Computational modeling in medicine
Part I: Introduction to mathematical oncology

S. Benzekry

Cours de formation doctorale
Université de Bordeaux
March 6, 2018

MONC
Modeling in ONCology

Mathematical medicine?

- First use of a mathematical model in medicine in 1760 by **D. Bernoulli**
- **Smallpox**: about 10% of death at that time (300–500 million deaths in the 20th century)

Is smallpox inoculation at small dose (vaccination) worthwhile given the risk of complications?

prob. infected → q ; mortality rate → $m(x)$; prob. smallpox death → p

$$\begin{cases} \frac{dS}{dx} = -qS - m(x)S \\ \frac{dR}{dx} = q(1-p)S - m(x)R \end{cases}$$

x = age

S(x) = susceptible

R(x) = recovered

TABLE I.

Ages par années.	Survivans selon M. Halley.	N'ayant pas eu la pet. vérole.	Ayant eu la pet. vérol.	Prenant la pet. vérole pendant ch. année.	Morts de la pet. vérole pendant chaq. ann.	Somme des morts de la pet. vérole.	Morts par d'autres maladies pend. chaq. année.
0	1300	1300	0				
1	1000	896	104	137	17,1	17,1	283
2	855	685	170	99	12,4	29,5	133
3	798	571	227	78	9,7	39,2	47
4	760	485	275	66	8,3	47,5	30
5	732	416	316	56	7,0	54,5	21
6	710	359	351	48	6,0	60,5	16
7	692	311	381	42	5,2	65,7	12,8
8	680	272	408	36	4,5	70,2	7,5
9	670	237	433	32	4,0	74,2	6
10	661	208	453	28	3,5	77,7	5,5
11	653	182	471	24,4	3,0	80,7	5
12	646	160	486	21,4	2,7	83,4	4,3
13	640	140	500	18,7	2,3	85,7	3,7
14	634	123	511	16,6	2,1	87,8	3,9
15	628	108	520	14,4	1,8	89,6	4,2
16	622	94	528	12,6	1,6	91,2	4,4
17	616	83	533	11,0	1,4	92,6	4,6
18	610	72	538	9,7	1,2	93,8	4,8
19	604	63	541	8,4	1,0	94,8	5
20	598	56	542	7,4	0,9	95,7	5,1
21	592	48,5	543	6,5	0,8	96,5	5,2
22	586	42,5	543	5,6	0,7	97,2	5,3
23	579	37	542	5,0	0,6	97,8	6,4
24	572	32,4	540	4,4	0,5	98,3	6,5

⇒ **Life expectancy** of 29 years (inoculation) VS 26 years (no inoculation)

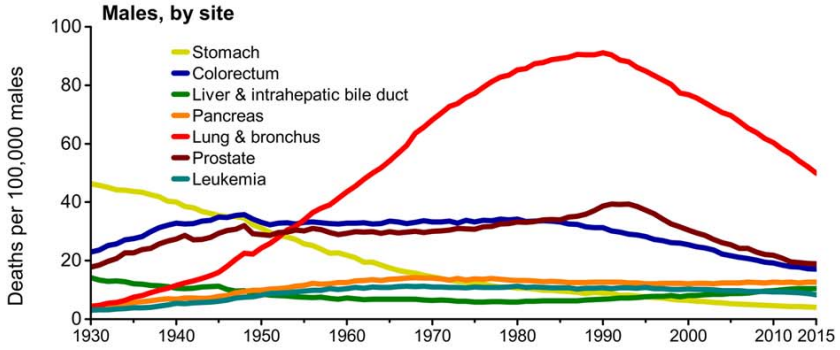
- Smallpox has been **eradicated** since 1980, in part thanks to a worldwide vaccination campaign

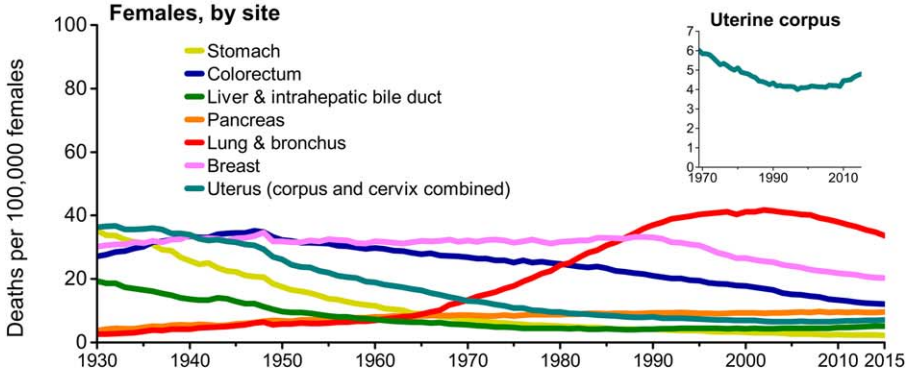
Bernoulli, Daniel « Essai d'une nouvelle analyse de la mortalité causée par la petite vérole et des avantages de l'inoculation pour la prévenir » Mémoires de mathématiques et de physique, Académie royale des sciences, 1760, p.1- 45

Cancer: a major public health concern

- Second leading **cause of death** worldwide (1 in 6 deaths, 8.8 million deaths in 2015)
- **First** cause of death in France (> 1 in 4 deaths) *InVS and INCa, 2011*
- Cumulative risks of **developing** a cancer: 30.9% in males and 23.3% in females
- Cumulative risks of **death** by cancer: 14.3% and 9%
- Most prevalent cancer types: **breast** in women, **prostate** in men
- Largest number of deaths: **lung** cancer
- One third of deaths from cancer are due to 5 leading **behavioral and dietary risks**: **tobacco** use (22%), high body mass index, low fruit and vegetable intake, lack of physical activity and alcohol use

Epidemiologial trends





Siegel, R. L., Miller, K. D., & Jemal, A. (2018). Cancer statistics, 2018. CA: a Cancer Journal for Clinicians, 68(1), 7–30.

