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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S. Benzekry

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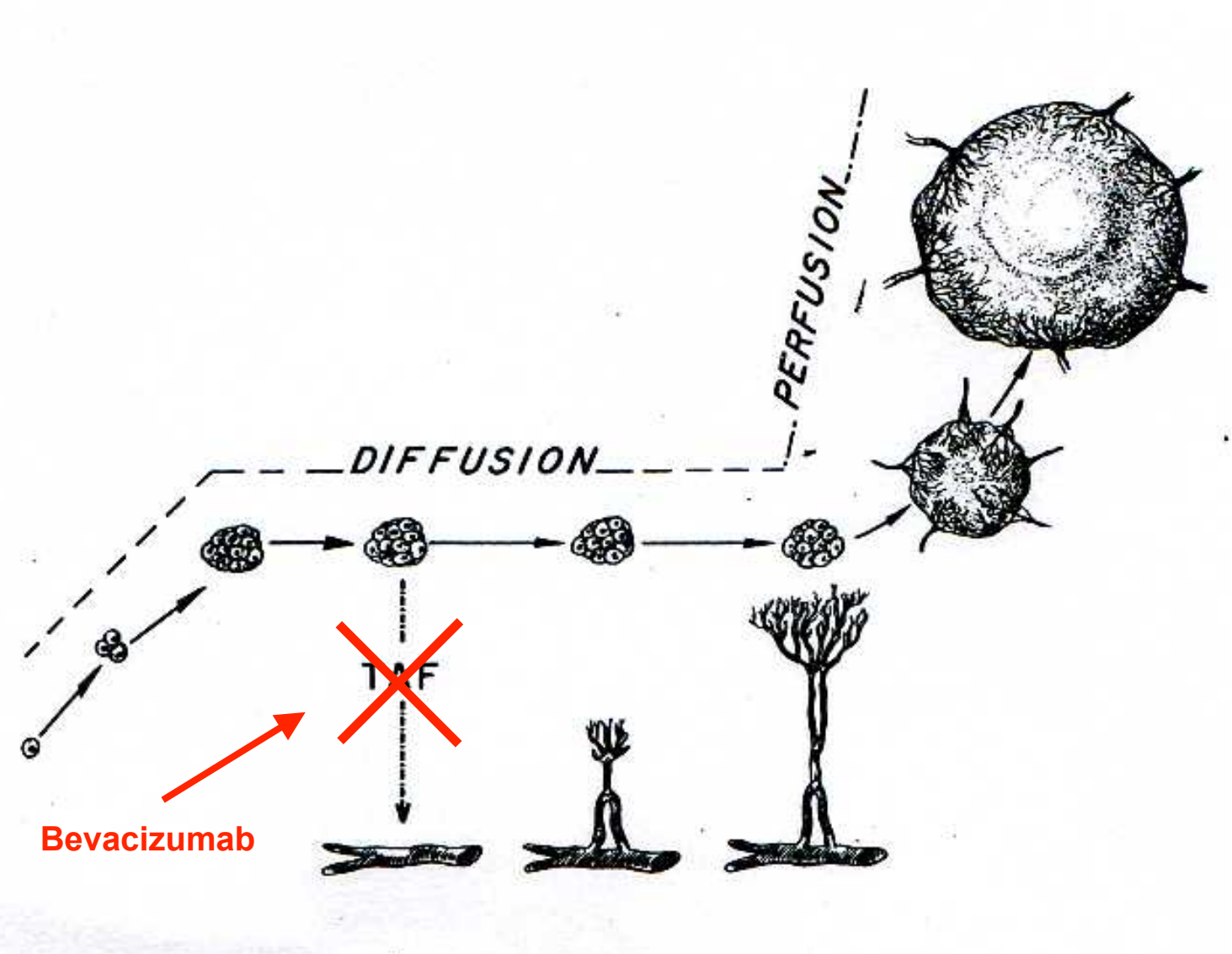
Mathematical perspectives in the biology and therapeutics of cancer

July 11, 2018

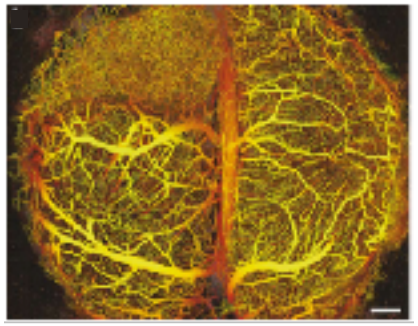
Angiogenesis



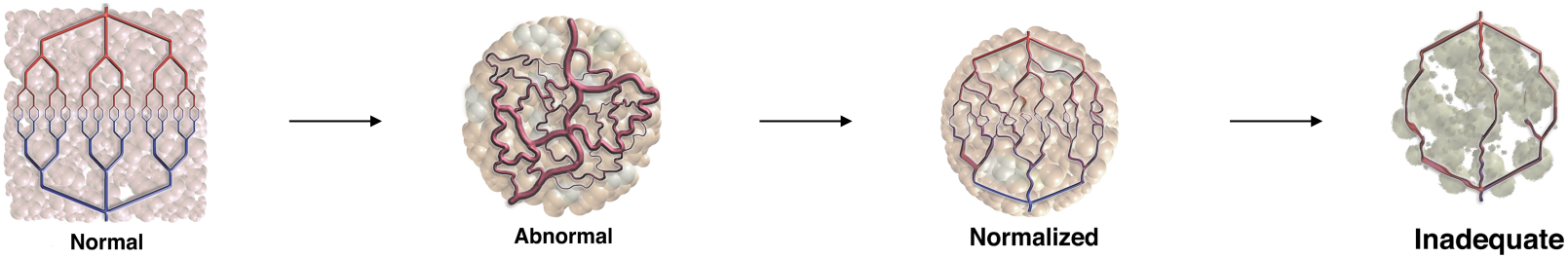
Folkman, N Engl J Med, 1971

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 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

