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# Mathematical Modeling and Prediction of Clinical Metastasis

Sébastien Benzekry

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# Mathematical Modeling and Prediction of Clinical Metastasis

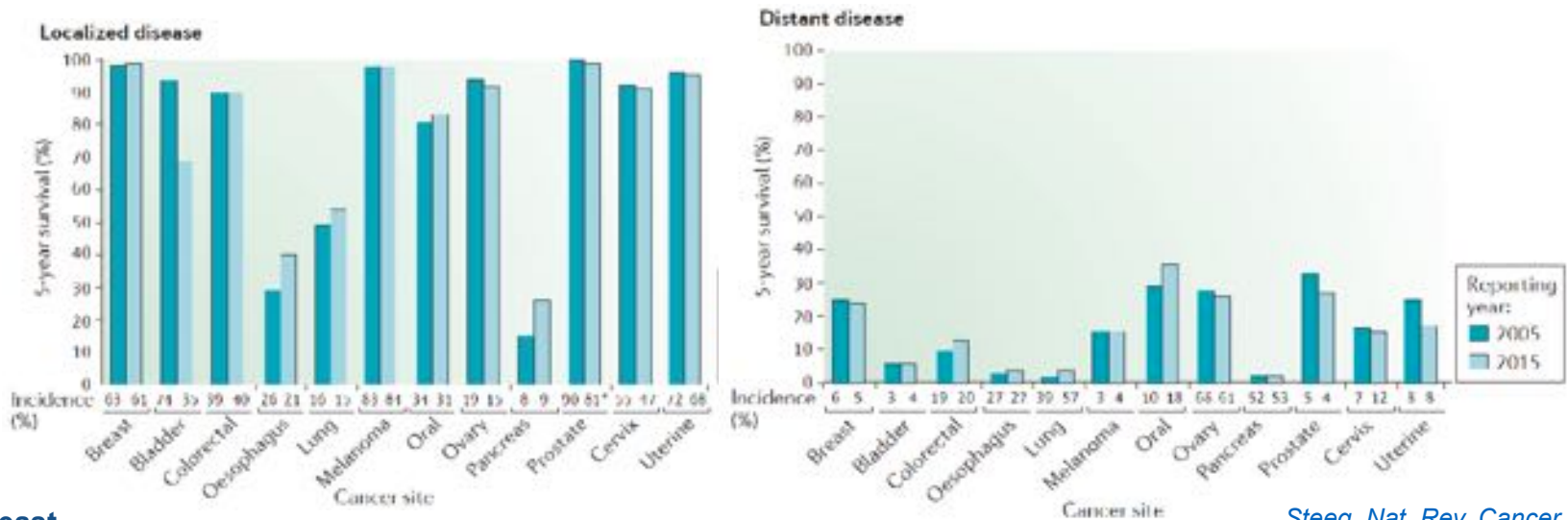
S. Benzekry

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*



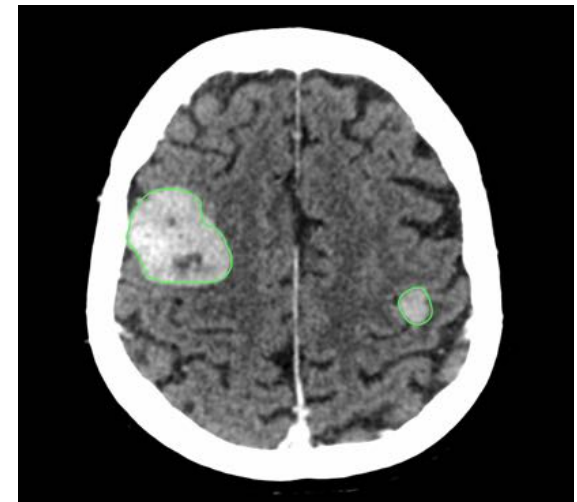
*Steeg, Nat. Rev. Cancer, 2016*

## 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



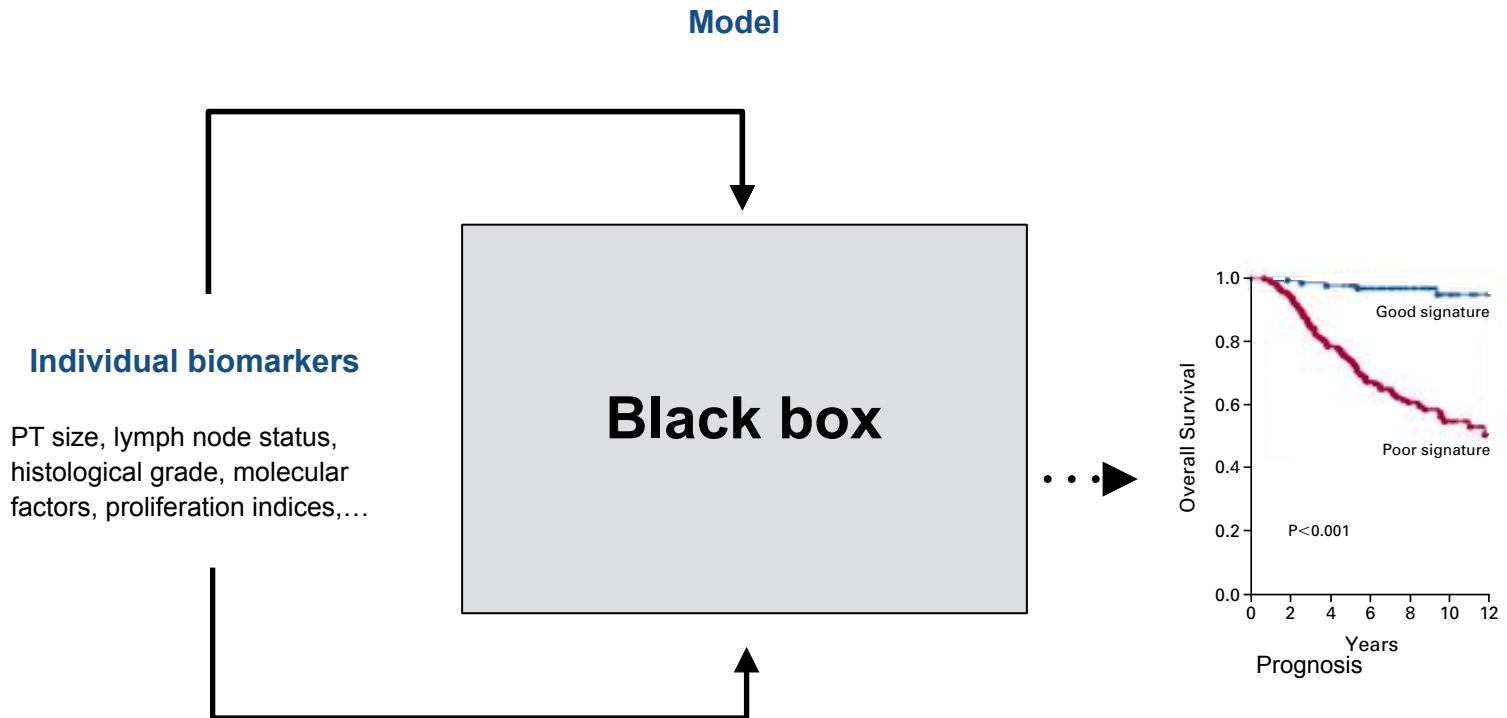
*Institut Bergonié, Bordeaux*

# 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



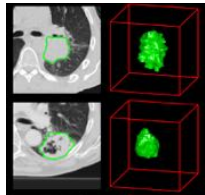
# Metastasis: a forgotten major player in modeling

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

## Clinical data

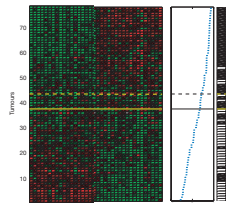
PT size, lymph node status, histological grade, molecular factors, proliferation indices,....

## Imaging data (Radiomics)



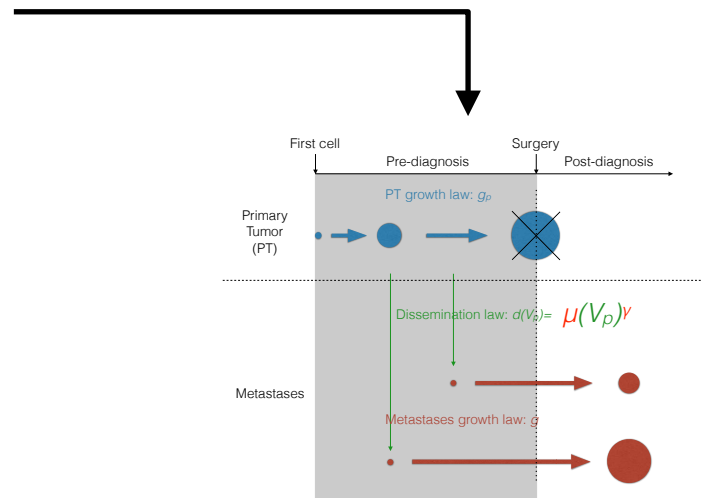
Aerts et al., Nat Commun, 2014

## Molecular data (-omics)



van't Veer et al., Nature, 2002

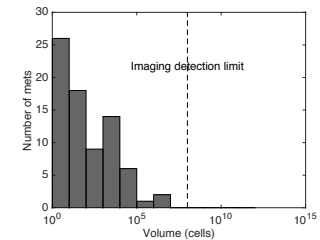
## Biologically-based model



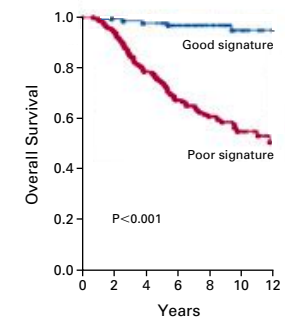
$$\frac{dV_p}{dt} = (\alpha_p - \beta_p \ln(V_p)) V_p$$

