



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

Sébastien Benzekry

► To cite this version:

Sébastien Benzekry. Data-driven mechanistic modeling of metastasis: cancer at the organism scale. RITS conference (Recherche en Imagerie et Technologies pour la Sante) of the French Society of Biomedical Engineering (SFGBM), May 2019, Tours, France. hal-02424452v2

HAL Id: hal-02424452

<https://inria.hal.science/hal-02424452v2>

Submitted on 27 Dec 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

S. Benzekry

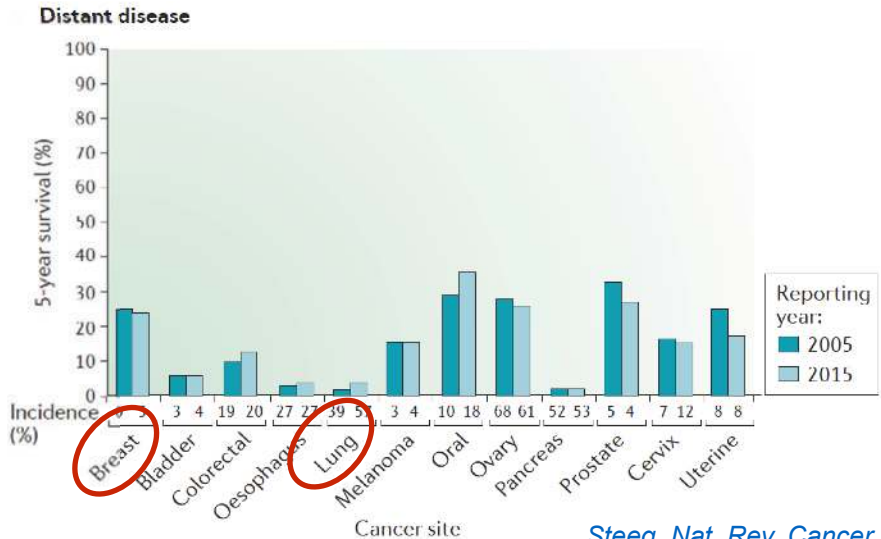
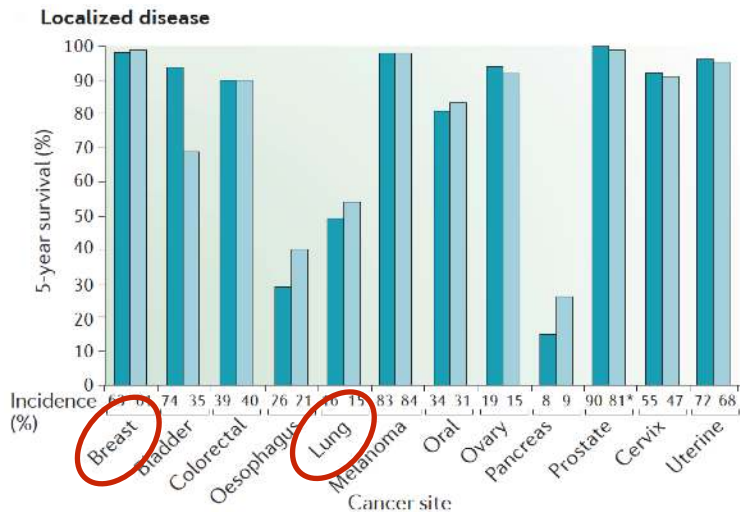
Inria Bordeaux Sud-Ouest

21 mai 2019



Metastasis (μετά = beyond, στάσιζ = place)