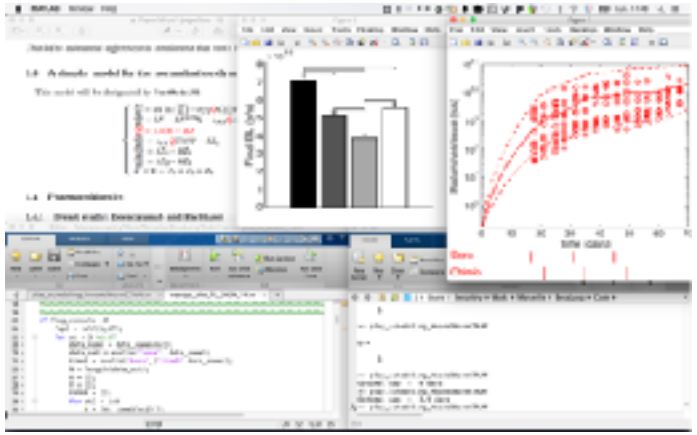
Lung cancer model

Experiment 1

Calibration

Experiment 2

Prediction



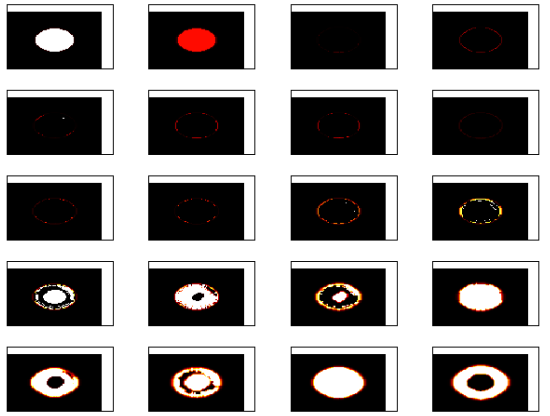
Modeling and Simulation

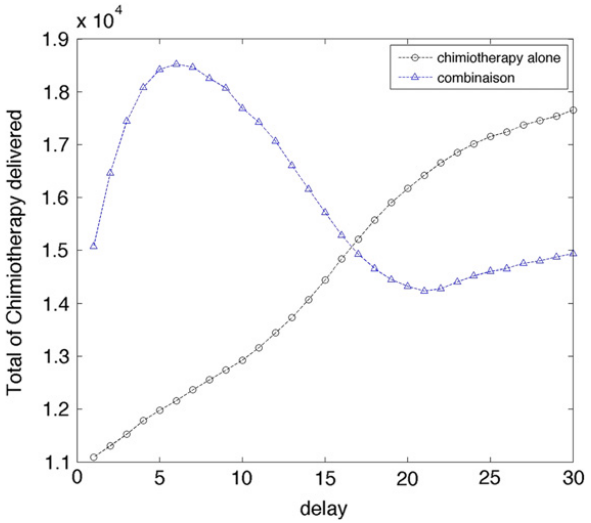
Imbs et al. (Benzekry), CPT: Pharmacometrics Syst Pharmacol, 2018

A first theoretical and complex model

Entity	Model equation
Density of P_1	$\frac{\partial P_1}{\partial t}+\frac{\partial P_1}{\partial a}+\nabla\cdot(\mathbf{v_{P_1}}P_1)=0\ P_1(a=0)=2P_2(a=a_{max,P_2})$
Density of P_2	$\frac{\partial P_2}{\partial t}+\frac{\partial P_2}{\partial a}+\nabla\cdot(\mathbf{v_{P_2}}P_2)=-P_2(a=a_{max,P_2})\frac{E_{max,C}[C]}{C_{50}+[C]}\ P_2(a=0)=fP_1(a=a_{max,P_1})+[\partial_t f]^+Q(t^-)$
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	$R=\frac{\int E}{Vol}\ \Pi=1-\frac{R^{\gamma_n}}{R^{\gamma_n}+R_{0.5}^{\gamma_n}}$,
Concentration of oxygen	$-\nabla(K_{[O_2]}\nabla[O_2])=-\sum_\phi\alpha_{[O_2],\phi}\phi\ [O_2]=\Pi C_{max}$ where $Es\geq\tau_v$
Concentration of VEGF	$\frac{\partial[V]}{\partial t}-\nabla\cdot(K_{[V]}\nabla[V])=\alpha_{[V]}Q_{[O_2]\leq\tau_{1,h}}-\beta_{[V]}E[V]-\delta_{[V]}[V]-[V]\frac{Emax_{[AA]}[AA]}{[AA]_{50}+[AA]}$
Concentration of chemo.	$-\nabla\cdot(K\nabla[C])=-\xi_{[C]}[C]\ [C]=\Pi\ P_{[C]}(t)$ where $Es\geq\tau_v$
Concentration of antiangiogenic	$-\nabla\cdot(K\nabla[AA])=-[V]\frac{Emax_{[AA]}[AA]}{v_{50}+[AA]}\ [AA]=\Pi P_{[AA]}(t)$ 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	Minimis 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
$Emax_{[AA]}$	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





