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Mechanistic modeling of the combination between cytotoxics and anti-angiogenics for sequence optimization

Sébastien Benzekry

QSPC 2022, Leiden, April 21st

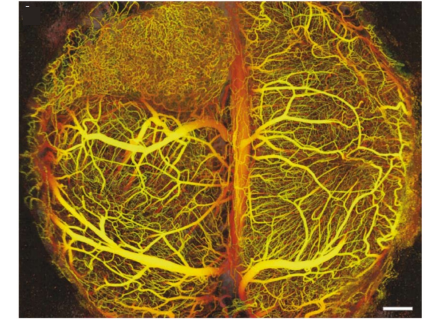
Inria – Inserm team COMPO
COMPUtational pharmacology and clinical Oncology
Centre Inria Méditerranée
Centre de Recherches en Cancérologie de Marseille

Outline

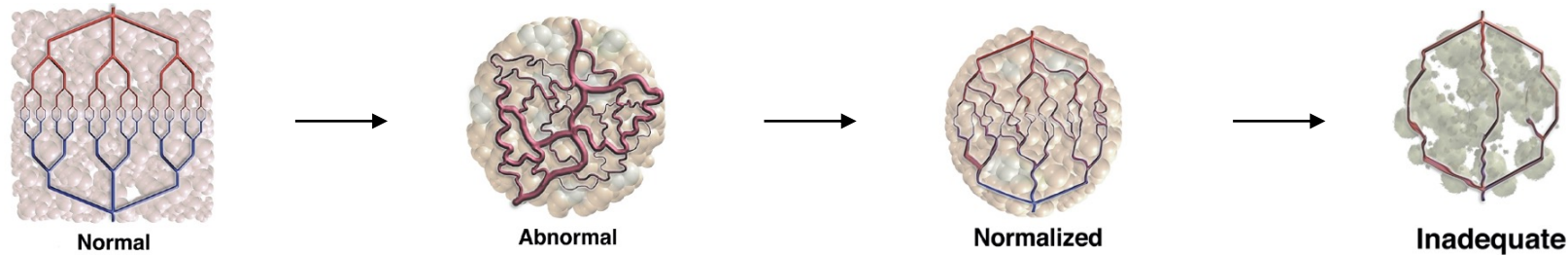
1. **Modeling at the tumor level**
2. **Modeling at the organism level : metastasis**
 1. Ortho-surgical models of post-surgical metastatic development
 2. Modeling neo-adjuvant treatment

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

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 with chemotherapy would achieve better efficacy

Current beva-chemo regimen are underpowered



Experimental therapeutics

Breast cancer model

Mollard et al. (Benzekry), Oncotarget 2017

Lung cancer model

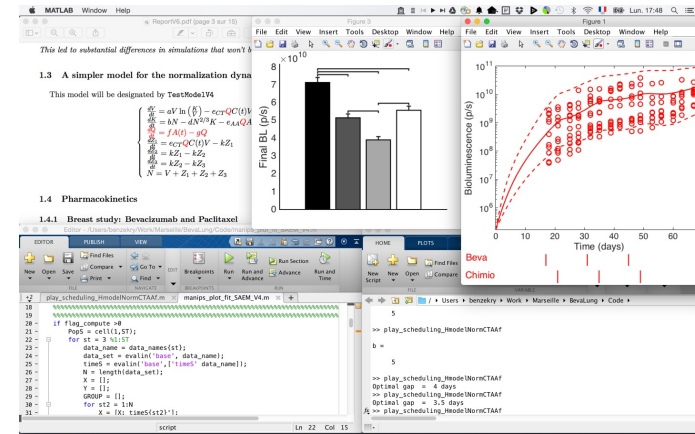
Experiment 1

Experiment 2

Calibration



Prediction



Modeling and Simulation

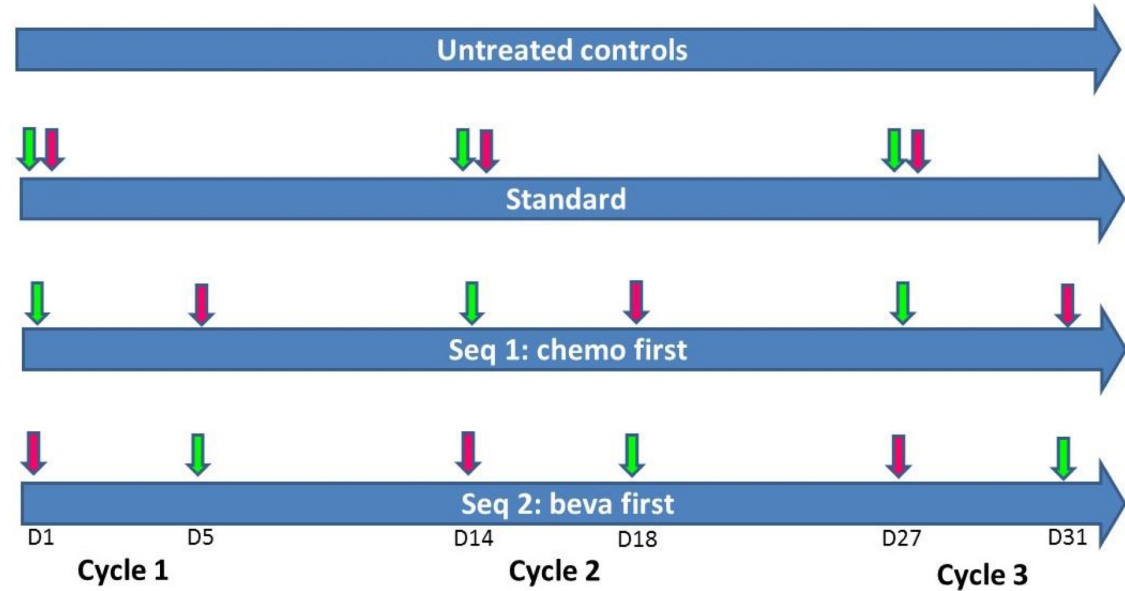
Imbs et al. (Benzekry), CPT: Pharmacometrics Syst Pharmacol, 2018

Schneider, B. K. et al. (Mochel), CPT: Pharmacometrics Syst Pharmacol, 2019

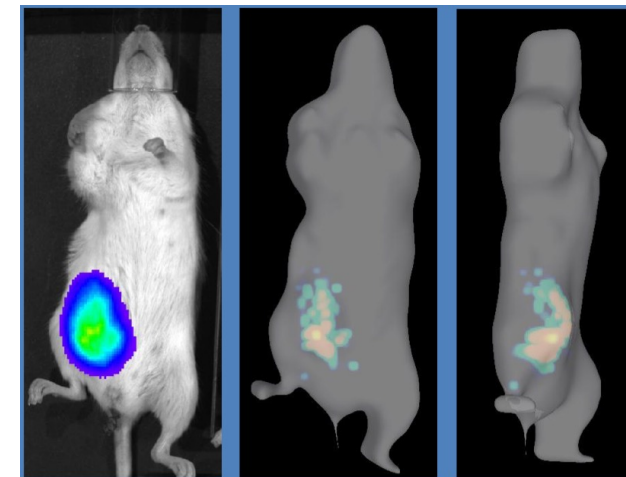
Experiment-1: 4 days gap



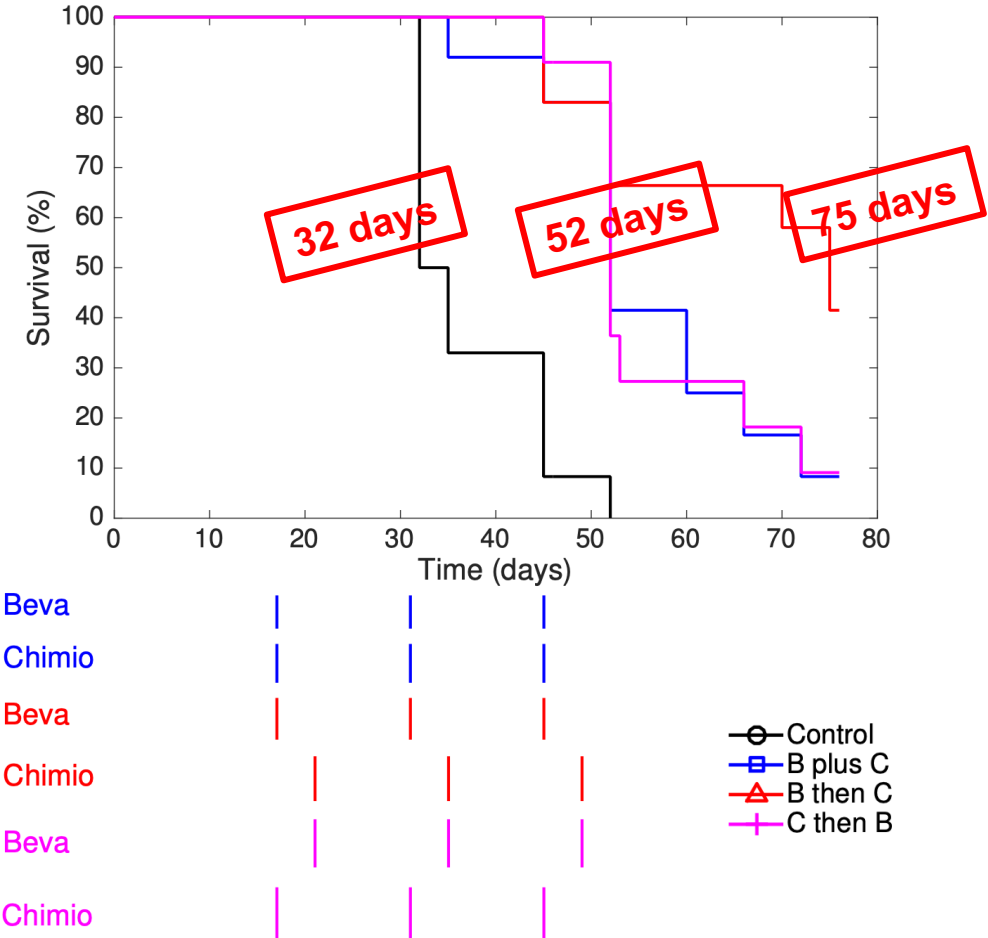
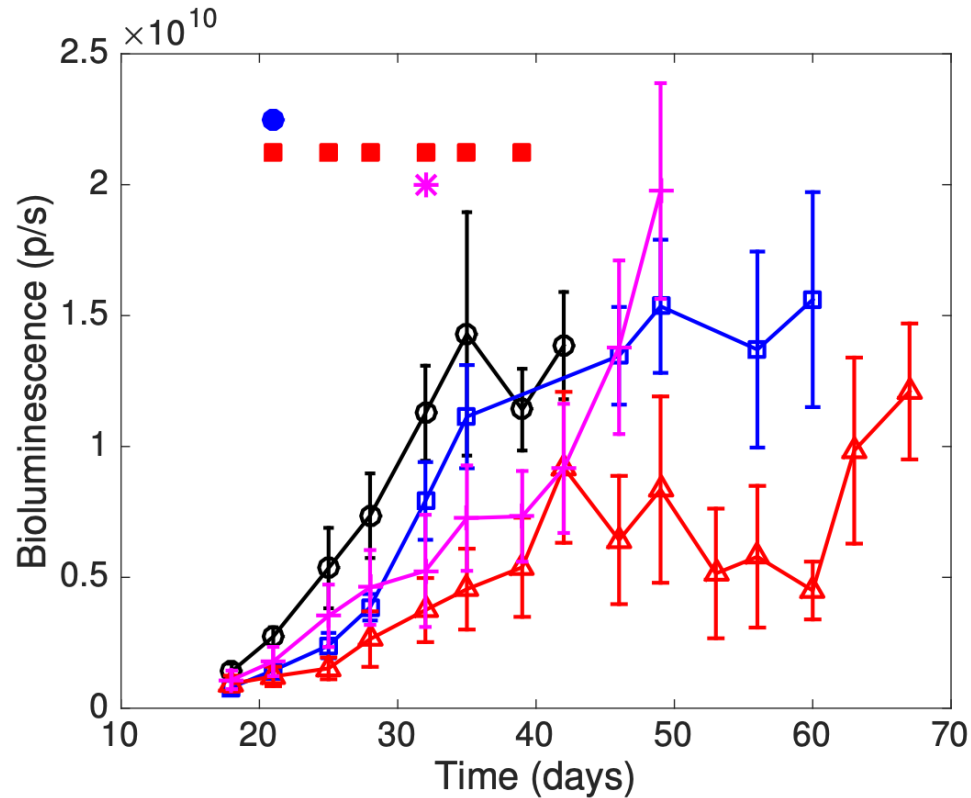
- ❖ Bevacizumab 20 mg/kg
 - ❖ Pemetrexed 100 mg/kg
 - ❖ Cisplatin 3 mg/kg
- } 3 cycles



