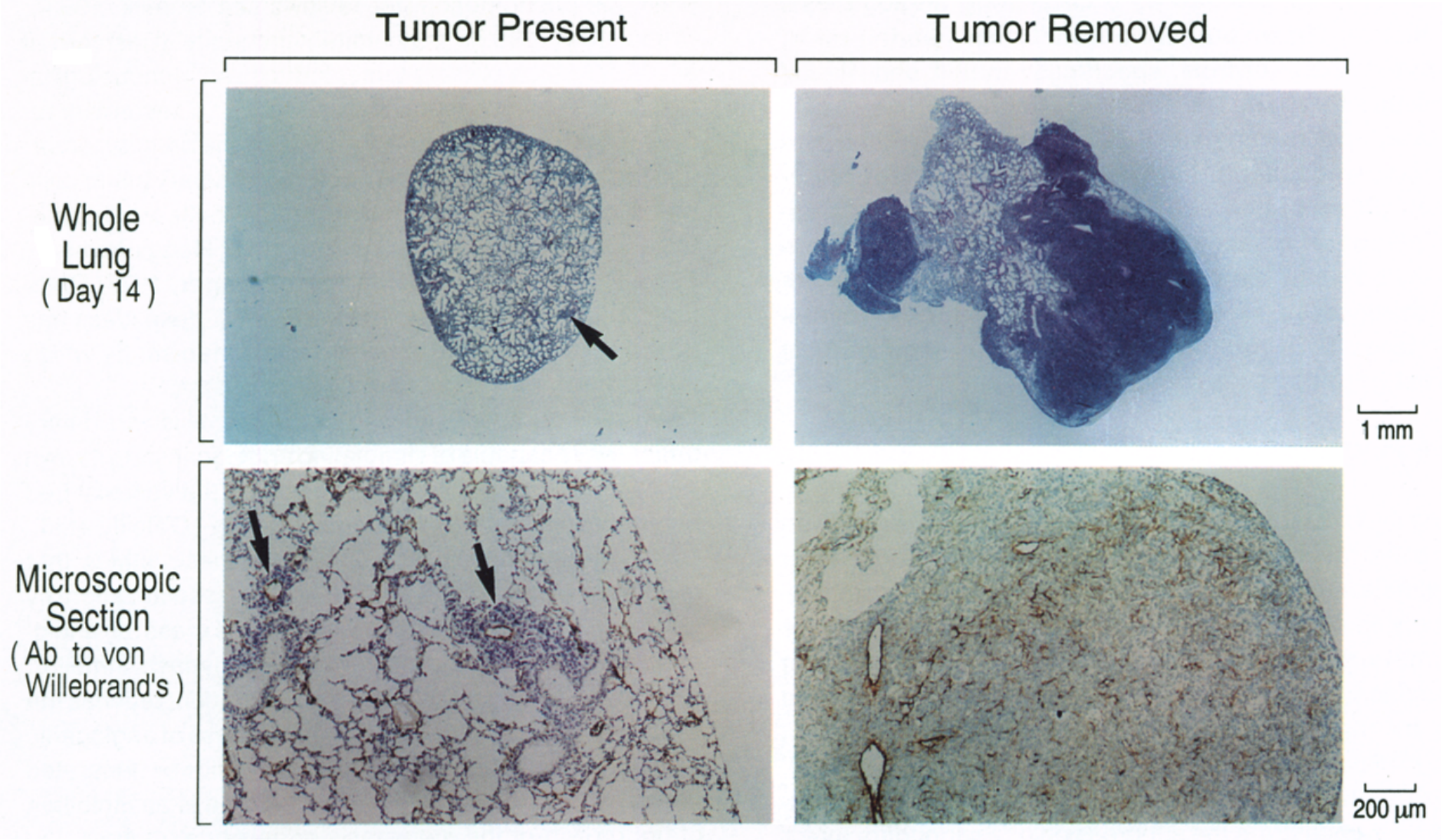


Figure 2. The Presence of a Primary Tumor Is Associated with an Inhibition of Neovascularization and Growth of Its Metastases

O'Reilly, Folkman et al., Angiostatin: A Novel Angiogenesis Inhibitor That Mediates te Suppression of Metastases by a Lewis Lung Carcinoma, *Cell 1994*