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

## 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

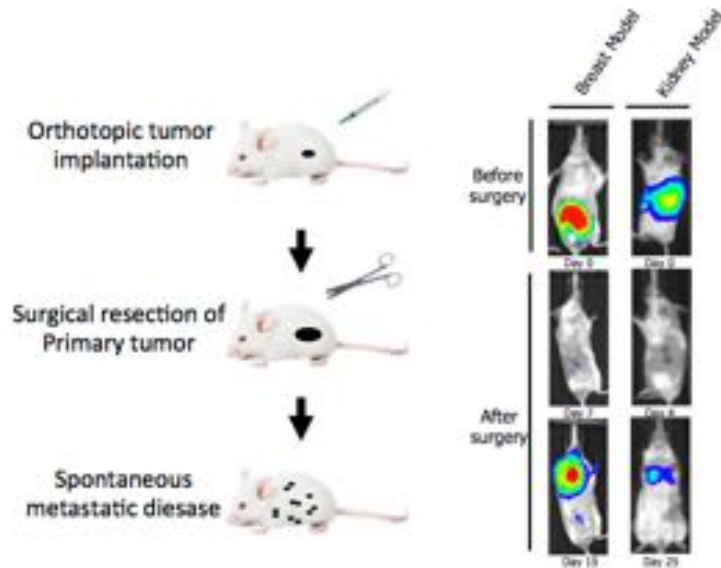


# Experimental data and questions



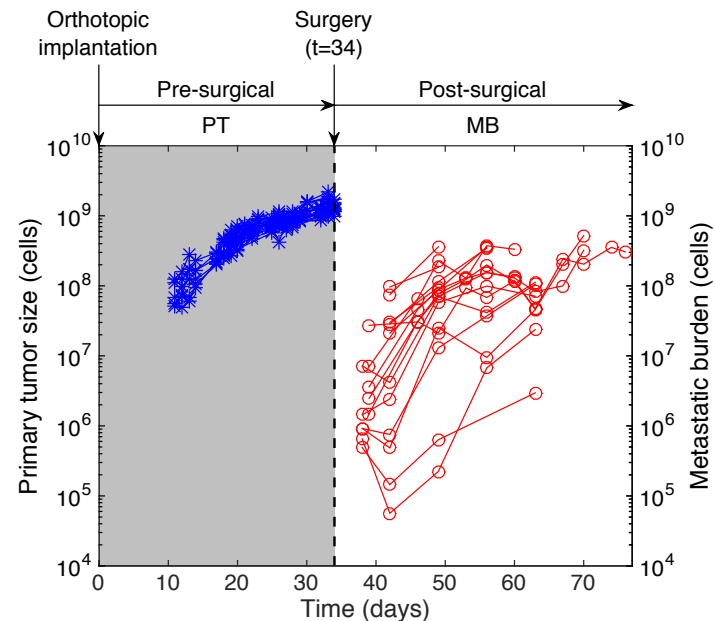
## Data

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

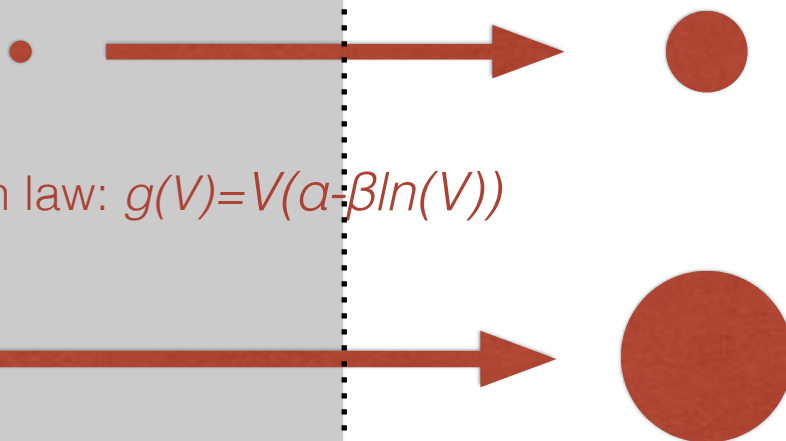
Primary  
Tumor  
(PT)



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<sup>-1</sup>]

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

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

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

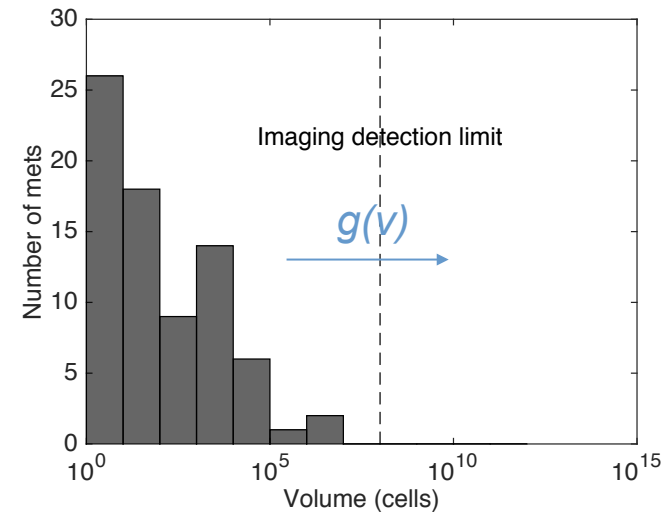
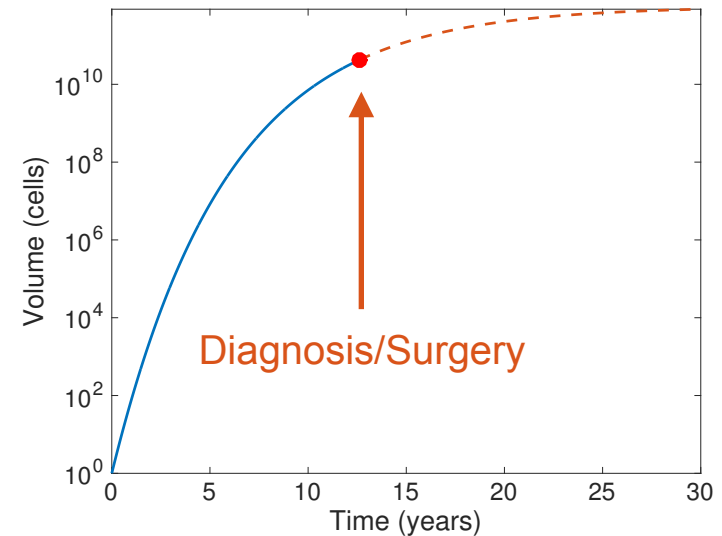
$$\partial_t \rho(t, v) + \partial_v (g(v) \rho(t, v)) = 0$$

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

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

→ 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

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

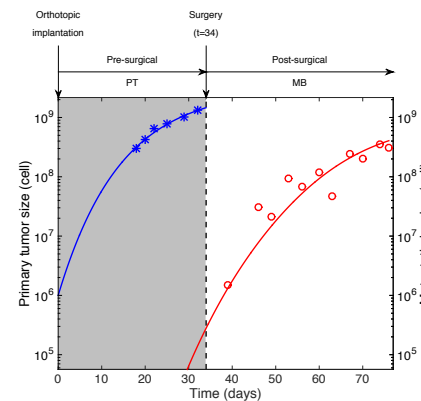
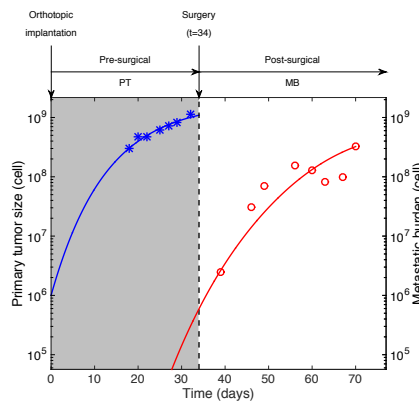
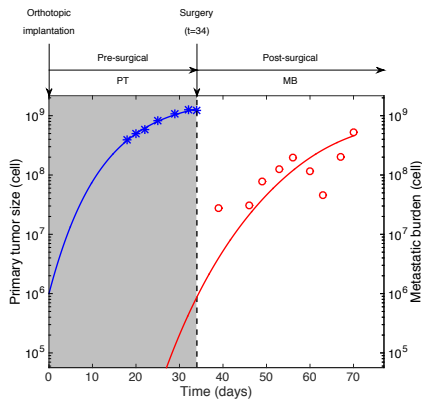
$$\theta^1, \dots, \theta^N \sim \mathcal{LN}(\theta_\mu, \theta_\omega), \quad \theta_\mu \in \mathbb{R}^p, \quad \theta_\omega \in \mathbb{R}^{p \times p}$$



Lavielle, CRC press, 2014

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

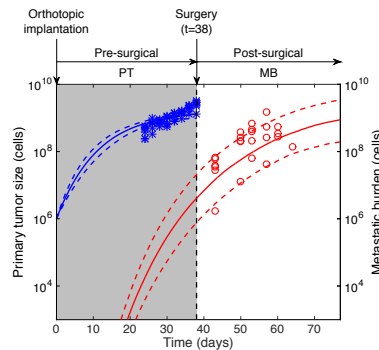
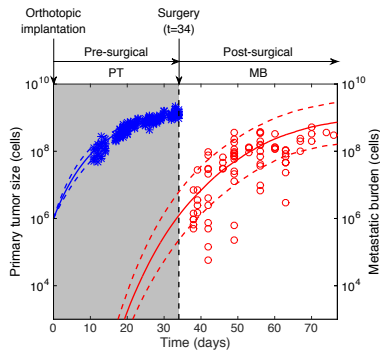
# The model fits at the individual and population levels



- \* 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  $\mu$  is a critical coefficient of inter-animal **variability** of metastatic potential (CV = 176%)

