



# Data-driven mechanistic modeling of metastasis: cancer at the organism scale

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# Data-driven mechanistic modeling of metastasis: cancer at the organism scale

S. Benzekry

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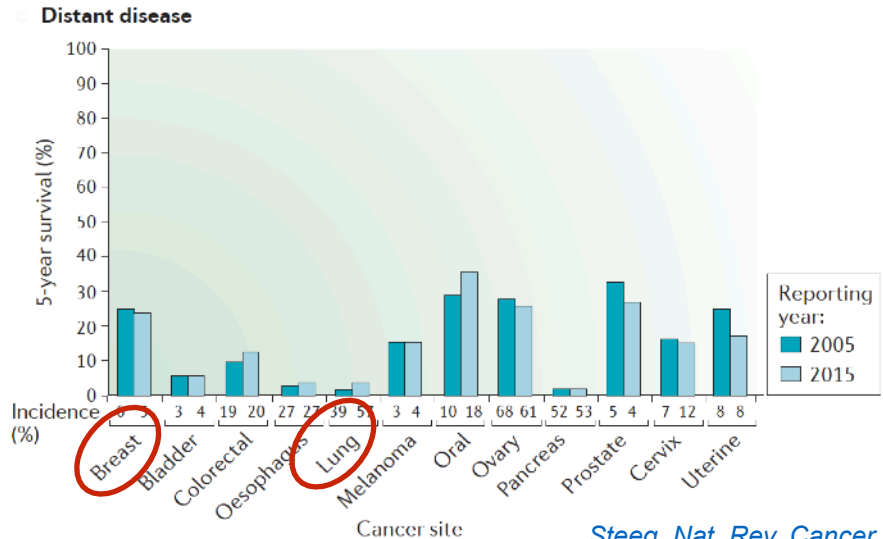
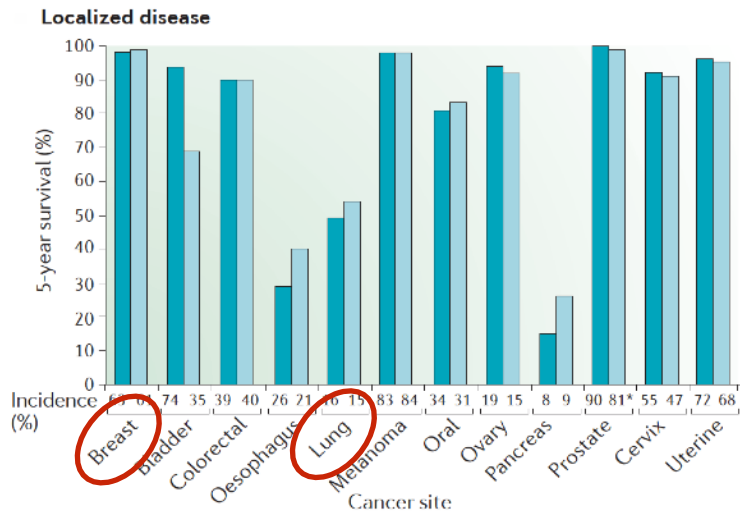
21 mai 2019





# Metastasis (μετά = beyond, στάσιζ = place)

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



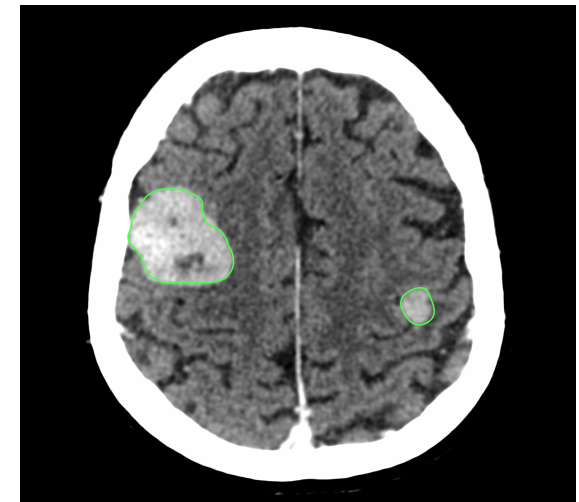
## • Breast

- 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

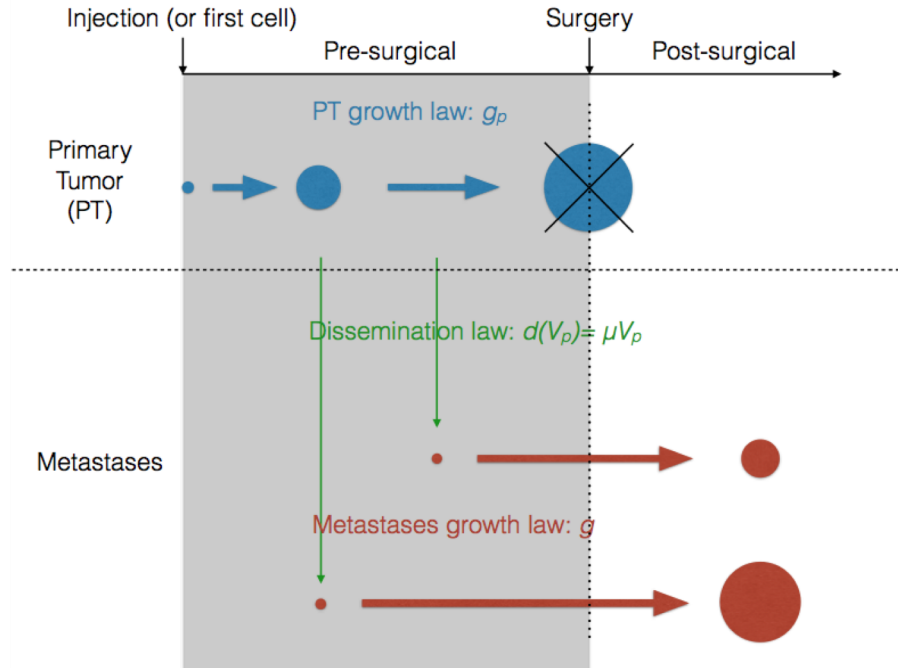
- 57% of cases are metastatic
- Decide whether to use **whole brain radiation therapy** or just (stereotactic) surgery
- Avoid cognitive impairment of the patient

