Combined *in vivo* and *in silico* quantitative modeling of post-surgery metastatic development and scheduling optimization of anti-cancer therapies

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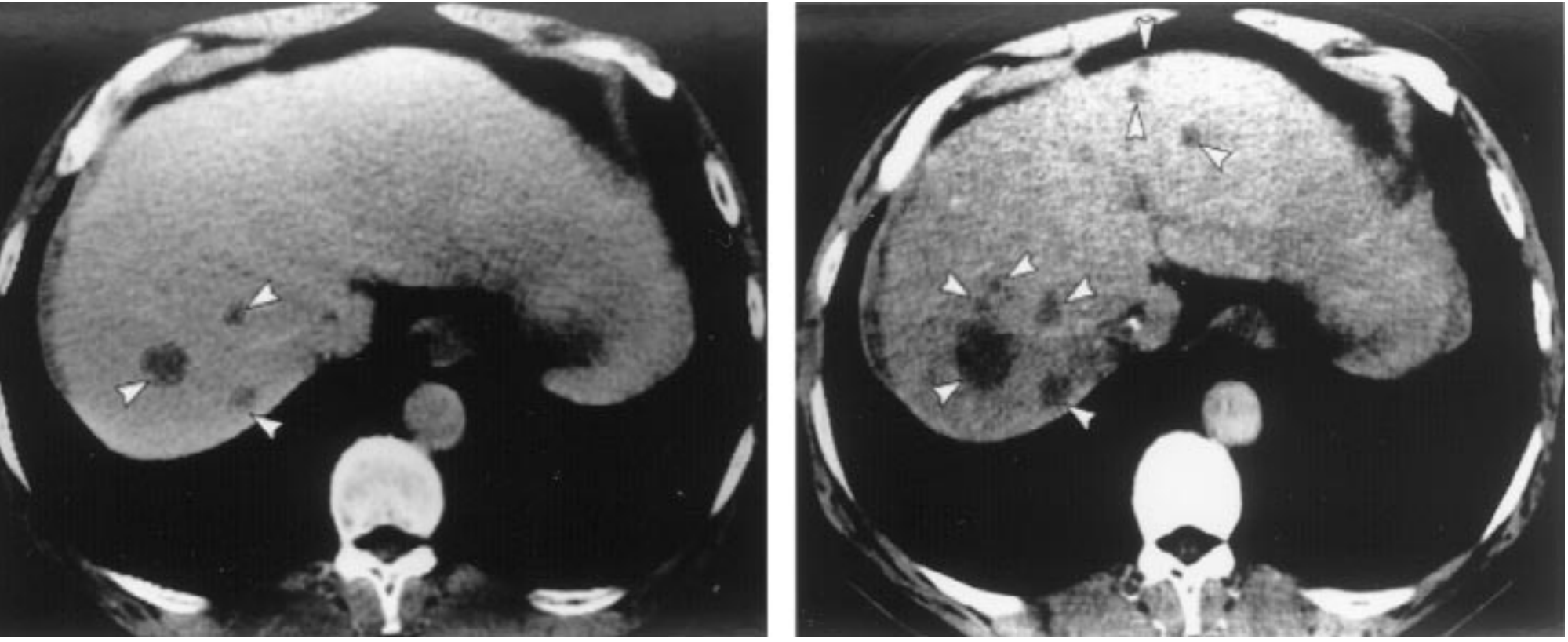
Metastases



Iwata et al., J Theor Biol 2000

Contrast-enhanced X-ray computed tomographies of the liver with multiple metastatic tumors. Interval : 127 days.

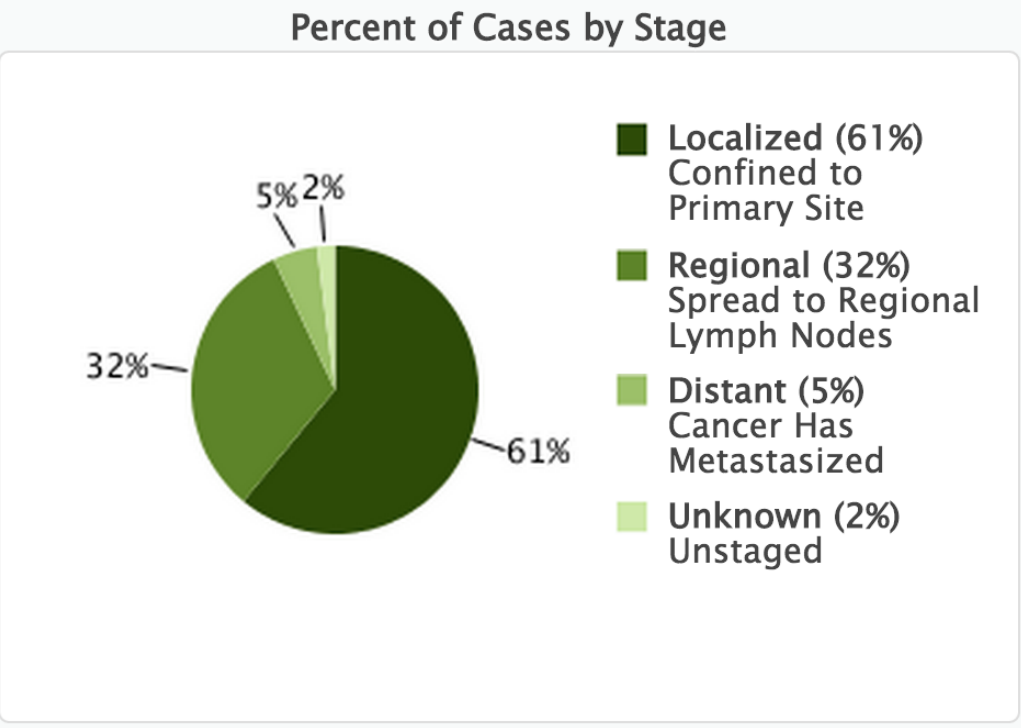
+ some of the metastases are **not visible**.

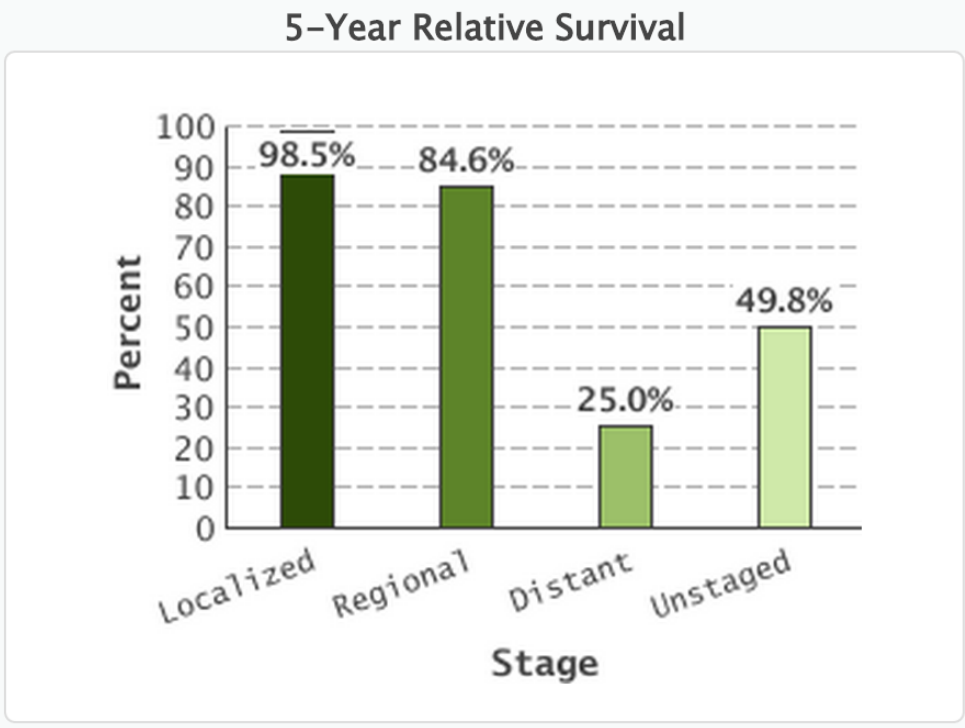
Metastasis (μετά=change, στάσις=place)

- Secondary tumors colonizing a distant organ
- "Metastasis remains the cause of **90%** of deaths from solid cancers" **Gupta and Massagué, Cell, 2006**
- Exciting **biological findings** amenable to dynamical/mathematical descriptions at the systemic scale in recent years:
  - Distant inhibition of angiogenesis by endogenous agents (endostatin,...) **O'Reilly, Folkman et al., Cell, 1994**
  - Self-seeding **Norton and Massagué, Nat Med, 2006**
  - Pre-metastatic niche **Kaplan et al., Nature 2005**
- Clinical **challenges**
  - What is the burden of **occult micro-metastases** at diagnosis?
  - What should be the extent of **post-surgery ("adjuvant") therapy**?
  - What is the **differential effect of therapies** on the primary tumor and the metastases? (AA therapies might accelerate mets? **Ebos et al., Cancer Cell, 2009**)
  - How to **optimize the scheduling** of anti-cancer agents?

Breast cancer epidemiology

- **Most common** invasive cancer in women (14% of new cancer cases)
- Overall **5-year survival**: 89.2%
- However, about 28% will **relapse** within 15 years **Brewster et al, J Natl Cancer Inst, 2008**
- **20 year** survival is (only) 44% **Litiere et al., Lancet Oncol, 2012**





Source: Surveillance, Epidemiology, and End Results (SEER) database, NCI

Breast cancer therapy

- Classical paradigm before the 1970's: disease "diffuses" from its primary location
  - $\Rightarrow$ **Extended** mastectomy **Halsted, Ann Surg, 1907**
- In the 1970s, realization that locally diagnosed PT might very likely have **already disseminated** (estimated incidence rate = 90%) **Fisher, Cancer, 1977**
  - $\Rightarrow$ **Breast conservative surgery**
  - $\Rightarrow$ Generalization of **adjuvant therapy** (chemotherapy, hormone therapy and more recently targeted therapies)

Clinical questions

- For **early breast cancer** (non-metastatic)

  Q1: How to estimate the amount of **residual distant disease** at diagnosis in order to **personalize** the adjuvant (chemo)-therapy?

- For **metastatic breast cancer**, no consensus on the utility of surgery. Ongoing clinical trials.

  Q2: What is the quantitative impact of **PT size/age/stage at resection** on the time-course of the post-surgical metastatic burden?

  Q3: How to **optimize the scheduling** of systemic anti-cancer agents (cytotoxic therapies, bio-therapies)?