Can mathematical models be of help in oncology?

- Novel **measurement methods** (especially from molecular biology and imaging) lead to accumulation of large amounts of biological and clinical data

Biological challenges

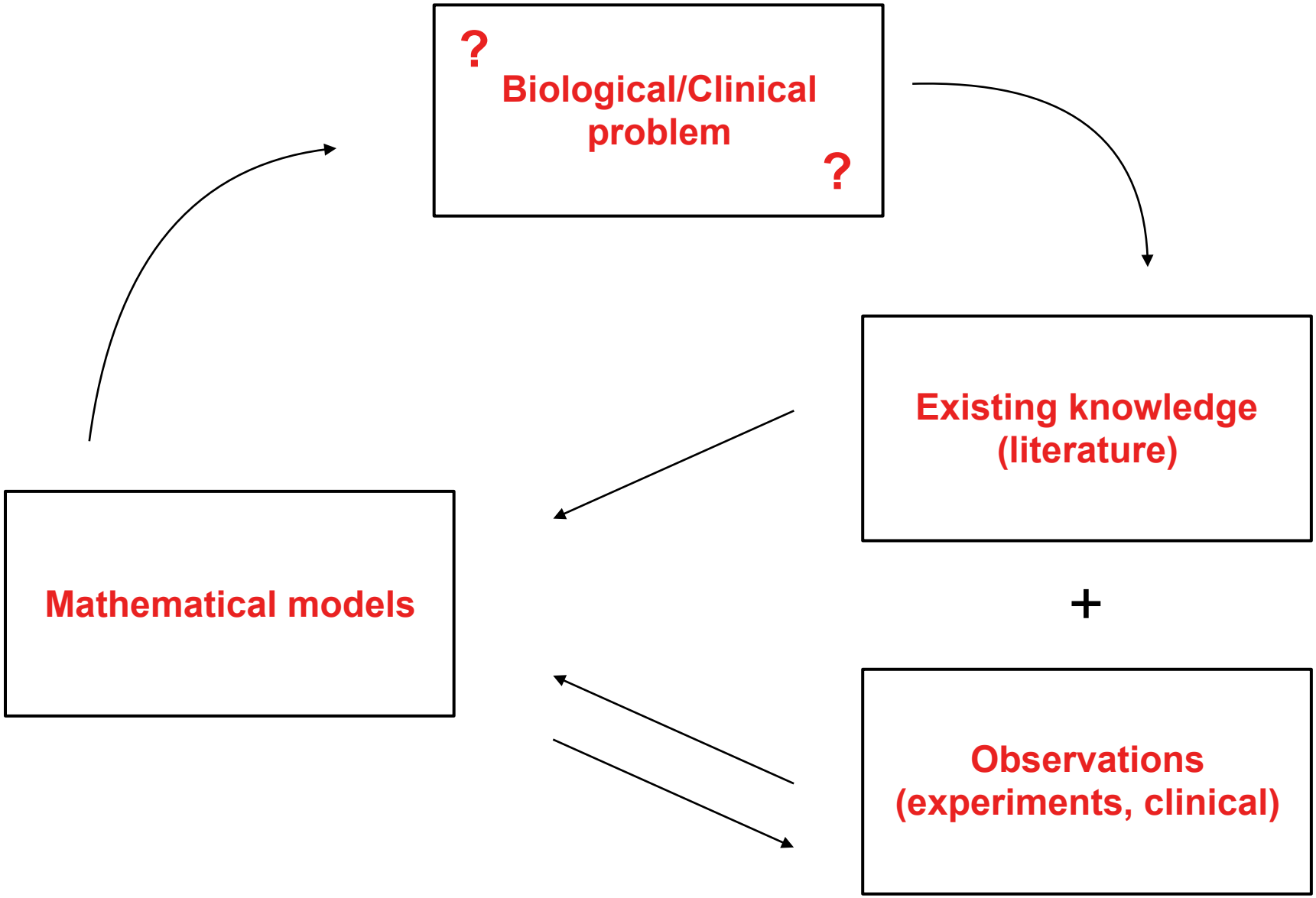
- **Understand** tumor growth
- General theories of **systemic dynamics** of cancer (metastasis, tumor-tumor interactions, cancer-immune dynamics,…)