*Steeg, Nat. Rev. Cancer, 2016*



*Institut Bergonié, Bordeaux*

# Mechanistic model of metastatic dissemination and growth



Growth rates of primary and secondary tumors  $g_p$  and  $g$

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

$$g(v) = (\alpha - \beta \ln(v)) v$$

Dissemination rate

$$d(V_p) = \mu V_p$$

Size distribution of the metastases  $\rho(t, v)$

$$\begin{cases} \partial_t \rho(t, v) + \partial_v (g(v) \rho(t, v)) = 0 \\ g(V_0) \rho(t, V_0) = d(V_p(t)) \\ \rho(0, v) = \rho^0 \end{cases}$$

Metastatic burden (total number of metastatic cells)

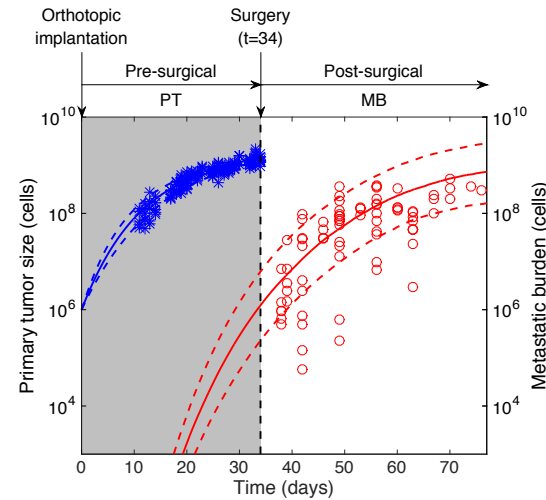
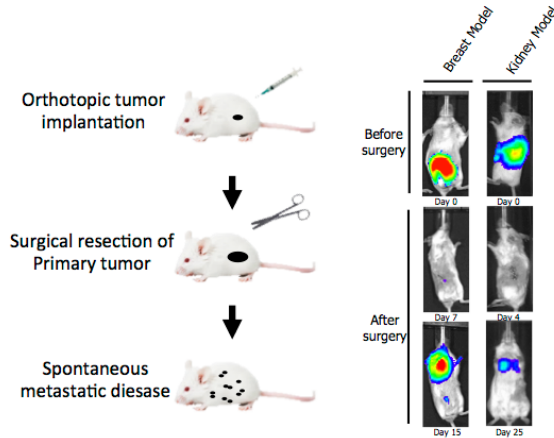
$$M(t) = \int_{V_0}^{+\infty} v \rho(t, v) dv = \int_0^t d(V_p(t-s)) V(s) ds$$



Ebos lab

Roswell Park Cancer Institute

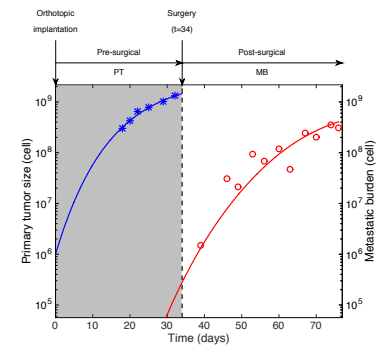
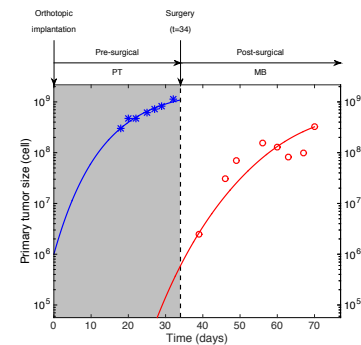
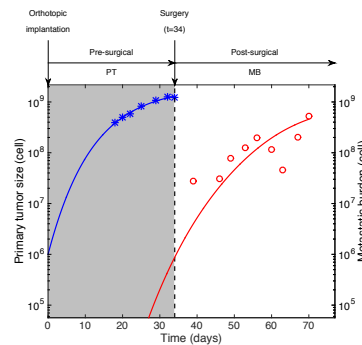
# Validation on animal data



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

Nonlinear **mixed-effects**  
statistical model for inter-  
animal variability

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



⇒ **same growth** for PT and mets:  $\alpha_p = \alpha$ ,  $\beta_p = \beta$

# Current work: implementing the mechanistic model into a statistical learning model

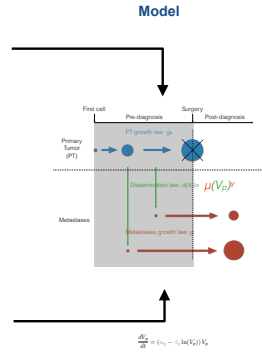
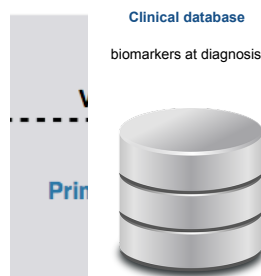
- Use the model for predictions of **time-to-relapse (TTR)**
- Implement clinical variables and biomarkers as **biologically meaningful** covariates

$$TTR^i = \inf \left\{ t > 0; N_{vis} \left( t, \theta^i \right) > 1 \right\}$$

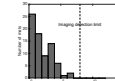
Parameter	Estimate	r.s.e. (%)	p-value
$\log \alpha_{pop}$	-8.883	10.151	
$\beta_{Ki67, \alpha}$	0.086	27.376	$2.59 \cdot 10^{-4}$
$\beta_{HER2, \alpha}$	0.029	42.833	0.020
$\beta_{CD44, \alpha}$	0.011	60.816	0.1
$\beta_{TRIO, \alpha}$	0.016	58.119	0.085
$\log \mu_{pop}$	-26.342	3.696	
$\beta_{EGFR, \mu}$	0.039	47.527	0.035
$\sigma$	0.606	23.104	
$\omega_{\alpha}$	2.062	22.715	
$\omega_{\mu}$	3.563	16.759	

