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Mathematical Modeling of Tumor-Tumor Distant Interactions Supports a Systemic Control of Tumor Growth

S. Benzekry

Inria team MONC, Bordeaux

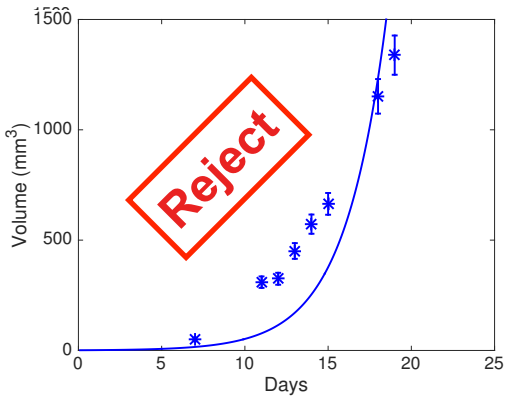
3rd Mathematical Biology Modeling days of Besançon

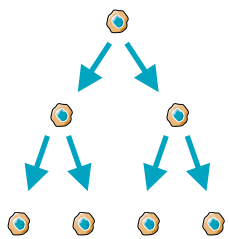
June 22, 2018

Tumor growth

What are **minimal** biological processes able to recover the **kinetics** of (experimental) tumor growth?