- **Human NSCLC H460-Luc+** xenograft
 - Subcutaneous graft
 - Matrigel support
- Follow-up
 - Bioluminescence imaging
 - Weight monitoring

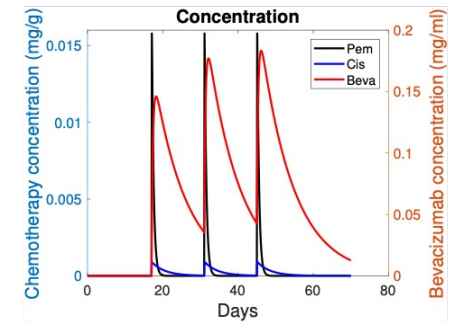
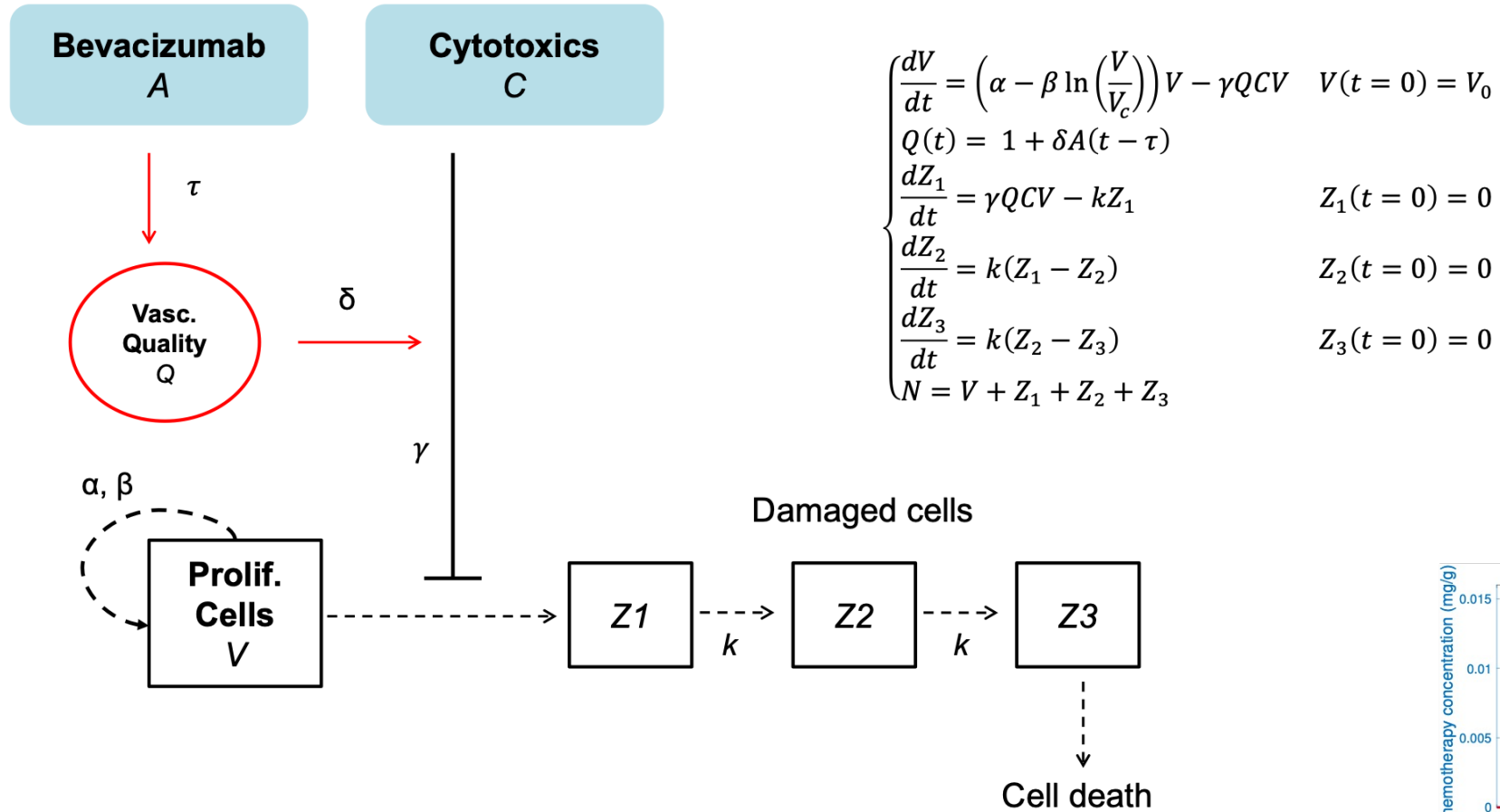


Sequential administration Beva then Chemo improves response and survival



-71.2% tumor size at study conclusion (day 60)

⇒ Sequential use increases **survival by 44%**

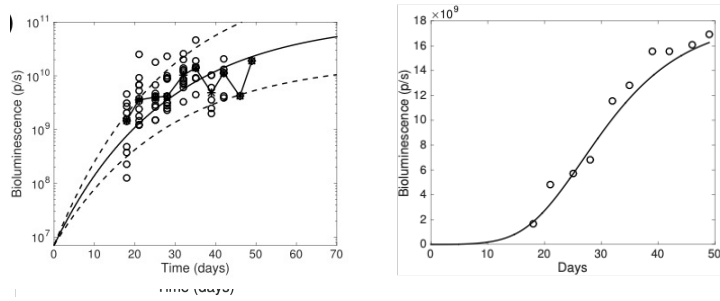


Simeoni et al., Rocchetti, *Cancer Res*, 2004
 Benzekry et al., CRAS, 2012
 Mollard et al., Benzekry, *Oncotarget*, 2017
 Imbs et al., Benzekry, *CPT: Pharmacometrics Syst Pharmacol*, 2018

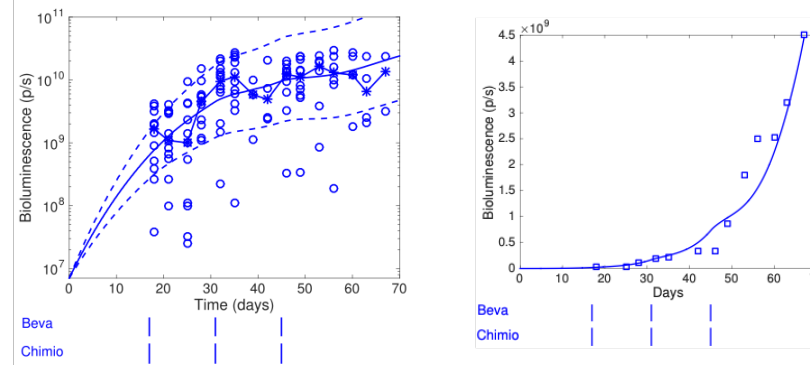
+ PK models for beva $A(t)$ and CT $C(t)$ concentrations

Model fits: individual + population level (NLME)