**Features selection based on Cox regression**

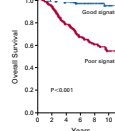
	p
tumor_size_clinical	0.00165
tumor_size_histological	0.4
grade	0.358
histology	0.0041
TNM_T	0.146
TNM_N	0.599
nb_invaded_ganglions	0.619
menopausal_status	0.000471
ER	0.543
PR	0.34
Ki67	3.09e-05
HER2	0.17
HER2_intensity	0.482
CK56	0.793
EGFR	0.016
VIM	0.226
ALDH1	0.674
CD24	0.894
CD44	0.397
E_cadherin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



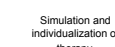
Prediction



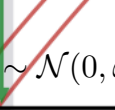
Diagnosis



Prognosis



Simulation and individualization of therapy

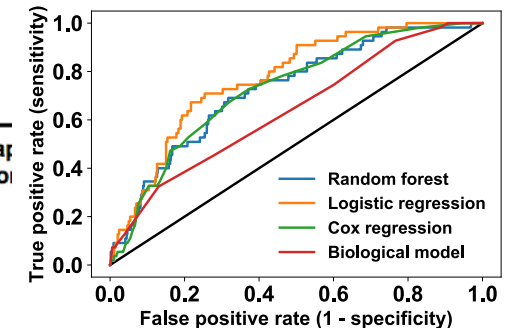


$$\ln(\mu^i) = \ln(\mu_{pop}) + \beta_{\mu}^T \mathbf{x}_{\mu}^i + \eta_{\mu}^i, \quad \eta_{\mu}^i \sim \mathcal{N}(0, \omega_{\mu}^2)$$

$$\ln(\alpha^i) = \ln(\alpha_{pop}) + \beta_{\alpha}^T \mathbf{x}_{\alpha}^i + \eta_{\alpha}^i, \quad \eta_{\alpha}^i \sim \mathcal{N}(0, \omega_{\alpha}^2)$$

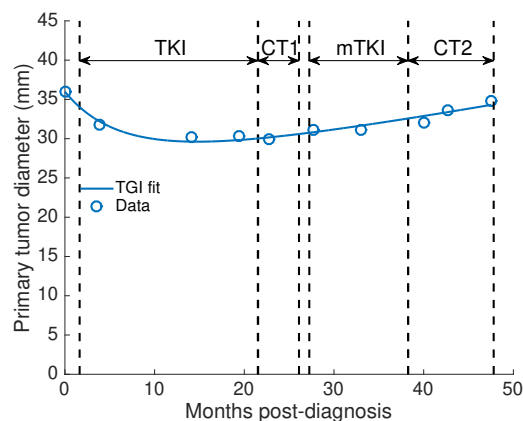
	AUROC	Accuracy	NPV	PPV
Random forest	0.727	87	91.7	22.5
Logistic regression	0.772	90.1	91	25
Cox regression	0.728	87.4	91.1	16.7
Bio-based	0.641	89.7	91.3	31.2