Objectives

- Design a minimally parameterized **mathematical theory/model** able to describe the data with identifiable parameters
- Validate the model against **preclinical and clinical data**
- **Qualitative and quantitative implications** for primary tumor size at diagnosis on survival
- Explore the effect of **systemic therapies**
- Define an **optimal control problem**

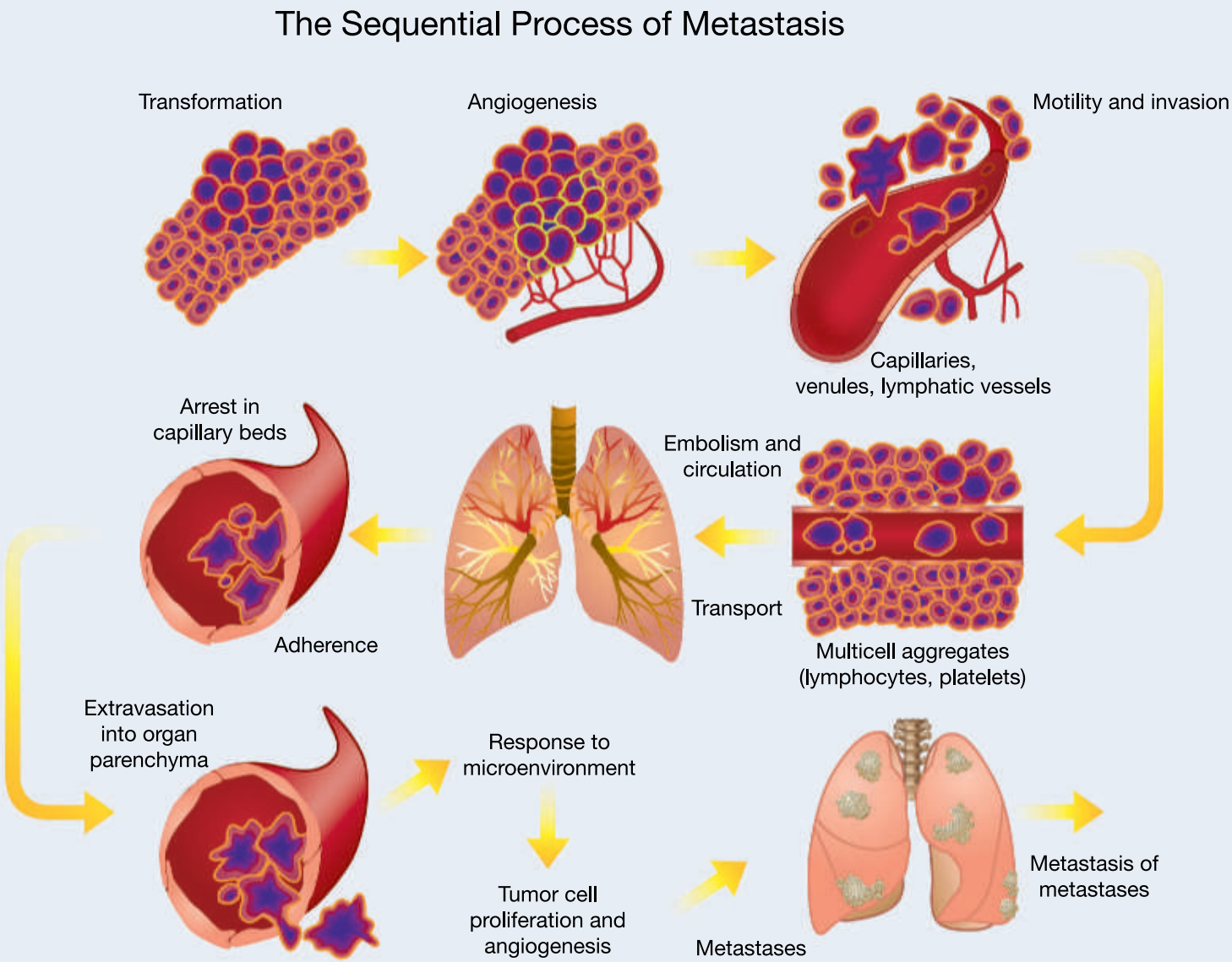
Outline

Theoretical modeling of metastatic development

An in vivo/in silico approach for postsurgical metastatic development
- Bioluminescence preclinical data of breast xenografts
- Clinical data of breast cancer metastatic relapse
- Quantitative impact of surgery on future metastatic development and survival

Therapy and scheduling optimization
- Modeling therapy
- An optimal control problem
- Concentrating VS diluting the dose

A short view at metastasis biology

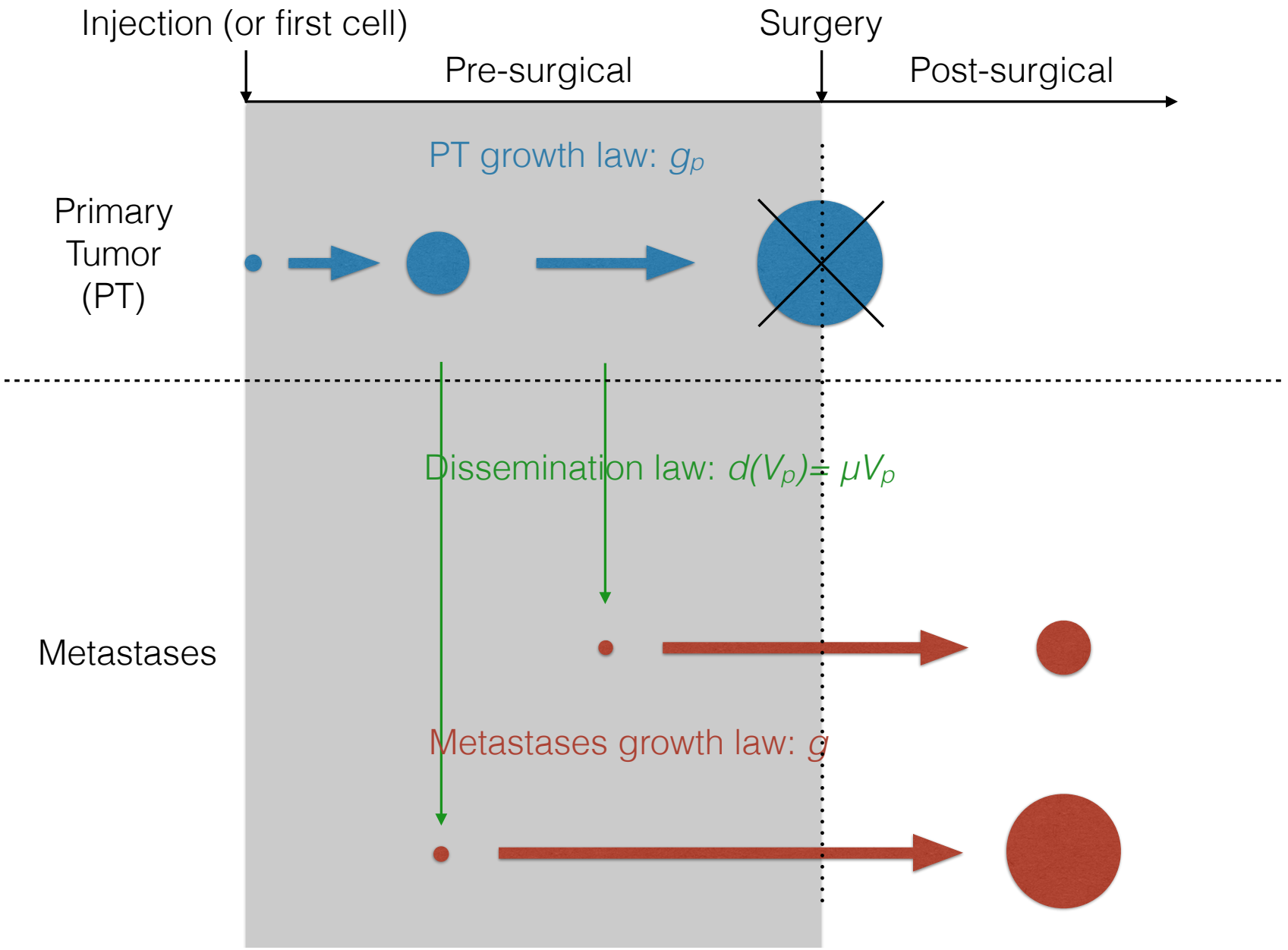


Talmadge and Fidler, Cancer Res, 2010

Mathematical models for metastasis

- Despite a large body of literature for tumor growth modeling, **relatively few models for mets**
- Early statistical models for clinical data of metastatic relapse probability **Blumenson, 1968**, then followed by **Koscielny, Tubiana and Guiguet, 1982, Retsky et al., 1997**
- Biologically-based, low-parameterized and experimentally-validated model for all the main steps of the metastatic process **Liotta, Saidel and Kleinerman, 1976**
- Semi-mechanistic models for description of the metastatic development at the organism scale **Bartoszynski, 1981, Yorke et al., 1993, Hanin 2006**, **Iwata, Kawasaki and Shigesada, 2000** (further studied and developed by **Barbolosi, Benabdallah, Hartung, Hubert, Verga, B. 2009-** and **Bethge, Schumacher and Wedemann, 2012**).
- More recently, theoretical investigations by **Scott, Gerlee et al., 2014** about the self-seeding and filter-flow approach
- ...

Model scheme



Mathematical formalism 1: growth

- Primary tumor V_p grows with rate $g_p(V_p)$ (Exponential, Gompertz, Gomp-Exp, power law,...)

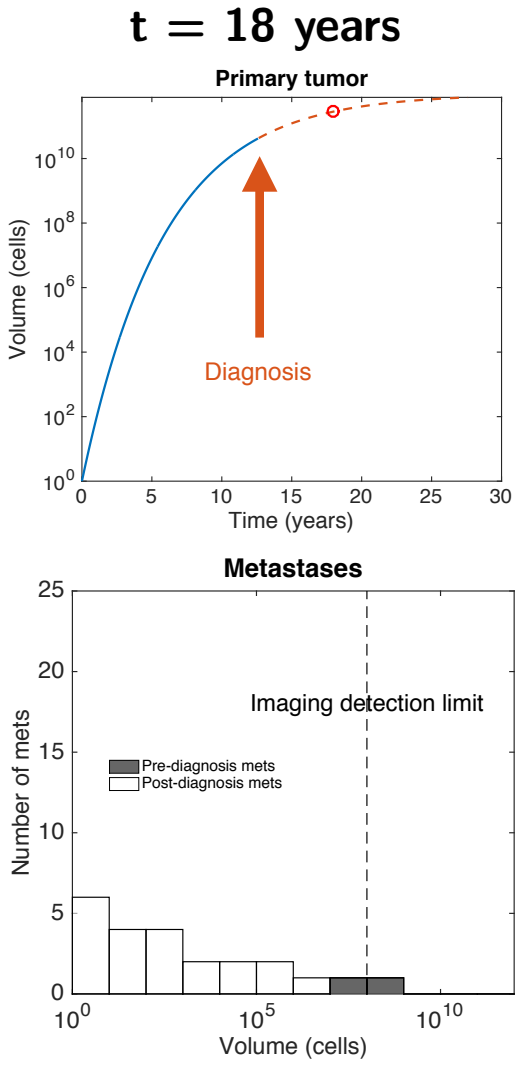
$$\frac{d}{dt}V_p = g_p(V_p), \quad V_p(t=0) = V_i$$

- **Population** of metastases structured in **volume** v described by a **density** $\rho(t, v)$

- Tumors grow in size with rate $g(v)$

$\Rightarrow$ Transport equation when tumors grow

$$\partial_t \rho(t, v) + \partial_v (g(v)\rho(t, v)) = 0$$



Mathematical formalism 2: dissemination

- Spread of new metastases with emission rate

$$d(V) = \mu V^{\gamma}$$

  μ = per day **probability** of a cell to **successfully** establish a distant colony, unit $[cell^{-1} \cdot day^{-1}]$