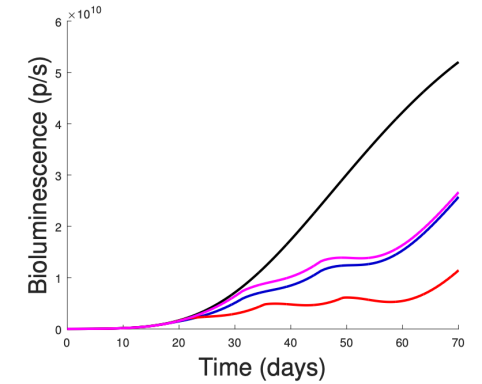
Control



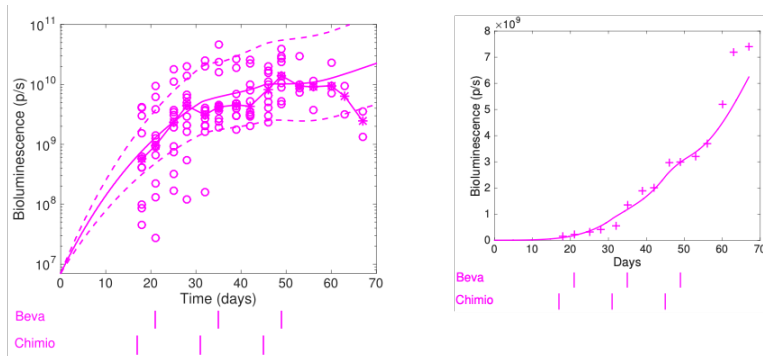
Simultaneous



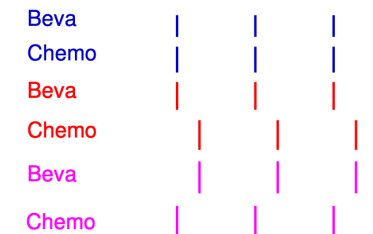
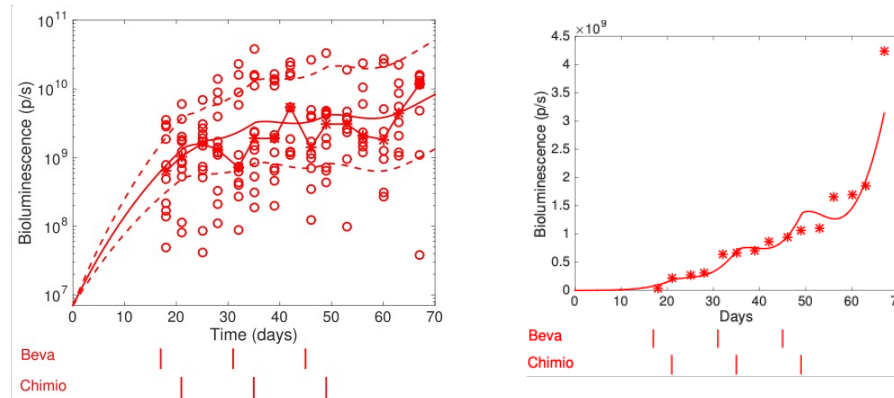
Median growth curves



Sequential C/B



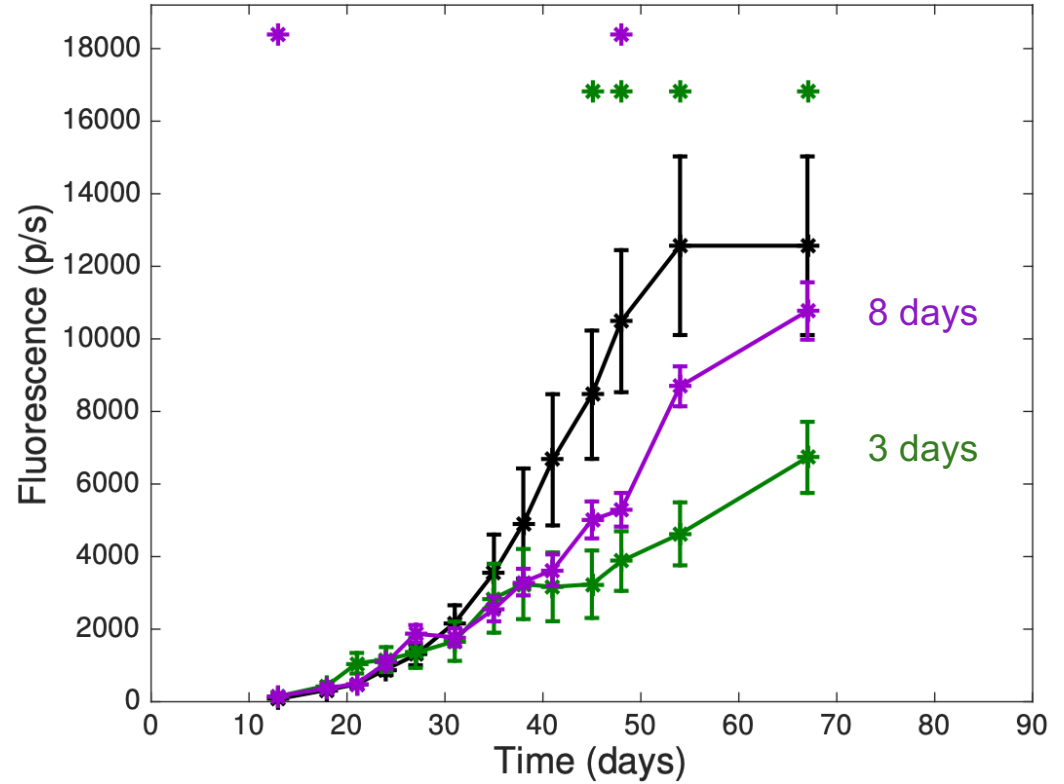
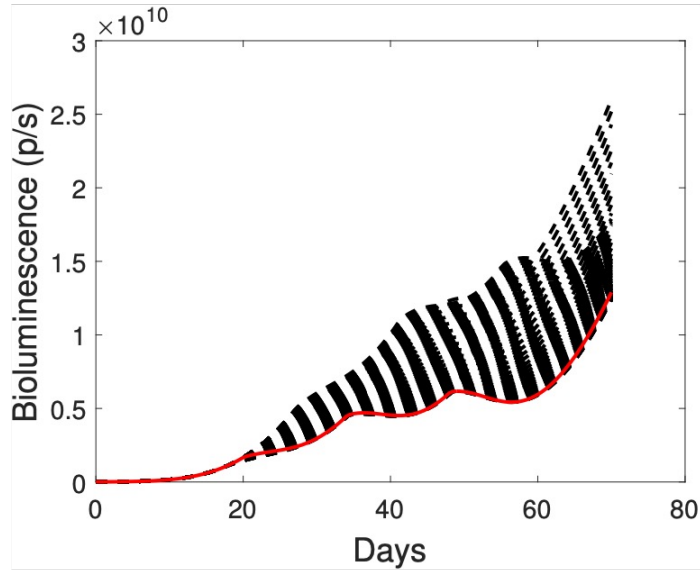
Sequential B/C



Parameters identifiability

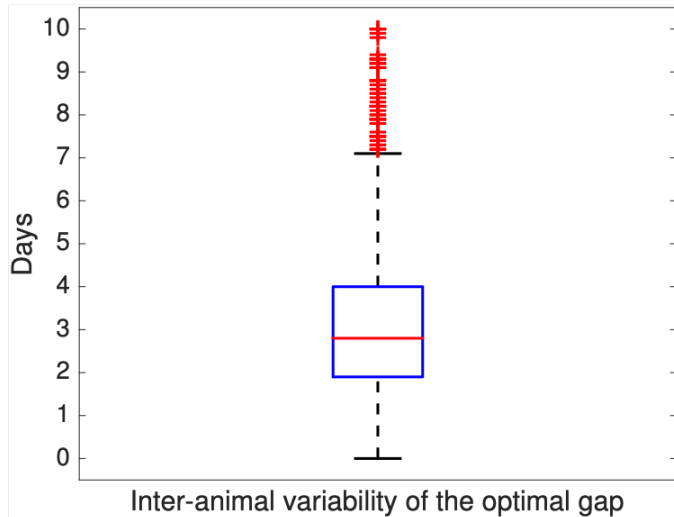
Parameters	Description	Units	Estimates	RSE ^a (%)	IAV ^b %
α	Proliferation rate	Day ⁻¹	0.767	8	8.62
β	Exponential decay rate of the relative tumor growth rate (Gompertz model)	Day ⁻¹	0.037	10	57.3
γ	Baseline effect of the chemotherapy	(mg/g) ⁻¹ .day ⁻¹	1	–	–
δ	Cytotoxics efficacy improvement following vascular normalization	(mg/mL) ⁻¹	1,200	36	0
τ	Delay parameter for dynamics of Q	Day	2	20	10
k	Delay of the tumor cell loss following chemotherapy	Day ⁻¹	0.3	–	–
Σ	Exponential error parameter	–	0.951	4	–