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

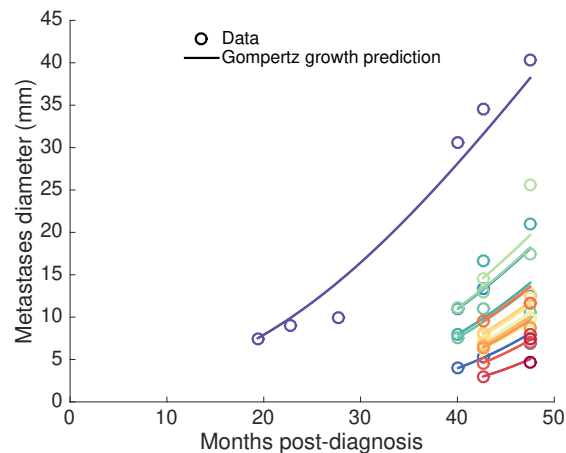


# Data of a NSCLC patient with brain mets

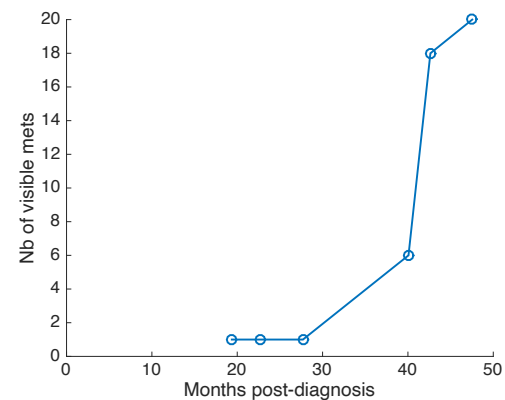
## Primary tumor size



## Metastases size



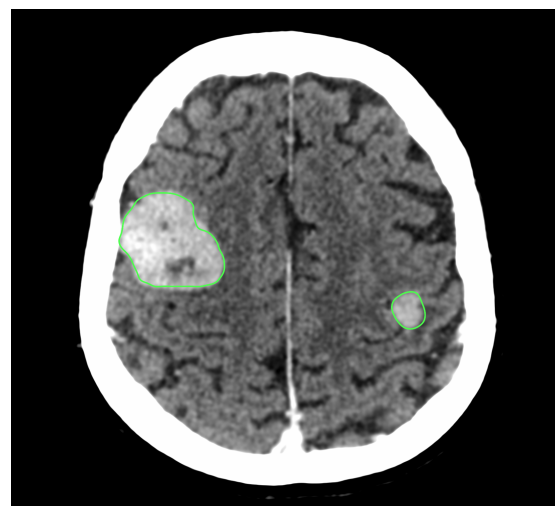
## Number of visible mets



## Lung CT



## Brain CT scan



First cancer cell

Diagnosis

