Mechanistic modeling of metastasis: cancer at the organism scale

S. Benzekry
Inria Bordeaux Sud-Ouest

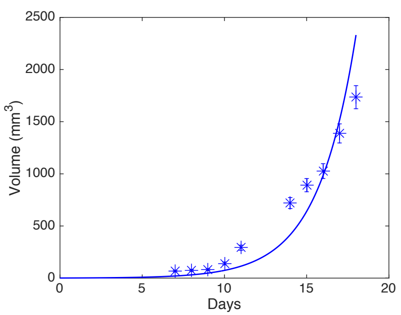
ISoP workshop
July 11th, 2019

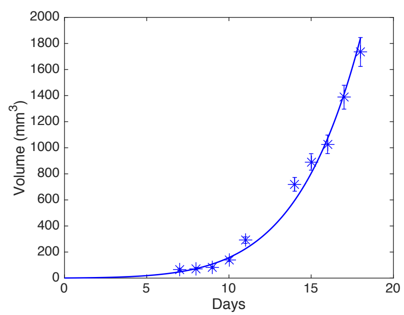
Modeling in ONCology

Can mathematical models be of help in oncology?

Understand (biology)

- **Theoretical** framework for description of the process
- Test different **hypotheses** and reject non-valid ones





Exponential

$$\frac{dV}{dt} = aV$$

Power law

$$\frac{dV}{dt} = aV^{\gamma}$$

Benzekry et al., PloS Comp Biol, 2014

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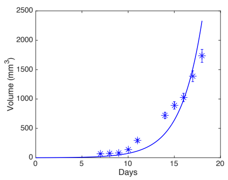
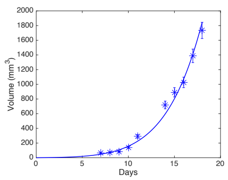


Exponential

$$\frac{dV}{dt} = aV$$

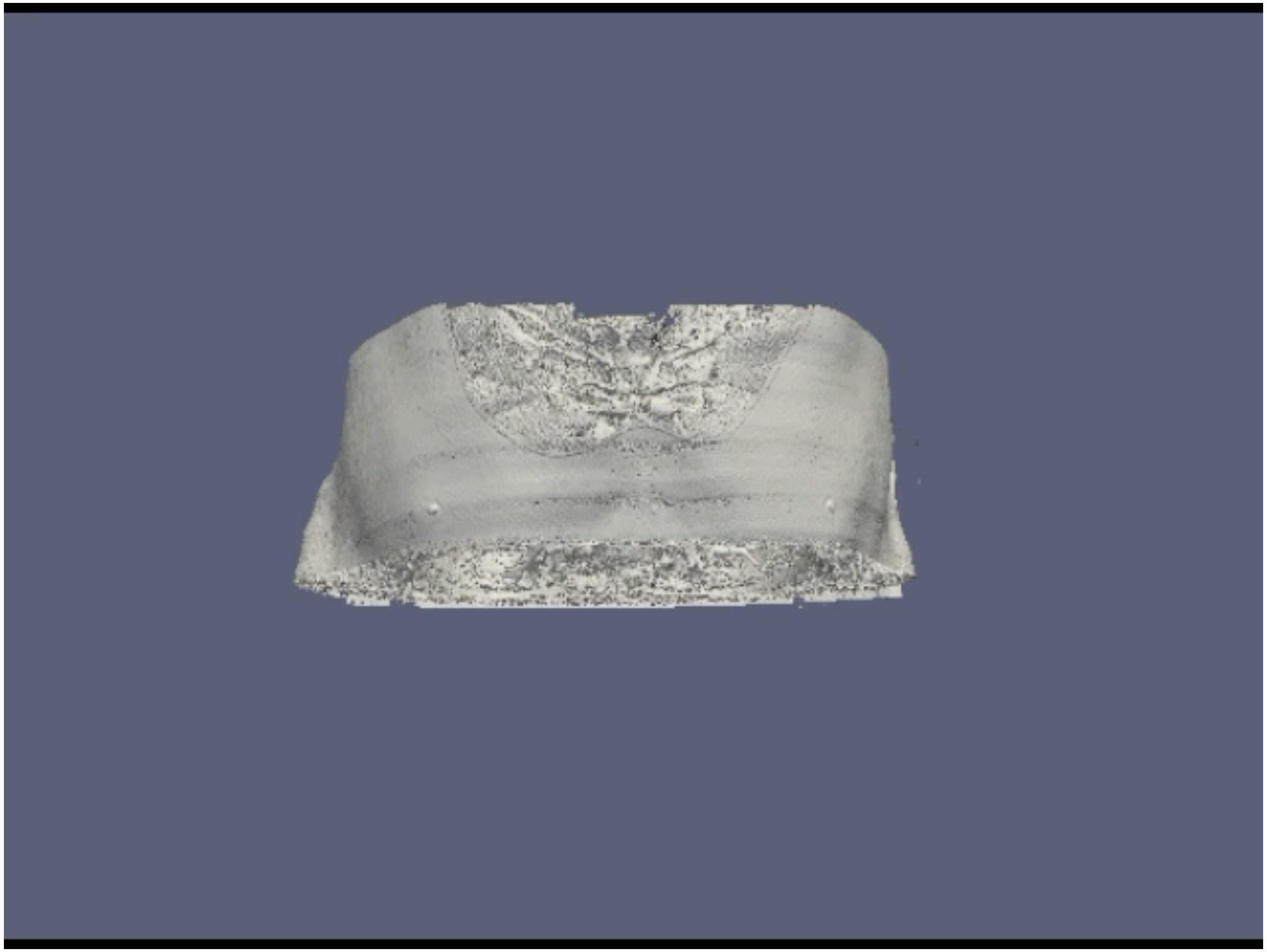


Power law

$$\frac{dV}{dt} = aV^{\gamma}$$

Predict and control (clinic)

- Predict tumor growth



Jouganous, Colin, Saut et al., 2014

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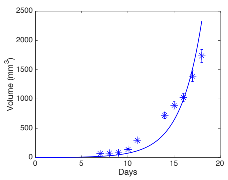