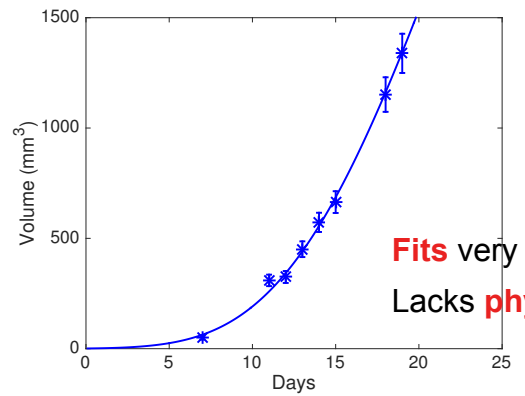
Exponential





$$\frac{dV}{dt} = aV$$

Gompertz

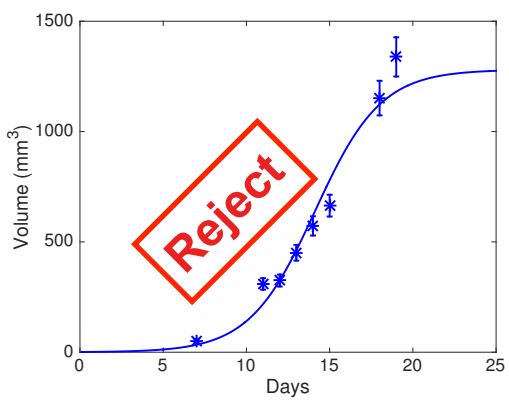


$$\frac{dV}{dt} = \alpha e^{-\beta t} V$$

Fits very well

Lacks **physiological** interpretation

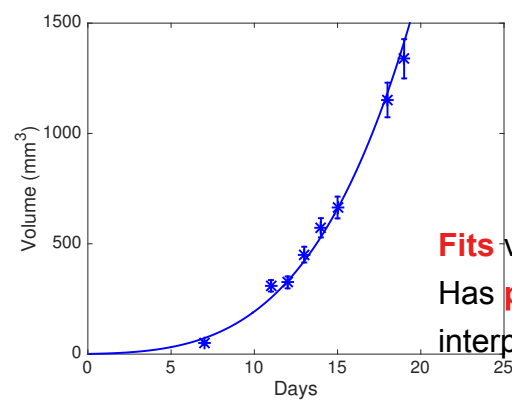
Logistic



Competition

$$\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right)$$

Power law



$$\frac{dV}{dt} = \alpha V^{\gamma}$$

Fits very well

Has **physiological** interpretation

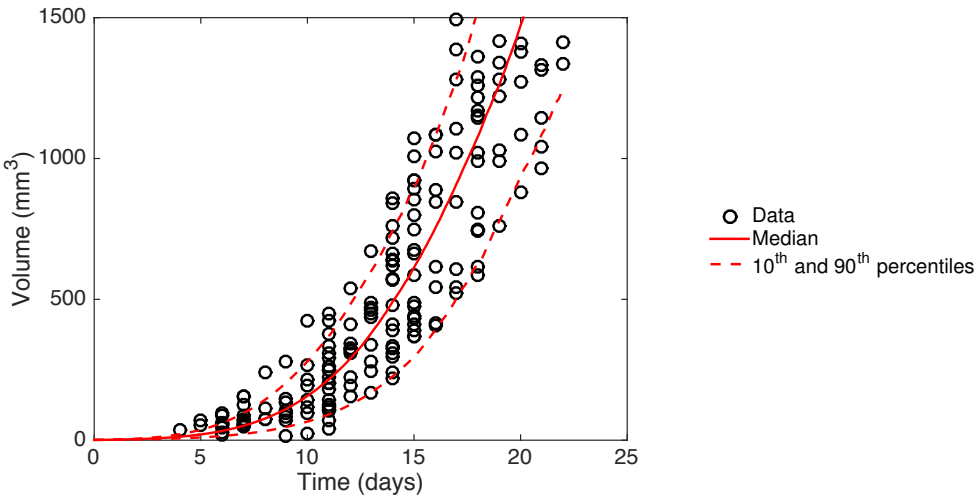
Benzekry et al., PloS Comp Biol, 2014

Population approach and its use for prediction

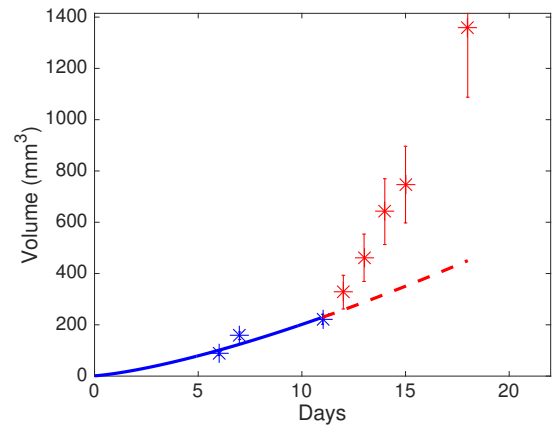
Nonlinear mixed-effects statistical modeling

$$y_j^i = M(t_j^i, \theta^i) + \varepsilon_j^i, \quad \varepsilon_j^i \sim \mathcal{N}(0, \sigma_j^i)$$

$$\theta^1, \cdots, \theta^N \sim \mathcal{LN}(\theta_{pop}, \theta_\omega), \quad \theta_{pop} \in \mathbb{R}^P, \theta_\omega \in \mathbb{R}^{P \times P}$$

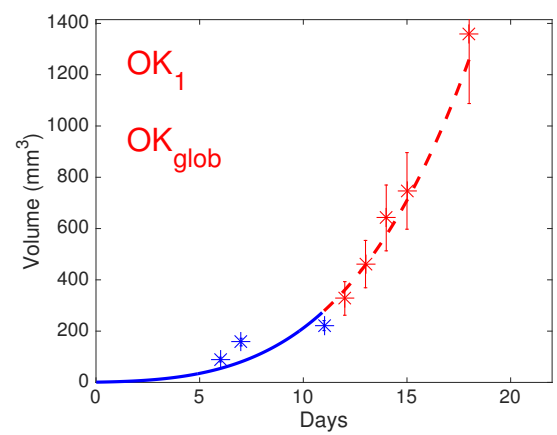


No a priori



With a priori

$$l(\theta^i) = \sum_{j=1}^{J^i} \frac{\left(y_j^i - M(t_j^i, \theta^i)\right)^2}{2\sigma^2} + \sum_{p=1}^{P} \frac{\left(\theta_p^i - \theta_{pop,p}\right)^2}{\theta_{\omega,p}^2} + C$$



Benzekry et al., PloS Comp Biol, 2014

Concomitant tumor resistance

- **Inhibition** of secondary **growth** by a primary mass
- Critical clinical implications in terms of **post-surgery metastatic acceleration**

