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Mathematical Modeling and Prediction of Clinical Metastasis

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► **To cite this version:**

Sébastien Benzekry. Mathematical Modeling and Prediction of Clinical Metastasis. Mathematical Challenges in the Analysis of Continuum Models for Cancer Growth, Evolution and Therapy, Nov 2018, Oaxaca, Mexico. hal-01969108

HAL Id: hal-01969108

<https://inria.hal.science/hal-01969108>

Submitted on 3 Jan 2019

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Mathematical Modeling and Prediction of Clinical Metastasis

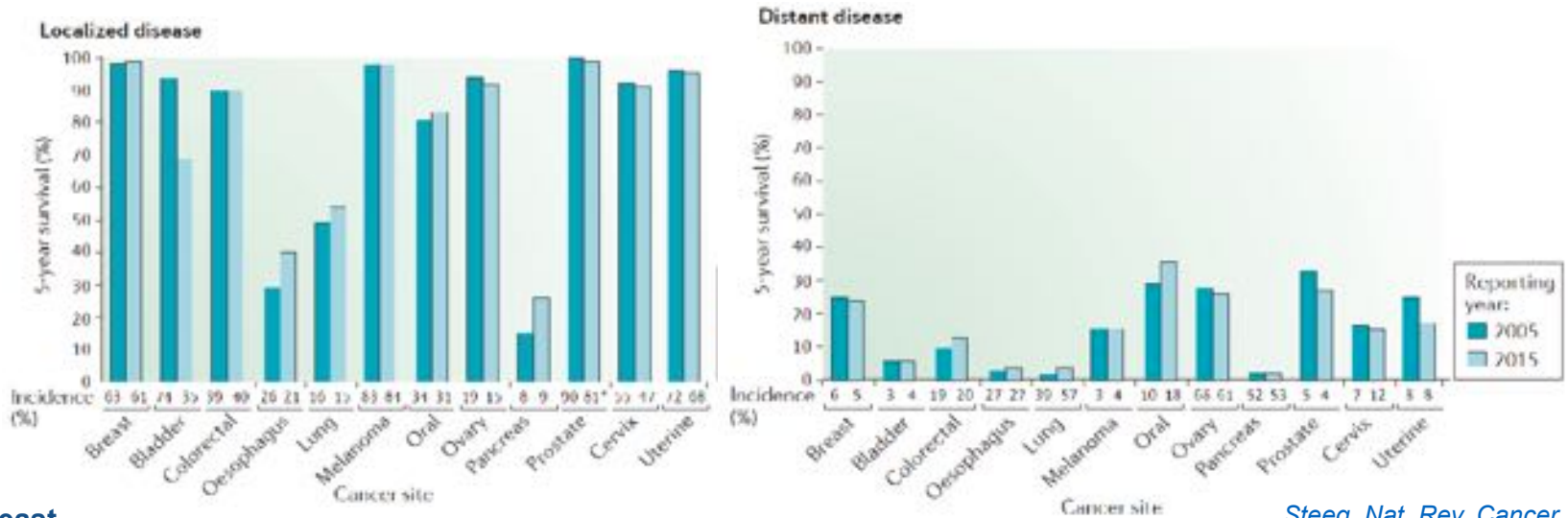
S. Benzekry

BIRS - CMO workshop
Oaxaca, Mexico

November 27, 2018

Metastasis (μετά = beyond, στάσιζ = place)

- Metastases are the **main cause of death** (>90%) from solid cancers *Lambert and Weinberg, Cell, 2017*



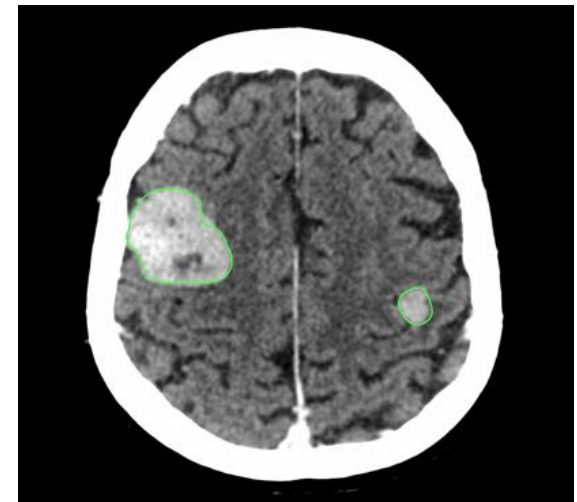
Steeg, Nat. Rev. Cancer, 2016

Breast

- 94% of cases are local or regional at diagnosis but 30% will relapse *Pollard, N Eng J Med, 2016*
- Estimate the amount of **residual distant disease** at diagnosis in order to **personalize** the adjuvant (chemo)-therapy
- Avoid unnecessary, heavy **toxicities**

Lung

- 57% of cases are metastatic
- Decide whether to use **whole brain radiation therapy** or just (stereotactic) surgery
- Avoid cognitive impairment of the patient



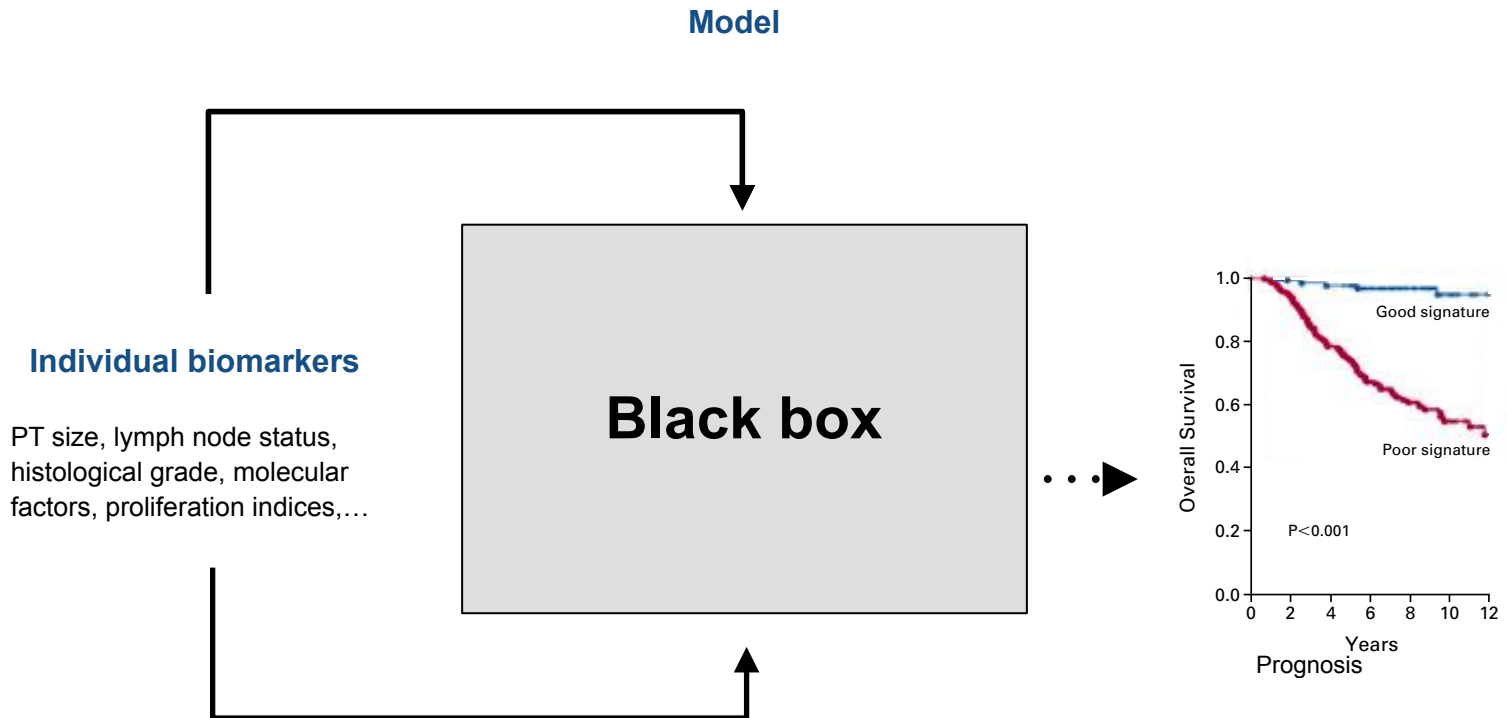
Institut Bergonié, Bordeaux

Some biological questions of interest to mathematical modeling

- **Minimal** model of metastatic dissemination and colonization able to reproduce the **systemic dynamics** of a solid cancer disease
- Investigate the relevance of several processes:
 - (early VS late event *Klein, Nat Rev Cancer, 2009*)
 - (metastases of metastases *Gudem et al., Nature, 2015*)
 - (dormancy *Chambers and Groom, Nat Rev Cancer, 2002*)
 - **tumor-tumor interactions**
 - (cancer-immune interactions)
 - **differential effect of therapy** *Ebos et al. (Kerbel), Cancer Cell, 2009*
 - ((pre-)metastatic niche *Peinado et al. (Lyden), Nature, 2005*)
 - systemic inhibition of angiogenesis *O'Reilly et al. (Folkman), Cell, 1990s*
 - (self-seeding *Norton, Nat Med, 2001*)

Metastasis: a forgotten major player in modeling

- The majority of mathematical modeling efforts in oncology are focused on (primary) **tumor growth**
- Existing models are based on a statistical, **biologically agnostic**, prediction of survival



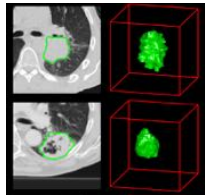
Metastasis: a forgotten major player in modeling

- The majority of mathematical modeling efforts in oncology are focused on (primary) **tumor growth**
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Clinical data

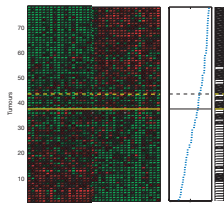
PT size, lymph node status, histological grade, molecular factors, proliferation indices,....

Imaging data (Radiomics)



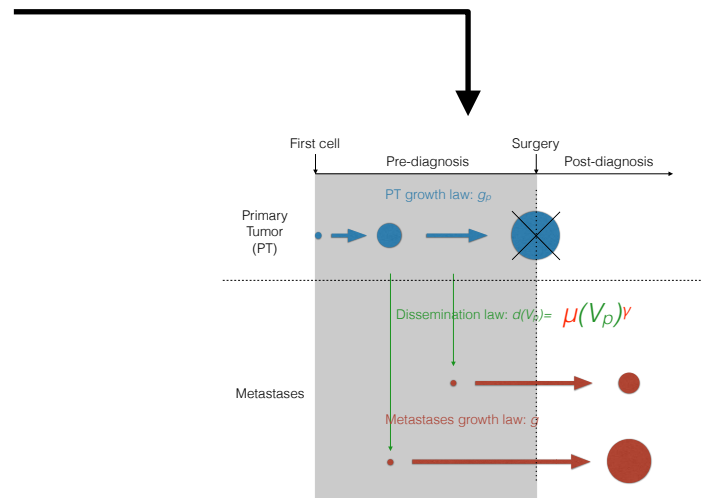
Aerts et al., Nat Commun, 2014

Molecular data (-omics)



van't Veer et al., Nature, 2002

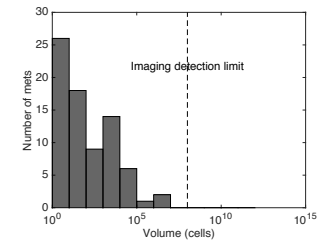
Biologically-based model



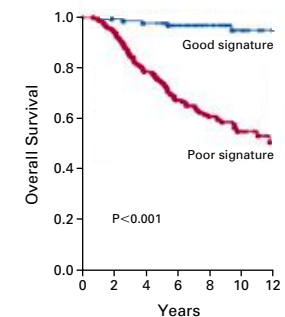
$$\frac{dV_p}{dt} = (\alpha_p - \beta_p \ln(V_p)) V_p$$

$$\begin{cases} \partial_t \rho(t, v) + \partial_v ((\alpha - \beta \ln(v)) v \rho(t, v)) = 0 \\ g(V_0) \rho(t, V_0) = \mu V_p(t)^\gamma \\ \rho(0, v) = 0 \end{cases}$$