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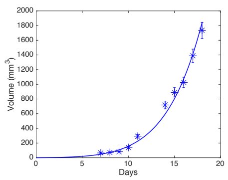
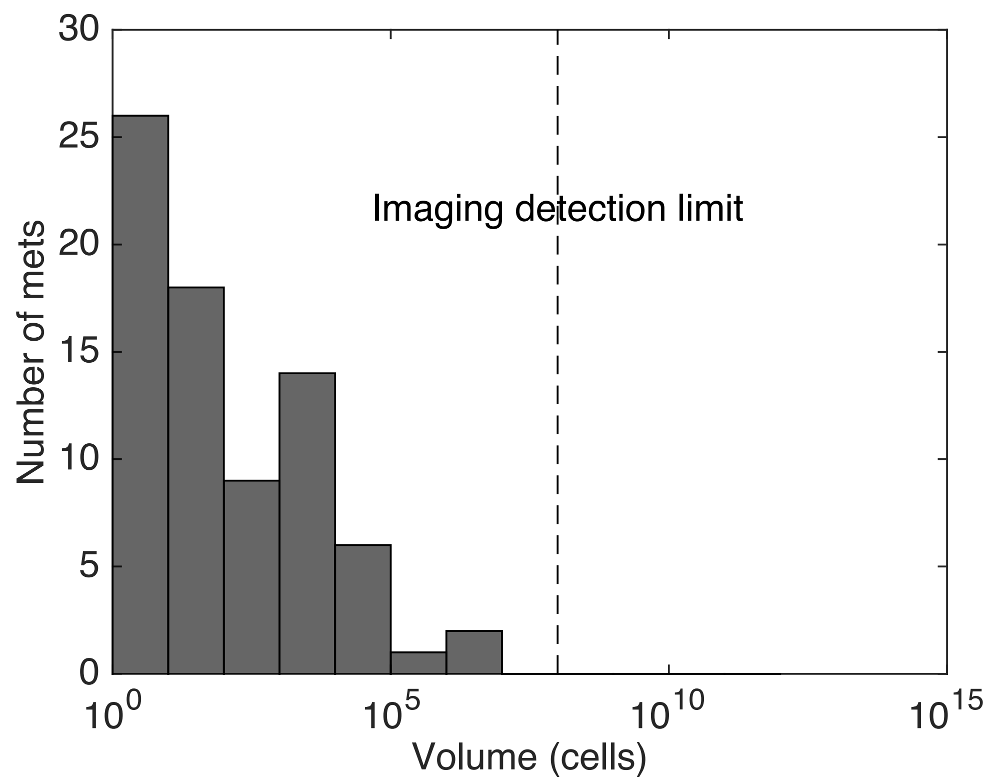


Power law

$$\frac{dV}{dt} = aV^{\gamma}$$

Predict and control (clinic)

- Predict **metastasis**
- **Personalize** (adjuvant) therapy



Benzekry et al., Cancer Res, 2016

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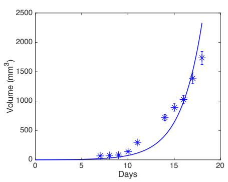
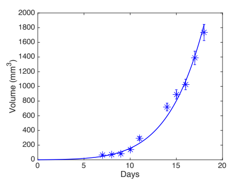
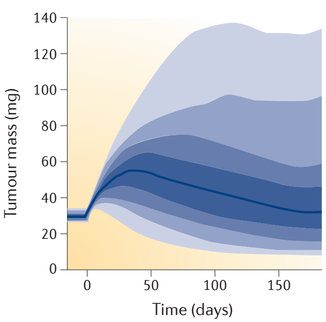


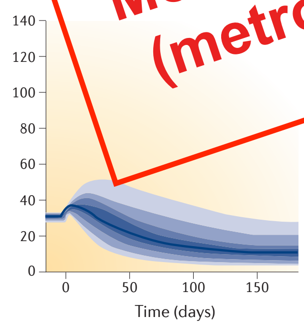
Exponential



Power law

Efficacy

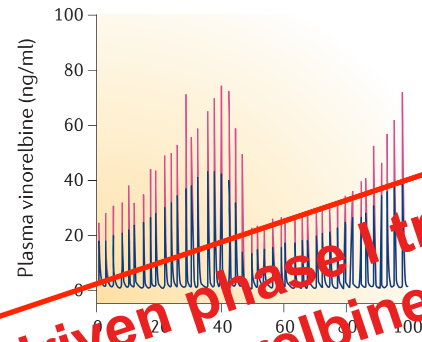


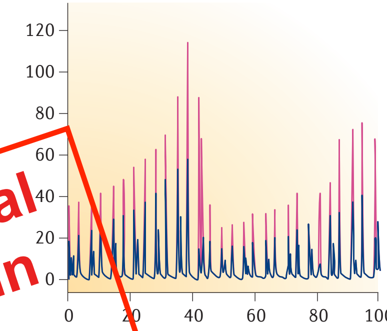


Predict and control (clinic)

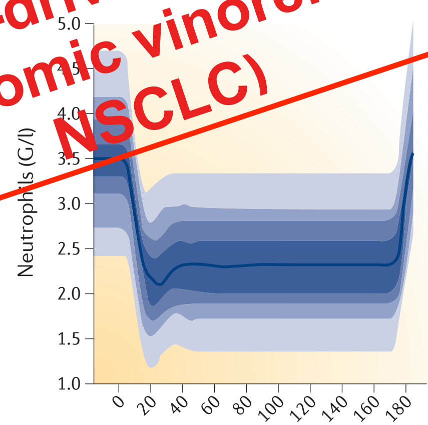
- Rational and individual design of **drug regimen**

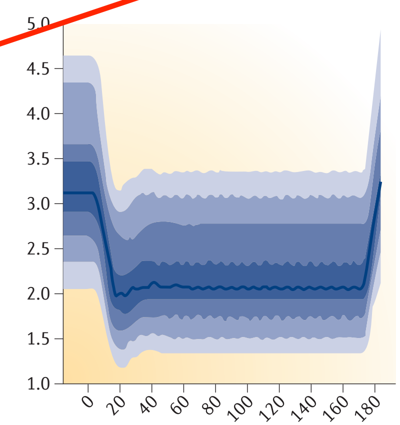
Empirical dosing	Model-based dosing
D1-D3-D5 50 mg	D1-D2-D4 60-30-60 mg





PK





Toxicity

Modeling-driven phase I trial (metronomic vinorelbine in NSCLC)

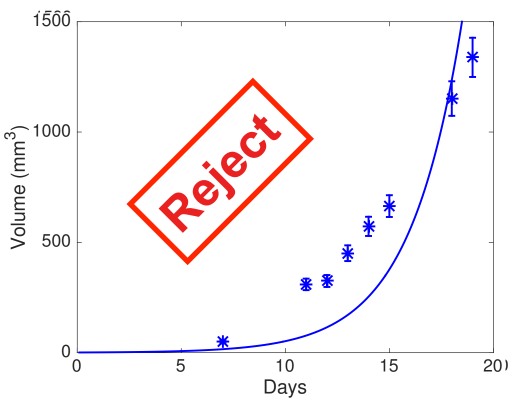
Barbolosi et al., Nat Rev Clin Onco., 2015

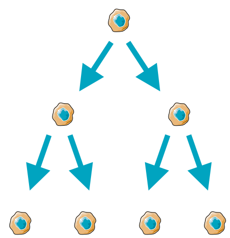
Tumor growth

Tumor growth

What are **minimal** biological processes able to recover the **kinetics** of (experimental) tumor growth?