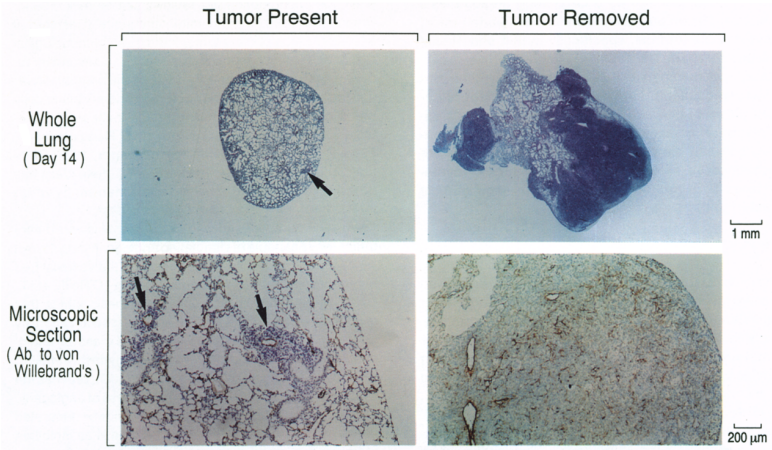


Figure 2. The Presence of a Primary Tumor Is Associated with an Inhibition of Neovascularization and Growth of Its Metastases

O'Reilly et al. (Folkman), Cell, 1994

Primary hypothesis: athrepsia (deprivation of **nutrients**)