Prediction of the optimal delay

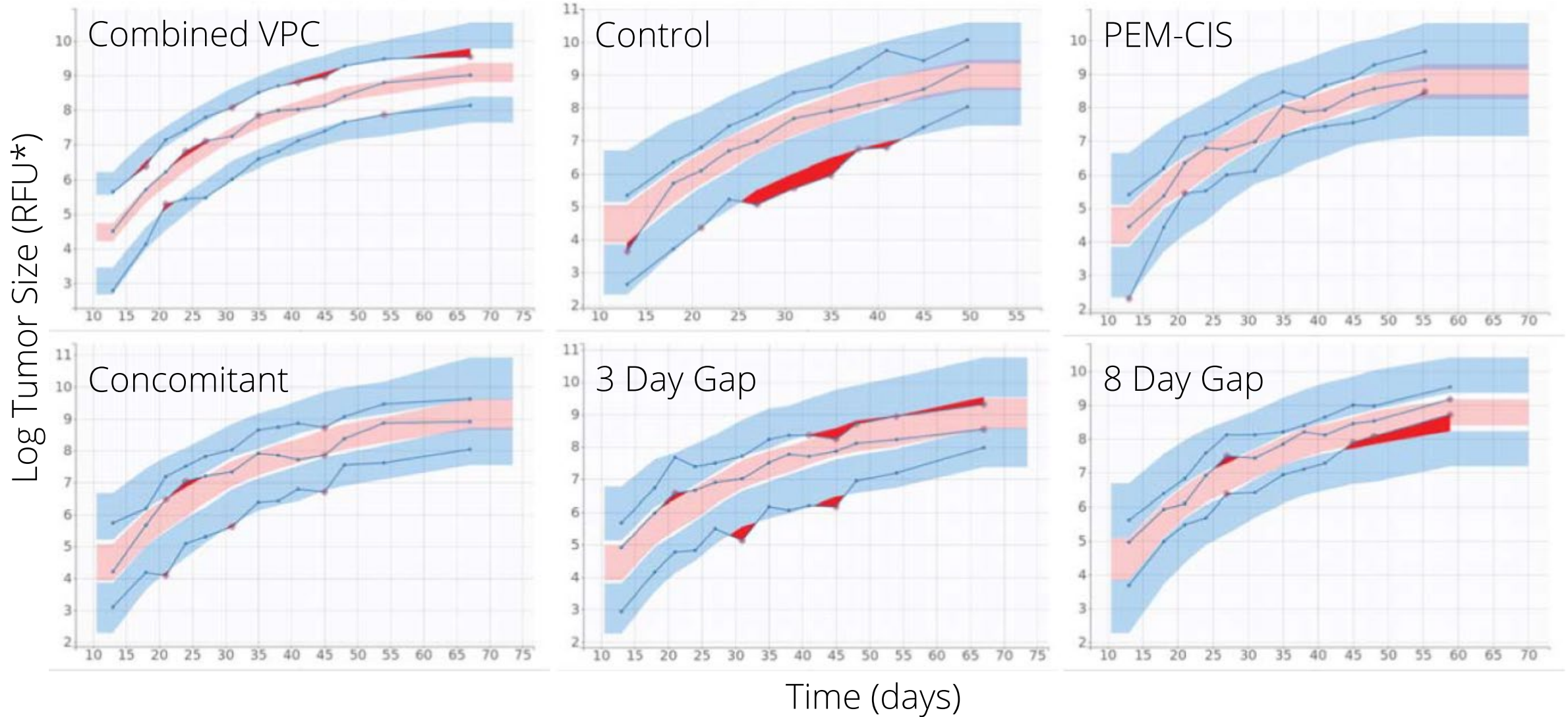


⇒ to be **tested experimentally**

⇒ **personalized** scheduling

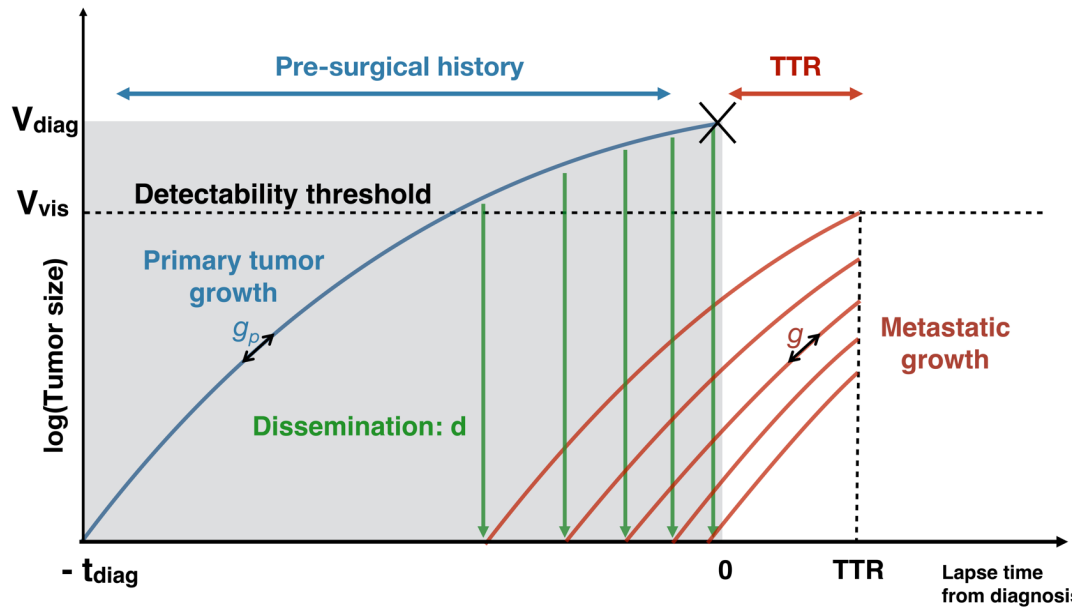


Model fit to the second experimental dataset



**Now, in real life, cancer patients treated
with systemic therapy are usually in
advanced stages**

What about the effect on metastases?



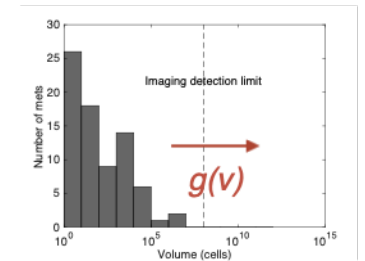
Growth rates of primary and secondary tumors g_p and g

$$\frac{dV_p}{dt} = g_p(t, V_p) \quad \text{ex: Gompertz}$$

Dissemination rate $d(V_p) = \mu V_p^\gamma$

Size distribution of the metastases $\rho(t, v)$ [Iwata et al., 2000]

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



Metastatic burden (total number of metastatic cells)

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

Number of metastases with size larger than the visible size V_{vis}

$$N_{vis}(t) = \int_{V_{vis}}^{+\infty} \rho(t, v) dv = \int_0^{t-\tau_{vis}} d(V_p(t)) dt$$

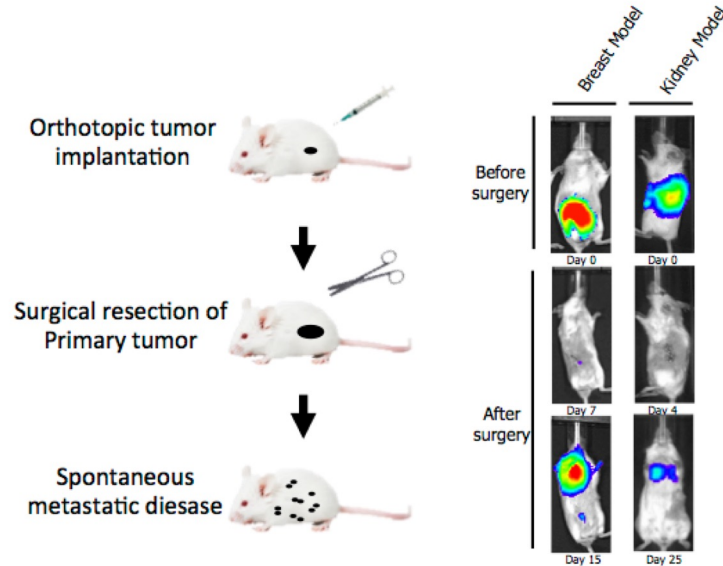
Time to relapse (TTR) = time from diagnosis to first visible met

$$TTR = \inf \{ t > 0 : N_{vis}(t_{diag} + t) \geq 1 \}$$

Experimental data and questions

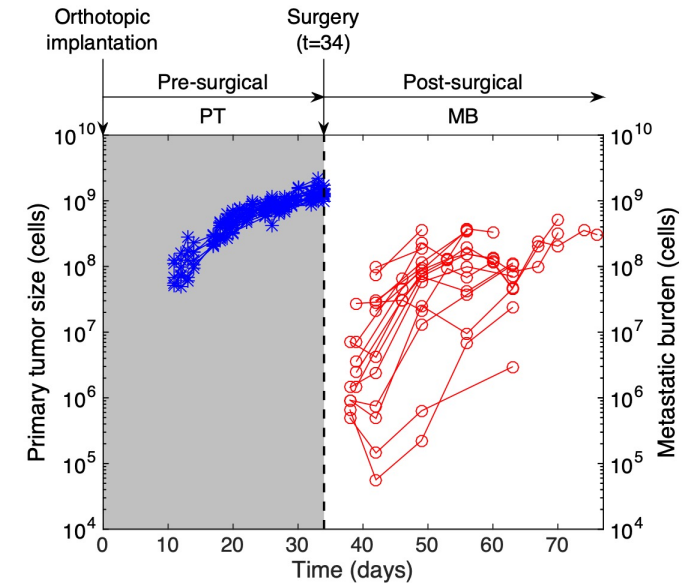
Data

- Clinically relevant ortho-surgical **animal models** of metastasis
- **Longitudinal** measurements of primary tumor size and total **metastatic burden**



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?