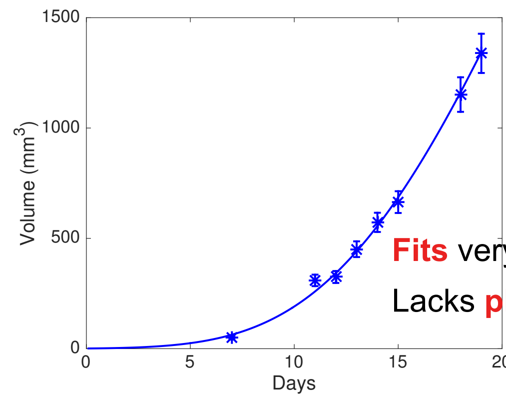
Exponential





$$\frac{dV}{dt} = aV$$

Gompertz

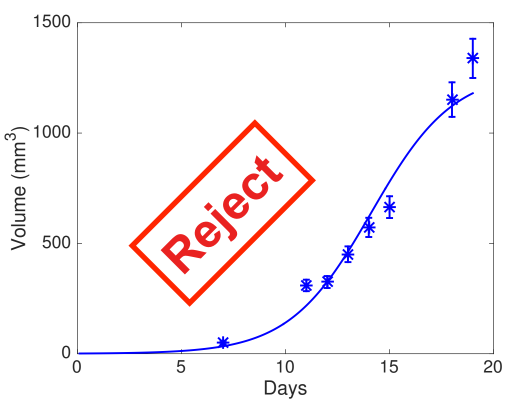


$$\frac{dV}{dt} = \alpha e^{-\beta t} V$$

Fits very well

Lacks **physiological** interpretation

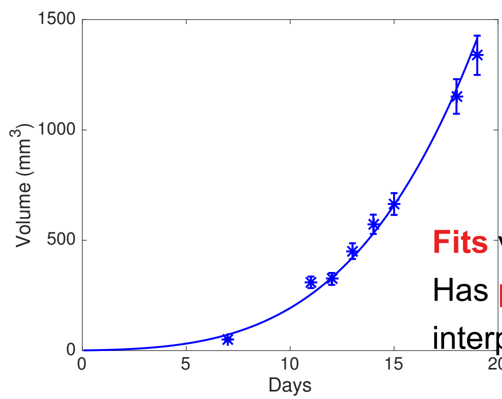
Logistic



Competition

$$\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right)$$

Power law



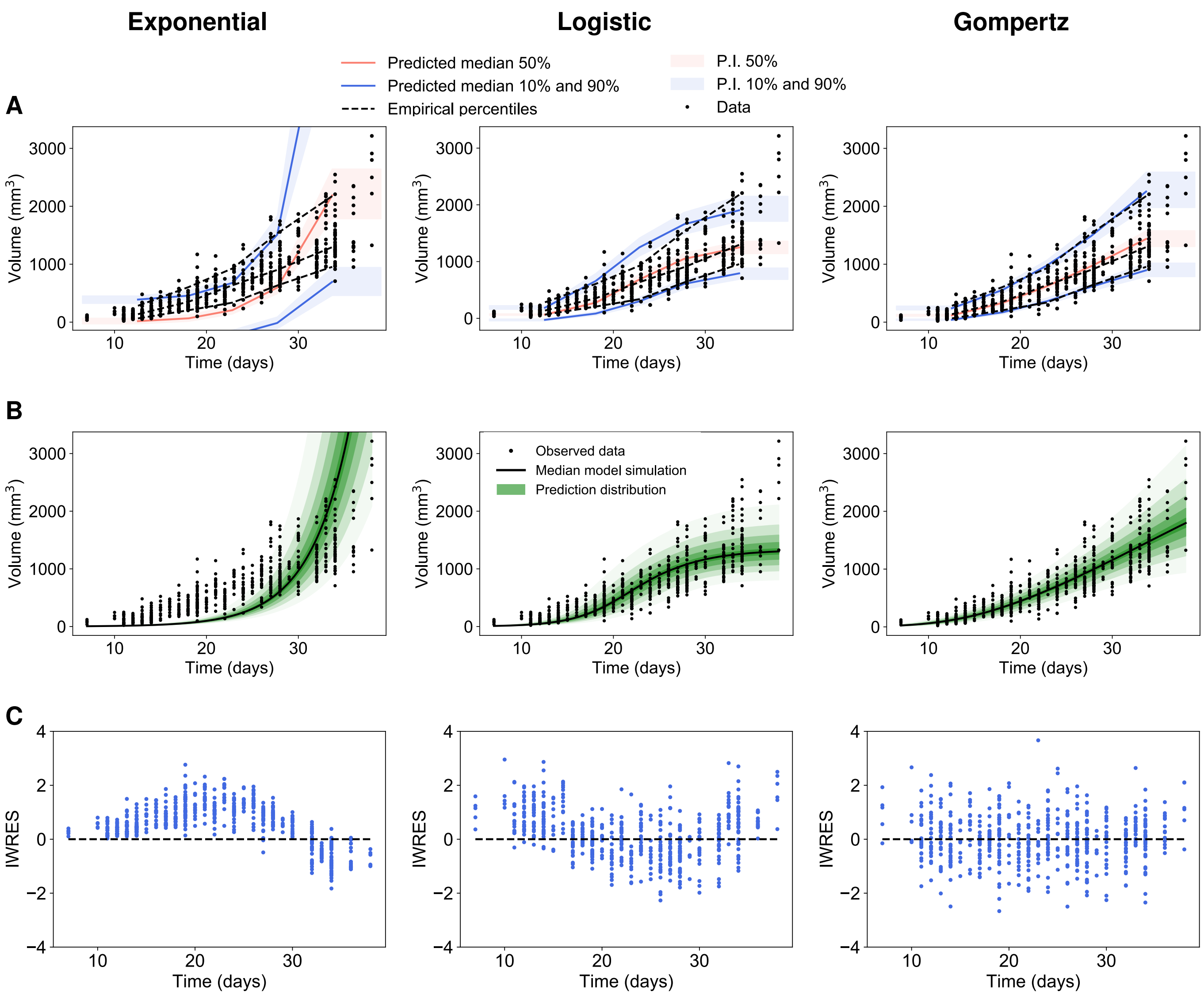
$$\frac{dV}{dt} = \alpha V^{\gamma}$$

