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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

Sébastien Benzekry

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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

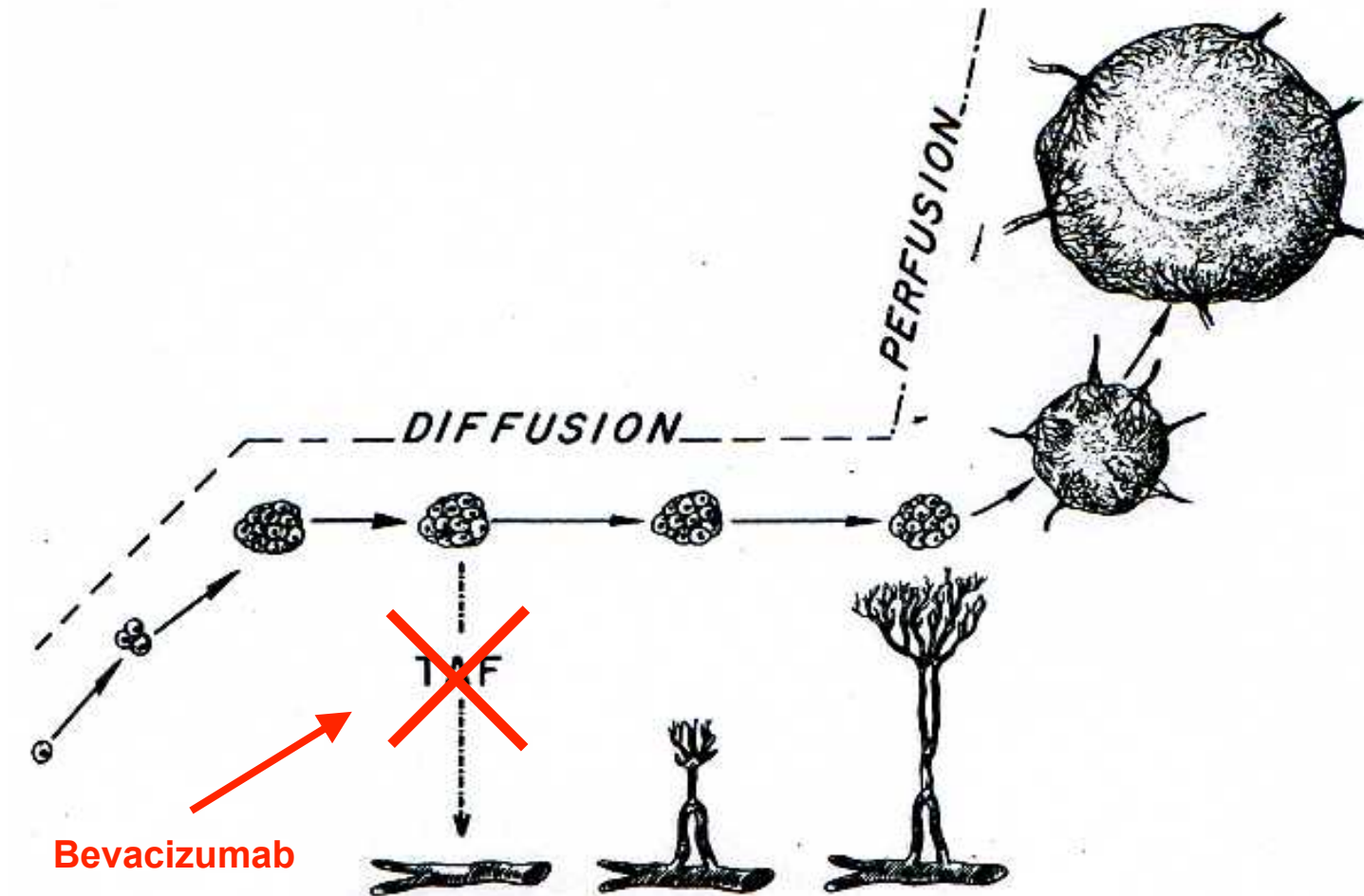
S. Benzekry

Inria team MONC, Bordeaux

Mathematical perspectives in the biology and therapeutics of cancer

July 11, 2018

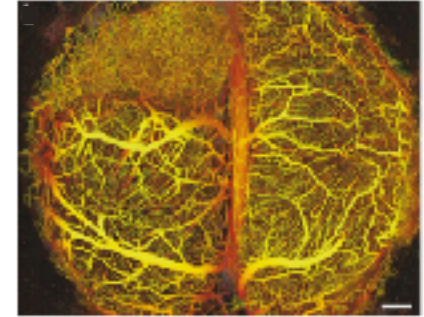
Angiogenesis



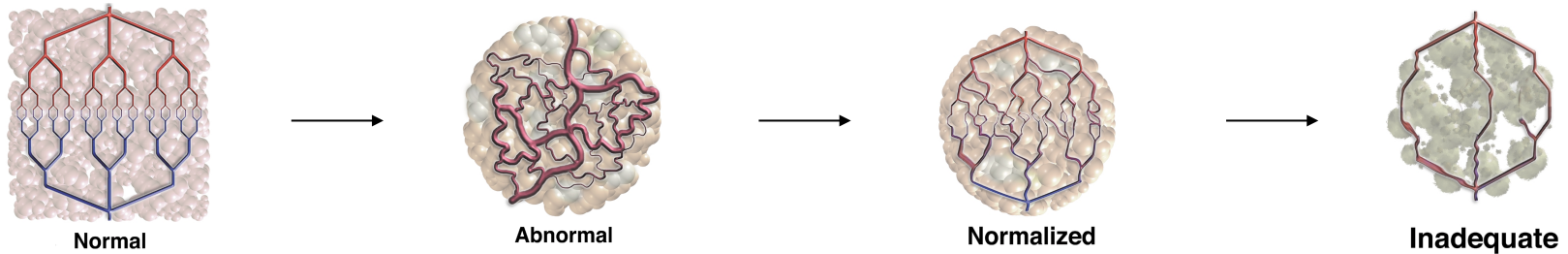
Bevacizumab

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

Breast cancer model

Mollard et al. (Benzekry), Oncotarget 2017

Lung cancer model

Experiment 1

Calibration



Experiment 2



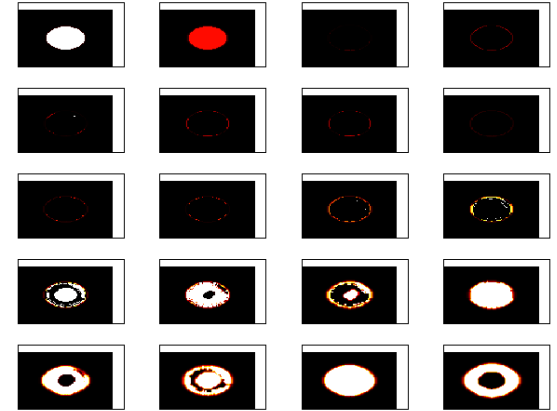
Prediction



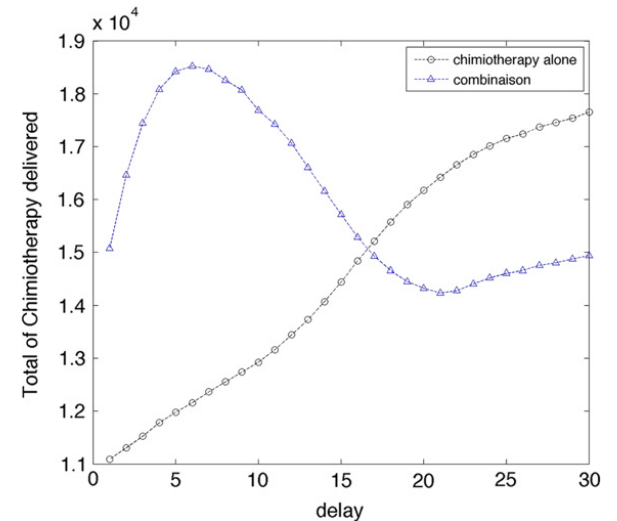
Modeling and Simulation

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
τ_0	Threshold of overcrowding	5×10^4	cell
$\tau_{1,h}$	Threshold of moderate hypoxia	4×10^{-7}	M
$\tau_{2,h}$	Threshold of severe hypoxia	4×10^{-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
μ	Rate of maturation for endothelial cells	0.5	cell/time-unit
τ_E	Minimum quantity of immature EC leading to maturation	5×10^2	cell
γ_n	Sigmoidal coefficient for the computation of vasculature quality	0.5	cell/mm ²
$R_{0.5}$	Density of EC leading to half of the maximal vasculature quality	8×10^{-3}	cell/mm ²
τ_v	Number of EC needed to form a functional blood vessel	4×10^4	cell
C_{max}	Oxygen concentration in blood	2×10^{-2}	M
K	Diffusion coefficient of molecules in the tissue	1-5	mm ² /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	0.25×10^{-4}	M/cell
$\xi_{[C]}$	Degradation rate of chemotherapy	1.25×10^{-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