Prediction



Diagnosis



Prognosis

Simulation and individualization of therapy

Outline

1. Modeling the dynamics of **metastatic burden** in clinically relevant ortho-surgical animal systems
2. **Clinical** applications
3. **Tumor-tumor interactions**

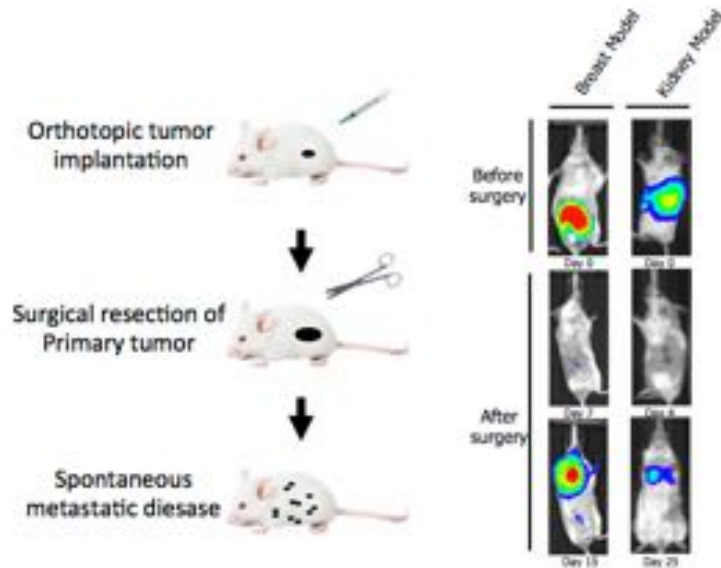
1. Modeling the dynamics of metastatic burden in clinically relevant ortho-surgical animal systems

Experimental data and questions



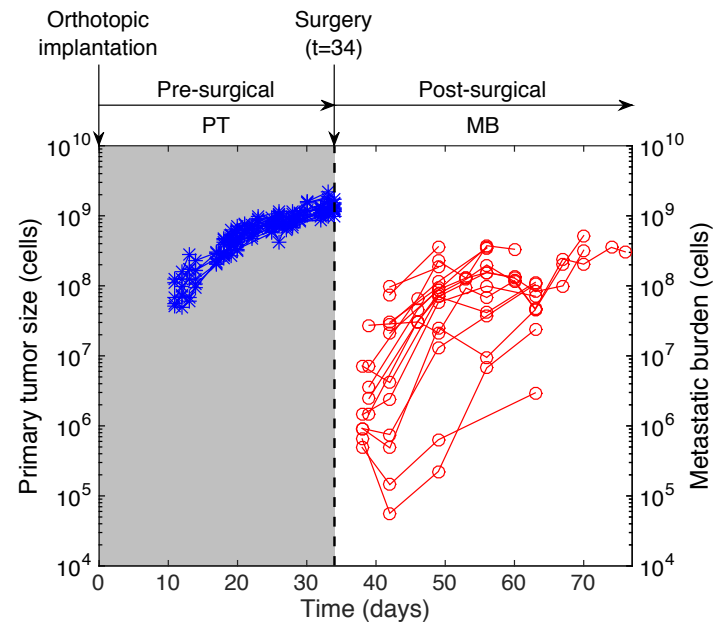
Data

- Clinically relevant ortho-surgical **animal models** of metastasis
- **Longitudinal** measurements of primary tumor size and total **metastatic burden**
- $n > 400$ animals



Questions

- Minimal model of metastatic development. **Dissemination** law? Differences between mets and primary tumor **growth**?
- Quantify the **inter-subject variability** of metastatic development
- What is the impact of the primary tumor size at surgery on metastatic development and survival?



Injection (or first cell)

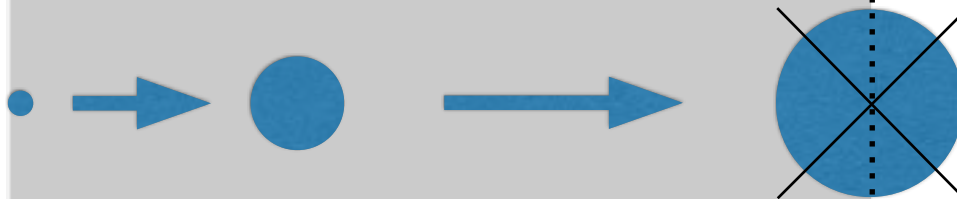
Surgery

Pre-surgical

Post-surgical

PT growth law: $g_p(V_p) = V_p(a_p - \beta_p \ln(V_p))$

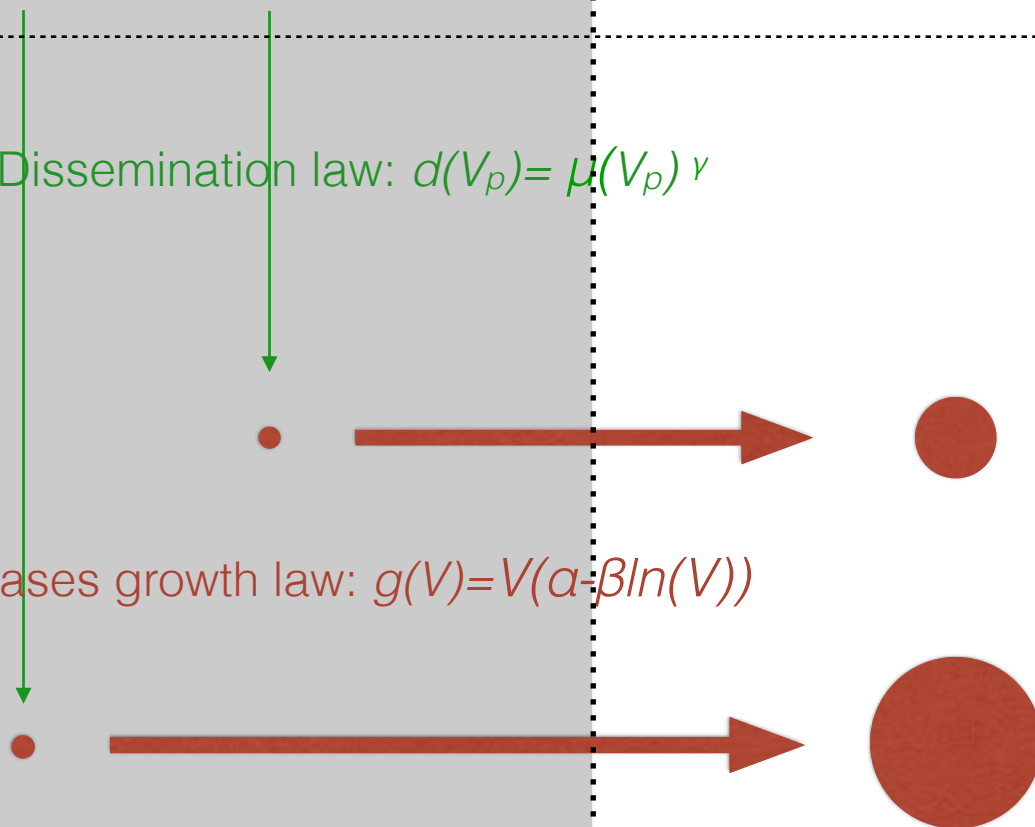
Primary
Tumor
(PT)



Dissemination law: $d(V_p) = \mu(V_p)^\nu$

Metastases

Metastases growth law: $g(V) = V(a - \beta \ln(V))$



Mathematical formalism

- Primary tumor V_p grows with rate g_p [size.day⁻¹]

$$\frac{d}{dt} V_p = g_p(V_p), \quad V_p(t=0) = V_i$$

- Population** of metastases represented by a **density** $\rho(t, v)$ [size⁻¹] structured in **size** v

- Secondary tumors **grow** in size with rate $g(v)$

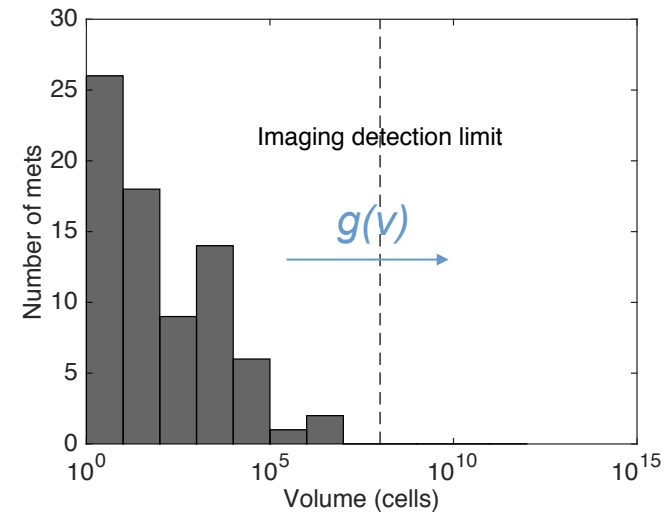
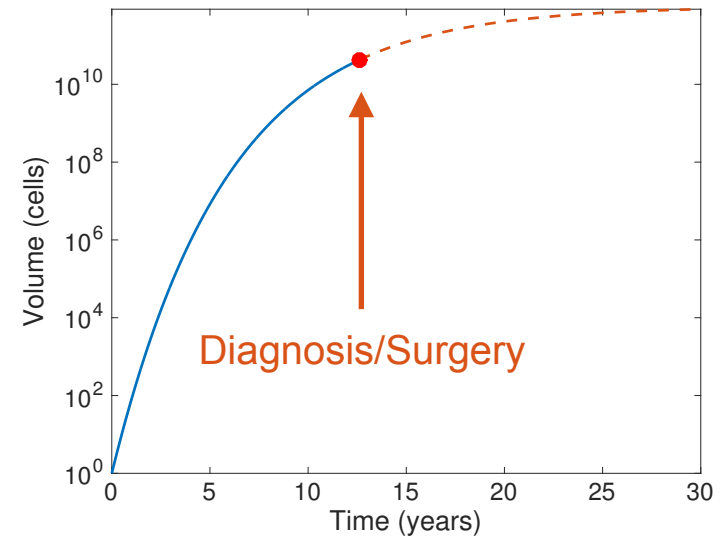
$$\partial_t \rho(t, v) + \partial_v (g(v) \rho(t, v)) = 0$$

- They are spread by the PT with **dissemination rate** $d(V_p(t))$ [day⁻¹]

$$g(V_0) \rho(t, V_0) = d(V_p(t)) \left(+ \int_{V_0}^{+\infty} d(v) \rho(t, v) dv \right)$$

→ fast computation of the metastatic burden

$$M(t) = \int_{V_0}^{+\infty} v \rho(t, v) dv = \int_0^t d(V_p(t-s)) V(s) ds$$



Statistical procedure: nonlinear mixed effects modeling

- Usual fitting methods consider each **time series independently**

$$y_i^j = M(t_i^j, \theta^j) + \varepsilon_i^j$$

Individual $1 \leq j \leq N$

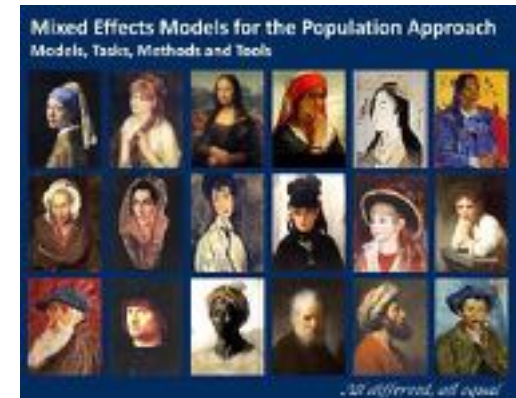
Time t_i

MLE \longrightarrow $\hat{\theta}^j = \min_{\theta^j} \sum (y_i^j - M(t_i, \theta^j))^2$