⇒ **Computational biology**

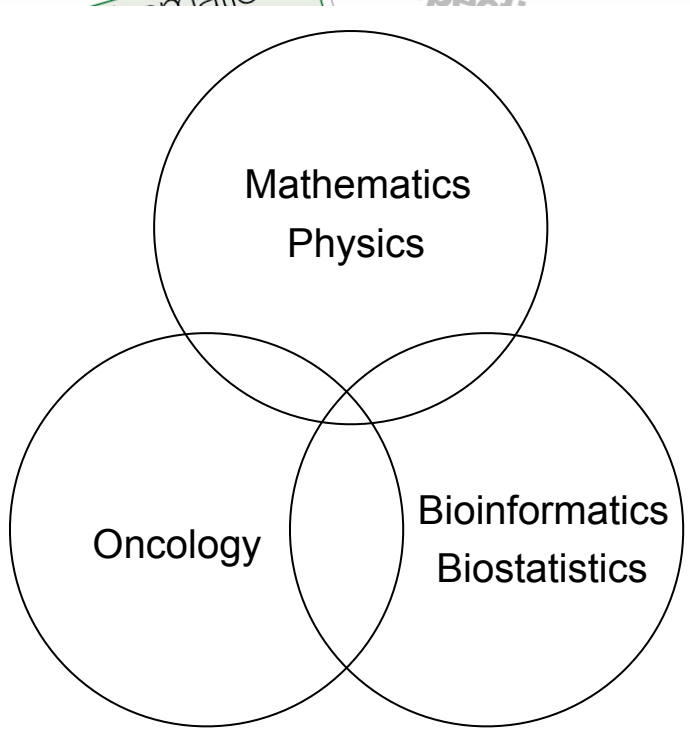
Clinical challenges

- Predict **tumor growth**
- Predict **metastasis**
- Predict **resistance**
- Optimize and **individualize** the therapy

⇒ **Personalized medicine**


?
Biological/Clinical problem
?
Existing knowledge (literature)
+
Observations (experiments, clinical)
Mathematical models

Mathematical oncology?



concepts

Leading Edge

Nature, 2003

Cancer summed up

Robert A. Gatenby and Philip K. Maini

Cell, 2014

Cell

Nat Rev Clin

Computational oncolog
mathematical modellir
regimens for precision

Dominique Barbolosi[1], Joseph Ciccolini[1], Bruno La
and Nicolas André[2,4,5]

Theory

Cell, 2008

Cell

Tumor Morphology and Phenotypic Evolution Driven by Selective Pressure from the Microenvironment

Alexander R.A. Anderson,[1,*] Alissa M. Weaver,[4] Peter T. Cummings,[2,3] and Vito Quaranta[4,*]

Outline

1. Tumor growth

2. Therapeutics

3. Metastases

1 Tumor growth

Outline

1. **Tumor growth**

    1.1. **Introduction**

    1.2. **Tumor growth laws**

    1.3. Angiogenesis and the Hahnfeldt model

    1.4. Tumor-tumor interactions

    1.5. Prediction

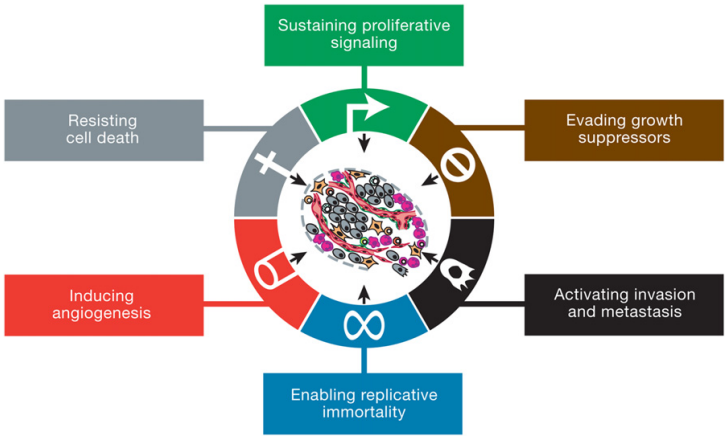
    1.6. Meningioma and heterogeneity

    1.7. Spatial models

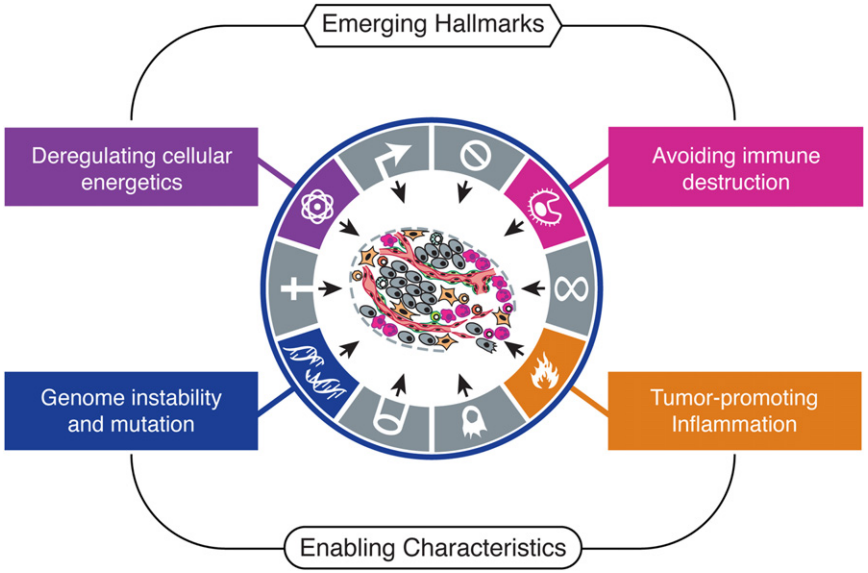
What is a cancer?

