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Mechanistic modeling of metastasis: cancer at the organism scale

Sébastien Benzekry

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Mechanistic modeling of metastasis: cancer at the organism scale

S. Benzekry
Inria Bordeaux Sud-Ouest

ISoP workshop
July 11th, 2019

Inria

M**NC**

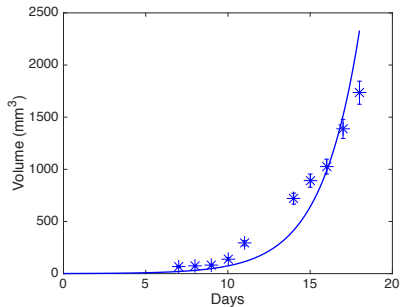
Modeling in **ONC**ology

Can mathematical models be of help in oncology?



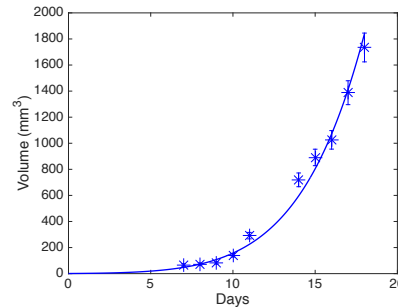
Understand (biology)

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



Exponential

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



Power law

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

Can mathematical models be of help in oncology?

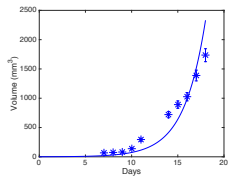


Predict and control (clinic)

- Predict tumor growth

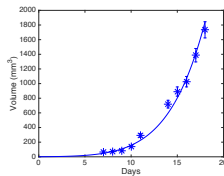
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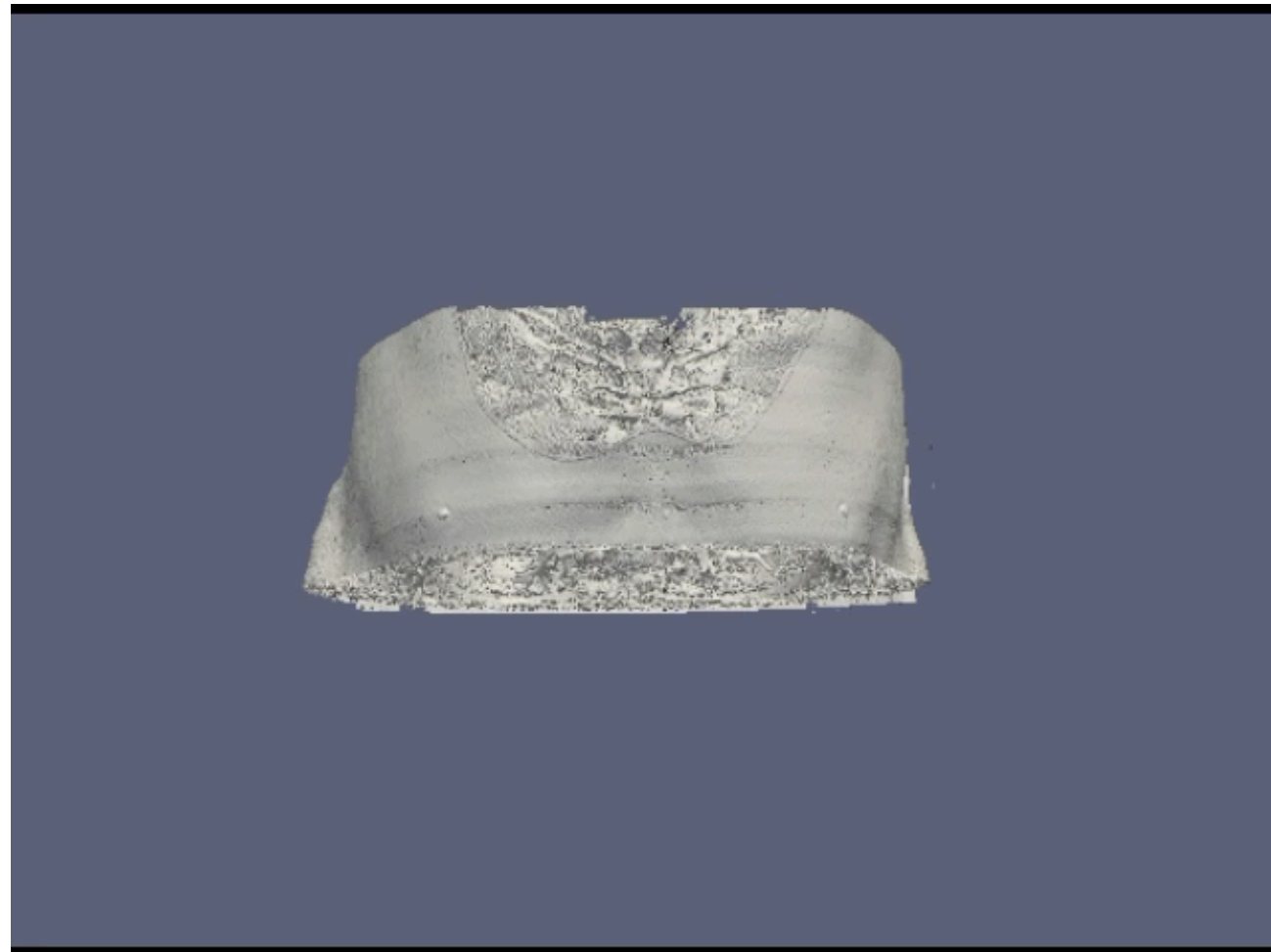
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Power law

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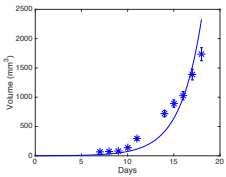
Can mathematical models be of help in oncology?



Predict and control (clinic)

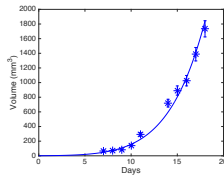
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Exponential

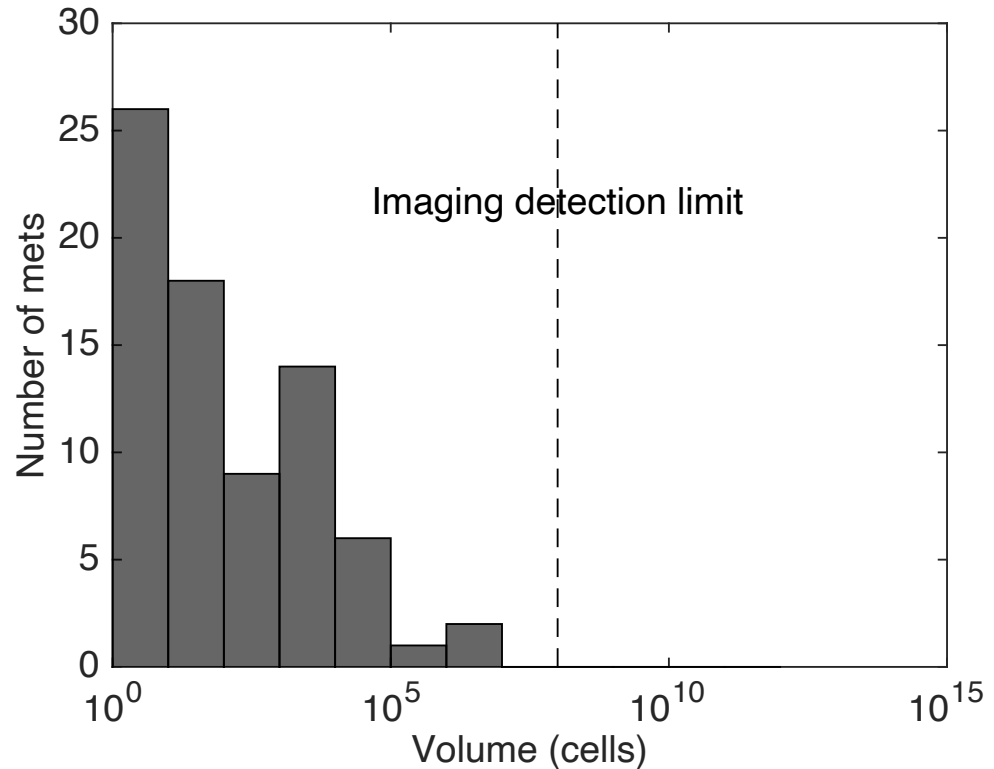
$$\frac{dV}{dt} = aV$$



Power law

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

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



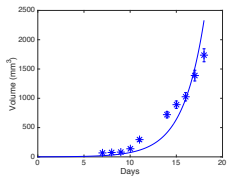
Can mathematical models be of help in oncology?



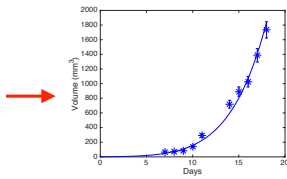
Predict and control (clinic)

Understand (biology)

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Exponential

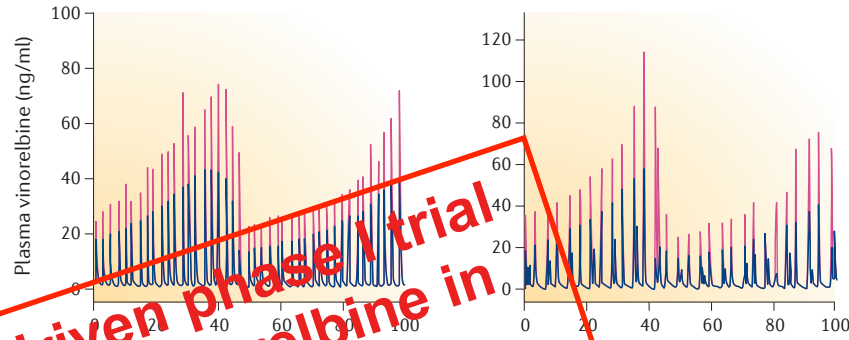


Power law

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

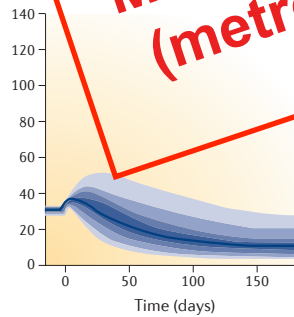
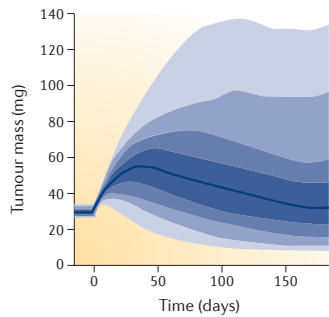
Empirical dosing
D1-D3-D5 50 mg

Model-based dosing
D1-D2-D4 60-30-60 mg

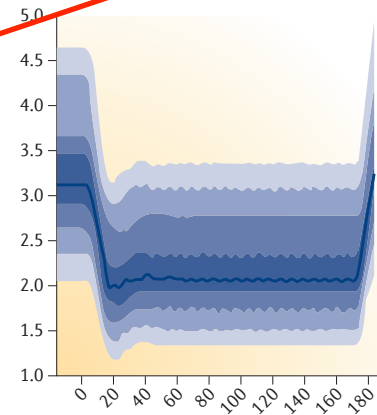
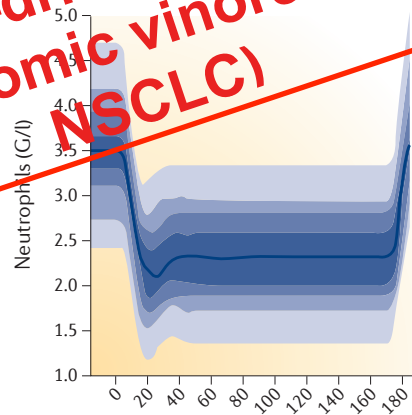


PK

Efficacy



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



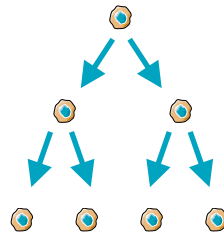
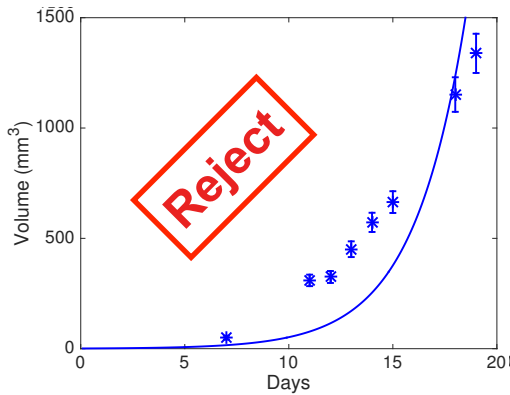
Toxicity

Tumor growth

Tumor growth

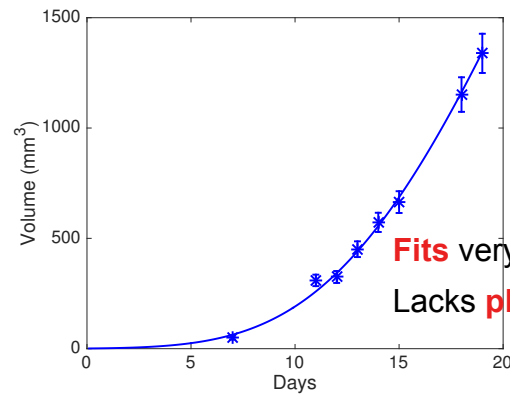
What are **minimal** biological processes able to recover the **kinetics** of (experimental) tumor growth?