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

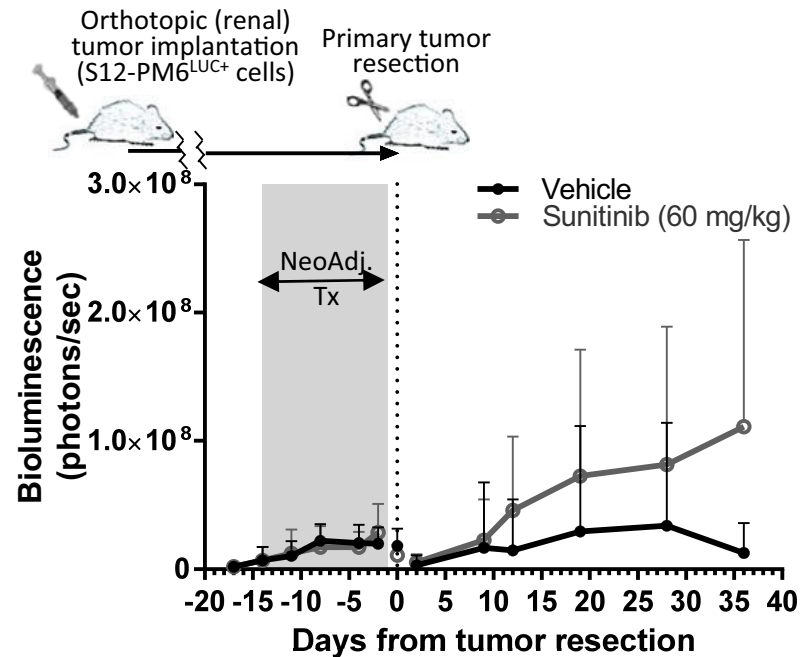


## Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

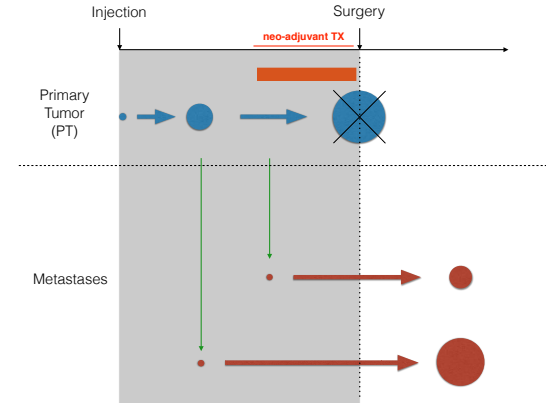
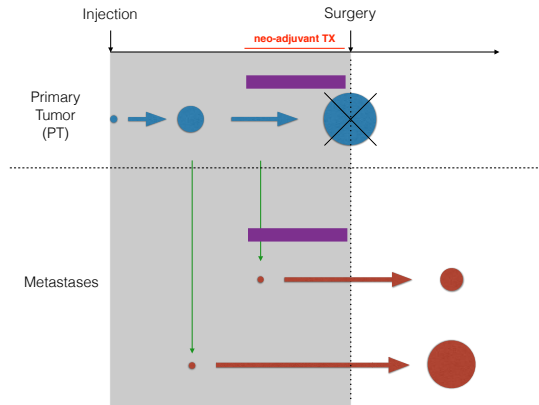
John M.L. Ebos,<sup>1,2</sup> Christina R. Lee,<sup>1</sup> William Cruz-Munoz,<sup>1</sup> Georg A. Bjarnason,<sup>3</sup> James G. Christensen,<sup>4</sup> and Robert S. Kerbel<sup>1,2,\*</sup>

## Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy

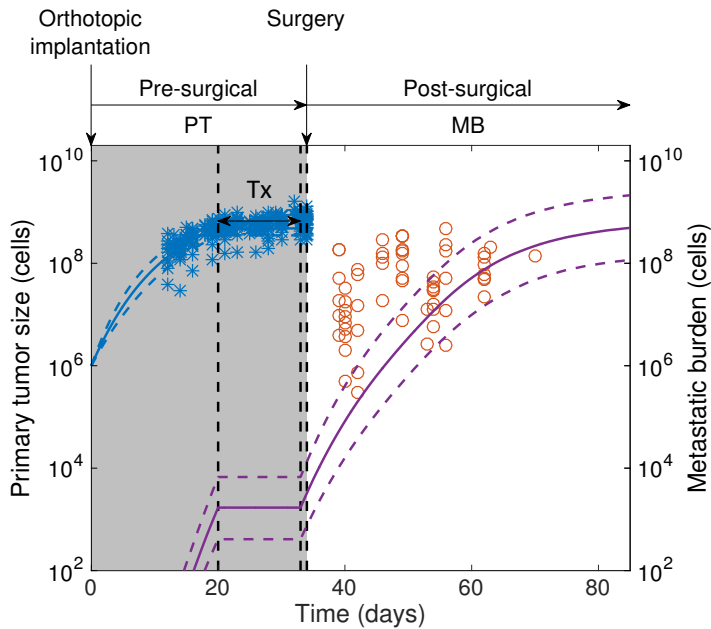
John M L Ebos<sup>1,2</sup>, Michalis Mastroi<sup>3</sup>, Christina R Lee<sup>2</sup>, Amanda Tracz<sup>1</sup>, John M Hudson<sup>2</sup>, Kristopher Attwood<sup>3</sup>, William R Cruz-Munoz<sup>2</sup>, Christopher Jedszko<sup>2</sup>, Peter Burns<sup>2,4</sup> & Robert S Kerbel<sup>2,4</sup>



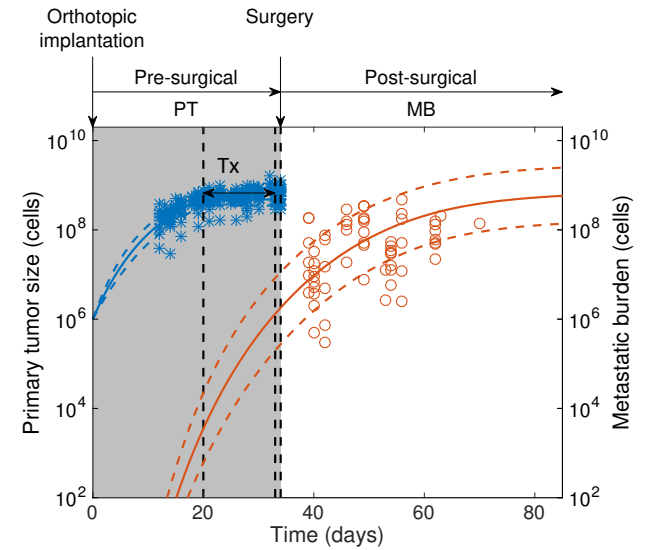
# Testing hypotheses for Sunitinib effect



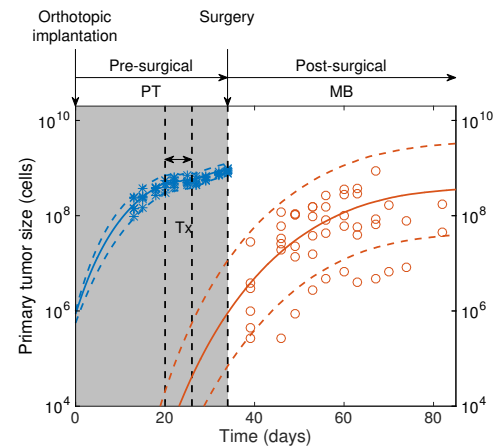
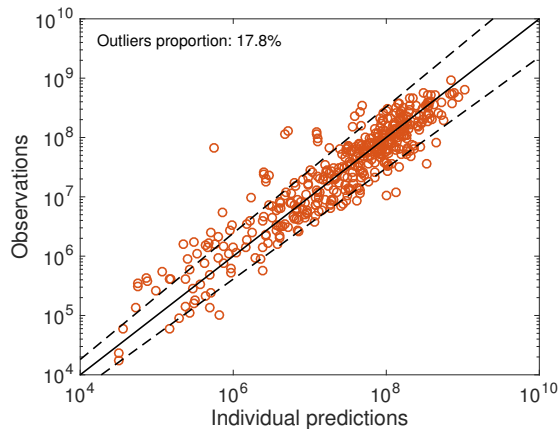
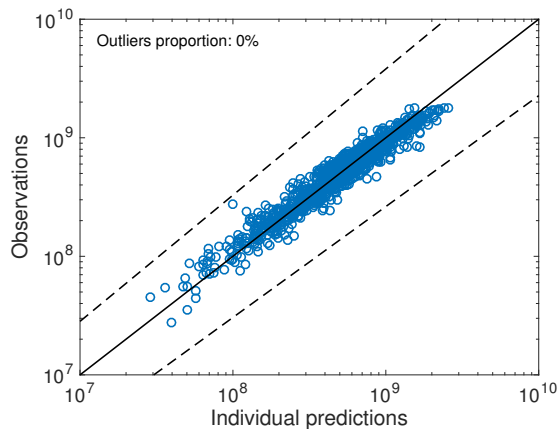
or



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

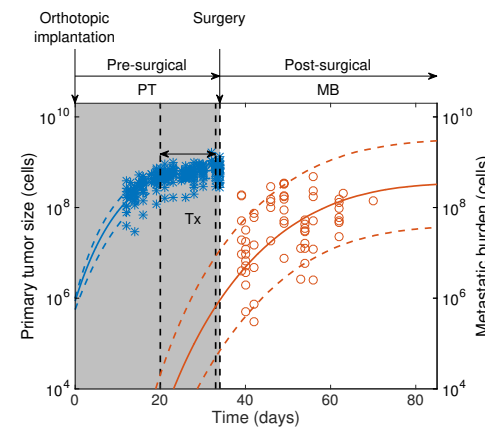


# A validated model of metastatic growth with neoadjuvant Sunitinib therapy



Su60(7D)

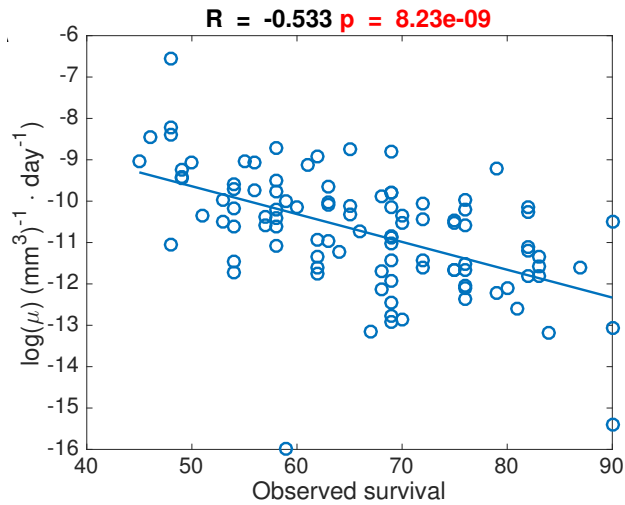
	Unit	Median value	CV (%)	r.s.e. (%)
$\mu$	$cell^{-1} \cdot day^{-1}$	2.12e-11	1.48e+03	17.3
$\alpha$	$day^{-1}$	1.94	18.1	2
$\beta$	$day^{-1}$	0.0911	19.7	2.21
$k$	$(mg/kg)^{-1}$	0.0372	32.1	6.34
$k_e$	$day^{-1}$	3.26 (fixed)	-	-