Fits very well

Has **physiological** interpretation

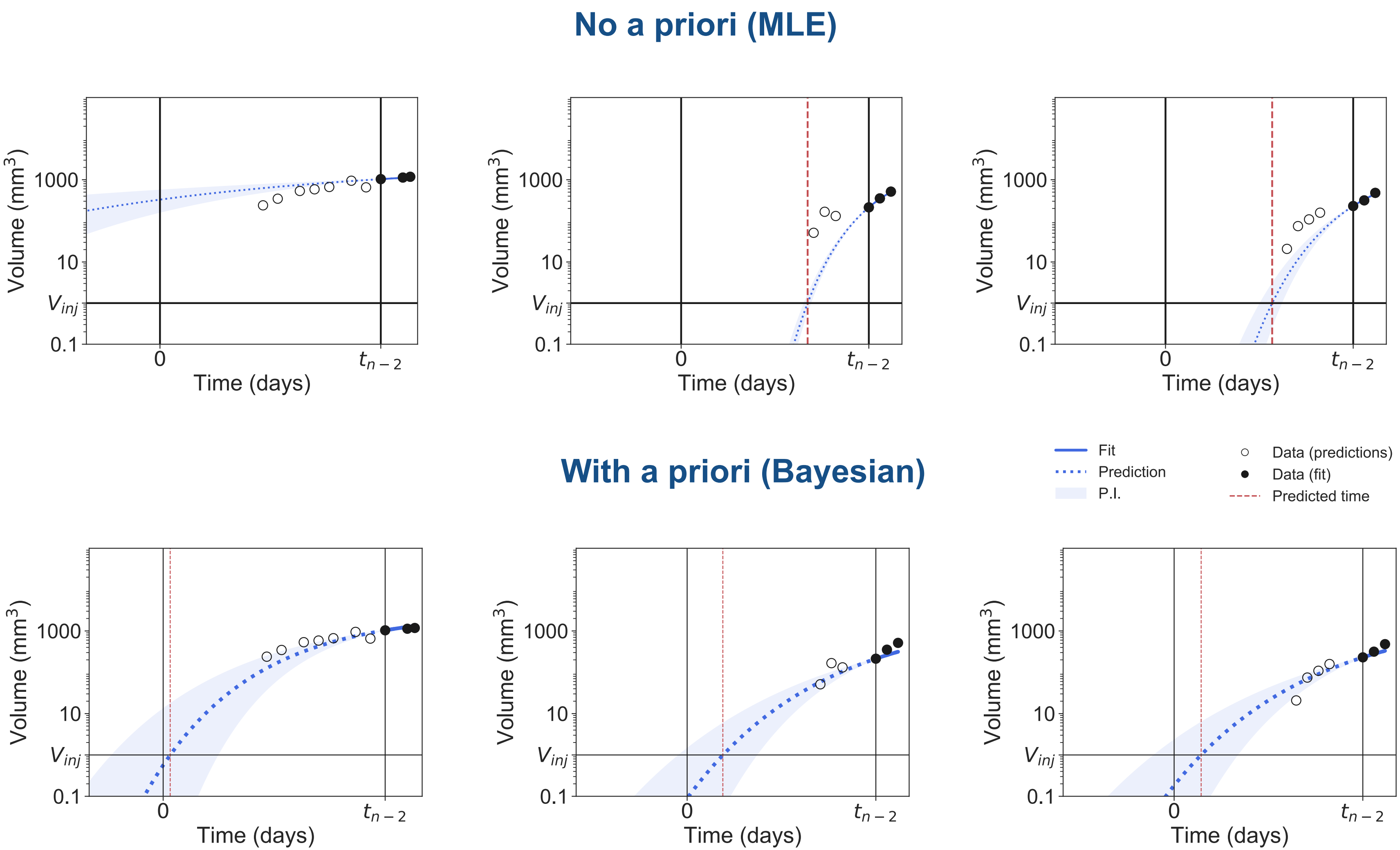
Benzekry et al., PloS Comp Biol, 2014

Population fit of tumor growth models



Vaghi et al. (Benzekry), bioRxiv, 2019

Bayesian estimation for prediction of tumor age

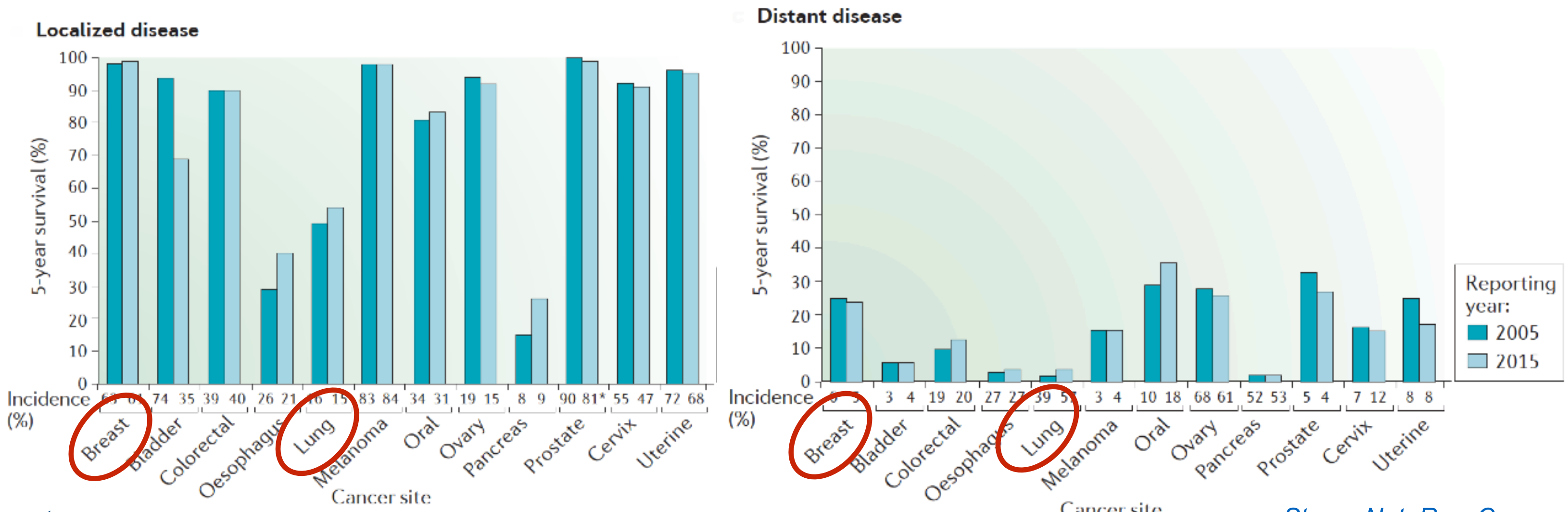


Vaghi et al. (Benzekry), bioRxiv, 2019

Metastasis

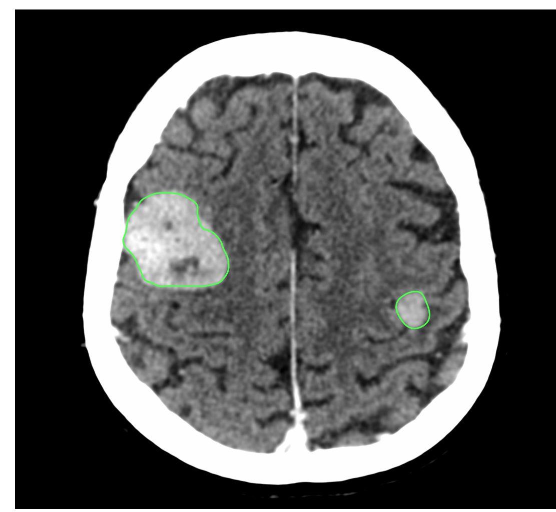
Metastasis (μετά = beyond, στάσιζ = place)

