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# Optimization of sequential administration of bevacizumab plus cytotoxics in non-small cell lung cancer by combining in vivo experiments and mathematical modeling

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# Optimization of sequential administration of bevacizumab plus cytotoxics in non-small cell lung cancer by combining in vivo experiments and mathematical modeling

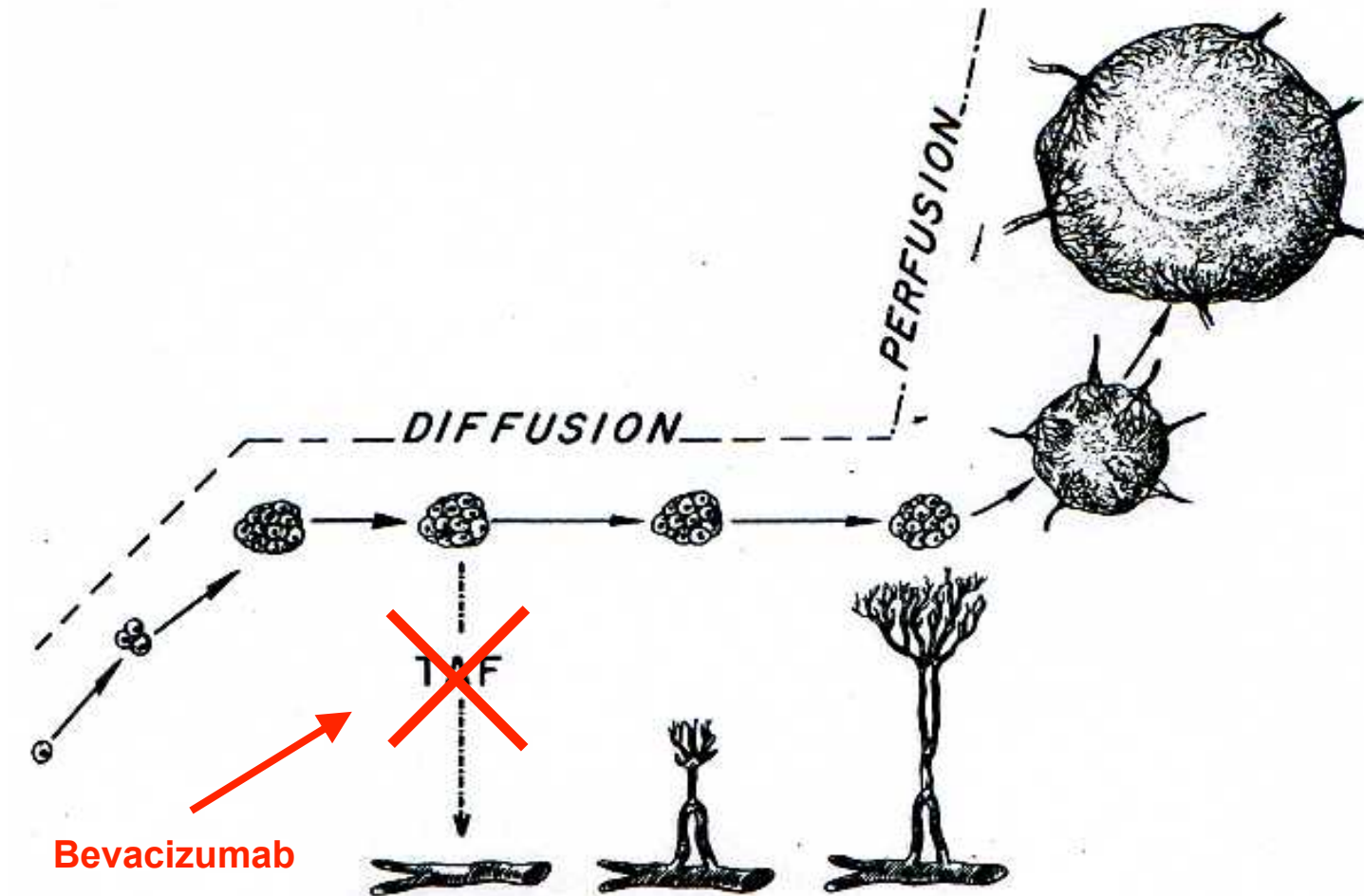
S. Benzekry

Inria team MONC, Bordeaux

Mathematical perspectives in the biology and therapeutics of cancer

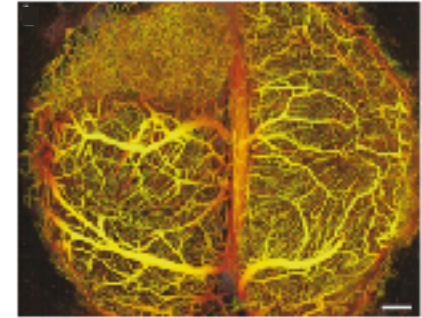
July 11, 2018

# Angiogenesis

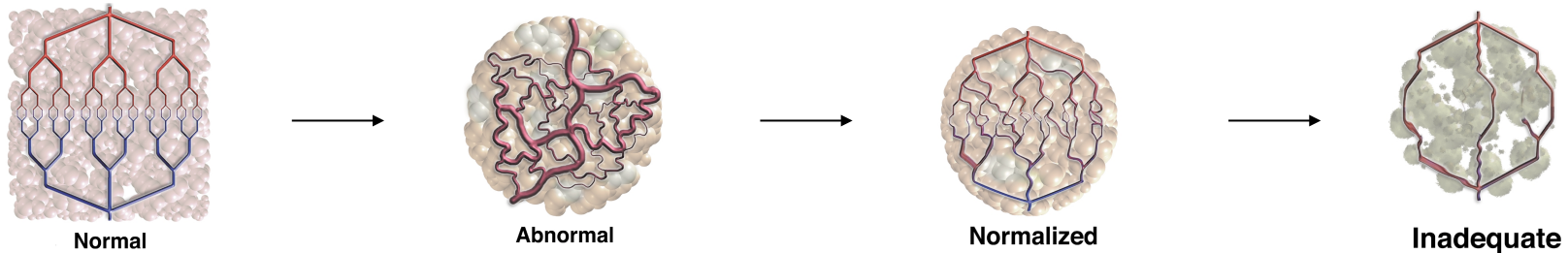


# Vascular normalization: a time window for improved pharmacokinetics?

- 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*

## 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

Modeling and Simulation

**Breast cancer model**

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

**Lung cancer model**

Experiment 1

Calibration



Experiment 2

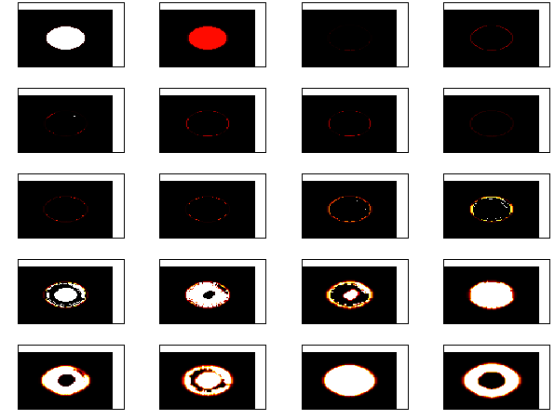


Prediction

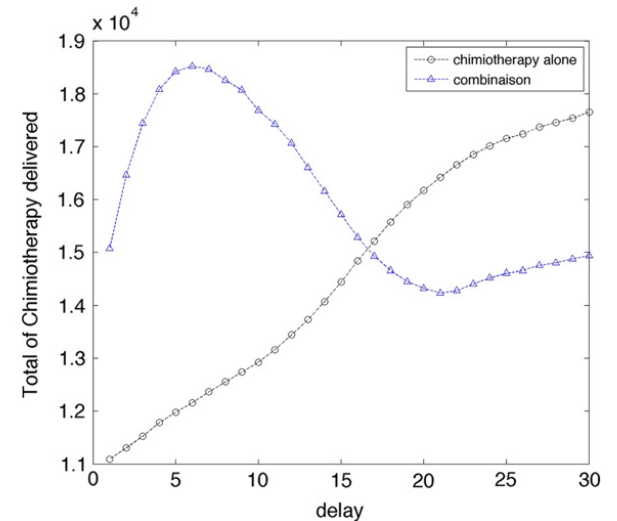


# A first theoretical and complex model

Entity	Model equation
Density of $P_1$	$\frac{\partial P_1}{\partial t} + \frac{\partial P_1}{\partial a} + \nabla \cdot (\mathbf{v}_{P_1} P_1) = 0 \quad P_1(a=0) = 2P_2(a = a_{max,P_2})$
Density of $P_2$	$\frac{\partial P_2}{\partial t} + \frac{\partial P_2}{\partial a} + \nabla \cdot (\mathbf{v}_{P_2} P_2) = -P_2(a = a_{max,P_2}) \frac{E_{max,C}[C]}{C_{50} + [C]} \quad P_2(a=0) = fP_1(a = a_{max,P_1}) + [\partial_t f]^+ Q(t^-)$
Density of $Q$	$\frac{\partial Q}{\partial t} + \nabla \cdot (\mathbf{v}_Q Q) = g(1-f)P_1(a = a_{max,P_1}) - \left[\frac{\partial f}{\partial t}\right]^+ Q(t^-) + \left[\frac{\partial g}{\partial t}\right]^- Q(t^-)$
Density of $A$	$\frac{\partial A}{\partial t} + \nabla \cdot (\mathbf{v}_A A) = (1-g)P_1(a = a_{max,P_1}) - \left[\frac{\partial g}{\partial t}\right]^- Q(t^-)$
Density of $H$	$\frac{\partial H}{\partial t} + \nabla \cdot (\mathbf{v}_H H) = 0$
Density of mature vessel cells	$\frac{\partial Es}{\partial t} = \mu \mathcal{H}(E + Es - \tau_E) E - a_{ES} Es$
Density of immature vessel cells	$\frac{\partial E}{\partial t} + \nabla \cdot (\chi E (1 - \frac{E}{N_E}) \nabla[V]) = pE \left(1 - \frac{E + Es}{N_E}\right) - a_E E - \mu \mathcal{H}(E + Es - \tau_E) E$
Quality of the vasculature	$R = \frac{\int E}{Vol} \quad \Pi = 1 - \frac{R^n}{R^n + R_{0.5}^n}$