Ehrlich, 1906

Non-immunogenic **systemic factors**

Dewys, Cancer Res 1972

Cytostatic circulating factor

Ruggiero et al., Br J Cancer 1985

Concomitant **immunity**

Bashford, 1908

CR occurs in **immune-deprived** mice

Gorelik, Int J Cancer 1981

Systemic inhibition of **angiogenesis**

O'Reilly et al. (Folkman), Cell 1994

Questions and experiment

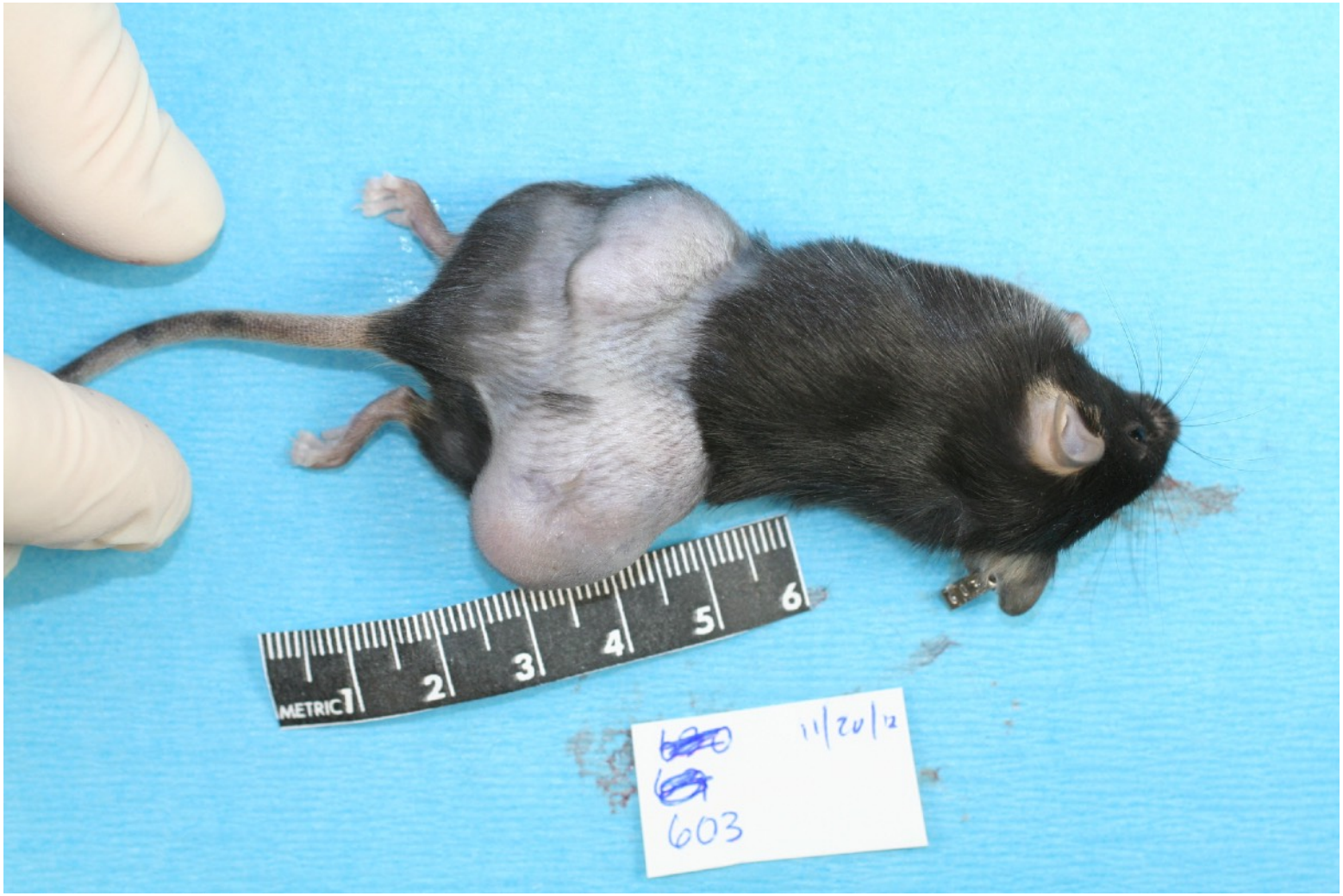
Questions

- **Quantitatively** distinguish between qualitatively valid **theories** of tumor-tumor interactions
- Establish and validate a **minimal model able to simulate tumor-tumor interactions**

Experiment

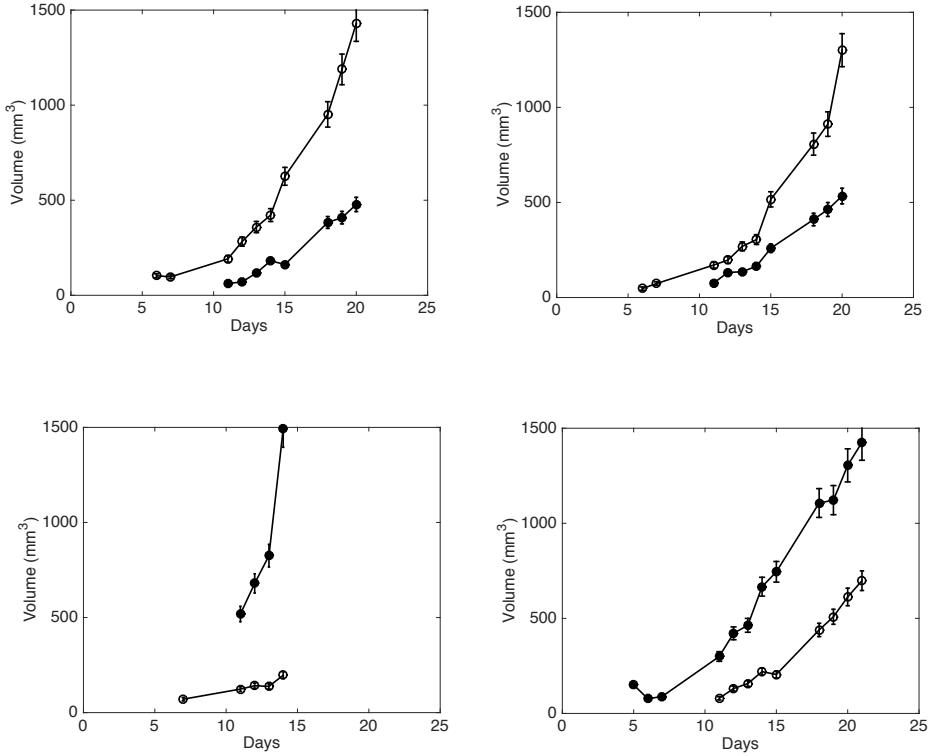
- Injection s.c. of **two tumors** of 10^6 LLC cells in C57/BL6 mice
- Two groups
  - Control: only one tumor
  - Group S: **simultaneous** injection of cells in two different sites