Exponential



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

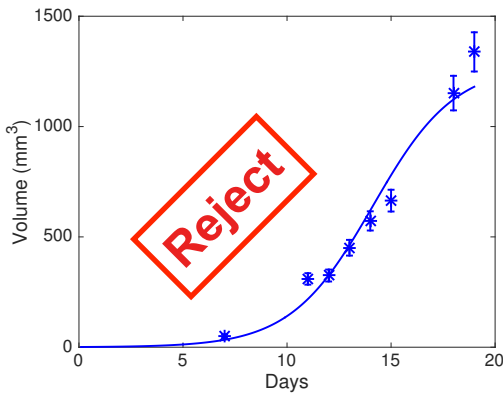
Gompertz



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

Fits very well
Lacks **physiological** interpretation

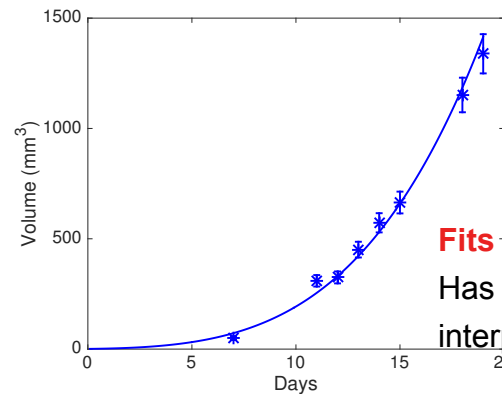
Logistic



Competition

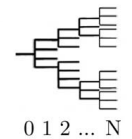
$$\frac{dV}{dt} = aV \left(1 - \frac{V}{K}\right)$$

Power law

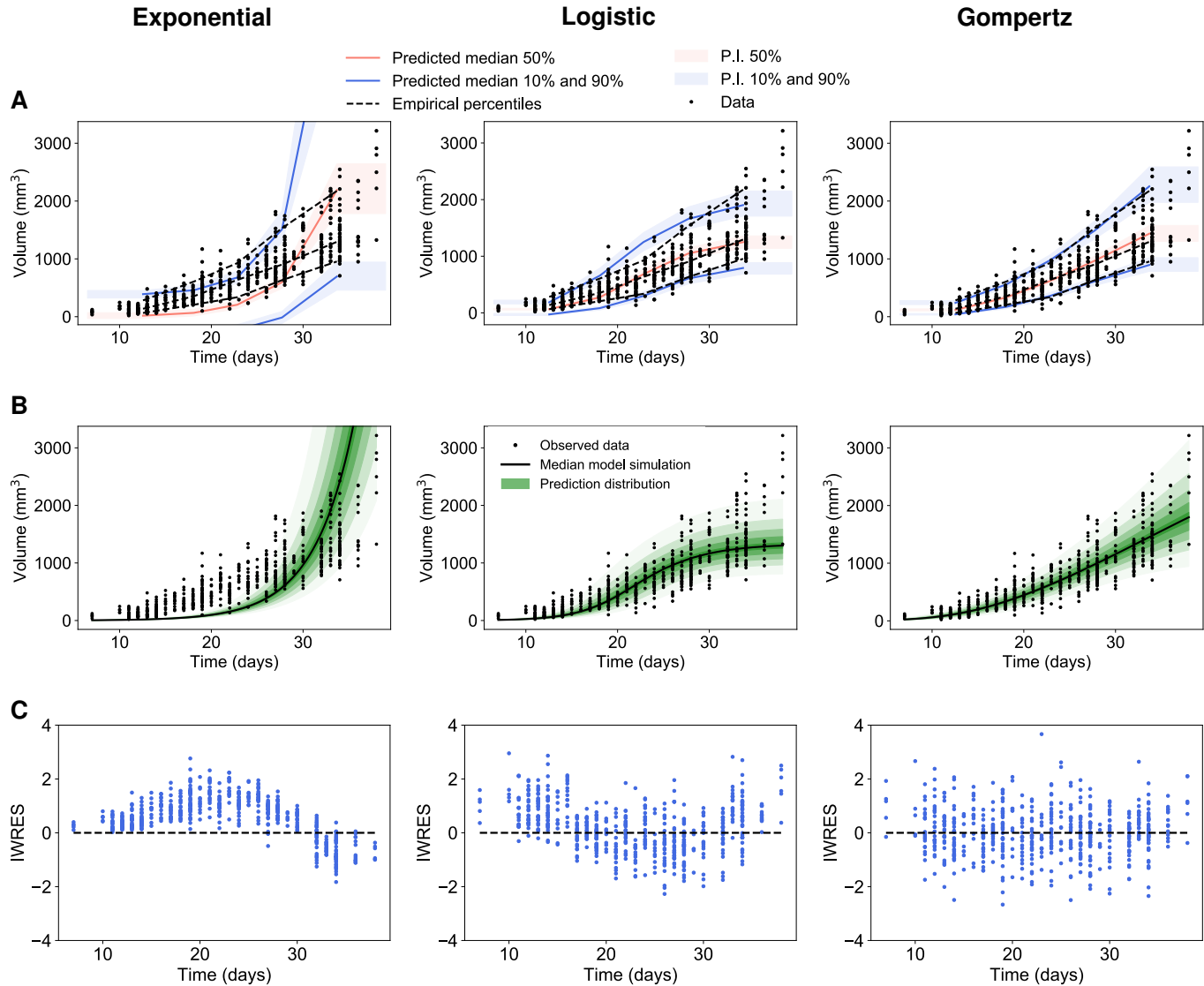


$$\frac{dV}{dt} = \alpha V^\gamma$$

Fits very well
Has **physiological** interpretation

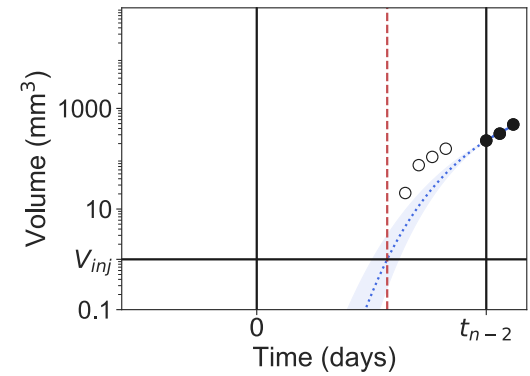
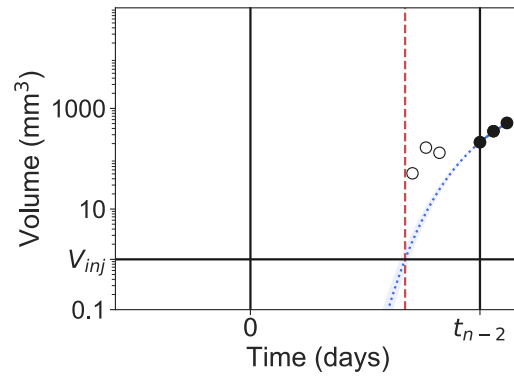
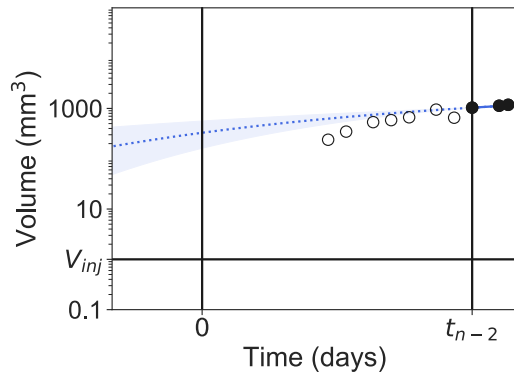


Population fit of tumor growth models

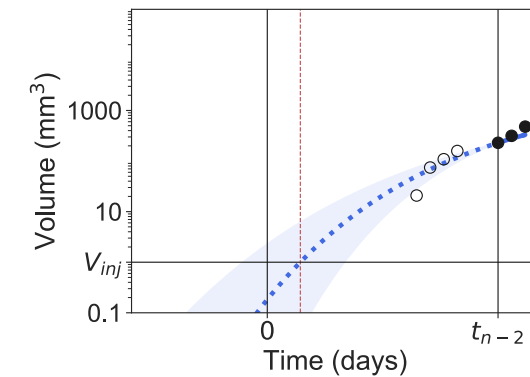
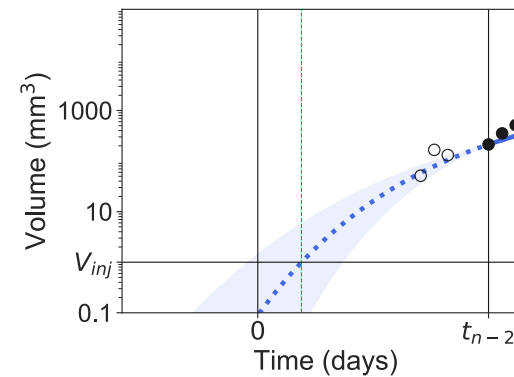
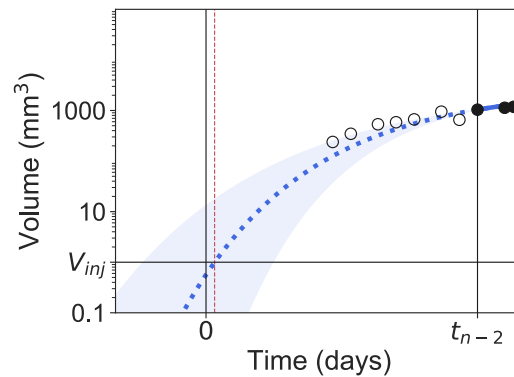


Bayesian estimation for prediction of tumor age

No a priori (MLE)



With a priori (Bayesian)

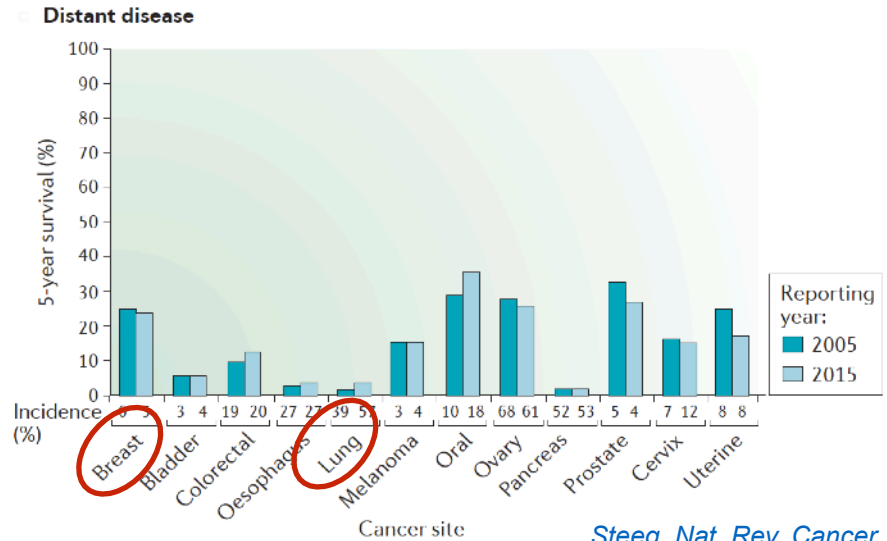
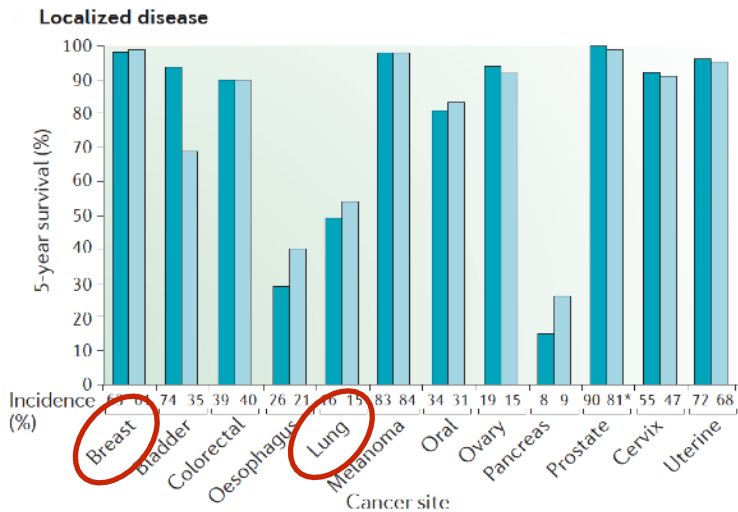