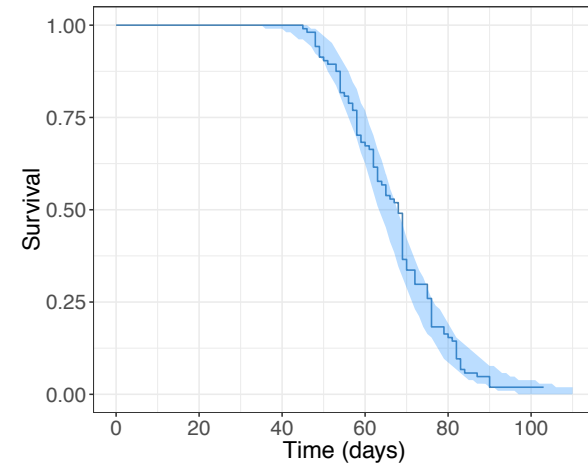
Su60(14D)



# Survival model: $\mu$ as a covariate



Model fit



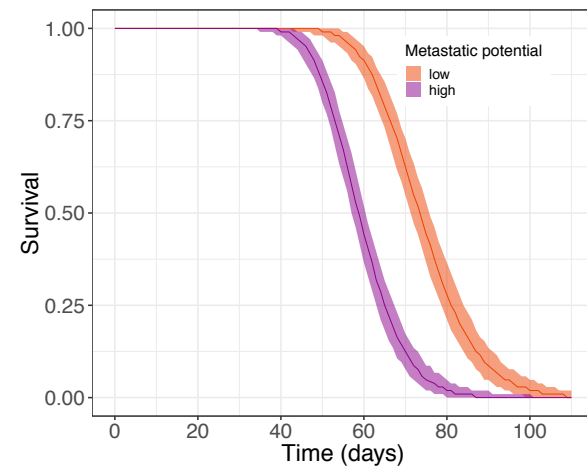
## Nonlinear mixed-effects survival model

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

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

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

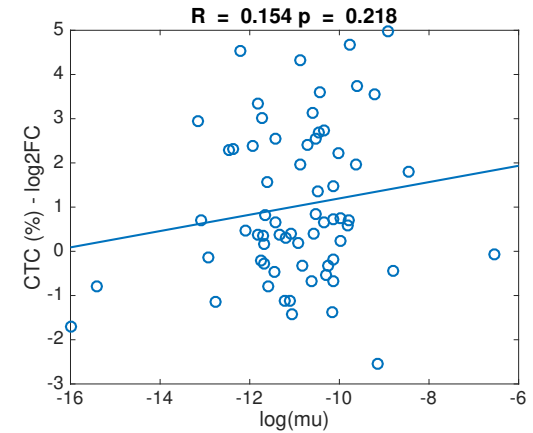
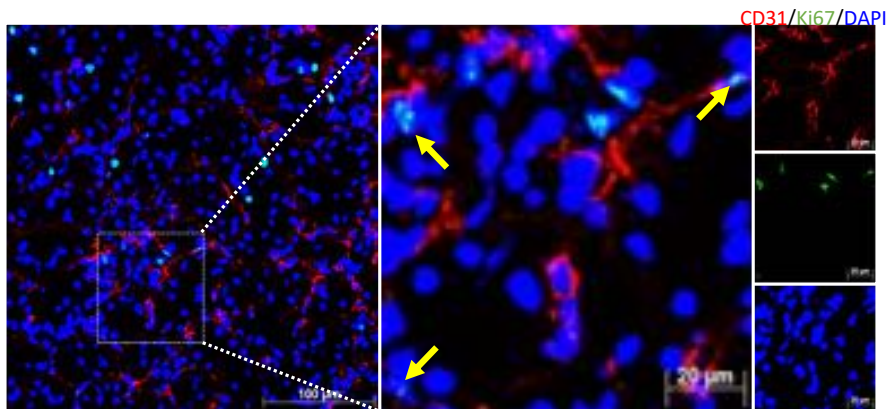
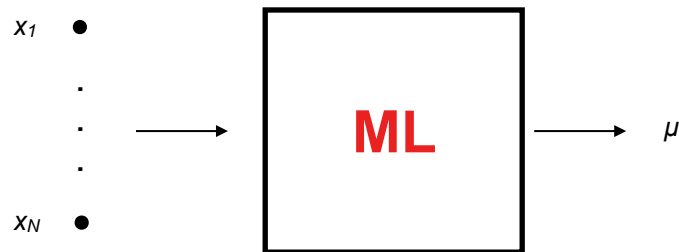
## Individual predictions of survival probability



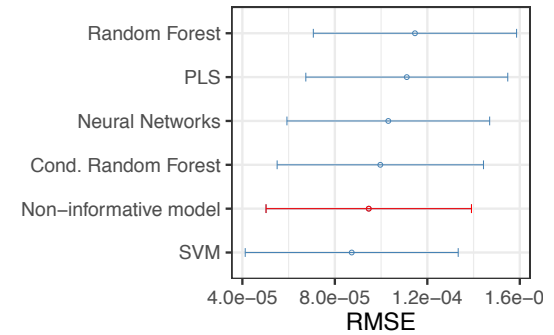
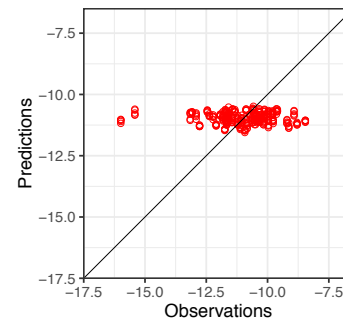
# Trying to predict $\mu$ from biomarkers using machine learning

## Biological measurements on multiple biomarkers

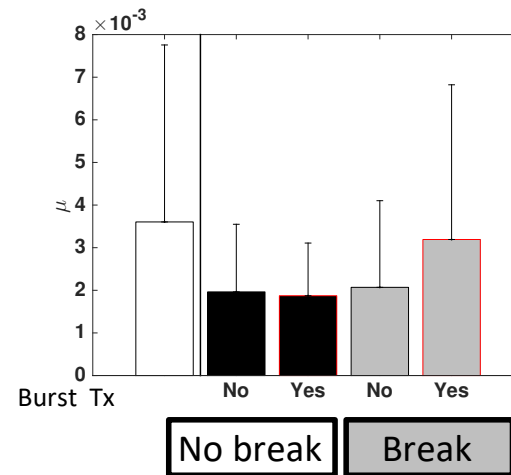
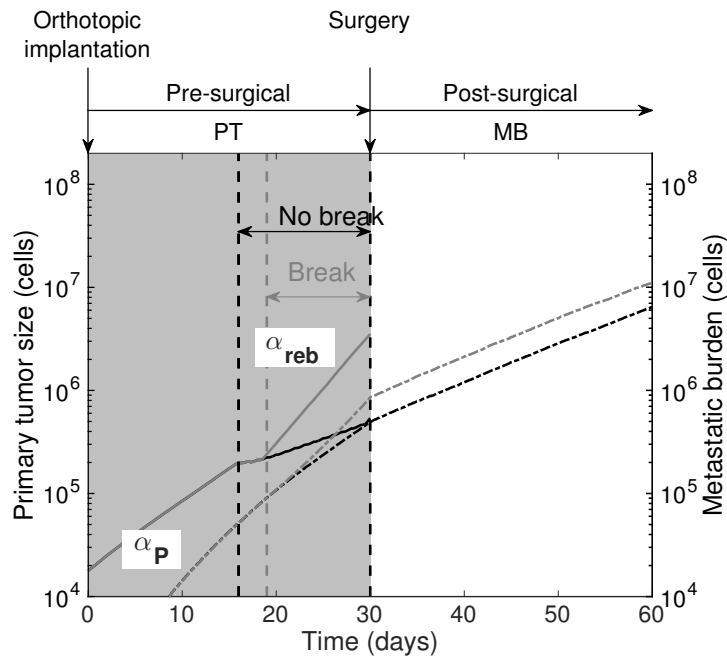
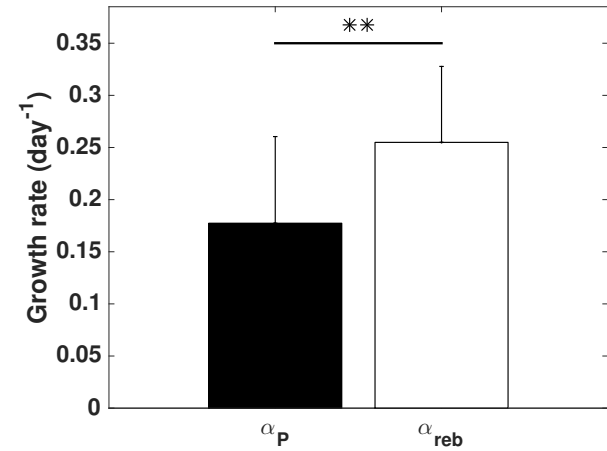
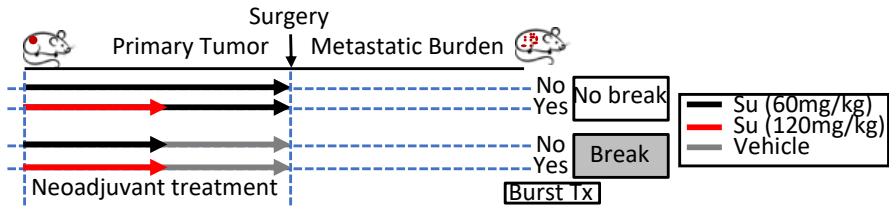
- Circulating tumor cells
- Proliferative (Ki67+) and endothelial cells (CD31+)
- Myeloid Derived Suppressor Cells (MDSCs)



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  $\mu$  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