- When only sparse data are available from subjects in the same **population**, one can fit **parameters distribution** all-in-once

$$y_i^j = M(t_i^j, \theta^j) + \varepsilon_i^j$$

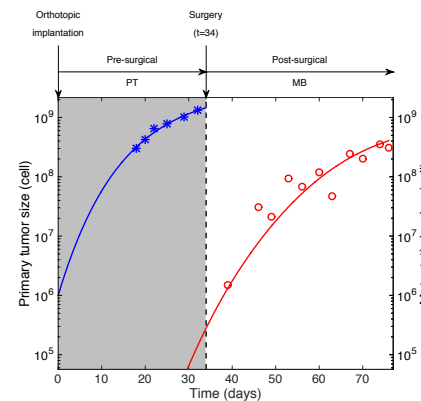
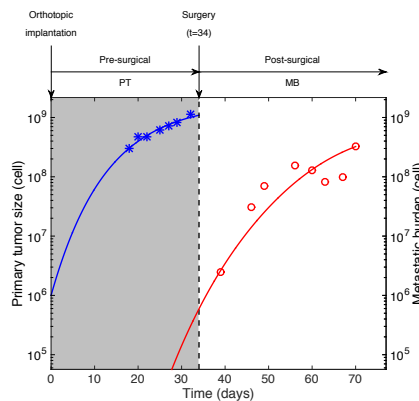
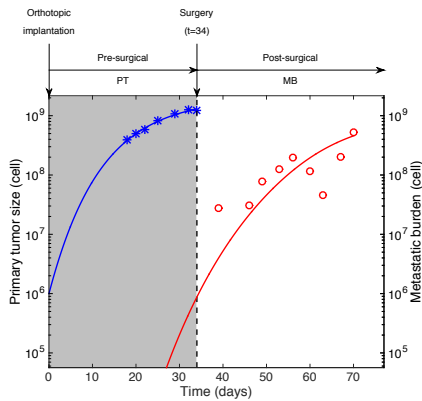
$$\theta^1, \dots, \theta^N \sim \mathcal{LN}(\theta_\mu, \theta_\omega), \quad \theta_\mu \in \mathbb{R}^p, \quad \theta_\omega \in \mathbb{R}^{p \times p}$$



Lavielle, CRC press, 2014

- Reduces the number of parameters from pxN to $p+p2$**

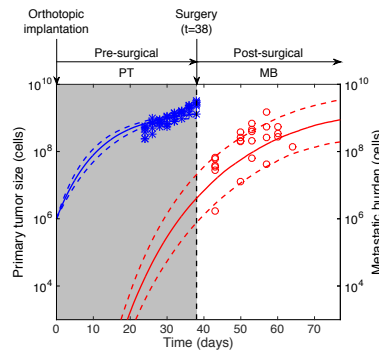
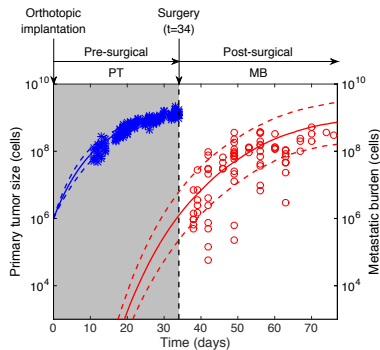
The model fits at the individual and population levels



- * Data primary tumor
- Median model primary tumor
- - - 10th and 90th percentiles model primary tumor
- o Data metastatic burden
- Median model metastatic burden
- - - 10th and 90th percentiles model metastatic burden

Fit

Prediction



Nonlinear mixed-effects statistical model for inter-animal variability

$$\theta^i = \theta_{pop} + \eta_i, \quad \eta_i \sim \mathcal{N}(0, \omega^2)$$

⇒ model with **same growth** for PT and mets

was the most parsimonious

⇒ good **practical identifiability** (all rse < 30%)

⇒ parameter μ is a critical coefficient of inter-animal **variability** of metastatic potential (CV = 176%)

Differential effects of anti-angiogenic therapies between primary tumor and metastases

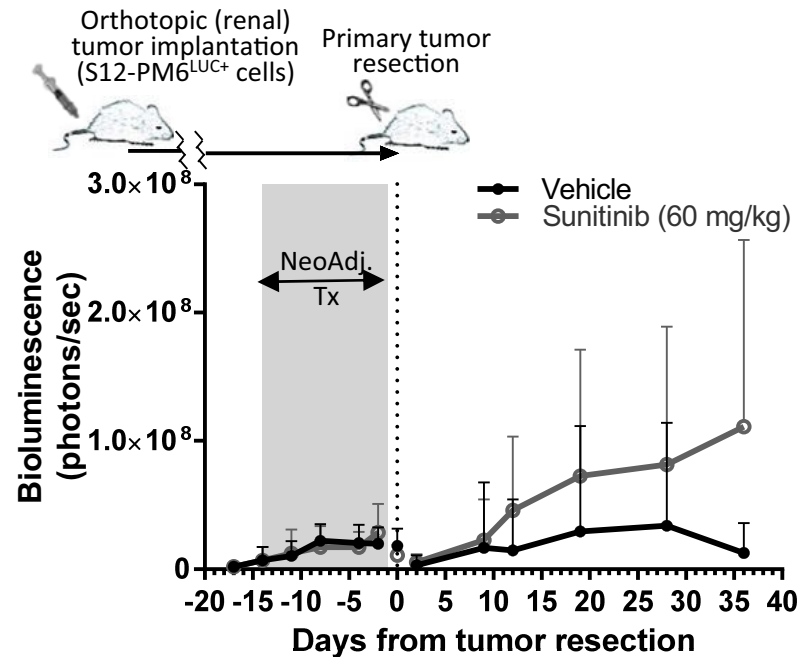


Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

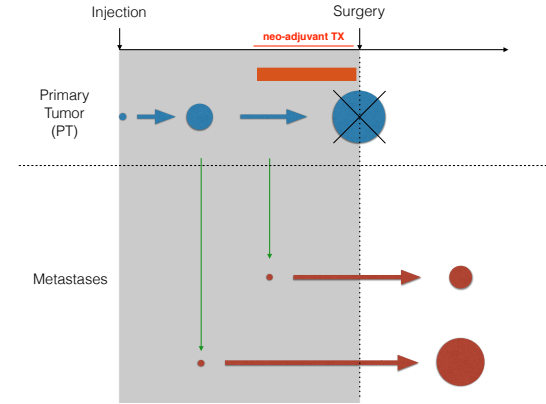
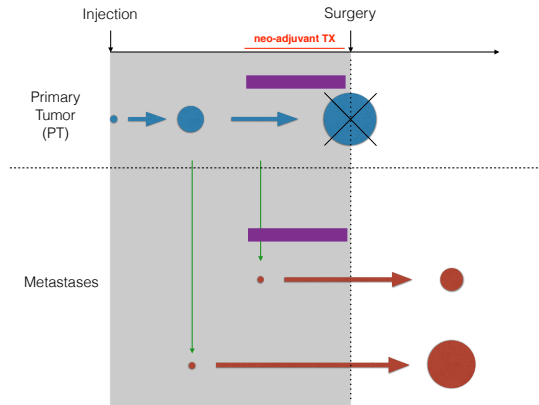
John M.L. Ebos,^{1,2} Christina R. Lee,¹ William Cruz-Munoz,¹ Georg A. Bjarnason,³ James G. Christensen,⁴ and Robert S. Kerbel^{1,2,*}

Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy

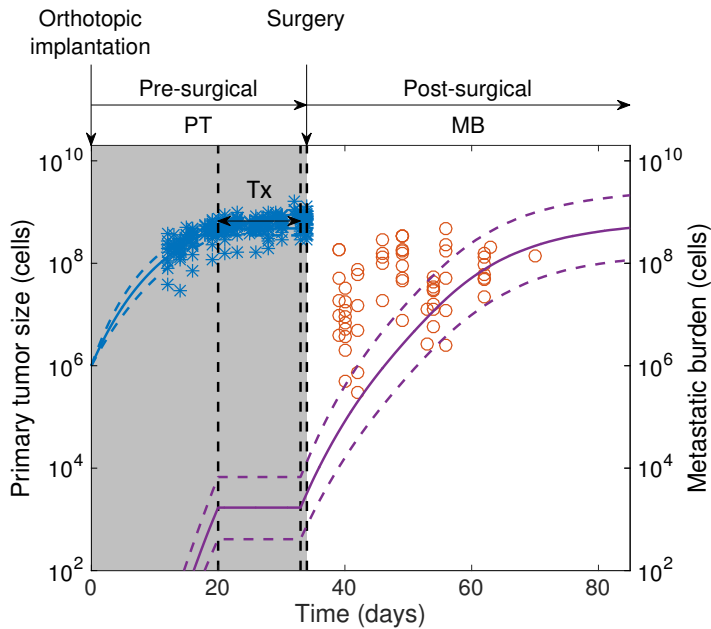
John M L Ebos^{1,2}, Michalis Mastroi³, Christina R Lee², Amanda Tracz¹, John M Hudson², Kristopher Attwood³, William R Cruz-Munoz², Christopher Jedszko², Peter Burns^{2,4} & Robert S Kerbel^{2,4}



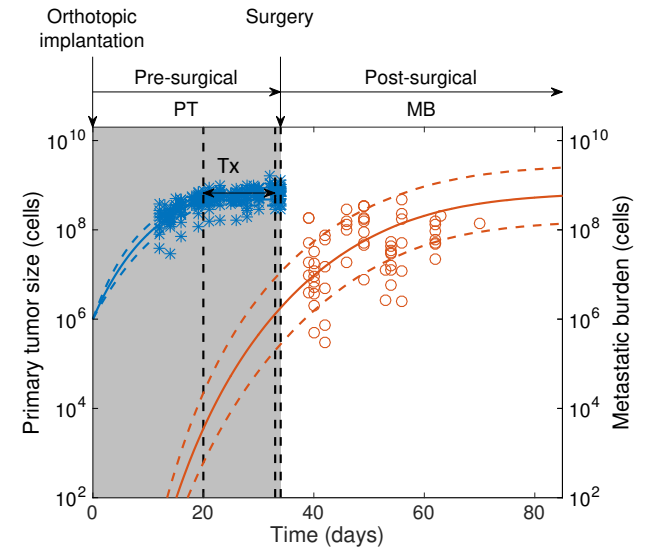
Testing hypotheses for Sunitinib effect



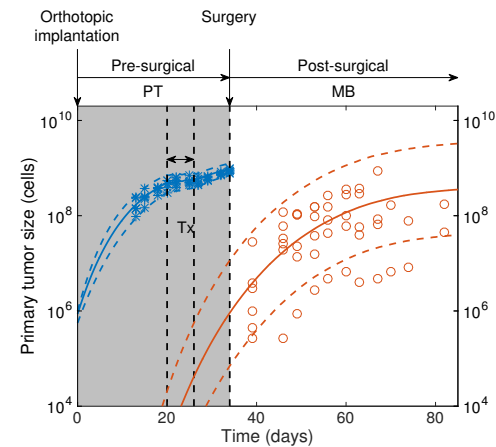
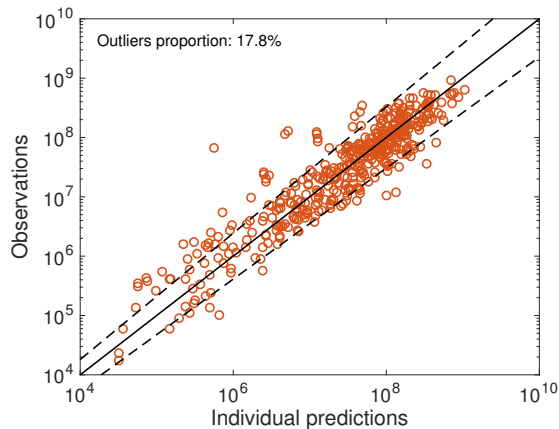
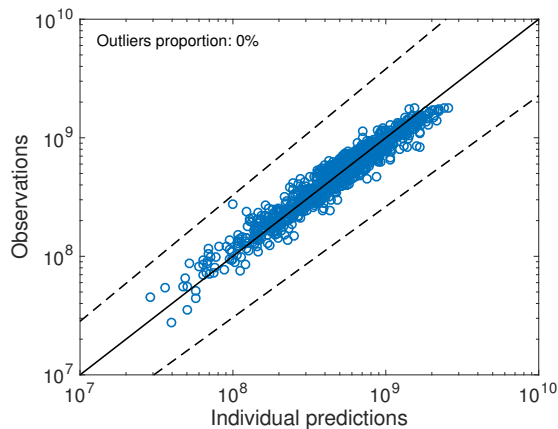
or