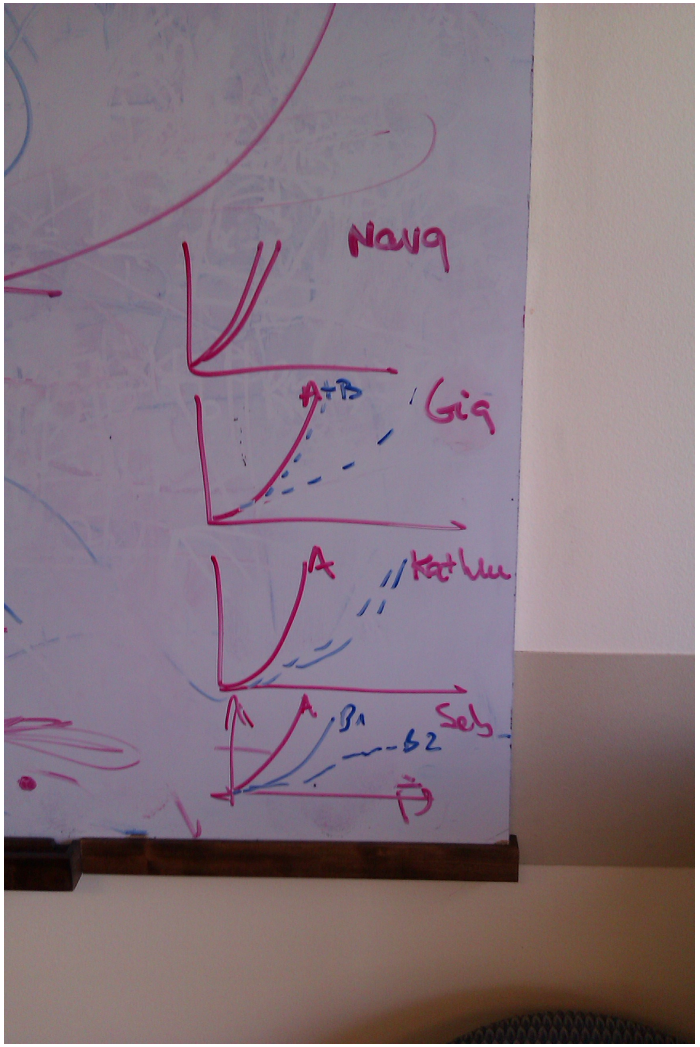
Objectives

- Are we able to give a mathematical description of the **dynamics of concomitant resistance**?
- Minimally parameterized, biologically and data-based mathematical model(s) of the process
- Test different **biological hypotheses** by confronting the (mathematical) theories to the empirical data