Concentration of oxygen	$-\nabla \cdot (K_{[O_2]} \nabla[O_2]) = -\sum_{\phi} \alpha_{[O_2],\phi} \phi \quad [O_2] = \Pi C_{max} \quad \text{where } Es \geq \tau_v$
Concentration of VEGF	$\frac{\partial [V]}{\partial t} - \nabla \cdot (K_{[V]} \nabla[V]) = \alpha_{[V]} Q_{[O_2] \leq \tau_{1,h}} - \beta_{[V]} E[V] - \delta_{[V]} [V] - [V] \frac{E_{max_{[AA]}}[AA]}{[AA]_{50} + [AA]}$
Concentration of chemo.	$-\nabla \cdot (K \nabla[C]) = -\xi_{[C]} [C] \quad [C] = \Pi P_{[C]}(t) \quad \text{where } Es \geq \tau_v$
Concentration of antiangiogenic	$-\nabla \cdot (K \nabla[AA]) = -[V] \frac{E_{max_{[AA]}}[AA]}{v_{50} + [AA]} \quad [AA] = \Pi P_{[AA]}(t) \quad \text{where } Es \geq \tau_v$



Parameter	Description	Value	Unit
$\tau_0$	Threshold of overcrowding	$5 \times 10^4$	cell
$\tau_{1,h}$	Threshold of moderate hypoxia	$4 \times 10^{-7}$	M
$\tau_{2,h}$	Threshold of severe hypoxia	$4 \times 10^{-9}$	M
$N_{max}$	Total density of tumor and/or healthy cells	$10^5$	cell
$a_{max,P_1}$	Maximum duration of phase $P_1$	5	time-unit
$a_{max,P_2}$	Maximum duration of phase $P_2$	8	time-unit
$\alpha_{[V]}$	Secretion rate of VEGF by quiescent cells	$10^{-8}$	M/cell
$\delta_{[V]}$	Consumption rate of VEGF by immature endothelial cells	0	M/cell
$\xi_{[V]}$	Degradation rate of VEGF	0	$M^{-1}$
$N_E$	Maximum number of endothelial cells	$10^5$	cell
$\mu$	Rate of maturation for endothelial cells	0.5	cell/time-unit
$\tau_E$	Minimum quantity of immature EC leading to maturation	$5 \times 10^2$	cell
$\gamma_n$	Sigmoidal coefficient for the computation of vasculature quality	0.5	cell/mm <sup>2</sup>
$R_{0.5}$	Density of EC leading to half of the maximal vasculature quality	$8 \times 10^{-3}$	cell/mm <sup>2</sup>
$\tau_v$	Number of EC needed to form a functional blood vessel	$4 \times 10^4$	cell
$C_{max}$	Oxygen concentration in blood	$2 \times 10^{-2}$	M
$K$	Diffusion coefficient of molecules in the tissue	1-5	mm <sup>2</sup> /time-unit
$\beta_{[O_2], P_1}$	Oxygen consumption of the $P_1$ tumor cells	$10^{-4}$	M/cell
$\beta_{[O_2], P_2}$	Oxygen consumption of the $P_2$ tumor cells	$10^{-4}$	M/cell
$\beta_{[O_2], Q}$	Oxygen consumption of the quiescent tumor cells	$0.25 \times 10^{-4}$	M/cell
$\xi_{[C]}$	Degradation rate of chemotherapy	$1.25 \times 10^{-4}$	M/time-unit
$E_{max_{[AA]}}$	Maximal effect of the antiangiogenic drug on VEGF	1	None
$v_{50}$	Amount of antiangiogenic drug producing half of the maximal effect	0.5	M
$E_{max, c}$	Maximal effect of the chemotherapy on $P_2$ cells	0.75	None
$C_{50}$	Amount of chemotherapy producing half of the maximal effect	0.2	M