Lignet, Benzekry et al. (Ribba), J Theor Biol, 2013

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

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

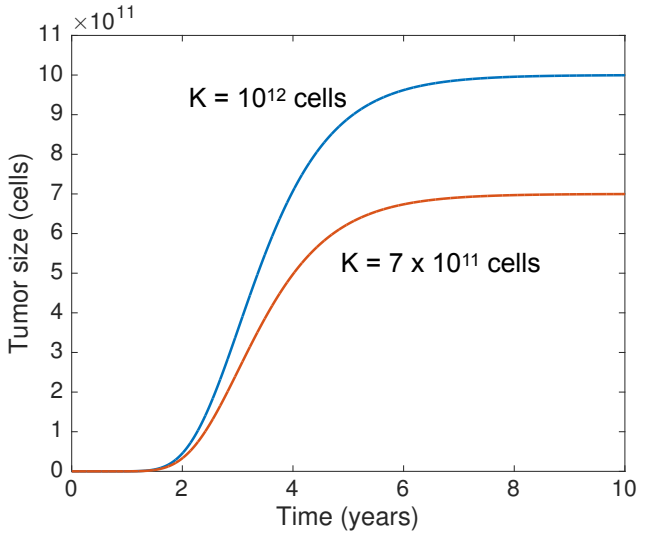
Vasculature = carrying capacity

neo-angiogenesis

Dynamical carrying capacity *K(t)*

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

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

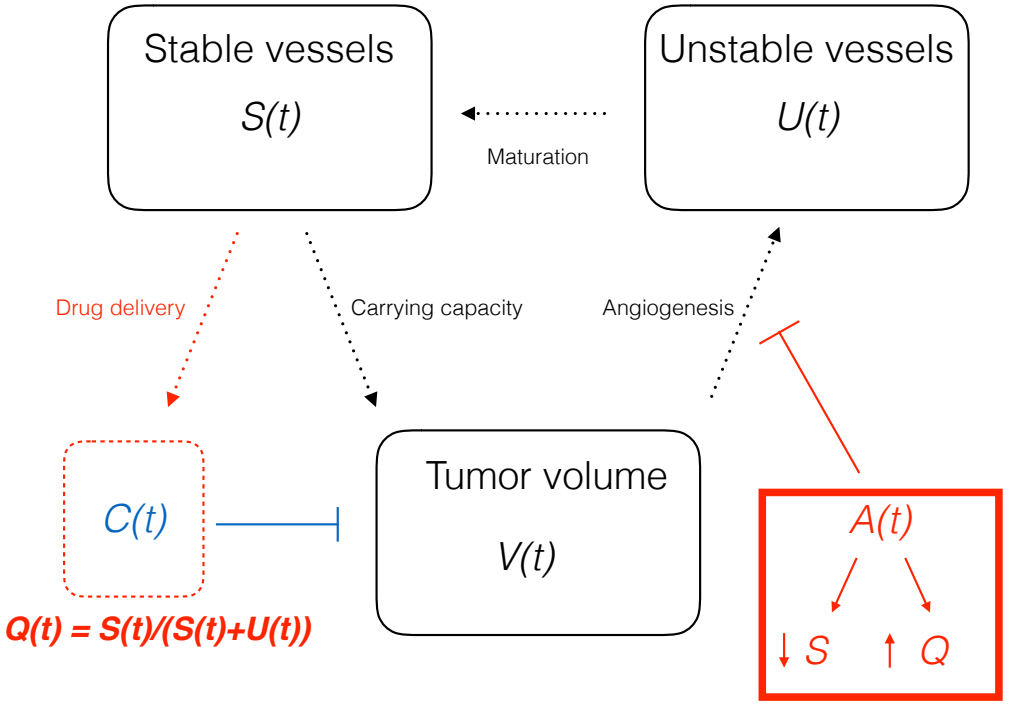


Hahnfeldt et al. (Folkman), Cancer Res, 1999

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

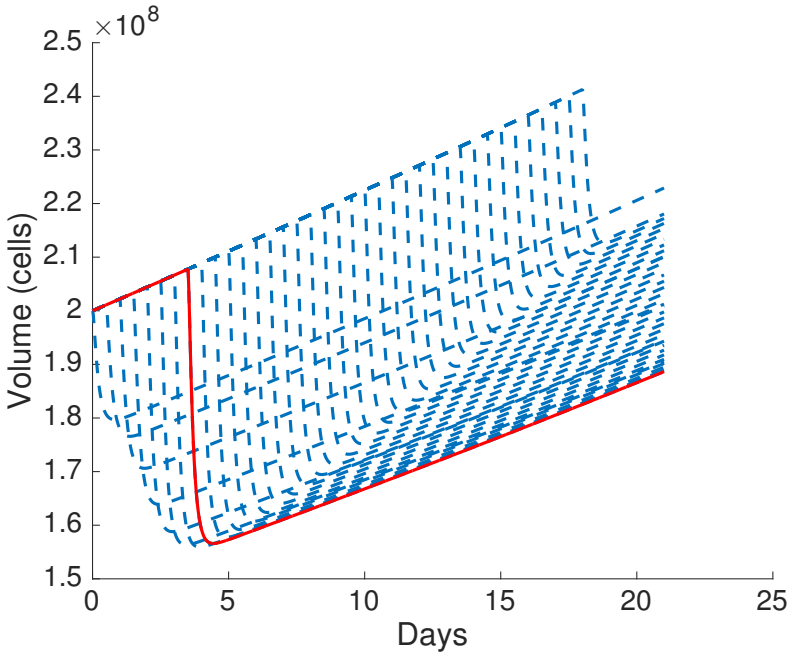
$$\begin{cases} \frac{dV}{dt} = aV\ln\left(\frac{S}{V}\right) - e_{CT}QSC(t)V \\ \frac{dU}{dt} = bV - dV^{2/3}U - \chi U - e_{AA}QSA(t)U \\ \frac{dS}{dt} = \chi U - \tau S \end{cases}$$