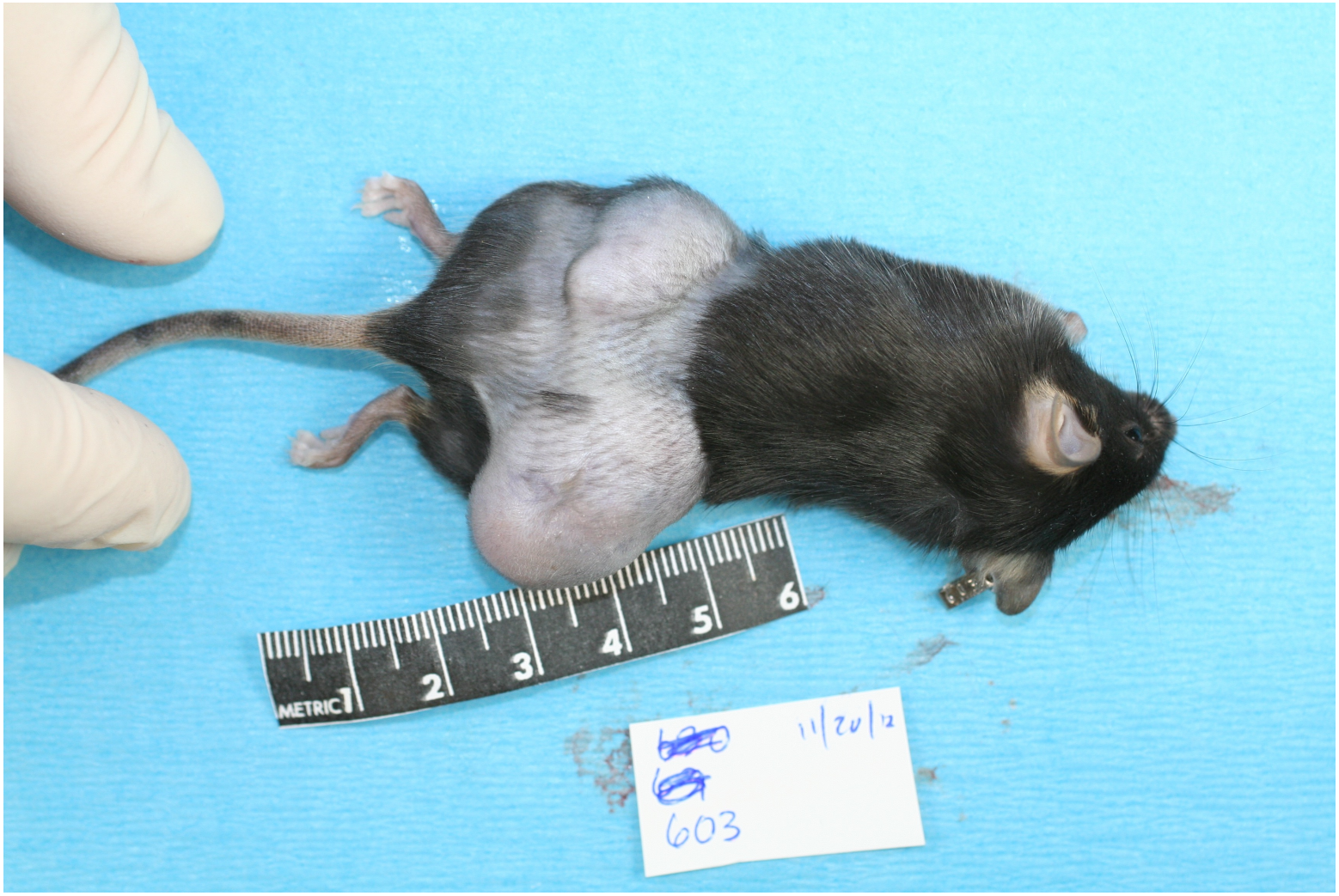
Experiment

- Injection s.c. of **two tumors** of 10^6 LLC cells in C57/BL6 mice
- Two groups
  - Control: only one tumor
  - Group S: **simultaneous** injection of cells in two different sites
- Record **tumor growth in time** at the two sites