- ★ Data PT
- Data MB
- Median PT
- Median MB
- - - 10th and 90th percentiles PT
- - - 10th and 90th percentiles MB
- simulation of therapy on metastases

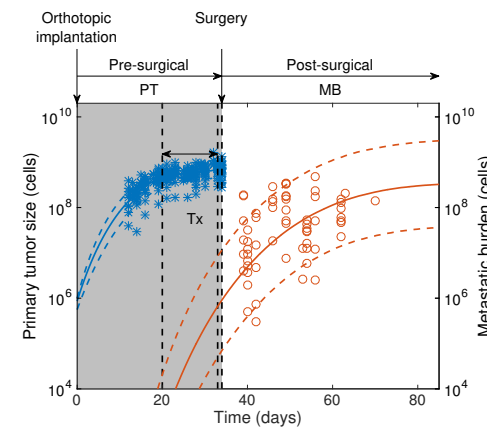


A validated model of metastatic growth with neoadjuvant Sunitinib therapy



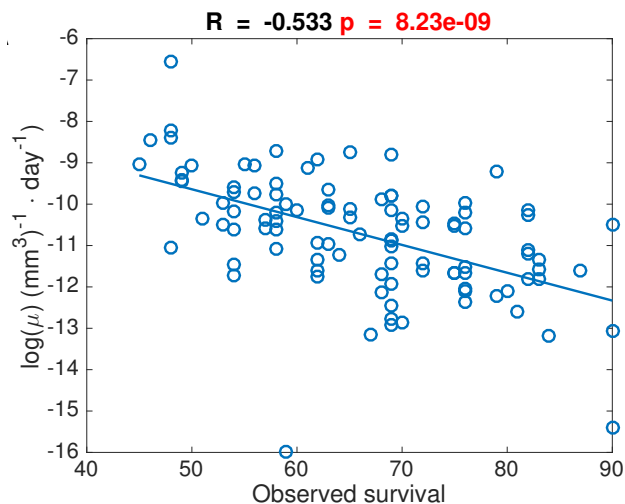
Su60(7D)

	Unit	Median value	CV (%)	r.s.e. (%)
μ	$cell^{-1} \cdot day^{-1}$	2.12e-11	1.48e+03	17.3
α	day^{-1}	1.94	18.1	2
β	day^{-1}	0.0911	19.7	2.21
k	$(mg/kg)^{-1}$	0.0372	32.1	6.34
k_e	day^{-1}	3.26 (fixed)	-	-

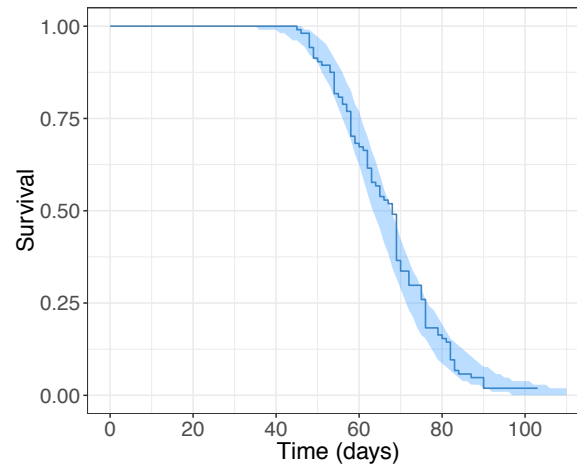


Su60(14D)

Survival model: μ as a covariate



Model fit



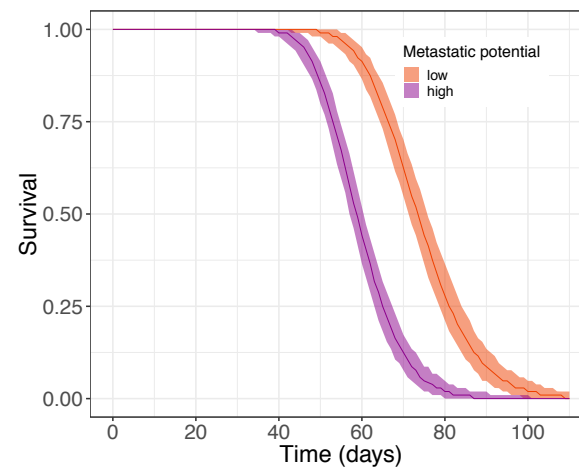
Nonlinear mixed-effects survival model

$$S^i(t) = \mathbb{P}(T^i \geq t) = e^{-\int_0^t h^i(s) ds}$$

$$h^i(t; T_e^i, s) = \frac{\frac{s}{T_e^i} \left(\frac{t}{T_e^i}\right)^{s-1}}{1 + \left(\frac{t}{T_e^i}\right)^s}$$

$$T_e^i = T_e^{pop} + \beta \mu^i + \eta^i, \quad \eta^i \sim \mathcal{N}(0, \omega)$$

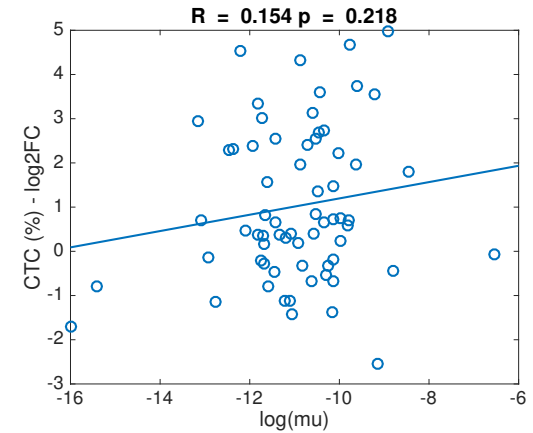
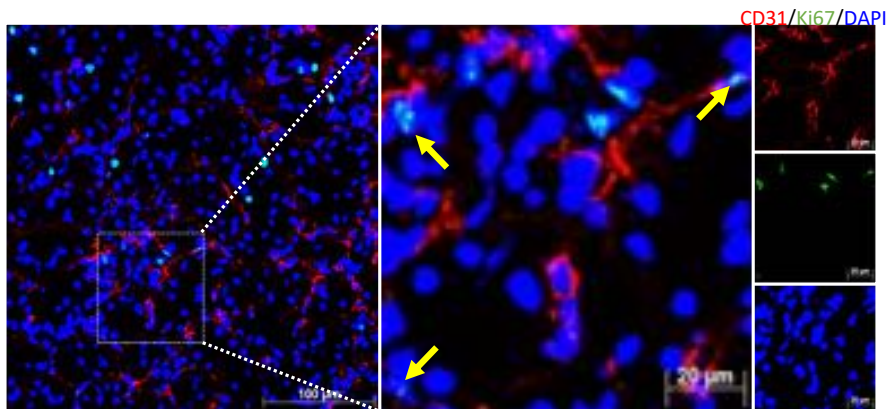
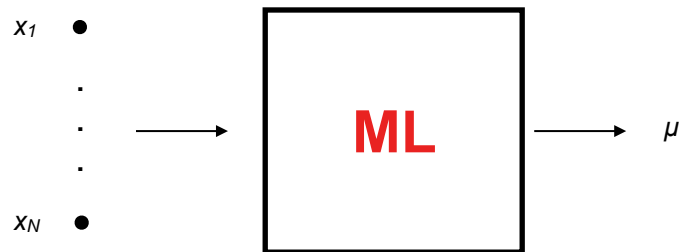
Individual predictions of survival probability



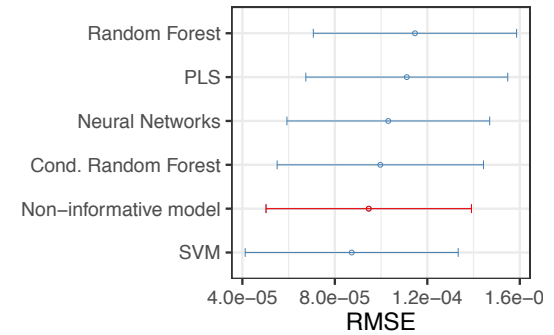
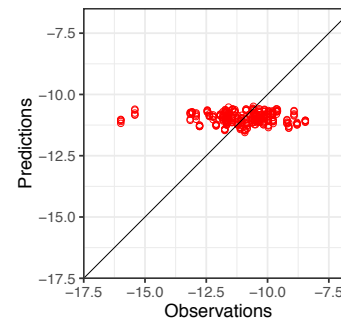
Trying to predict μ from biomarkers using machine learning

Biological measurements on multiple biomarkers

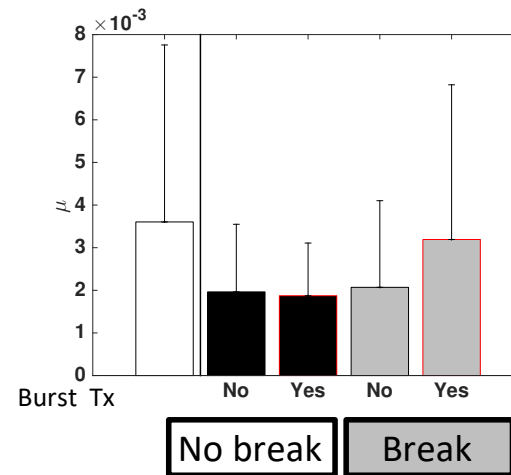
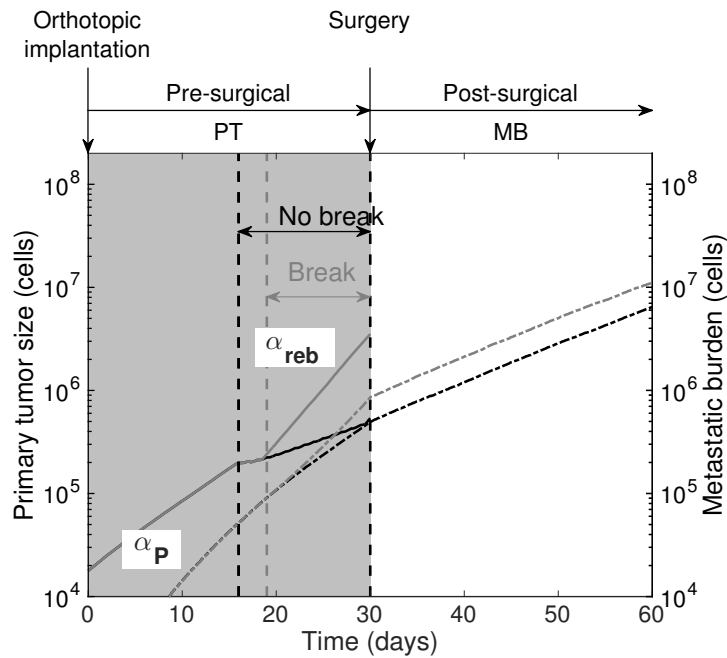
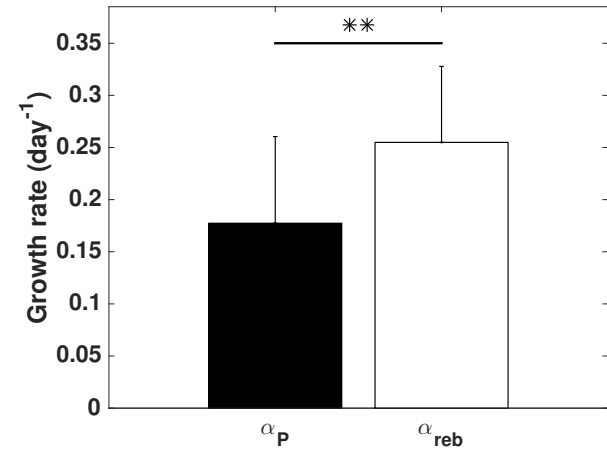
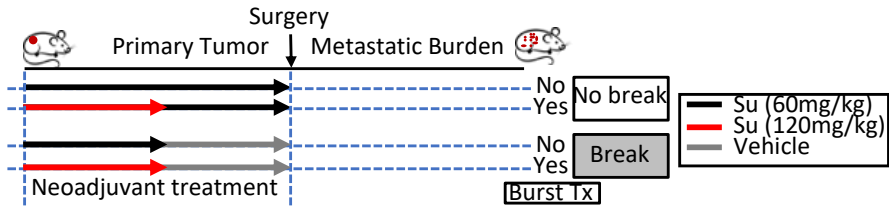
- Circulating tumor cells
- Proliferative (Ki67+) and endothelial cells (CD31+)
- Myeloid Derived Suppressor Cells (MDSCs)