- Tumor = malignant **neoplasm**. neo = new, plasma = formation
- Usually assumed that it departs from a cell undergoing several genetic and epigenetic changes leading to **abnormal proliferation**

Hallmarks of cancer

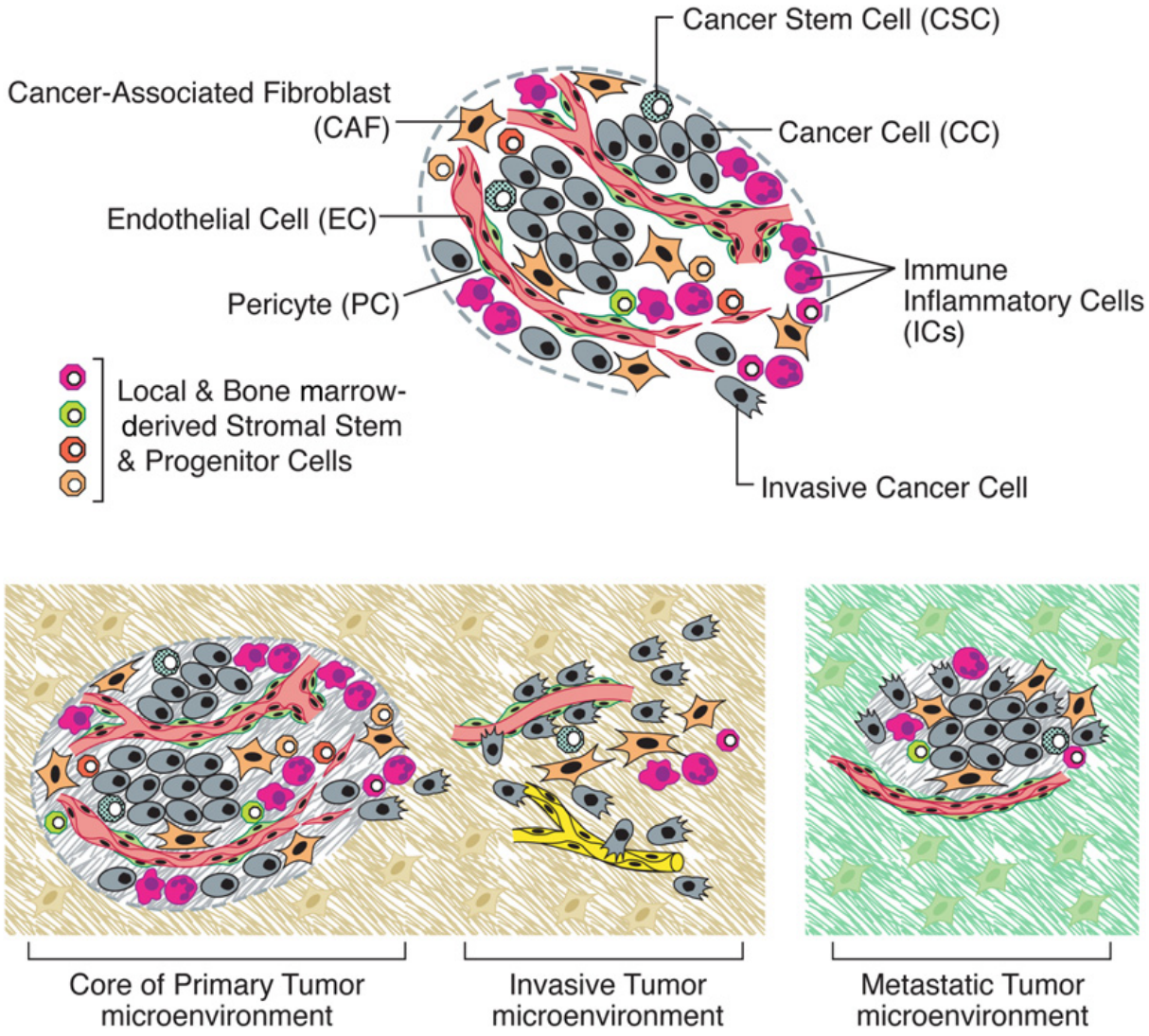


Hanahan and Weinberg, Cell, 2000



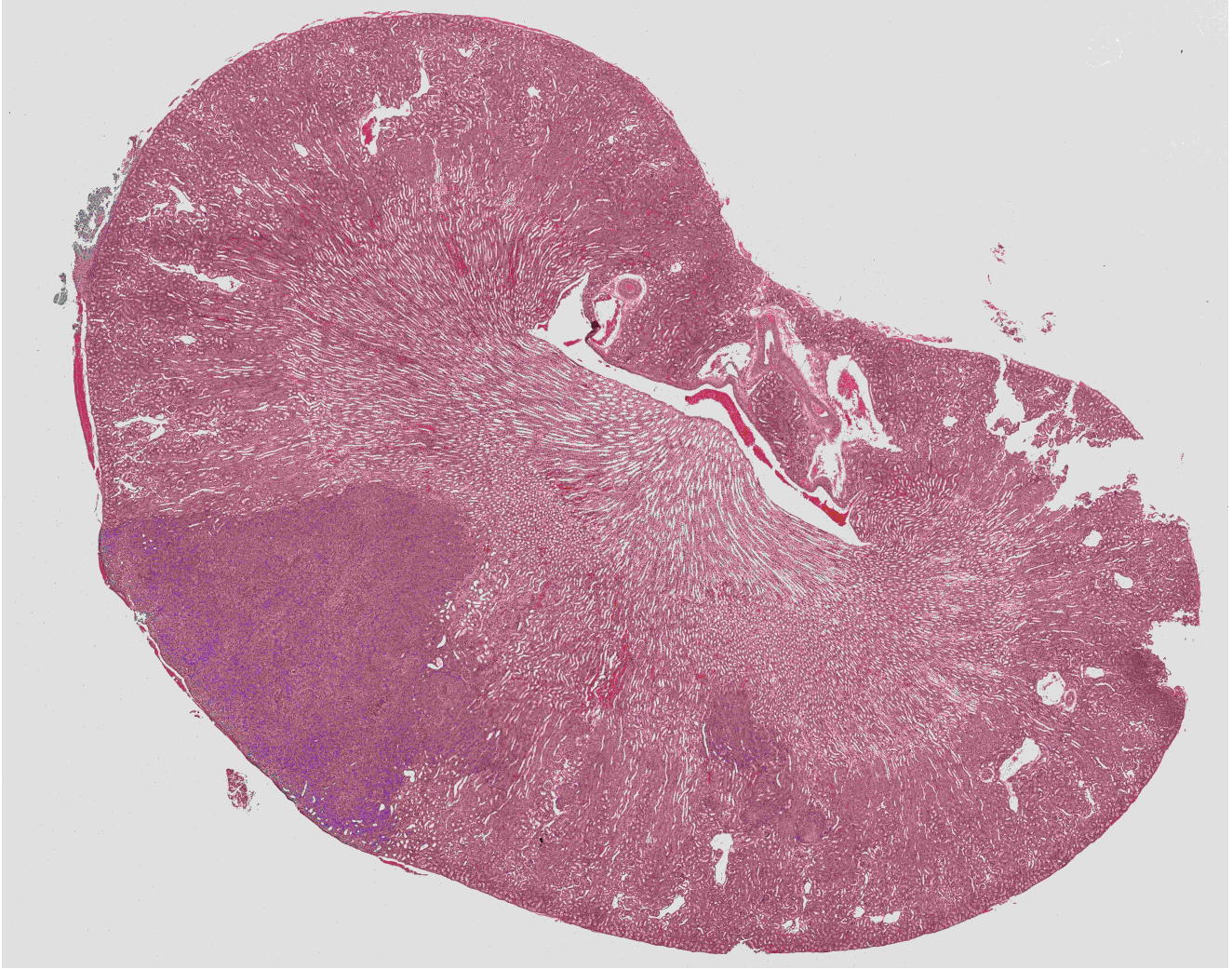
Hanahan and Weinberg, Cell, 2011

Microenvironment



Hanahan and Weinberg, Cell, 2011

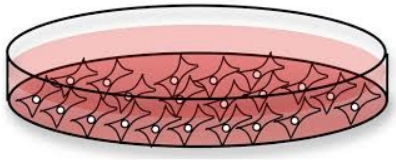
A kidney tumor observed by Hematoxylin and Eosin staining



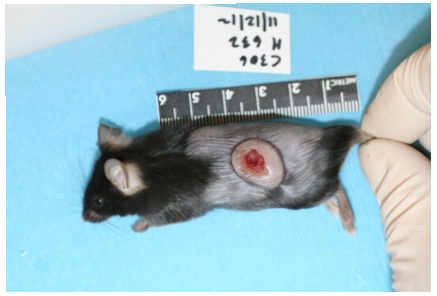
We will focus here on **carcinomas:** solid cancers from epithelial origin

Quantification of Tumor Growth

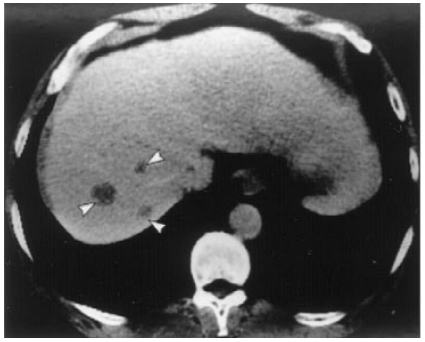
- **In vitro**
  - 2D proliferation assays
  - 3D Tumor spheroids. Limited maximal size (mm)



- **In vivo** animal models
  - **Subcutaneous/orthotopic** implant
  - **Iso/xenograft** (requires immune-deficient mice)
  - Genetically engineered mice



- **Imaging** techniques (gives human data)
  - Mammographies
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI)
  - Functional imaging (PET)

