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

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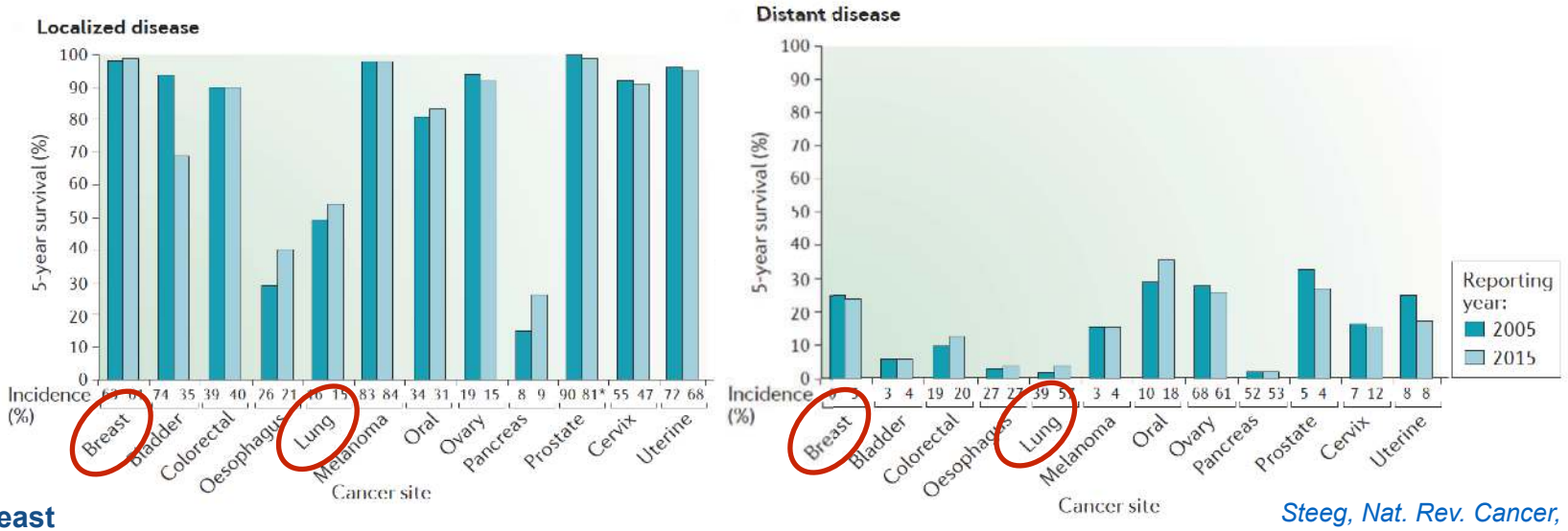
21 mai 2019

Inria informatics mathematics

MONC Modeling in ONCology

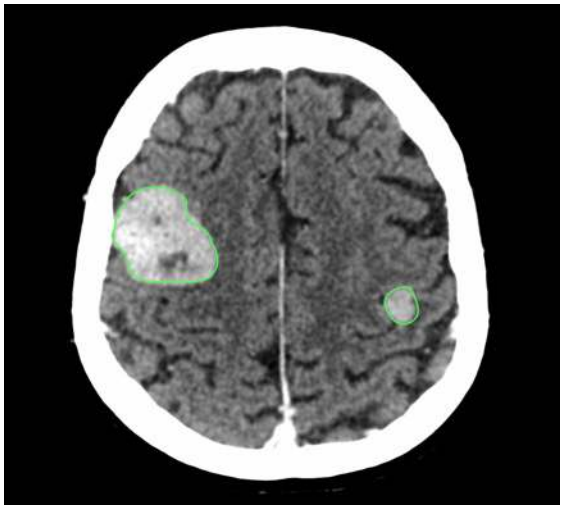
Metastasis (μετά = beyond, στάσιζ = place)

- 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



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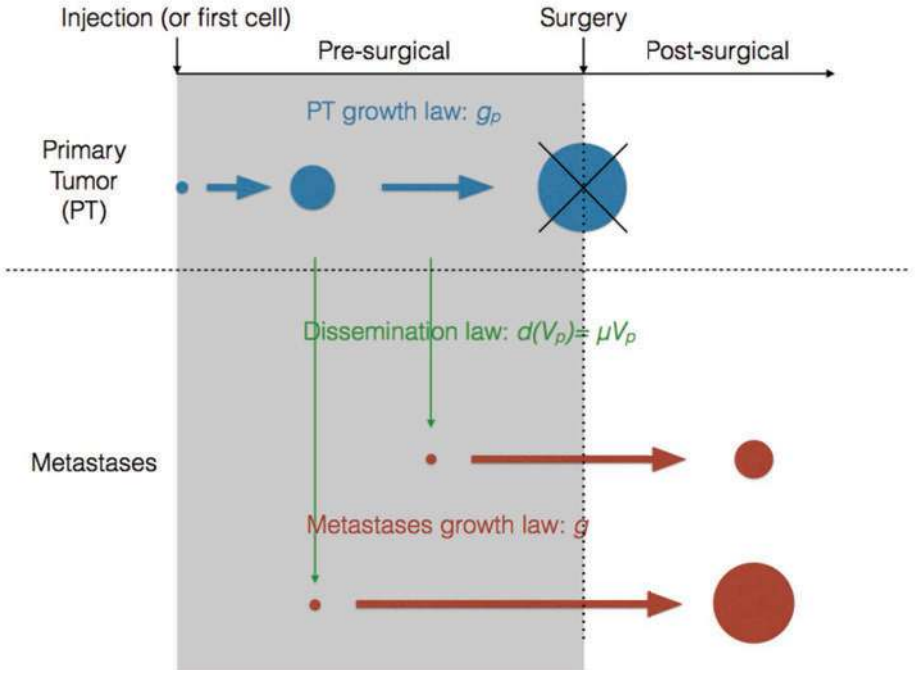
Mechanistic model of metastatic dissemination and growth