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

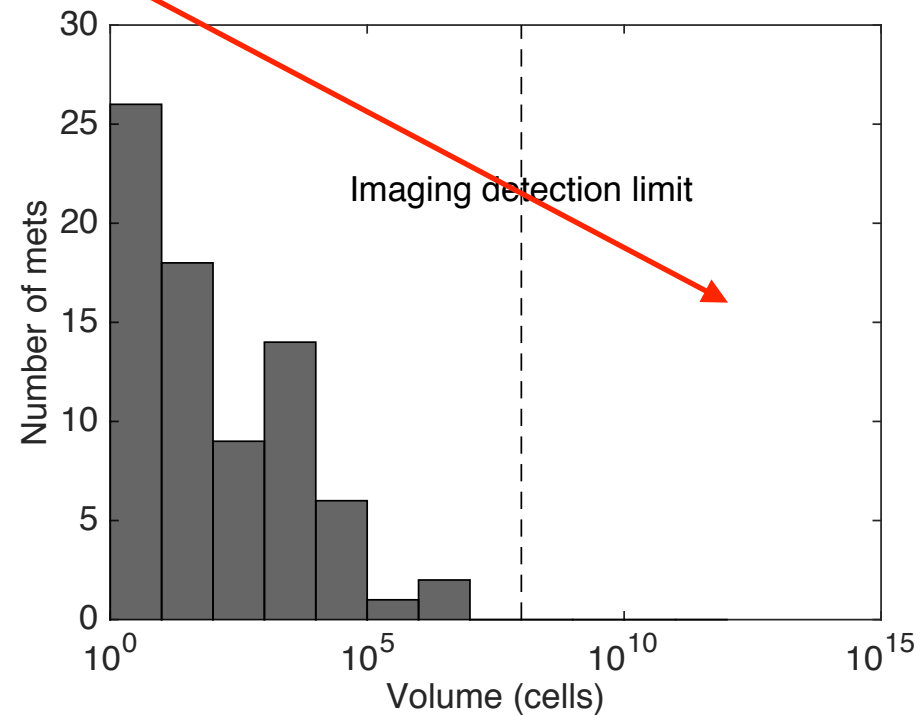
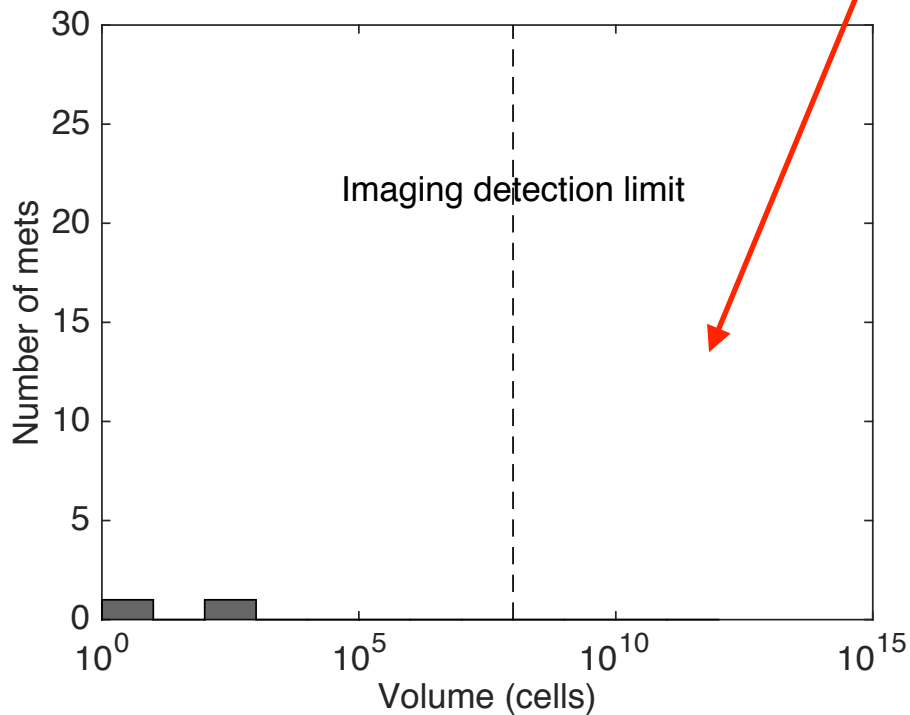


# Diagnosis personalization

Virtual patient with  
median  $\mu$

Virtual patient with  
large  $\mu$  (90th prct)

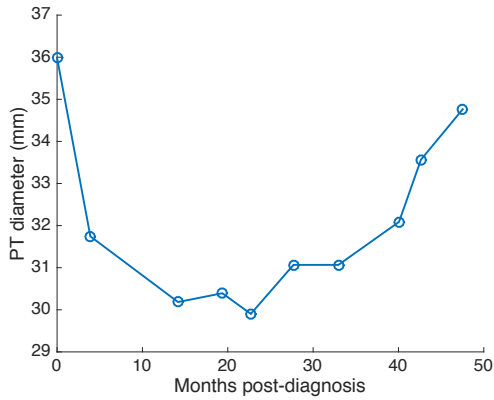
Nothing visible



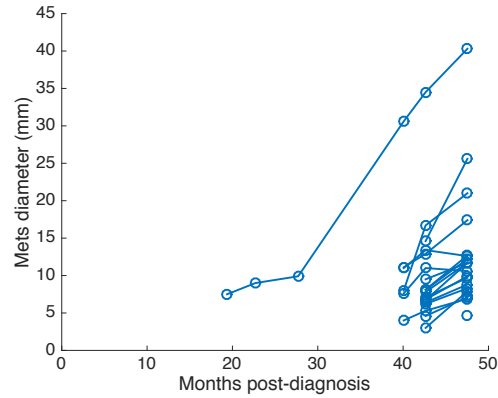
Breast cancer patient with primary tumor of 4.32 cm