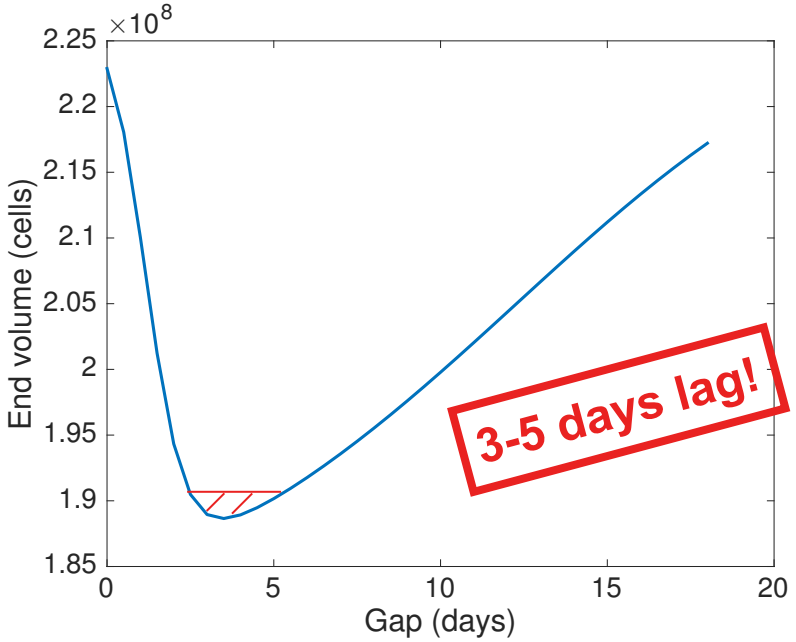


$$Q = \frac{S}{S+U}$$

Benzekry et al. (Hubert), CRAS, 2012

A priori simulations of the model suggest optimal sequence

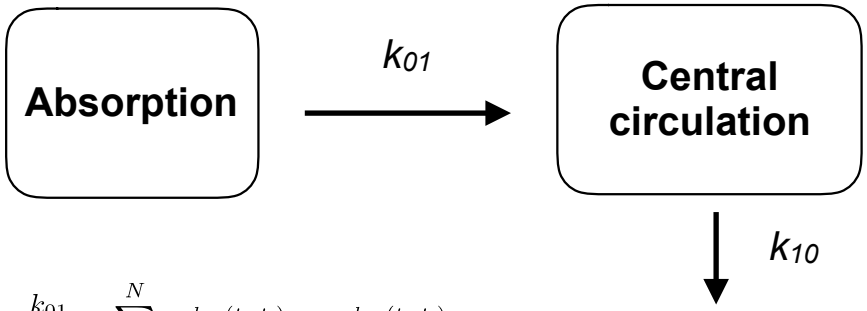




Anti-angiogenics first, then cytotoxics

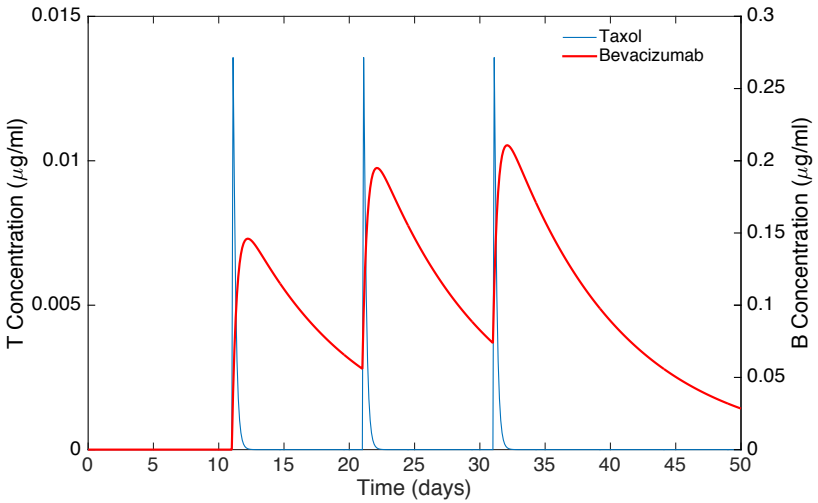
Benzekry et al., A new mathematical model for optimizing the combination between antiangiogenic and cytotoxic drugs in oncology, CRAS, 2012

Pharmacokinetics models

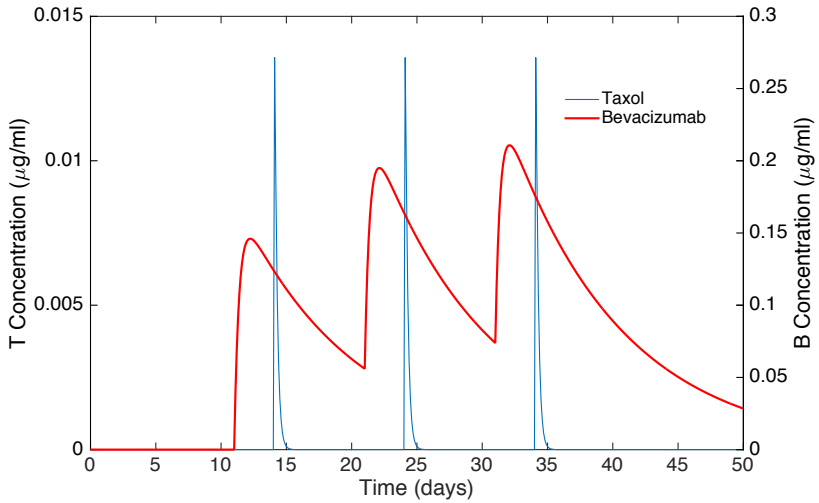


$$C(t) = \frac{D}{V}\frac{k_{01}}{k_{01}-k_{10}}\sum_{i=1}^{N} e^{-k_{10}(t-t_i)} - e^{-k_{01}(t-t_i)} 1_{t \geq t_i}$$