treatment

Growth law:  $g_p(V_p) = V_p(\alpha_p - \beta_p \ln(V_p))$

Primary  
Tumor

**Delay?**

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

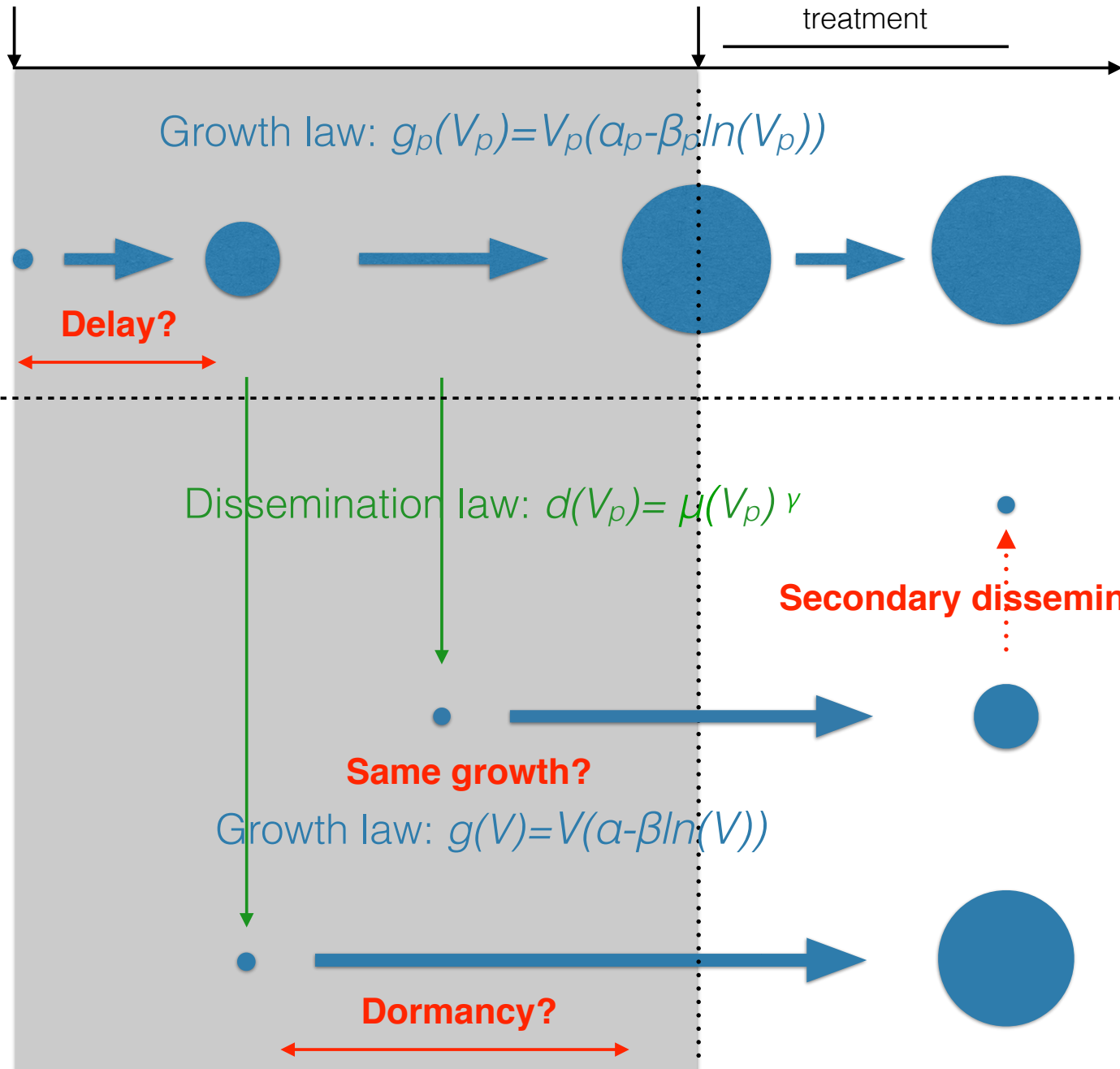
Brain  
Metastases

**Same growth?**

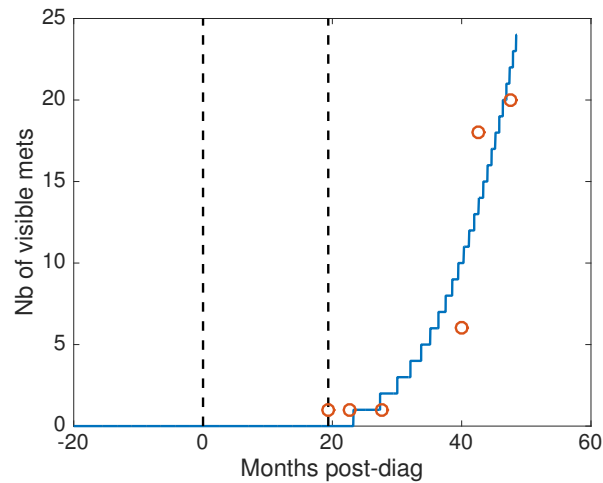
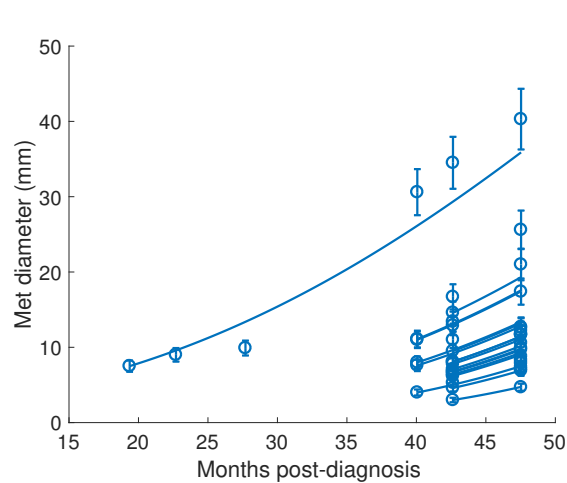
Growth law:  $g(V) = V(\alpha - \beta \ln(V))$