Growth rates of primary and secondary tumors g_p and g

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

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

Dissemination rate

$d(V_p) = \mu V_p$

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

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

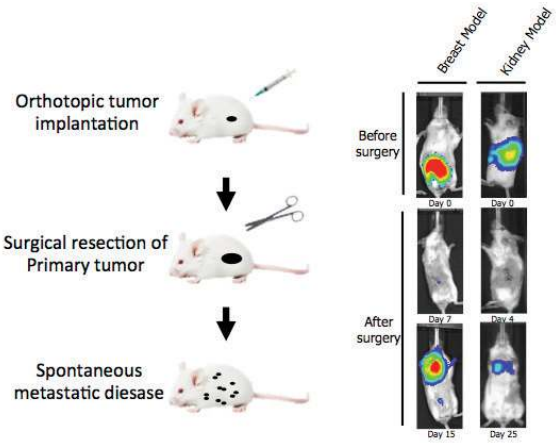
Metastatic burden (total number of metastatic cells)

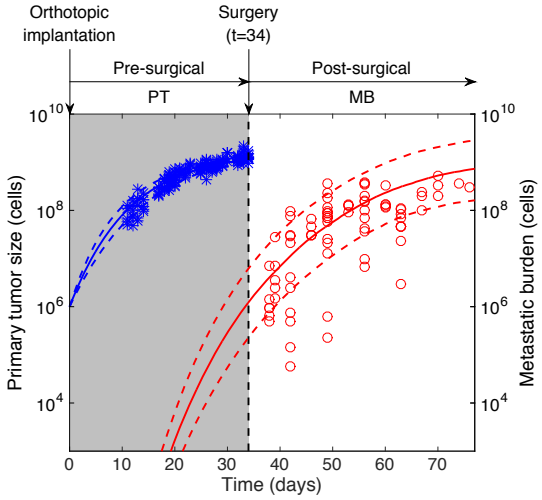
$$M(t) = \int_{V_0}^{+\infty} v\rho(t,v)dv = \int_0^t d\left(V_p(t-s)\right) V(s)ds$$

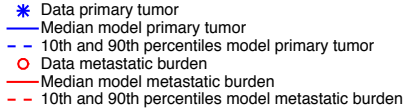
Iwata, Kawasaki, Shigesada, J Theor Biol, 2000

Validation on animal data

Ebos lab
Roswell Park Cancer Institute

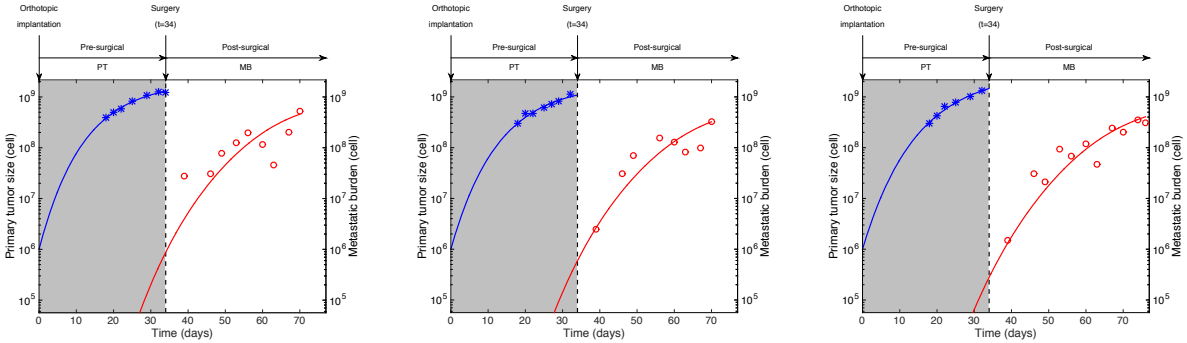






Nonlinear **mixed-effects** statistical model for inter-animal variability

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



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

Benzekry et al. (Ebos), Cancer Res, 2016

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

- Use the model for predictions of **time-to-relapse (TTR)**

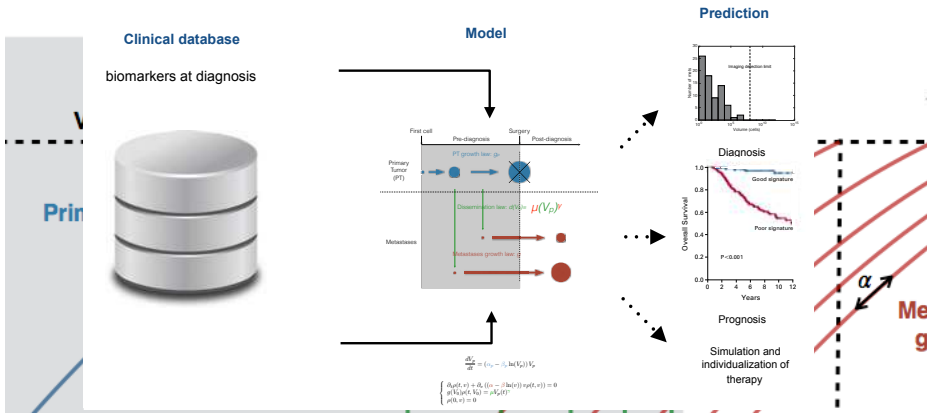
$$TTR^i = \inf\left\{t > 0; N_{vis}\left(t, \theta^i\right) > 1\right\}$$

- Implement clinical variables and biomarkers as **biologically meaningful** covariates