- Fit
- ⋯ Prediction
- P.I.
- Data (predictions)
- Data (fit)
- - - Predicted time

Metastasis

Metastasis (μετά = beyond, στάσιζ = place)

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



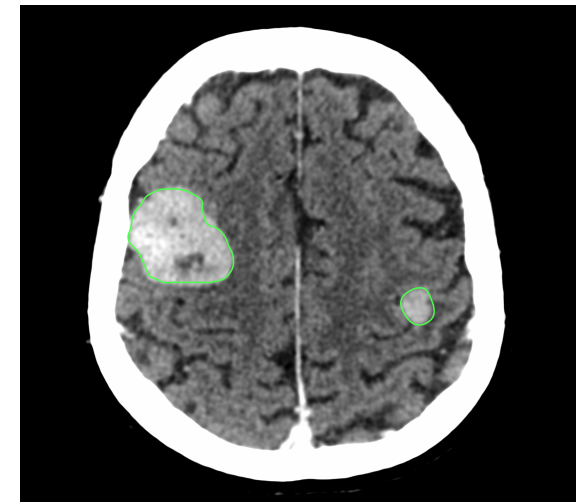
Breast

- 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

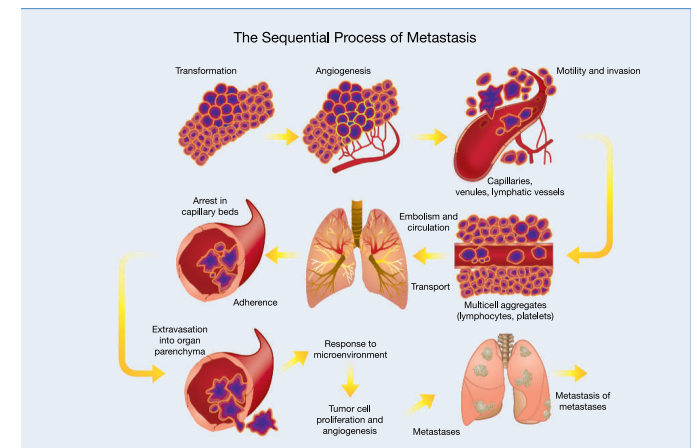
Steeg, Nat. Rev. Cancer, 2016



Institut Bergonié, Bordeaux

Some biological questions of interest to mathematical modeling

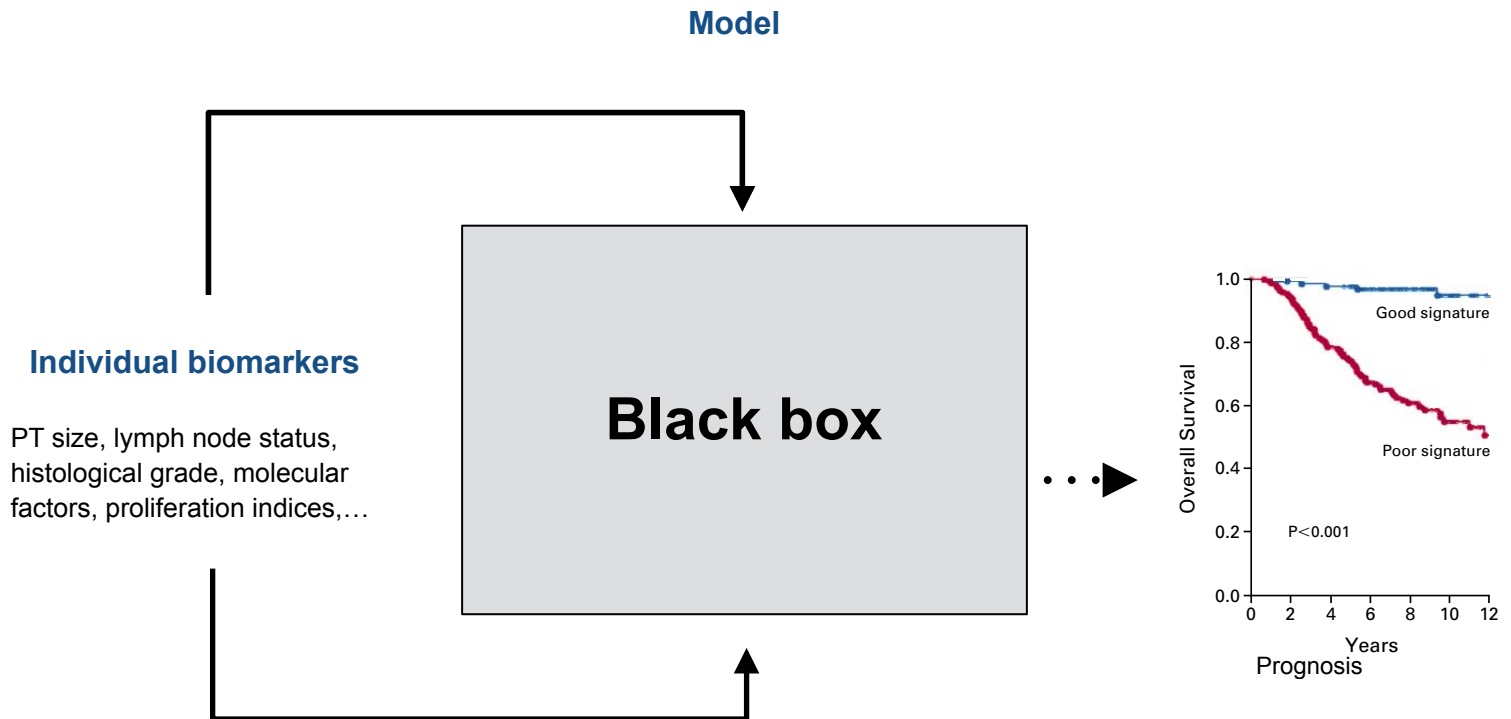
- **Minimal** model of metastatic dissemination and colonization able to reproduce the **systemic dynamics** of a solid cancer disease
- Investigate the relevance of several processes:
 - (early VS late event [Klein, Nat Rev Cancer, 2009](#))
 - (metastases of metastases [Gudem et al., Nature, 2015](#))
 - (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



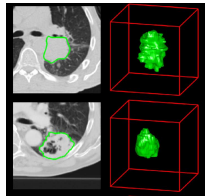
Metastasis: a forgotten major player in modeling

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Clinical data

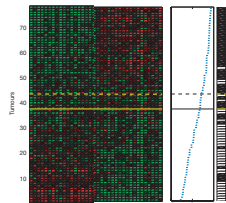
PT size, lymph node status, histological grade, molecular factors, proliferation indices,....

Imaging data (Radiomics)



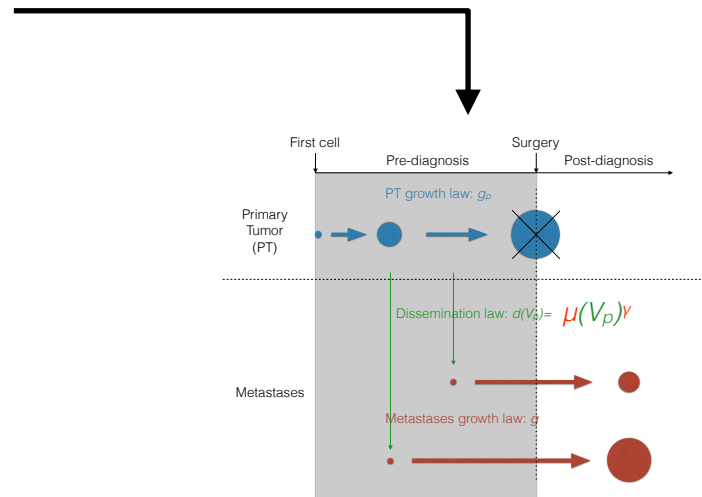
Aerts et al., Nat Commun, 2014

Molecular data (-omics)



van't Veer et al., Nature, 2002

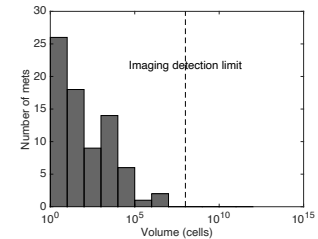
Biologically-based model



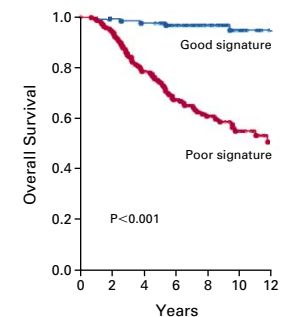
$$\frac{dV_p}{dt} = (\alpha_p - \beta_p \ln(V_p)) V_p$$

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

Prediction



Diagnosis



Prognosis

Simulation and individualization of therapy

Injection (or first cell)

Surgery

Pre-surgical

Post-surgical

PT growth law: $g_p(V_p) = V_p(a_p - \beta_p \ln(V_p))$

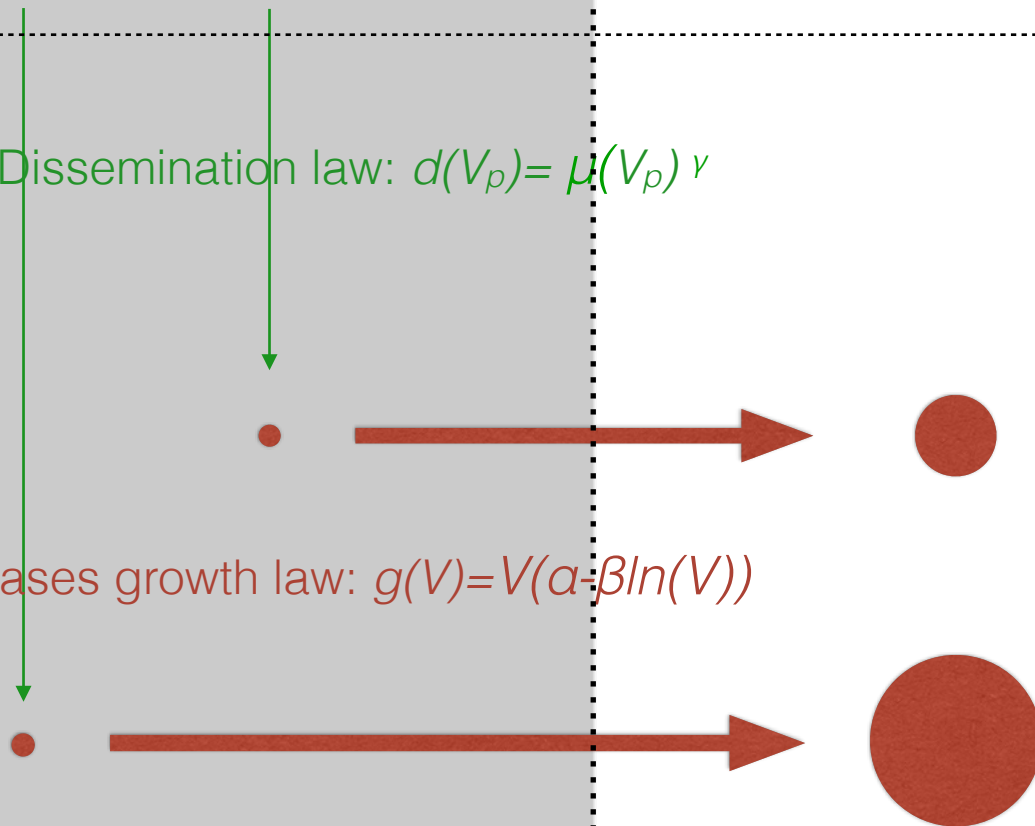
Primary
Tumor
(PT)



Dissemination law: $d(V_p) = \mu(V_p)^\nu$

Metastases

Metastases growth law: $g(V) = V(a - \beta \ln(V))$



Mathematical formalism

- Primary tumor V_p grows with rate g_p [size.day⁻¹]