Cond. Random forest



Impact of treatment breaks



2. Clinical application

Metastatic relapse probability in a breast cancer clinical dataset

Diameter of PT (cm)	Prop. of relapse (Data)	Prop. of relapse (Model)
$1 \leq D \leq 2.5$	27.1	27.3
$2.5 < D \leq 3.5$	42.0	43.1
$3.5 < D \leq 4.5$	56.7	56.6
$4.5 < D \leq 5.5$	66.5	65.6
$5.5 < D \leq 6.5$	72.8	74.0
$6.5 < D \leq 7.5$	83.8	80.1
$7.5 < D \leq 8.5$	81.3	84.5

- 20 year follow-up of 2648 patients *Koscielny et al., Br J Cancer, 1984*
- **Assumptions**
 - (lognormal) distribution of μ for **inter-individual variability**
 - Doubling time from median values of the literature (7 months) *Coumans et al., BMC Cancer 2013*
 - Maximal reachable size = 10^{12} cells \approx 1 kg *Klein, Nat Rev Cancer, 2009*
- Probability of developing a met = probability of having one at diagnosis

$$\mathbb{P}(\text{Mets}) = \mathbb{P}\left(\mu \int_0^{T_1} V_p(t) > 1\right)$$

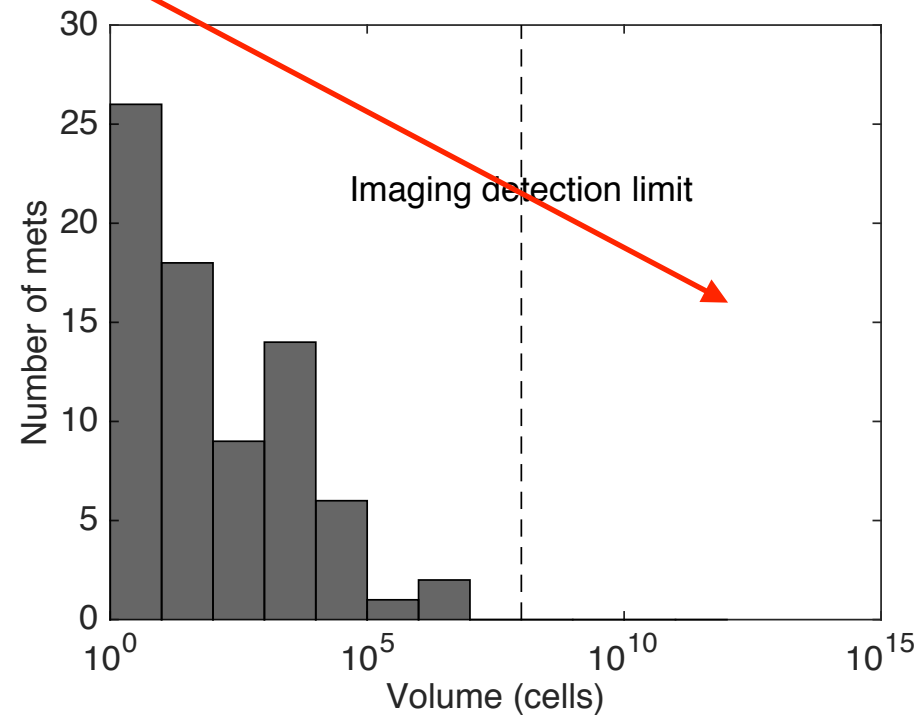
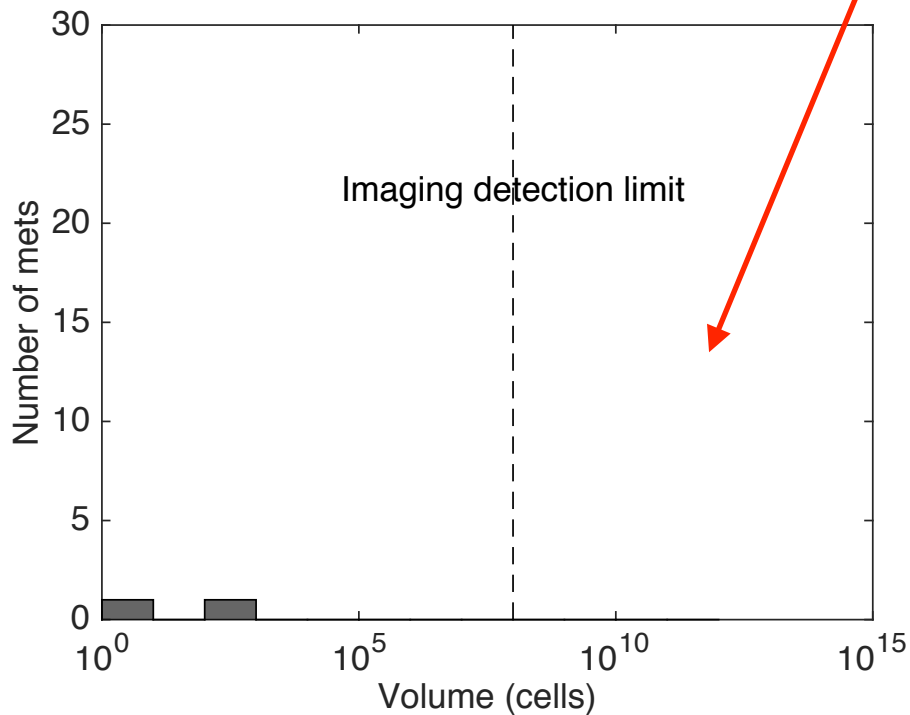


Diagnosis personalization

Virtual patient with
median μ

Virtual patient with
large μ (90th prct)

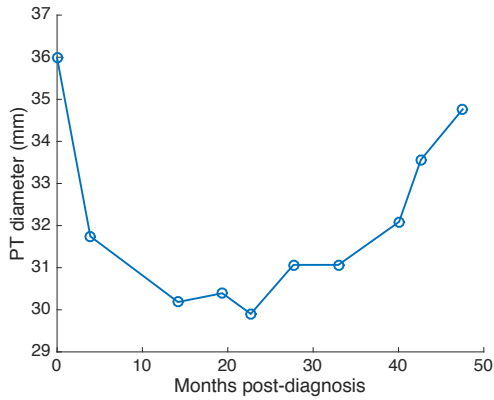
Nothing visible



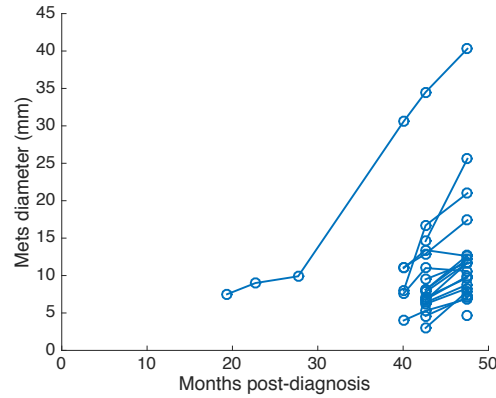
Breast cancer patient with primary tumor of 4.32 cm