## Simplified model for the anti-angiogenic therapy: the Hahnfeldt-Folkman approach

$$\begin{cases} \frac{dV}{dt} = aV \ln\left(\frac{K}{V}\right) \\ \frac{dK}{dt} = bV - dV^{2/3}K - eA(t)K \end{cases}$$

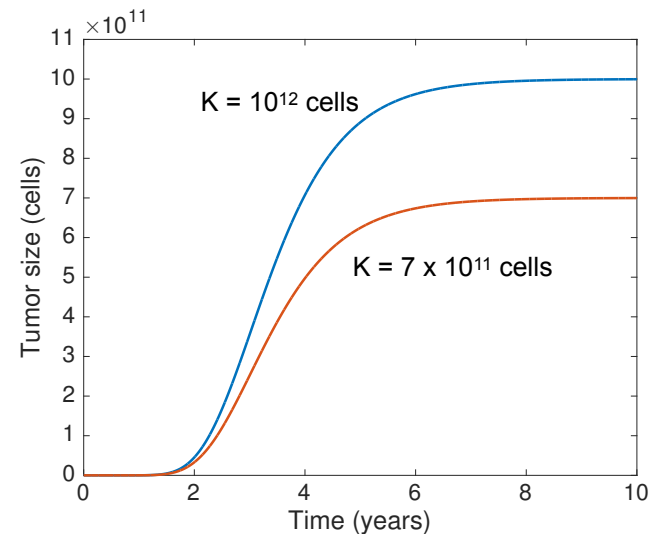
Hahnfeldt-Folkman effect:  $K = f(A(t))$

Dynamics of  $K$  are governed by a balance between **angiogenic stimulation and inhibition** (both endogenous and exogenous)