$\mathbf{x^i}$

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



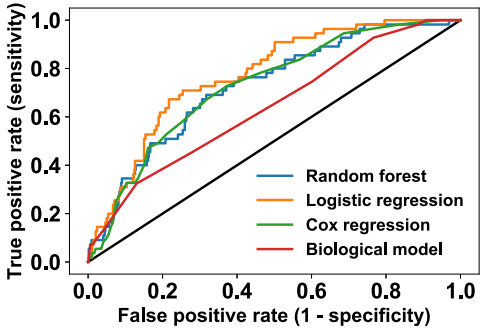
$$\ln\left(\mu^i\right) = \ln\left(\mu_{pop}\right) + \beta_\mu^T \mathbf{x_\mu^i} + \eta_\mu^i, \quad \eta_\mu^i \sim \mathcal{N}(0, \omega_\mu^2)$$

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

Parameter	Estimate	r.s.e. (%)	p-value
$\log \alpha_{pop}$	-8.883	10.151	
$\beta_{\text{Ki67},\alpha}$	0.086	27.376	$2.59 \cdot 10^{-4}$
$\beta_{\text{HER2},\alpha}$	0.029	42.888	0.026
$\beta_{\text{CD44},\alpha}$	0.011	60.816	0.1
$\beta_{\text{TRIO},\alpha}$	0.016	58.119	0.085
$\log \mu_{pop}$	-26.342	3.696	
$\beta_{\text{EGFR},\mu}$	0.039	47.527	0.035
σ	0.606	23.104	
ω_α	2.062	22.715	
ω_μ	3.563	16.759	

	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

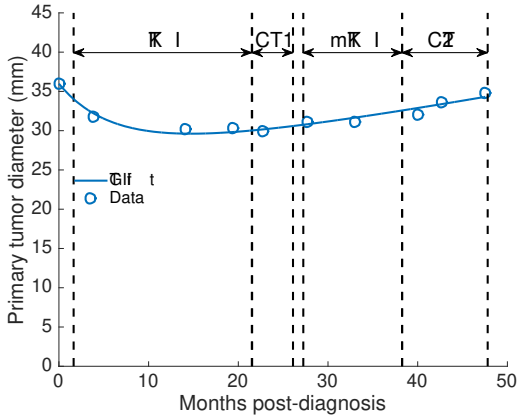
AUROC = Area Under the ROC curve, NPV = Negative Predictive Value
PPV = Positive Predictive Value