A mouse with two tumors

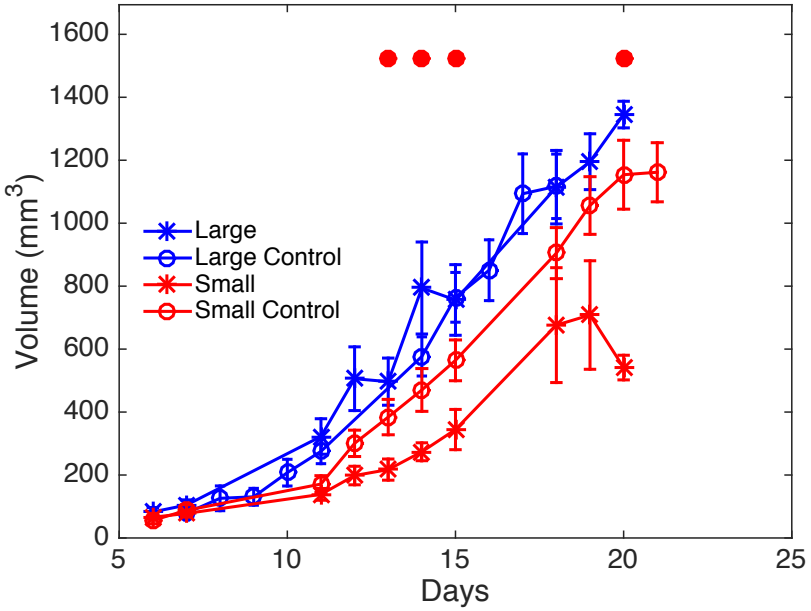


One tumor has normal growth and the other is suppressed

Individual growth kinetics



Small/Large in two-tumor bearing animals VS artificially paired small/large controls

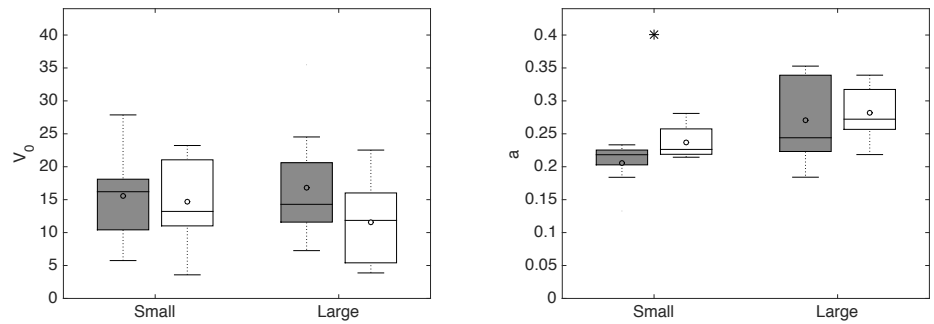


Benzekry et al., Cancer Res, 2017

Single-tumor growth models

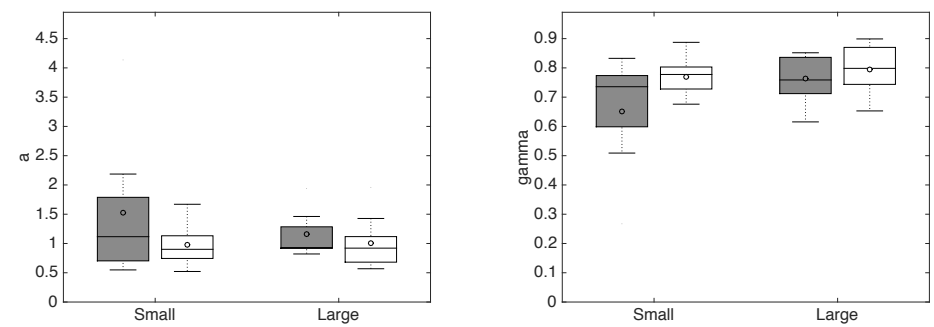
Exponential V0

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



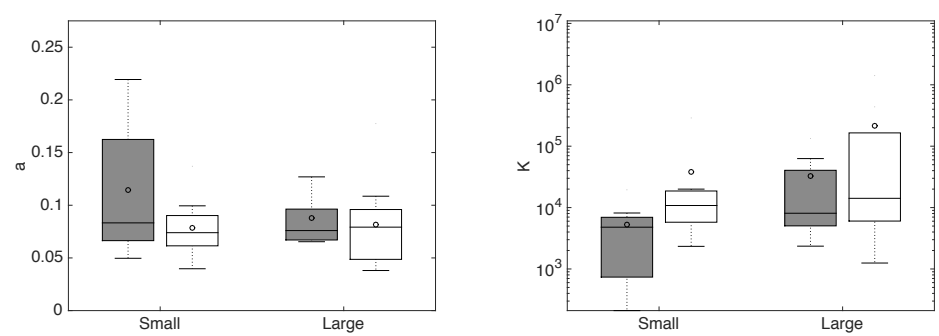
Power law

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



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 models

- Requirements:
  - **Symmetry:** same parameters for tumor 1 and tumor 2
  - Should resume to **single tumor growth** in the absence of the other tumor
- Main assumption for the difference between the two tumors: difference in **the initial take** ($V_{0,1}$ = 1, $V_{0,2}$ = 0.75)
- Difference in the growth kinetics should not result from difference in V_0
- Model selection (rejection) criteria: goodness-of-fit + parameter identifiability