Vasculature = carrying capacity

neo-angiogenesis  
↓

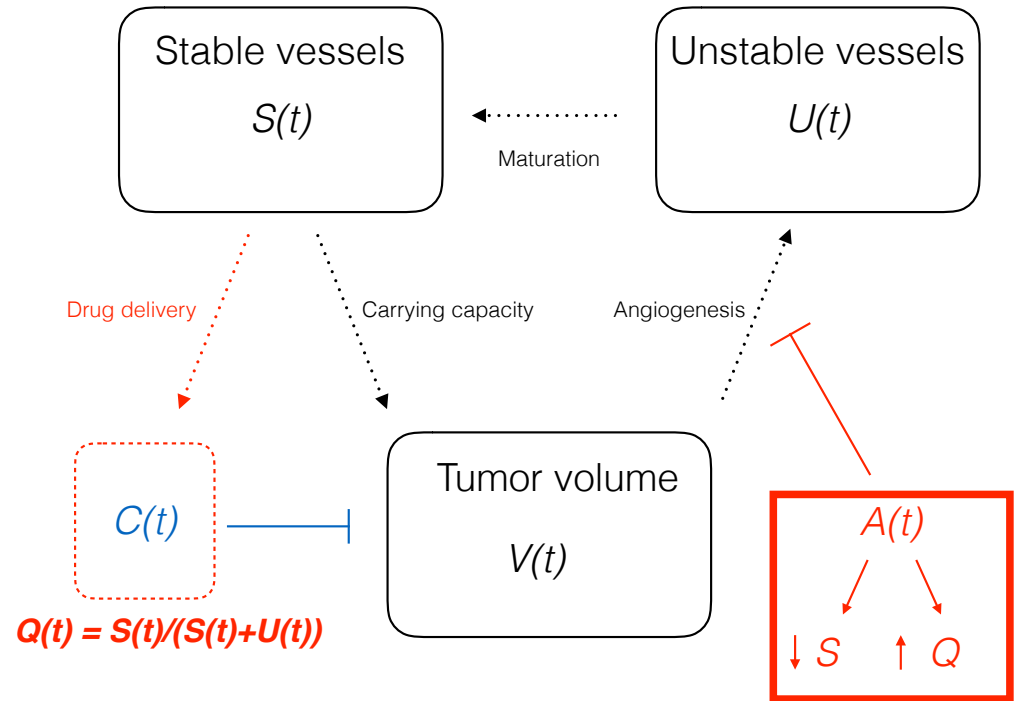
**Dynamical** carrying capacity  $K(t)$



# Modeling the combination of chemotherapy and bevacizumab

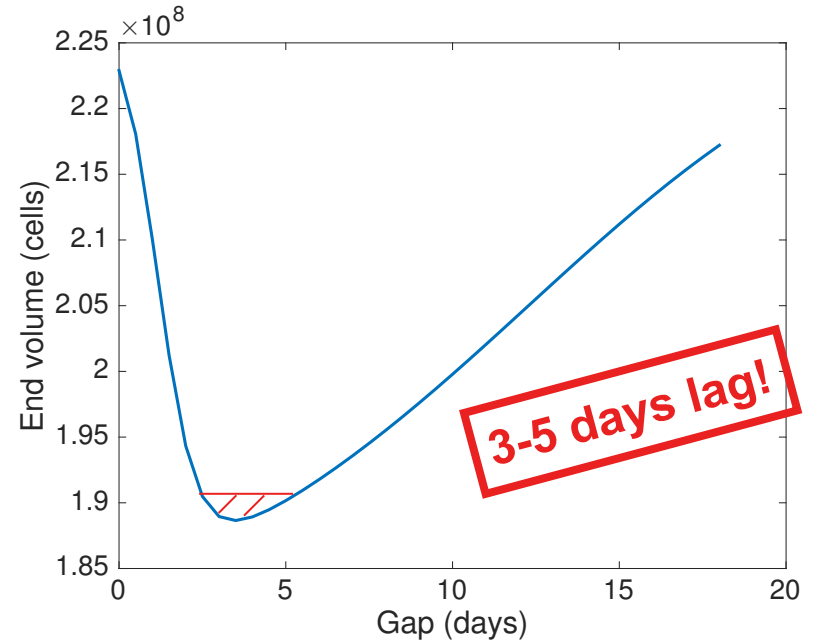
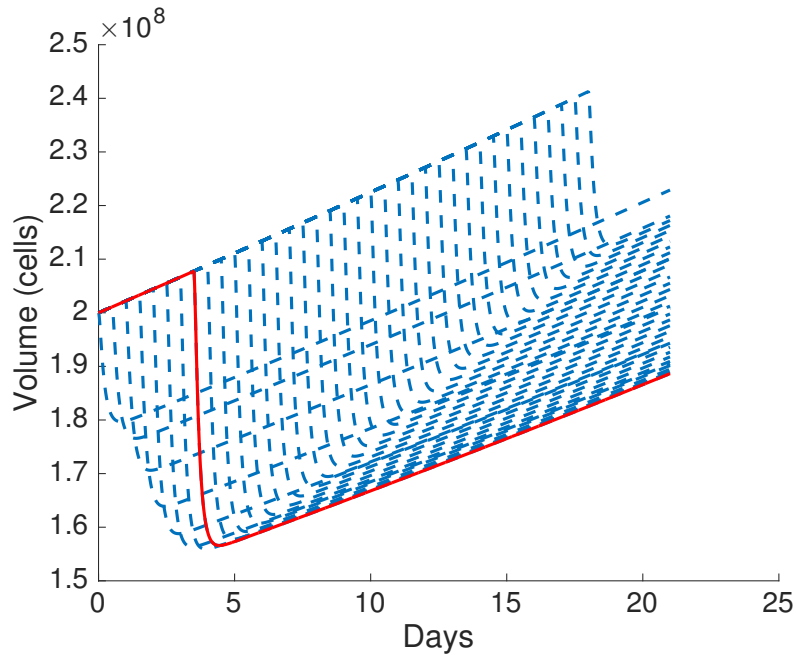
Idea: define a dynamical index of quality of the vasculature  $Q$  by dividing the vasculature into **stable** and **unstable** compartments

$$\begin{cases} \frac{dV}{dt} = aV \ln\left(\frac{S}{V}\right) - e_{CT} Q S C(t) V \\ \frac{dU}{dt} = bV - dV^{2/3} U - \chi U - e_{AA} Q S A(t) U \\ \frac{dS}{dt} = \chi U - \tau S \end{cases}$$



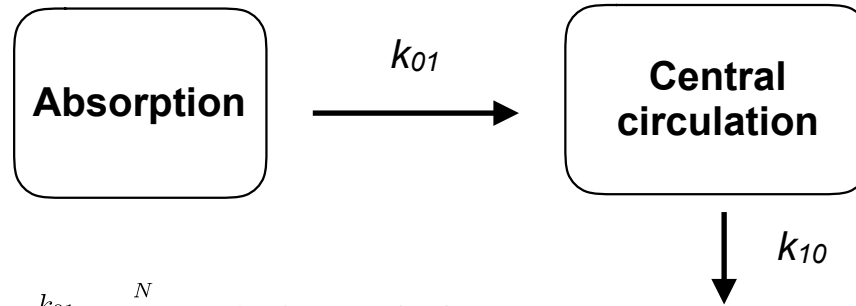
$$Q = \frac{S}{S + U}$$

## A priori simulations of the model suggest optimal sequence



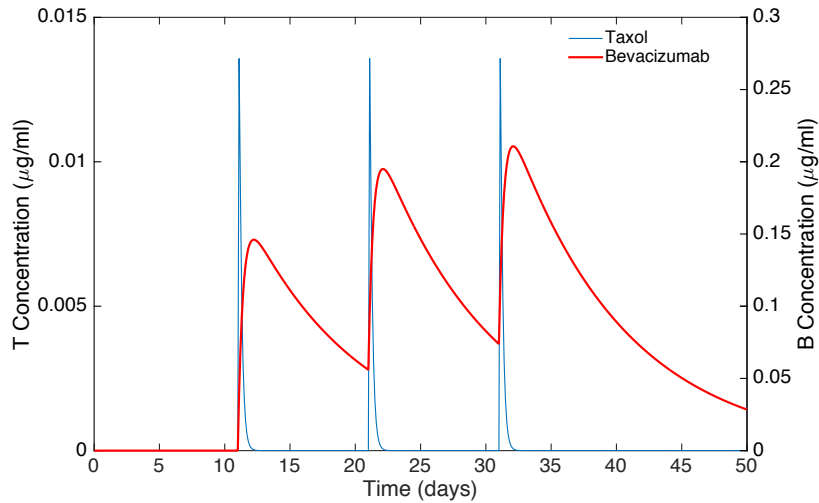
... ► **Anti-angiogenics first, then cytotoxics**

# Pharmacokinetics models

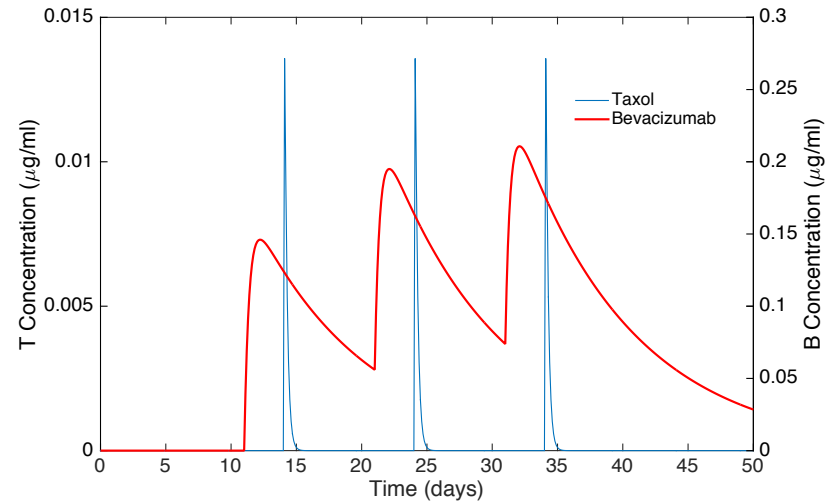


$$C(t) = \frac{D}{V} \frac{k_{01}}{k_{01} - k_{10}} \sum_{i=1}^N e^{-k_{10}(t-t_i)} - e^{-k_{01}(t-t_i)} \mathbb{1}_{t \geq t_i}$$