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



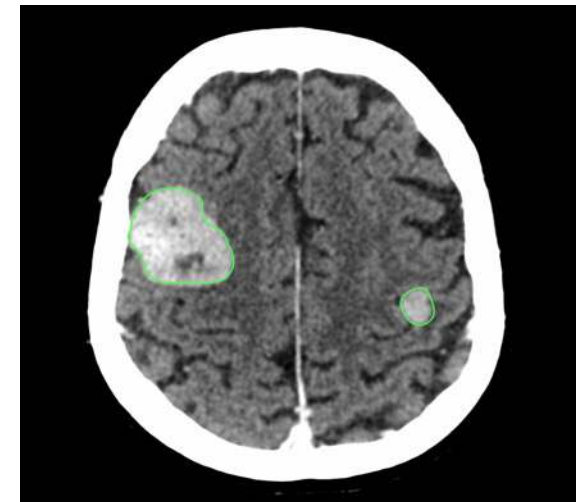
Steeg, Nat. Rev. Cancer, 2016

• 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**

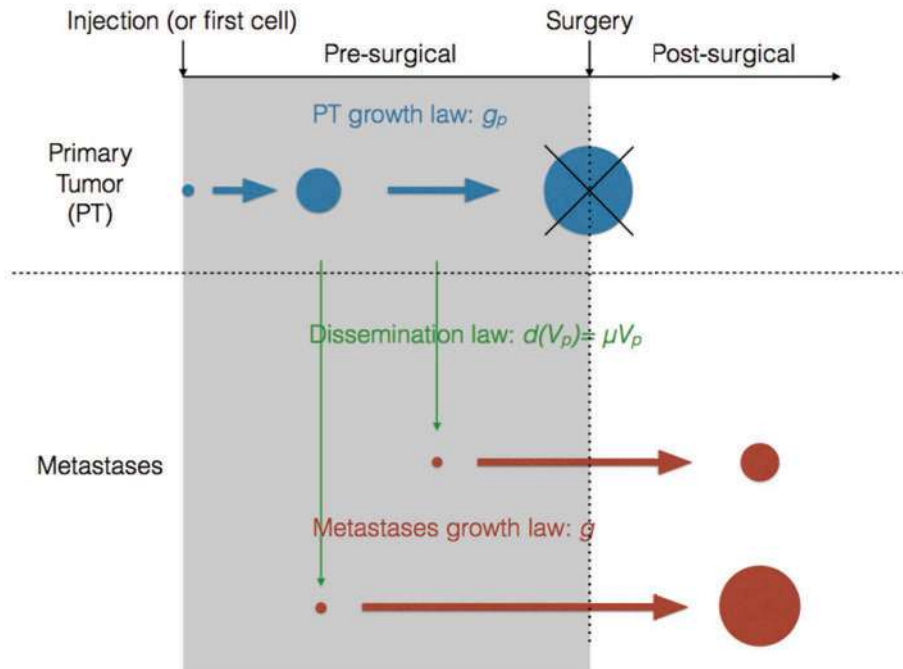
• Lung

- 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

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)

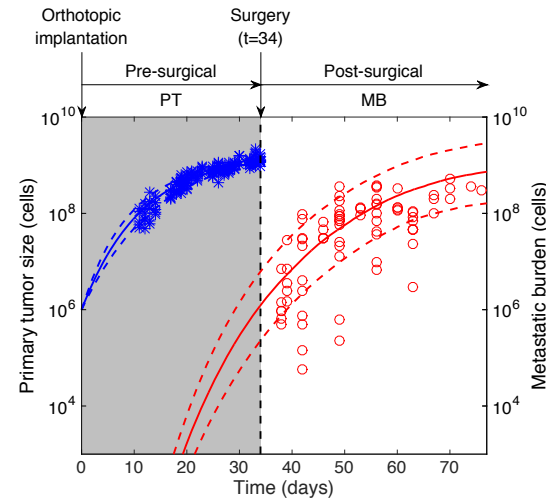
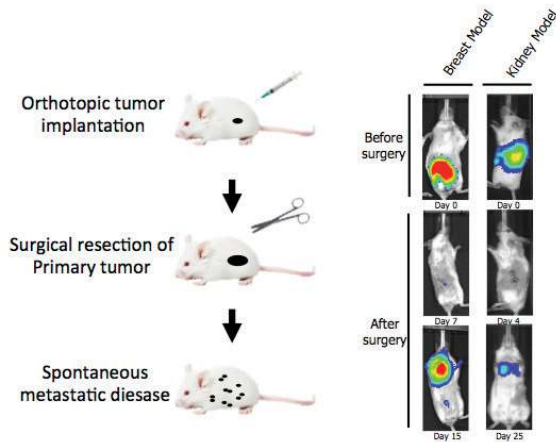
$$M(t) = \int_{V_0}^{+\infty} v \rho(t, v) dv = \int_0^t d(V_p(t-s)) V(s) ds$$

Validation on animal data



Ebos lab

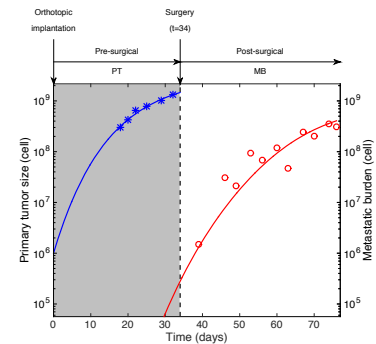
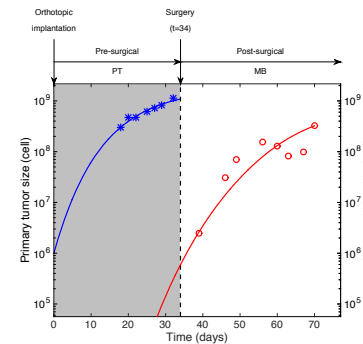
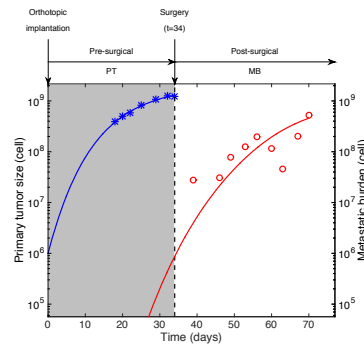
Roswell Park Cancer Institute



- * 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: $\alpha_p = \alpha$, $\beta_p = \beta$