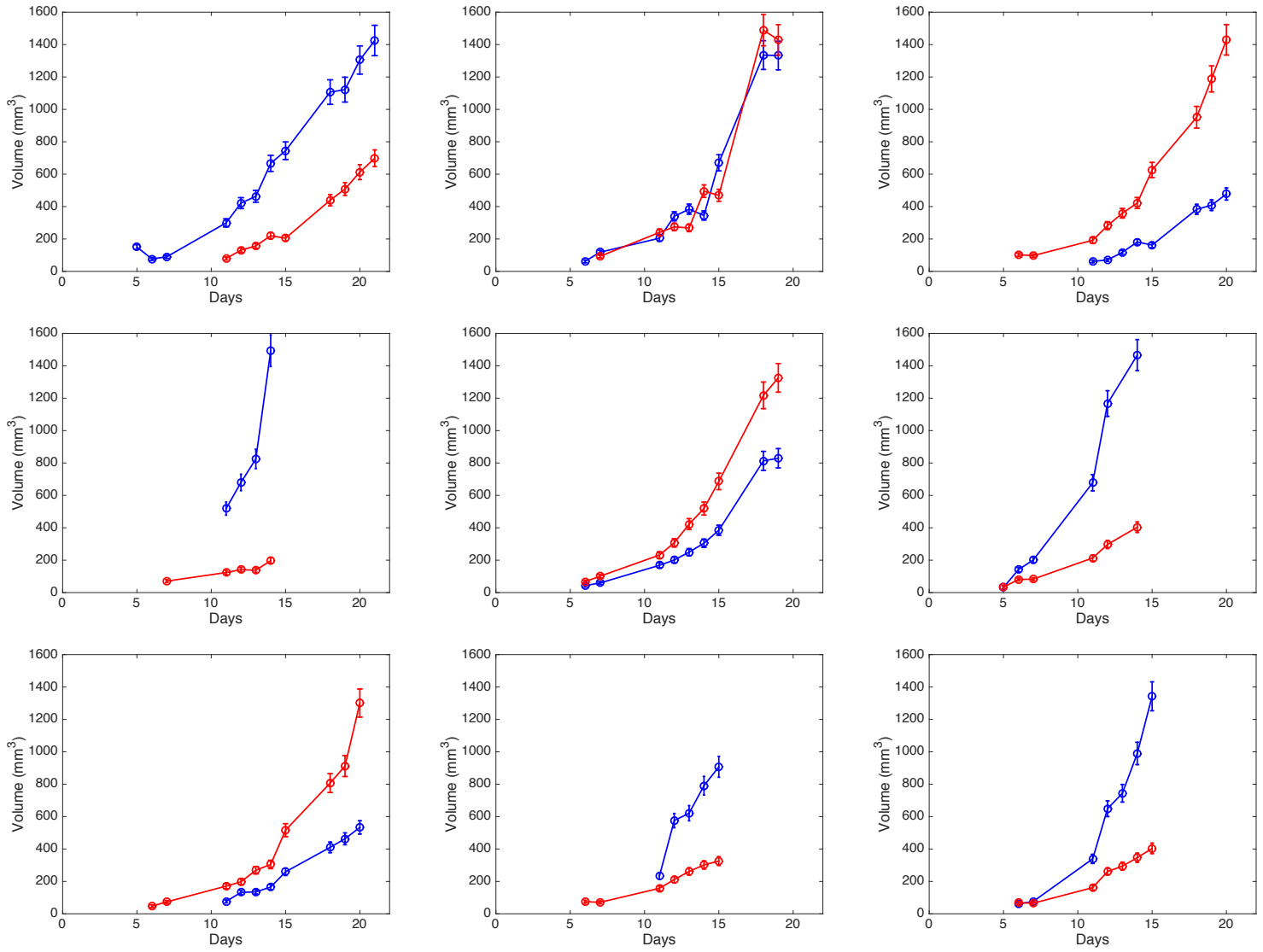
Bets



A mouse with two tumors

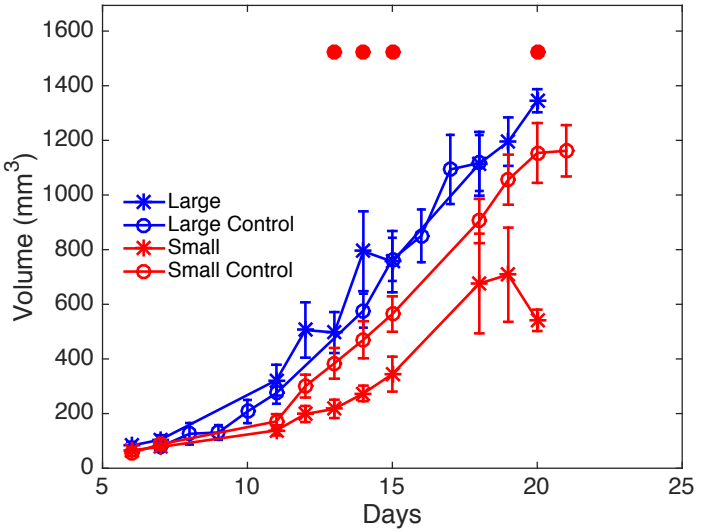


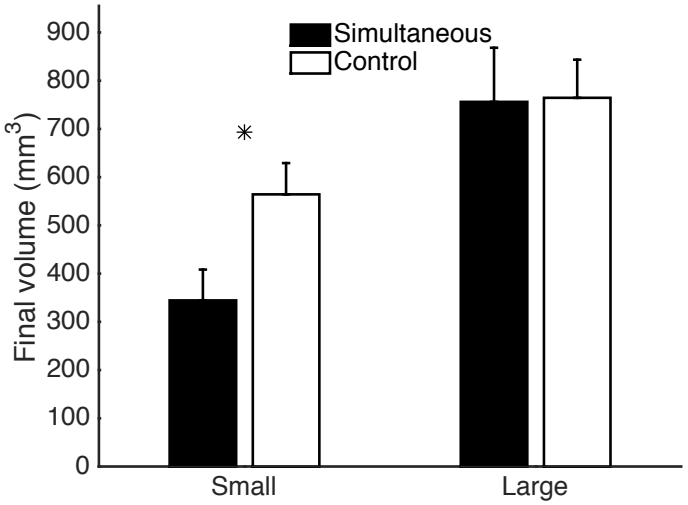
Something happens. One tumor has normal volume and the other is smaller



Statistical confirmation

- We want to test: is the **couple** ($L_S(t)$, $R_S(t)$) statistically different from a **couple** of two tumors growing independently?
- Generate an **artificial group of double independent tumors** by randomly dividing the control group (n=20) in 2 and pairing couples of growth curves from each subgroup
- Compare the large/small tumors of group S to the large/small tumors of the virtual control group

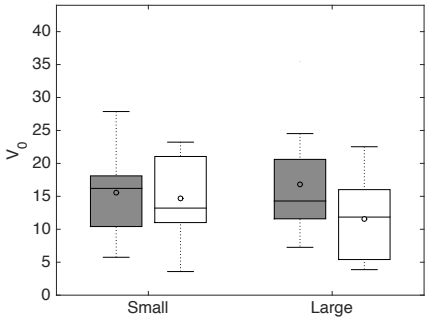


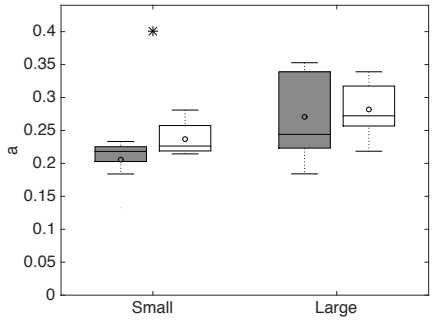


Single-tumor growth models

Exponential V_0

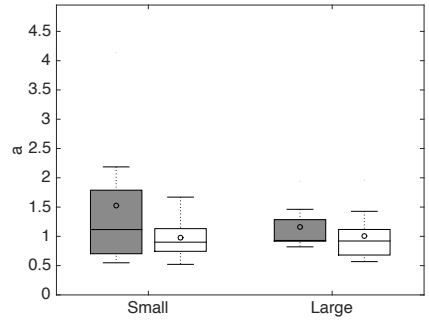
$$\begin{cases} \frac{dV}{dt} = aV \\ V(t=0) = V_0 \end{cases}$$