- Metastases are the **main cause of death** (>90%) from solid cancers *Lambert and Weinberg, Cell, 2017*



Steeg, Nat. Rev. Cancer, 2016

- **Breast**
  - 94% of cases are local or regional at diagnosis but 30% will relapse
    Pollard, N Eng J Med, 2016
  - Estimate the amount of **residual distant disease** at diagnosis in order to **personalize** the adjuvant (chemo)-therapy
  - Avoid heavy **toxicities** for low risk patients
- **Lung**
  - 57% of cases are metastatic
  - Decide whether to use **whole brain radiation therapy** or just (stereotactic) surgery
  - Avoid cognitive impairment of the patient

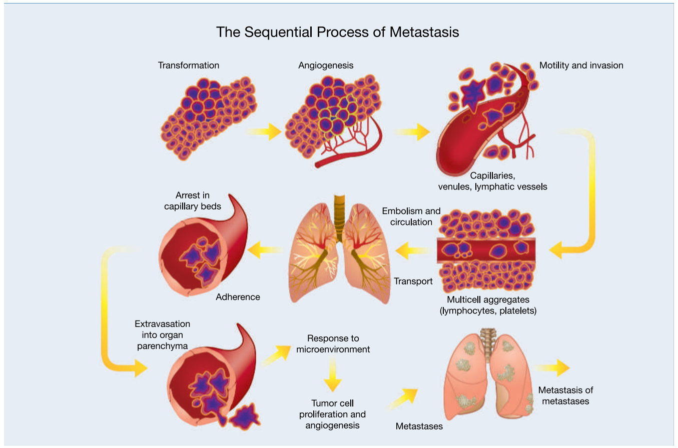


Institut Bergonié, Bordeaux

Some biological questions of interest to mathematical modeling

- **Minimal** model of metastatic dissemination and colonization able to reproduce the **systemic dynamics** of a solid cancer disease

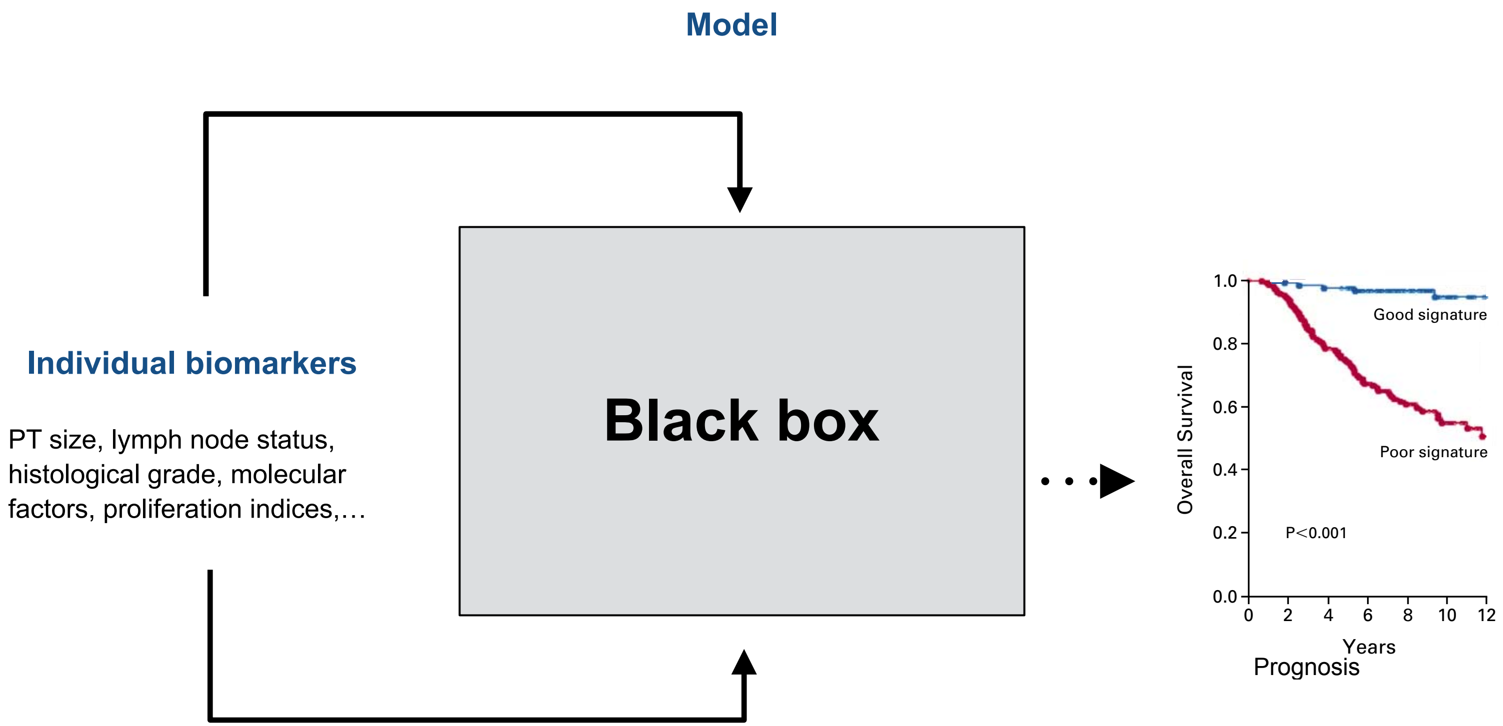
- Investigate the relevance of several processes:
  - (early VS late event *Klein, Nat Rev Cancer, 2009*)
  - (metastases of metastases *Gundem et al., Nature, 2015*)
  - (dormancy *Chambers and Groom, Nat Rev Cancer, 2002*)
  - **tumor-tumor interactions**
  - (cancer-immune interactions)
  - **differential effect of therapy** *Ebos et al. (Kerbel), Cancer Cell, 2009*
  - ((pre-)metastatic niche *Peinado et al. (Lyden), Nature, 2005*)
  - systemic inhibition of angiogenesis *O'Reilly et al. (Folkman), Cell, 1990s*
  - (self-seeding *Norton, Nat Med, 2001*)



Talmadge and Fidler, Cancer Res, 2010

Metastasis: a forgotten major player in modeling

- The majority of mathematical modeling efforts in oncology are focused on (primary) **tumor growth**
- Existing models are based on a statistical, **biologically agnostic**, prediction of survival



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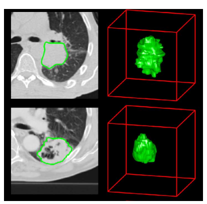
Clinical data

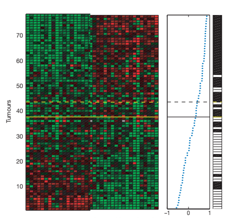
PT size, lymph node status, histological grade, molecular factors, proliferation indices,…

Imaging data (Radiomics)