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

- Population** of metastases represented by a **density** $\rho(t, v)$ [size⁻¹] structured in **size** v

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

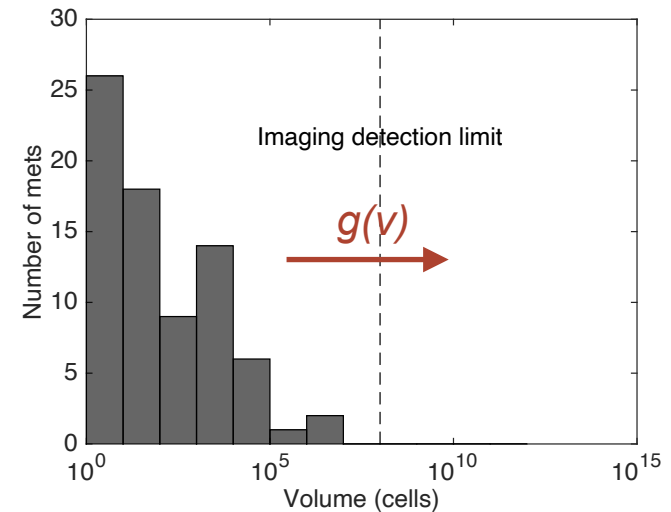
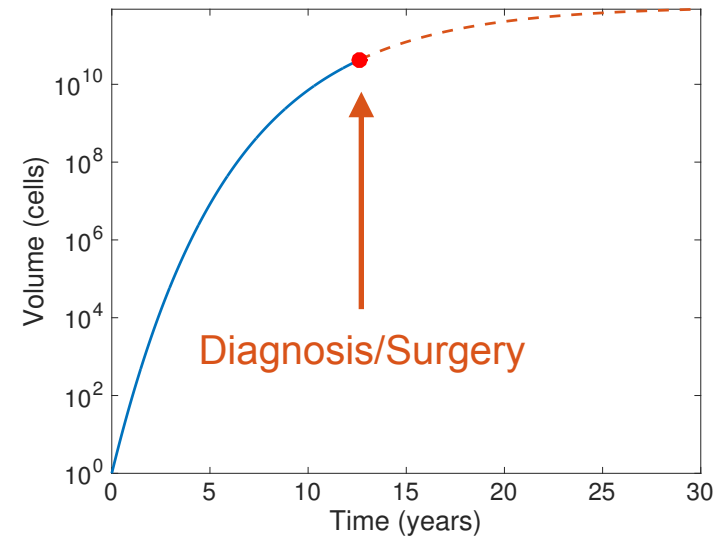
$$\partial_t \rho(t, v) + \partial_v (g(v) \rho(t, v)) = 0$$

- 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

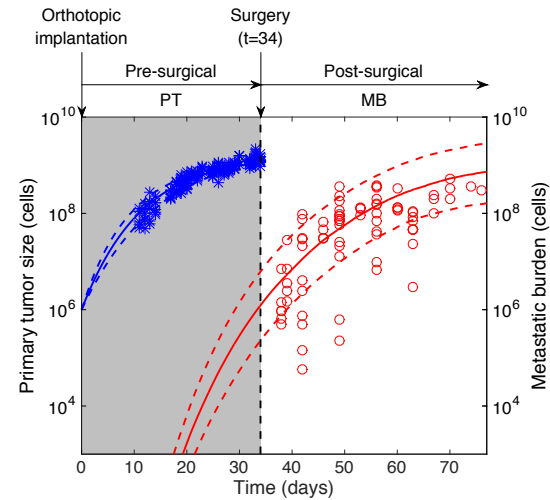
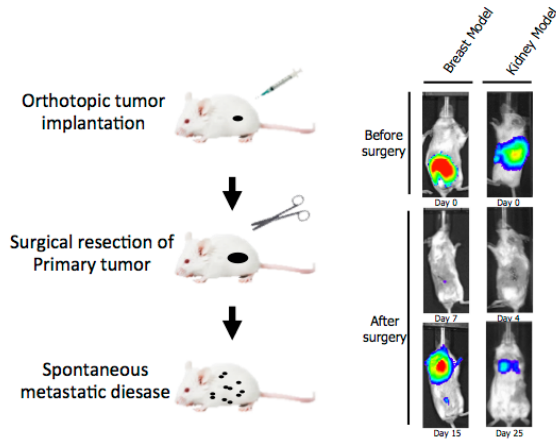
$$M(t) = \int_{V_0}^{+\infty} v \rho(t, v) dv = \int_0^t d(V_p(t-s)) V(s) ds$$





Ebos lab
Roswell Park Cancer Institute

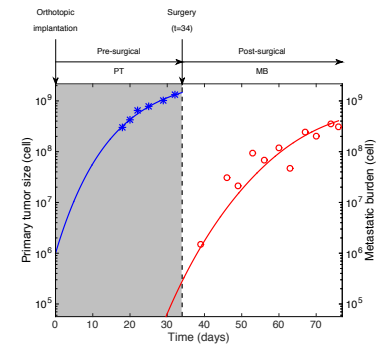
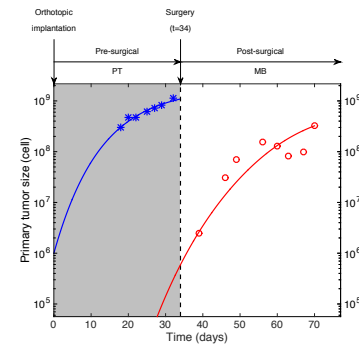
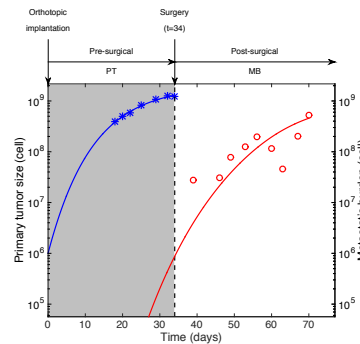
Validation on animal data



- * Data primary tumor
- Median model primary tumor
- - - 10th and 90th percentiles model primary tumor
- Data metastatic burden
- Median model metastatic burden
- - - 10th and 90th percentiles model metastatic burden

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

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



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

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

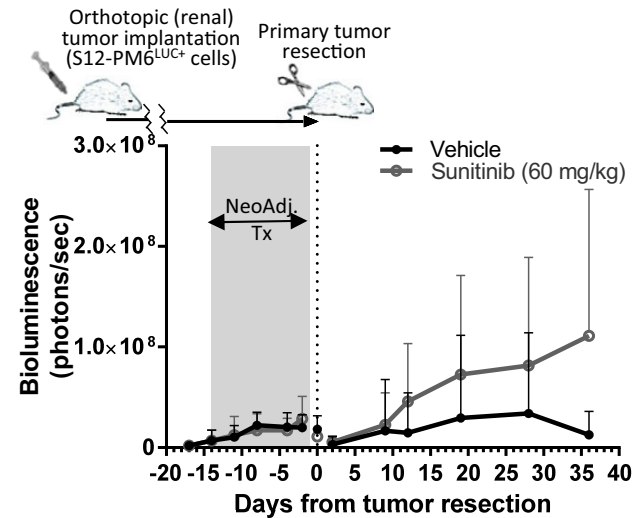
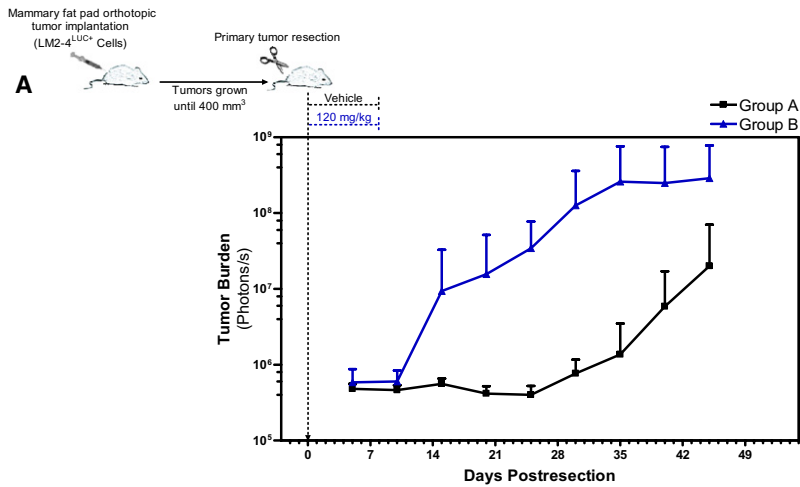


Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

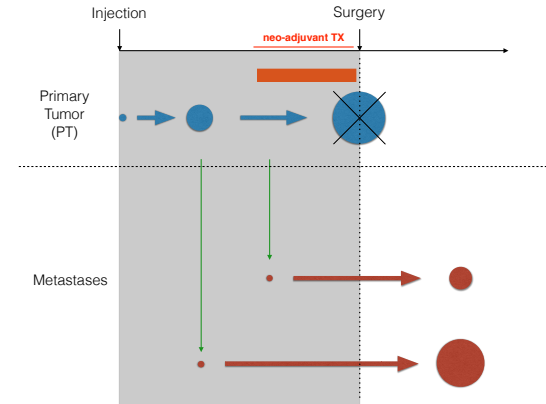
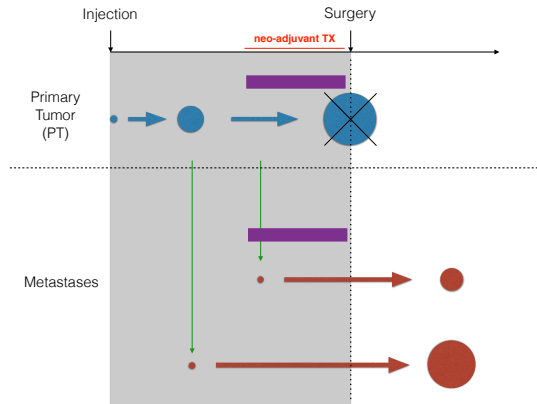
John M.L. Ebos,^{1,2} Christina R. Lee,¹ William Cruz-Munoz,¹ Georg A. Bjarnason,³ James G. Christensen,⁴ and Robert S. Kerbel^{1,2,*}

Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy

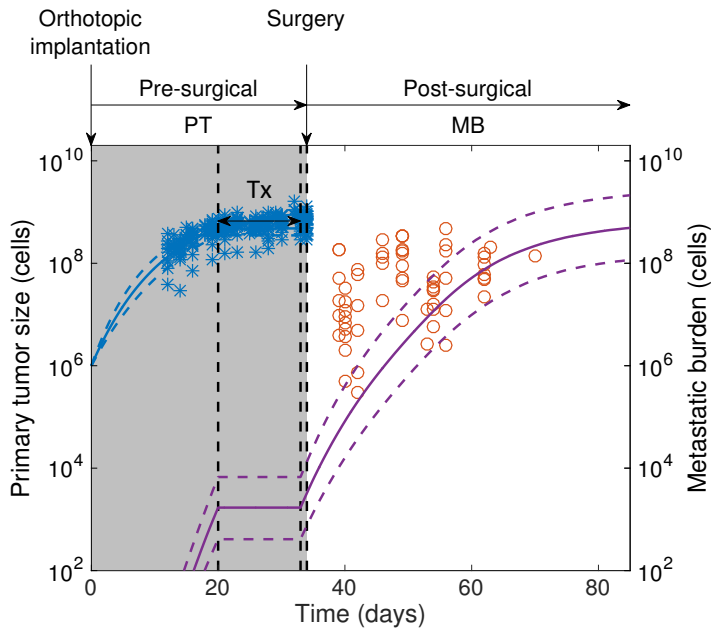
John M L Ebos^{1,2}, Michalis Mastroi¹, Christina R Lee², Amanda Tracz¹, John M Hudson², Kristopher Attwood³, William R Cruz-Munoz², Christopher Jedszko², Peter Burns^{2,4} & Robert S Kerbel^{2,4}