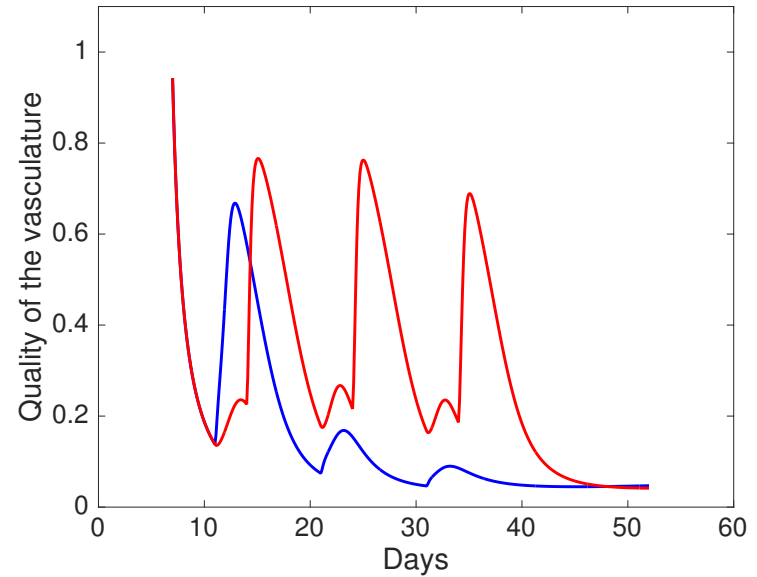
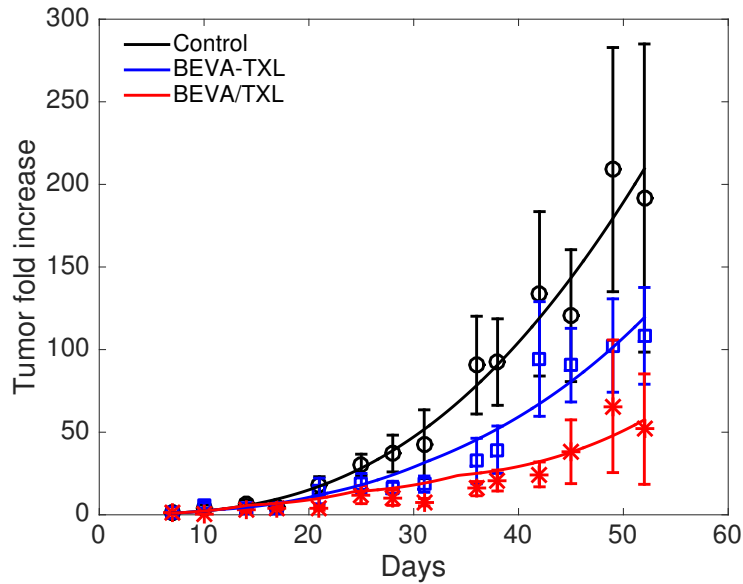
Concomitant



Sequential



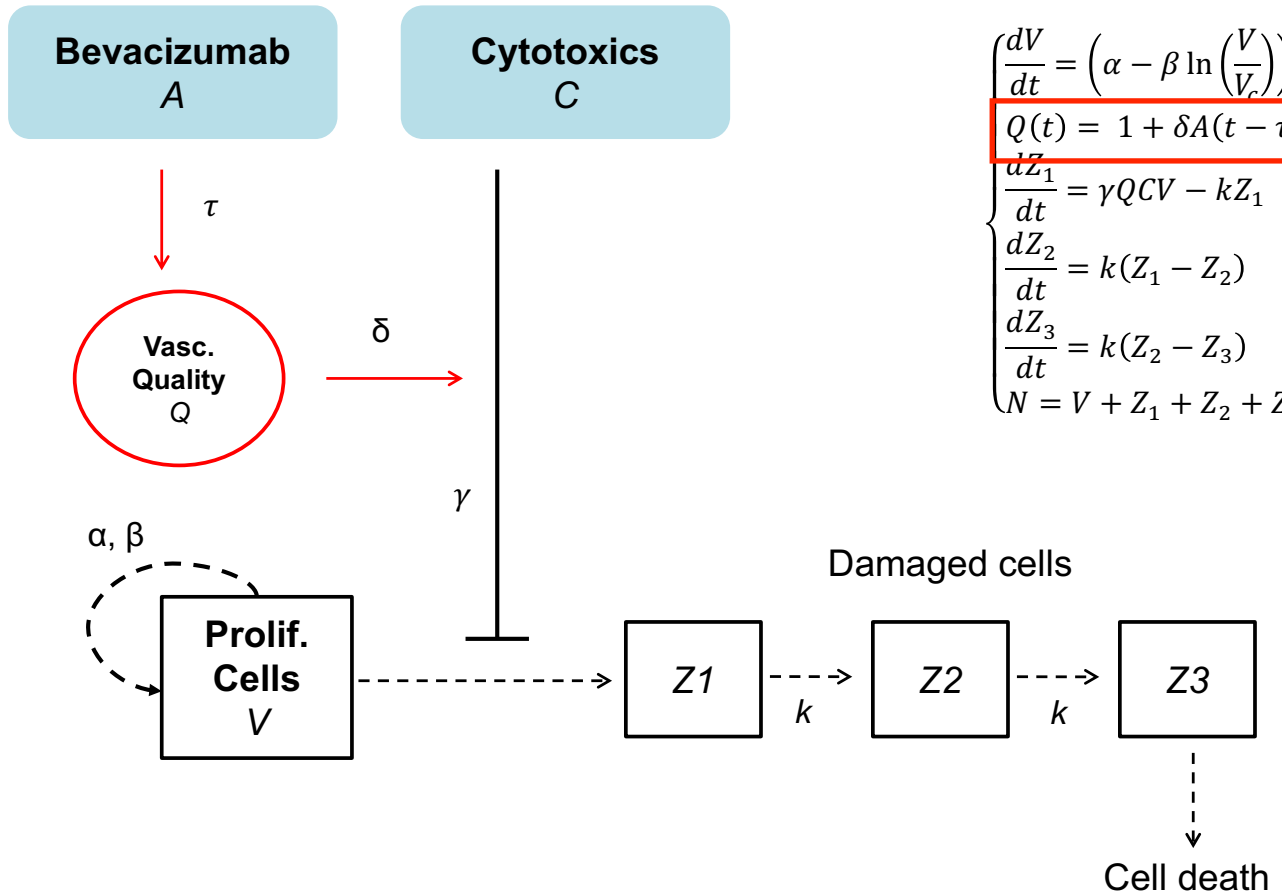
## Confrontation to experimental data



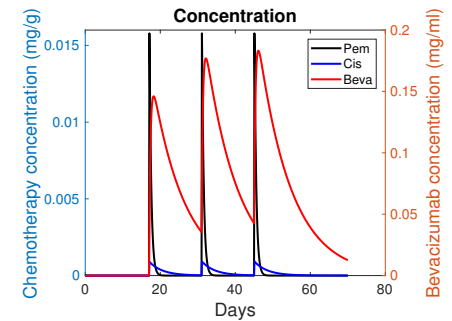
Par.	Unit	Estimate	SE (%)
a	day <sup>-1</sup>	0.0703	0.0328
b	day <sup>-1</sup>	86.8	463
d	day <sup>-1</sup>	0.0745	0.508
$\chi$	day <sup>-1</sup>	0.00203	0.0164
$\tau$	day <sup>-1</sup>	0	-
$U_0$	-	5	50.5
$S_0$	-	82.4	116
$e_{TXL}$	ml·mg <sup>-1</sup> ·day <sup>-1</sup>	13.9	84.3
k	day <sup>-1</sup>	8.45x10 <sup>-9</sup>	0.552
$e_{BEVA}$	ml·mg <sup>-1</sup> ·day <sup>-1</sup>	0.494	2.73

Identifiability issues!