# Data of a NSCLC patient with brain mets

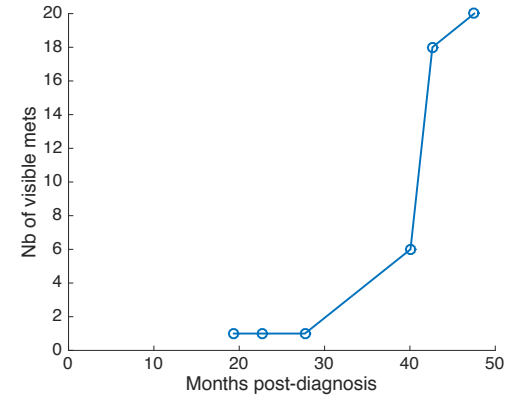
## Primary tumor size



## Metastases size



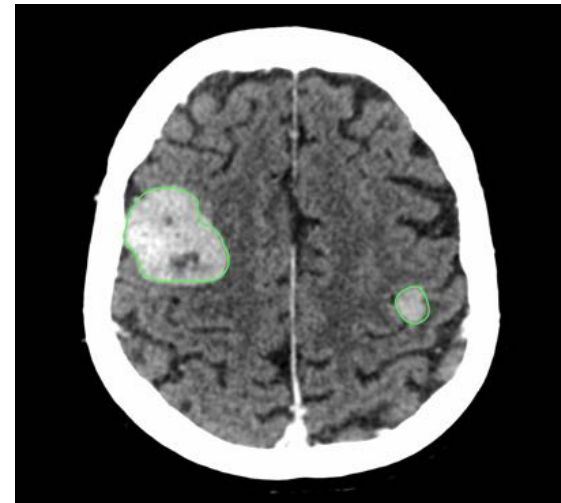
## Number of visible mets



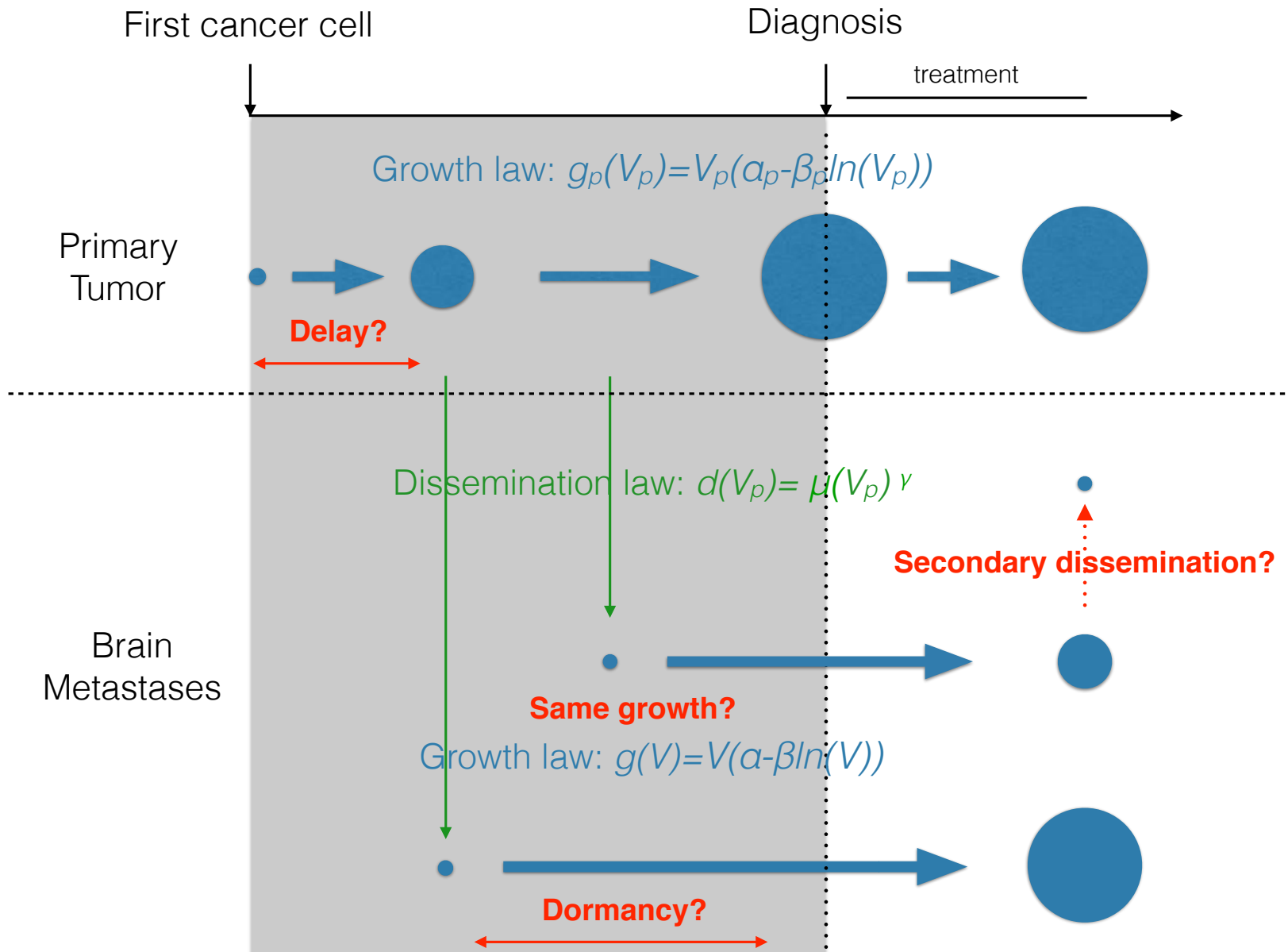
## Lung CT



## Brain CT scan

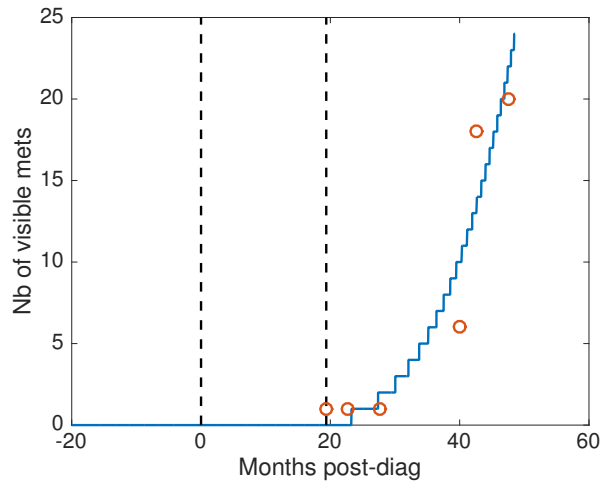
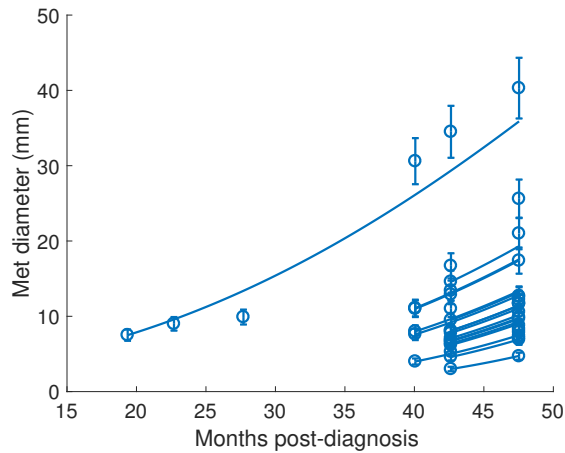


# Different biological scenari





# The model with dormancy could describe best the data

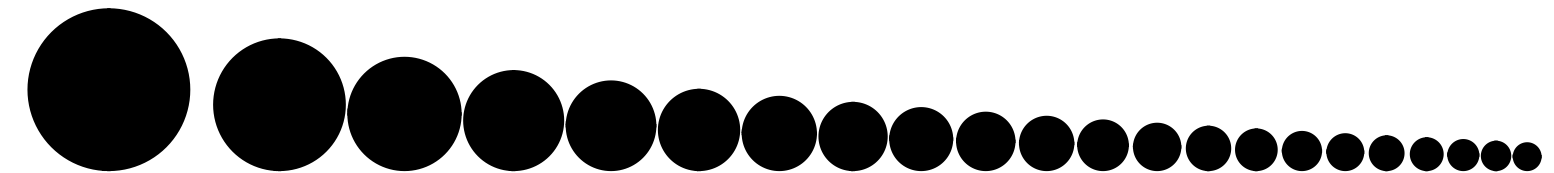


## Objective function

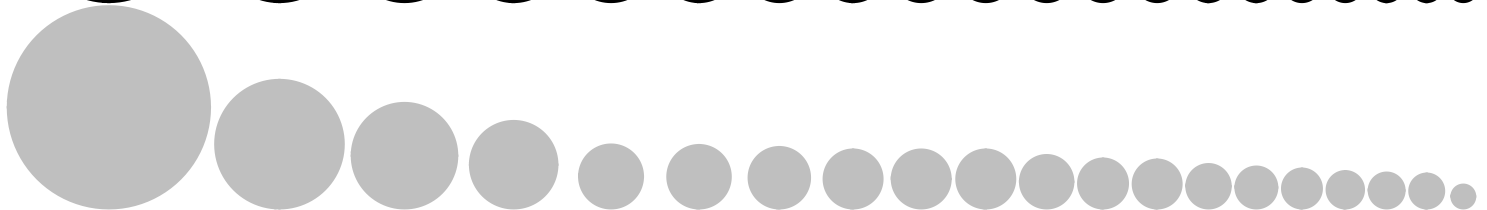
Model	Patient 1	Patient 2
Base	5.51	2.53
Secondary	5.43	2.3
Delay	5.23	1.53
Dormancy	4.93	1.71
Diff. growth	4.95	1.79

Dormancy estimated to 133 days  $\pm$  4.2%

Model



Data

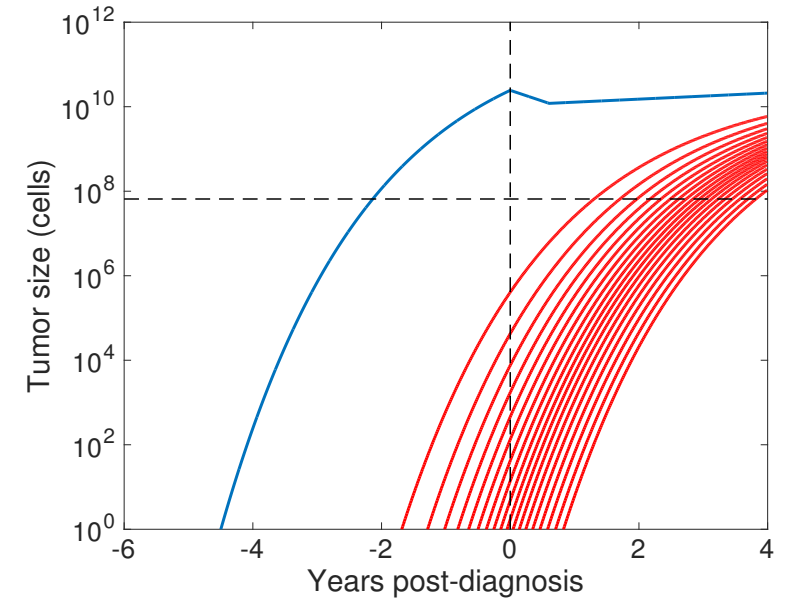
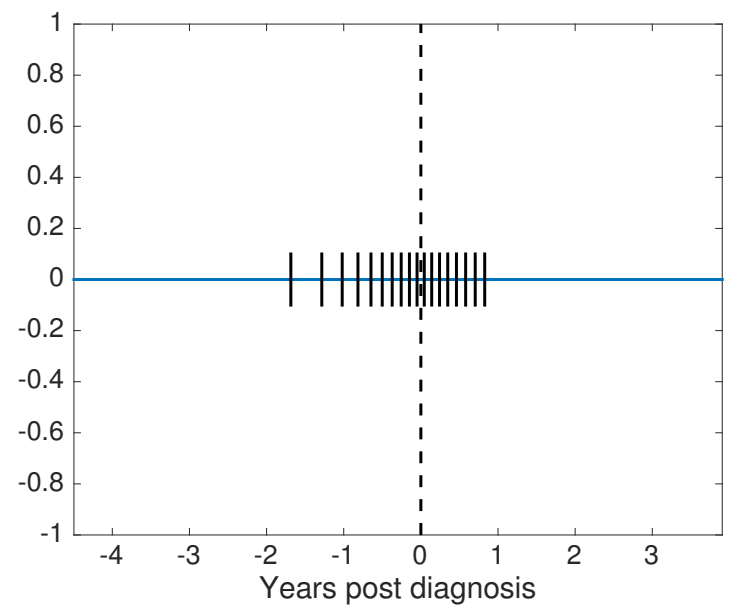
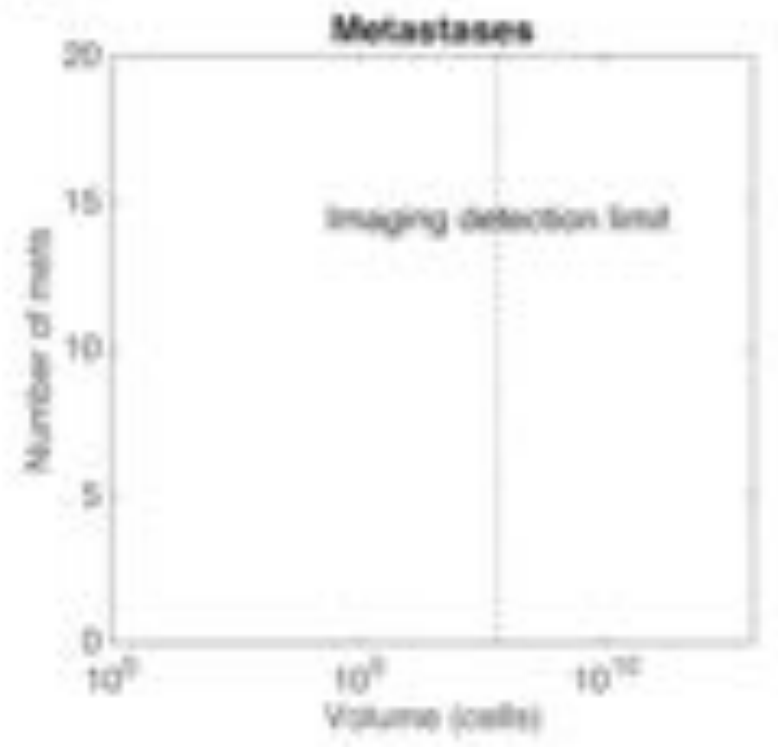
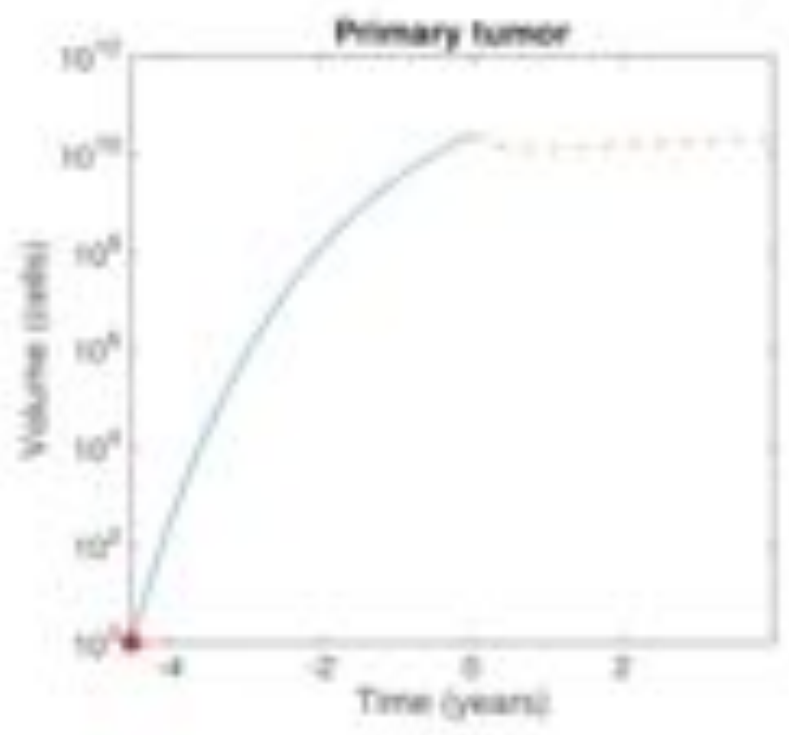


t = -55 months  
— 10 mm

Primary  
tumor  
(lung)