Results

Methodology: mixed-effects modeling

Individual i

Time t_j

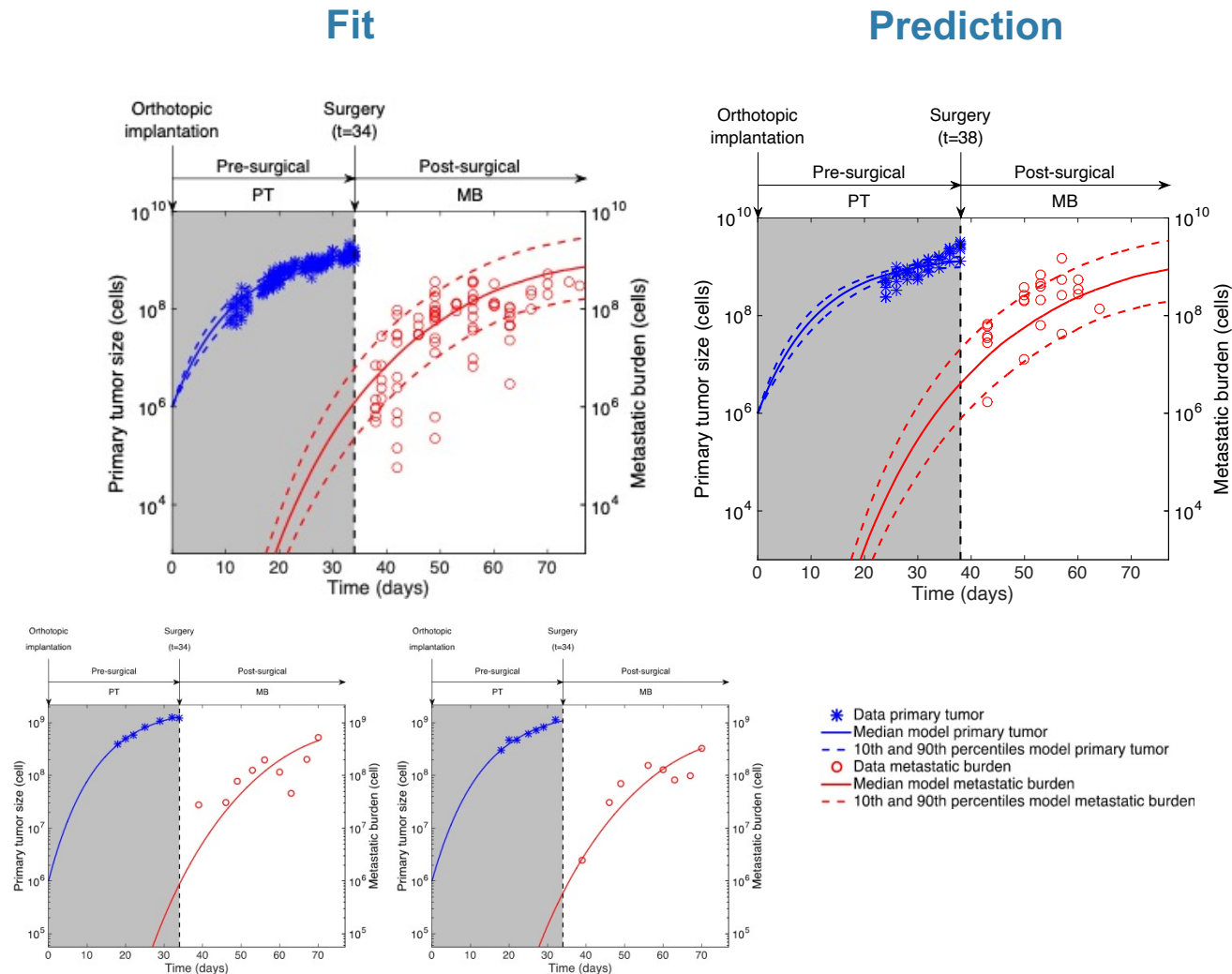
$$y_j^i = M(t_j^i, \theta^i) + \varepsilon_j^i, \quad \varepsilon_j^i \sim \mathcal{N}(0, \sigma_j^i)$$

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

- Likelihood maximization performed using the SAEM algorithm
- **Main difficulty:** PDE model
- **Solution:** fast Fourier transform for computation of metastatic burden

Results:

- g = Gompertz for breast, exponential for kidney, $\gamma = 1$
- **same growth** for PT and mets
- good practical **identifiability** (all rse < 30%)
- parameter μ is critical for inter-animal variability (CV = 176%)
- insights on quantitative **link between PT size and proba of relapse**



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



Cancer Cell
Report

Published online: October 31, 2014

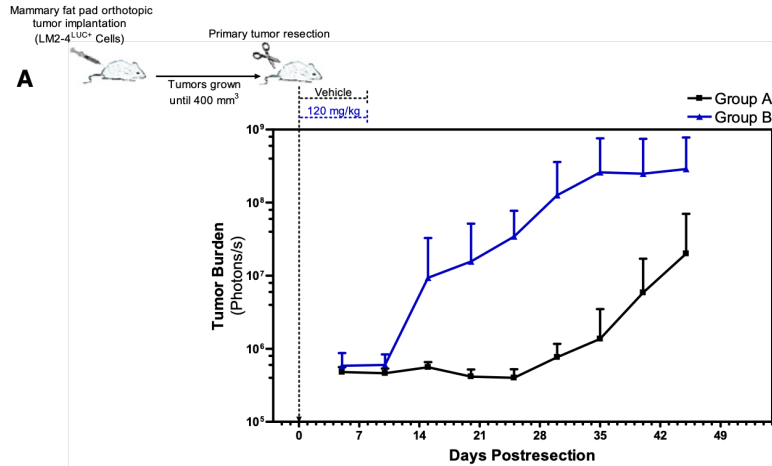
Research Article



EMBO
Molecular Medicine

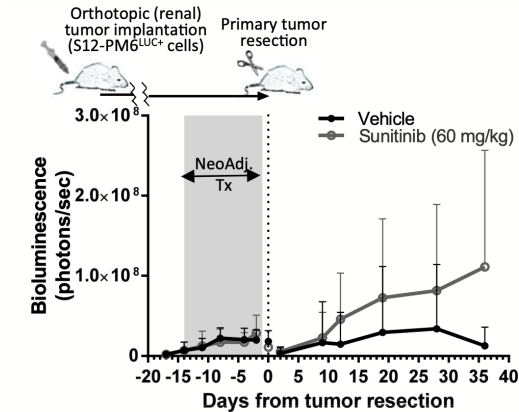
Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

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

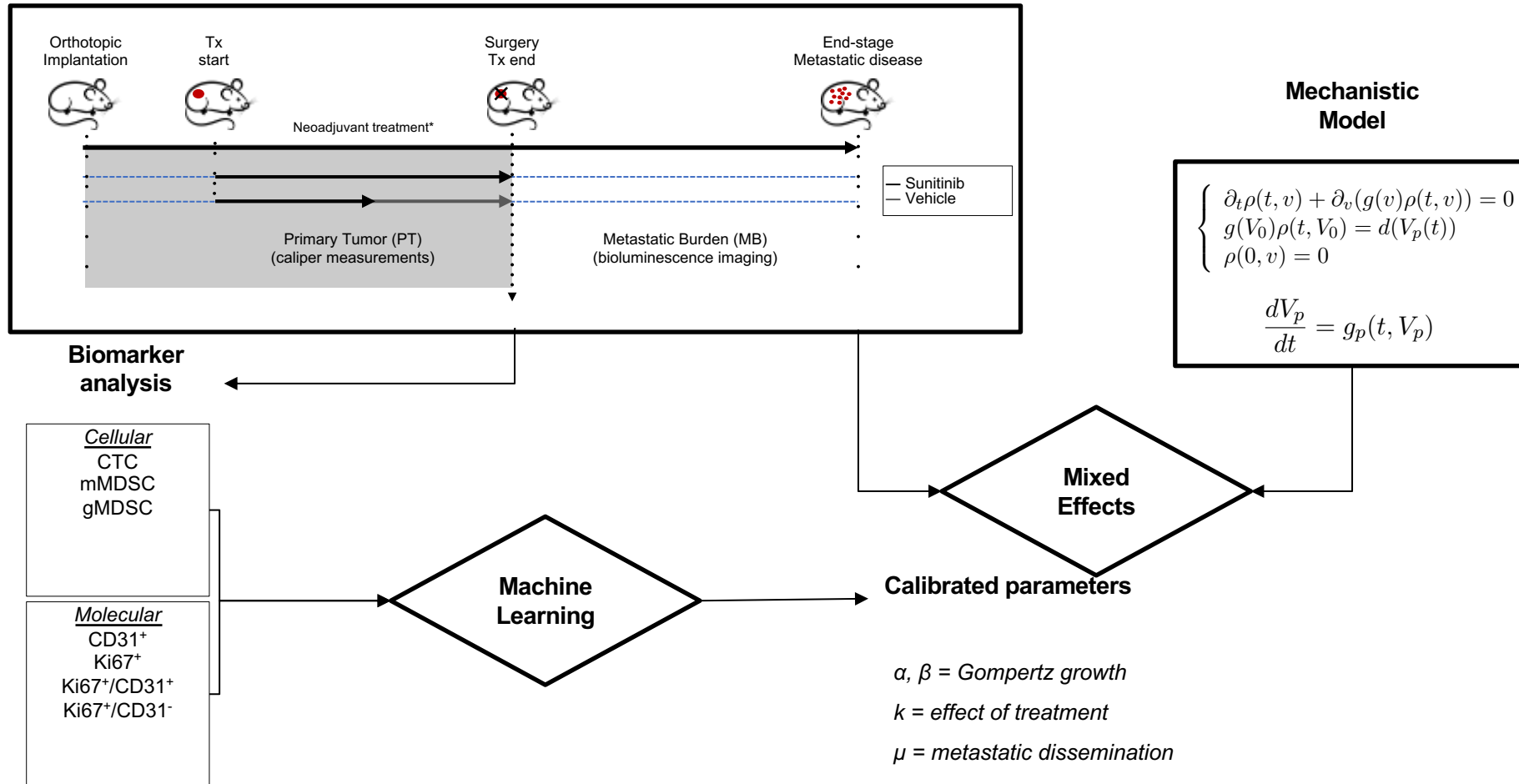
John M L Ebos^{1,*}, Michalis Mastri¹, Christina R Lee², Amanda Tracz¹, John M Hudson², Kristopher Attwood³, William R Cruz-Munoz², Christopher Jedszko², Peter Burns^{2,4} & Robert S Kerbel^{2,4}



Aims

- Test possible hypotheses for the **differential effects** of sunitinib on primary tumor and metastases
- Build a **minimal kinetics-pharmacodynamics (K-PD) model** of neoadjuvant sunitinib treatment
- Assess the predictive power of biomarkers on the model parameters using **machine learning** algorithms