# 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

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

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

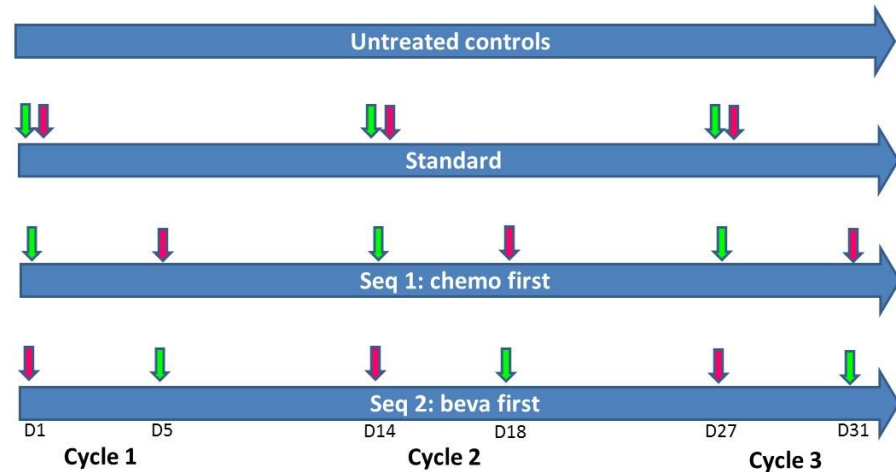


# Non-small cell lung: calibration experiment

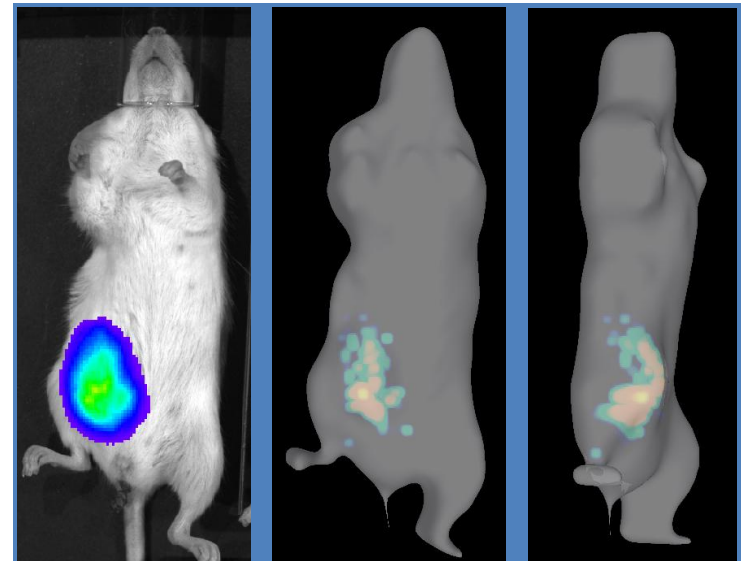


- ❖ Bevacizumab 20 mg/kg
- ❖ Pemetrexed 100 mg/kg
- ❖ Cisplatin 3 mg/kg

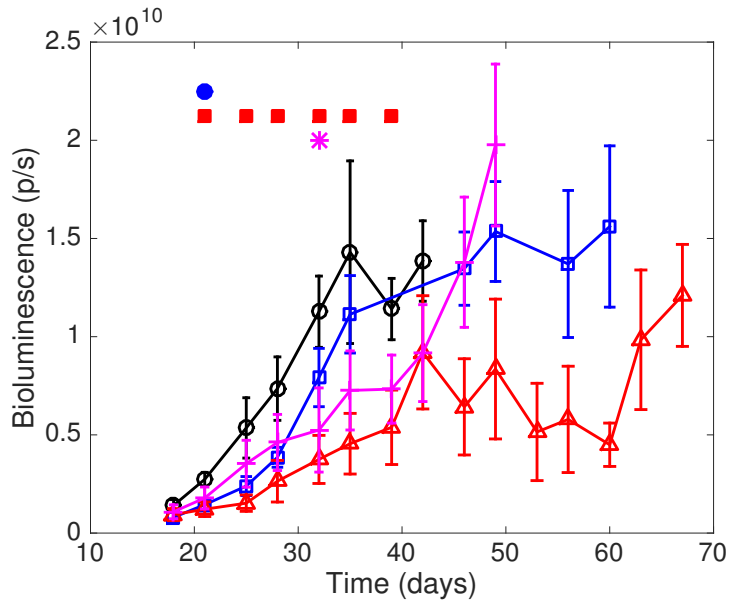
} 3 cycles



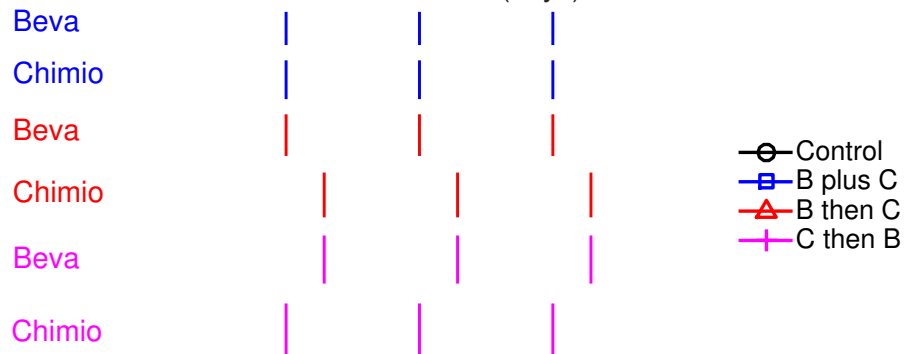
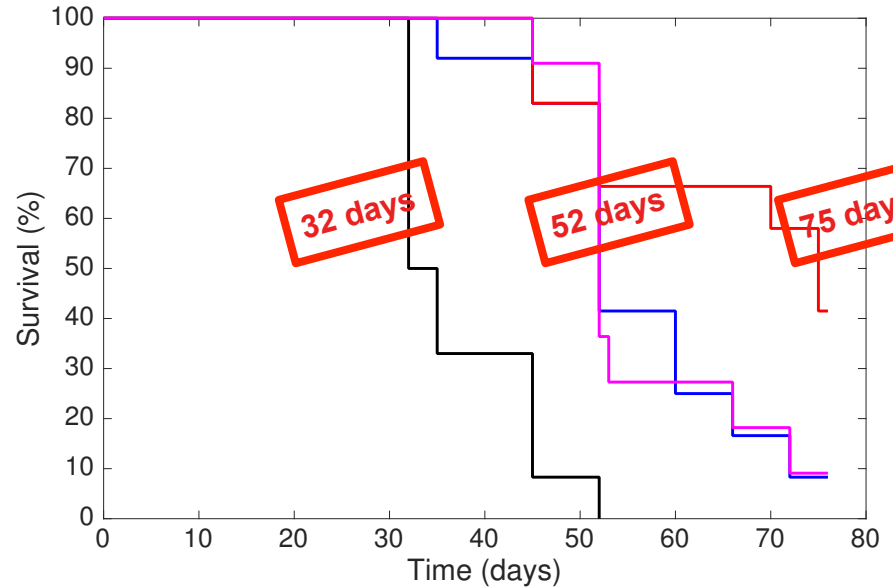
- **Human NSCLC** H460-Luc+ xenograft
  - Subcutaneous graft
  - Matrigel support
- Follow-up
  - Bioluminescence imaging
  - Weight monitoring