Metastases (Brain)

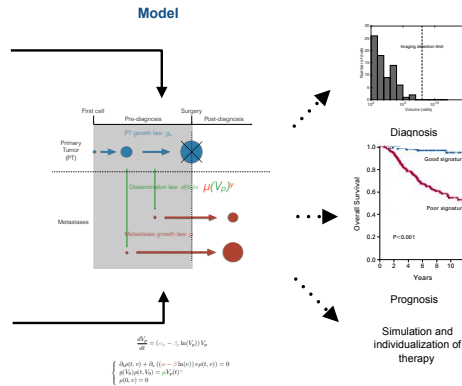
$t = -4.5$  years



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

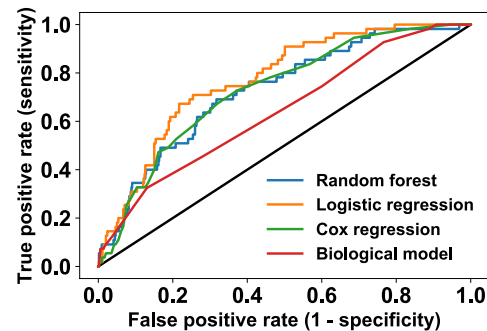
- Use the model for predictions of **time-to-relapse** and survival
- Implement clinical variables and biomarkers as **biologically meaningful** covariates
- Predict metastasis for localized **breast** cancer patients (~10% relapse at 5 years) to advise for **adjuvant therapy**

Clinical database  
biomarkers at diagnosis



	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**

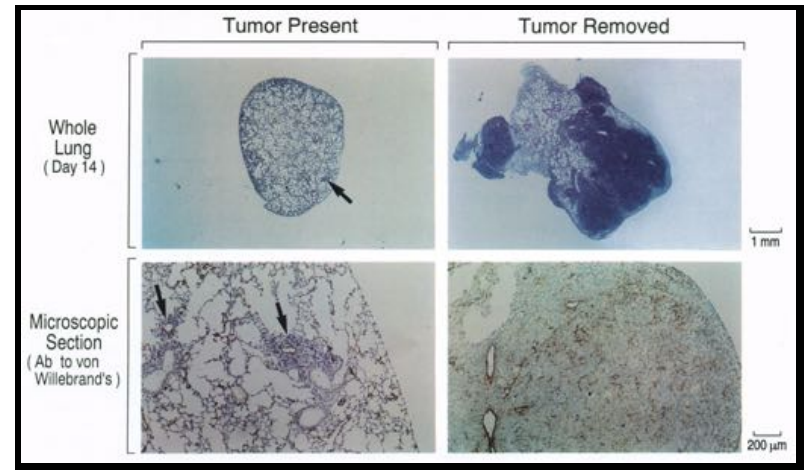
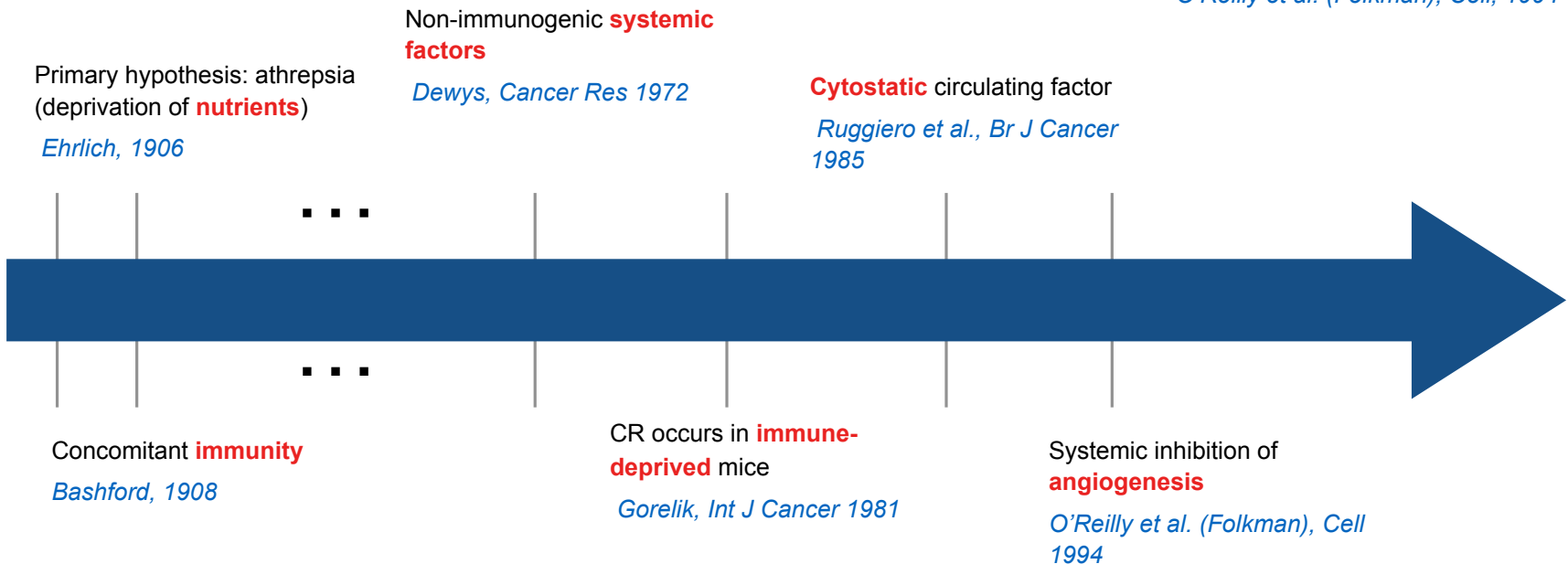


Figure 2. The Presence of a Primary Tumor Is Associated with an Inhibition of Neovascularization and Growth of Its Metastases