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

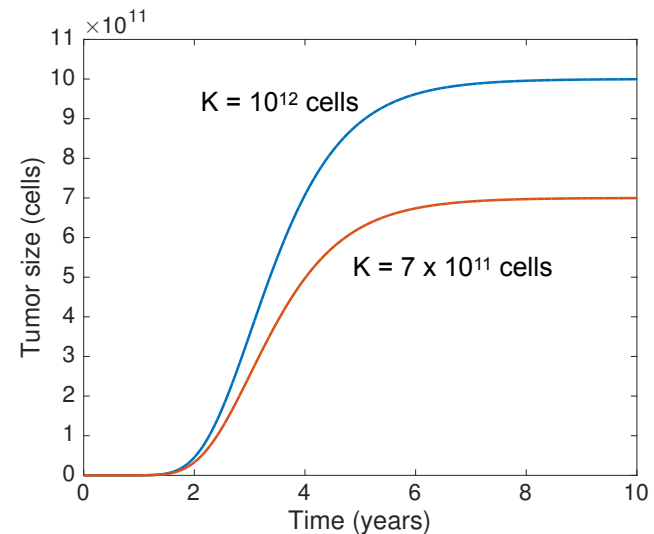
Hahnfeldt-Folkman effect: $K = f(A(t))$

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

Vasculature = carrying capacity

neo-angiogenesis
↓

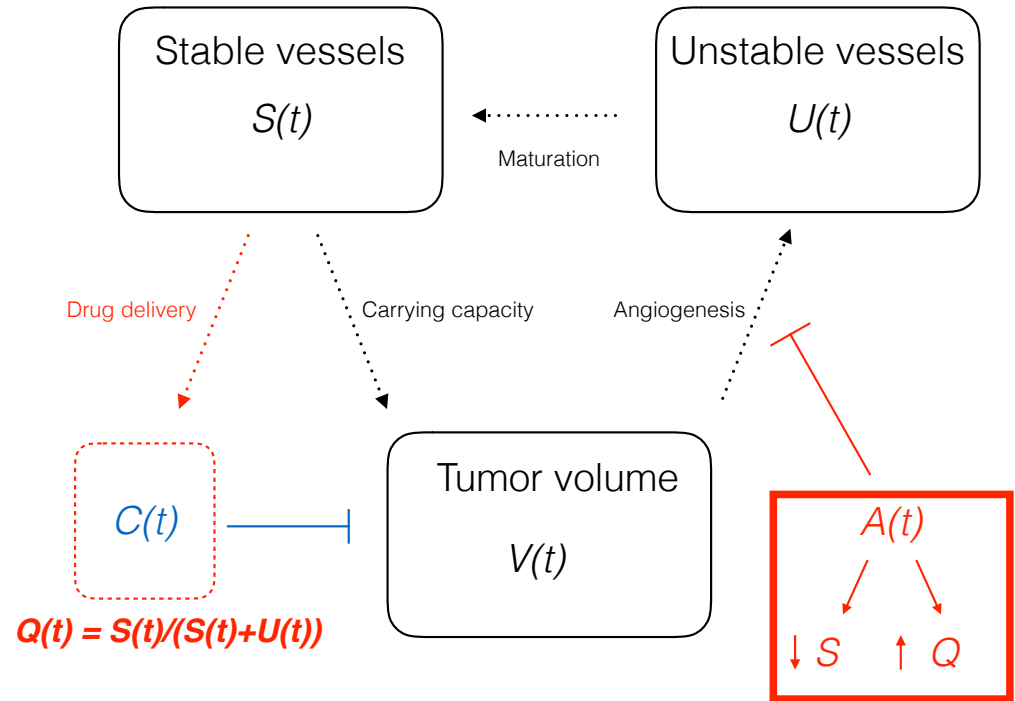
Dynamical carrying capacity $K(t)$



Modeling the combination of chemotherapy and bevacizumab

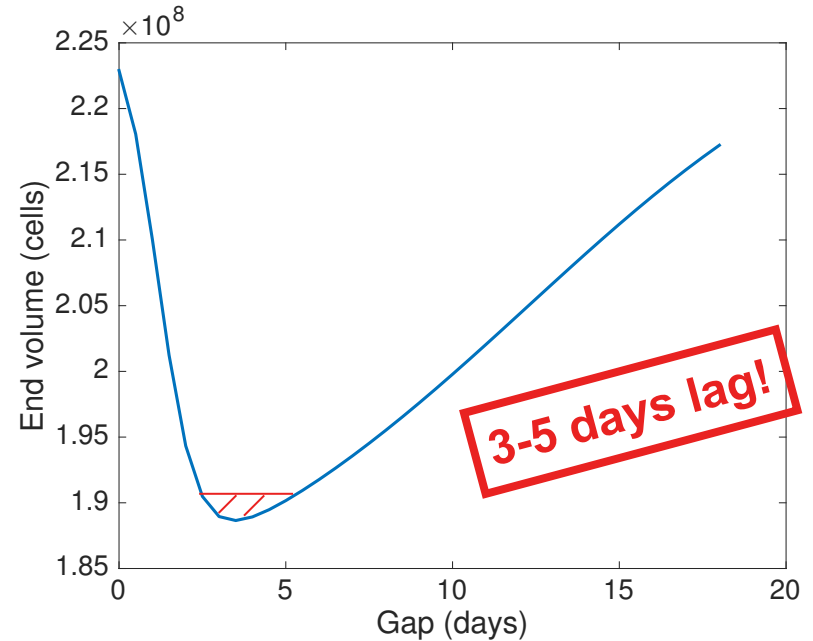
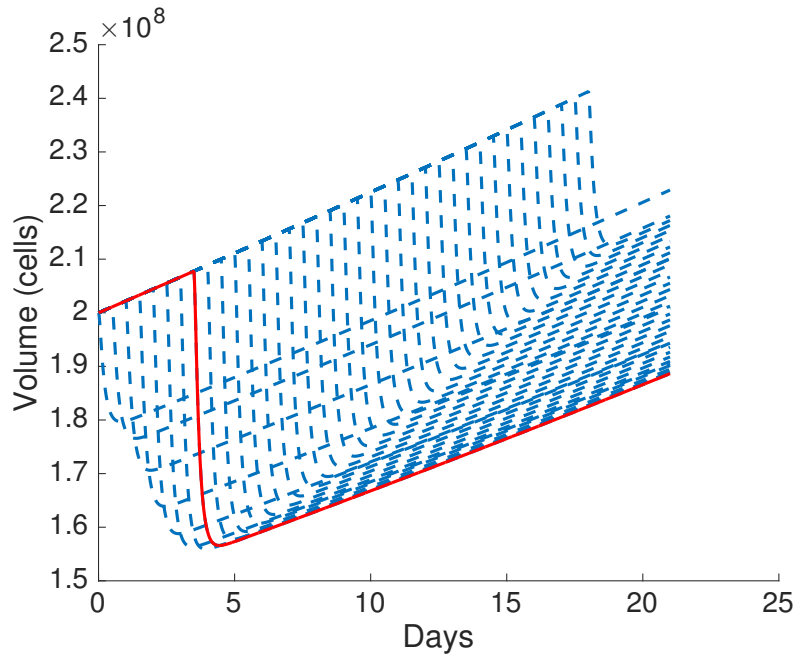
Idea: define a dynamical index of quality of the vasculature Q by dividing the vasculature into **stable** and **unstable** compartments