Concomitant



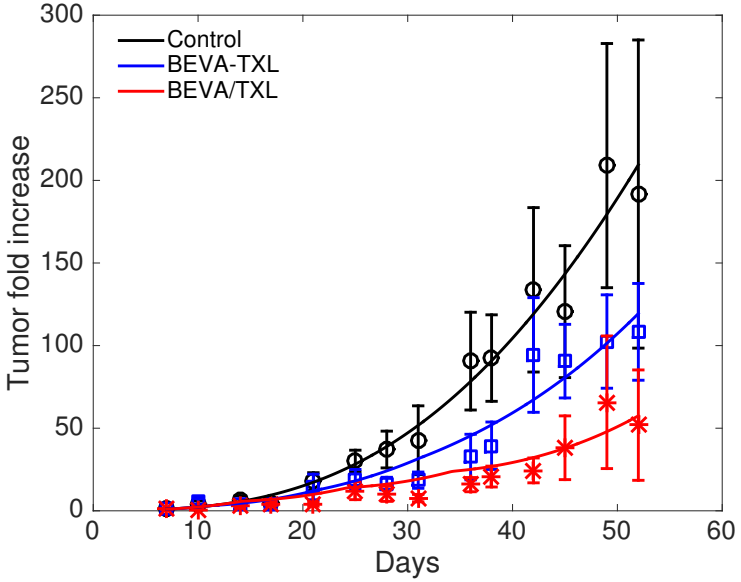
Sequential

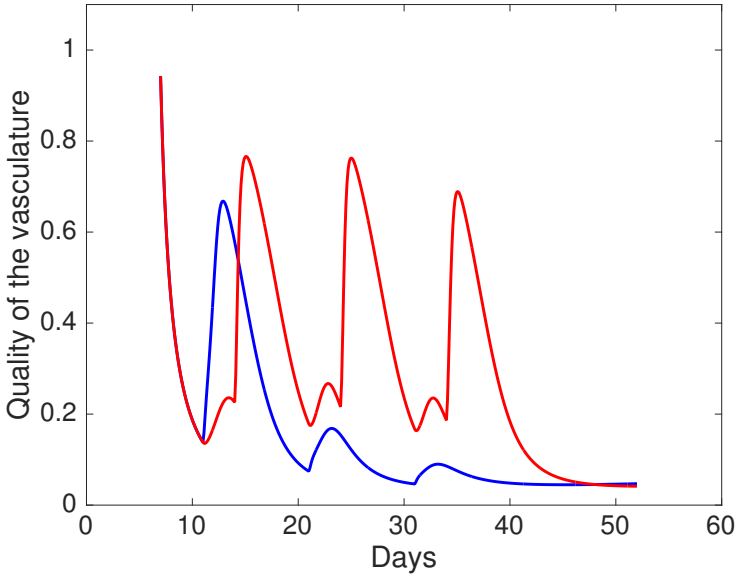


Innocenti F. et al., Drug Metab Dispos Biol Fate Chem, 1995

Lin et al., J Pharmacol Exp Ther. 1999

Confrontation to experimental data



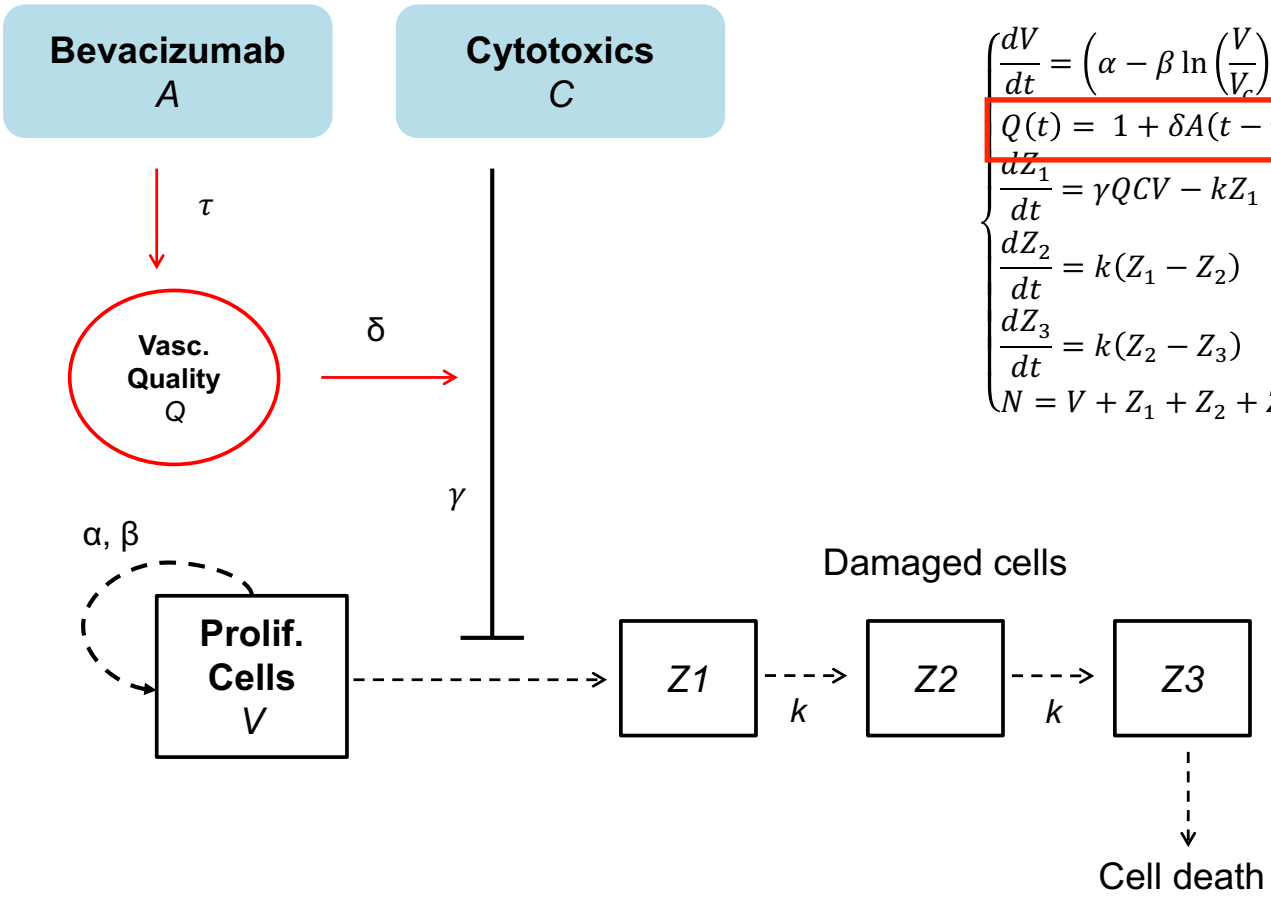


Par.	Unit	Estimate	SE (%)
a	day^{-1}	0.0703	0.0328
b	day^{-1}	86.8	463
d	day^{-1}	0.0745	0.508
χ	day^{-1}	0.00203	0.0164
τ	day^{-1}	0	-
U_0	-	5	50.5
S_0	-	82.4	116
e_{TXL}	$ml \cdot mg^{-1} \cdot day^{-1}$	13.9	84.3
k	day^{-1}	8.45×10^{-9}	0.552
e_{BEVA}	$ml \cdot mg^{-1} \cdot day^{-1}$	0.494	2.73

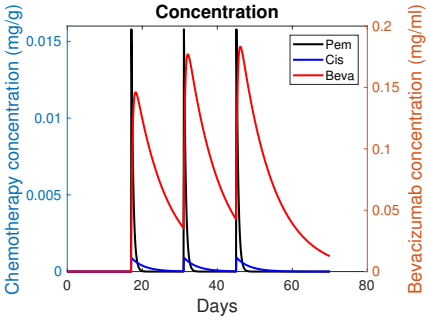
Identifiability issues!