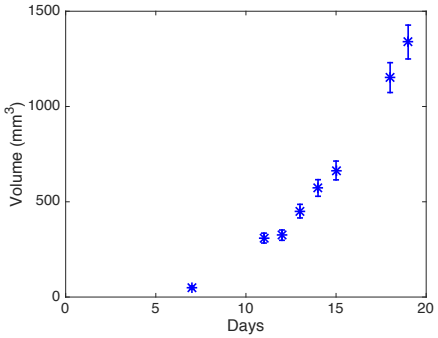


Background on quantitative analysis of tumor growth curves

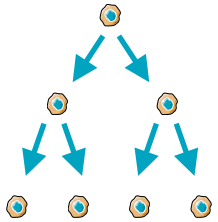
- Study of biological **growth processes** has a long history
- Started in the 1950's for human tumor growth dynamics *Collins et al., Am J Roentgenol Radium Ther Nucl Med, 1956*
- One general observation is that the **relative growth rate decreases in time** *Laird, Br J Cancer, 1965, Steel, Br J Cancer,1966, Spratt, Cancer, 1993*
- The most widely used model is the **Gompertz model**, but there is a wide array of empiric, **ODE-based**, growth models
- For experimental tumor growth, first appears in *Casey, Am J Cancer, 1934*
- Applicability for tumor growth generally confirmed on large animal data sets *Laird, Br J Cancer, 1964,1965* and human breast cancer data *Norton, Cancer Res, 1988*

Fit methodology: likelihood maximization

Data



Theory



(Structural) model

$$V: \begin{array}{ccc} \mathbb{R}\times\mathbb{R}^p & \longrightarrow & \mathbb{R} \\ (t,\theta) & \longmapsto & V(t,\theta) \end{array}$$

(Statistical) observation model

$$V_j = V(t_j;\theta) + \sigma_j \varepsilon_j \qquad \varepsilon_j \sim \mathcal{N}(0,1)$$

σ_j = std of the measurement error

- constant
- proportional

Likelihood

$$L(\theta) = p(V_1,\cdots,V_n;\theta) = \prod_{j=1}^{n} p(V_j;\theta) = \prod_{j=1}^{n} \frac{1}{\sigma_j\sqrt{2\pi}} e^{-\frac{\left(V_j - V(t_j,\theta)\right)^2}{2\sigma_j^2}}$$

log

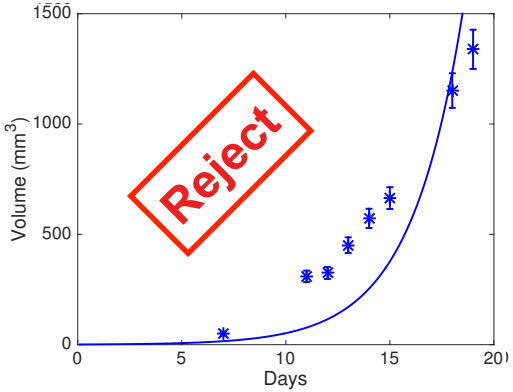
$$l(\theta) = -\sum_{j=1}^{n} \frac{\left(V_j - V(t_j,\theta)\right)^2}{2\sigma_j^2} - \sum_{j=1}^{n} \ln(\sigma_j)$$

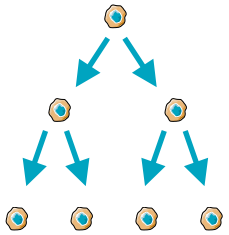
$$\hat{\theta} = \underset{\theta}{\operatorname{argmax}}\, l(\theta)$$

Tumor growth

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

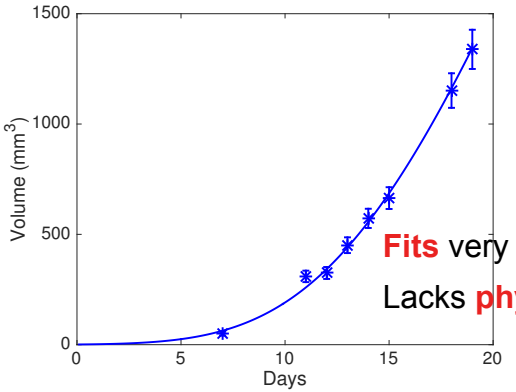
Exponential





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

Gompertz

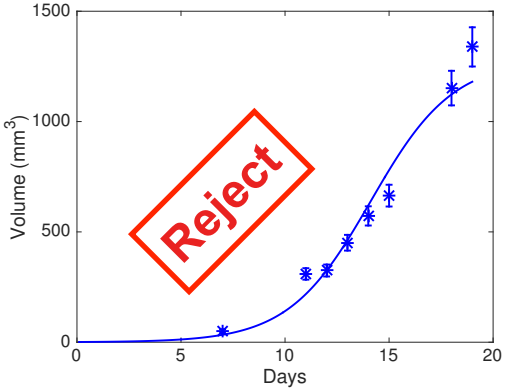


$$\frac{dV}{dt} = \alpha e^{-\beta t} V$$

Fits very well

Lacks **physiological** interpretation

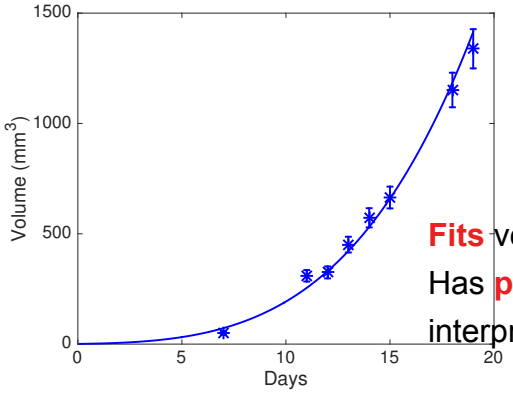
Logistic



Competition

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

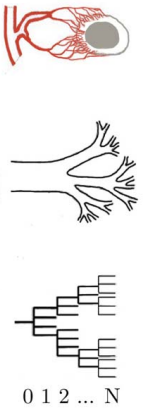
Power law



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

Fits very well

Has **physiological** interpretation



Benzekry et al., PloS Comp Biol, 2014

Goodness of fit metrics

Sum of Squared Errors

$$SSE^i = \sum_{j=1}^{n^i} \left(\frac{V_j^i - V(t_j^i, \hat{\theta}^i)}{\hat{\sigma}_j^i} \right)^2$$