# Sequential administration Beva then Chemo improves response and survival



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



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

# Population approach for model calibration: nonlinear mixed effects modeling

- Classical nonlinear regression considers each **time series independently**

$$Y_i^j = M(t_i^j, \beta^j) + \varepsilon_i^j, \quad \varepsilon_i^j \sim \mathcal{N}(0, \sigma_i^j)$$

$$\xrightarrow{\text{MLE}} \hat{\beta}^j = \min_{\beta} \sum (y_i^j - M(t_i^j, \beta))^2$$

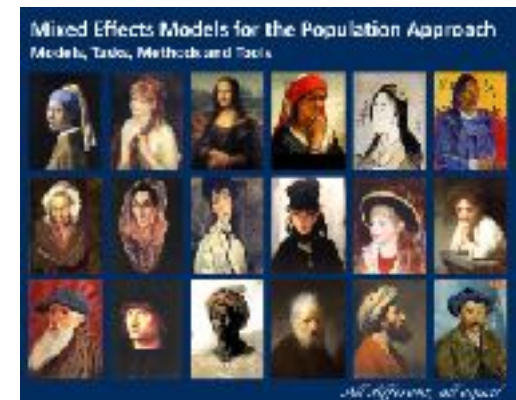
Individual  $1 \leq j \leq N$

Time  $t_i$

- When only sparse data are available from subjects in the same **population**, one can fit the **parameters distribution** all-in-once

$$Y_i^j = M(t_i^j, \beta^j) + \varepsilon_i^j$$

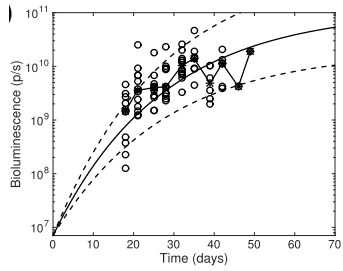
$$\beta^1, \dots, \beta^N \sim \mathcal{LN}(\beta_{\mu}, \beta_{\omega}), \quad \beta_{\mu} \in \mathbb{R}^p, \quad \beta_{\omega} \in \mathbb{R}^{p \times p}$$



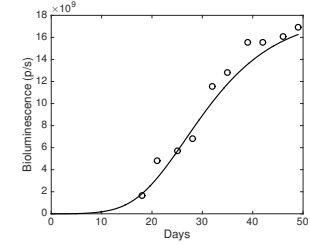
Lavielle, CRC press, 2014

- Reduces the number of parameters from  $pxN$  to  $p+p^2$**

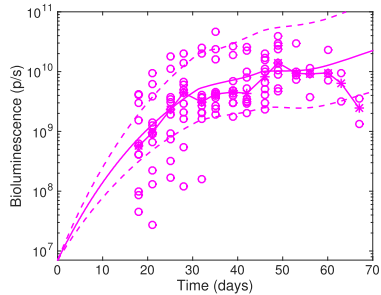
# Control



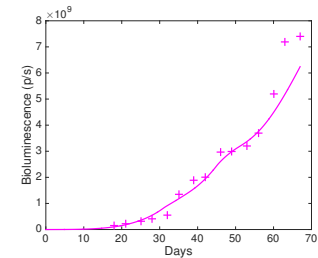
# Model fits: individual + population level (NLME)



Sequential C/B

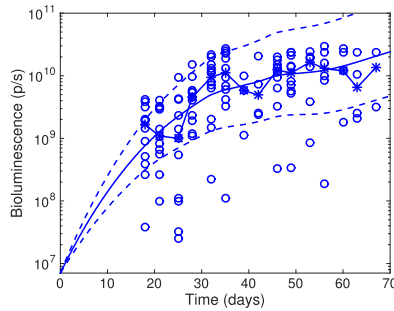


Beva  
Chimio



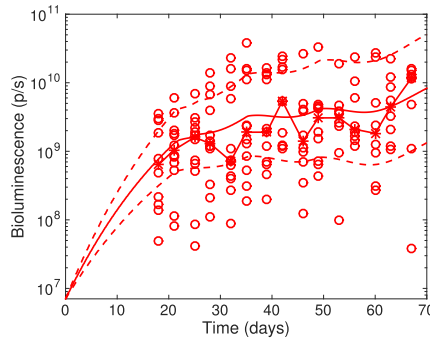
Beva  
Chimio

# Simultaneous

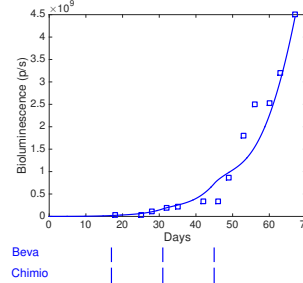


Beva  
Chimio

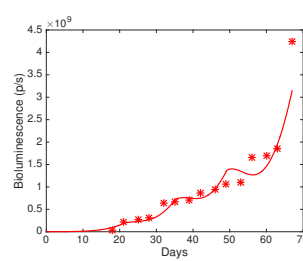
# Sequential B/C



Beva  
Chimio



Beva  
Chimio



Beva  
Chimio

# Median growth curves

Parameters	Description	Units	Estimates	RSE (%)	AV (%)
$\alpha$	Proliferation rate	day <sup>-1</sup>	0.767	8	8.62
$\beta$	Exponential decay rate of the relative tumor growth rate (Gompertz model)	day <sup>-1</sup>	0.037	10	57.3
$\gamma$	Baseline effect of the chemotherapy	(mg/g) <sup>-1</sup> .day <sup>-1</sup>	-	-	-
$\delta$	Cytotoxic efficacy improvement following vascular normalization	(mg/mL) <sup>-1</sup>	1200	36	0
$\tau$	Delay parameter for dynamics of $Q$ .	day	2	20	10
$k$	Delay of the tumor cell loss following chemotherapy	day <sup>-1</sup>	0.3	-	0
$\sigma$	Exponential error parameter	-	0.951	4	-