Mollard et al. (Benzekry), Oncotarget 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

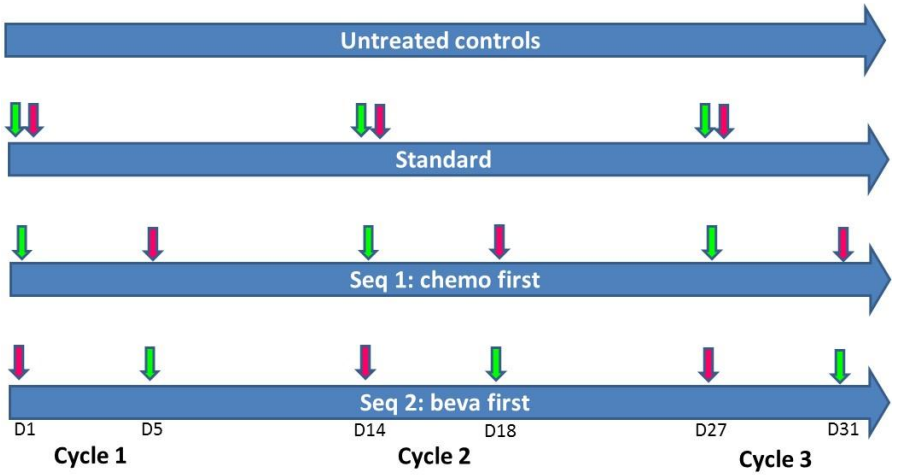
Imbs et al., Benzekry, CPT: Pharmacometrics Syst Pharmacol, 2018

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

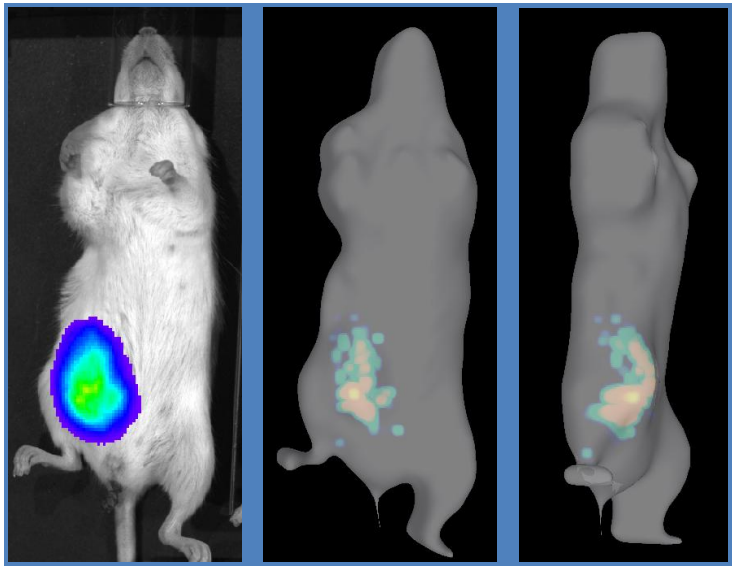
Non-small cell lung: calibration experiment

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

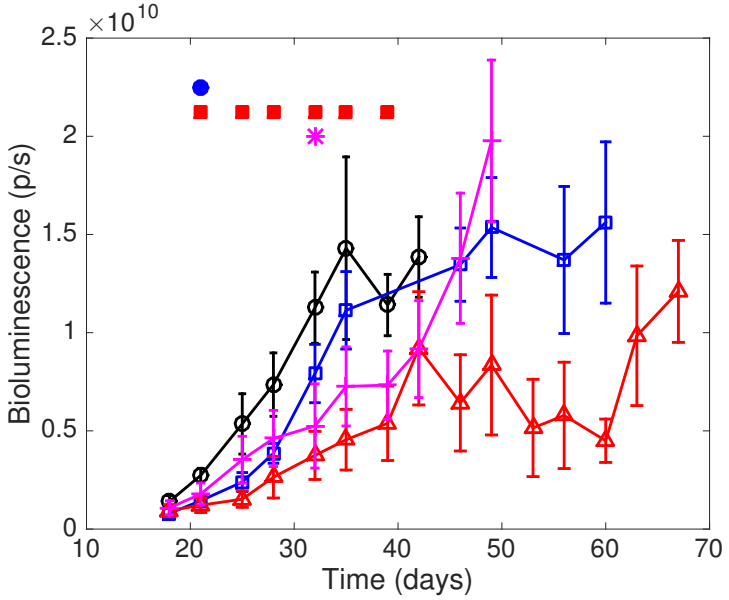
} 3 cycles



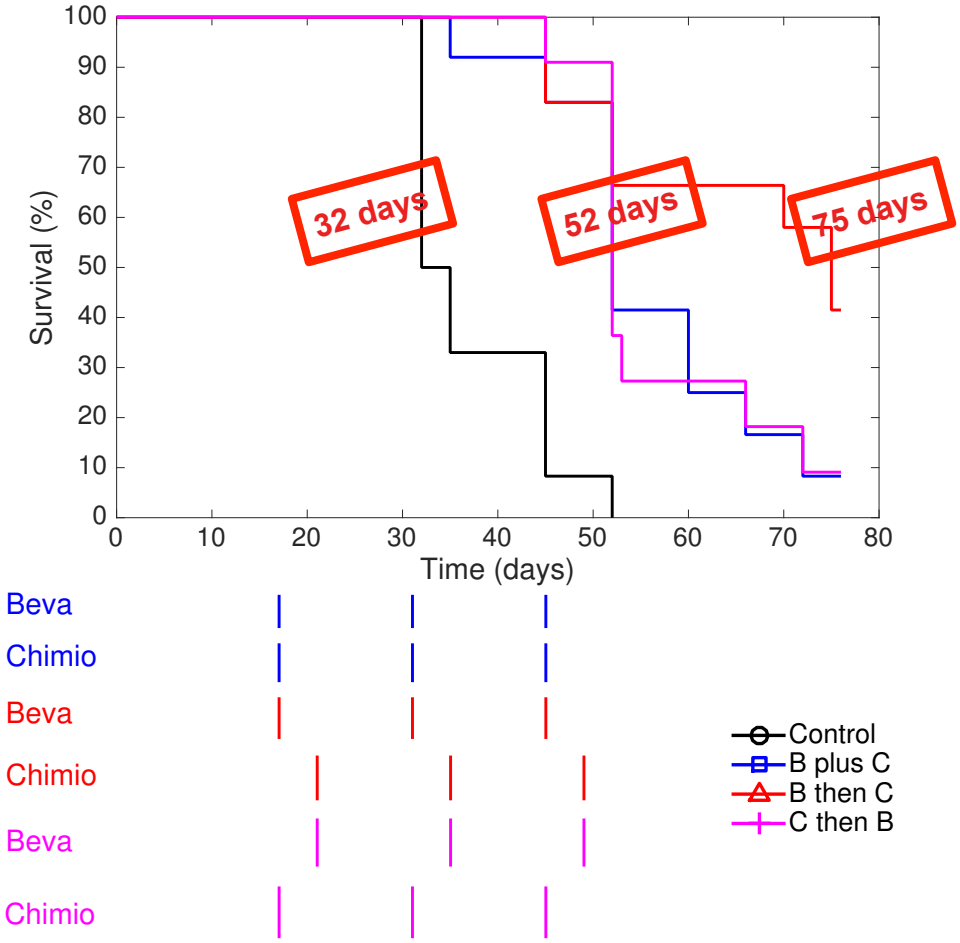
- **Human NSCLC** H460-Luc+ xenograft
  - Subcutaneous graft
  - Matrigel support
- Follow-up
  - Bioluminescence imaging
  - Weight monitoring