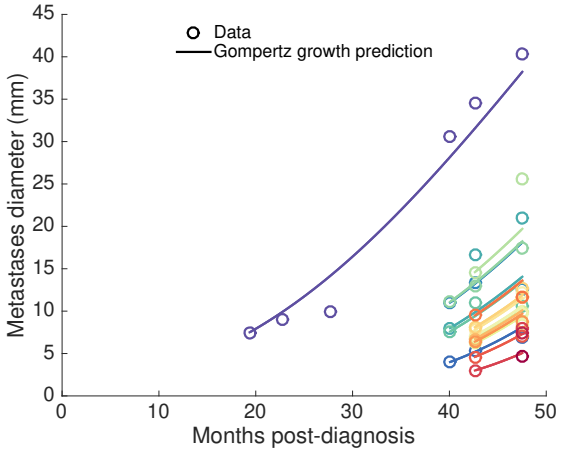
Nicolò et al., in preparation, 2019

Data of a NSCLC patient with brain mets

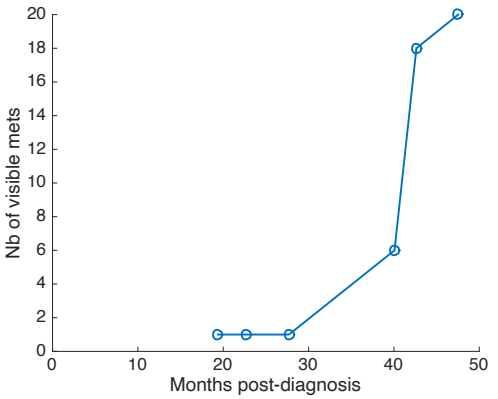
Primary tumor size



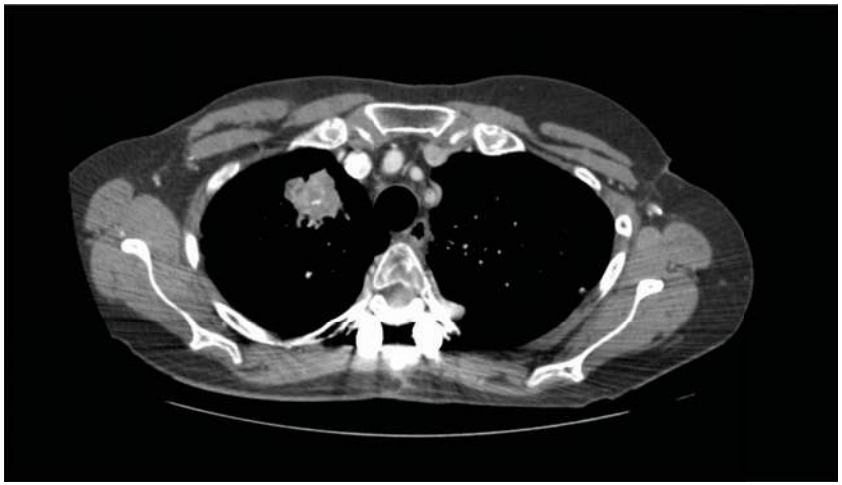
Metastases size