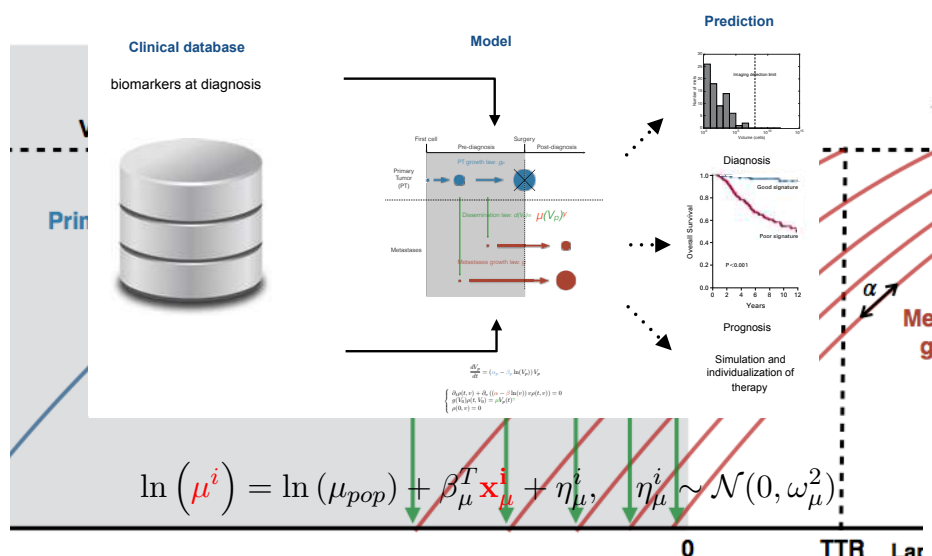
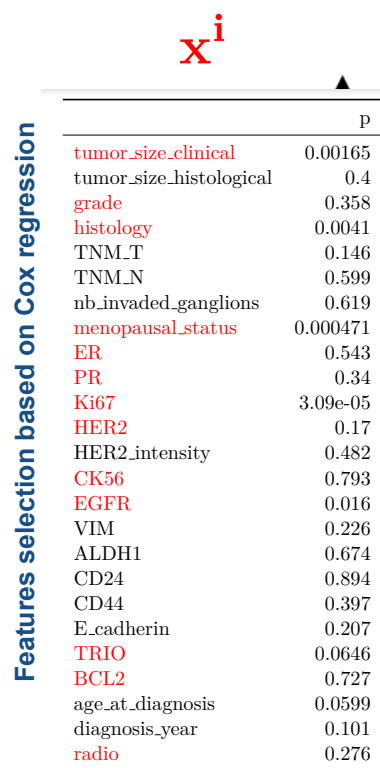
Current work: implementing the mechanistic model into a statistical learning model

- Use the model for predictions of **time-to-relapse (TTR)** $TTR^i = \inf \left\{ t > 0; N_{vis} \left(t, \theta^i \right) > 1 \right\}$
- Implement clinical variables and biomarkers as **biologically meaningful** covariates

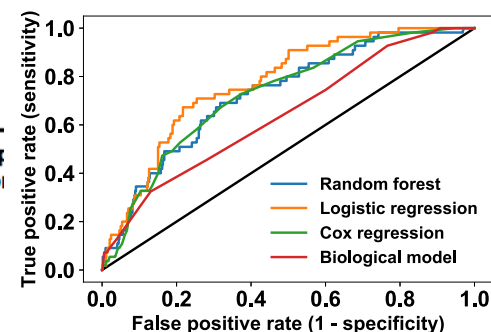
Parameter	Estimate	r.s.e. (%)	p-value
$\log \alpha_{pop}$	-8.883	10.151	
$\beta_{Ki67,\alpha}$	0.086	27.376	$2.59 \cdot 10^{-4}$
$\beta_{HER2,\alpha}$	0.029	42.689	0.020
$\beta_{CD44,\alpha}$	0.011	60.816	0.1
$\beta_{TRIO,\alpha}$	0.016	58.119	0.085
$\log \mu_{pop}$	-26.342	3.696	
$\beta_{EGFR,\mu}$	0.039	47.527	0.035
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

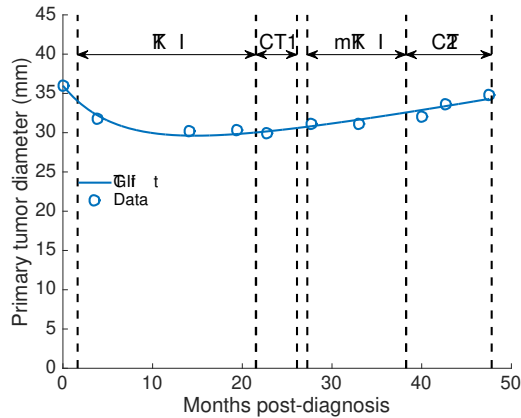


$$\ln(\alpha^i) = \ln(\alpha_{pop}) + \beta_\alpha^T \mathbf{x}_\alpha^i + \eta_\alpha^i, \quad \eta_\alpha^i \sim \mathcal{N}(0, \omega_\alpha^2)$$