Modeling schematic

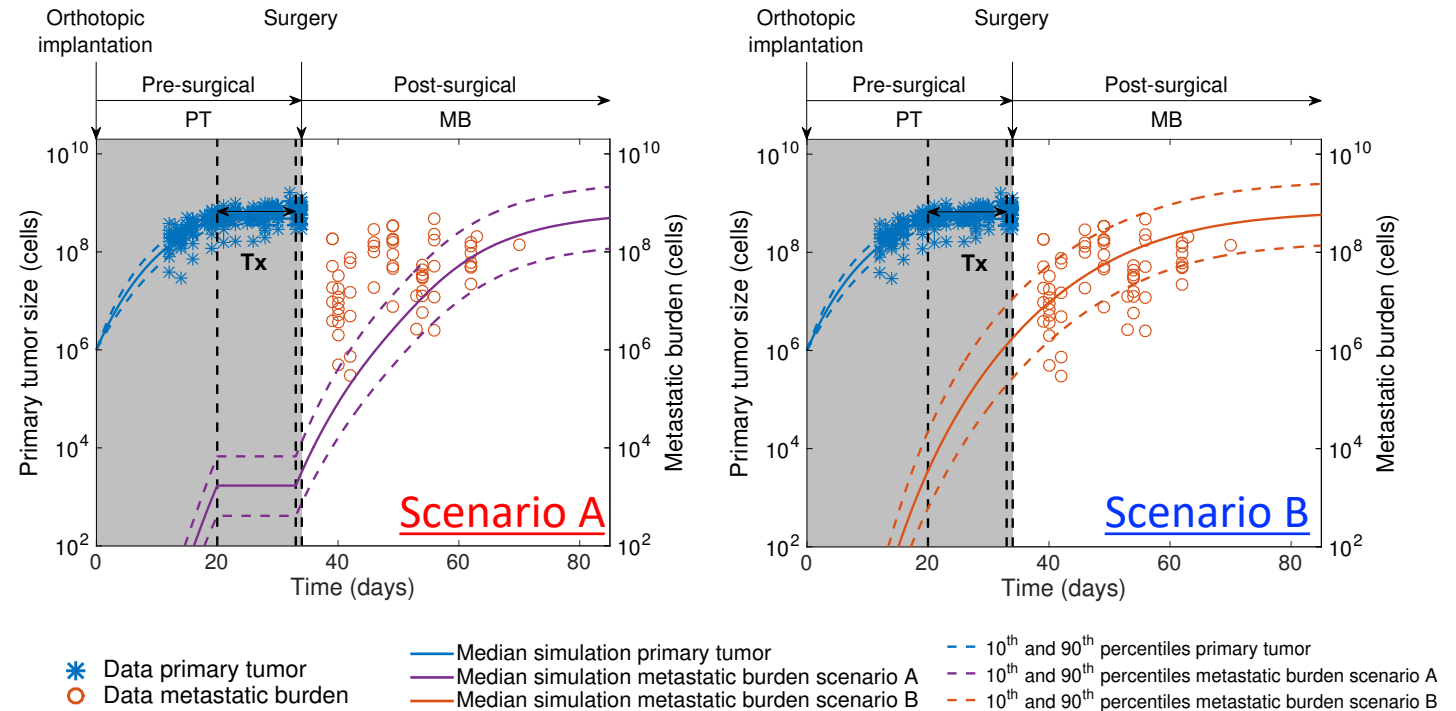
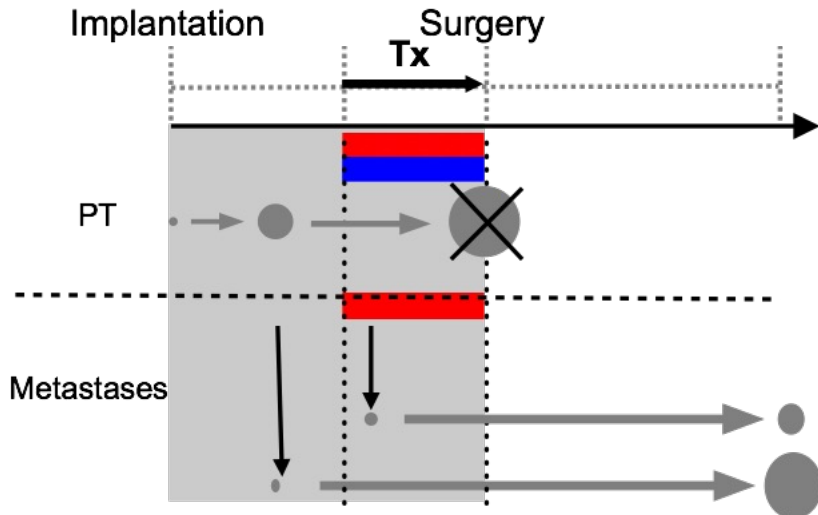


Simulations of the effect of neoadjuvant sunitinib treatment on metastases suggest no effect on growth of metastases

- Parameter values from the previous study on control groups \Rightarrow simulations are pure mechanistic predictions
- In first approximation, the effect of the drug was modeled by setting the tumor growth rate to zero during the phase of treatment

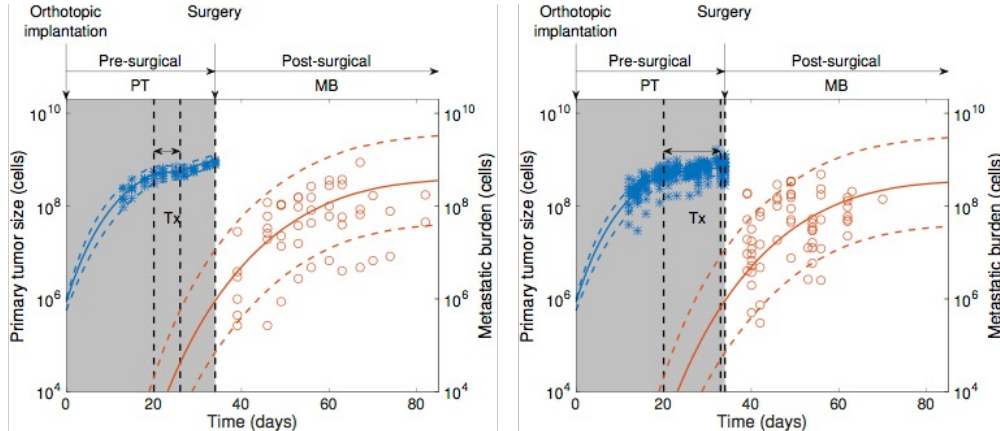
Tx Effects

- Scenario A**
PT and MB growth arrest
- Scenario B**
PT growth arrest only



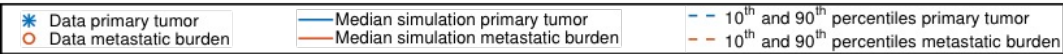
A K-PD model for the effect of Sunitinib

$$g_p^{treat}(t, v) = g_p(t, v)(1 - kC(t))$$



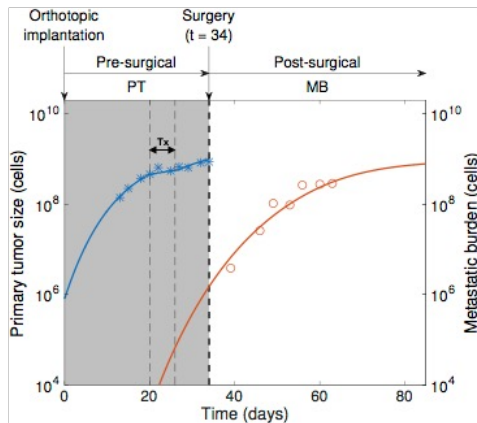
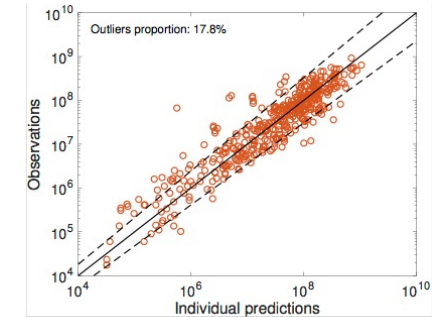
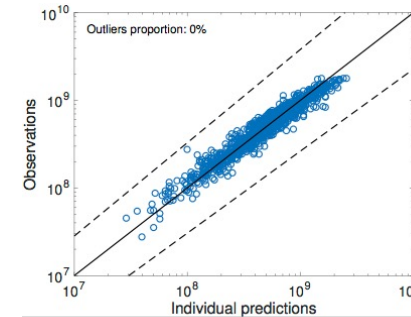
Su60(7D)

Su60(14D)

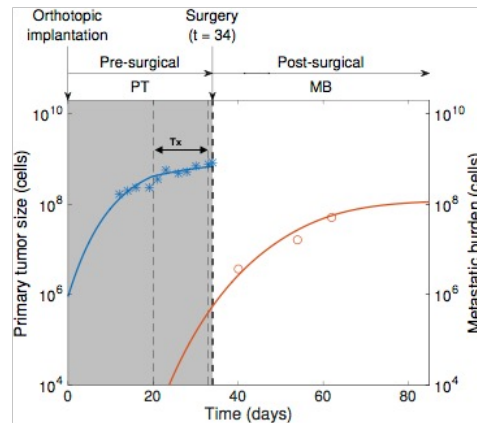


Primary tumor

Metastatic burden



Su60(7D)