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



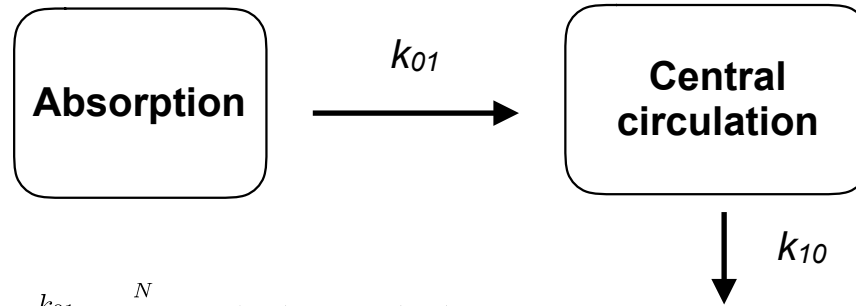
$$Q = \frac{S}{S + U}$$

A priori simulations of the model suggest optimal sequence



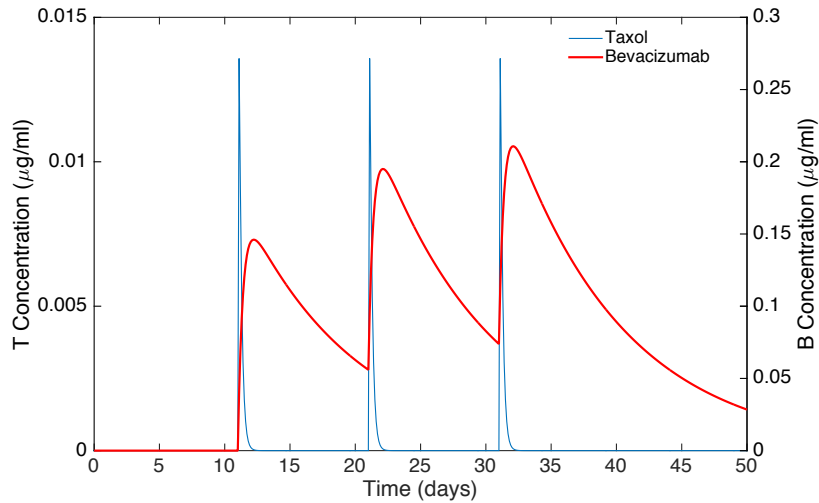
... ► **Anti-angiogenics first, then cytotoxics**

Pharmacokinetics models

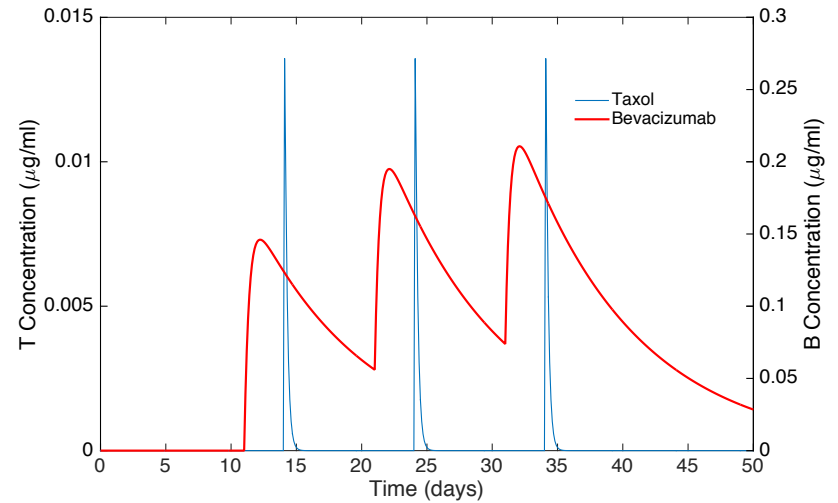


$$C(t) = \frac{D}{V} \frac{k_{01}}{k_{01} - k_{10}} \sum_{i=1}^N e^{-k_{10}(t-t_i)} - e^{-k_{01}(t-t_i)} \mathbb{1}_{t \geq t_i}$$

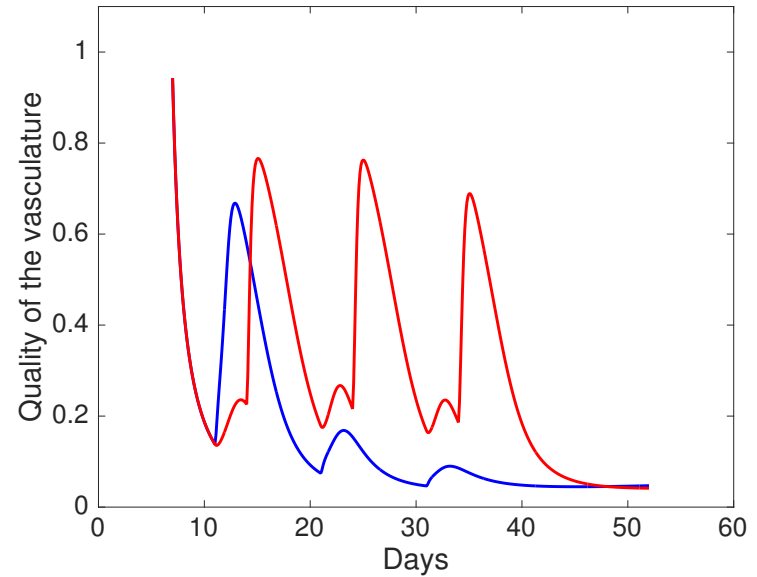
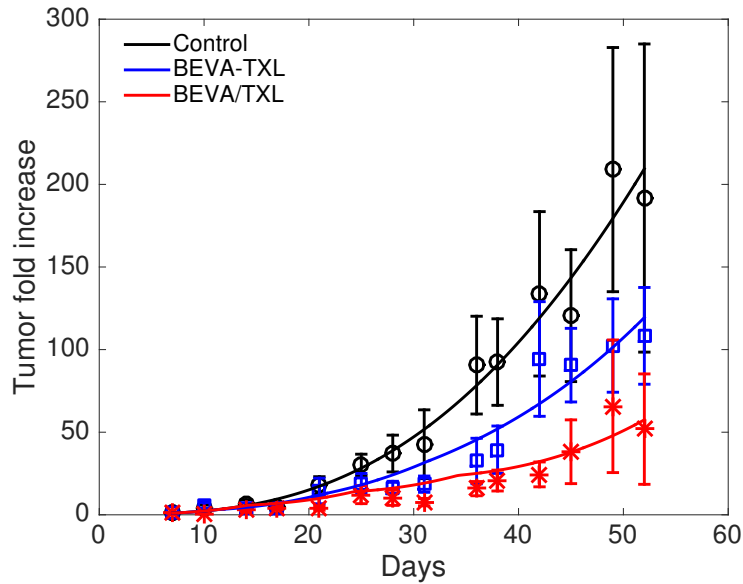
Concomitant