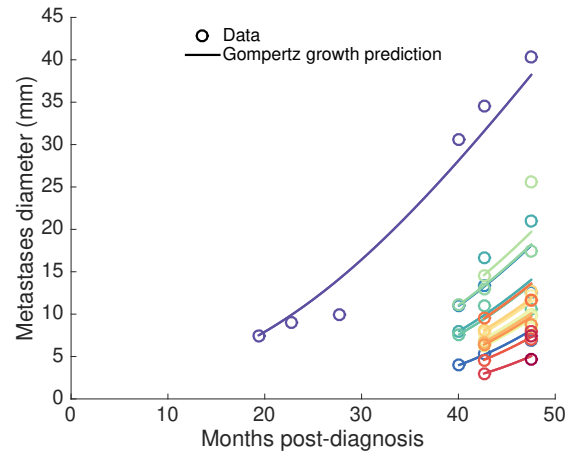


Data of a NSCLC patient with brain mets

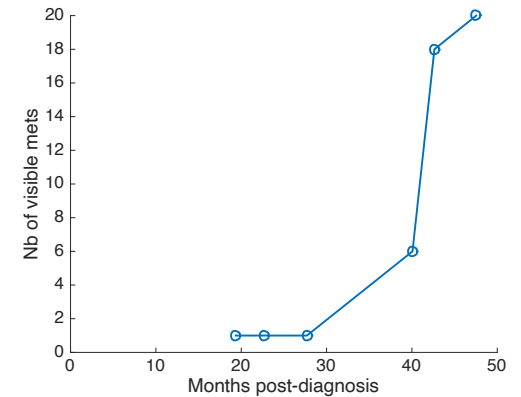
Primary tumor size



Metastases size



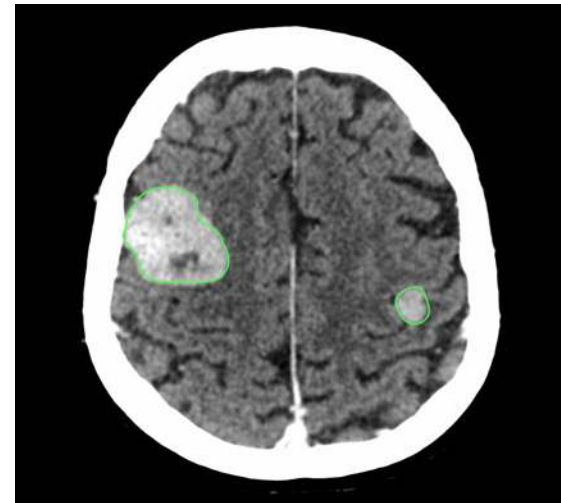
Number of visible mets



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

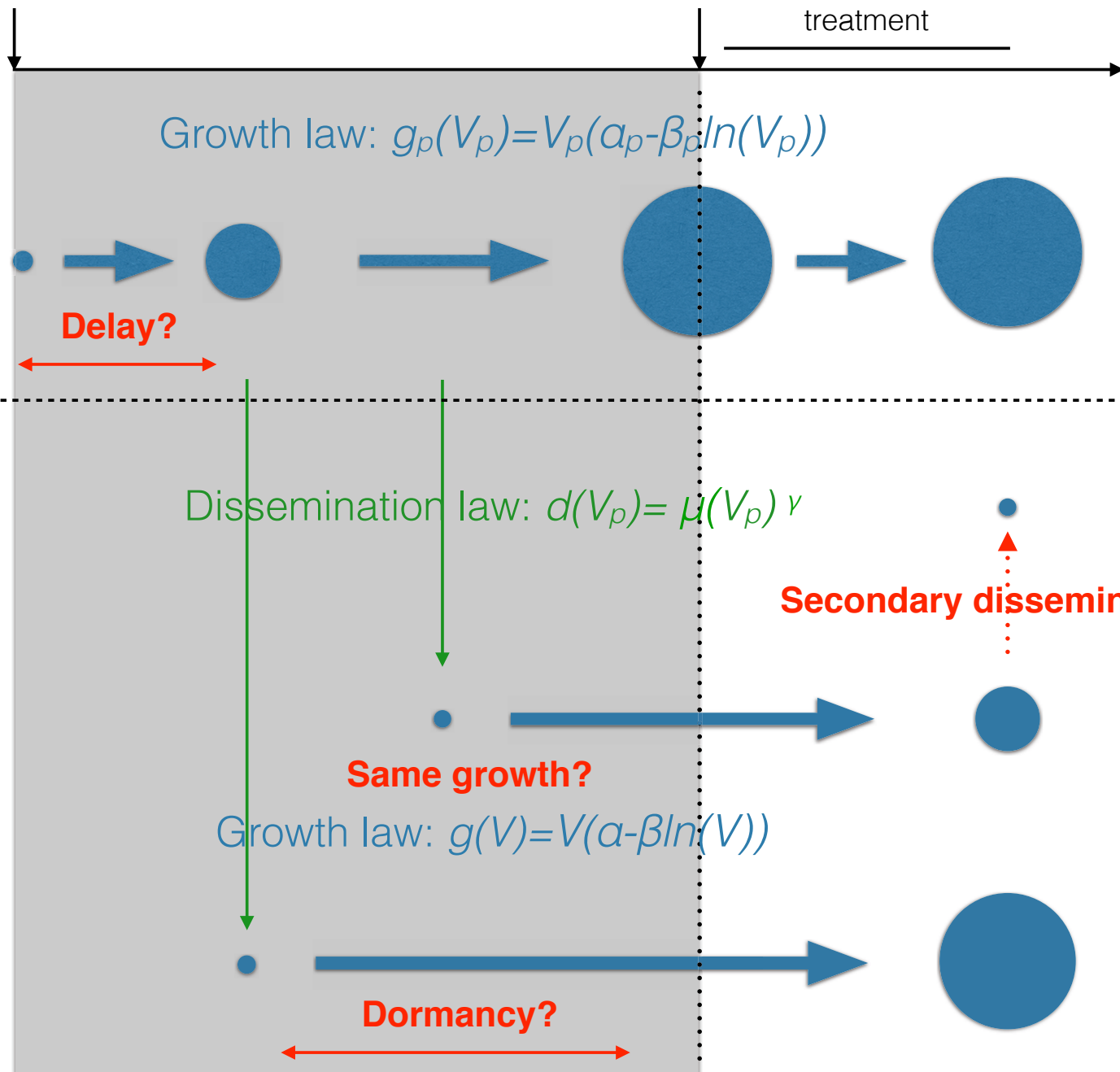
Brain
Metastases

Same growth?