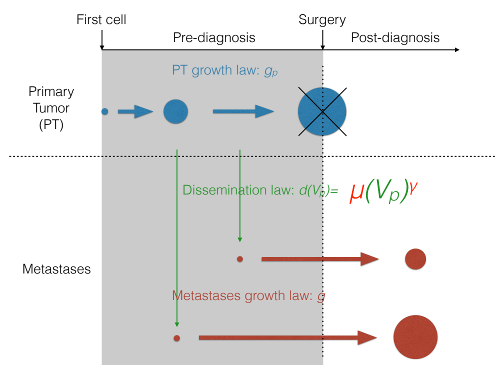
Aerts et al., Nat Commun, 2014

Molecular data (-omics)



van't Veer et al., Nature, 2002

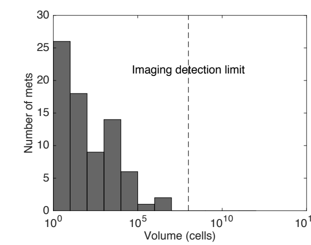
Biologically-based model



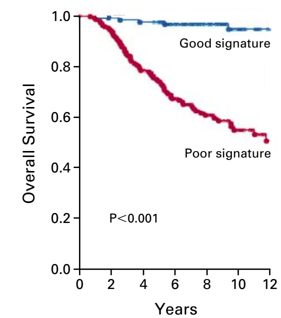
$$\frac{dV_p}{dt} = (\alpha_p - \beta_p \ln(V_p))\, V_p$$

$$\begin{cases} \partial_t \rho(t,v) + \partial_v \left((\alpha - \beta \ln(v))\, v \rho(t,v) \right) = 0 \\ g(V_0)\rho(t,V_0) = \mu V_p(t)^\gamma \\ \rho(0,v) = 0 \end{cases}$$

Prediction

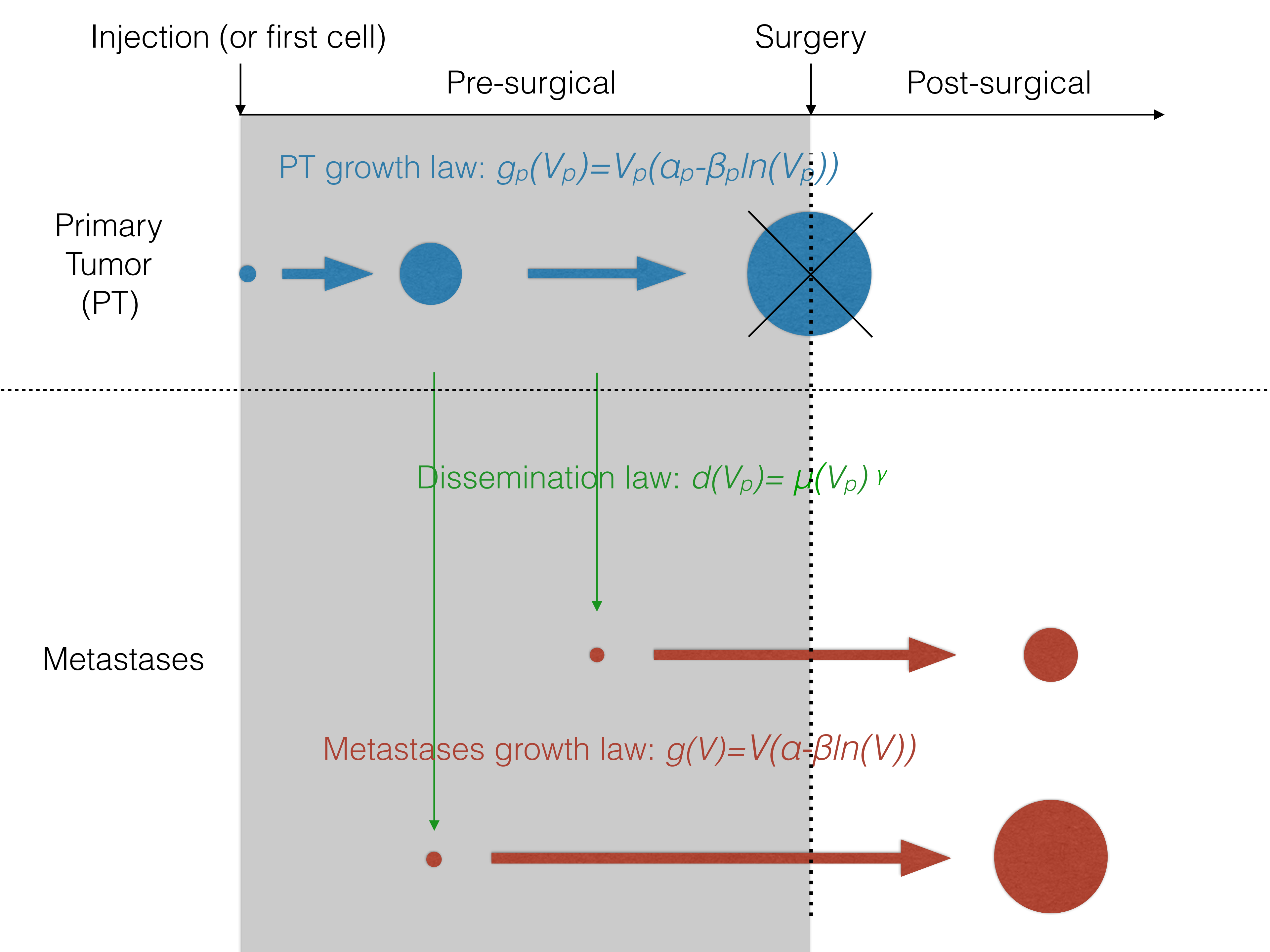


Diagnosis



Prognosis

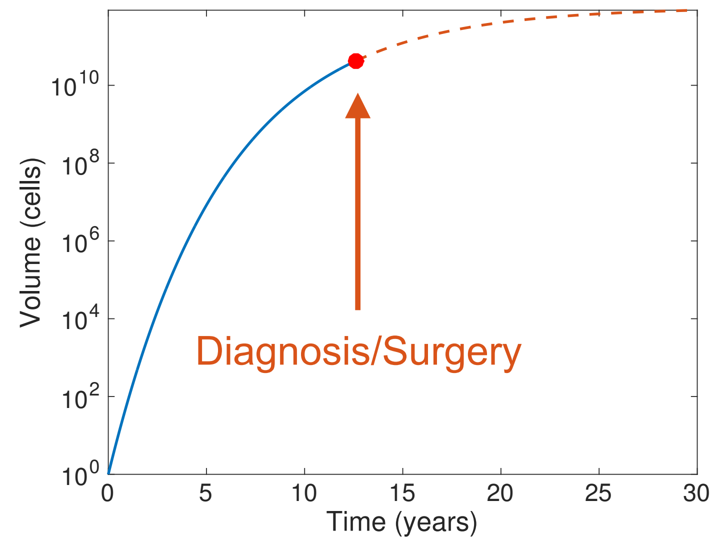
Simulation and individualization of therapy