Sequential



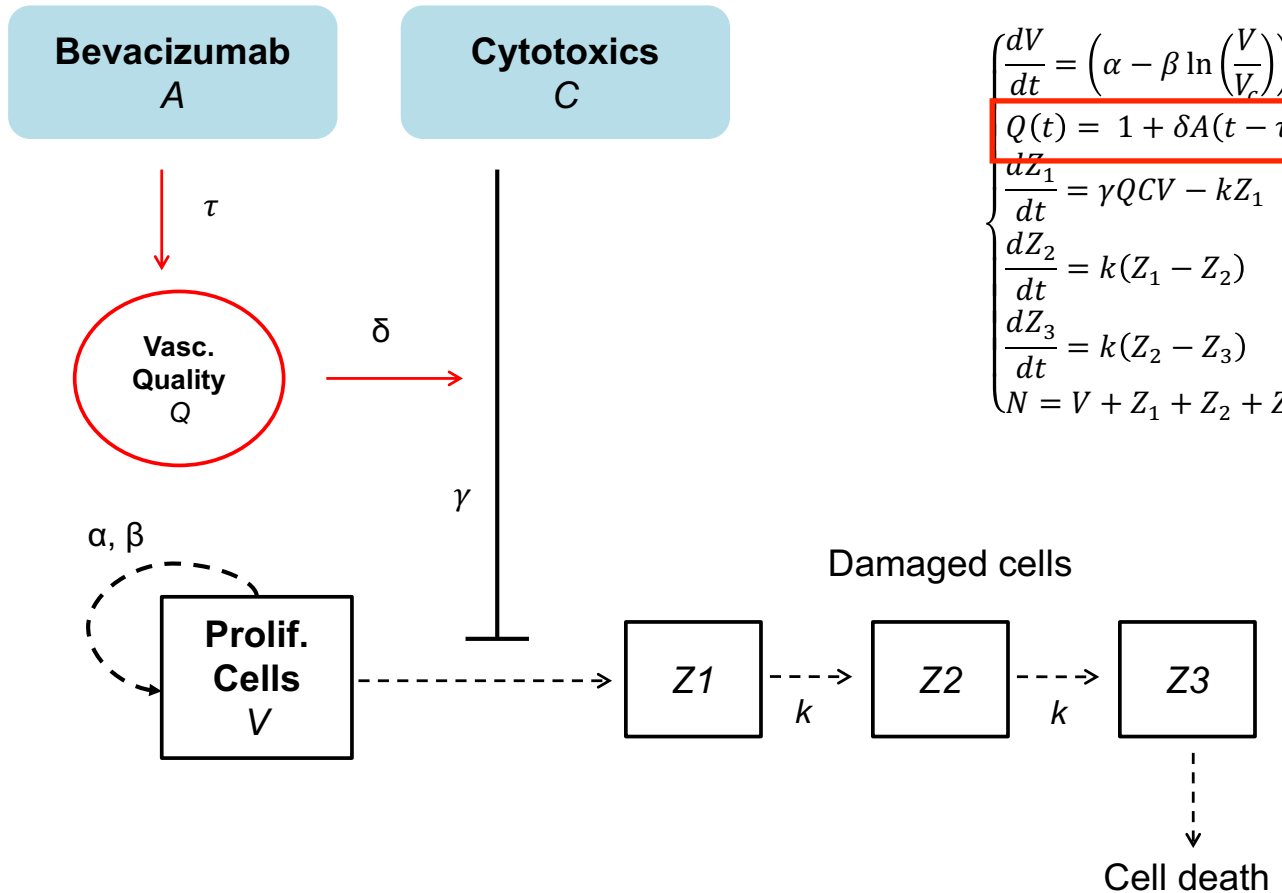
Confrontation to experimental data



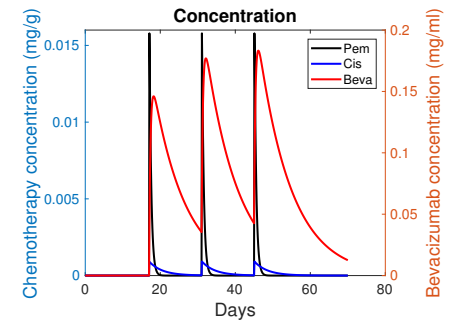
Par.	Unit	Estimate	SE (%)
a	day ⁻¹	0.0703	0.0328
b	day ⁻¹	86.8	463
d	day ⁻¹	0.0745	0.508
χ	day ⁻¹	0.00203	0.0164
τ	day ⁻¹	0	-
U_0	-	5	50.5
S_0	-	82.4	116
e_{TXL}	ml·mg ⁻¹ ·day ⁻¹	13.9	84.3
k	day ⁻¹	8.45x10 ⁻⁹	0.552
e_{BEVA}	ml·mg ⁻¹ ·day ⁻¹	0.494	2.73