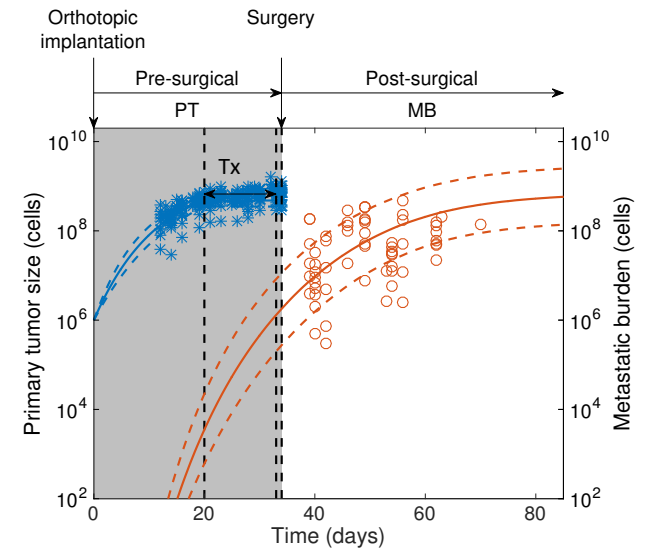
Testing hypotheses for neo-adjuvant TKI effect



or



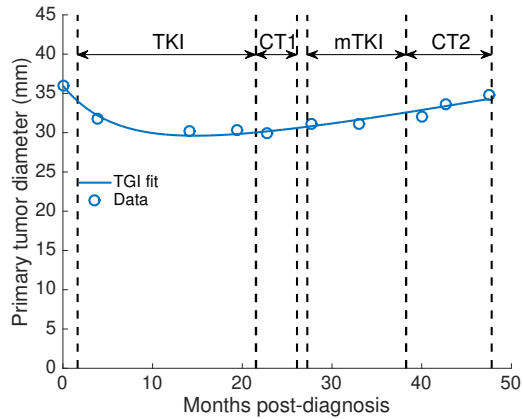
- ★ Data PT
- Data MB
- Median PT
- Median MB
- - - 10^{th} and 90^{th} percentiles PT
- - - 10^{th} and 90^{th} percentiles MB
- simulation of therapy on metastases



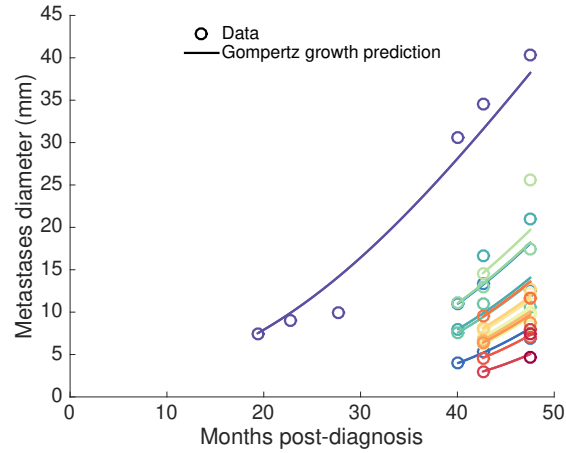
Clinical application - Brain Metastasis from NSCLC

Data of a NSCLC patient with brain mets

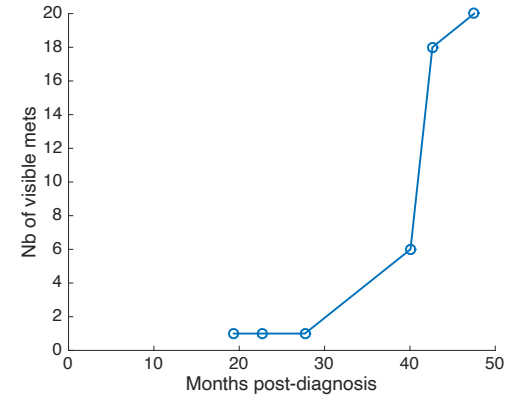
Primary tumor size



Metastases size



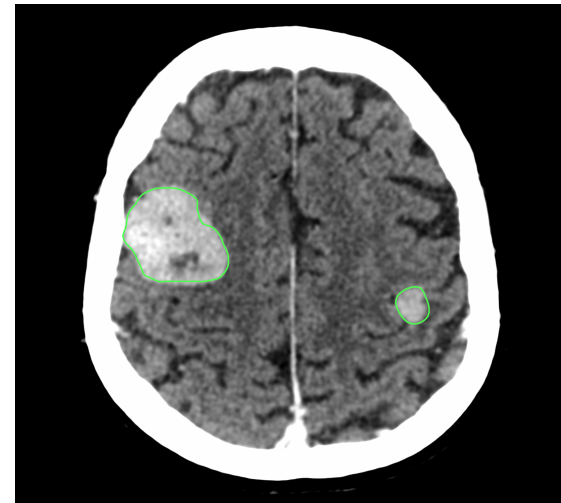
Number of visible mets



Lung CT



Brain CT scan



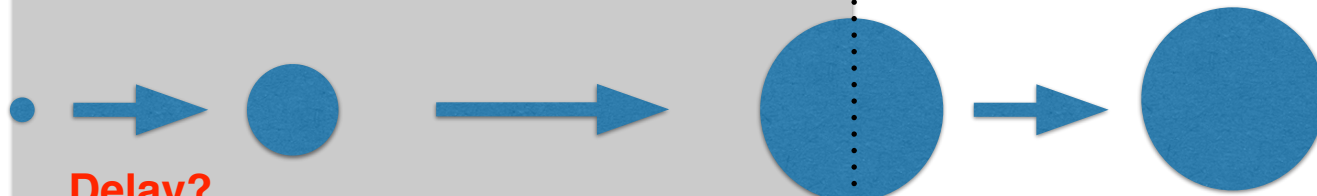
First cancer cell

Diagnosis

treatment

$$\text{Growth law: } g_p(V_p) = V_p(\alpha_p - \beta_p \ln(V_p))$$

Primary
Tumor



Delay?

$$\text{Dissemination law: } d(V_p) = \mu(V_p)^\gamma$$

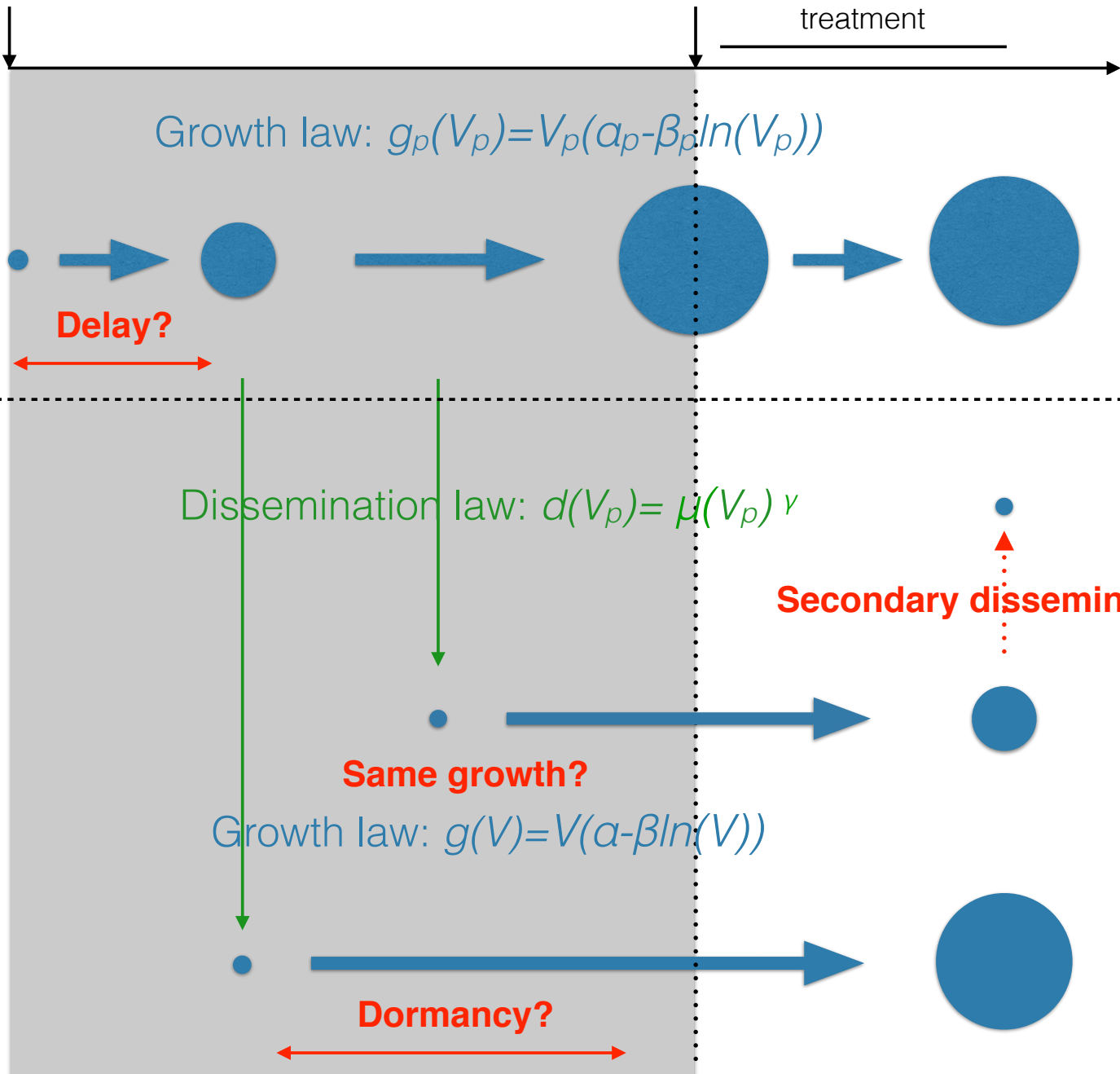
Brain
Metastases

Secondary dissemination?

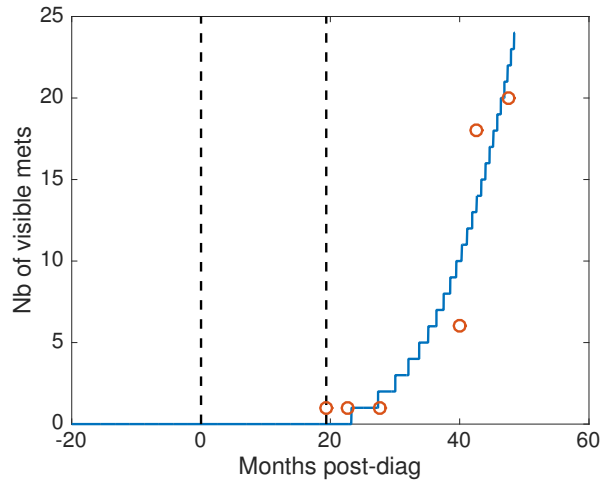
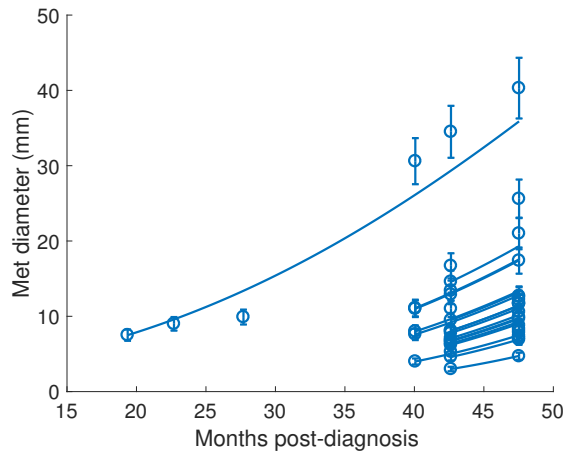
Same growth?

$$\text{Growth law: } g(V) = V(\alpha - \beta \ln(V))$$

Dormancy?