Injection (or first cell)
Surgery
Pre-surgical
Post-surgical
PT growth law: $g_p(V_p)=V_p(\alpha_p-\beta_p ln(V_p))$
Primary Tumor (PT)
Dissemination law: $d(V_p)= \mu(V_p)^{\gamma}$
Metastases
Metastases growth law: $g(V)=V(\alpha-\beta ln(V))$

Mathematical formalism

- Primary tumor V_p grows with rate g_p [size.day^{-1}]

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



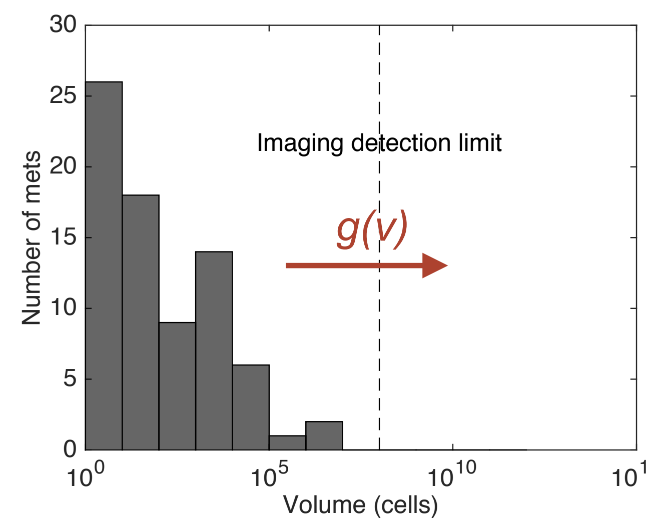
- **Population** of metastases represented by a **density** ***ρ(t,v)*** [size^{-1}] structured in **size *v***

- Secondary tumors grow in size with rate *g(v)*

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

- They are spread by the PT with **dissemination rate** *d(V$_p$(t))* [day^{-1}]

$$g(V_0)\rho(t,V_0) = d(V_p(t)) \left(+ \int_{V_0}^{+\infty} d(v)\rho(t,v)dv \right)$$



→ fast computation of the metastatic burden

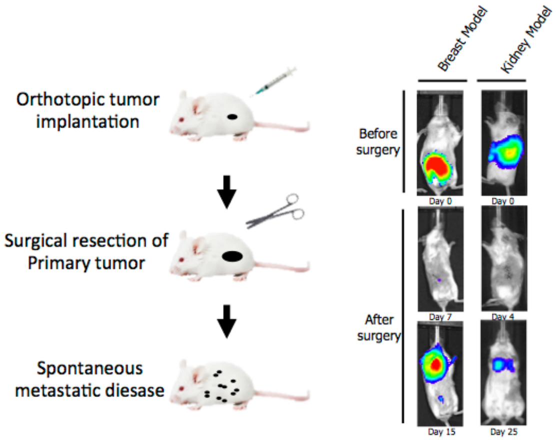
$$M(t) = \int_{V_0}^{+\infty} v\rho(t,v)dv = \int_0^t d\left(V_p(t-s)\right) V(s)ds$$

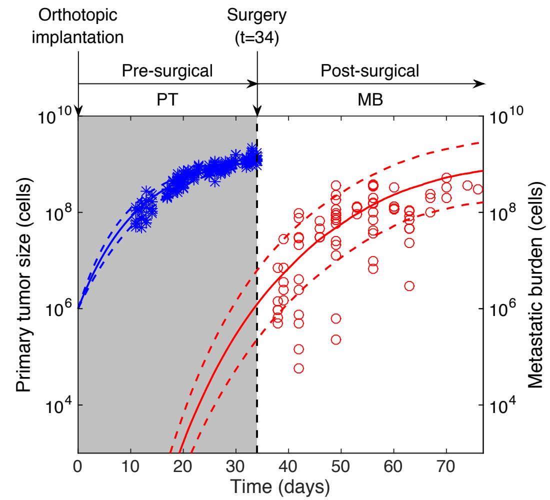
Iwata, Kawasaki, Shigesada, J Theor Biol, 2000

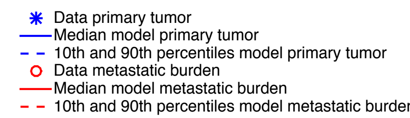
Validation on animal data

Ebos lab

Roswell Park Cancer Institute

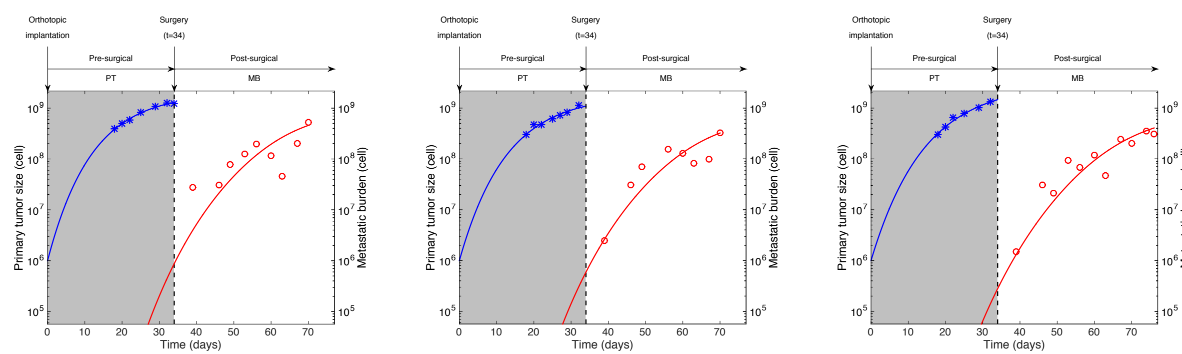






Nonlinear **mixed-effects** statistical model for inter-animal variability

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



$\Longrightarrow$ **same growth** for PT and mets: $\alpha_p = \alpha$, $\beta_p = \beta$

Benzekry et al. (Ebos), Cancer Res, 2016

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

Cancer Cell
Report

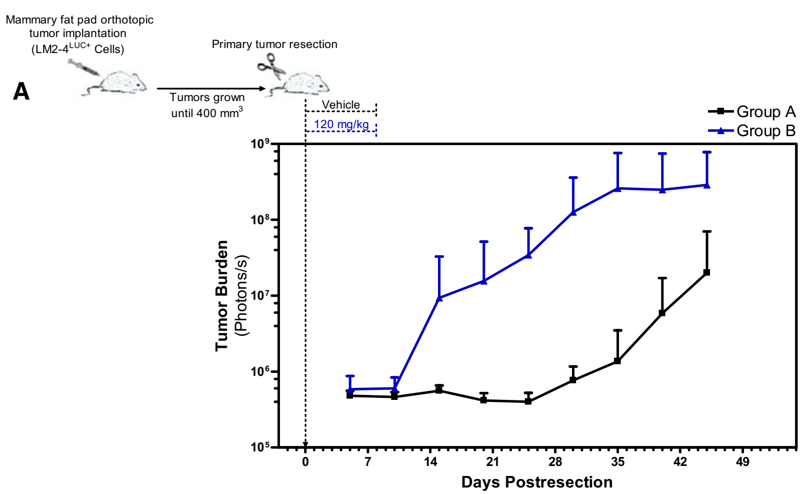
Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