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

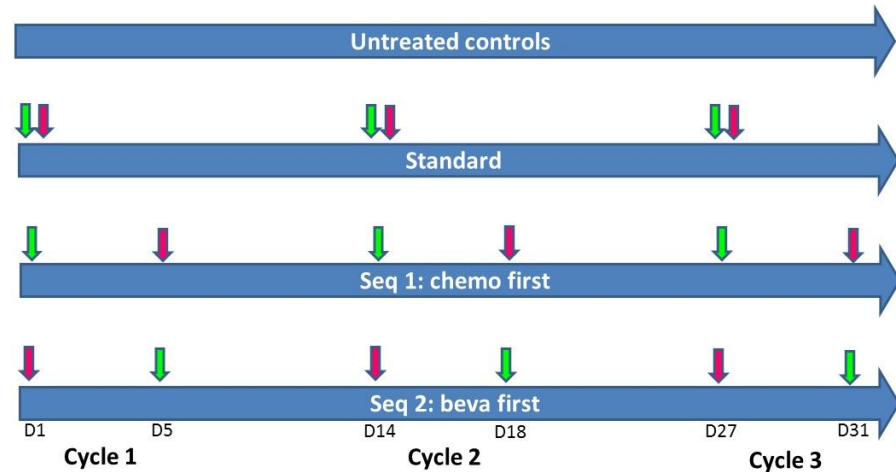
+ PK models for beva $A(t)$ and CT $C(t)$ concentrations

Non-small cell lung: calibration experiment

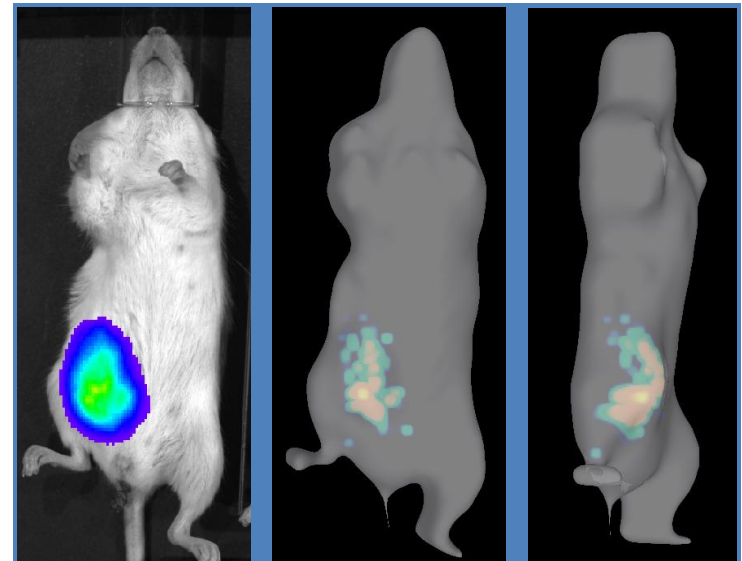


- ❖ Bevacizumab 20 mg/kg
- ❖ Pemetrexed 100 mg/kg
- ❖ Cisplatin 3 mg/kg

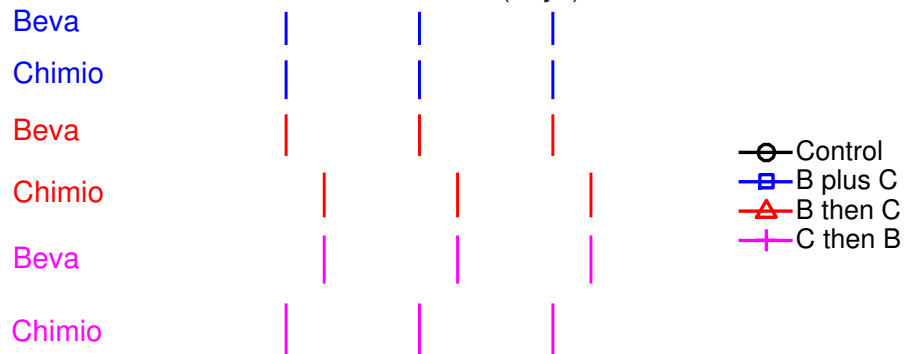
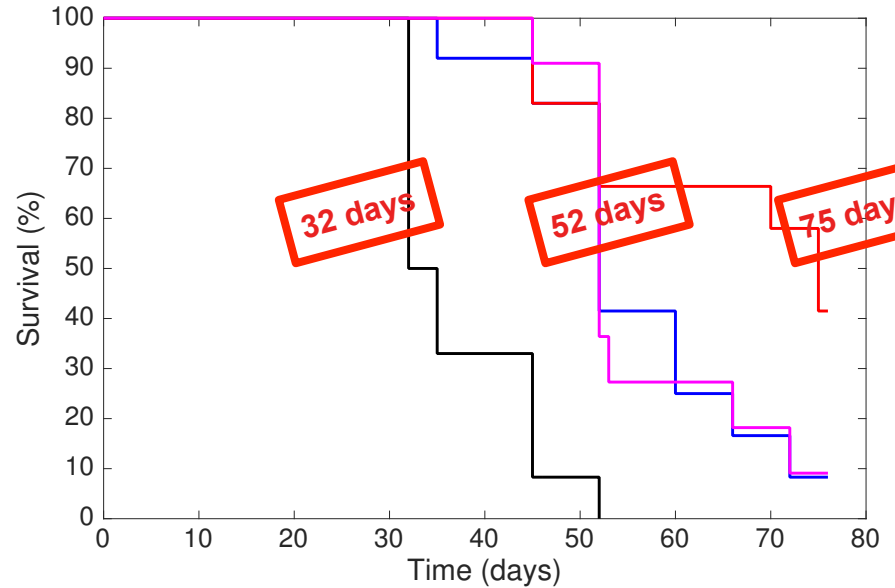
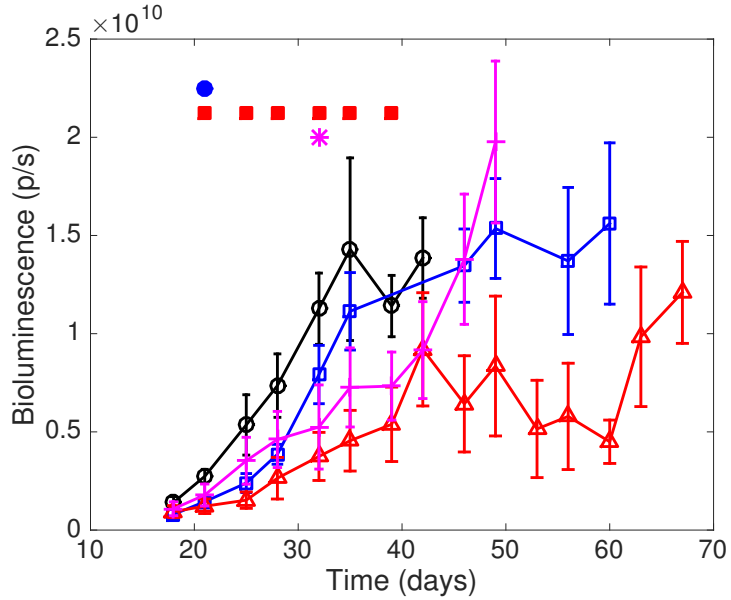
} 3 cycles