  γ = $\frac{1}{3}$ of fractional dimension of the vasculature (non-identifiable from real data, in applications $\gamma = 1$)

- Entering flux of new metastases at V_0 (size of one cell)

$$g(V_0)\rho(t, V_0) = \underbrace{d(V_p(t))}_{\text{primary mets}} + \underbrace{\int_{V_0}^{+\infty} d(v)\rho(t, v)dv}_{\text{secondary mets (often negligible)}} \qquad [day^{-1}]$$

Iwata, Kawasaki and Shigesada, J Theor Biol, 2000

Model equations

Primary tumor

$$\frac{d}{dt} V_p(t) = g_p(V_p(t)), \quad V_p(t=0) = V_i$$

Metastases

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

$$\text{Number of metastases} = \int_{V_0}^{+\infty} \rho(t,v)dv = \mu \int_0^t V_p(s)ds$$

$$\text{Metastatic burden} = \int_{V_0}^{+\infty} v\rho(t,v)dv = \mu \int_0^t V_p(s)V(t-s)ds$$

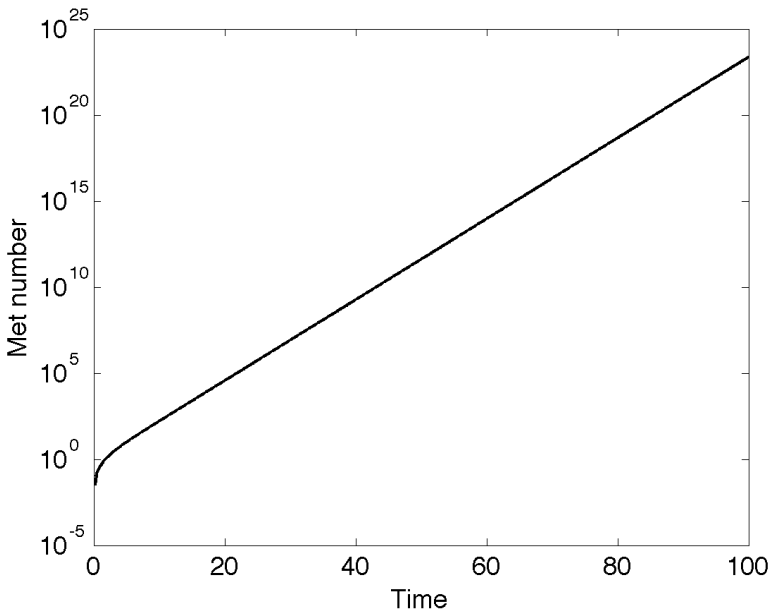
- Existence and uniqueness of solutions **Barbolosi, Benabdallah, Hubert, Verga, Math Biosc 2009**

Asymptotic behavior

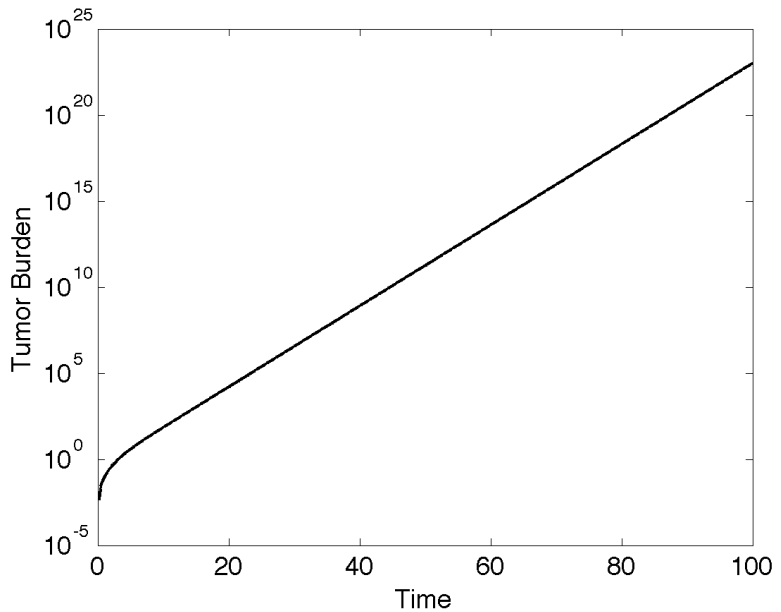
$$\rho(t, v) \sim e^{\lambda_0 t}\Phi(v)$$

$\lambda_0 =$ valeur propre principale de l'opérateur, Φ vecteur propre associé, Ψ vecteur propre adjoint

$$\int_0^{+\infty} d(V(\tau))e^{-\lambda_0 \tau}d\tau = 1, \quad \frac{d}{d\tau}V = g(V),\ V(0) = V_0$$



Number of metastases



Metastatic mass

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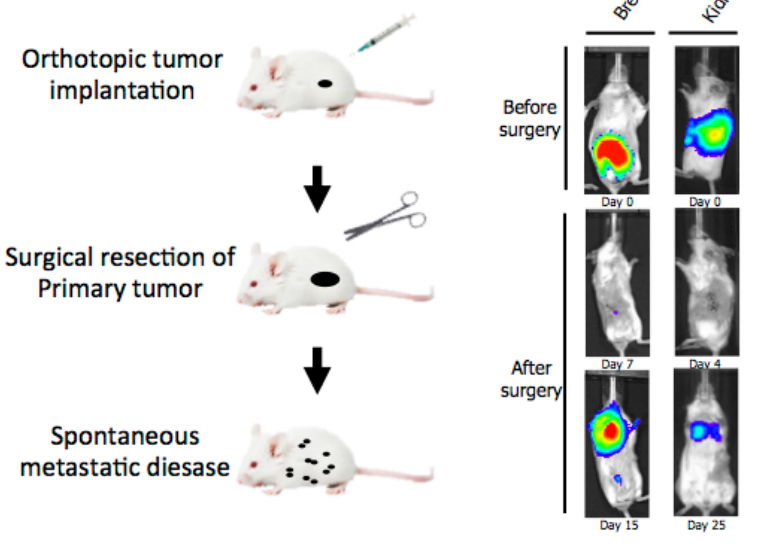
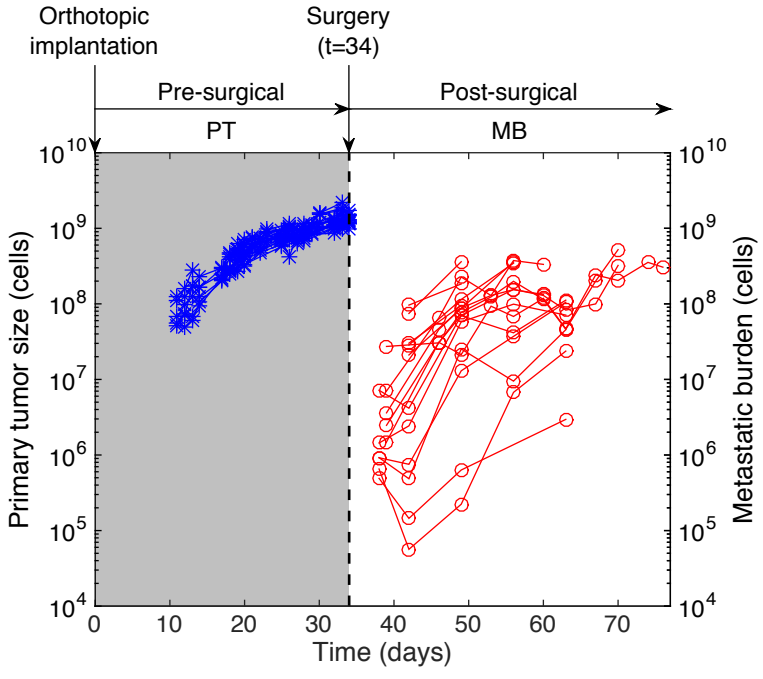
Ortho-surgical animal models of metastasis

- Intra-vital process
- Necessary to consider **surgery** of the primary tumor (PT) for clinical relevance

- Hard to generate **spontaneous metastases**
- Role of the immune system





Ebos, Kerbel et al., EMBO 2014, Cancer Cell 2009

Statistical procedure: nonlinear mixed-effects modeling

Sparse longitudinal data from individuals belonging to the **same population**
Usually

$$y_i^j = f(t_i^j, \theta^{\mathbf{j}}) + \varepsilon_i^j$$

$$\text{For each } j,\ \hat{\theta}^j = \min_{\theta^j} \sum \left(y_i^j - f(t_i, \theta^j)\right)^2 ,$$

individual $1 \leq j \leq N$
time t_i
Observation y_i^j
Model f depending on $\theta \in \mathbb{R}^p$
Error ε_i^j i.i.d $\sim \mathcal{N}(0, \sigma_i)$

In mixed-effects modeling:

$$y_i^j = f(t_i^j, \theta^{\mathbf{j}}) + \varepsilon_i^j$$

$$\theta^{\mathbf{j}} \textbf{ i.i.d}, \sim \mathcal{LN}(\theta_\mu, \theta_\cdot)$$

$$\theta_\mu \in \mathbb{R}^p,\ \theta_\Omega \in \mathbb{R}^{p \times p} \Rightarrow \left(\hat{\theta_\mu}, \hat{\theta_\Omega}\right) = \text{argmax } LLH$$

Goes from $p \times N$ parameters to $p^2 + p$ parameters and uses the data from the **entire population**!

Best model structure

Mechanistic assumptions

- Various structures tested for relationship of the PT and mets growth for optimal **trade-off between goodness-of-fit and identifiability**
- **Same growth** between PT and mets
- Growth model = Gomp-Exp