The model with dormancy could describe best the data

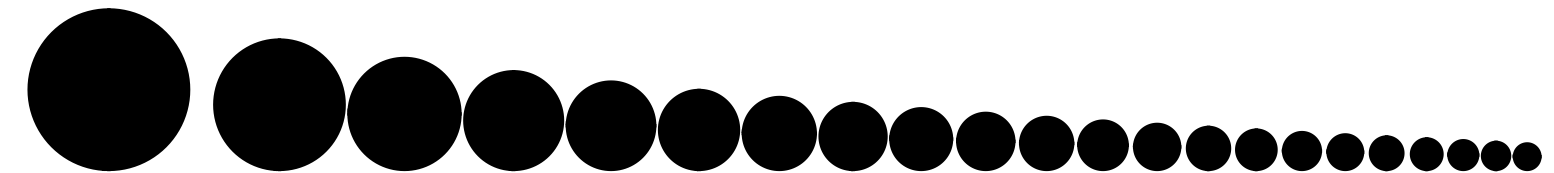


Objective function

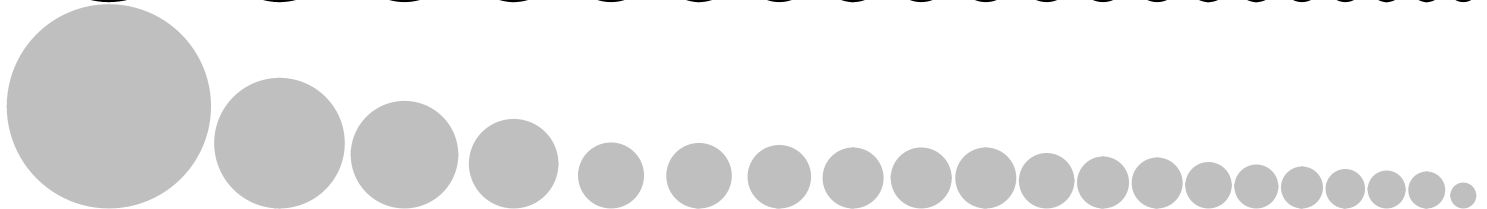
| Model | Patient 1 | Patient 2 |
|--------------|-----------|-----------|
| Base | 5.51 | 2.53 |
| Secondary | 5.43 | 2.3 |
| Delay | 5.23 | 1.53 |
| Dormancy | 4.93 | 1.71 |
| Diff. growth | 4.95 | 1.79 |

Dormancy estimated to 133 days \pm 4.2%

Model



Data



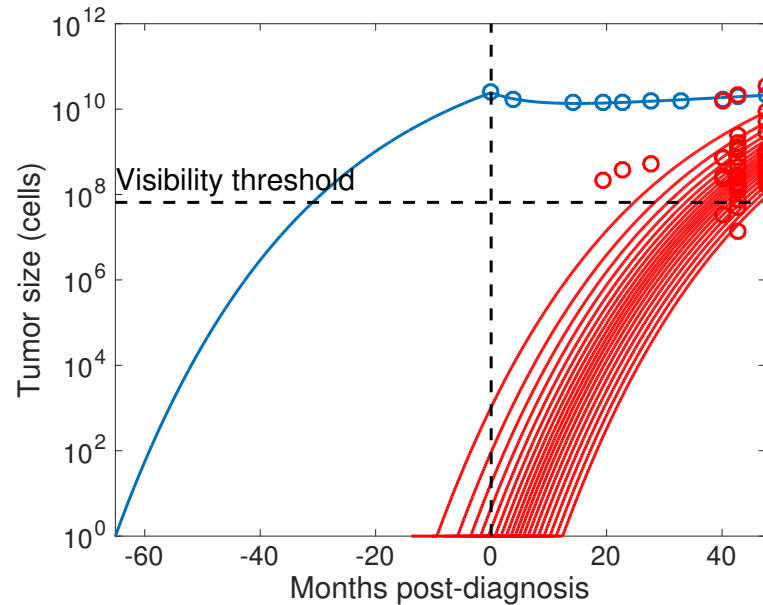
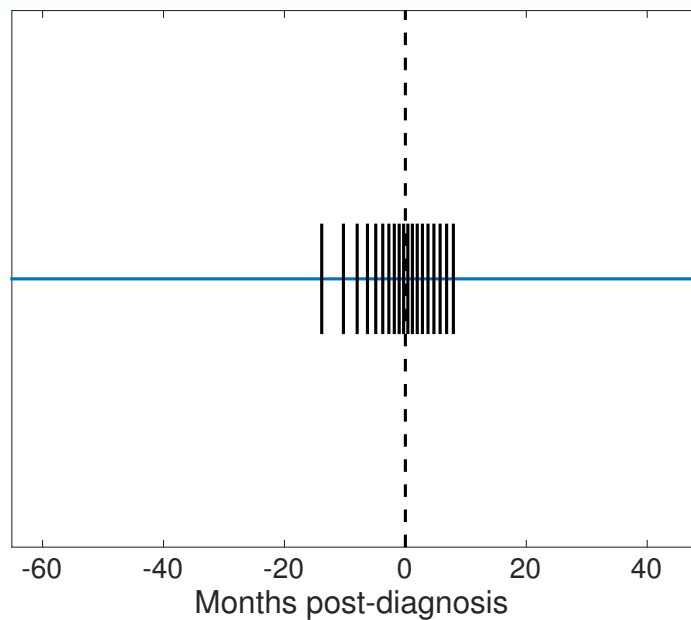
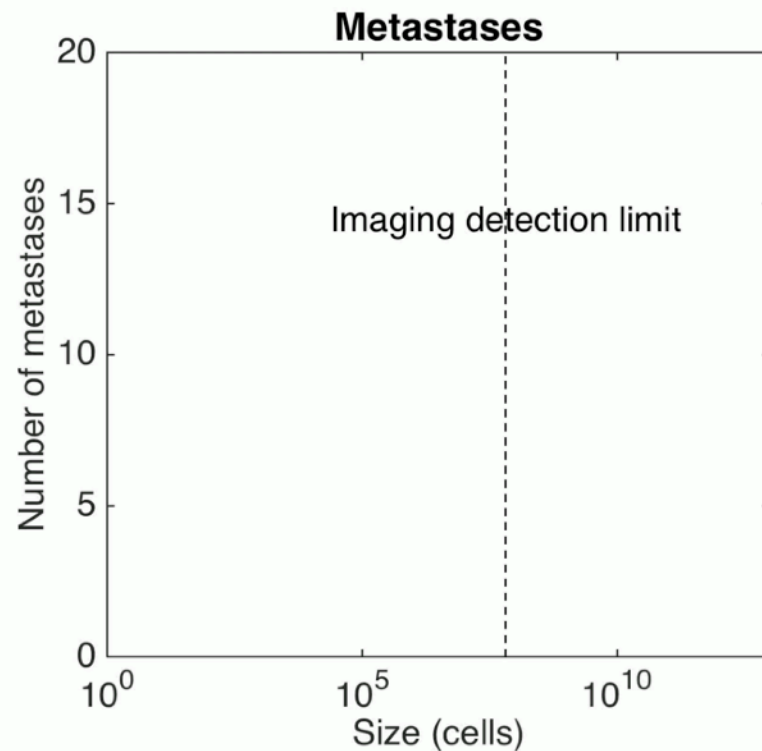
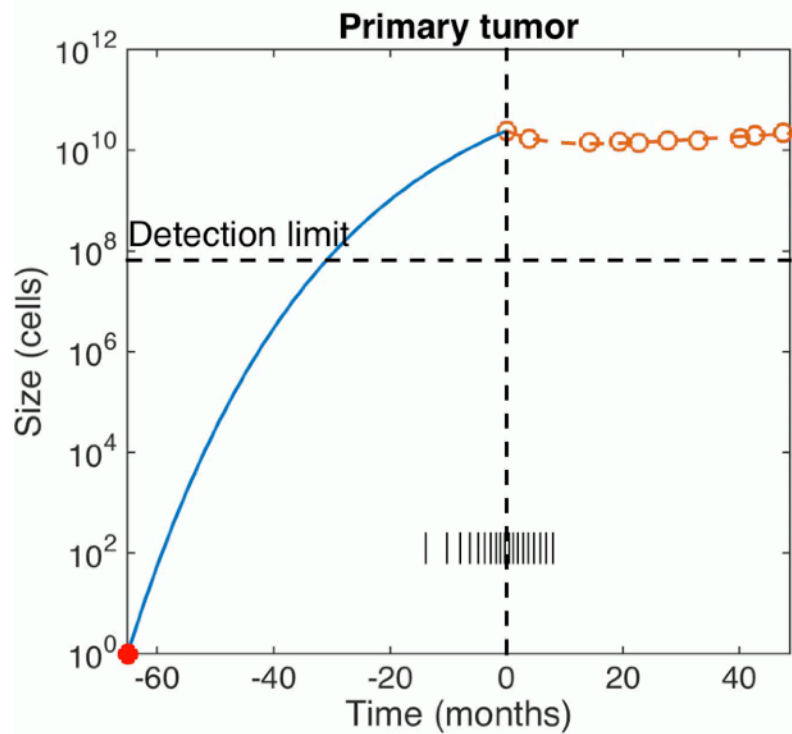
t = -55 months
— 10 mm

*

Primary
tumor
(lung)

Metastases (brain)

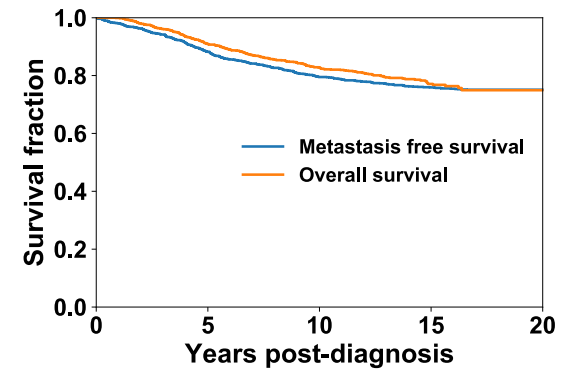
t = -65.1 months



Clinical application - Metastatic relapse in breast cancer

Clinical data of individual breast metastatic relapse

K = 25 features



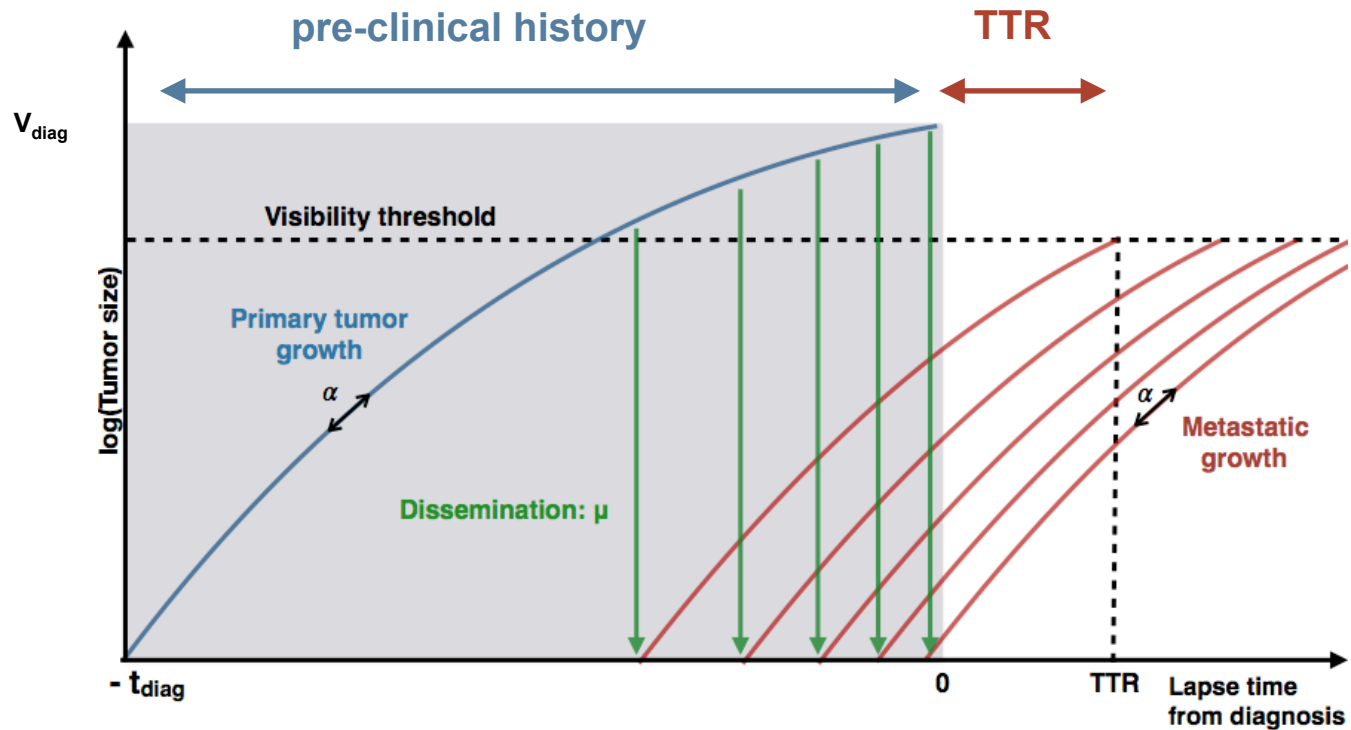
outcome

n = 1057 patients (642 w/o adj)