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**

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

MLE →

$$\hat{\beta}^j = \min_{\beta} \sum \left(y_i^j - M(t_i^j, \beta)\right)^2$$

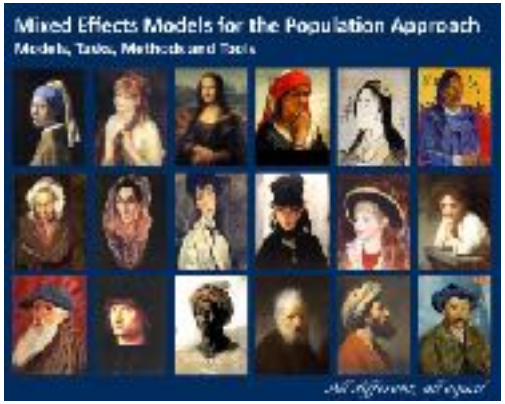
Individual $1 \le j \le N$

Time t_i

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

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

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

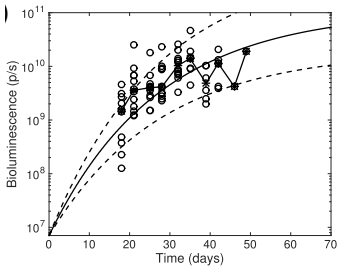


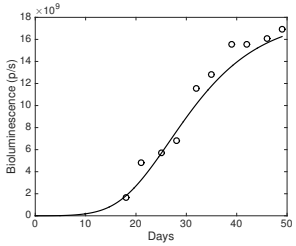
Lavielle,CRC press, 2014

- **Reduces the number of parameters from *pxN to p+p²***

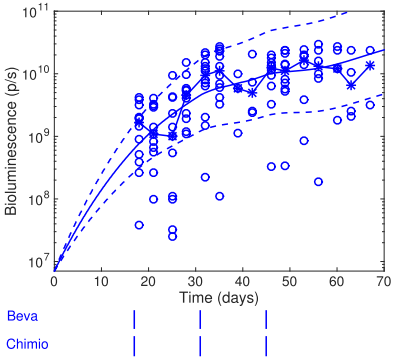
Model fits: individual + population level (NLME)