Data of a NSCLC patient with brain mets

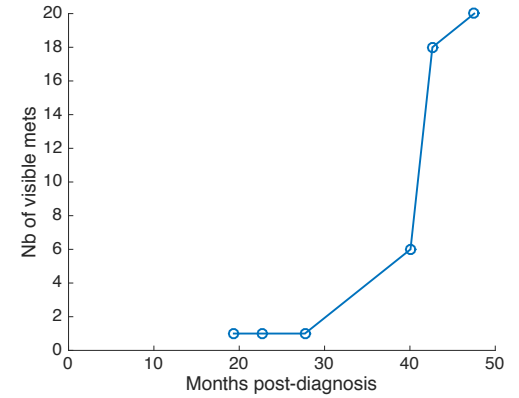
Primary tumor size



Metastases size



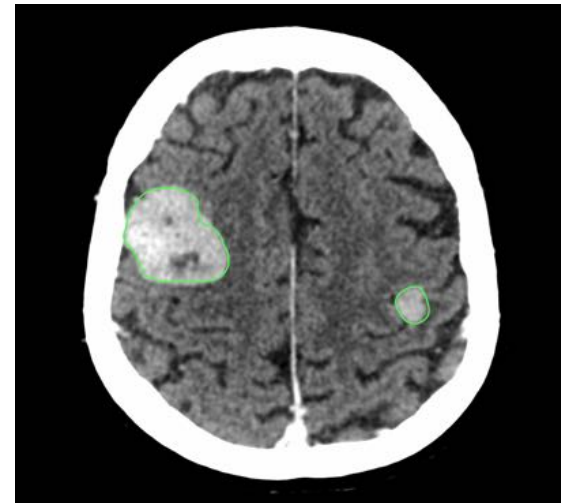
Number of visible mets



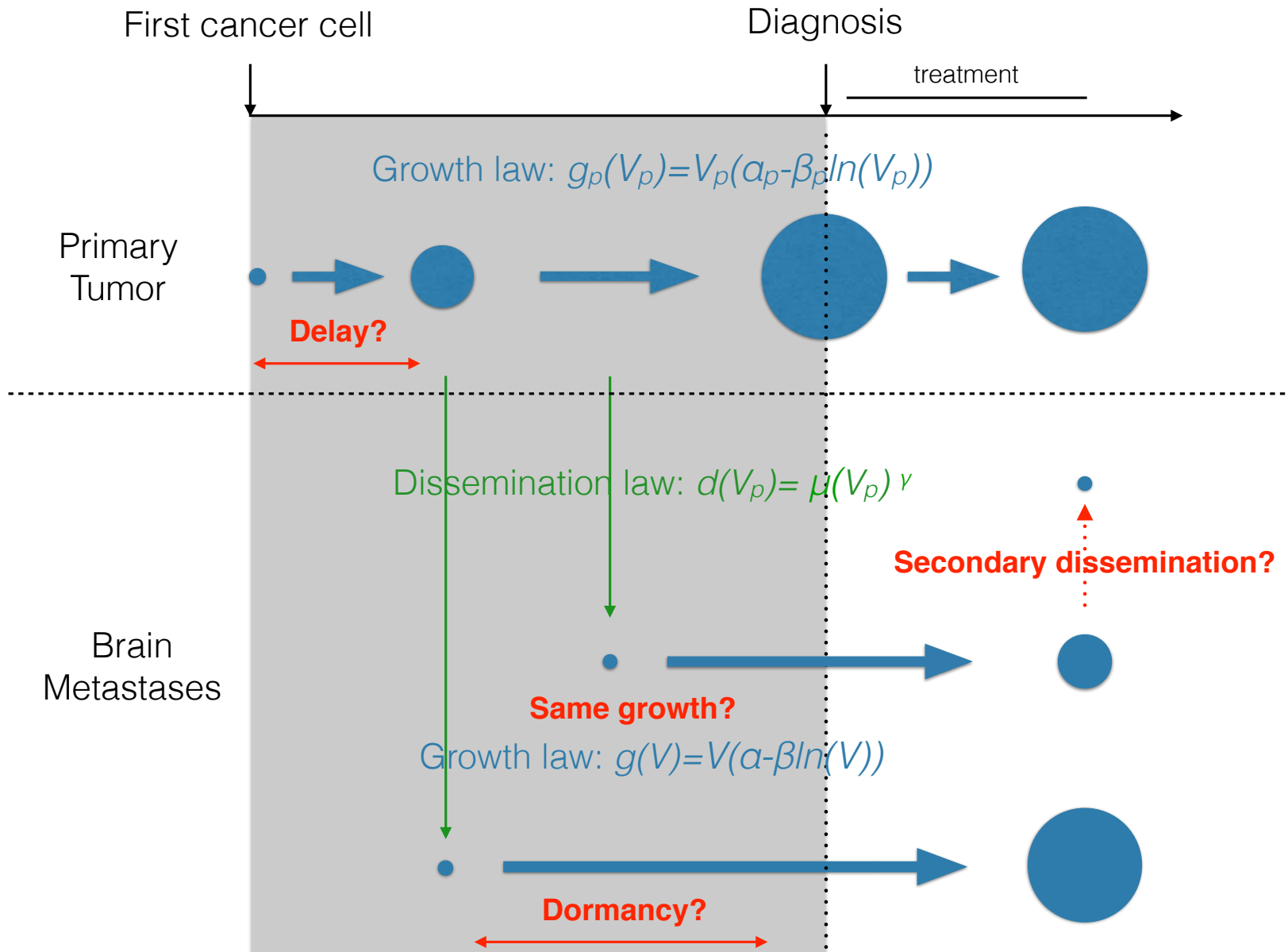
Lung CT



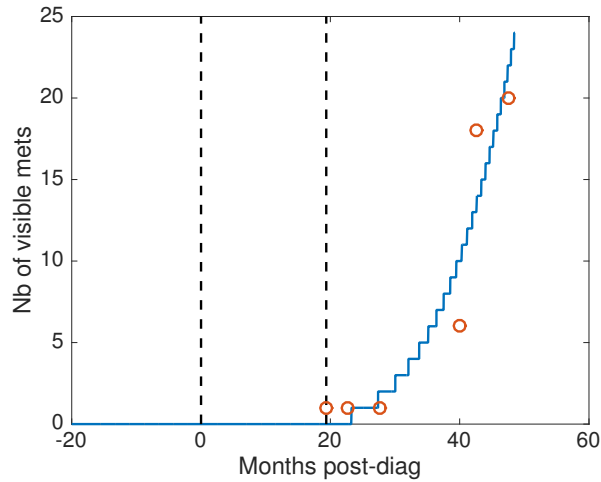
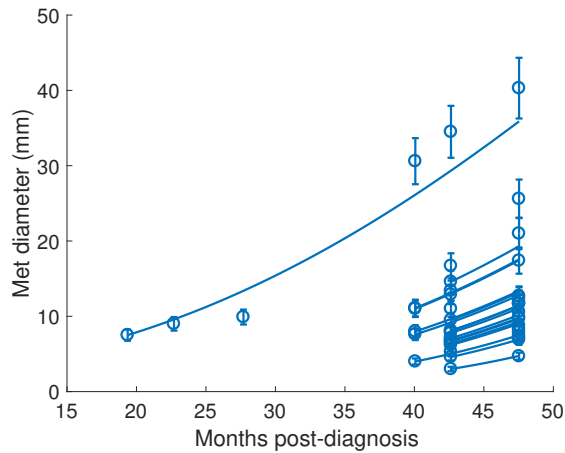
Brain CT scan



Different biological scenari



The model with dormancy could describe best the data

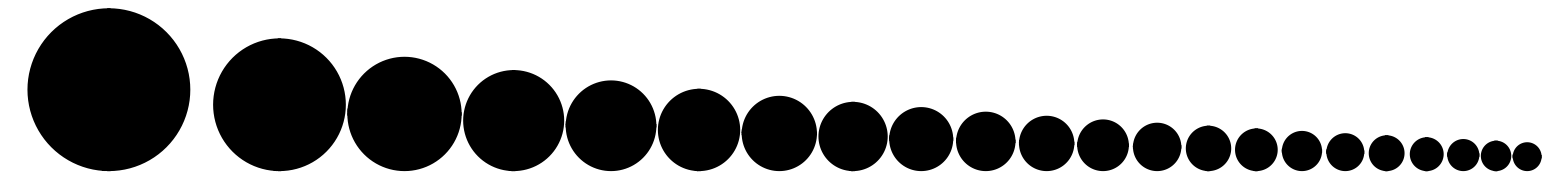


Objective function

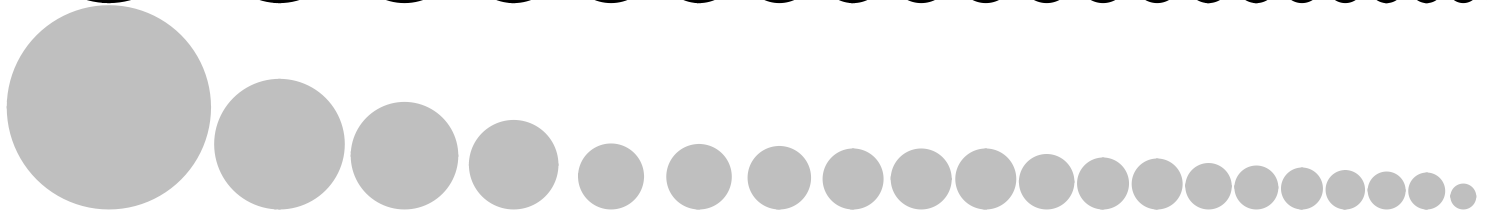
Model	Patient 1	Patient 2
Base	5.51	2.53
Secondary	5.43	2.3
Delay	5.23	1.53
Dormancy	4.93	1.71
Diff. growth	4.95	1.79

Dormancy estimated to 133 days \pm 4.2%

Model



Data



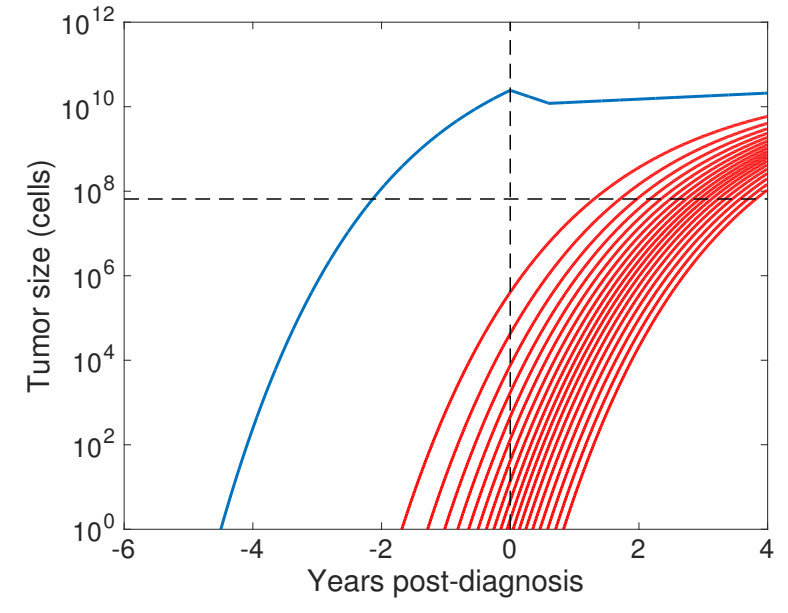
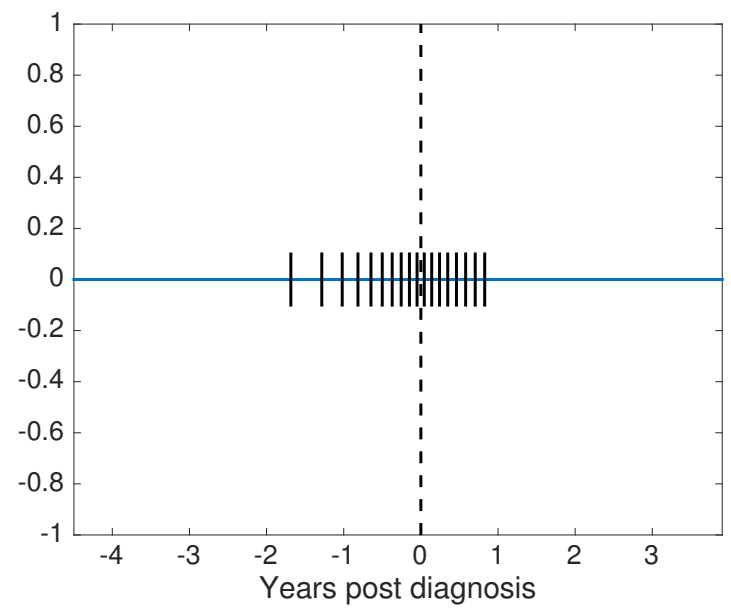
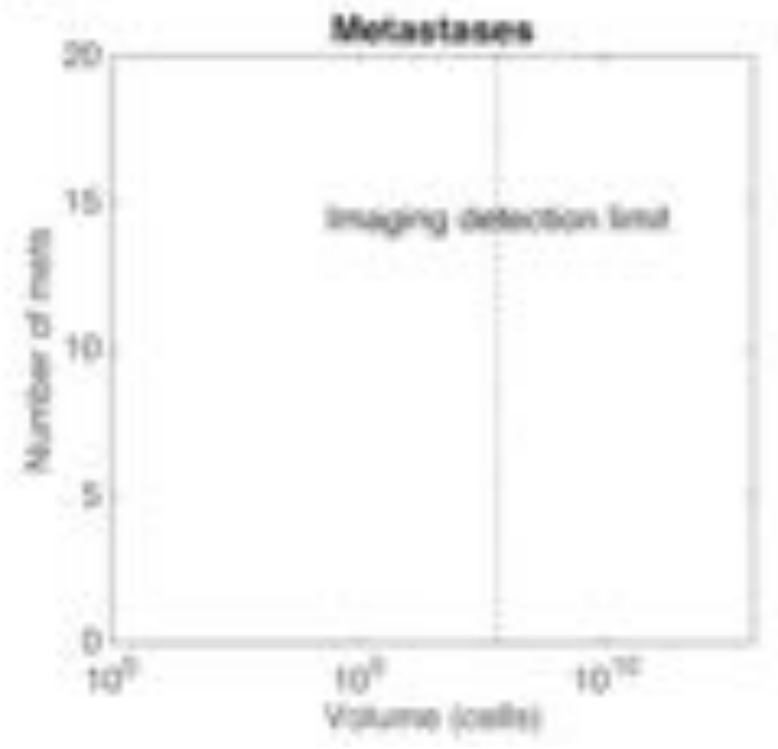
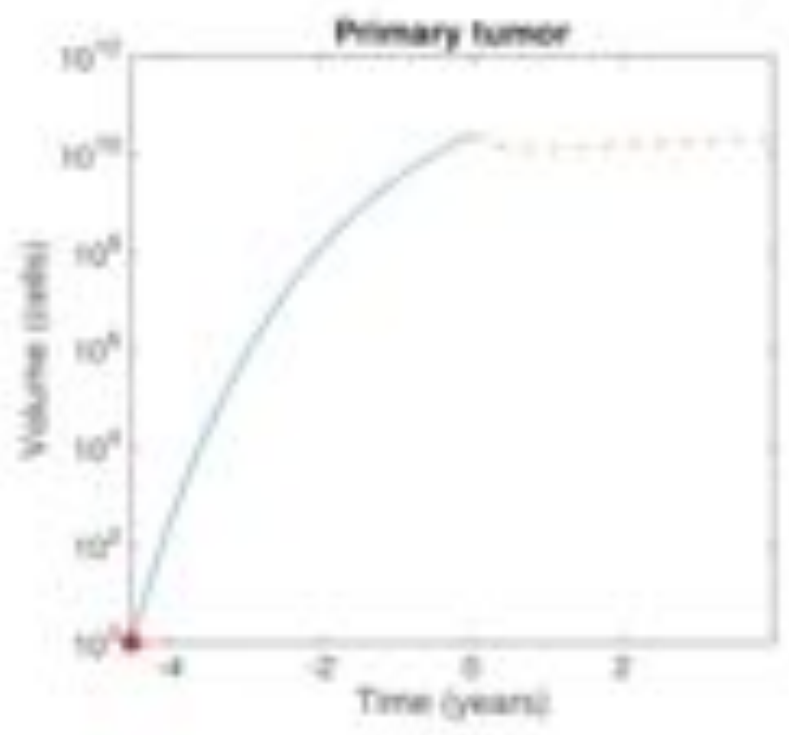
t = -55 months
— 10 mm