$$Gomp(v) = (\alpha - \beta \ln(v))\, v$$

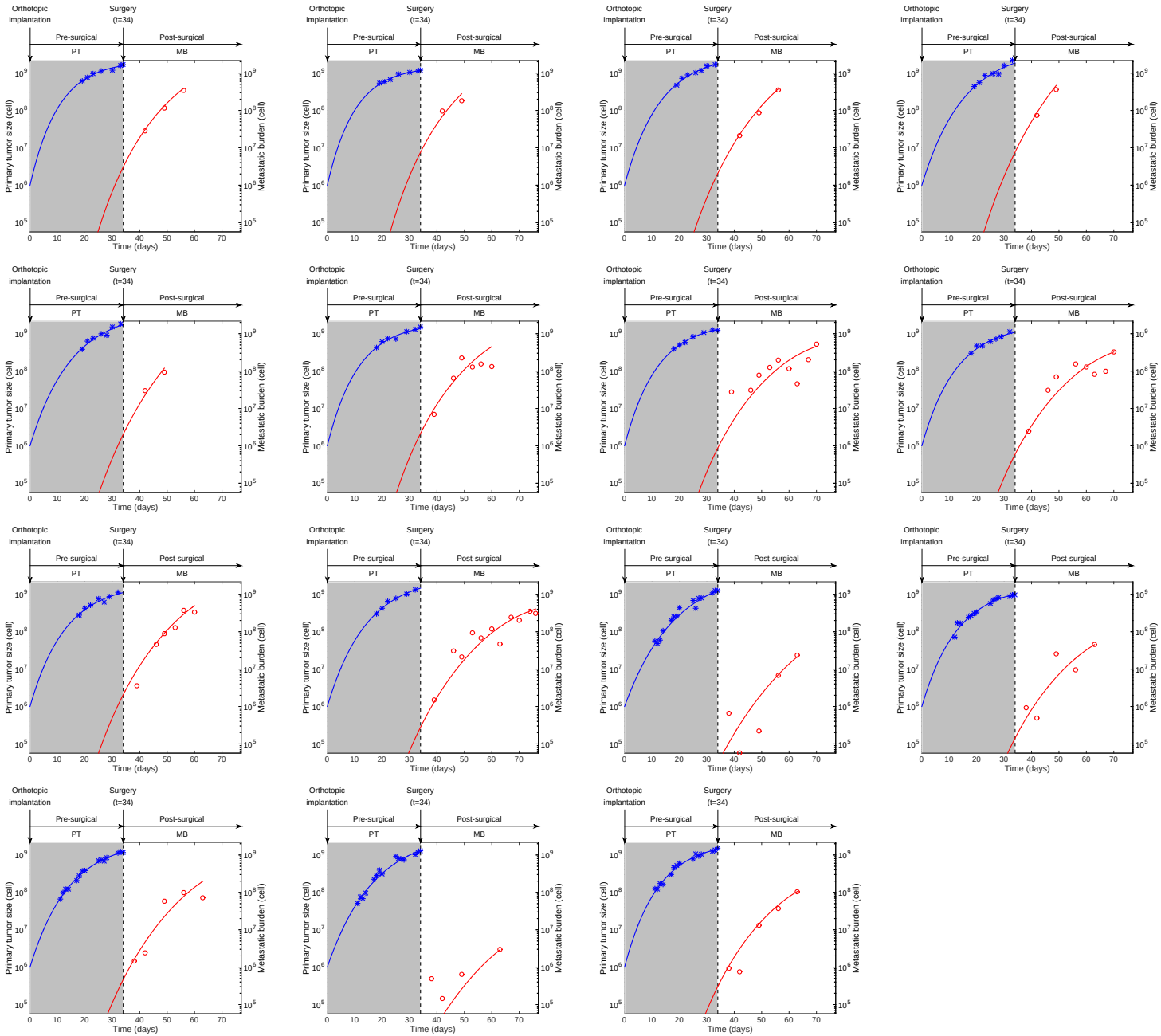
$$g_p(v) = g(v) = \min(Gomp(v), \lambda v)$$

- λ = *in vitro* proliferation rate (measured)

Statistical assumptions

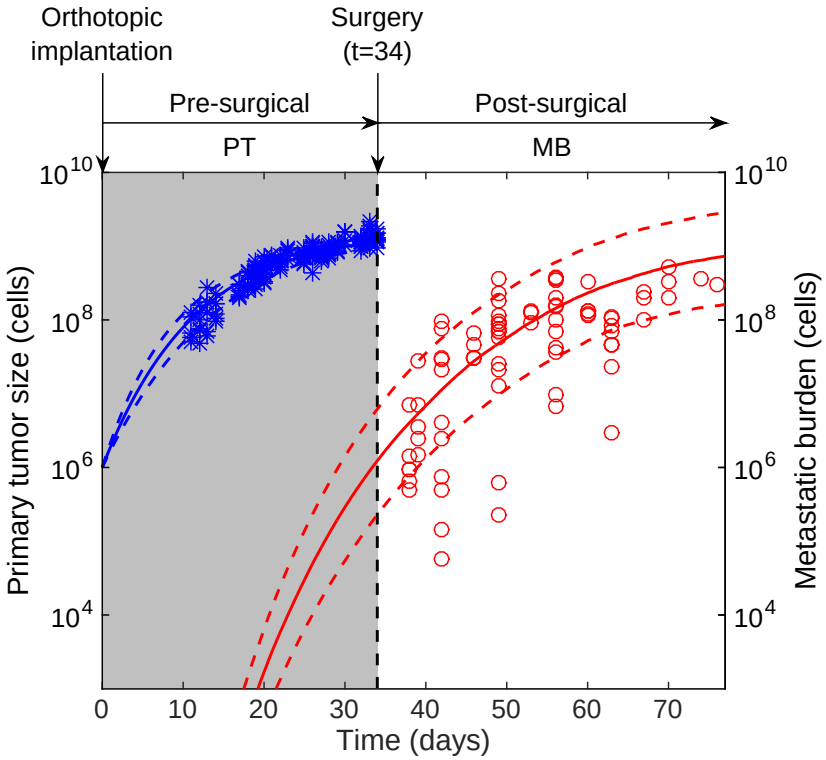
- PT and mets fitted together (3 parameters)
- **Proportional** statistical error model
- **Lognormal** population distribution of the parameters

Individual fits

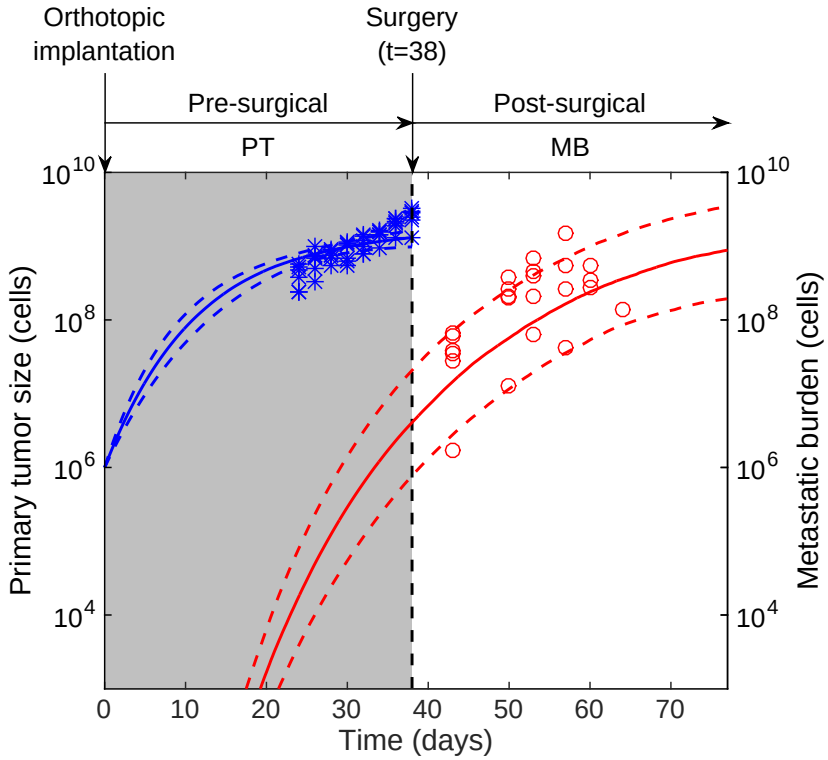


Fit and prediction of bioluminescence preclinical data

Fit



Prediction



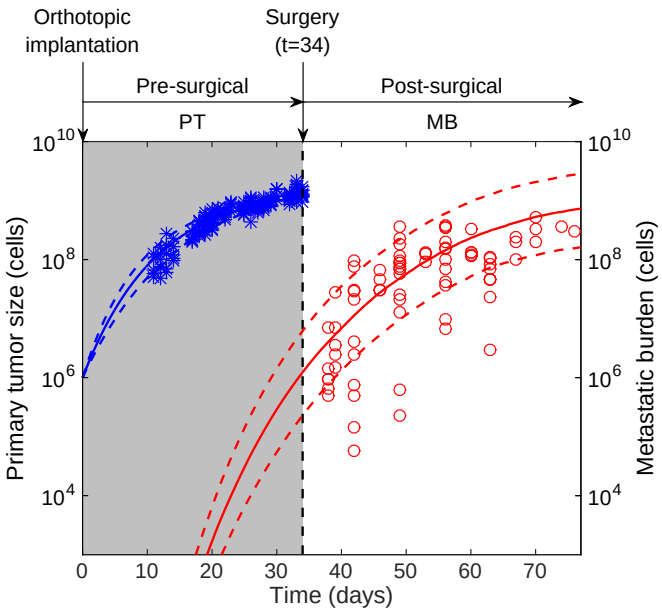
Data PT
Median model PT
Model prct PT
Data Met
Model median Met
Model prct Met