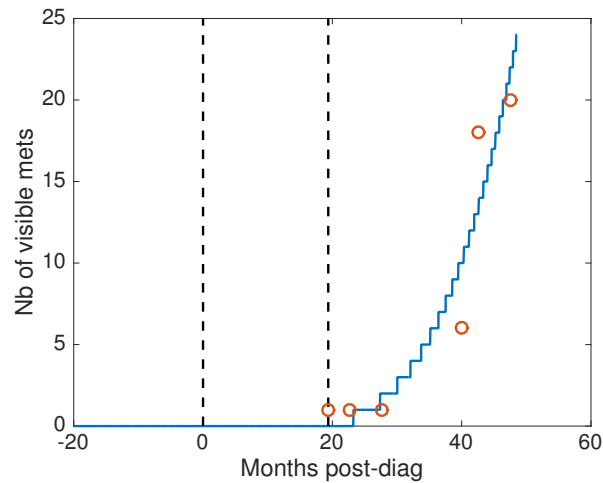
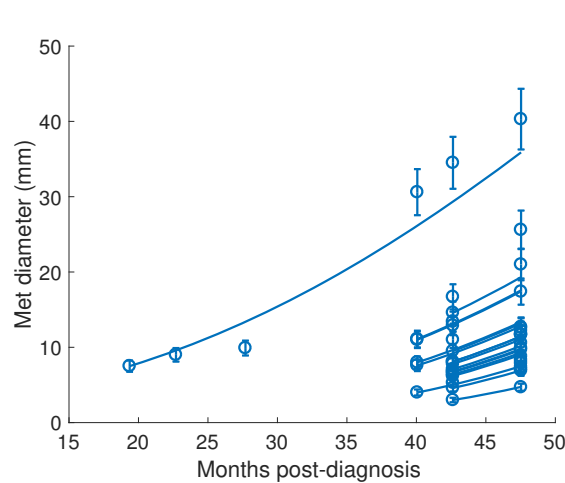
Growth law: $g(V) = V(\alpha - \beta \ln(V))$

Secondary dissemination?

Dormancy?



The model with dormancy could describe best the data



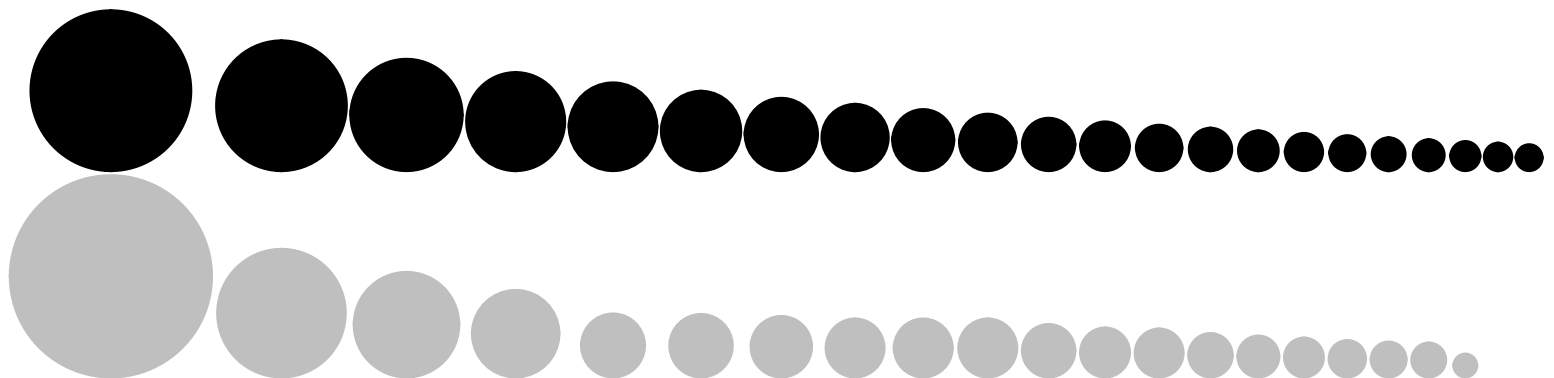
Objective function

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

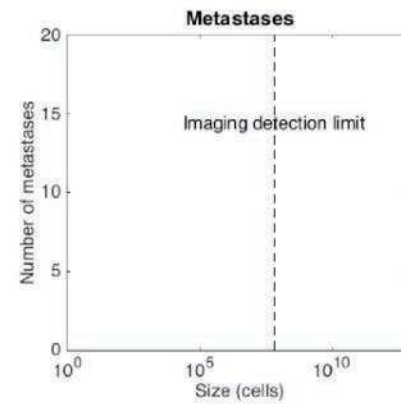
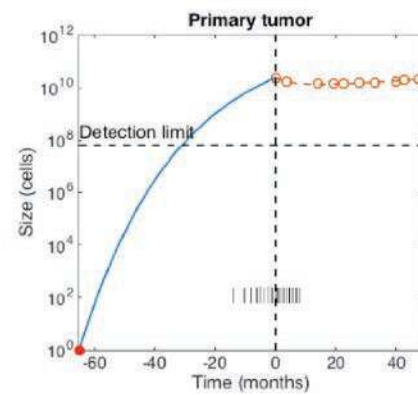
— 10 mm

*

Primary
tumor
(lung)

Metastases (brain)