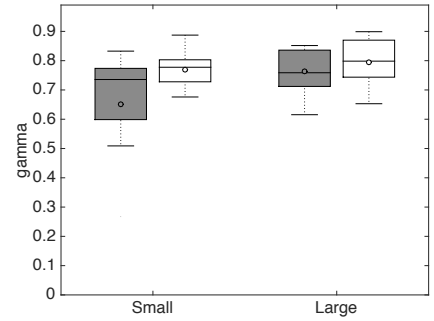




Power law

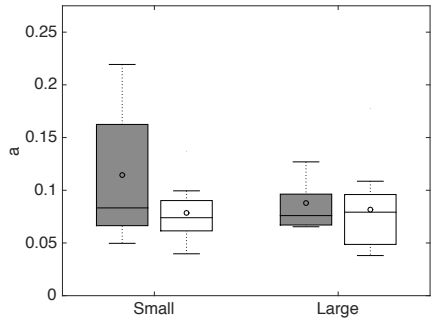
$$\begin{cases} \frac{dV}{dt} = aV^{\gamma} \\ V(t=0) = 1\ mm^3 = 10^6\ cells \end{cases}$$

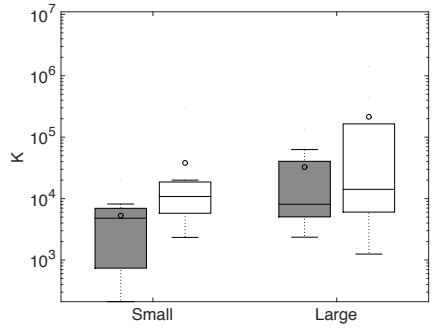




Gompertz

$$\begin{cases} \frac{dV}{dt} = aV \ln\left(\frac{K}{V}\right) \\ V(t=0) = 1\ mm^3 = 10^6\ cells \end{cases}$$





Simultaneous
Control

Two-tumors modeling

Two-tumors models

- Asymmetric inhibition

$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K}{V_1}\right), \quad V_1(t=0) = 1 \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K}{V_2}\right) - eI(V_1, V_2), \quad V_2(t=0) = 1 \end{cases}$$

was able to fit the data
but **biologically unrealistic**

Two-tumors models

- Asymmetric inhibition

$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K}{V_1}\right), & V_1(t=0) = 1 \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K}{V_2}\right) - eI(V_1, V_2), & V_2(t=0) = 1 \end{cases}$$

was able to fit the data
but **biologically unrealistic**

Two-tumors models

- Asymmetric inhibition

$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K}{V_1}\right), & V_1(t=0) = 1 \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K}{V_2}\right) - eI(V_1, V_2), & V_2(t=0) = 1 \end{cases}$$

REJECTED

was able to fit the data
but **biologically unrealistic**

- Symmetric direct inhibition

$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K}{V_1}\right) - eI_1(V_1, V_2), & V_1(t=0) = 1 \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K}{V_2}\right) - eI_2(V_1, V_2), & V_2(t=0) = V_{0,2} \end{cases}$$

  - Same growth and inhibition parameters for V_1 and V_2
  - Symmetry: $I_1(V_2,V_1)=I_2(V_1,V_2)$
  - Three possibilities for the shape of $I_1(V_1,V_2)$ shown here: V_1V_2 (1), V_2 (2), $(V_1+V_2)V_1$ (3)

Hypothesis for the origin of dissymmetry between V_1 and V_2

➡ comes from the initial number of cells that « take »

Two-tumors models

- Indirect (angiogenesis-related) inhibition

$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K_1}{V_1}\right), & V_1(t=0) = 1 \\ \frac{dK_1}{dt} = bV_1 - dV_1^{2/3}K_1 - eI_1(V_1, V_2), & K_1(t=0) = K_0 \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K}{V_2}\right), & V_2(t=0) = V_{0,2} \\ \frac{dK_2}{dt} = bV_2 - dV_2^{2/3}K_2 - eI_2(V_1, V_2) & K_2(t=0) = K_0 \end{cases}$$