Akaike Information Criterion

$$AIC^i = -2l(\hat{\theta}^i) + 2p$$

number of parameters

Model	SSE	AIC	RMSE	R2	p > 0.05	#
Power law	**0.164(0.0158 - 0.646)[1]**	**-18.4(-43.2 - 1.63)[1]**	**0.415(0.145 - 0.899)[1]**	**0.97(0.801 - 0.998)[1]**	100	2
Gompertz	0.176(0.019 - 0.613)[2]	-16.9(-48.2 - 1.1)[2]	0.433(0.156 - 0.875)[2]	0.971(0.828 - 0.997)[2]	100	2
Logistic	0.404(0.0869 - 0.85)[3]	-5.41(-18.4 - 3.88)[3]	0.665(0.331 - 1)[3]	0.908(0.712 - 0.989)[3]	100	2
Exponential	1.9(0.31 - 3.56)[4]	10.7(-5.38 - 23.1)[4]	1.4(0.595 - 1.95)[4]	0.69(0.454 - 0.944)[4]	15	1

Root Mean Squared Errors

$$RMSE^i = \sqrt{\frac{1}{n-p} SSE^i}$$

R^2

$$R^{2,j} = 1 - \frac{\sum_j \left(V_j^i - V(t_j^i; \hat{\theta}^i) \right)^2}{\sum_j \left(V_j^i - \overline{V^i} \right)^2}$$

Parameter values and identifiability

Model	Par.	Unit	Median value (CV)	NSE (%) (CV)
Power law	α	$\text{mm}^{3(1-\gamma)} \cdot \text{day}^{-1}$	0.886 (30.8)	8.17 (52.5)
	γ	-	0.788 (7.56)	2.28 (58.6)
Gompertz	α_0	day^{-1}	1.68 (23.5)	6.11 (82.9)
	β	day^{-1}	0.0703 (28)	8.35 (92.9)
Logistic	a	day^{-1}	0.474 (13.3)	2.93 (23.3)
	K	mm^3	1.92e+03 (36.7)	15.8 (28.7)
Exponential	a	day^{-1}	0.356 (12.9)	2.53 (19.4)
Generalized logistic	a	$[day^{-1}]$	2555 (148)	2.36e+05 (137)
	K	$[mm^3]$	4378 (307)	165 (220)
	α	-	0.0001413 (199)	2.36e+05 (137)

NSE = Normalized Standard Error ⟷ practical identifiability

$$\hat{\theta} \sim \mathcal{N}\left(\theta^*, \hat{\sigma}^2 \left(J \cdot J^T\right)^{-1}\right)$$

$$se\left(\hat{\theta}^k\right) = \sqrt{\hat{\sigma}^2 \left(J \cdot J^T\right)_{k,k}}$$