B., Ebos et al., Cancer Research, 2015

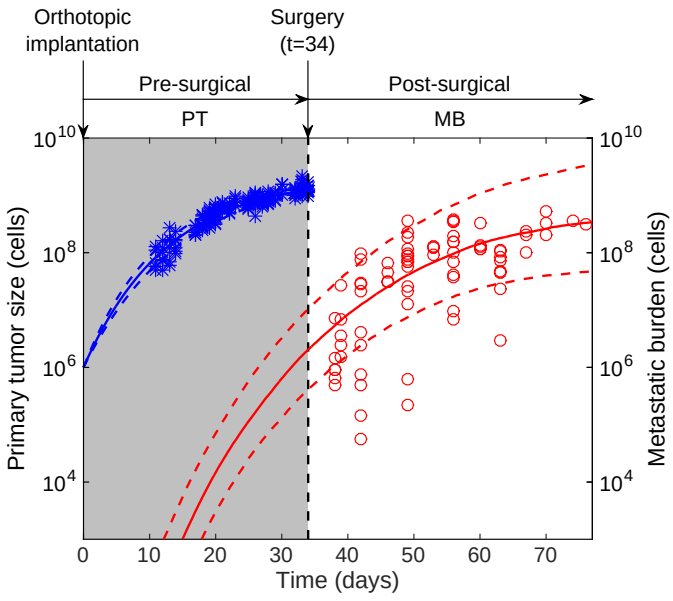
Hartung et al., Cancer Research, 2014

Goodness-of-fit/Identifiability trade-off

Same growth

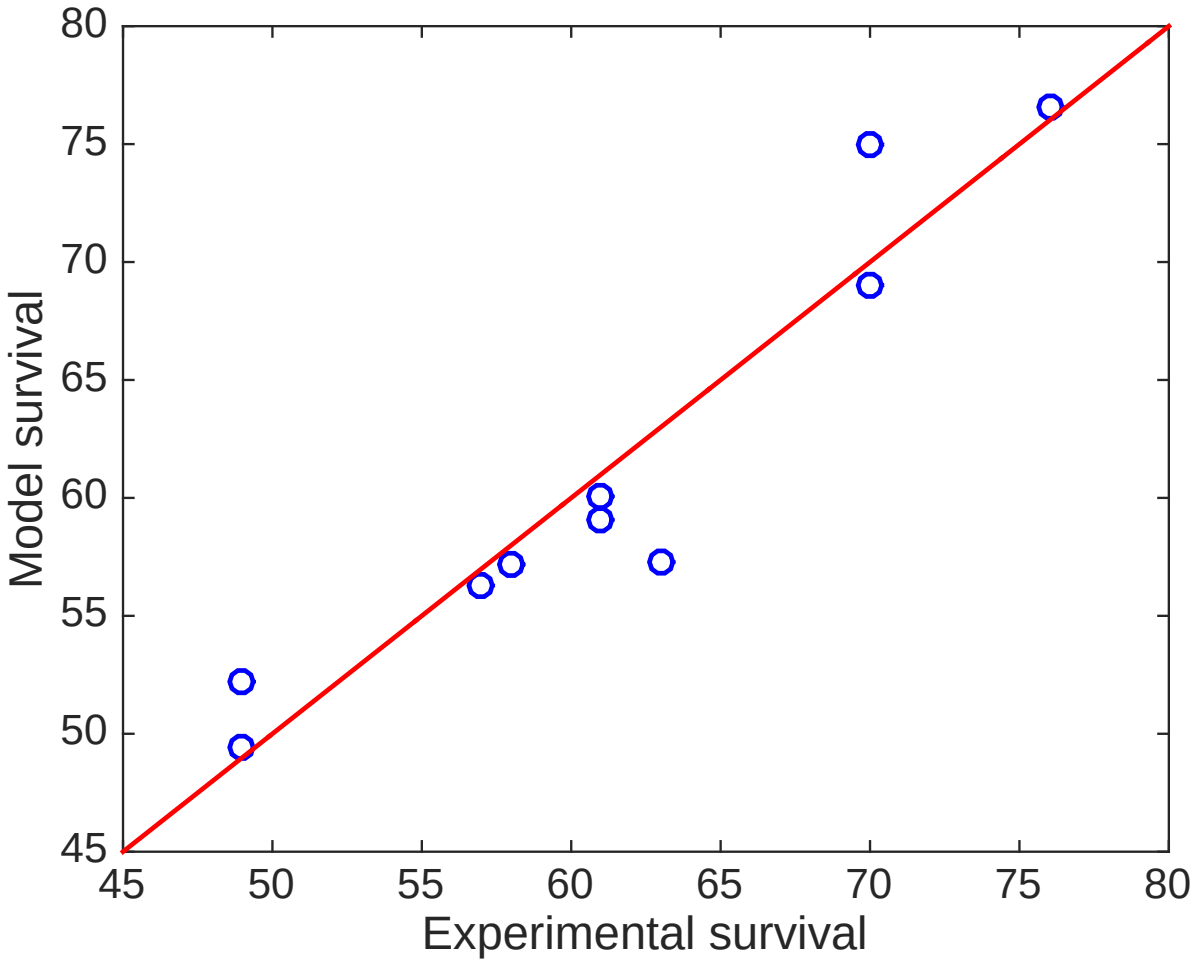


Different growth alpha fixed



Model	Par.	Unit	Median value (CV)	NSE (%)
Diff growth alpha fixed	α_P	day^{-1}	0.605 (9.83)	3.57
	β_P	day^{-1}	0.0786 (12.2)	4.86
	μ	$cell^{-1} \cdot day^{-1}$	3.01e-09 (820)	72.1
	β	day^{-1}	0.0816 (15.7)	5.06
Same growth	α	day^{-1}	0.664 (16.3)	4.76
	β	day^{-1}	0.0893 (21.3)	6.21
	μ	$cell^{-1} \cdot day^{-1}$	4.43e-11 (176)	26.5

Predicted versus experimental survival



The model survival was defined as the time to reach a given lethal burden of 4×10^9 p/s, i.e.

$$\inf \left\{ t > 0; M(t) > 4 \times 10^9 \right\}$$

Clinical data

20 year follow-up of 2648 **breast cancer** patients

Koscielny, Tubiana et al., Br J Cancer, 1984

Diameter of PT (cm)	Prop. of relapse (Data)	Prop. of relapse (Model)
$1-2.5$	27.1	25.5
$2.5-3.5$	42.0	42.3
$3.5-4.5$	56.7	56.3
$4.5-5.5$	66.5	65.9
$5.5-6.5$	72.8	74.3
$6.5-7.5$	83.8	80.8
$7.5-8.5$	81.3	85.7

$p = 0.023$

Pearson's χ^2 test for goodness-of-fit

- **Gompertz growth** of PT, doubling time at 1 gram = 7 months and carrying capacity = 10^{12} cells (1 kg)
- Recover cancer **inception time** - T_1 from PT volume at diagnosis
- Lognormal distribution of μ for **inter-individual** variability
- Probability of metastatic relapse = probability of having one at diagnosis

$$\mathbb{P}(\textbf{Mets}) = \mathbb{P}\left(\mu \int_0^{T_1} V_p(t) > 1\right)$$

$$\mu_{median} = 7 \times 10^{-12} cell^{-1} \cdot day^{-1}$$

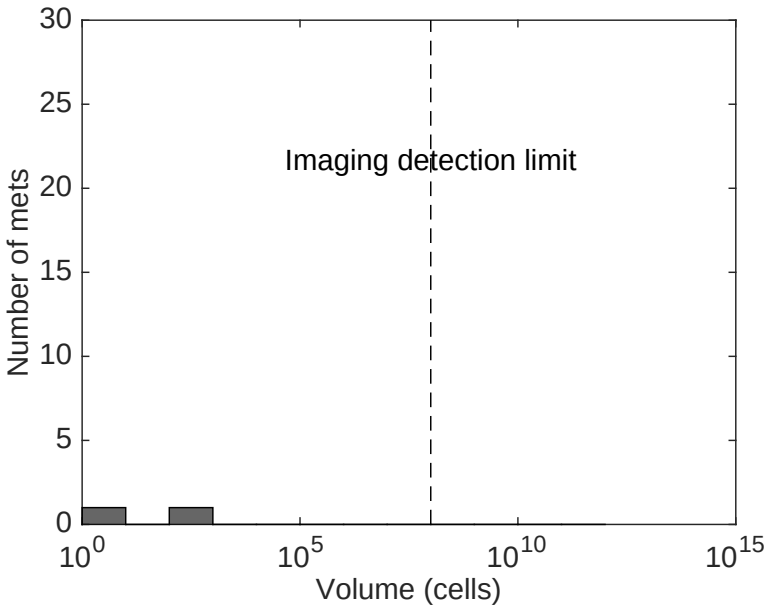
Parameters: quantification of metastatic potential

Data	Growth model	Location	Par.	Unit	Estimate (CV)	95 % CI
In vitro (Breast)	Exp.		λ	day^{-1}	0.837 (-)	(0.795 - 0.879)
Preclinical Breast	Gomp-Exp.	PT	V_i	$cell$	1.00×10^6 (-)	-
			α	day^{-1}	0.664 (16.3)	(0.605 - 0.729)
			β	day^{-1}	0.0893 (21.3)	(0.0791 - 0.101)
		Met	V_0	p/s	10 (-)	-
			μ	$cell^{-1} \cdot day^{-1}$	4.43×10^{-11} (176)	$(2.70 \times 10^{-11}$ - $7.27 \times 10^{-11})$
Preclinical Kidney	Exp.	PT	V_i	p/s	1.63×10^5 (45.5)	$(9.40 \times 10^4$ - $2.83 \times 10^5)$
			α	day^{-1}	0.21 (60.3)	(0.151 - 0.292)
		Met	V_0	p/s	10 (-)	-
			α	day^{-1}	0.307 (201)	(0.133 - 0.707)
			μ	$cell^{-1} \cdot day^{-1}$	0.0415 (397)	(0.0181 - 0.0948)
Clinical Breast	Gomp.	PT	V_i	$cell$	1 (-)	
			α	day^{-1}	0.013 (-)	
			β	day^{-1}	0.000471 (-)	
		Met	V_0	$cell$	1 (-)	
			μ	$cell^{-1} \cdot day^{-1}$	7.00×10^{-12} (1.04×10^4)	

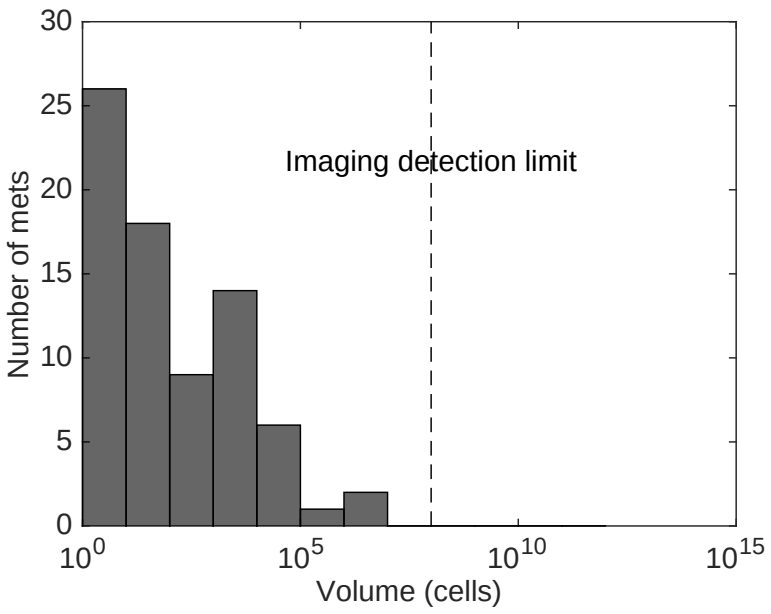
Simulation of the cancer history

Size distribution of metastases at diagnosis (D=4cm)

Median μ



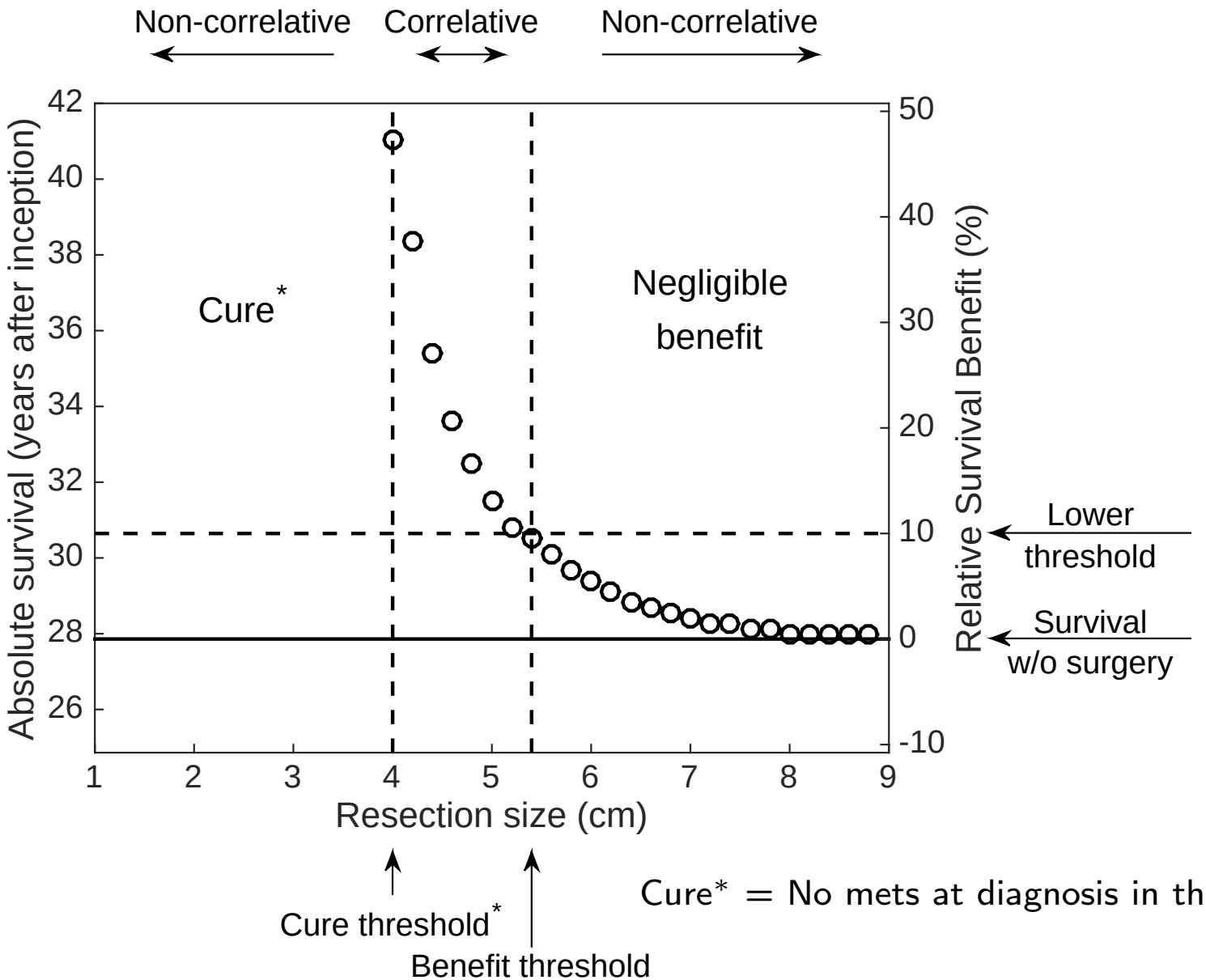
Large μ (90th percentile)



For the simulations a stochastic version of the model is employed (inhomogeneous Poisson process for the emission of new metastases).