*

Primary
tumor
(lung)

Metastases (Brain)

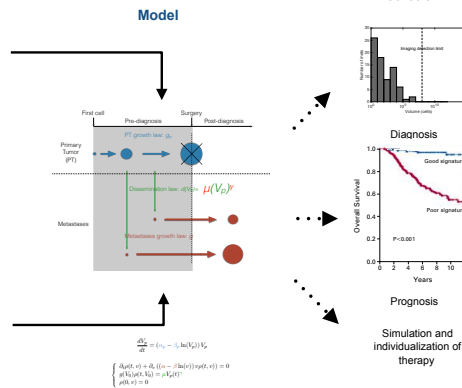
$t = -4.5$ years



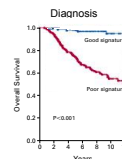
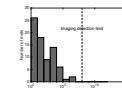
Current work: implementing the mechanistic model into a biostatistical model at the population scale

- Use the model for predictions of **time-to-relapse** and survival
- Implement clinical variables and biomarkers as **biologically meaningful** covariates
- Predict metastasis for localized **breast** cancer patients (~10% relapse at 5 years) to advise for **adjuvant therapy**

Clinical database
biomarkers at diagnosis



Prediction

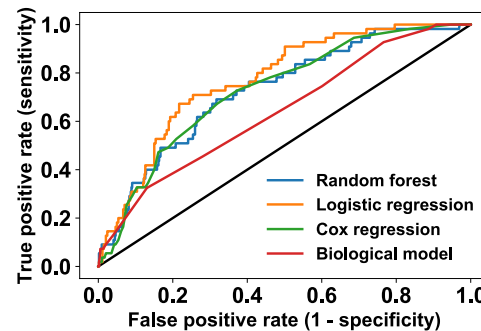


Prognosis

Simulation and individualization of therapy

	AUROC	Accuracy	NPV	PPV
Random forest	0.727	87	91.7	22.5
Logistic regression	0.772	90.1	91	25
Cox regression	0.728	87.4	91.1	16.7
Bio-based	0.641	89.7	91.3	31.2

AUROC = Area Under the ROC curve, NPV = Negative Predictive Value
PPV = Positive Predictive Value



	P
tumor_size_clinical	0.00165
tumor_size_histological	0.4
grade	0.358
histology	0.0041
TNM_T	0.146
TNM_N	0.599
nb_invaded_ganglions	0.619
menopausal_status	0.000471
ER	0.543
PR	0.34
Ki67	3.09e-05
HER2	0.17
HER2_intensity	0.482
CK56	0.793
EGFR	0.016
VIM	0.226
ALDH1	0.674
CD24	0.894
CD44	0.397
E_cadherin	0.207
TRIO	0.0646
BCL2	0.727
age_at_diagnosis	0.0599
diagnosis_year	0.101
radio	0.276

Features selection based on Cox regression

3. Tumor-tumor interactions: a dynamical study of concomitant resistance

Concomitant tumor resistance

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

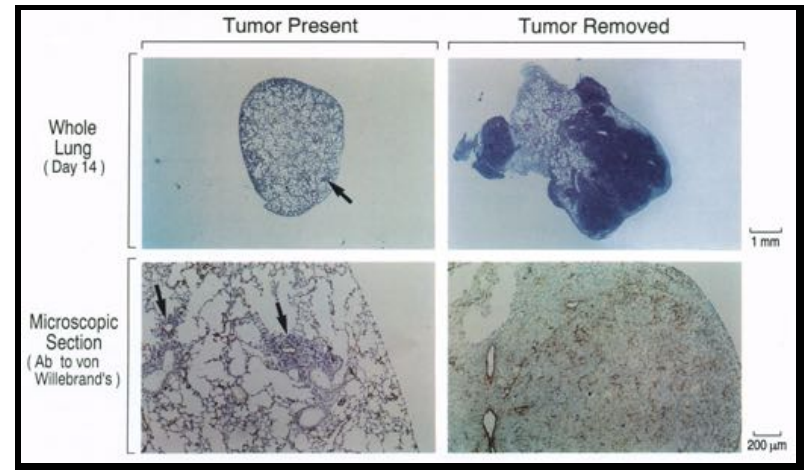
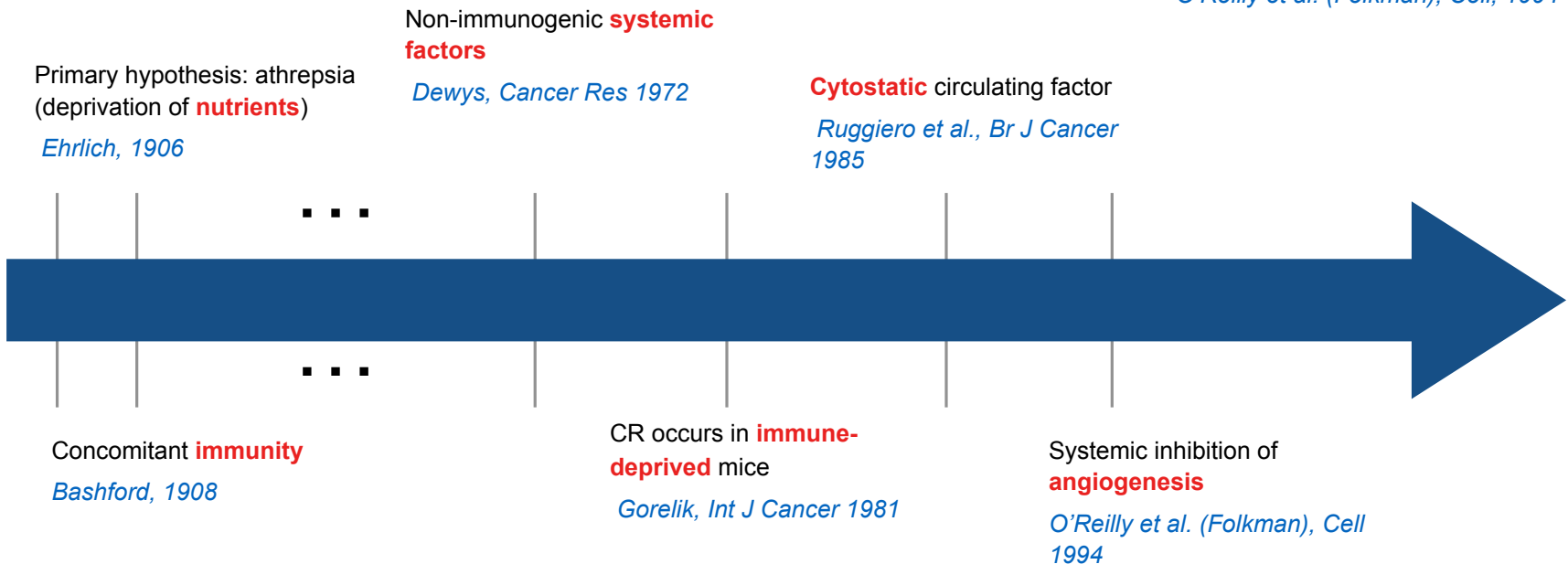


Figure 2. The Presence of a Primary Tumor Is Associated with an Inhibition of Neovascularization and Growth of Its Metastases

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



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

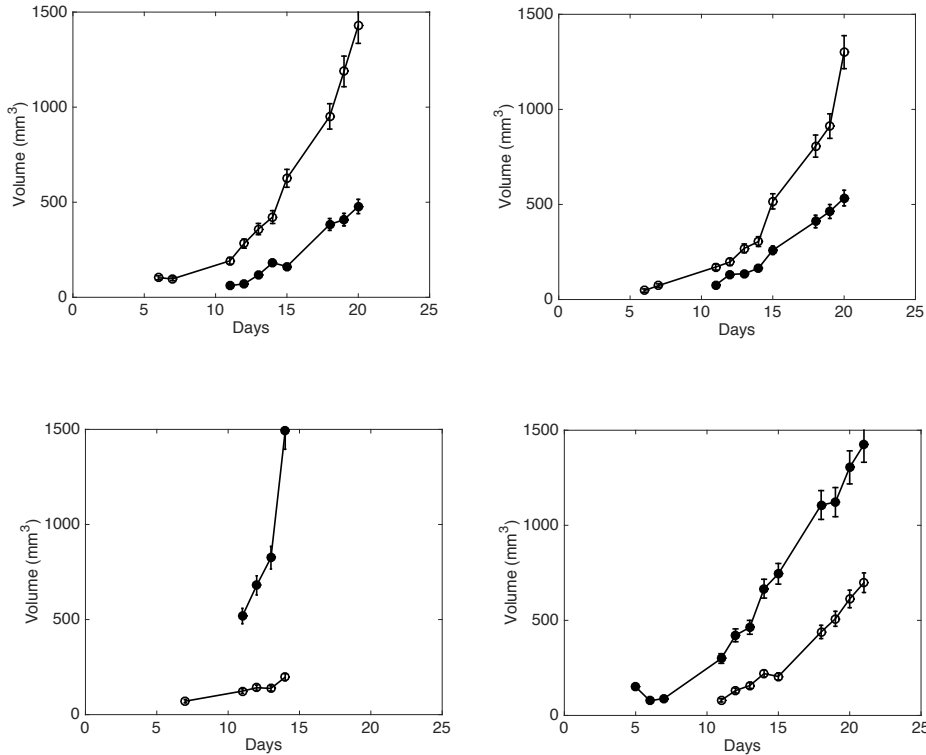
- Injection s.c. of **two tumors** of 10^6 LLC cells in C57/BL6 mice
- Two groups
 - Control: only one tumor
 - Group S: **simultaneous** injection of cells in two different sites