- Based on the Hahnfeldt model

  Hahnfeldt et al., Cancer Res, 1999 with

  dynamic carrying capacity *K*

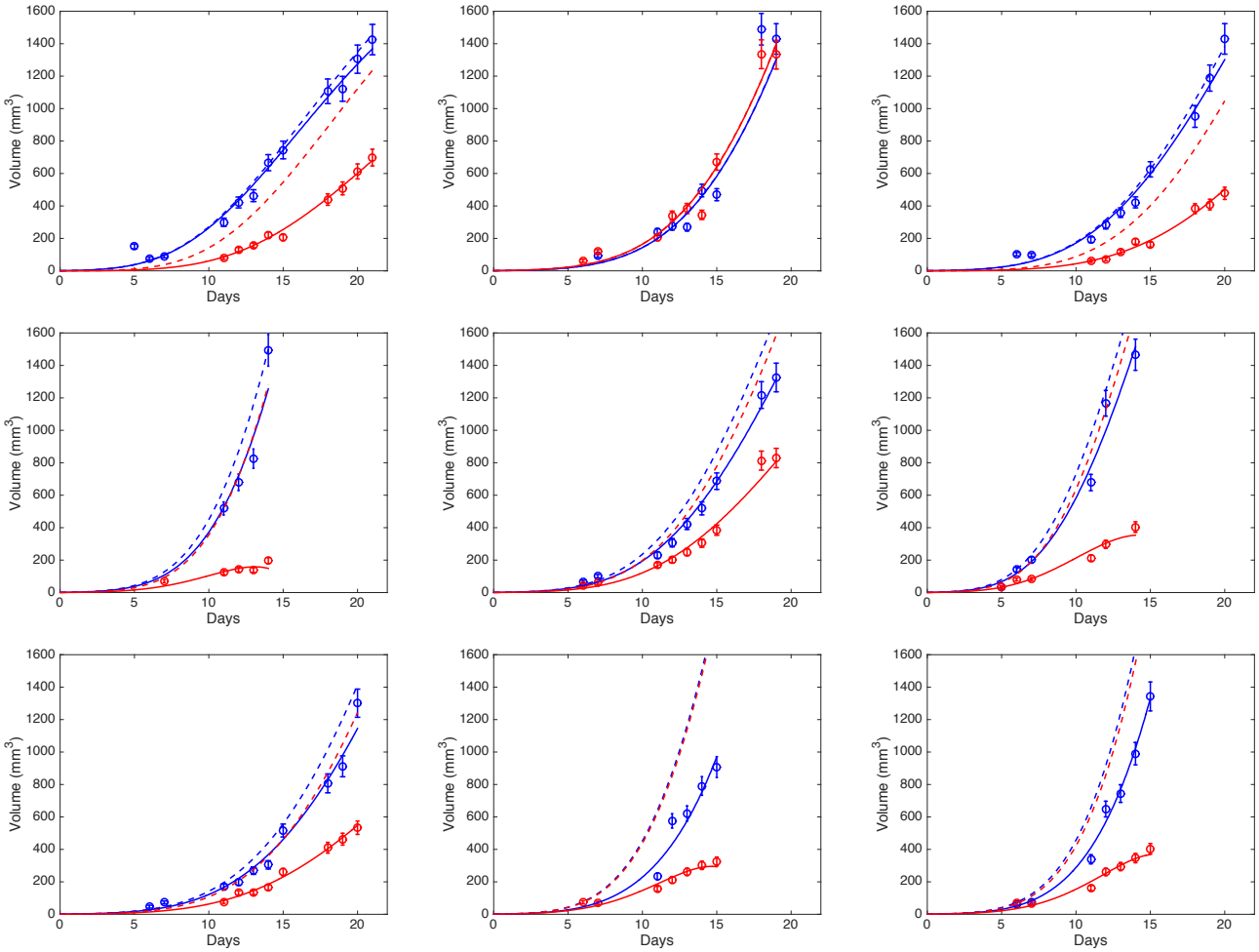
- Parameters *d* and K_0 were fixed

- Competition (athrepsia hypothesis)

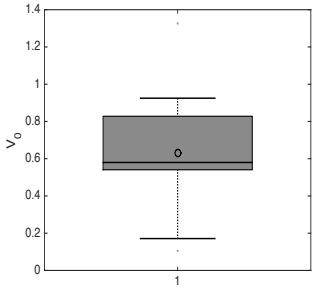
$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K}{V_1+V_2}\right), & V_1(t=0) = 1 \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K}{V_1+V_2}\right), & V_2(t=0) = V_{0,2} \end{cases}$$