Nonlinear impact of PT size at surgery on survival

median μ



Cure* = No mets at diagnosis in the simulation

Summary

- A biologically-based, **minimally parameterized**, mathematical model for metastatic development links pre-surgical tumor growth and post-surgical **metastatic burden dynamics**
- **Validation** against preclinical and clinical data sets
- **Same growth law** between PT and mets, **equal probability** among the PT cells of successful establishment of a distant colony and **no secondary dissemination** was a sufficient theory to explain the data
- Inter-animal/individual metastatic propensity can be reduced to variability of **one critical parameter** μ
- Nonlinear dependence of survival on primary tumor size at diagnosis suggests existence of a **threshold for efficacy of surgery** and provides a way to compute it

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Chemotherapy = reduction of the growth speed

$$g(V) = aV \ln\left(\frac{K}{V}\right) - C(t)V$$

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$$g(V) = aV \ln\left(\frac{K}{V}\right) - C(t)V$$

Toward taking into account inter-individual variability

- Simulation of 10 **virtual patients** with breast cancer
- Chemotherapy : 6 cycles of 21 days **Viens & al., 2001**
- Number of visible metastases ($> 10^8$ cel.) 5 years after the end of the treatment.

Patient	m	# metastases	Patient	m	# metastases
$n^\circ 1$	1.7×10^{-8}	0	$n^\circ 6$	7.0×10^{-8}	0
$n^\circ 2$	1.9×10^{-8}	0	$n^\circ 7$	1.3×10^{-7}	**1**
$n^\circ 3$	2.7×10^{-8}	0	$n^\circ 8$	2.7×10^{-7}	**2**
$n^\circ 4$	5.0×10^{-8}	0	$n^\circ 9$	4.0×10^{-7}	**3**
$n^\circ 5$	6.1×10^{-8}	0	$n^\circ 10$	6.1×10^{-7}	**4**

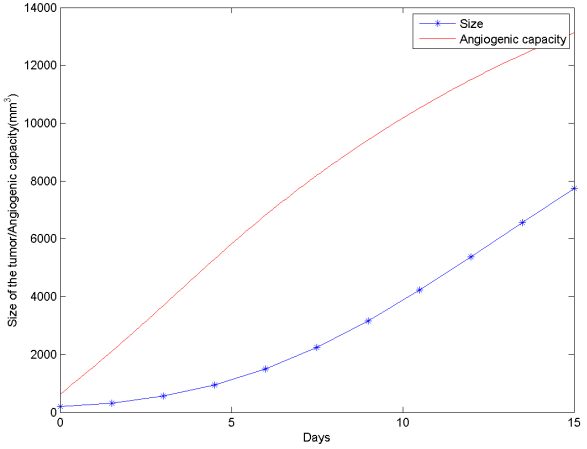
Anti-angiogenic treatments

Hahnfeldt et al., 1999

$$\frac{dV}{dt} = aV \ln\left(\frac{K}{V}\right)$$

Consider K as a **variable** representing the **vasculature**

$$\frac{dK}{dt} = \underbrace{cV}_{\text{Stimulation by the tumor}} \quad \underbrace{- dV^{\frac{2}{3}} K}_{\text{Inhibition}}$$



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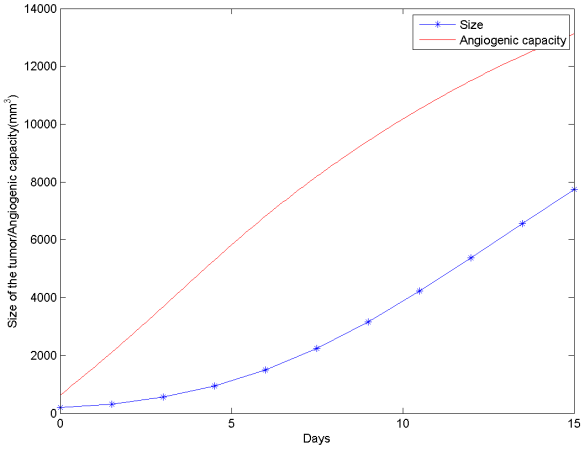
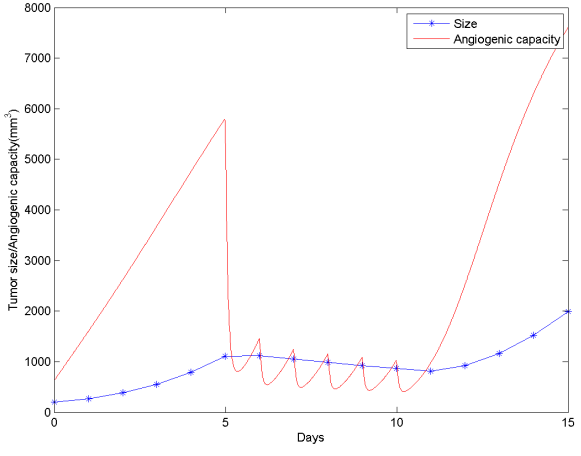


Treatment

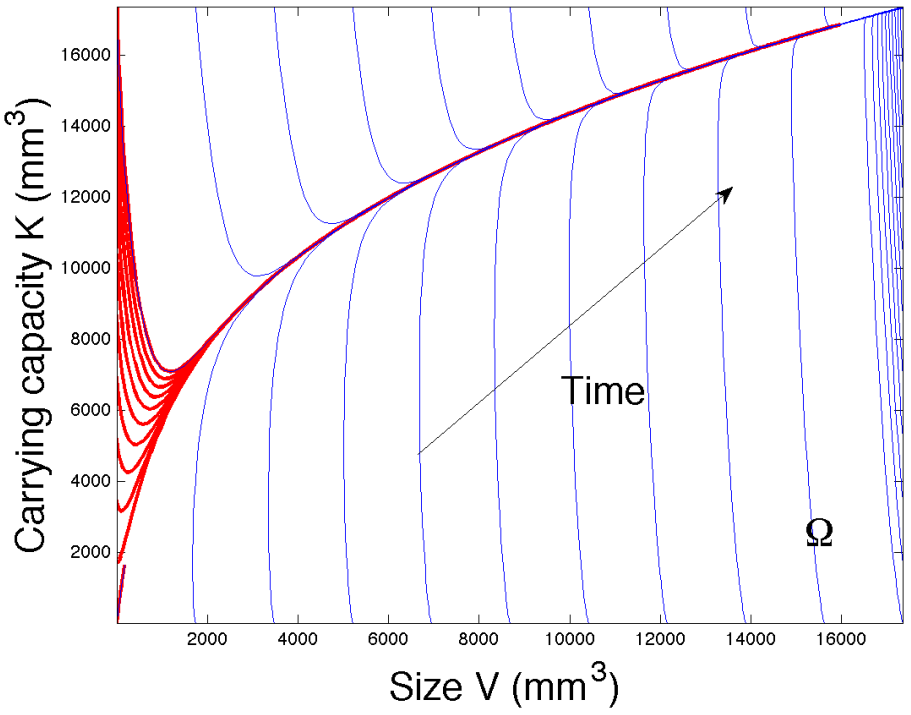
$$\frac{dV}{dt} = aV \ln\left(\frac{K}{V}\right) - \underbrace{f\,C(t)V}_{\text{cytotoxic}}$$

$$\frac{d\theta}{dt} = cV - dV^{\frac{2}{3}}K - \underbrace{e\,A(t)K}_{anti-angiogenic}$$



Hahnfeldt et al., 1999

Transport equation for the metastases population



$$\Omega =]V_0, b[^2 \,, \; b = \left(\frac{c}{d}\right)^{\frac{3}{2}}$$

$$G = \begin{pmatrix} aV \ln\left(\frac{K}{V}\right) \\ cV - dV^{\frac{2}{3}}K \end{pmatrix}$$

$$\overline{G} = G - Bu(t)$$

$$u(t) = (C(t), A(t))$$

$$\rho(t, V, K)$$

Conservation law

$$\partial_t \rho + \mathrm{div}(\rho \overline{\mathrm{G}}) = 0$$

Boundary condition. Birth of new metastases

Birth rate of new metastases of parameter $\sigma \in \partial\Omega$ per meta of size V and carrying capacity K per unit of time : $\mathbf{b}(\sigma, V, K)$

We assume that the metastases are born with size 1 cell (V_0) and same carrying capacity K_0

$$b(\sigma, V, K) = \delta_{\sigma=(V_0,K_0)} d(V, K)$$

We take :

$$d(V, K) = \mu V^{\gamma}$$

Metastatic model with angiogenesis

B., 2011

$$\begin{cases} \partial_t \rho + \mathrm{div}(\overline{\mathrm{G}}\rho) = 0 \\ -\overline{G}(t,\sigma)\cdot\nu(\sigma)\rho(t,\sigma) = \delta_{\sigma=(V_0,K_0)}\left\{\int_\Omega d(V)\rho(t,V,K)dVdK + d(V_p(t))\right\} \\ \rho(0) = \rho^0 \end{cases}$$

- Renewal equation in **dimension 2** for the trait $X = (V, K)$
- Theoretical and numerical **analysis** has been performed : well-posedness, regularity, asymptotic behavior, error estimate