A mouse with two tumors

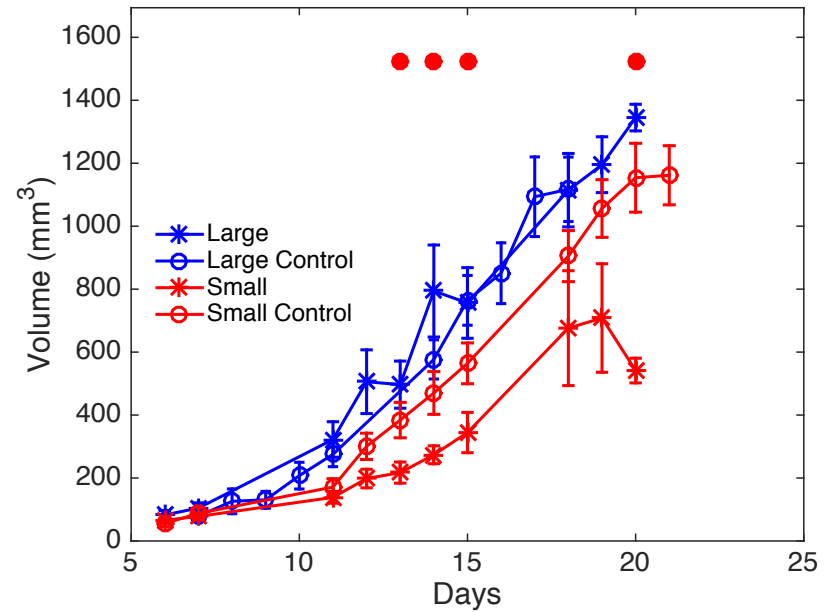


One tumor has normal growth and the other is suppressed

Individual growth kinetics



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



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

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

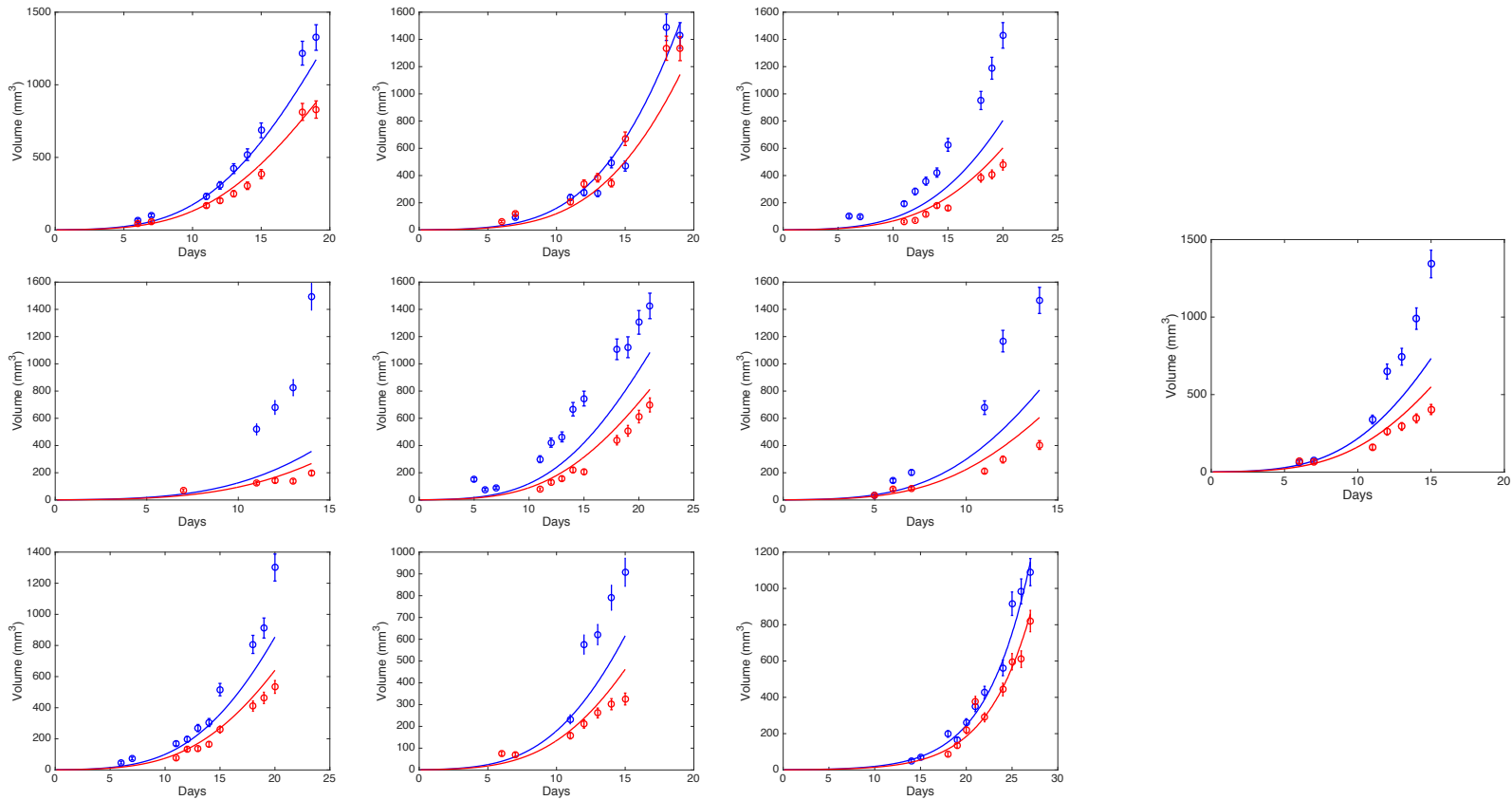
Angiogenesis inhibition

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

Proliferation inhibition

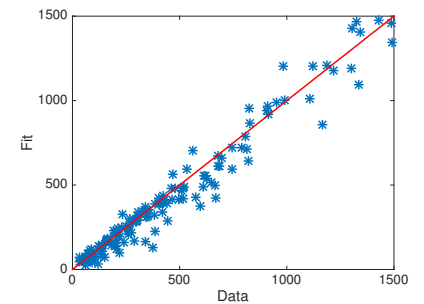
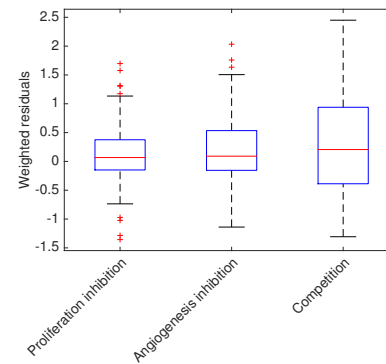
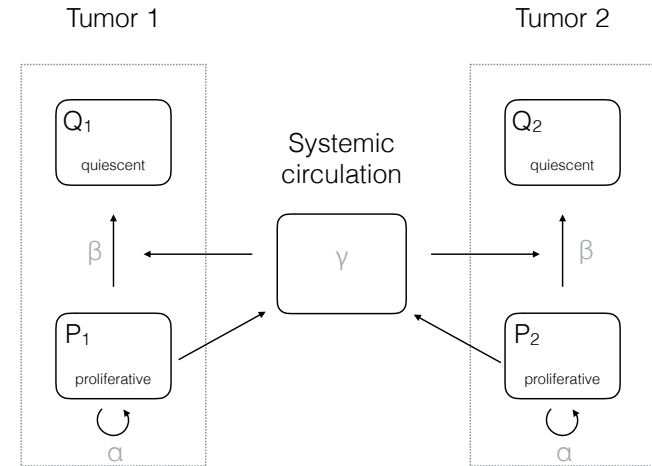
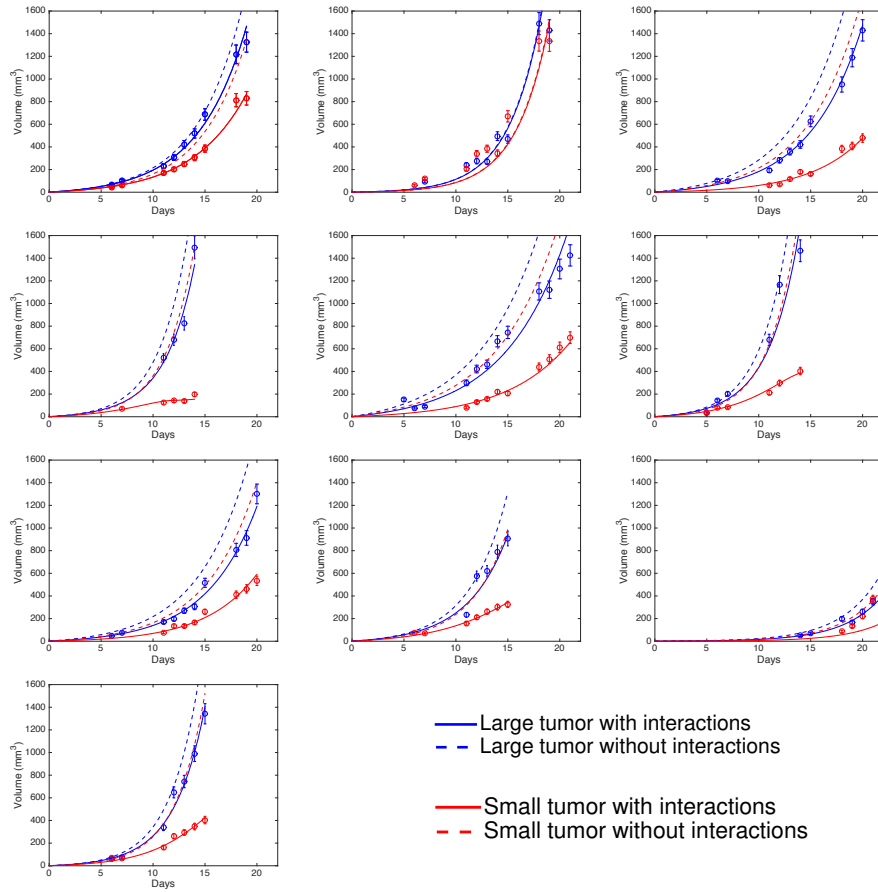
$$\begin{cases} \frac{dP_1}{dt} = \alpha P_1 - (\beta P_1 + \gamma(P_1 + P_2)) 1_{P_1 > 0}, & P_1(t=0) = V_{0,1} \\ \frac{dQ_1}{dt} = \beta P_1 + \gamma(P_1 + P_2), & Q_1(t=0) = 0 \\ \frac{dP_2}{dt} = \alpha P_2 - (\beta P_2 + \gamma(P_1 + P_2)) 1_{P_2 > 0}, & P_2(t=0) = V_{0,2} \\ \frac{dQ_2}{dt} =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

The competition model did not fit



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

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

Conclusion

- A general modeling framework for **modeling metastases**
- Statistical nonlinear **mixed-effects modeling** very useful for parameter estimations
- Simplified model (growth + dissemination) able to describe available clinically relevant **preclinical data** of dynamics of total metastatic burden
- **Same growth** for primary tumor and mets in breast animal model
- A **patient-specific key parameter μ** is critical in the quantification of patient-specific metastatic aggressiveness
- Could be clinically useful for guiding **adjuvant therapy** (chemotherapy/WBRT)
- Application to clinical data of **number and size** of brain mets suggested **dormancy** in NSCLC
- **Quantitative** exploration of classical theories for metastatic colonization and **tumor-tumor interactions**

Acknowledgements

Biology

- Preclinical data of ortho-surgical animal models of metastases

*J. Ebos *A. Tracz
*M. Matri



Roswell Park Cancer Institute, Buffalo, NY, USA

- Two-tumors study

*C. Lamont *L. Hlatky
*P. Hahnfeldt

Center of Cancer and Systems Biology, Boston, MA, USA

Clinic

- Brain metastasis from lung tumors

*F. Chomy

Bergonié Institute, Bordeaux, FR



*F. Barlesi *X. Muracciole

SMARTc team, CRCM, Inserm, CNRS, Marseille, FR

Modeling

*C. Nicolò



*D. Barbolosi

Thank you for your attention!