Beva

Chemo

Beva

Chemo

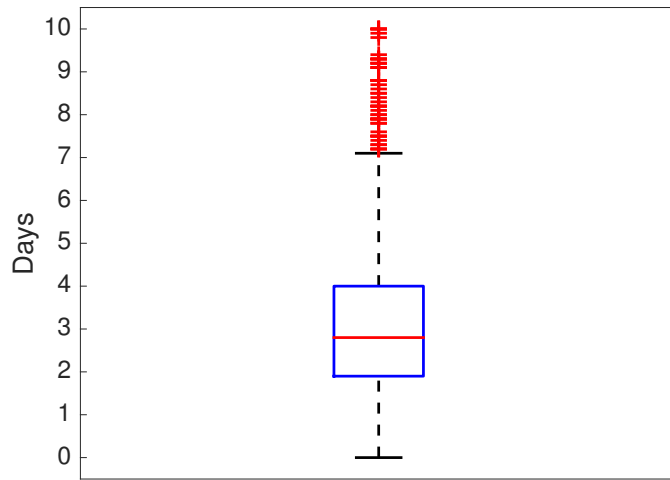
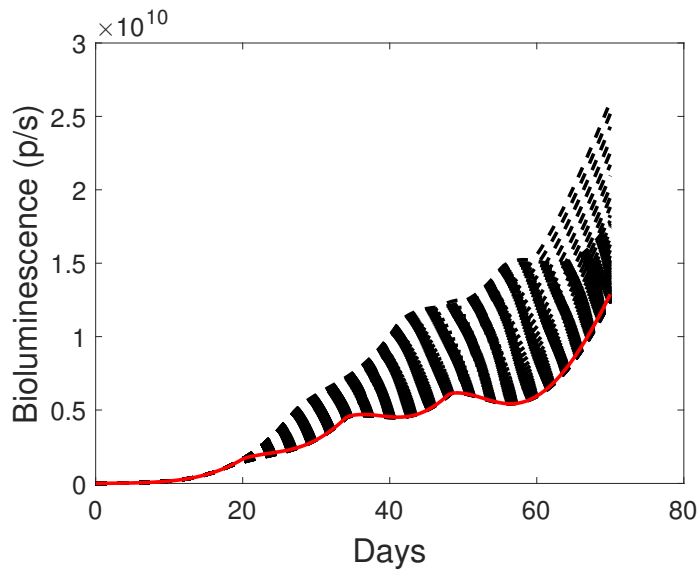
Beva

Chemo

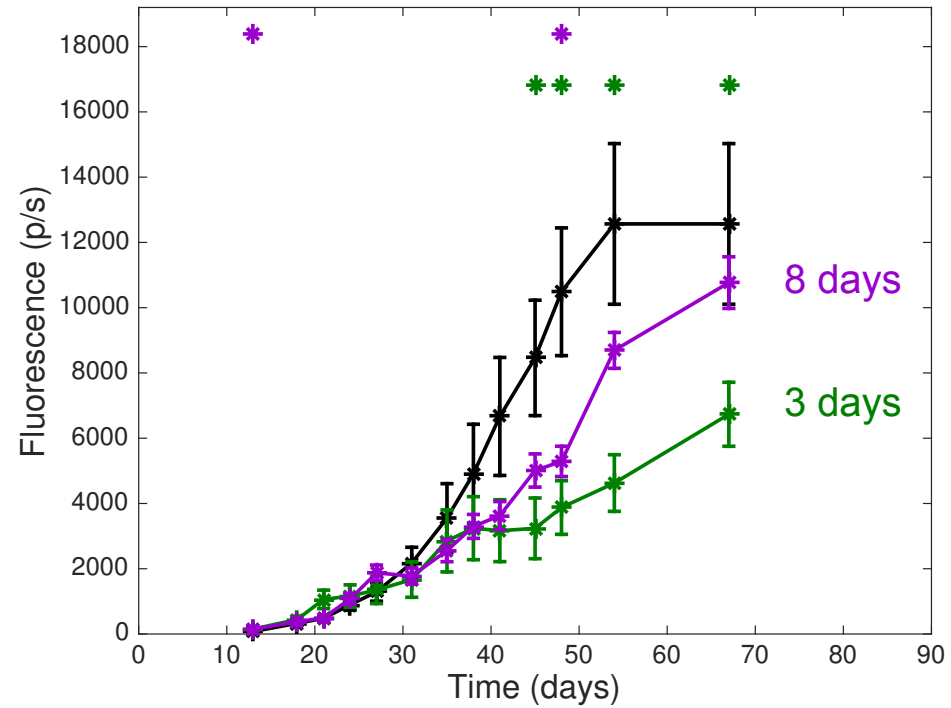
Beva

Chemo

# Prediction of the optimal delay



Inter-animal variability of the optimal gap



⇒ to be **tested experimentally**

⇒ **personalized** scheduling

# Conclusion

- In order to be confronted to empirical data and yield robust predictions, mathematical models must **remain simple** and **well dimensioned** with the data
- Mathematical modeling can be used to **identify optimized drug regimen** for combination therapies among a large number of scenarios that cannot be all tested experimentally
- This is of increasing relevance in modern oncology where **an always larger arsenal of anti-cancer agents** becomes available to oncologists (cf. immune-oncology in combination)
- **Nonlinear mixed-effects modeling** is a powerful statistical approach for pooling together population data that arise from studies in experimental and clinical oncology
- Subsequent patient-specific bayesian estimation of the parameters can be used for **personalized scheduling**

Integrated Systems and Technologies: *Mathematical Oncology*

**Mathematical Modeling of Cancer Immunotherapy and Its Synergy with Radiotherapy**

Raphael Serre<sup>1</sup>, Sebastien Benzekry<sup>2</sup>, Laetitia Padovani<sup>3</sup>, Christophe Meille<sup>4</sup>, Nicolas André<sup>1,5,6</sup>, Joseph Ciccolini<sup>1</sup>, Fabrice Barlesi<sup>1,7</sup>, Xavier Muracciole<sup>3</sup>, and Dominique Barbolosi<sup>1</sup>

Cancer Research

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## Translational/Bedside - Lung cancer



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Dr. C. Mascaux



Dr. P. Tomasini



Dr. A. Boyer

## Translational/Bench



Dr. J. Ciccolini



S. Giacometti



Dr. S. Mollard



Dr. C. Serdjebi