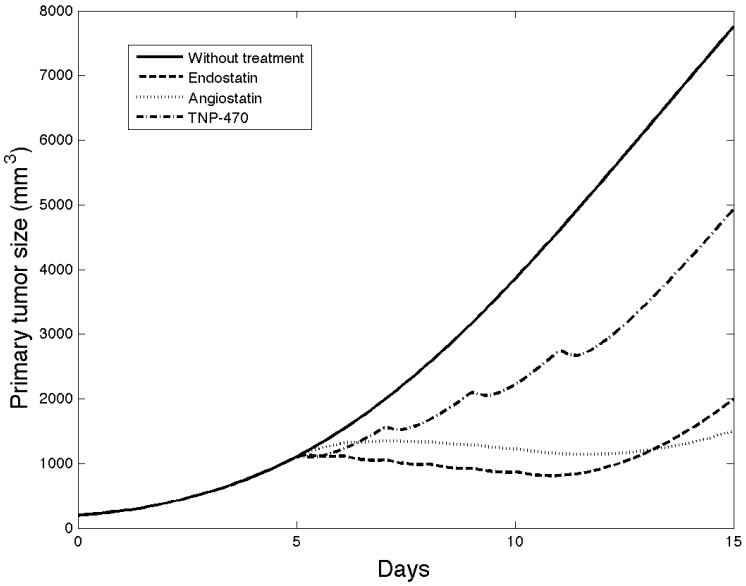
B., JEE, 2011

B., M2AN, 2012

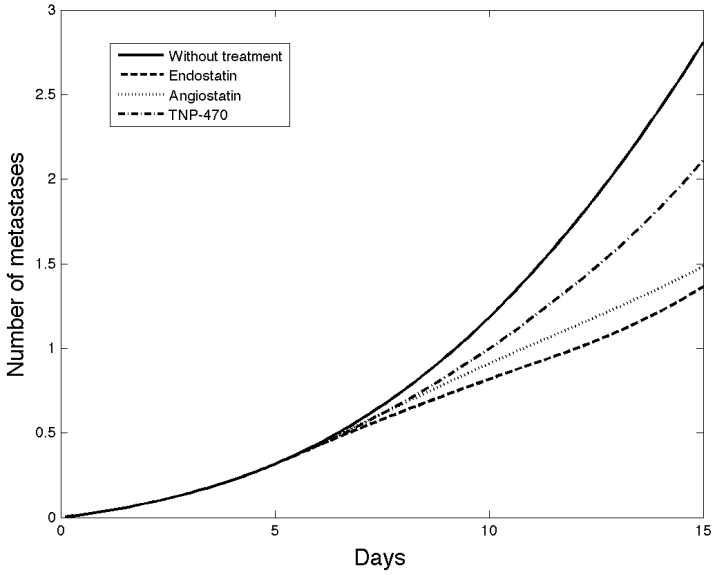
Anti-angiogenic monotherapy

Testing the drugs from Hahnfeldt et al., 99 (mice data)

Endostatin 20 mg/kg/day, Angiostatin 20 mg/kg/day, TNP-470 30 mg/kg/q.o.d



Primary tumor

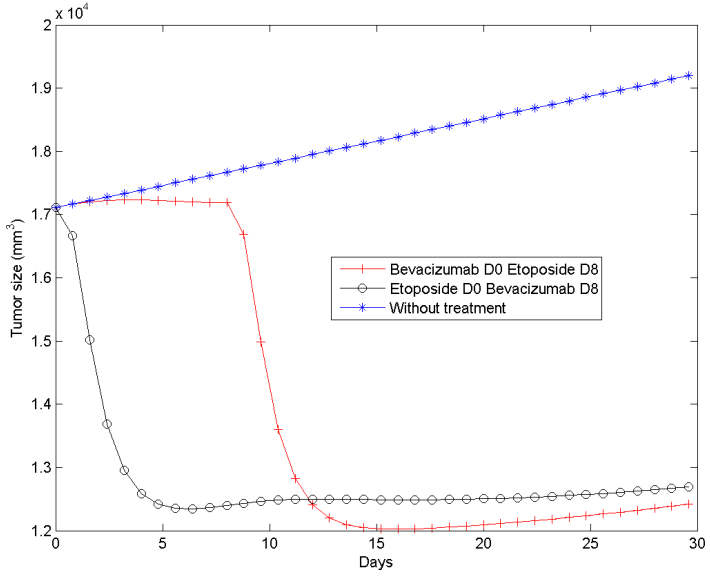


Metastases

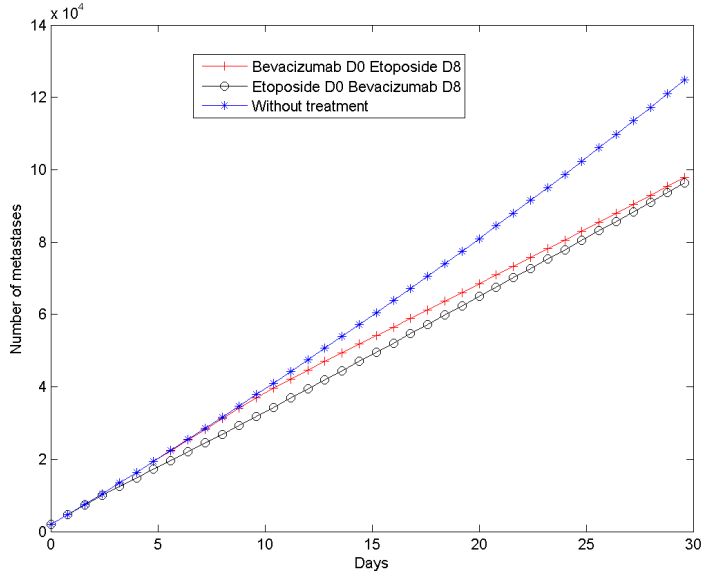
CT/AA combination. Order of administration?

Etoposide (CT)/Bevacizumab (AA) combination

Bevacizumab D0 Etoposide D8 VS Etoposide D0 Bevacizumab D8



Primary tumor



Metastases

In these two first examples, the best protocol/drug is **not the same** for the primary tumor and for the number of metastases.

Theoretical modeling of metastatic development

An in vivo/in silico approach for postsurgical metastatic development

- Bioluminescence preclinical data of breast xenografts
- Clinical data of breast cancer metastatic relapse
- Quantitative impact of surgery on future metastatic development and survival

Therapy and scheduling optimization

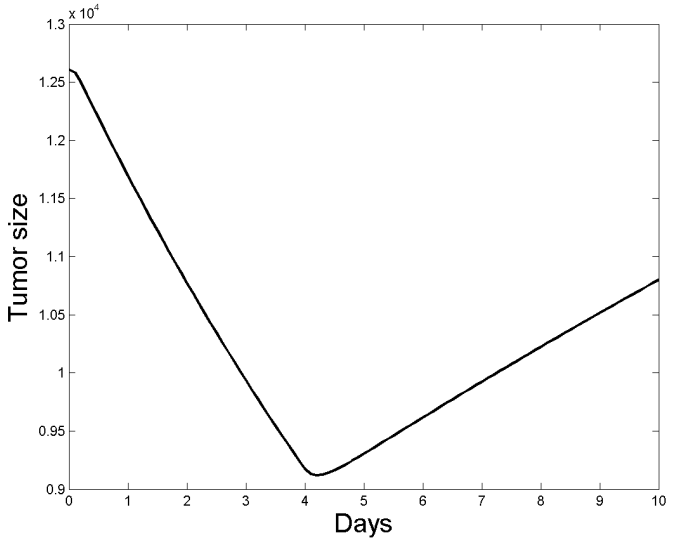
- Modeling therapy
- An optimal control problem
- Concentrating VS diluting the dose

On the primary tumor

$$X_p := (V_p, K_p), \quad \dot{X}_p(t;u) = G(X_p) - B(X_p)u(t)$$

Two possible criteria to be minimized for the primary tumor size

$$J_T(u) = V_p(T;u) \quad \textbf{and} \quad J_m(u) = \min_{t\in[0\,T]} V_p(t;u)$$



On the primary tumor

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$$J_T(u) = V_p(T;u) \quad \textbf{and} \quad J_m(u) = \min_{t\in[0\,T]} V_p(t;u)$$

Toxicity constraints

$$\mathcal{U}_{ad} = \left\{ \begin{pmatrix} 0 \\ 0 \end{pmatrix} \leq u(t) \leq \begin{pmatrix} c_{max} \\ a_{max} \end{pmatrix} \ \forall t \ \textbf{and} \ \int_0^T u(t)dt \leq \begin{pmatrix} C_{max} \\ A_{max} \end{pmatrix} \right\}$$

Optimal control problem : find $u^* \in \mathcal{U}_{ad}$ such that $J_m(u^*) \leq J_m(u)$ for all $u \in \mathcal{U}_{ad}$, studied in

U. Ledzewicz and H. Schättler, SIAM J. on Control and Optimization, 2007

A. d'Onofrio, U. Ledzewicz, H. Maurer and H. Schättler, Math. Biosc., 2009

A. Ergun, K. Camphausen, L. M. Wein, Bull. Math. Biol., 2003

On the metastases

- Two new criteria

$$J(u) = \underbrace{\int_\Omega \rho(T, V, K; u) dV dK}_{\textbf{Total number of metastases}}$$

$$J_M(u) = \underbrace{\int_\Omega V\rho(T, V, K; u) dV dK}_{\textbf{Metastatic mass}}$$

- Optimal control problem

Find $(u^*, u_M^*) \in \mathcal{U}_{ad}$ such that

$$J(u^*) = \min_{u\in\mathcal{U}_{ad}} J(u) \textbf{ and } J_M(u_M^*) = \min_{u\in\mathcal{U}_{ad}} J_M(u)$$

Is there a **difference** in the optimal

minimizer **between the metastatic**

and primary tumor criteria?

Existence of an optimal solution

Theorem

Under some regularity assumptions **there exists** $(u^*, u_M^*) \in \mathcal{U}_{ad}$ *such that*

$$J(u^*) \leq J(u), \quad \forall u \in \mathcal{U}_{ad}, \quad J_M(u_M^*) \leq J_M(u), \quad \forall u \in \mathcal{U}_{ad}$$

The proof is based on the following proposition

Proposition

Under some regularity assumptions $\rho(u) \in W^{1,\infty}(Q)$ *and there exists a continuous function* C *such that, for all* $u \in \mathcal{U}_{ad}$

$$||\rho(u)||_{W^{1,\infty}(Q)} \leq C(||u||_{L^\infty(Q)})$$

Optimality system for J

Proposition

Let u^* be a solution of the optimal control problem. We have the following **optimality system** *:*

$$\begin{cases} \partial_t \rho^* + \operatorname{div}(\rho^* G(u^*)) = 0 \\ -G \cdot \nu \rho^*(t, \sigma; u^*) = \delta_{\sigma=(v_0, \kappa_0)} \left\{ \int_\Omega d(X) \rho^*(t, X; u^*) dX + d(X_p(t; u^*)) \right\} \\ \rho^*(0, X; u^*) = \rho^0 \end{cases}$$

$$\begin{cases} -\partial_t p^* - G(u^*) \nabla p^* - d \int_{\partial\Omega} N(\sigma) p^*(t, \sigma) d\sigma = 0 \\ p^*(T) = -1. \end{cases}$$

$$\int_0^T \int_\Omega p^* \operatorname{div}(\rho^* B(X) \cdot (v - u^*)) \, dX \, dt \leq 0, \quad \forall v \in \mathcal{U}_{ad}.$$