| menopausal_status | ER | PR | Ki67 | HER2 | HER2_intensity | CK56 | EGFR | VIM | ALDH1 |
|-------------------|-----|-----|------|------|----------------|------|------|-----|-------|
| Post-ménopause | 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ménopause | 40 | 95 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |
| Activité génitale | 87 | 10 | 26 | 0 | 0 | 0 | 0 | 80 | 0 |
| Post-ménopause | 100 | 100 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post-ménopause | 0 | 0 | 16 | 82 | +++ | 0 | 0 | 0 | 0 |
| Activité génitale | 100 | 95 | 12 | 0 | 0 | 0 | 0 | 0 | 1 |
| Activité génitale | 56 | 100 | 17 | 0 | 0 | 0 | 0 | 0 | 0 |
| Activité génitale | 57 | 85 | 23 | 100 | +++ | 0 | 0 | 0 | 0 |
| Post-ménopause | 80 | 5 | 20 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post-ménopause | 0 | 0 | 15 | 100 | +++ | 0 | 5 | 0 | 0 |
| Post-ménopause | 100 | 80 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post-ménopause | 30 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post-ménopause | 0 | 0 | 15 | 40 | +++ | 0 | 0 | 0 | 0 |
| Ménopause | 0 | 80 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post-ménopause | 0 | 0 | 27 | 0 | 0 | 0 | 30 | 0 | 1 |
| Post-ménopause | 0 | 0 | 56 | 0 | 0 | 80 | 60 | 100 | 0 |
| Activité génitale | 50 | 92 | 2 | 1 | + | 0 | 0 | 0 | 0 |
| Post-ménopause | 0 | 47 | 5 | 0 | 0 | 0 | 0 | 80 | 0 |
| Post-ménopause | 65 | 0 | 10 | 0 | 0 | 0 | 0 | 60 | 0 |
| Post-ménopause | 100 | 50 | 11 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ménopause | 20 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Activité génitale | 90 | 6 | 5 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post-ménopause | 100 | 3 | 5 | 0 | 0 | 0 | 0 | 0 | 0 |
| Activité génitale | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ménopause | 80 | 100 | 5 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post-ménopause | 100 | 85 | 25 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post-ménopause | 10 | 45 | 11 | 13 | +++ | 0 | 0 | 0 | 0 |
| Post-ménopause | 66 | 1 | 2 | 40 | ++ | 0 | 0 | 0 | 0 |

| date_metastatic_relapse | date_death_or_loss |
|-------------------------|---------------------|
| 854 | 0 |
| censored | |
| 1999-02-04 00:00:00 | 1998-04-26 00:00:00 |
| | 1999-01-06 00:00:00 |
| | 1993-10-21 00:00:00 |
| | 2004-06-15 00:00:00 |
| 1990-09-04 00:00:00 | 2006-03-21 00:00:00 |
| 1993-02-08 00:00:00 | 2002-04-05 00:00:00 |
| 1999-12-15 00:00:00 | 2006-11-23 00:00:00 |
| | 1997-11-02 00:00:00 |
| | 2006-09-15 00:00:00 |
| 1995-03-08 00:00:00 | 2003-03-29 00:00:00 |
| | 2003-12-02 00:00:00 |
| 1990-04-06 00:00:00 | 1990-10-20 00:00:00 |
| 1994-11-02 00:00:00 | 2003-10-14 00:00:00 |
| | 2004-11-19 00:00:00 |
| | 2006-09-30 00:00:00 |
| | 1991-07-31 00:00:00 |
| | 1995-07-05 00:00:00 |
| | 2005-12-08 00:00:00 |
| | 2005-05-23 00:00:00 |
| | 2007-09-06 00:00:00 |
| | 2006-09-06 00:00:00 |
| | 2001-02-09 00:00:00 |
| | 2005-07-23 00:00:00 |
| | 1993-08-12 00:00:00 |
| | 1995-01-01 00:00:00 |
| | 1993-02-08 00:00:00 |

Mechanistic modeling of time to relapse



- Number of metastases with size larger than the visible size V_{vis} (= 0.5 cm)

$$N_{\text{vis}}(t) = \int_{V_{\text{vis}}}^{+\infty} \rho(t, v) dv = \int_0^{t-\tau_{\text{vis}}} d(V_p(t)) dt$$

τ_{vis} = time to reach V_{vis}

- **Time to relapse (TTR)** defined as the time elapsed from diagnosis to the appearance of a first visible metastasis

$$TTR = \inf \{t > 0 : N_{\text{vis}}(t_{\text{diag}} + t) \geq 1\}$$

- Parameter β fixed such that carrying capacity = 10^{12} cells

Mixed-effects statistical model

$$\ln(T^i) = \ln\left(TTR\left(V_{diag}^i; \alpha^i, \mu^i\right)\right) + \varepsilon^i, \quad \varepsilon^i \sim \mathcal{N}(0, \sigma^2) \quad (\text{Observation model})$$

$$S(t|\alpha^i, \mu^i) = \mathbb{P}(T^i > t|\alpha^i, \mu^i)$$

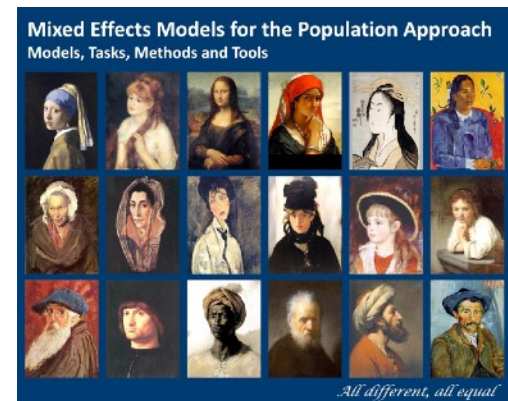
Survival function to account for **censoring** in the likelihood

$$\ln(\alpha^i) = \ln(\alpha_{pop}) + \eta_{\alpha}^i, \quad \eta_{\alpha}^i \sim \mathcal{N}(0, \omega_{\alpha}^2)$$

$$\ln(\mu^i) = \ln(\mu_{pop}) + \eta_{\mu}^i, \quad \eta_{\mu}^i \sim \mathcal{N}(0, \omega_{\mu}^2)$$

fixed effects

random effects

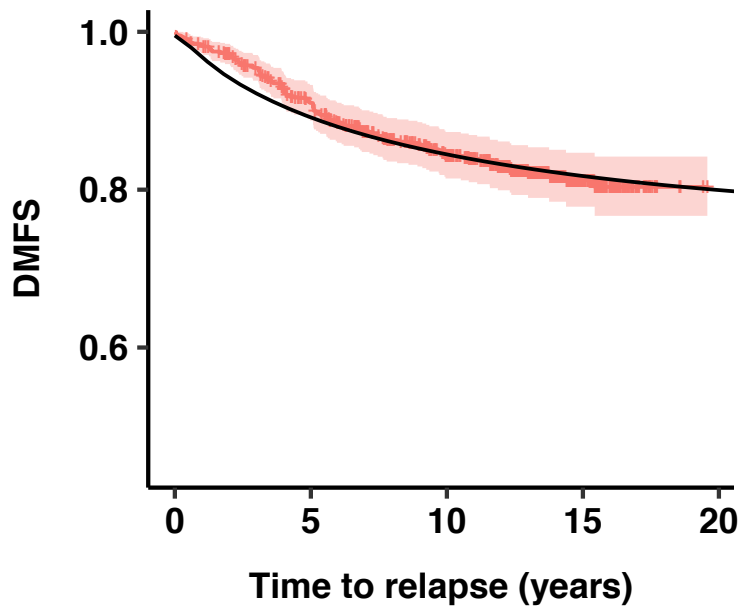


Lavielle, CRC press, 2014

Likelihood maximization performed using the *saemix* R package (SAEM algorithm)

Comets, Lavenu, Lavielle, *J Stat Softw*, 2017

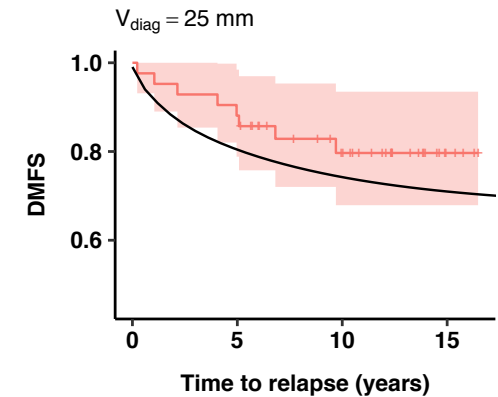
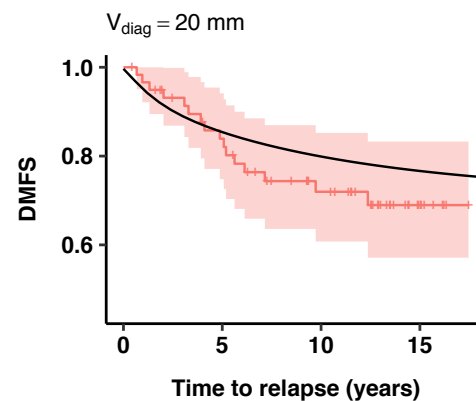
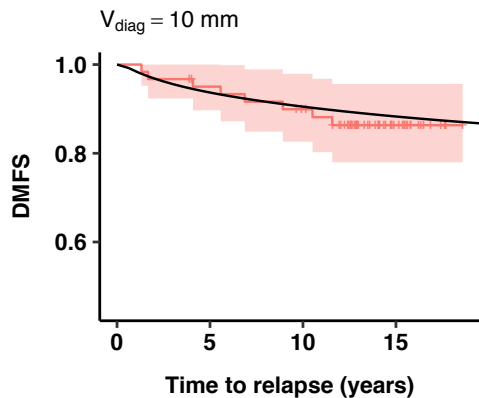
Descriptive power: fit to the data



—+— Kaplan–Meier estimate

— Model fit

| Parameter | Estimate | r.s.e. (%) |
|---------------------|----------|------------|
| $\log \alpha_{pop}$ | -6.337 | 12.635 |
| $\log \mu_{pop}$ | -26.814 | 3.683 |
| σ | 0.542 | 28.409 |
| ω_{α} | 3.373 | 36.435 |
| ω_{μ} | 3.780 | 15.876 |



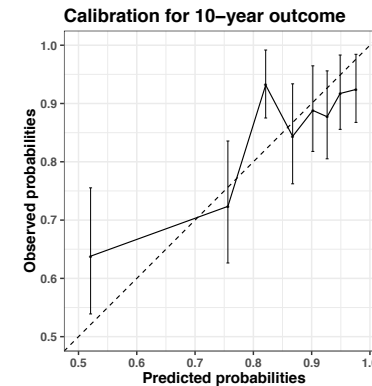
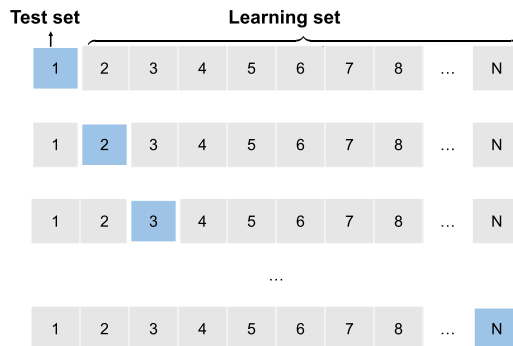
Predictive power: covariates

$$\ln(\mu^i) = \ln(\mu_{pop}) + \beta_{\mu}^T \mathbf{x}_{\mu}^i + \eta_{\mu}^i, \quad \eta_{\mu}^i \sim \mathcal{N}(0, \omega_{\mu}^2)$$

$$\ln(\alpha^i) = \ln(\alpha_{pop}) + \beta_{\alpha}^T \mathbf{x}_{\alpha}^i + \eta_{\alpha}^i, \quad \eta_{\alpha}^i \sim \mathcal{N}(0, \omega_{\alpha}^2)$$