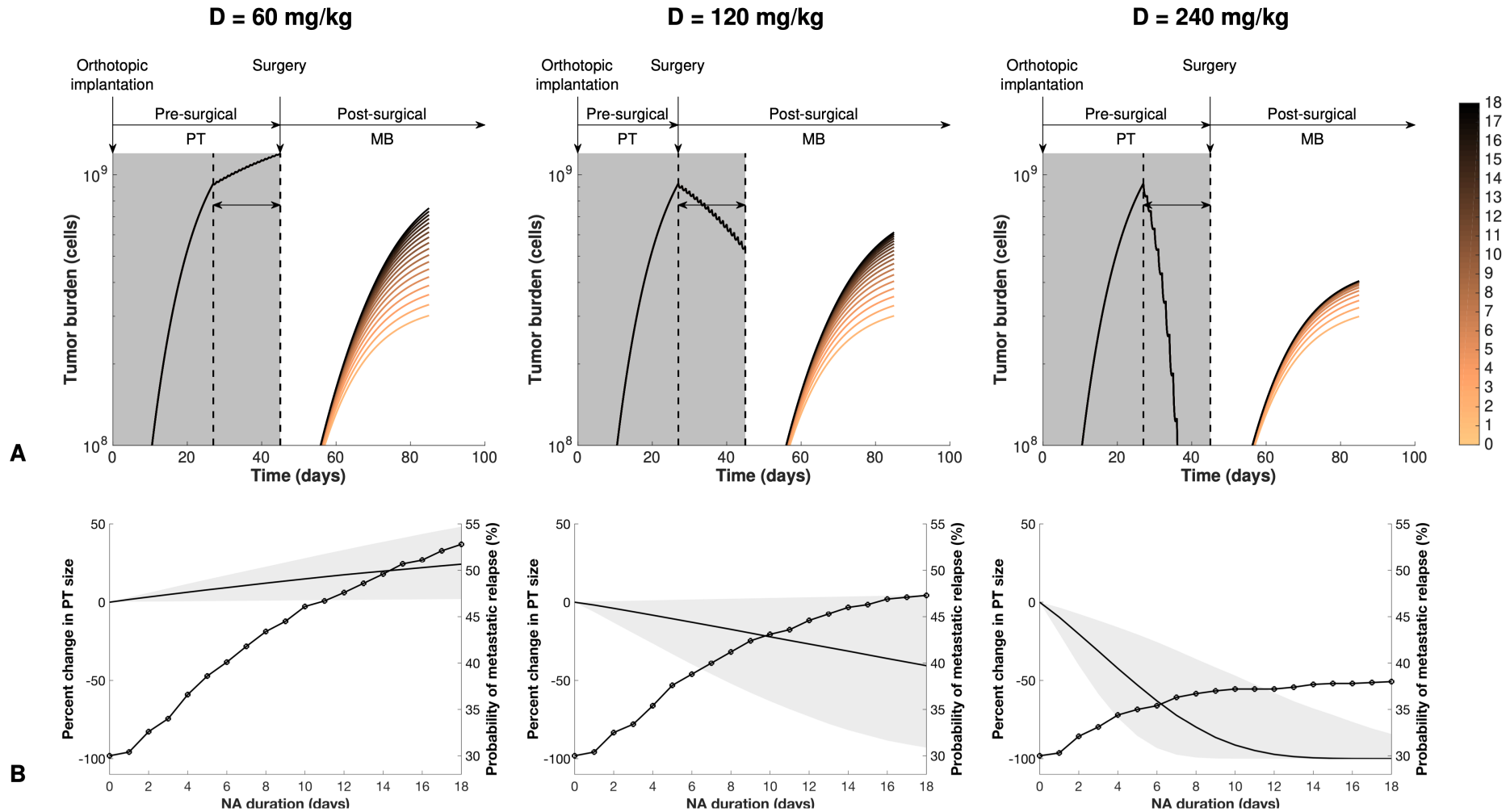


Su60(14D)

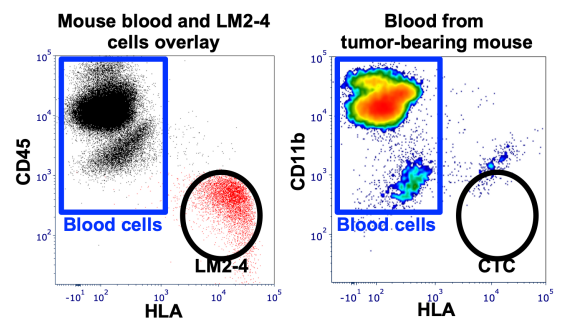
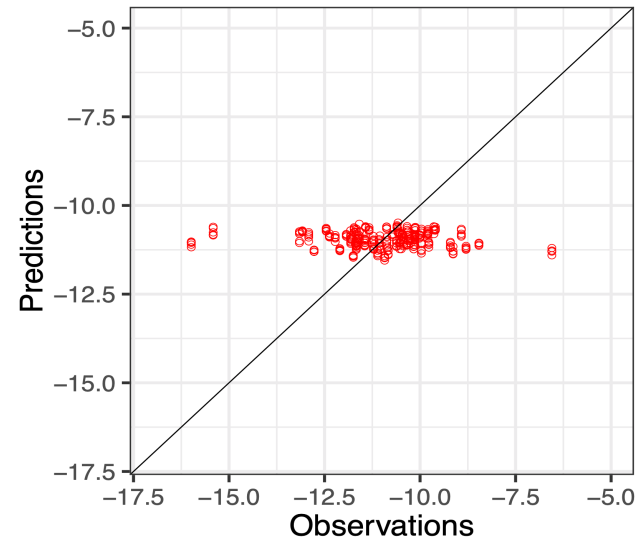
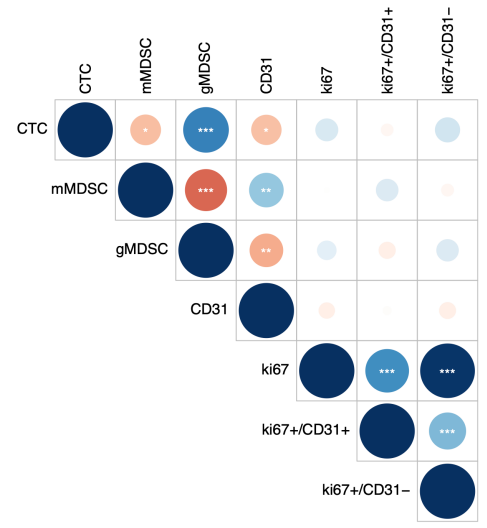
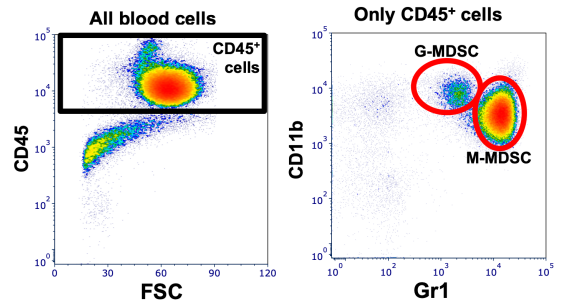
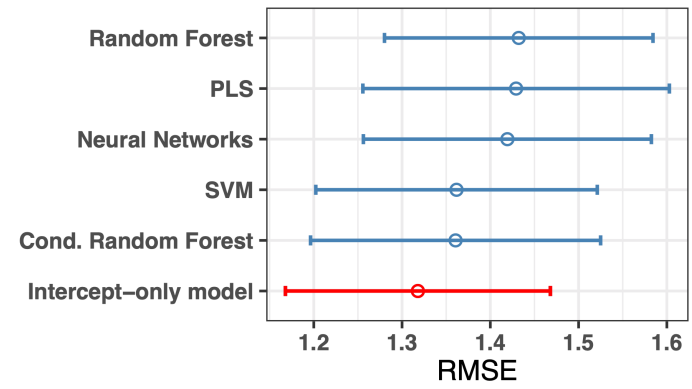
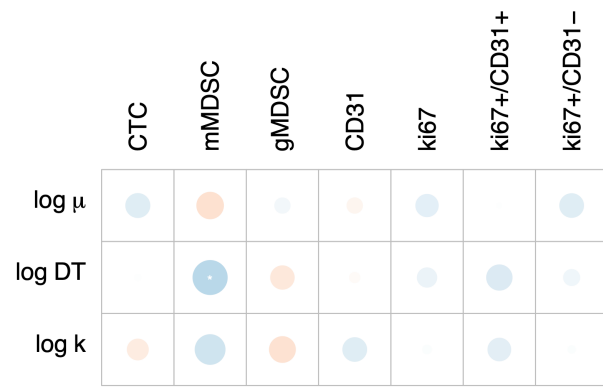
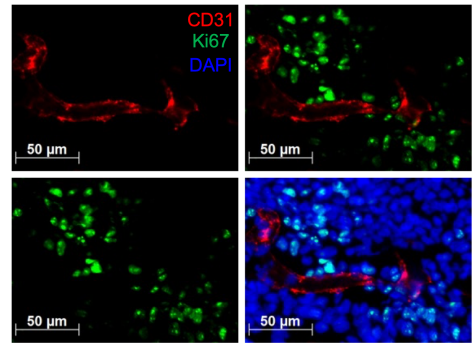
Parameter (Unit)	Meaning	Median	CV (%)	r.s.e. (%)
μ (cell ⁻¹ · day ⁻¹)	dissemination coefficient	$2.12 \cdot 10^{-11}$	$1.48 \cdot 10^3$	17.3
α (day ⁻¹)	gompertzian growth parameter	1.94	18.1	2
β (day ⁻¹)	gompertzian growth parameter	0.0911	19.7	2.21
λ (day ⁻¹)	in vitro proliferation rate	0.837 (fixed)	-	-
k (L/mg)	drug efficacy	0.446	32.1	6.34
k_e (day ⁻¹)	drug elimination rate	3.26 (fixed)	-	-
V_d (L/kg)	volume of distribution	12 (fixed)	-	-

η -shrinkage < 20% for each parameter \Rightarrow the individual parameter estimates can be considered reliable

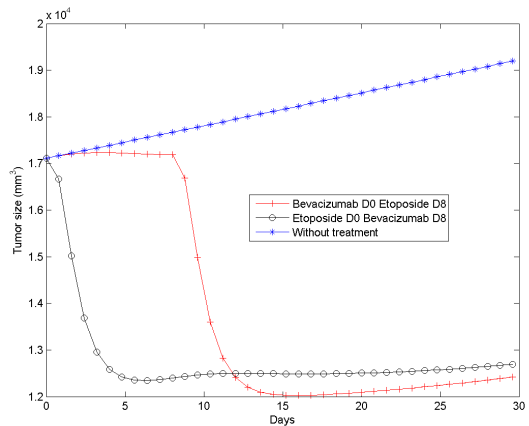
Increased duration of neo-adjuvant treatment could substantially increase probability of metastatic relapse



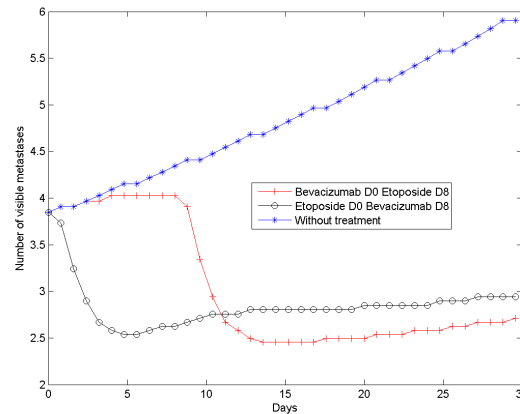
The biomarkers considered in this study have limited predictive power for metastatic potential as defined by μ