- One parameter (degree of freedom) less than the other models

Direct inhibition (2) fit

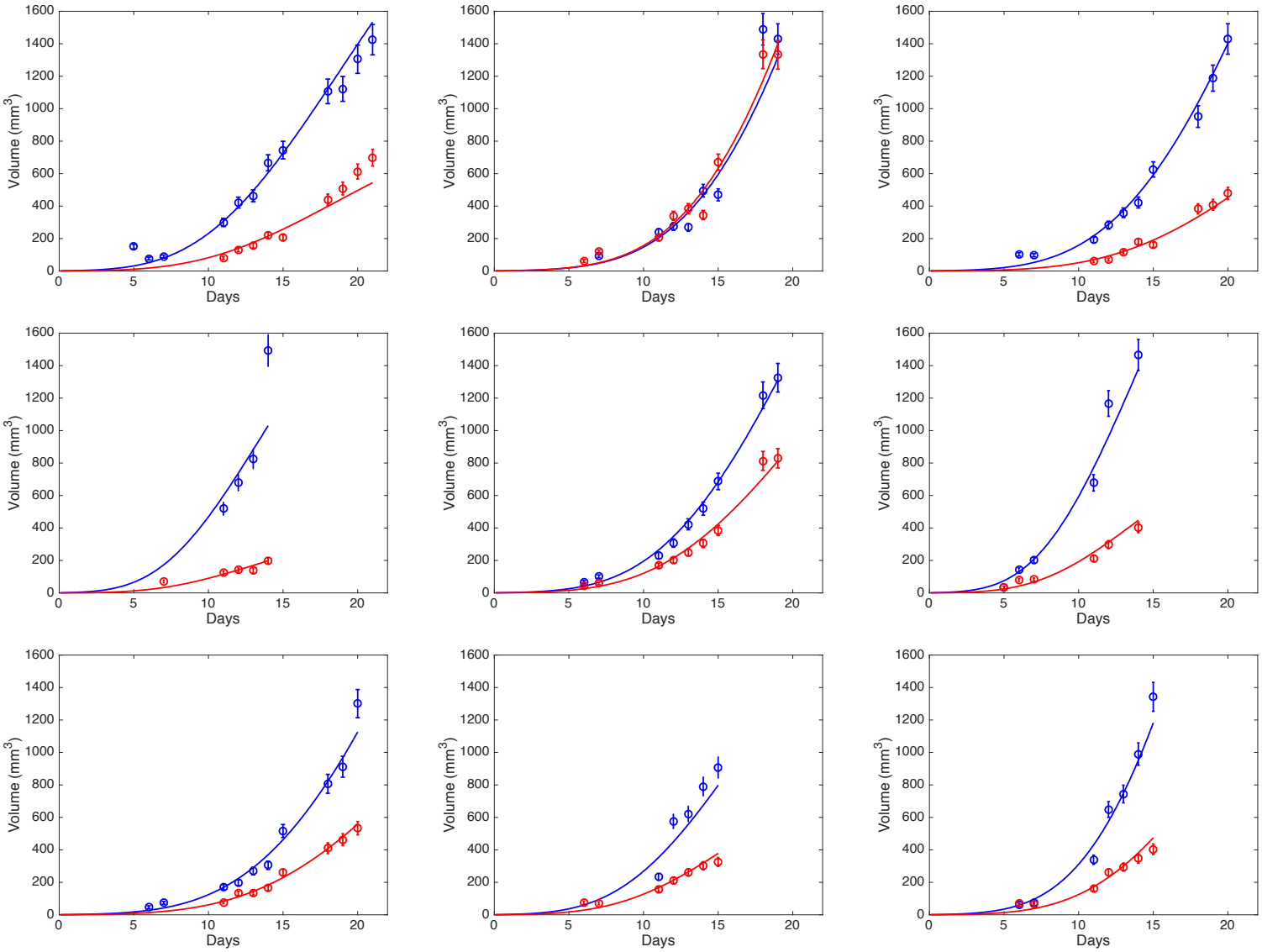


Model
Model with e=0



- Gives **satisfactory fit**
- Behavior when $e = 0$ is realistic
- Kinetic differences between V_1 and V_2 are **mostly due to inhibition** (and not to difference in $V_{0,2}$)

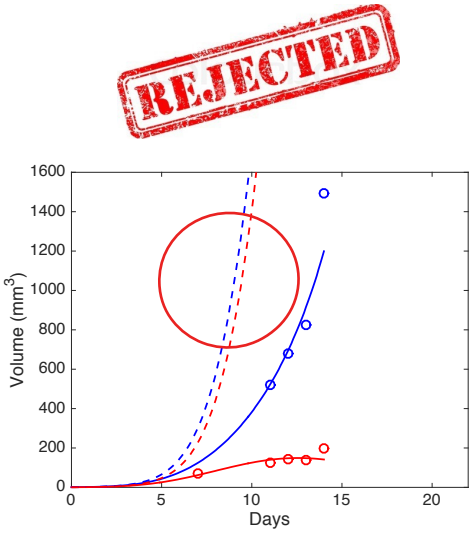
Competition model



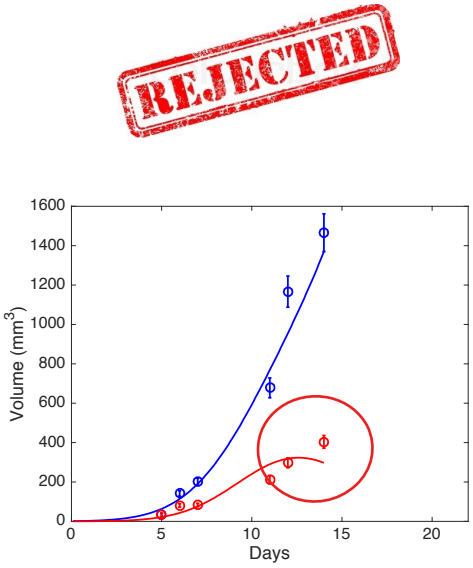
- Also gives **satisfactory fit** (and thus, possible explanatory hypothesis)