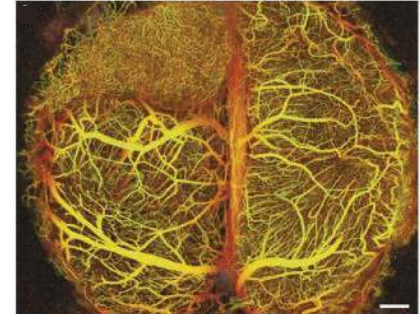
$t = -65.1$ months



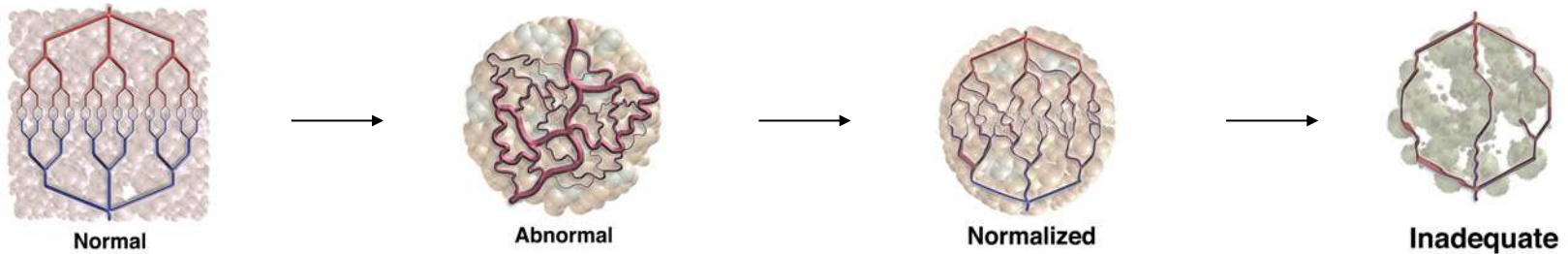
2 Combination bevacizumab - chemotherapy