Theoretical simulations of CT/AA combination in the metastatic setting

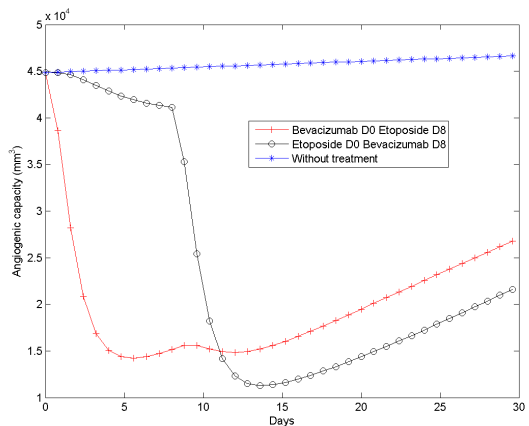


A

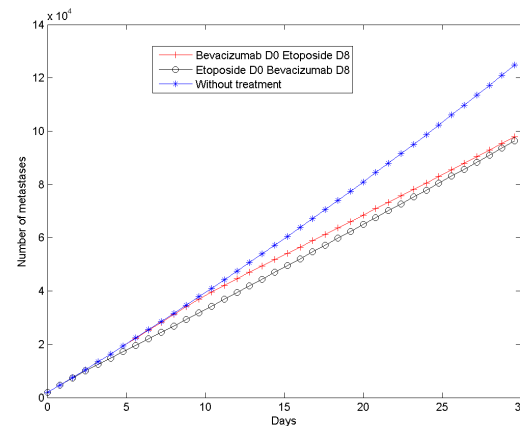


B

⇒ Impact of the CT/AA sequence on outcome might differ between the primary tumor and the metastases



C



D

Discussion

- Construction of a semi-mechanistic model for the **combination of CT and AA** drugs in oncology
- Based on a biological mechanism of transient **vascular normalization** following bevacizumab treatment
- The model was able to quantify experimentally-observed differences between CT/AA and AA/CT sequential administrations
- **Predictions** of the model in terms of optimal sequence were confirmed in a second set of experiments
- **Systemic therapies** should be further modeled at the **systemic (organism) scale**
 - Include the **dissemination** process in addition to growth
 - Consider not just one tumor but a **population of tumors** (cf individual lesion TGI models, e.g. *Mercier et al., J PK PD, 2020*)
 - In addition, there are **tumor-tumor systemic interactions** (cf *Benzekry et al., Cancer Res, 2017*)
- A modeling framework for populations of tumors was proposed and compared to experimental data
 - **Post-surgical** metastatic development in untreated animals
 - Extension to the **neoadjuvant** setting

Acknowledgments

Experimental therapeutics

J. Ciccolini

S. Mollard

A. Boyer

S. Giacommetti



Preclinical data of ortho-surgical animal models of metastasis

J. Ebos

M. Matri

A. Tracz



Modeling

D.C. Imbs

R. El Cheikh

J. Mochel

C. Nicolò

B. Schneider



Multiple **open positions** in COMPO !!

- Tenure researcher
- Postdoc
- **PhD**
- Engineer



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@SBenzekry

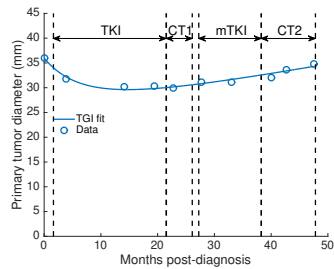
Thank you for your attention !

Results: individual clinical data

Methodology

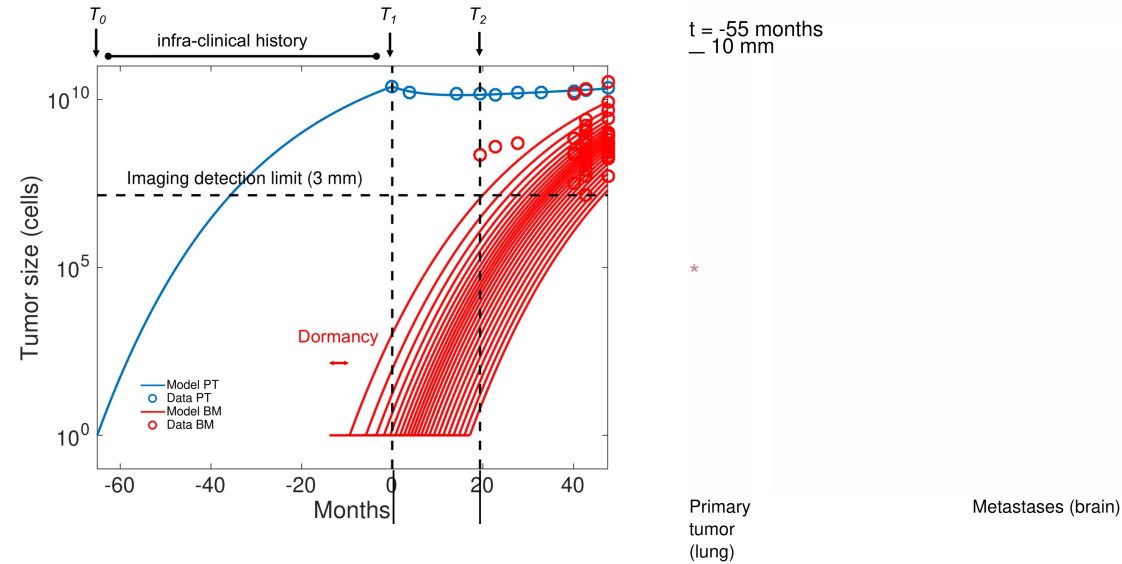
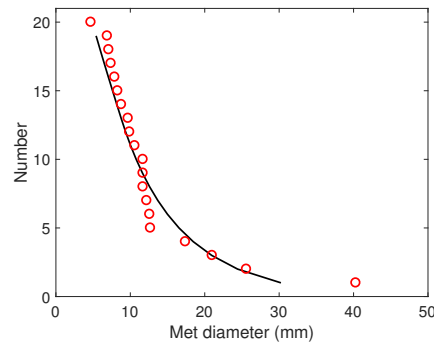
Primary tumor

$$\frac{dS_p}{dt} = \alpha_1 S_p - \kappa e^{-\frac{t-T_d}{t_{res}}} \ln 2 S_p, \quad \forall t \geq T_d.$$



Metastases

$$f(t, v) = \int_v^{+\infty} \rho(t, u) du = N(t - \tau(v))$$



- Main difficulties:

no data on PT pre-treatment + fit PDE to discrete data

Results

- Dormancy, estimated to 133 days \pm 4.2%
- Good fit of the entire longitudinal data (47 BM sizes over 6 time points) with only **3 parameters**.
- Onset of BM 14-19 months before diagnosis

Model



Data



Ongoing (collab. TU München)

- Extend to larger cohort: **complex** treatment histories
- Include effect of **treatment** $\Rightarrow g(t, v) \Rightarrow$ nontrivial difficulties for param estimation

Results: prediction of clinical metastatic relapse

Methodology

- Reduce to two parameters: growth (α) and dissemination (μ)

$$\ln(T^i) = \ln(TTR(V_{diag}^i; \alpha^i, \mu^i)) + \varepsilon^i, \quad \varepsilon^i \sim \mathcal{N}(0, \sigma^2) \quad S(t|\alpha^i, \mu^i) = \mathbb{P}(T^i > t|\alpha^i, \mu^i)$$

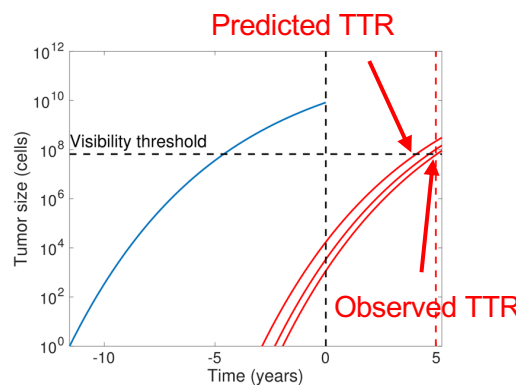
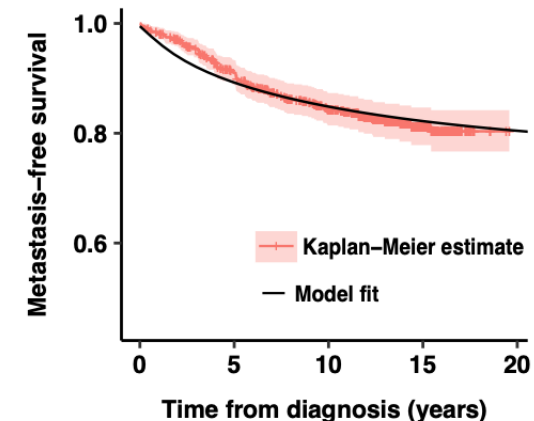
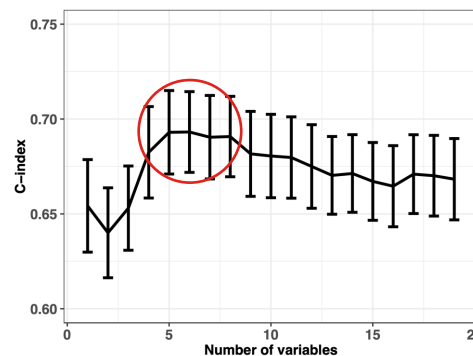
$$\ln(\mu^i) = \ln(\mu_{pop}) + \beta_{\mu}^T \mathbf{x}_{\mu}^i + \eta_{\mu}^i, \quad \eta_{\mu}^i \sim \mathcal{N}(0, \omega_{\mu}^2)$$

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

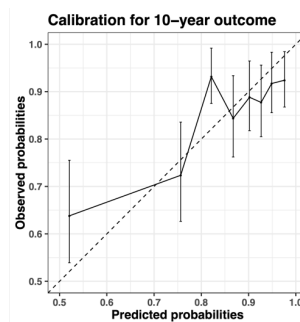
- Main difficulties: selection of covariates + survival data
- Solution: random survival forest + adapt for censoring

Results

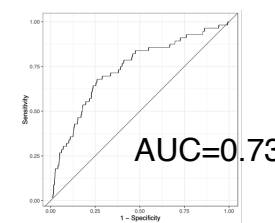
- Similar predictive power for mechanistic VS classical Cox or survival random forest (c-index = 0.63-0.70 vs 0.67-0.71 vs 0.67-0.72) or other ML
- Gives mechanistic insights on metastatic biology



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
σ	0.606	23.104	
ω_{α}	2.062	22.715	
ω_{μ}	3.563	16.759	



Mechanistic



Random survival forest