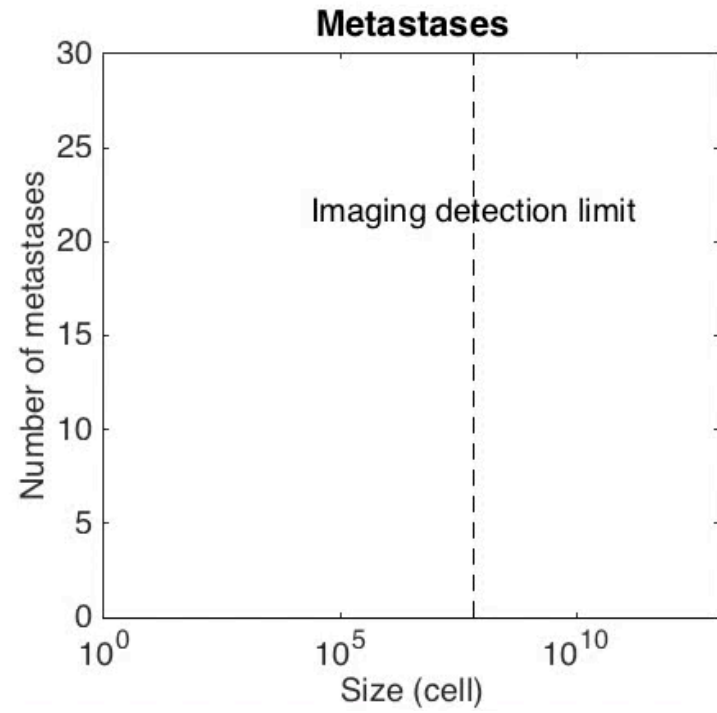
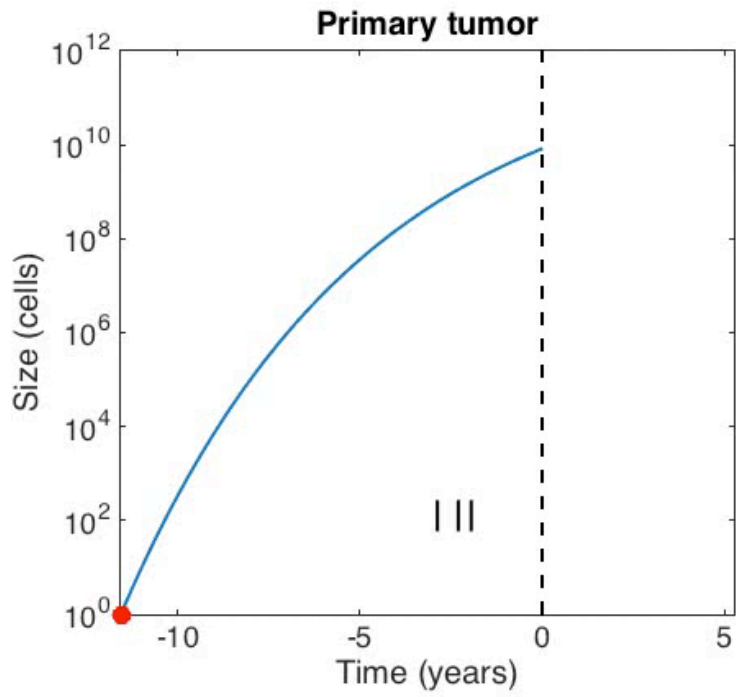
| Parameter | Estimate | r.s.e. (%) | p-value |
|------------------------|----------|------------|----------------------|
| $\log \alpha_{pop}$ | -8.883 | 10.151 | |
| $\beta_{Ki67, \alpha}$ | 0.086 | 27.376 | $2.59 \cdot 10^{-4}$ |
| $\beta_{HER2, \alpha}$ | 0.029 | 42.833 | 0.020 |
| $\beta_{CD44, \alpha}$ | 0.011 | 60.816 | 0.1 |
| $\beta_{TRIO, \alpha}$ | 0.016 | 58.119 | 0.085 |
| $\log \mu_{pop}$ | -26.342 | 3.696 | |
| $\beta_{EGFR, \mu}$ | 0.039 | 47.527 | 0.035 |
| σ | 0.606 | 23.104 | |
| ω_{α} | 2.062 | 22.715 | |
| ω_{μ} | 3.563 | 16.759 | |

c-index = 0.62 (10-folds cross-validation)

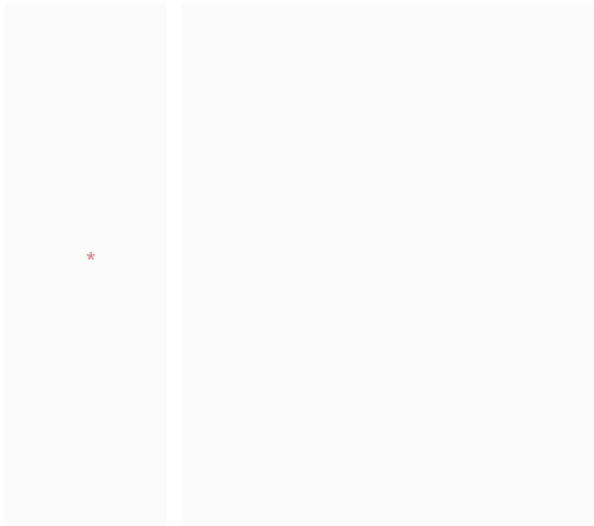


| Patient ID | Tumor size (mm) | Ki67 | HER2 | CD44 | TRIO | EGFR | Observed TTR (cens) | Predicted TTR | Prediction error (days) |
|------------|-----------------|------|------|------|------|------|---------------------|---------------|-------------------------|
| 47 | 20 | 32 | 100 | 0 | 0 | 50 | 739 (1) | 447 | 292 |
| 255 | 25 | 1 | 60 | 90 | 60 | 0 | 1812 (1) | 1609 | 203 |
| 143 | 18 | 60 | 0 | 50 | 0 | 0 | 2798 (1) | 434 | 2364 |
| 12 | 10 | 20 | 0 | 23 | 0 | 0 | 5970 (0) | $+\infty$ | - |

t = -11.6 years

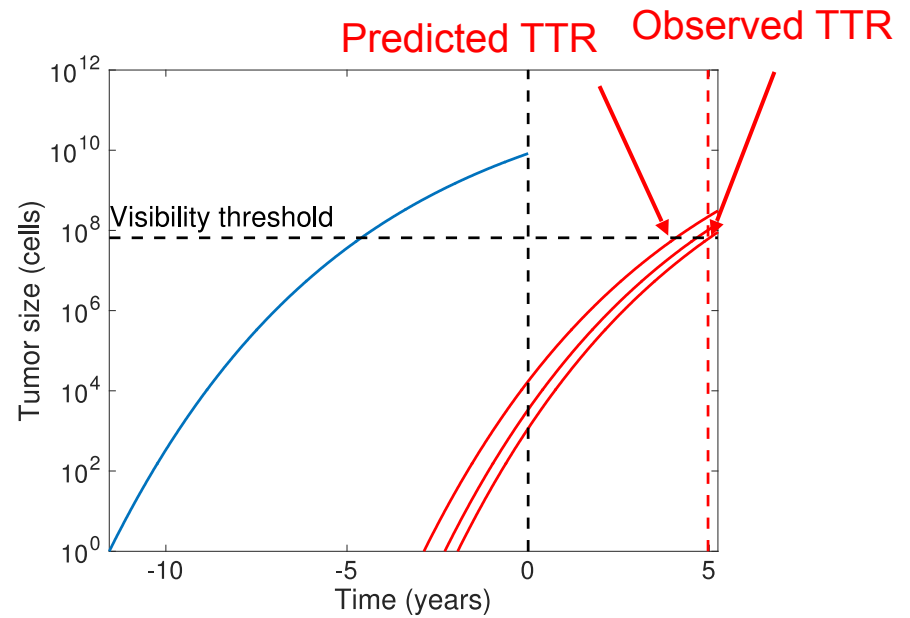


t = -141 months
— 10 mm



Primary tumor

Metastases



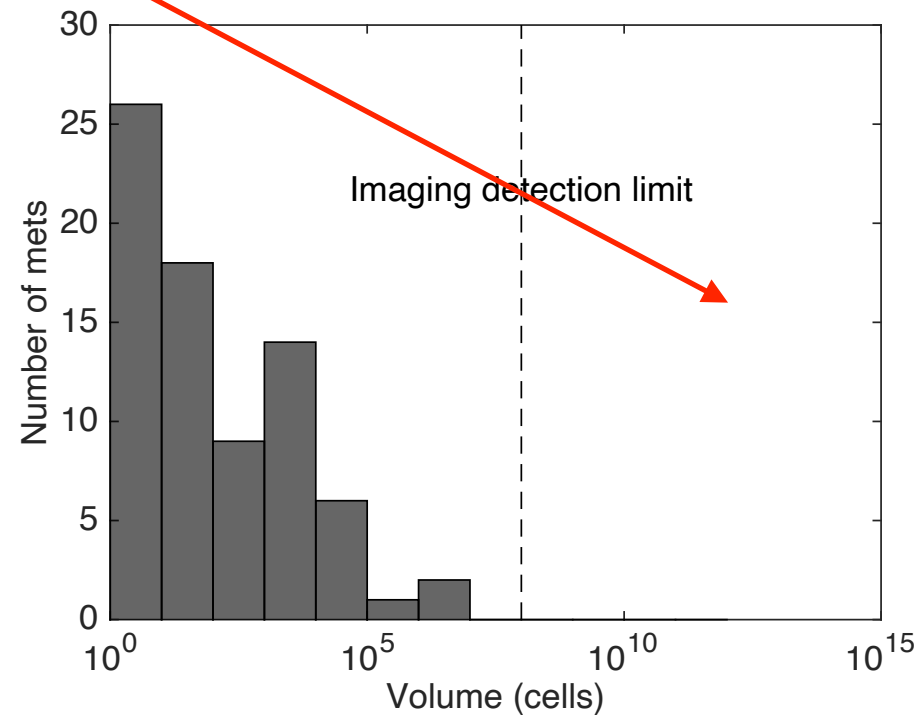
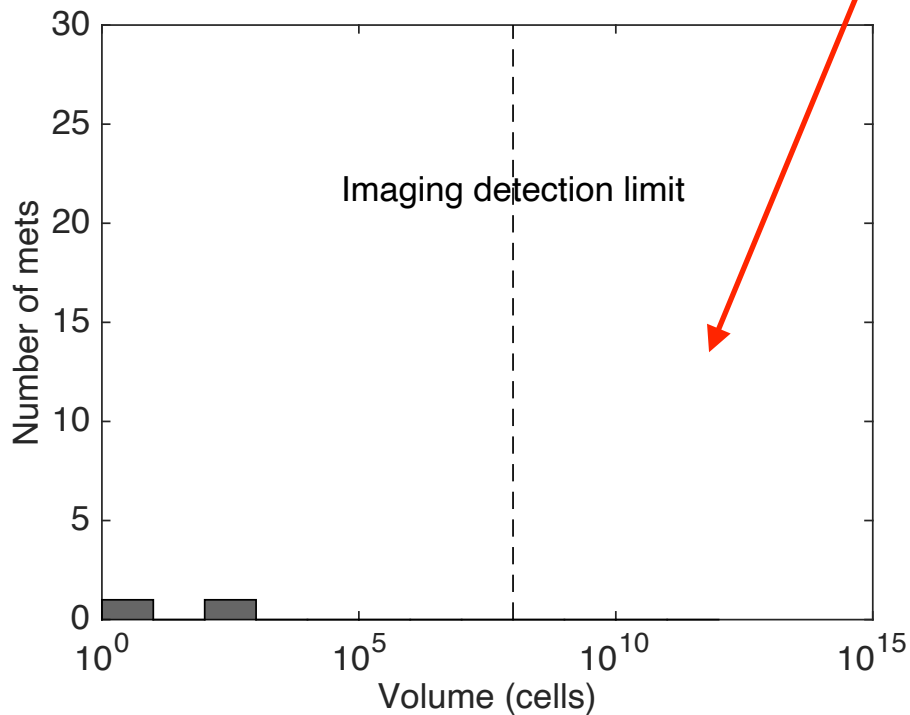


Diagnosis personalization

Virtual patient with
median μ

Virtual patient with
large μ (90th prct)

Nothing visible



Breast cancer patient with primary tumor of 4.32 cm

Chemotherapy personalization

Toward taking into account inter-individual variability

- 10 virtual patients with breast cancer detected at stage **T1N0M0**. Size of the tumor at detection: 1 gram.
- Chemotherapy : 6 cycles of 21 days (75mg of DTX and 100mg d'EPI) *Viens & al., J. Clin. Onc. 2001*
- Number of visible metastases ($> 10^8$ cel.) 5 years after the end of the treatment

Adapt the number of cycles to each patient

| μ | Protocole de Viens | | |
|----------------------|----------------------|----------------------|-----------------------|
| | 6 cycles 126 days | 9 cycles 189 days | 12 cycles 252 days |
| 1.3×10^{-7} | 1 | 0 | * |
| 2.7×10^{-7} | 2 | 1 | 0 |
| 4.0×10^{-7} | 3 | 2 | 1 |
| 6.1×10^{-7} | 5 | 4 | 3 |

Acknowledgements

Biology

- Preclinical data of ortho-surgical animal models of metastases

*J. Ebos

*A. Tracz

*M. Matri



Roswell Park Cancer Institute, Buffalo, NY, USA

- Beva + cytotoxics study



Dr. J. Ciccolini

Clinic

- Brain metastasis from lung tumors

*F. Chomy

Bergonié Institute, Bordeaux, FR



*F. Barlesi

*X. Muracciole

AP-HM, Marseille, FR

Modeling

*C. Nicolò



*D. Barbolosi



That's all Folks!

Thanks for listening!