**Secondary dissemination?**

**Dormancy?**



# The model with dormancy could describe best the data

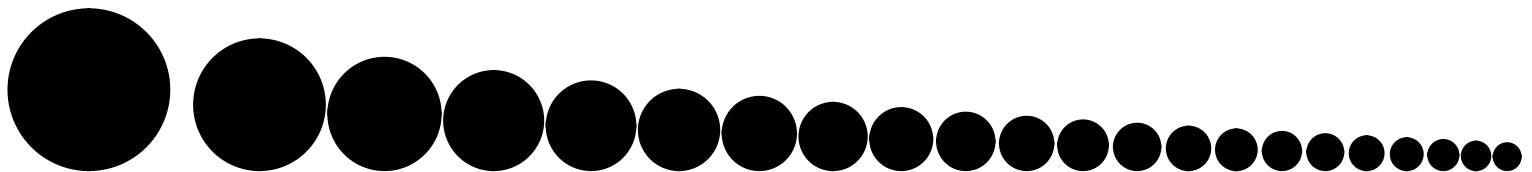


## Objective function

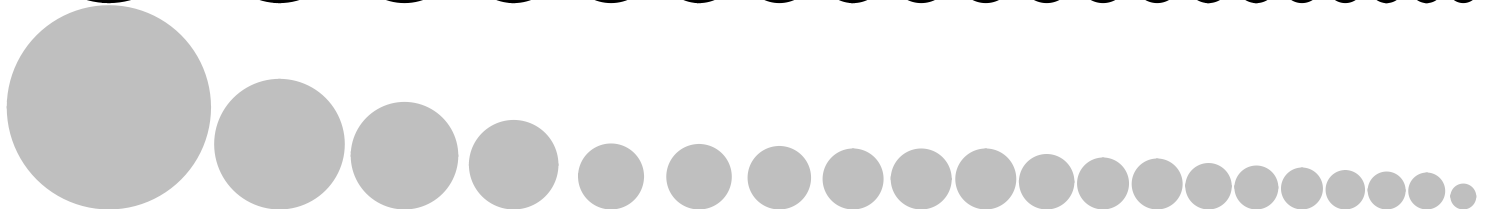
Model	Patient 1	Patient 2
Base	5.51	2.53
Secondary	5.43	2.3
Delay	5.23	1.53
Dormancy	4.93	1.71
Diff. growth	4.95	1.79

Dormancy estimated to 133 days  $\pm$  4.2%

Model



Data



$t = -65$  months

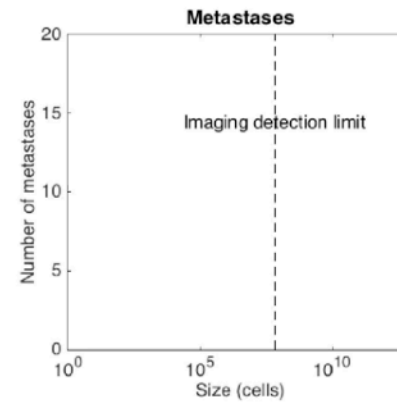
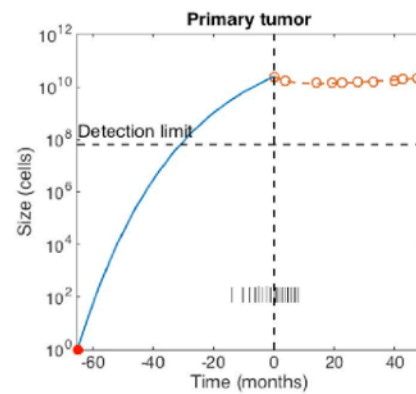
— 10 mm

\*

Primary  
tumor  
(lung)

Metastases (brain)

$t = -65.1$  months

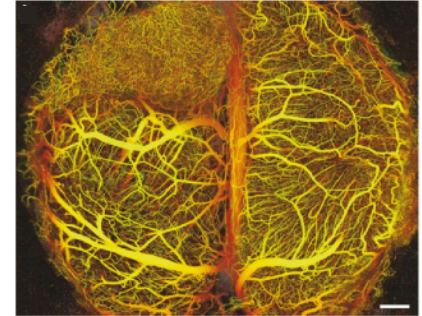




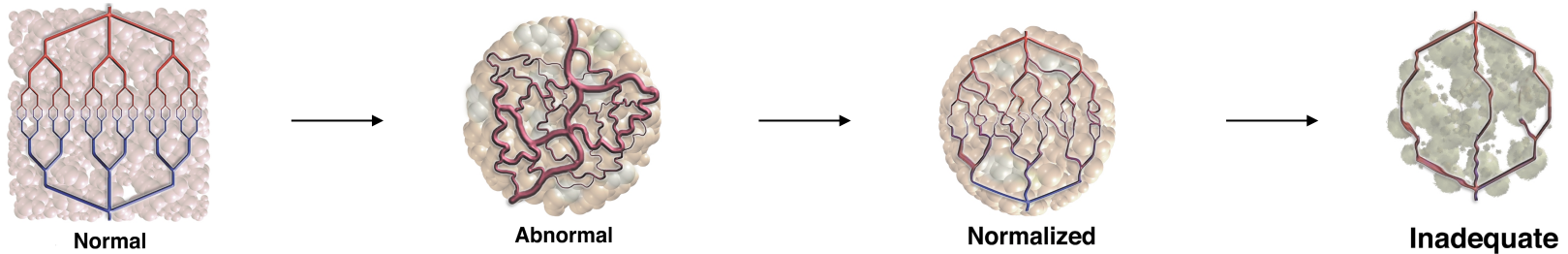
## 2 Combination bevacizumab - chemotherapy