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



Experimental therapeutics

Breast cancer model

Mollard et al. (Benzekry), Oncotarget 2017

Lung cancer model

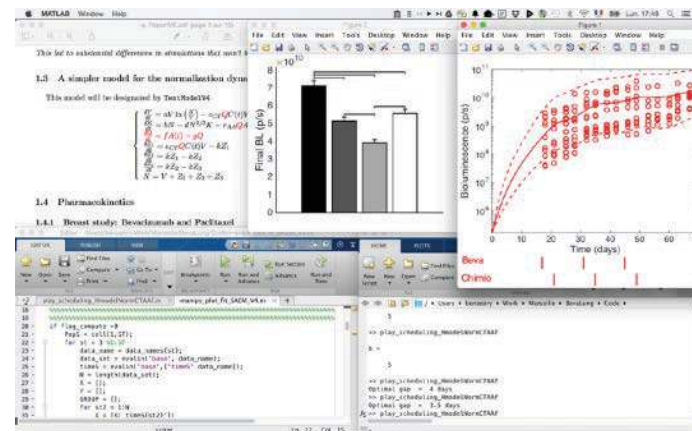
Experiment 1

Calibration



Experiment 2

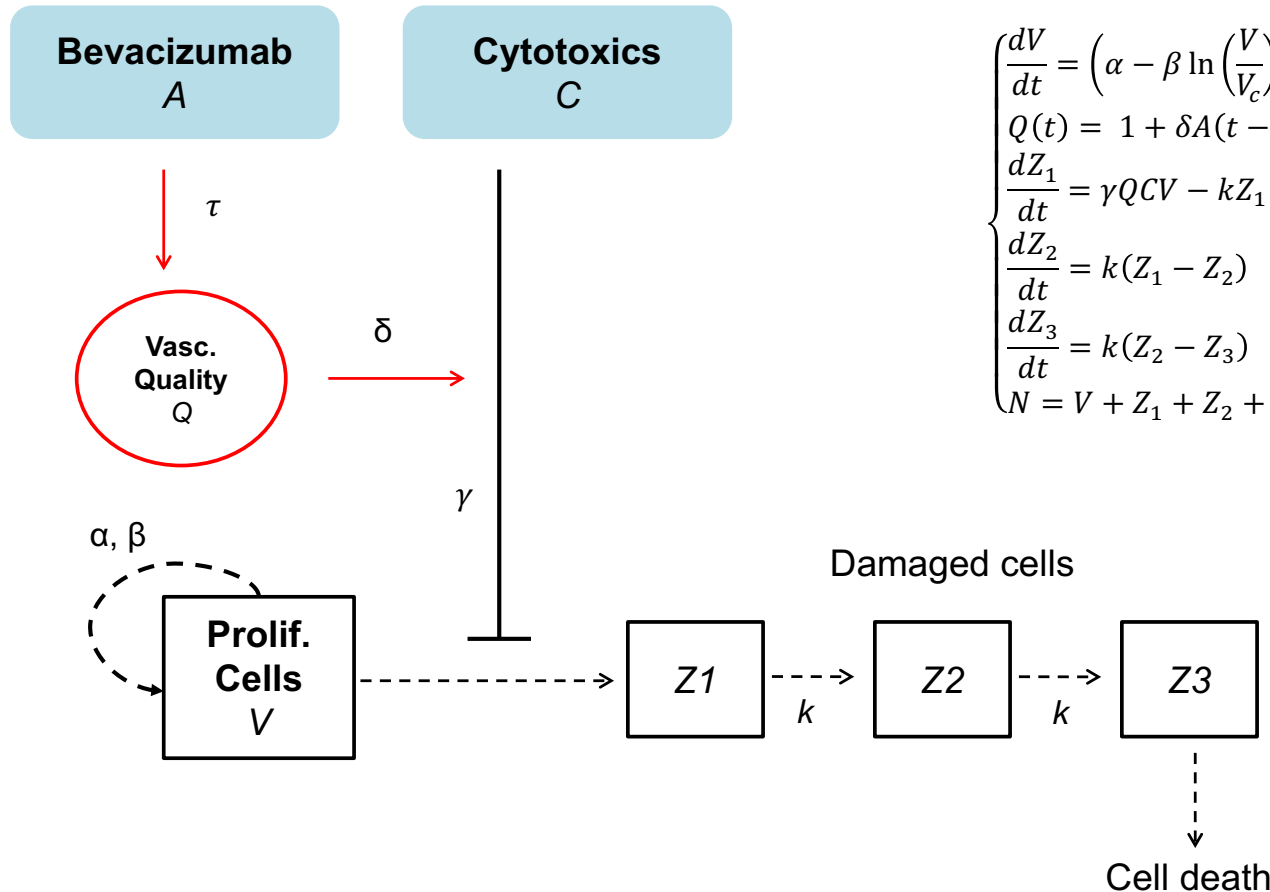
Prediction



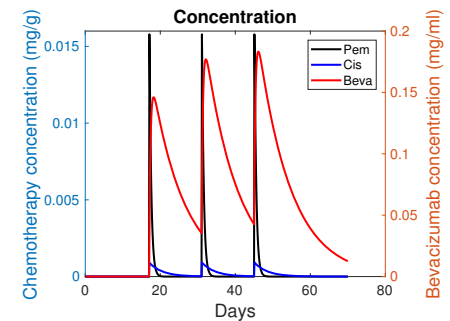
Modeling and Simulation

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

Semi-mechanistic mathematical model



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



Simeoni et al., Rocchetti, Cancer Res, 2004

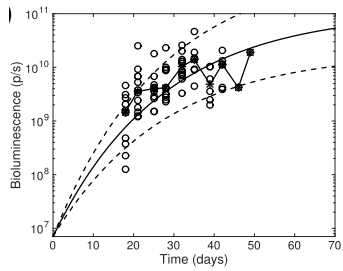
Benzekry et al., CRAS, 2012

Mollard et al., Benzekry, Oncotarget, 2017

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

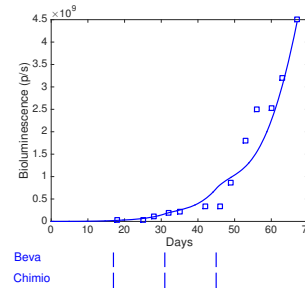
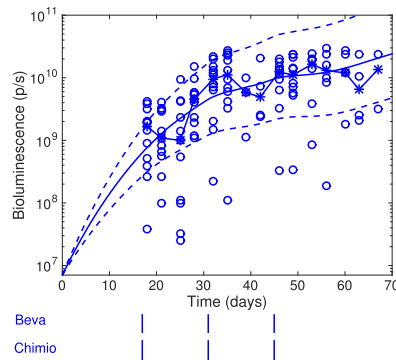
+ PK models for beva $A(t)$ and CT $C(t)$ concentrations

Control

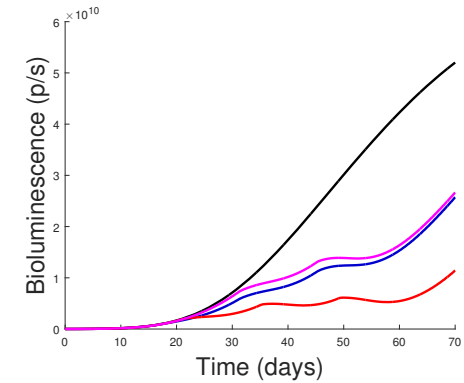


Model fits: individual + population level (NLME)

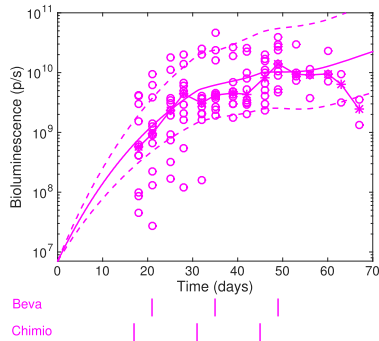
Simultaneous



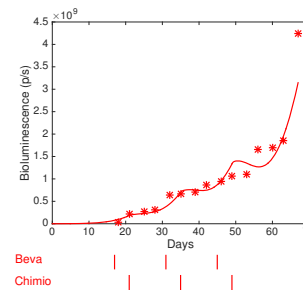
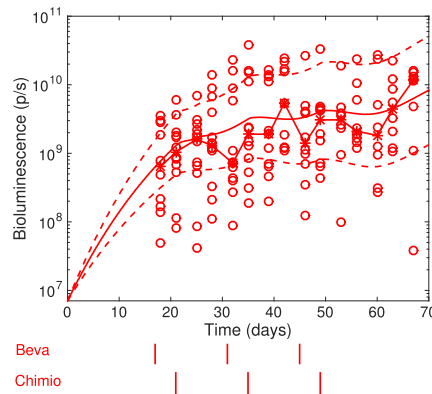
Median growth curves