Competition

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

Angiogenesis inhibition

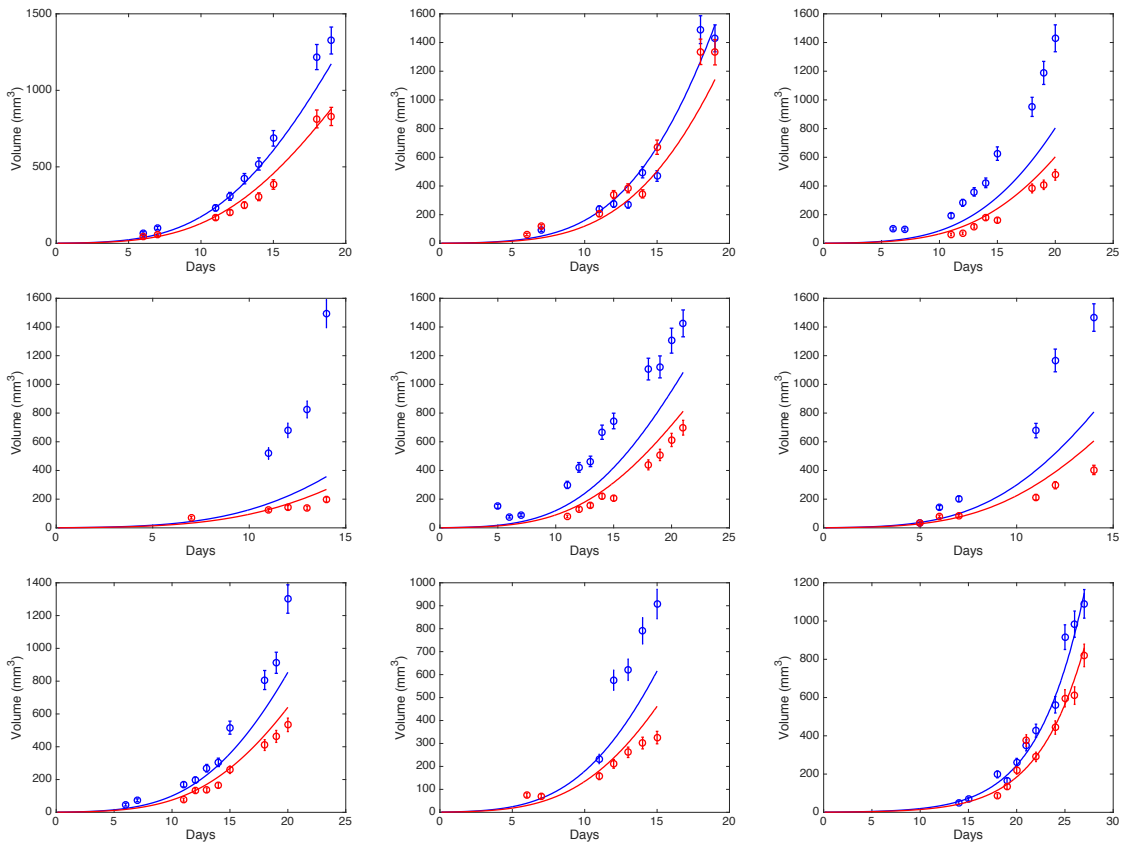
$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K_1}{V_1}\right), & V_1(t=0) = V_{0,1} \\ \frac{dK_1}{dt} = bV_1 - dV_1^{\frac{2}{3}}K_1 - eV_2 1_{K_1>K_0}, & K_1(t=0) = K_0 \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K_2}{V_2}\right), & V_2(t=0) = V_{0,2} \\ \frac{dK_2}{dt} = bV_2 - dV_2^{\frac{2}{3}}K_2 - eV_1 1_{K_2>K_0}, & K_2(t=0) = K_0 \end{cases}$$