# Vascular normalization: a time window for improved pharmacokinetics?

- Bevacizumab = anti-VEGF monoclonal antibody  $\Rightarrow$  **anti-angiogenic** action (first approved in 2004)
- Only proved clinical efficacy when **combined (concomitantly) with cytotoxics**
- Possible explanation: transient **normalization** of the otherwise abnormal (leaky, tortuous) vascular architecture



*Vakoc et al., Jain, 2009, Nat Med*



*Jain, Nat Med, 2001*

## Therapeutic question

What is the **optimal time gap** between administration of bevacizumab and cytotoxic chemotherapy? How to capture **inter-individual variability** for designing **personalized therapies**?

**Hypothesis: sequential use of bevacizumab associated with chemotherapy would achieve better efficacy and modeling support could help to define the optimal time-window**

Current beva-chemo  
regimen are  
underpowered



**Breast cancer model**

*Mollard et al. (Benzekry), Oncotarget 2017*

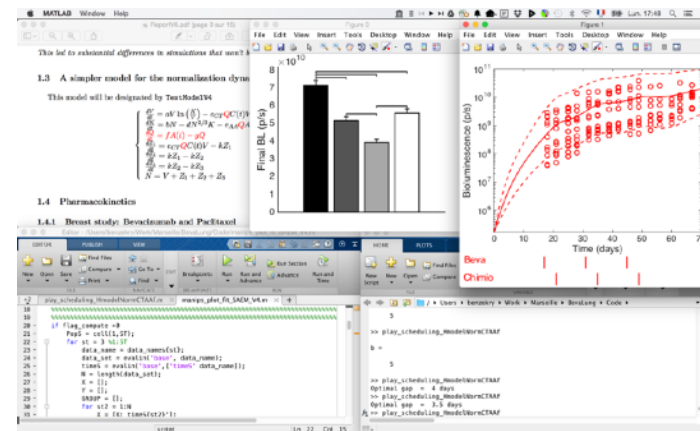
**Lung cancer model**

Experiment 1

Calibration

Experiment 2

Prediction

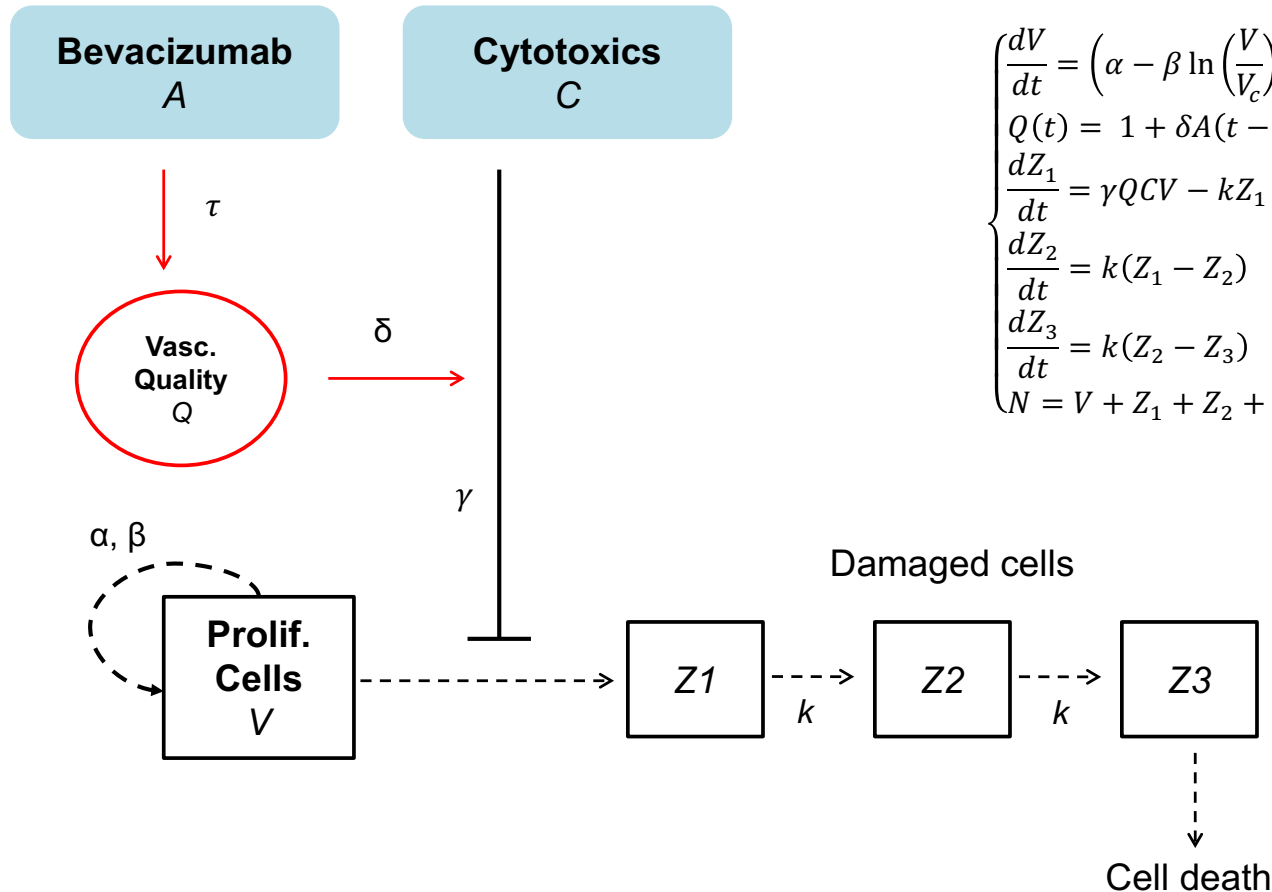


Experimental therapeutics

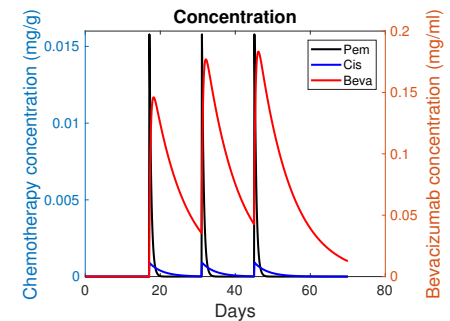
Modeling and Simulation

*Imbs et al. (Benzekry), CPT: Pharmacometrics Syst Pharmacol, 2017*

# Semi-mechanistic mathematical model



$$\begin{cases} \frac{dV}{dt} = \left( \alpha - \beta \ln \left( \frac{V}{V_c} \right) \right) V - \gamma Q C V & V(t=0) = V_0 \\ Q(t) = 1 + \delta A(t - \tau) \\ \frac{dZ_1}{dt} = \gamma Q C V - k Z_1 & Z_1(t=0) = 0 \\ \frac{dZ_2}{dt} = k(Z_1 - Z_2) & Z_2(t=0) = 0 \\ \frac{dZ_3}{dt} = k(Z_2 - Z_3) & Z_3(t=0) = 0 \\ N = V + Z_1 + Z_2 + Z_3 \end{cases}$$



Simeoni et al., Rocchetti, Cancer Res, 2004

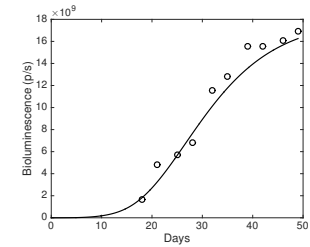
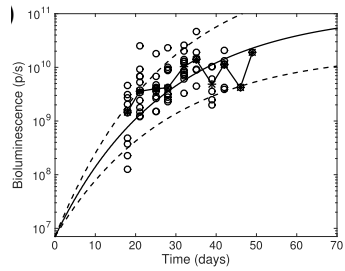
Benzekry et al., CRAS, 2012

Mollard et al., Benzekry, Oncotarget, 2017

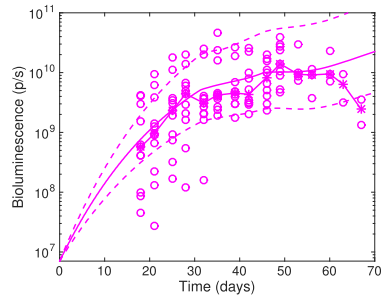
Imbs et al., Benzekry, CPT: Pharmacometrics Syst Pharmacol, 2018