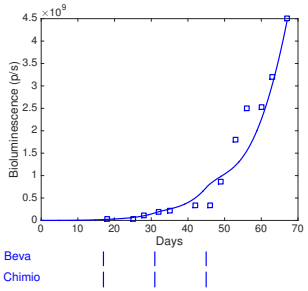
Control



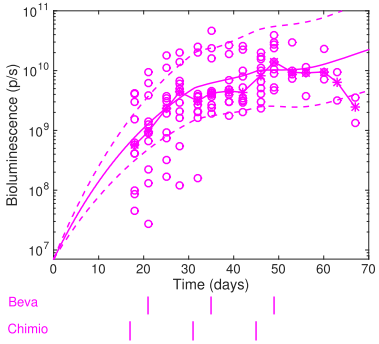


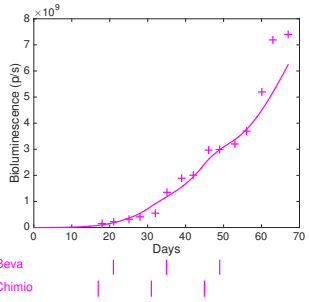
Simultaneous



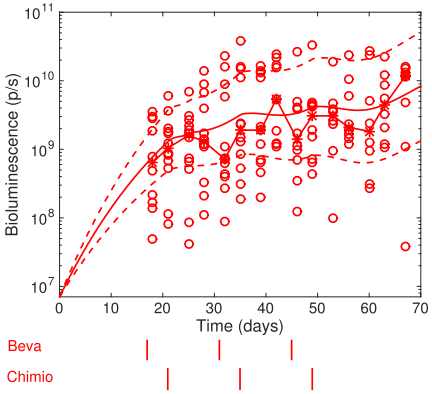


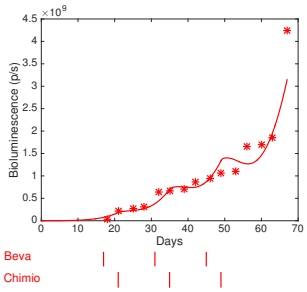
Sequential C/B



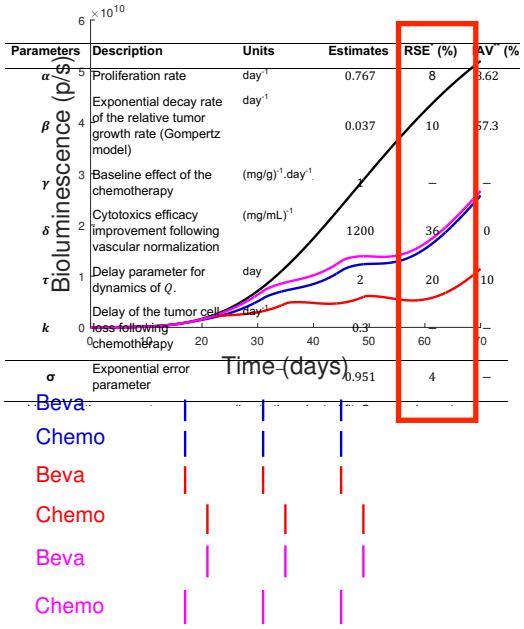


Sequential B/C





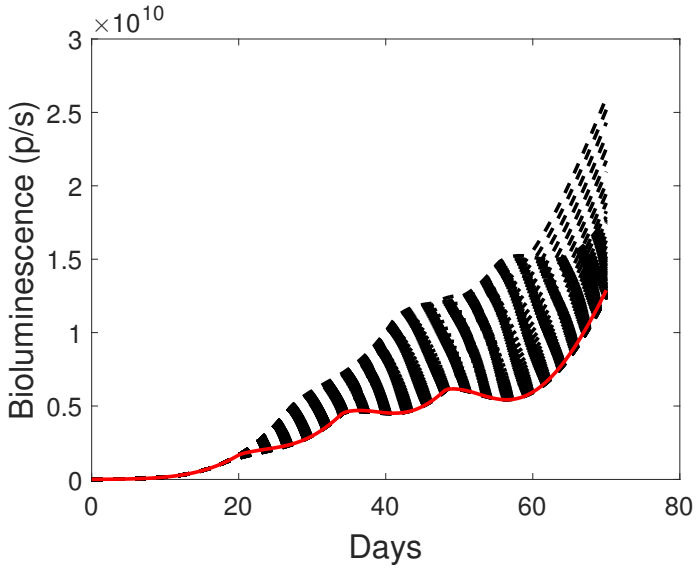
Median growth curves

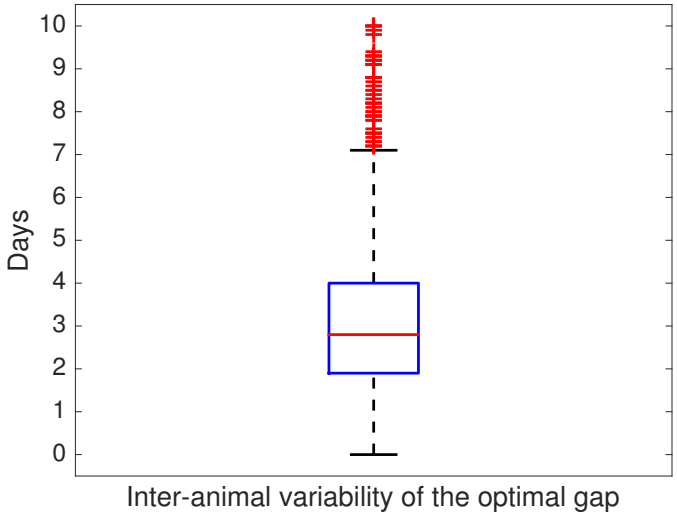


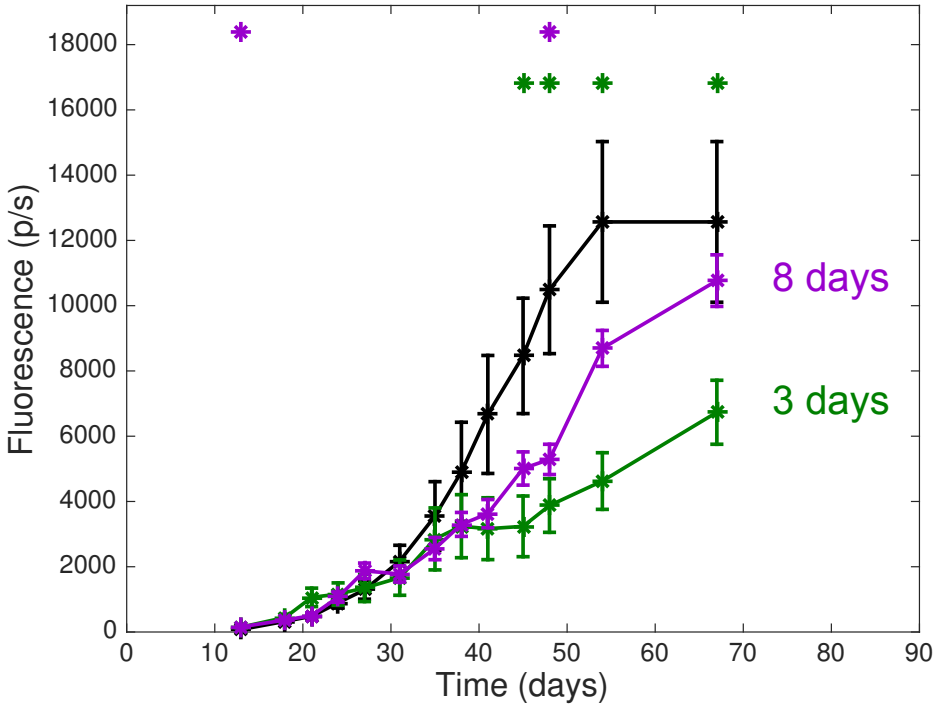
Parameters	Description	Units	Estimates	RSE (%)	IAV (%)
α	Proliferation rate	day^{-1}	0.767	8	3.62
β	Exponential decay rate of the relative tumor growth rate (Gompertz model)	day^{-1}	0.037	10	57.3
γ	Baseline effect of the chemotherapy	$(mg/g)^{-1}.day^{-1}$	1	–	–
δ	Cytotoxics efficacy improvement following vascular normalization	$(mg/mL)^{-1}$	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	–	–
σ	Exponential error parameter		0.951	4	–

Imbs et al., Benzekry, CPT: PSP, 2018

Prediction of the optimal delay







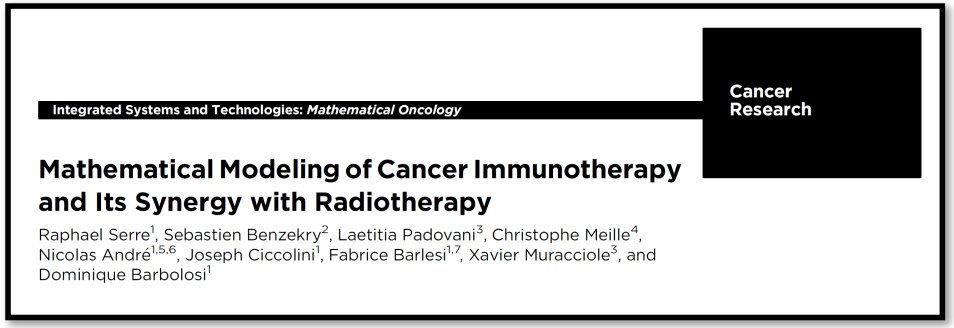
⇒ to be **tested experimentally**

⇒ **personalized** scheduling

Imbs et al., Benzekry, 2018, CPT: PSP

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**



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