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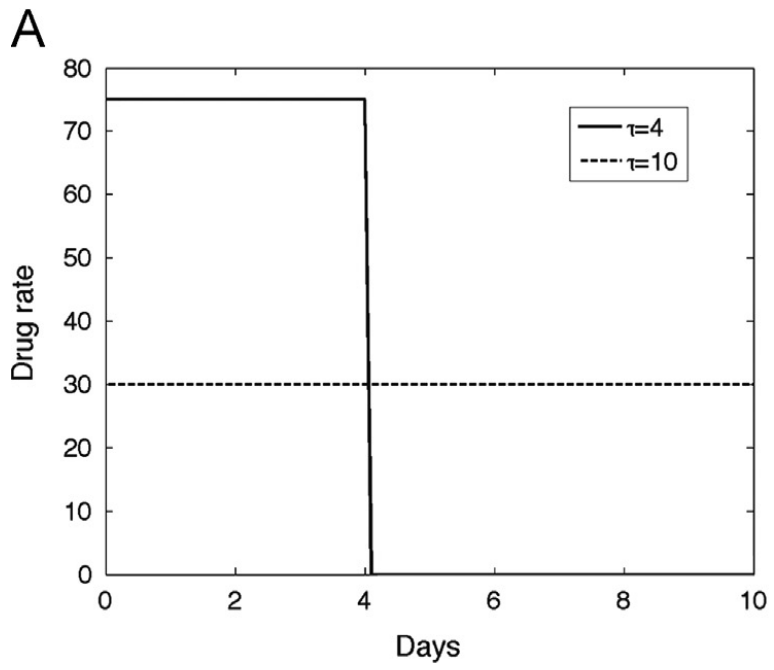
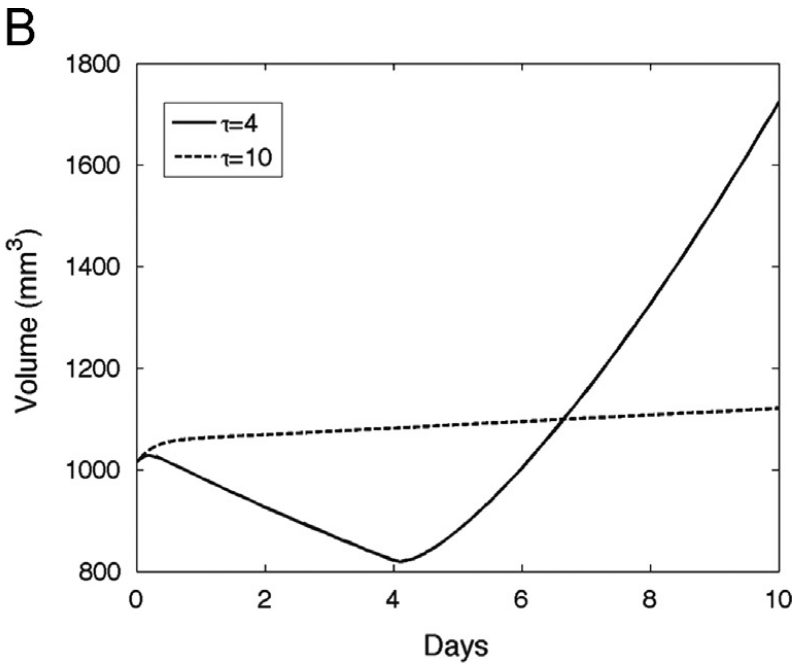
Concentrating VS diluting the dose

Simpler situation: constant administration then 0 **Ledzewicz & al., 10**

Same total AUC $= (C_{max}, A_{max})$
Variable = durations $= (t_C, t_A)$

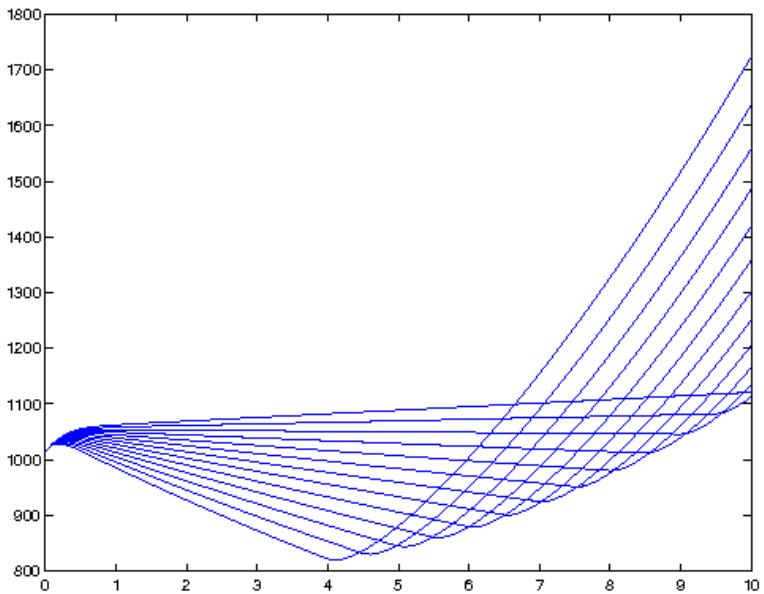


Drug administration

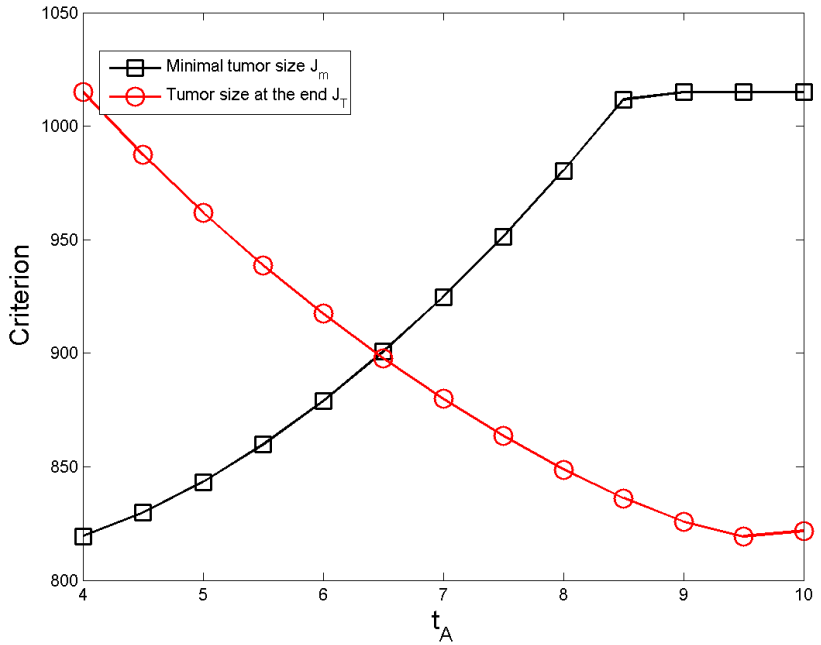


Primary tumor

AA monotherapy. Primary tumor



Growth time curves



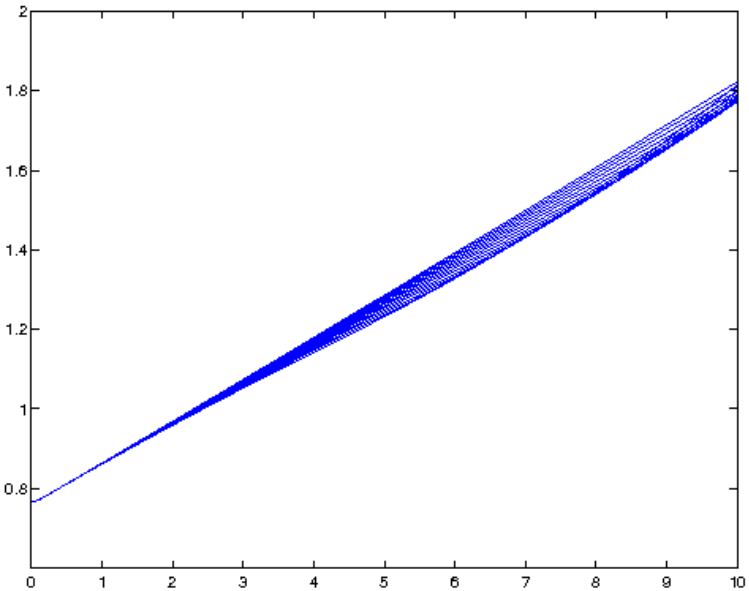
Criteria

- Better **short term** tumoral reduction J_m with **MTD** (Maximum Tolerated Dose, $t_A = 4$)

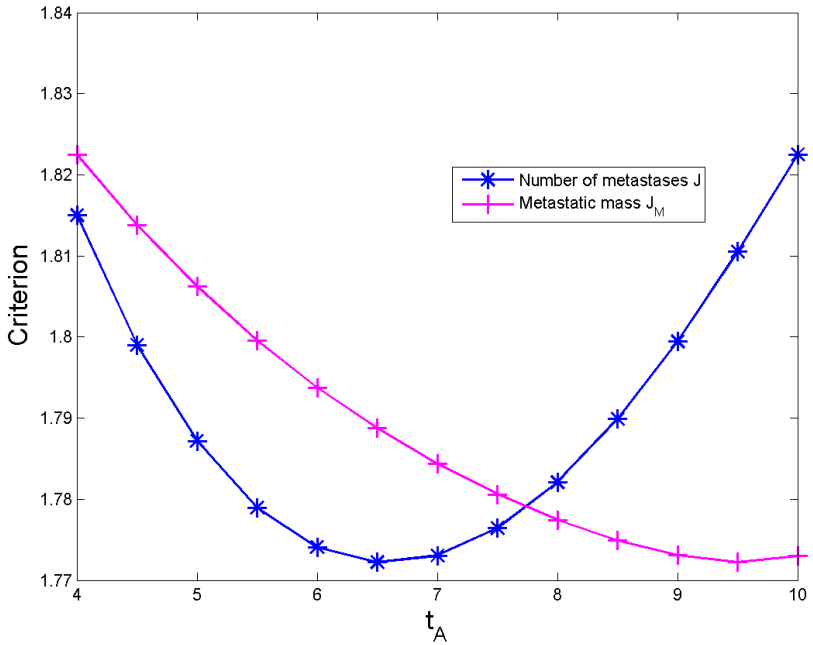
- Better **long term** tumoral reduction J_T with **metronomic** ($t_A = 4$)

(for these values of parameters and initial conditions)

AA monotherapy. Metastases



Time curves



Criteria

- **Nontrivial optimal scheduling** for the number of mets
- Metastatic mass J_M is qualitatively the same as tumor size J_T

Benzekry and Hahnfeldt, J Theor Biol, 2013

Quantification of the effect of scheduling optimization

Criterion	Min size J_m	End size J_T	Nb mets J	**Mass $\mathbf{J}_M$**
Min /Max reduction in %	-19/0	+10/+70	+132/+138	**+33/+154**

- The scheduling has a strong impact on the tumoral criteria and on the **metastatic mass**
- Impact on the number of metastases is much smaller

Benzekry and Hahnfeldt, J Theor Biol, 2013

Summary

- **Scheduling is important**
- Number of metastases and primary tumor criteria yield **different optimal strategies** : strong dose/short time (Maximum Tolerate Dose), small dose/large time (metronomic), nontrivial minimum value
- Optimal schedule can **differ between primary tumor and metastases** (parallels experimental findings: **Ebos et al. EMBO 2014, Cancer Cell, 2009**).

Thank you for listening!

This work was done in collaboration with

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- **Florence Hubert** McF
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