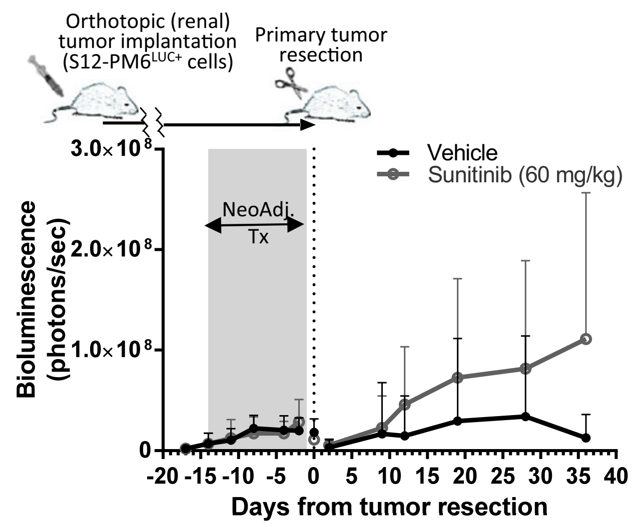
John M.L. Ebos,[1,2] Christina R. Lee,[1] William Cruz-Munoz,[1] Georg A. Bjarnason,[3] James G. Christensen,[4] and Robert S. Kerbel[1,2,*]

Published online: October 31, 2014
Research Article
TRANSPARENT PROCESS
OPEN ACCESS
EMBO Molecular Medicine

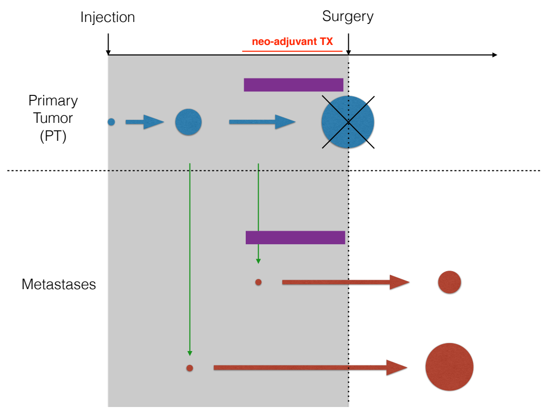
Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy

John M L Ebos[1,*], Michalis Mastri[1], Christina R Lee[2], Amanda Tracz[1], John M Hudson[2], Kristopher Attwood[3], William R Cruz-Munoz[2], Christopher Jedeszko[2], Peter Burns[2,4] & Robert S Kerbel[2,4]





Testing hypotheses for neo-adjuvant TKI effect



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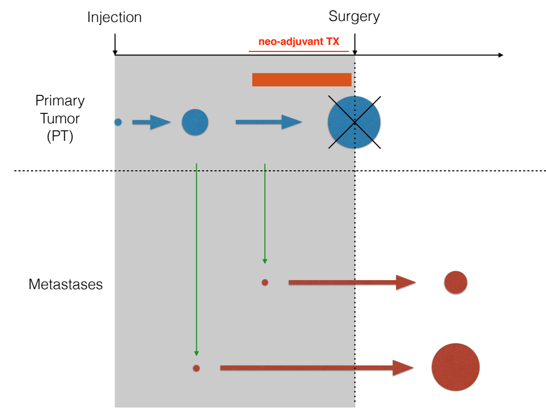

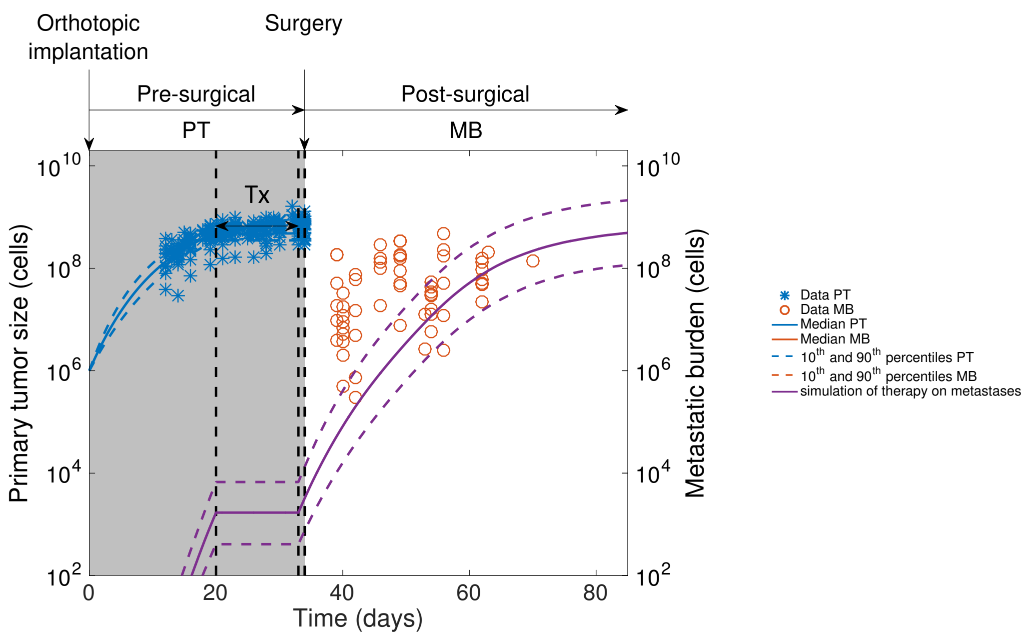

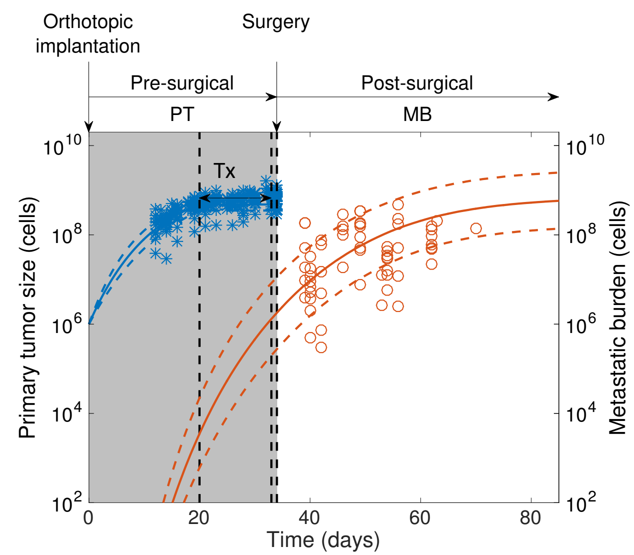

Clinical application - Brain Metastasis from NSCLC