*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

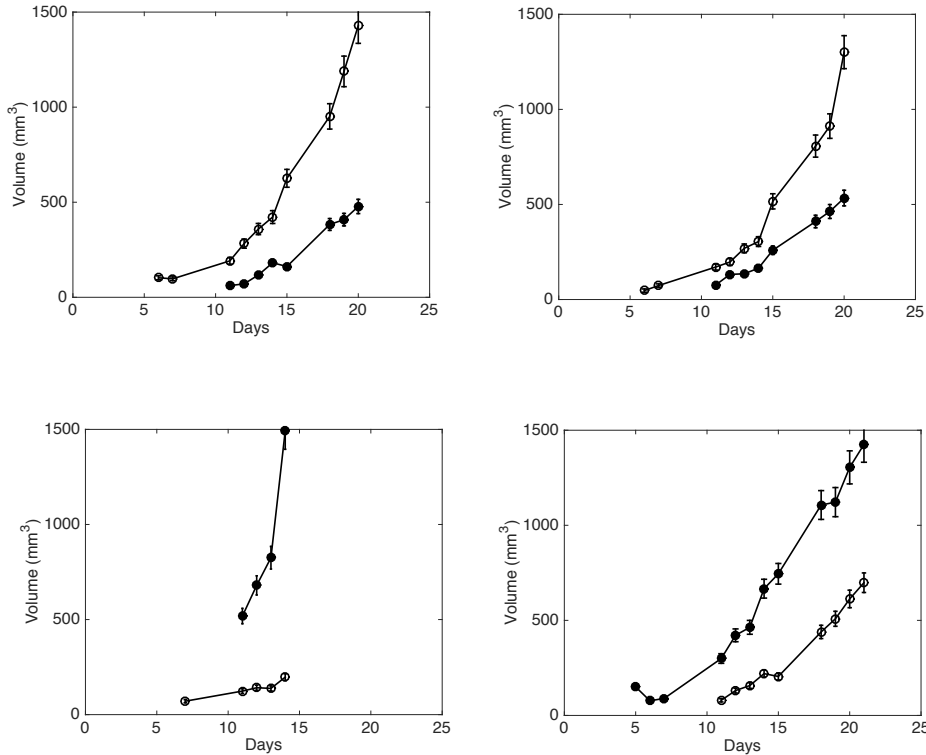
# A mouse with two tumors



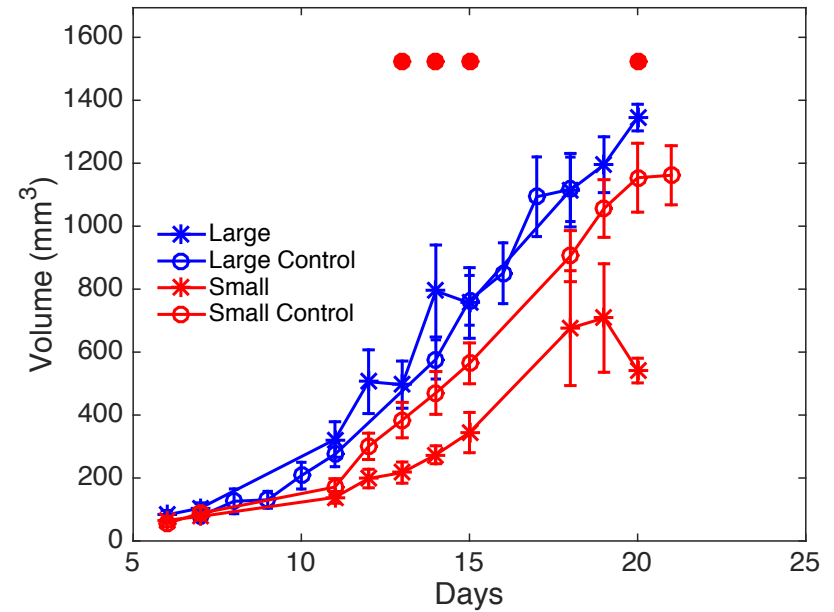


# One tumor has normal growth and the other is suppressed

## 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

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

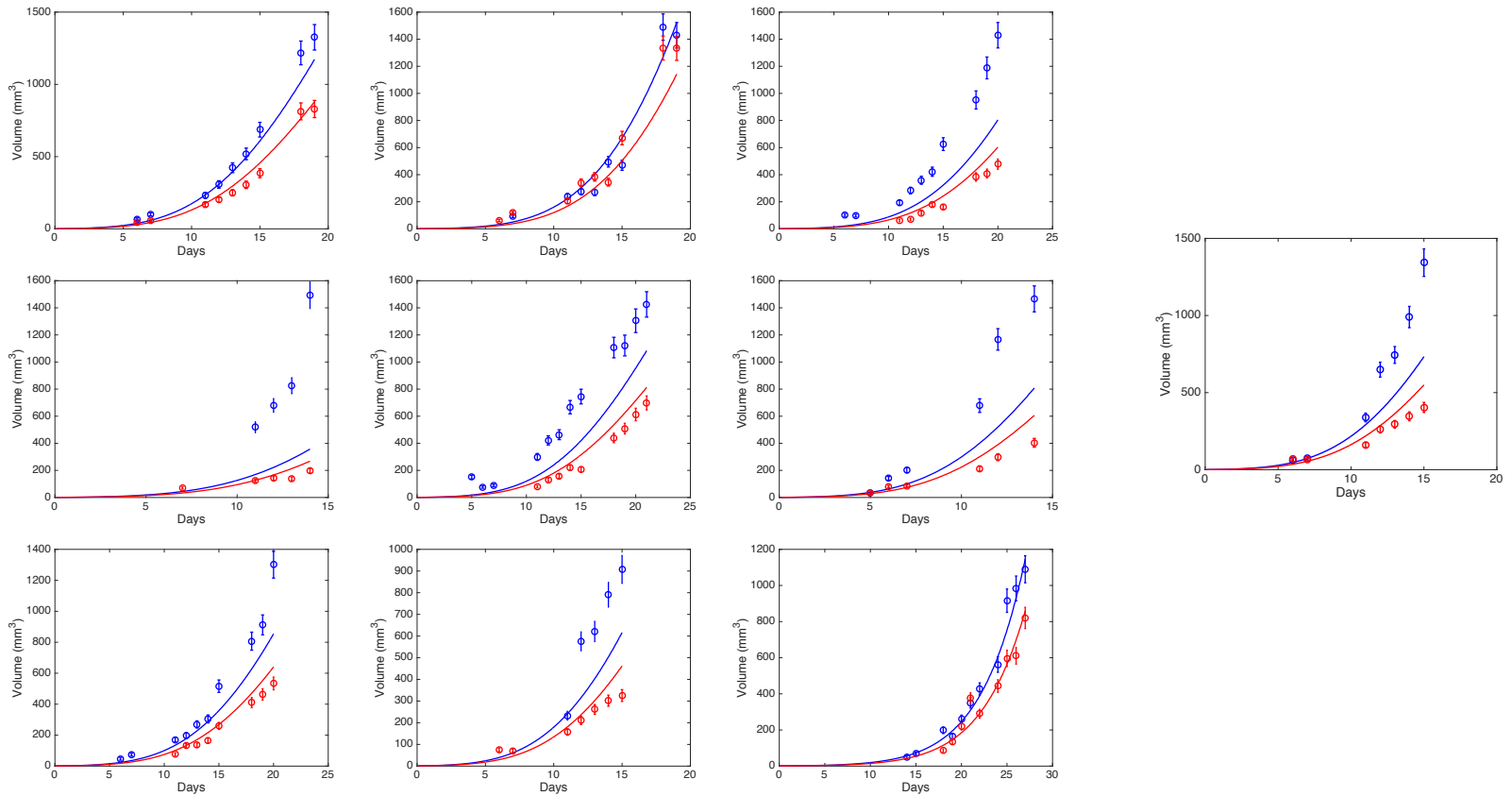
## Angiogenesis inhibition

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

## Proliferation inhibition

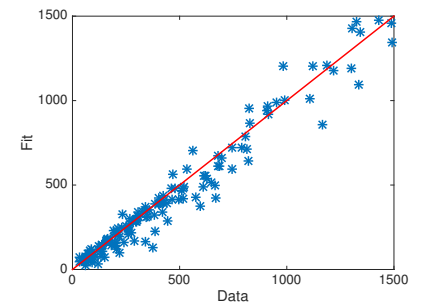
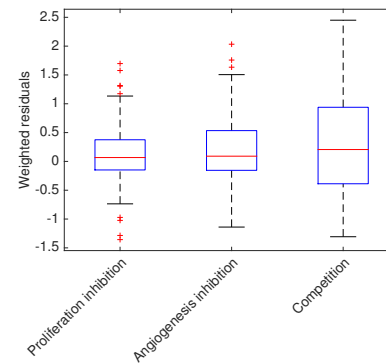
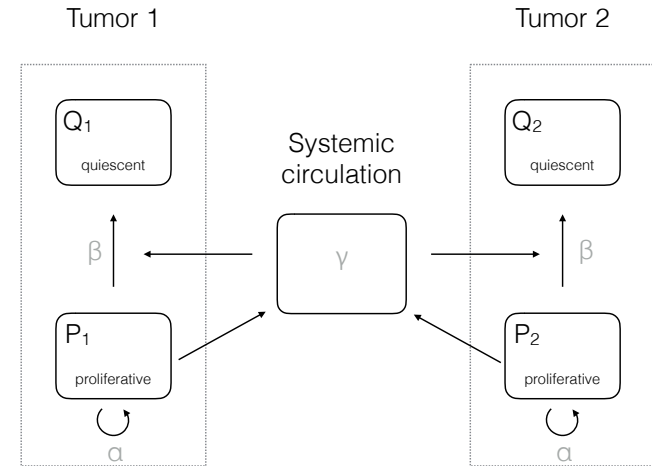
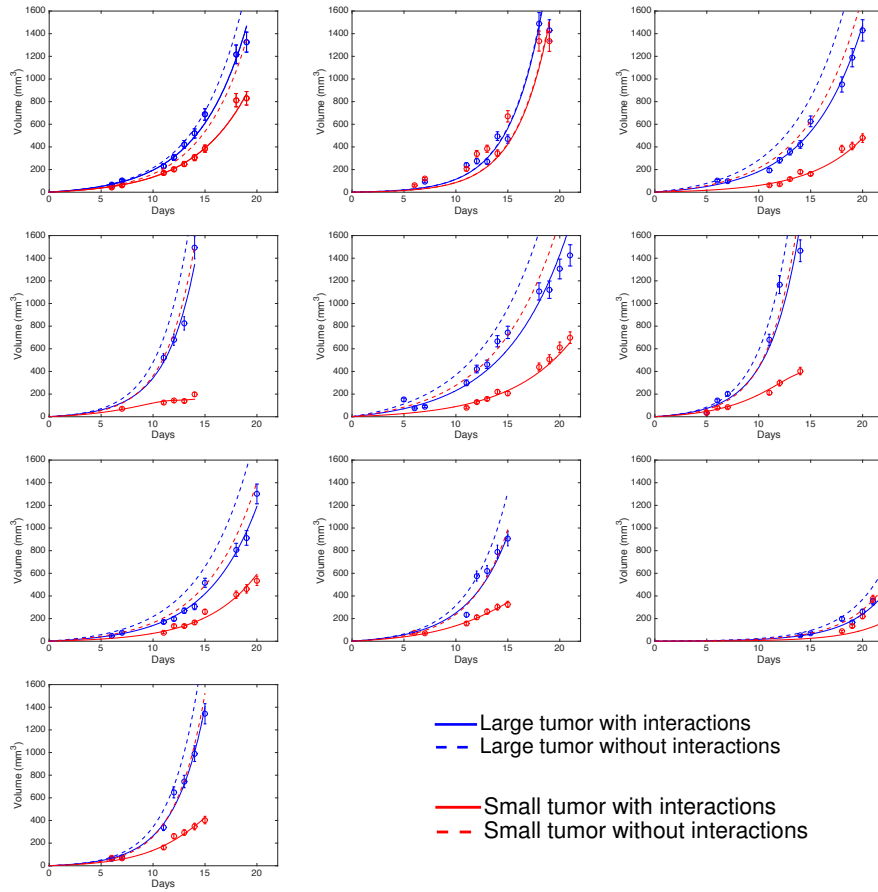
$$\begin{cases} \frac{dP_1}{dt} = \alpha P_1 - (\beta P_1 + \gamma(P_1 + P_2)) 1_{P_1 > 0}, & P_1(t=0) = V_{0,1} \\ \frac{dQ_1}{dt} = \beta P_1 + \gamma(P_1 + P_2), & Q_1(t=0) = 0 \\ \frac{dP_2}{dt} = \alpha P_2 - (\beta P_2 + \gamma(P_1 + P_2)) 1_{P_2 > 0}, & P_2(t=0) = V_{0,2} \\ \frac{dQ_2}{dt} =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

# 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	$\alpha$	day <sup>-1</sup>	5.77 (67.4)	17.5
	$\beta$	day <sup>-1</sup>	5.07 (49.3)	21.2
	$\gamma$	-	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  $\mu$**  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**

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- Preclinical data of ortho-surgical animal models of metastases

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\*M. Mastri



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\*P. Hahnfeldt

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

## *Clinic*

- Brain metastasis from lung tumors

\*F. Chomy

**Bergonié Institute, Bordeaux, FR**



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

## *Modeling*

\*C. Nicolò



\*D. Barbolosi

# Thank you for your attention!