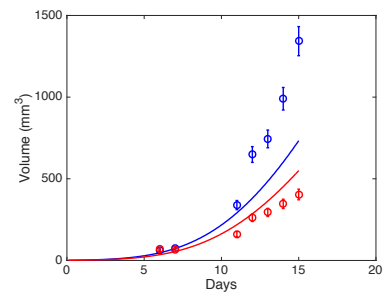
Proliferation inhibition

$$\begin{cases} \frac{dP_1}{dt} = \alpha P_1 - (\beta P_1 + \gamma(P_1+P_2))1_{P_1>0}, & P_1(t=0) = V_{0,1} \\ \frac{dQ_1}{dt} = \beta P_1 + \gamma(P_1+P_2), & Q_1(t=0) = 0 \\ \frac{dP_2}{dt} = \alpha P_2 - (\beta P_2 + \gamma(P_1+P_2))1_{P_2>0}, & P_2(t=0) = V_{0,2} \\ \frac{dQ_2}{dt} = \beta P_2 + \gamma(P_1+P_2), & Q_2(t=0) = 0 \end{cases}$$

Benzekry et al., Cancer Res, 2017

The competition model did not fit

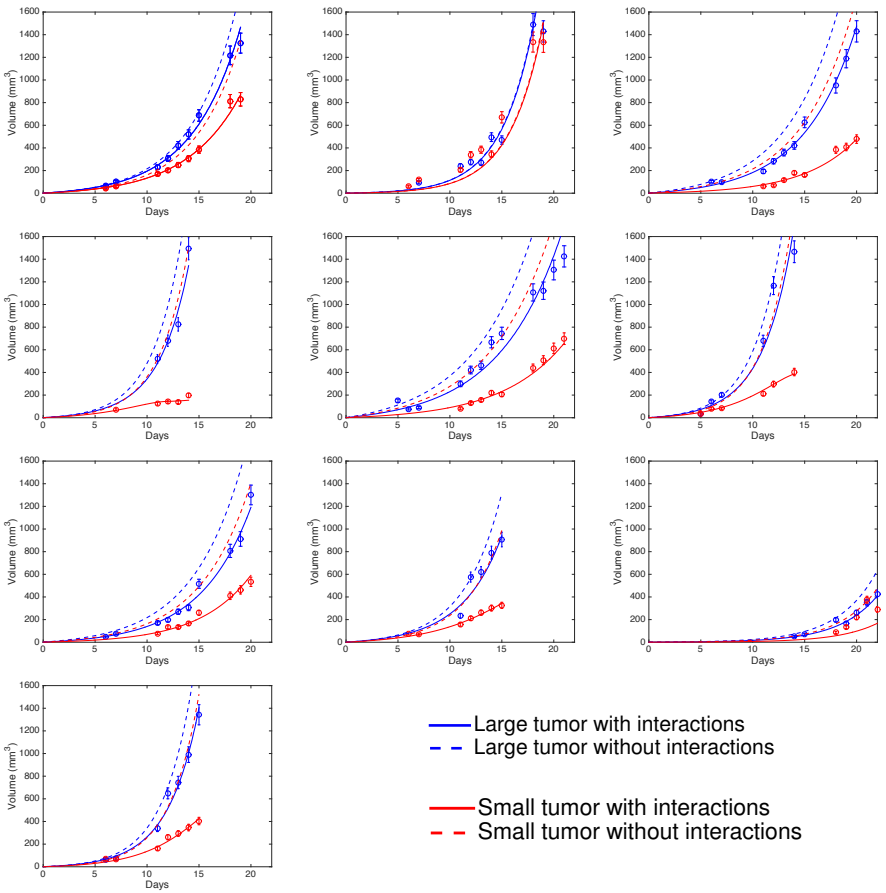


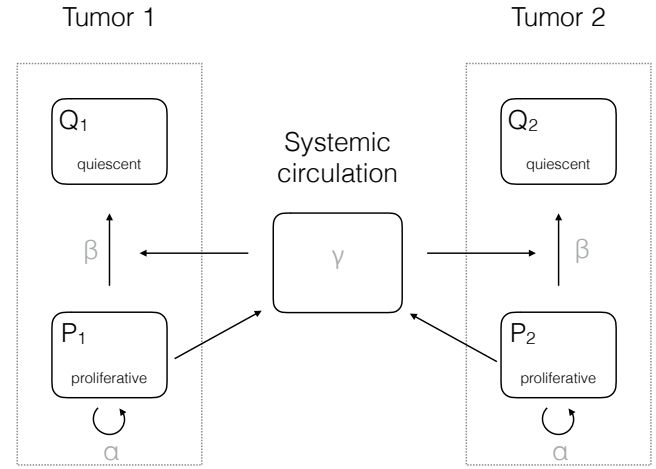


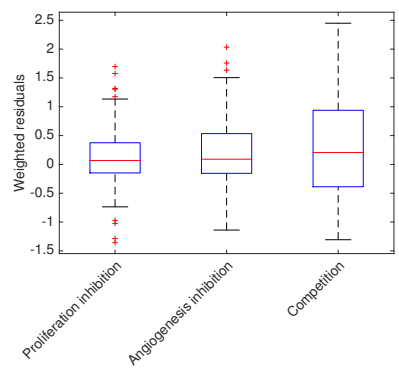
$$\begin{cases} \dfrac{dV_1}{dt} = aV_1 \ln\left(\dfrac{K}{V_1 + V_2}\right), & V_1(t=0) = V_{0,1} \\ \dfrac{dV_2}{dt} = aV_2 \ln\left(\dfrac{K}{V_1 + V_2}\right), & V_2(t=0) = V_{0,2} \end{cases}$$

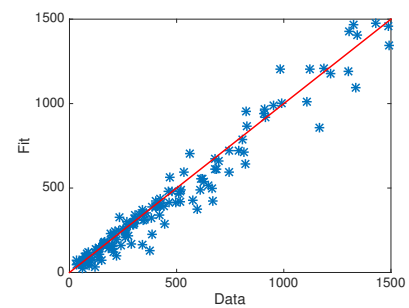
Benzekry et al., Cancer Res, 2017

The « inhibition of proliferation » model fitted best









Model	Par.	Unit	Median value (CV)	RSE (%)
Proliferation inhibition	α	day^{-1}	5.77 (67.4)	17.5
	β	day^{-1}	5.07 (49.3)	21.2
	γ	-	0.074 (2.69e+03)	2.47

Model	SSE	AIC	RMSE	R2	#
Proliferation inhibition	**0.204(0.0319 - 0.461)**[1]	**-14.2(-54 - -8.28)**[1]	**0.453(0.182 - 0.688)**[1]	**0.961(0.902 - 0.987)**[1]	3
Angiogenesis inhibition	0.336(0.154 - 0.772)[2]	-5.07(-27.5 - 5.67)[2]	0.588(0.4 - 0.891)[2]	0.957(0.645 - 0.986)[2]	3
Competition	0.666(0.141 - 2.2)[3]	0.71(-33.2 - 13.1)[3]	0.828(0.383 - 1.5)[3]	0.694(-0.0757 - 0.964)[3]	2

Summary

- « Proliferation inhibition » model was able to adequately fit the data and provides with a **simple** (3 parameters), **identifiable, biologically grounded model**.