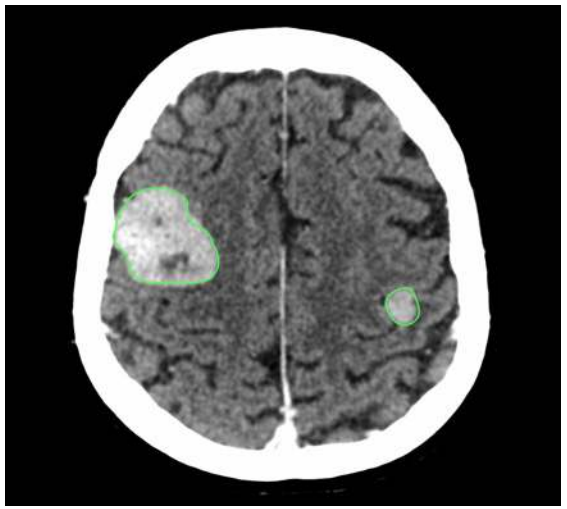
Number of visible mets



Lung CT



Brain CT scan



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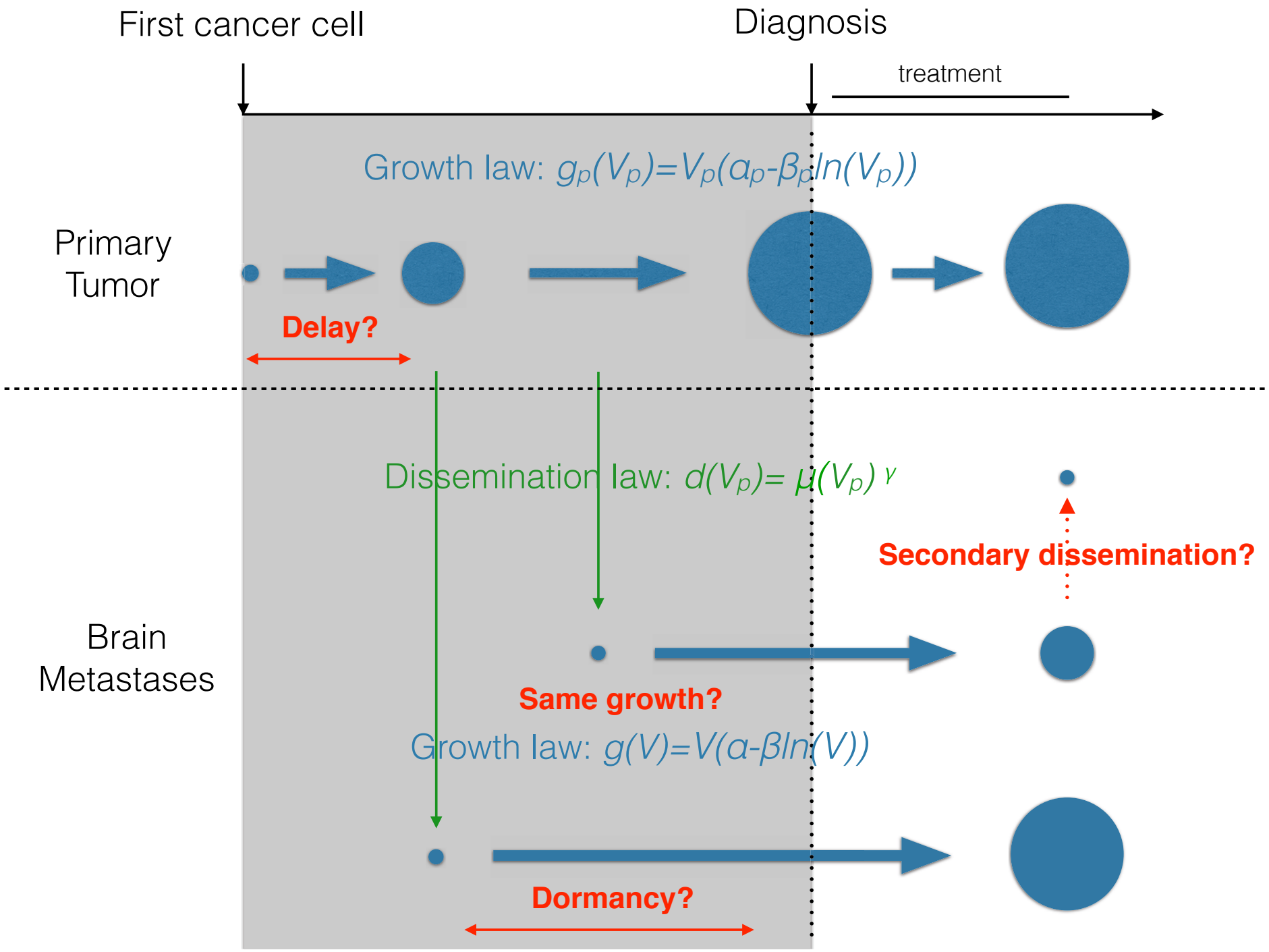
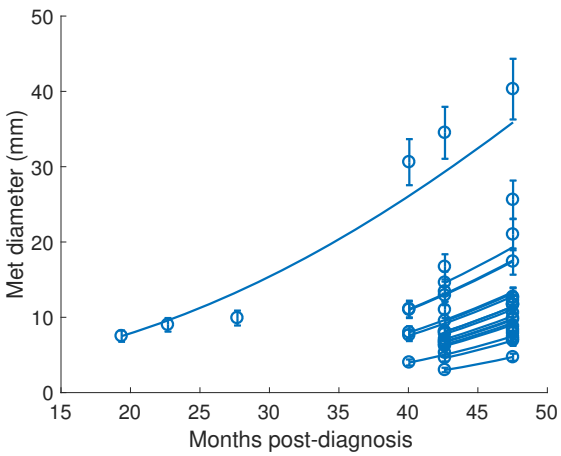
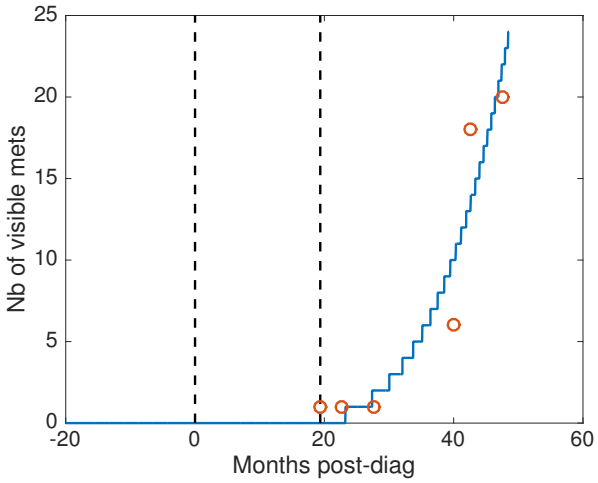