- **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

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

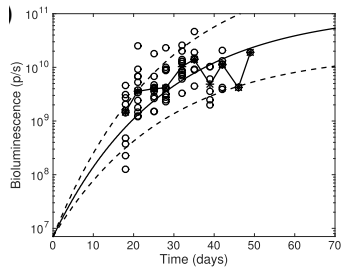
$$\beta^1, \dots, \beta^N \sim \mathcal{LN}(\beta_{\mu}, \beta_{\omega}), \quad \beta_{\mu} \in \mathbb{R}^p, \quad \beta_{\omega} \in \mathbb{R}^{p \times p}$$



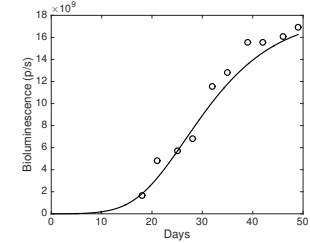
Lavielle, CRC press, 2014

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

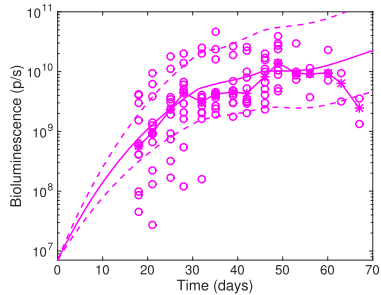
Control



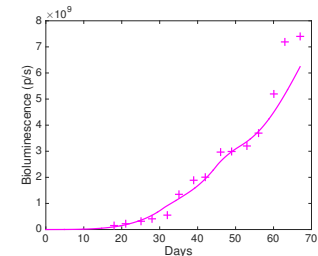
Model fits: individual + population level (NLME)



Sequential C/B

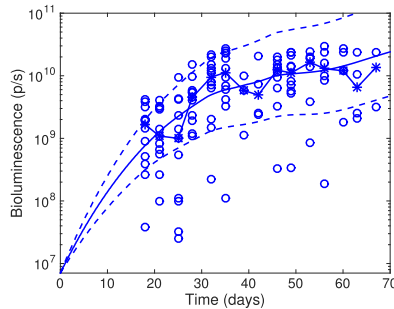


Beva
Chimio



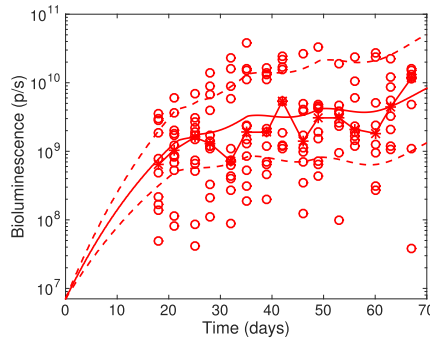
Beva
Chimio

Simultaneous

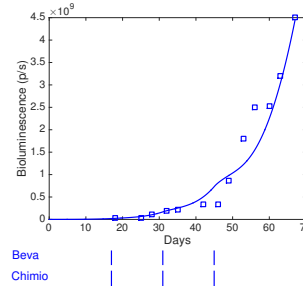


Beva
Chimio

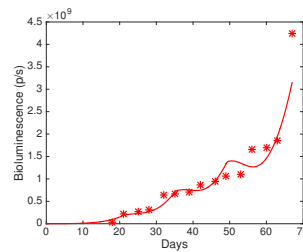
Sequential B/C



Beva
Chimio



Beva
Chimio



Beva
Chimio

Median growth curves

Parameters	Description	Units	Estimates	RSE (%)	AV (%)
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		-	-
δ	Cytotoxic efficacy improvement following vascular normalization	(mg/mL) ⁻¹	1200	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		0
σ	Exponential error parameter		0.951	4	-