- « Angiogenesis inhibition » model was **also able** to fit the data, but to a lesser extent.
- « Competition model » was not able to fit the data, thus allowing to **reject this theory/model** as being sufficient to explain the data.
- Our model gives a dynamical valid explanation of the **CR paradox** (= if a tumor is able to inhibit the growth of a distant one, how can it grow at the same time?)

Perspective: integrate this model for tumor-tumor interactions into the **organism-level** for the dynamics of the metastatic population

Conclusion

- A general modeling framework for **modeling metastases**

- Simplified model (growth + dissemination) able to describe available clinically relevant **preclinical data** of dynamics of total metastatic burden

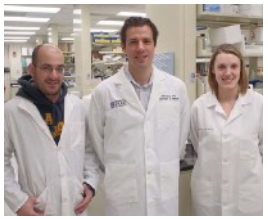
- **Quantitative** exploration of classical theories for metastatic colonization and **tumor-tumor interactions** and st

- A **patient-specific key parameter μ** was critical in the quantification of patient-specific metastatic aggressiveness

Acknowledgements

- Preclinical data of ortho-surgical animal models of metastases

  J. Ebos, M. Mastri, Roswell Park Cancer Institute, Buffalo, NY, USA



- One and two-tumors study

  Center of Cancer and Systems Biology, Boston, MA, USA
  C. Lamont, P. Hahnfeldt, L. Hlatky

- Biology of the kidney metastases to the lung

  L. Cooley, W. Souleyreau, A. Bikfalvi
  LAMC, Inserm, Bordeaux, FR

  E. Ribot
  RMSB, CNRS

Thank you for your attention!