First cancer cell
Diagnosis
treatment
Growth law: $g_p(V_p)=V_p(\alpha_p-\beta_p \ln(V_p))$
Primary Tumor
Delay?
Dissemination law: $d(V_p)=\mu(V_p)^{\gamma}$
Secondary dissemination?
Brain Metastases
Same growth?
Growth law: $g(V)=V(\alpha-\beta \ln(V))$
Dormancy?

The model with dormancy could describe best the data





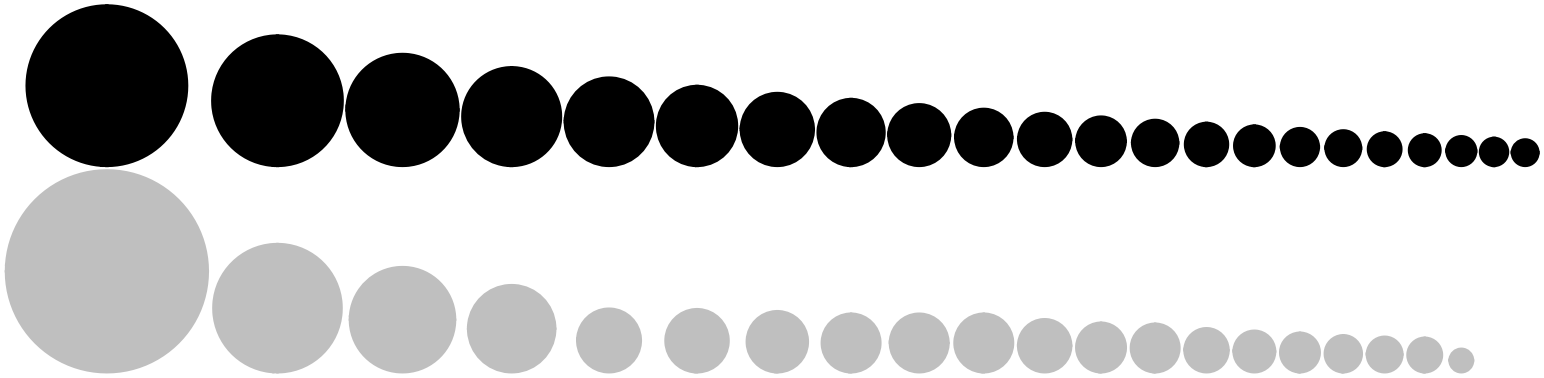
Objective function

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 ± 4.2%

Model

Data



Bilous et al. (Benzekry), biorXiv, 2018

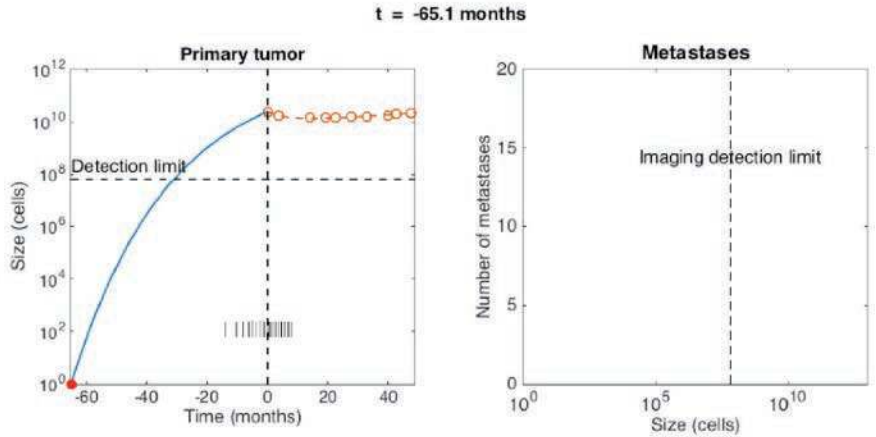
t = -65 months

10 mm

*

Primary tumor (lung)

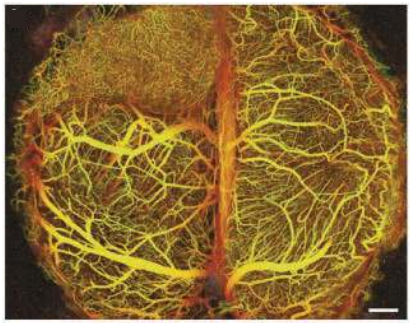
Metastases (brain)



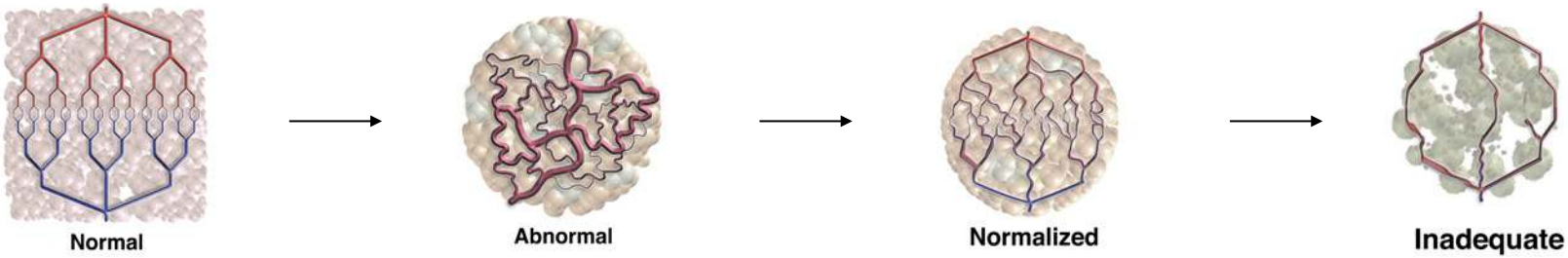
2 Combination bevacizumab - chemotherapy

Vascular normalization: a time window for improved pharmacokinetics?