Beva

Chemo

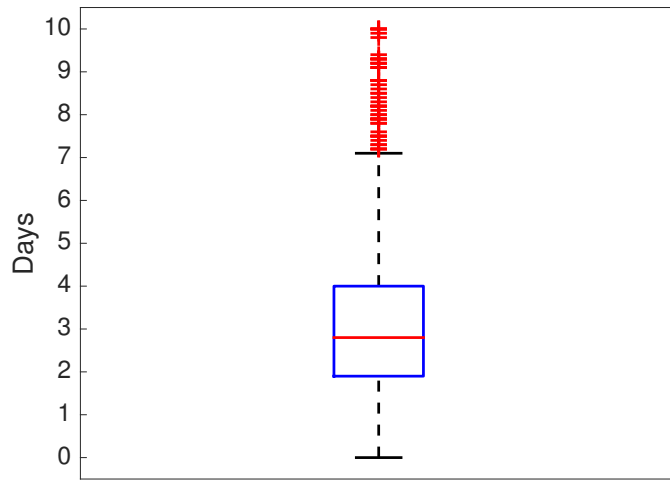
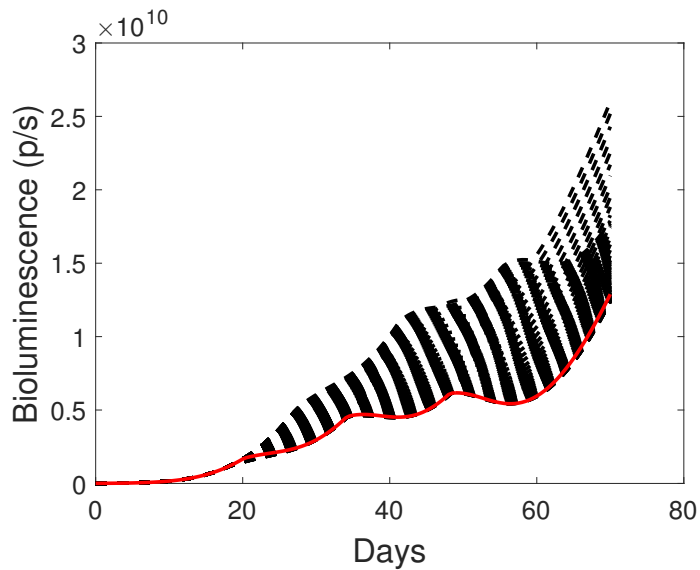
Beva

Chemo

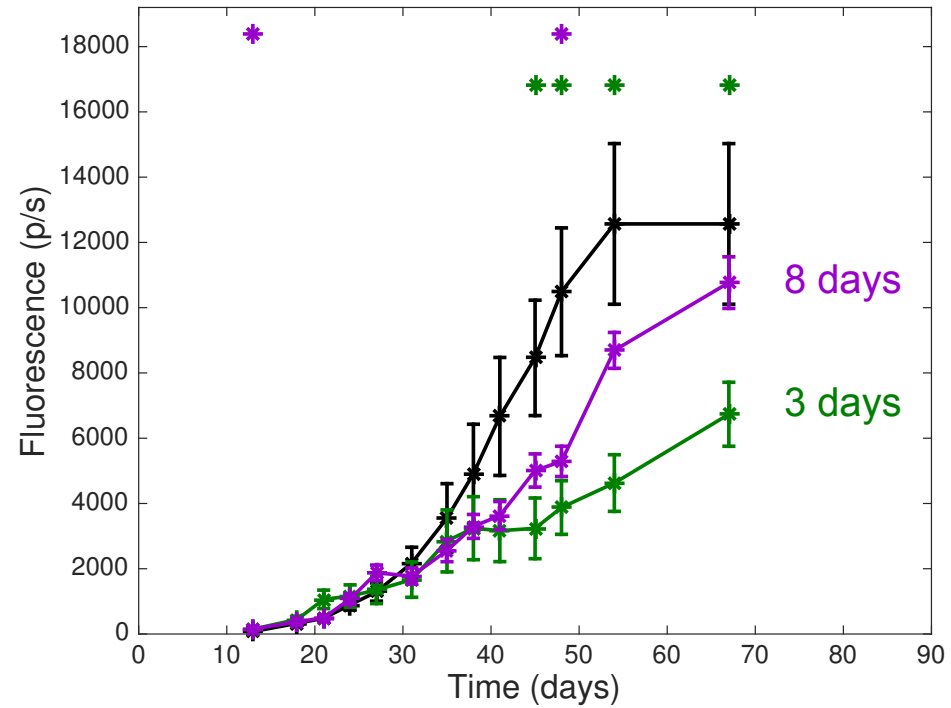
Beva

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*

Cancer Research

Mathematical Modeling of Cancer Immunotherapy and Its Synergy with Radiotherapy

Raphael Serre¹, Sebastien Benzekry², Laetitia Padovani³, Christophe Meille⁴, Nicolas André^{1,5,6}, Joseph Ciccolini¹, Fabrice Barlesi^{1,7}, Xavier Muracciole³, and Dominique Barbolosi¹

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Modeling & Simulation



Pr. D. Barbolosi



Dr DC Imbs



Dr R. El Cheikh

Translational/Bedside - Lung cancer



Pr. F. Barlesi



Dr. C. Mascaux



Dr. P. Tomasini



Dr. A. Boyer

Translational/Bench



Dr. J. Ciccolini



S. Giacometti



Dr. S. Mollard



Dr. C. Serdjebi