Models able to fit

- Criterias for rejection of a model:
  - Inaccurate visual goodness-of-fit
  - Yielding biologically unrealistic behavior when *e = 0*



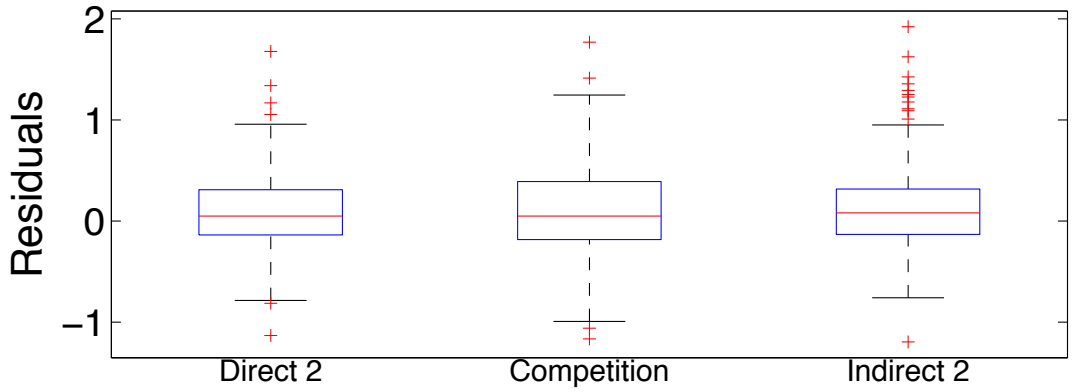
Index	1	2	3
I_1	V_2V_1	V_2	$(V_1+V_2)V_1$
I_2	V_1V_2	V_1	$(V_1+V_2)V_2$
Direct Inhibition	x	o	x
Indirect Inhibition	x	o	x
Competition	o		



Goodness-of-fit metrics

Model	SSE	AIC	RMSE	R2	p > 0.05	#
Direct 2	**0.183(0.102 - 0.388)[1]**	**-17.6(-31.2 - -6.08)[1]**	**0.428(0.324 - 0.63)[1]**	**0.973(0.934 - 0.991)[1]**	100	4
Competition	0.241(0.102 - 0.398)[2]	-15.8(-33 - -3.96)[2]	0.492(0.326 - 0.635)[2]	0.956(0.871 - 0.99)[3]	100	3
Indirect 2	0.273(0.151 - 0.506)[3]	-10.9(-24.1 - -1.58)[3]	0.523(0.393 - 0.715)[3]	0.967(0.934 - 0.986)[2]	100	4

SSE = Sum of Squared Errors, AIC = Akaike Information Criterion, RMSE= Root Mean Squared Errors



Parameter values/identifiability

Model	Par.	Unit	Median value (CV)	NSE (%)	95% CI
Direct 2	a	-	0.0957 (21.9)	11.3	
	K	-	1.02e+04 (90.2)	46.5	
	$V_{0,2}$	-	0.58 (64.4)	8.9	
	e	-	0.048 (91.5)	2.35	**(0.044, 0.052)**
Competition	a	-	0.0988 (28.8)	11.2	
	K	-	8.52e+03 (82.2)	42.1	
	$V_{0,2}$	-	0.402 (63.1)	12.5	
Indirect 2	a	-	0.206 (35.8)	7.81	
	b	-	18.7 (32.1)	13.2	
	$V_{0,2}$	-	0.685 (45.3)	11.8	
	e	-	4.07 (57.8)	1.36	**(3.96, 4.18)**

NSE = Normalized Standard error

CV = Coefficient of Variation

Summary

- In mice bearing two tumors implanted simultaneously, **tumor growth is suppressed in one of the two tumors**
- Single tumor growth models were not able to explain the dynamical discrepancies
- New quantitative and **identifiable** mathematical models of tumor-tumor growth interactions were developed and able to match the data. **20+ models tested**
- Possible explanation of dissymmetry: difference in number of cells that take
- Based only on tumor growth kinetics we could not clearly discriminate between **three possible theories**: competition, direct or indirect (angiogenesis) inhibition
- But we could discriminate the shape of the inhibition term: $I_1(V_1, V_2) = V_2$