- Bevacizumab = anti-VEGF monoclonal antibody ⇒ **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

Experimental therapeutics

Breast cancer model

Mollard et al. (Benzekry), Oncotarget 2017

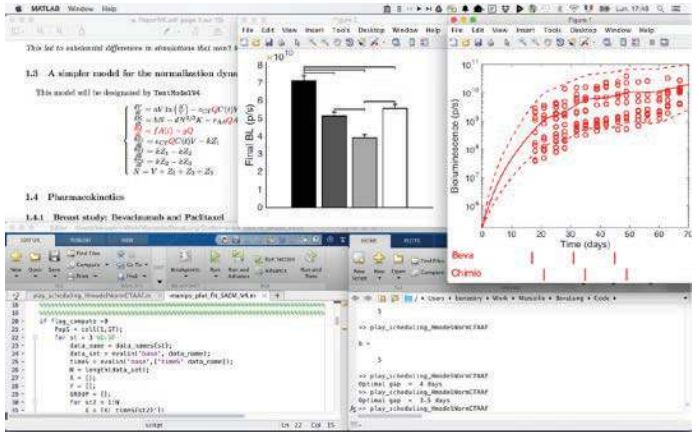
Lung cancer model

Experiment 1

Calibration

Experiment 2

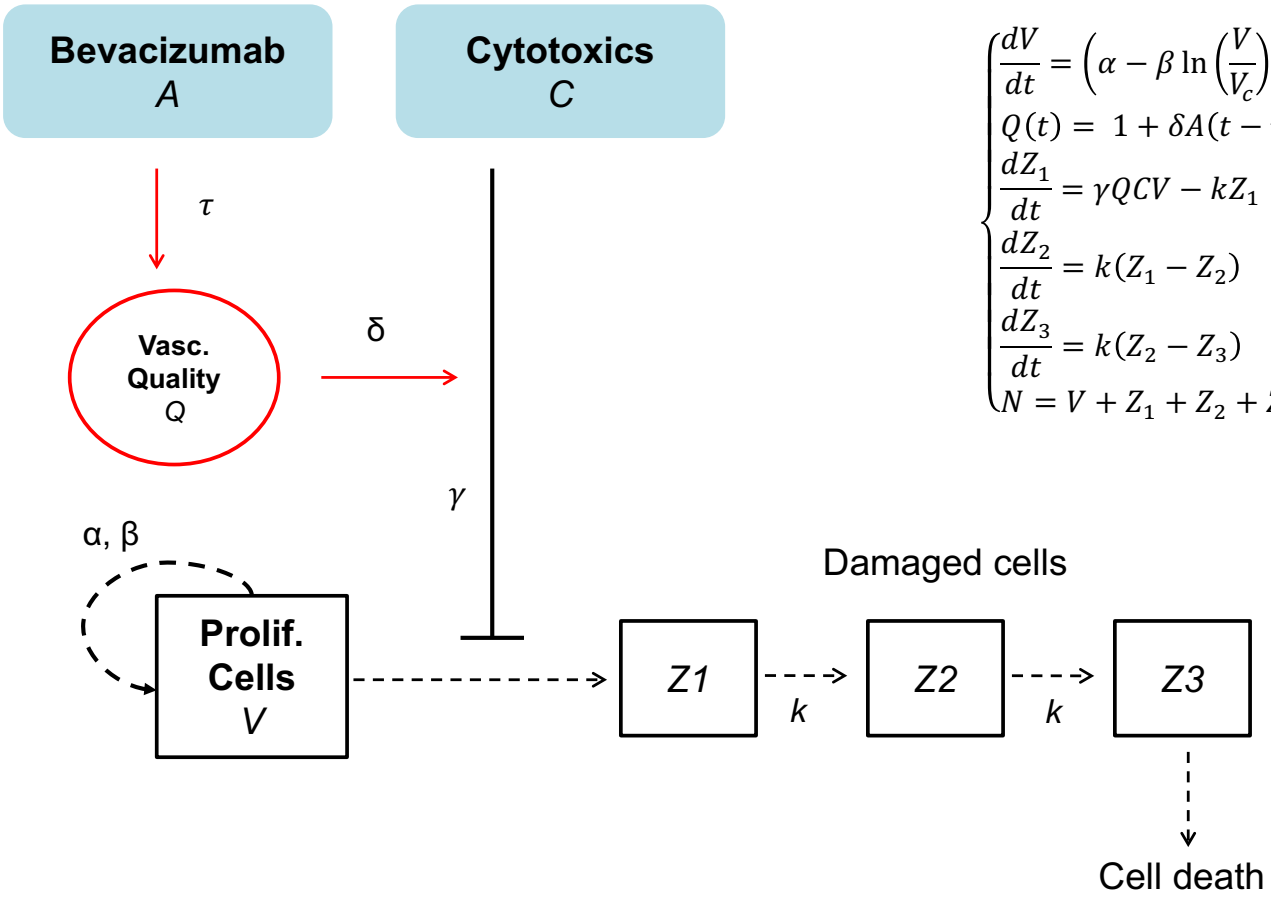
Prediction



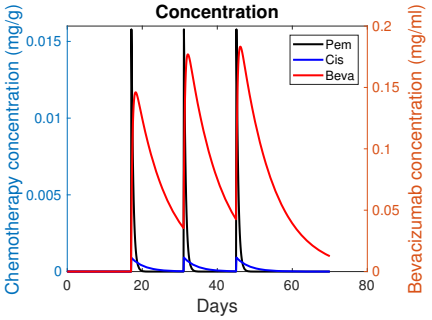
Modeling and Simulation

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

Semi-mechanistic mathematical model



$$\begin{cases} \dfrac{dV}{dt} = \left(\alpha - \beta \ln\left(\dfrac{V}{V_c}\right)\right) V - \gamma QCV & V(t=0) = V_0 \\ Q(t) = 1 + \delta A(t-\tau) & \\ \dfrac{dZ_1}{dt} = \gamma QCV - kZ_1 & Z_1(t=0) = 0 \\ \dfrac{dZ_2}{dt} = k(Z_1 - Z_2) & Z_2(t=0) = 0 \\ \dfrac{dZ_3}{dt} = k(Z_2 - Z_3) & Z_3(t=0) = 0 \\ N = V + Z_1 + Z_2 + Z_3 & \end{cases}$$

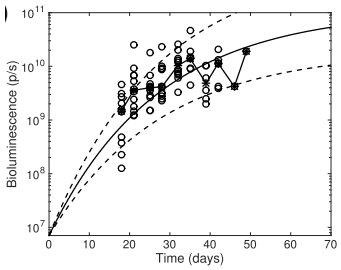


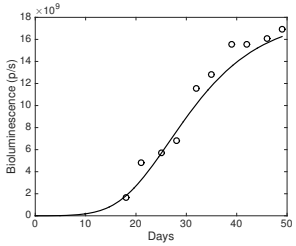
Simeoni et al., Rocchetti, Cancer Res, 2004
Benzekry et al., CRAS, 2012
Mollard et al., Benzekry, Oncotarget, 2017
Imbs et al., Benzekry, CPT: Pharmacometrics Syst Pharmacol, 2018

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

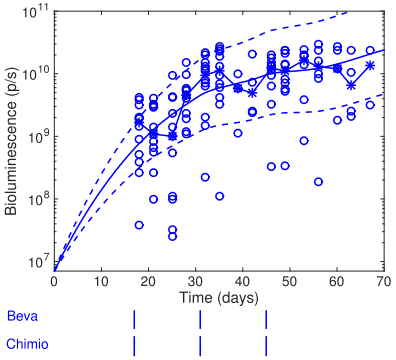
Model fits: individual + population level (NLME)