+ PK models for beva  $A(t)$  and CT  $C(t)$  concentrations

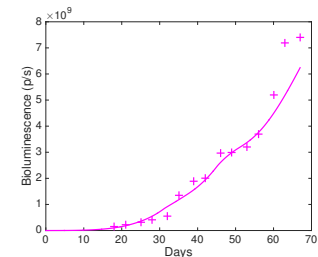
## Control



## Sequential C/B



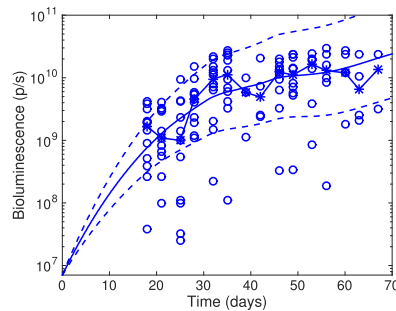
Beva  
Chimio



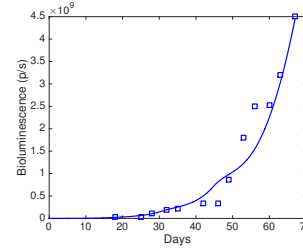
Beva  
Chimio

# Model fits: individual + population level (NLME)

## Simultaneous

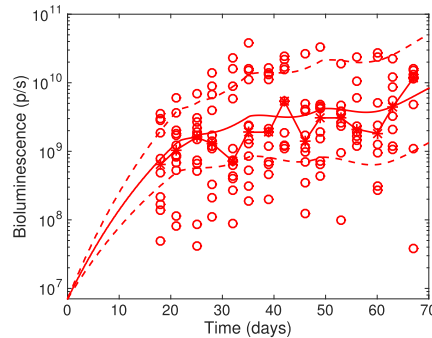


Beva  
Chimio

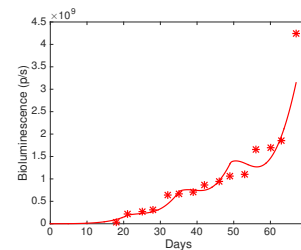


Beva  
Chimio

## Sequential B/C

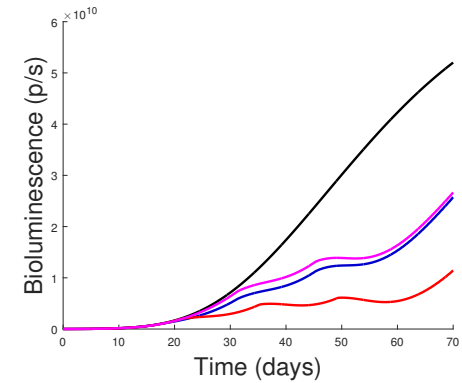


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Chimio



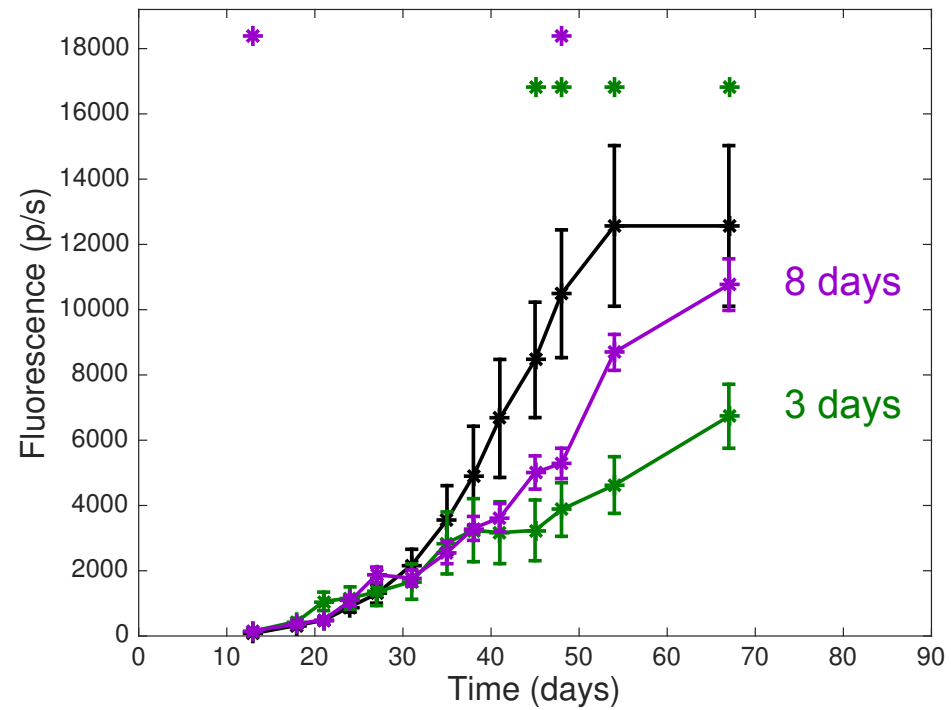
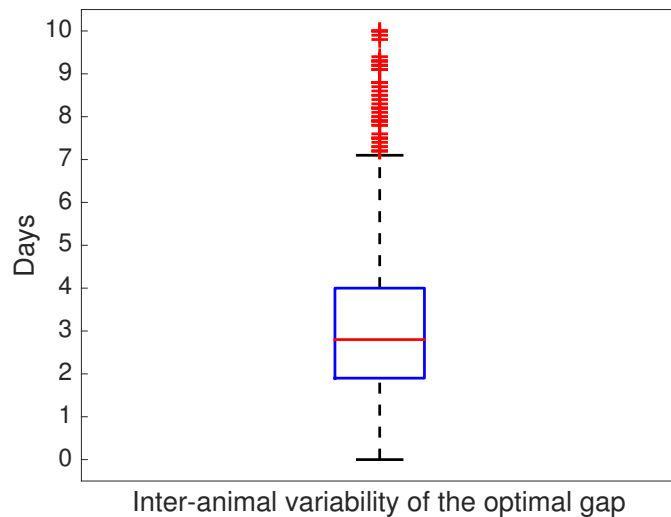
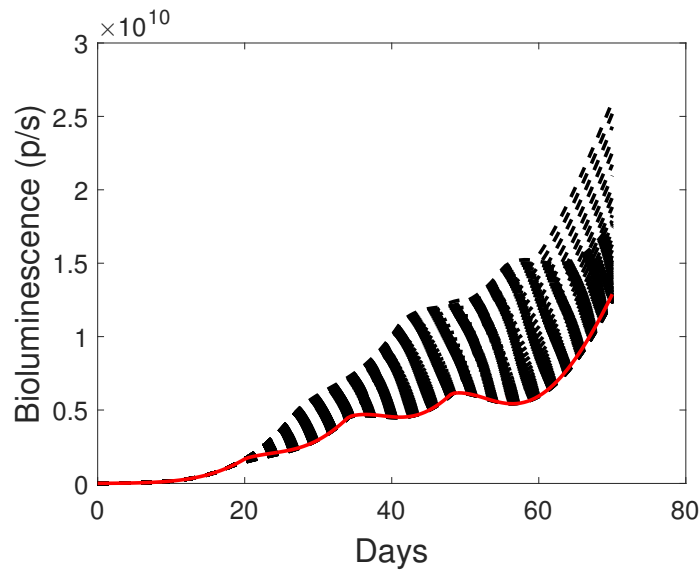
Beva  
Chimio

## Median growth curves



Beva  
Chemo  
Beva  
Chemo  
Beva  
Chemo

# Prediction of the optimal delay



⇒ to be **tested experimentally**

⇒ **personalized** scheduling

# Acknowledgements

## Biology

- Preclinical data of ortho-surgical animal models of metastases

\*J. Ebos

\*A. Tracz

\*M. Mastri



**Roswell Park Cancer Institute, Buffalo, NY, USA**

- Beva + cytotoxics study



Dr. J. Ciccolini

## Clinic

- Brain metastasis from lung tumors

\*F. Chomy

**Bergonié Institute, Bordeaux, FR**



\*F. Barlesi

\*X. Muracciole

**AP-HM, Marseille, FR**

## Modeling

\*C. Nicolò



\*D. Barbolosi



**Thanks for listening!**

*That's all Folks!*

**We are looking for postdocs!**

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