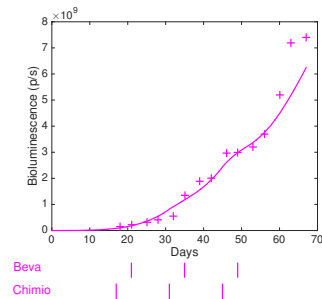
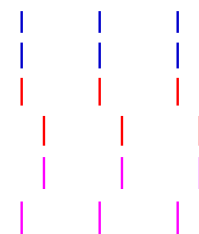
Sequential C/B



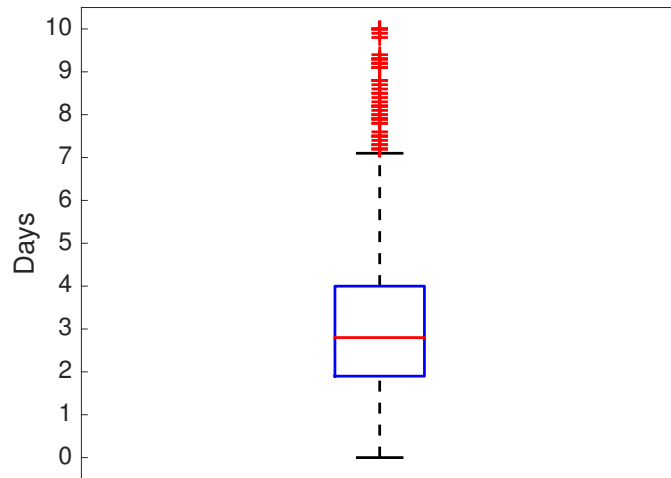
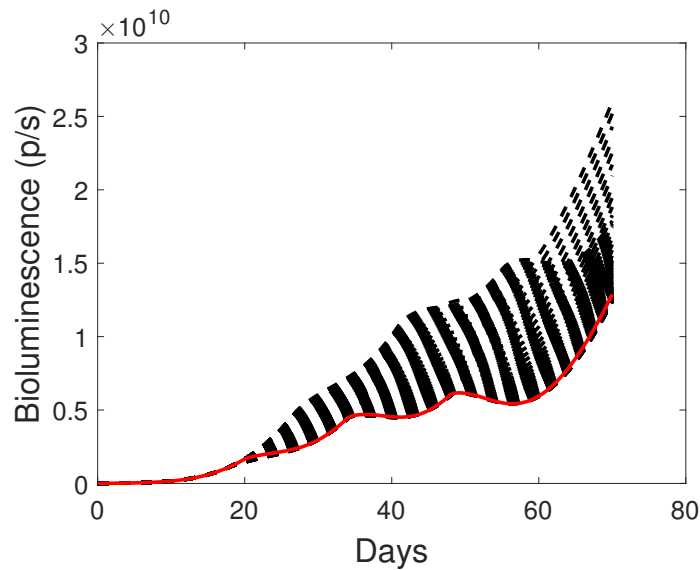
Sequential B/C



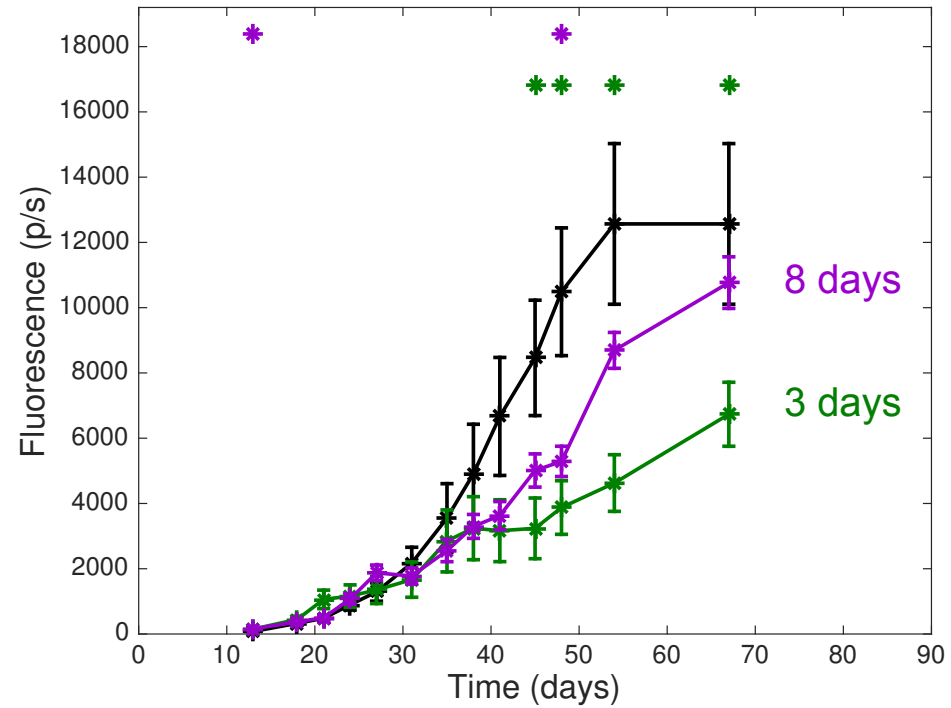
Beva
Chemo
Beva
Chemo
Beva
Chemo



Prediction of the optimal delay



Inter-animal variability of the optimal gap



⇒ to be **tested experimentally**

⇒ **personalized** scheduling

Acknowledgements

Biology

- Preclinical data of ortho-surgical animal models of metastases

*J. Ebos

*A. Tracz

*M. Matri



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!

sebastien.benzekry@inria.fr