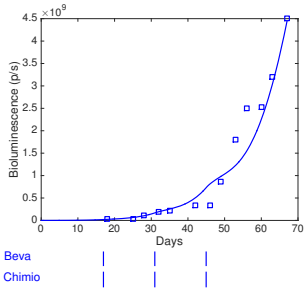
Control



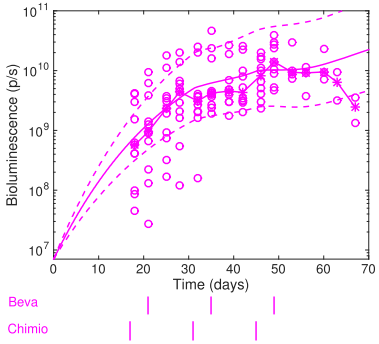


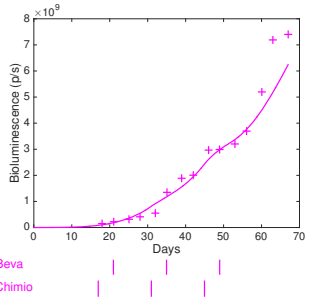
Simultaneous



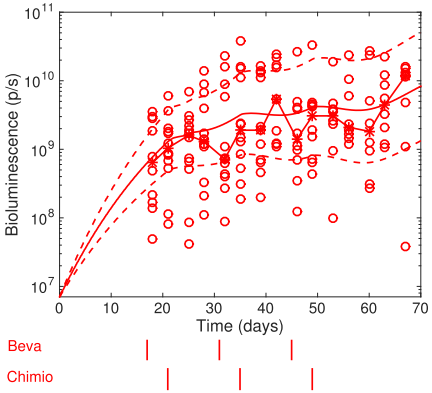


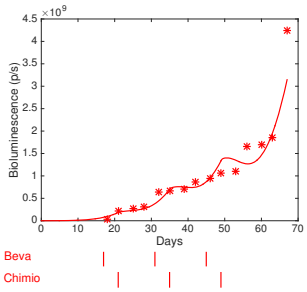
Sequential C/B



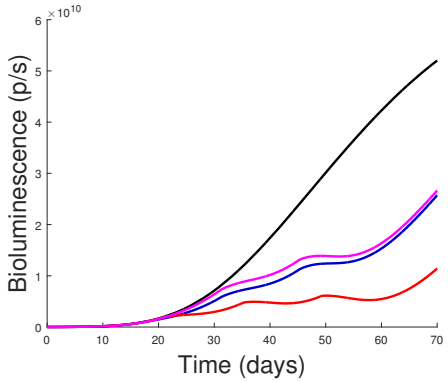


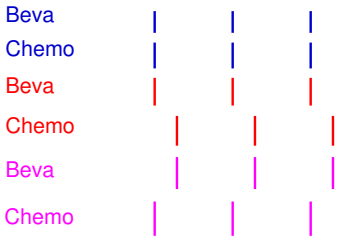
Sequential B/C





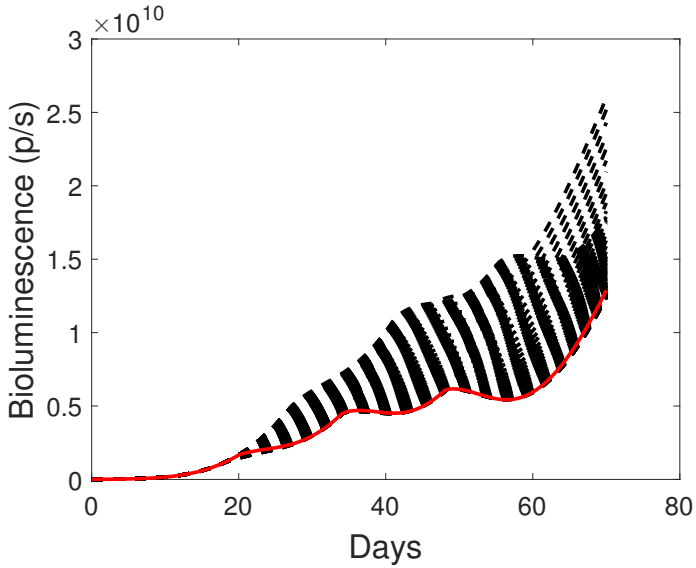
Median growth curves

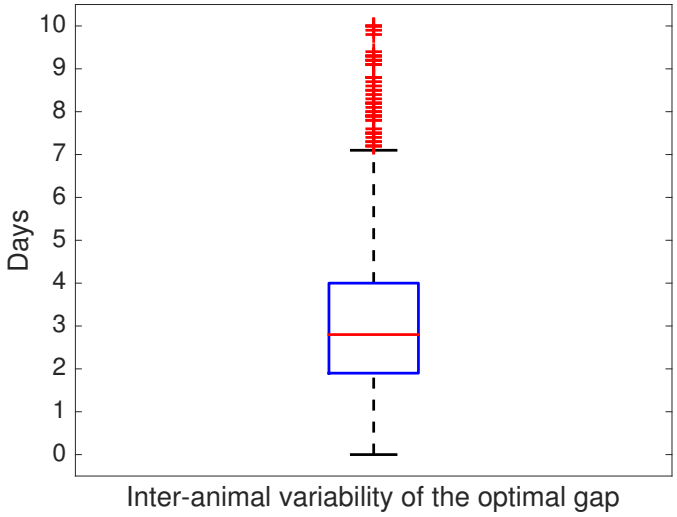


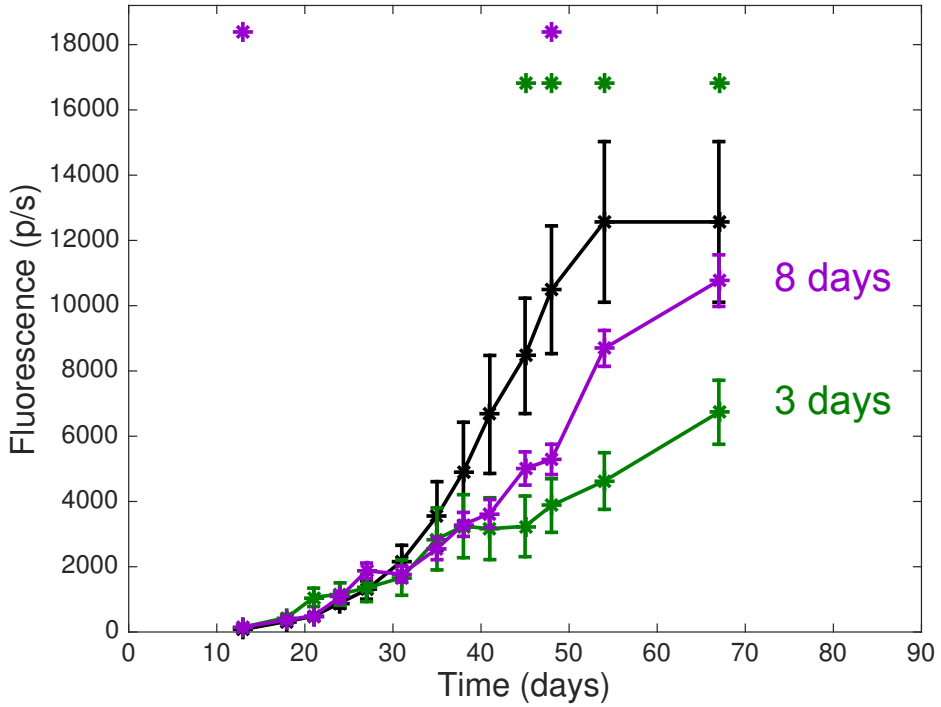


Imbs et al., Benzekry, CPT: Pharmacometrics and Systems Pharmacology, 2017

Prediction of the optimal delay







⇒ to be **tested experimentally**

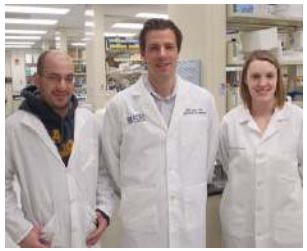
⇒ **personalized** scheduling

Imbs et al., Benzekry, 2017, CPT: Pharmacometrics and Systems Pharmacology

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

SMART C
SIMULATION MODELING ADAPTIVE RESPONSE FOR THERAPEUTICS IN CANCER

Dr. J. Ciccolini

Clinic

- Brain metastasis from lung tumors

✶F. Chomy **Bergonié Institute, Bordeaux, FR**

✶X. Muracciole

AP-HM, Marseille, FR

✶F. Barlesi

Modeling

✶C. Nicolò

✶D. Barbolosi


Thanks for listening!
That's all Folks!
We are looking for postdocs!
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