Outline

1. **Tumor growth**

    1.1. Introduction

    1.2. Tumor growth laws

    1.3. Angiogenesis and the Hahnfeldt model

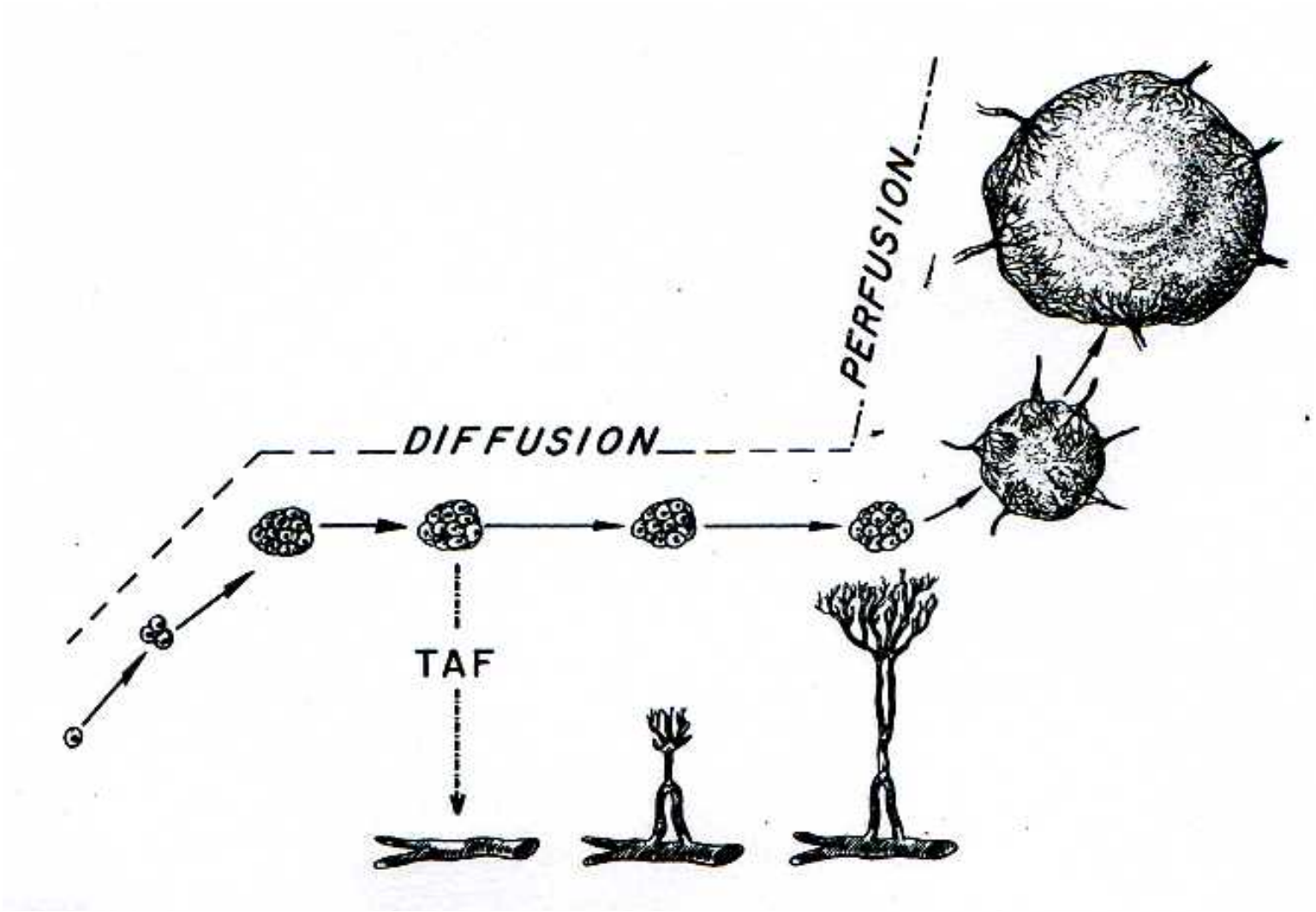
    1.4. Tumor-tumor interactions

    1.5. Prediction

    1.6. Meningioma and heterogeneity

    1.7. Spatial models

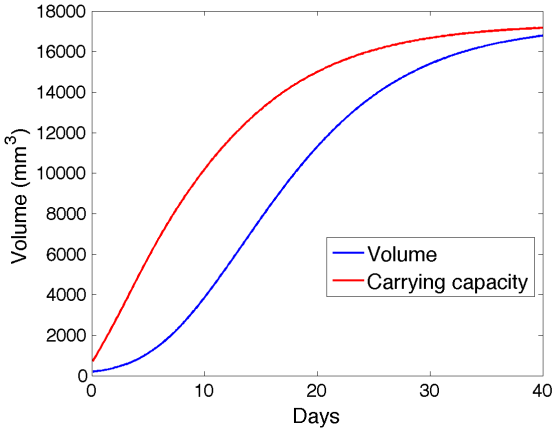
Angiogenesis



J. Folkman, Tumor angiogenesis: therapeutic implications, N Engl J Med, 1971

A model integrating angiogenesis

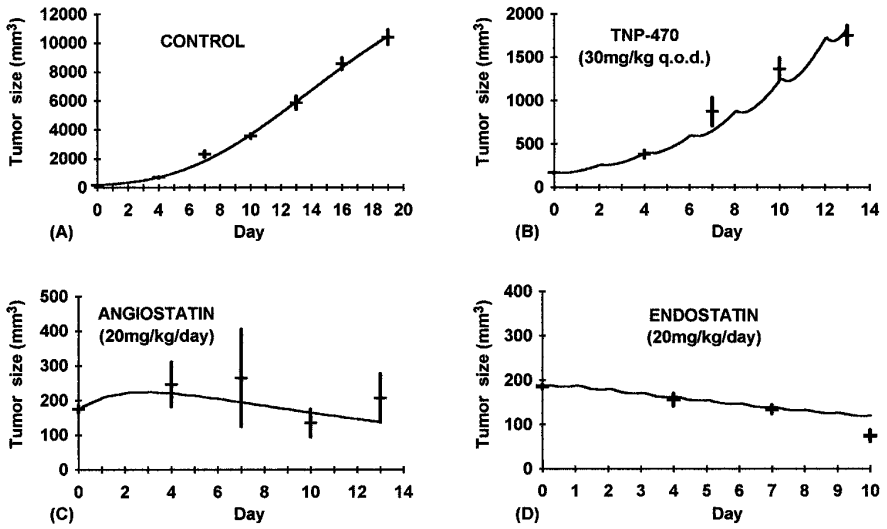
- **Dynamic carrying capacity**
- Biophysical derivation of the balance between pro and anti-angiogenic factors
- Allows integration of the action of **anti-angiogenic drugs**
- Also gives a framework for understanding **post-vascular dormancy**



$$\begin{cases} \frac{dV}{dt} = aV \ln\left(\frac{K}{V}\right) \\ \frac{dK}{dt} = bV - dV^{2/3}K \\ K(t=0) = K_0 \end{cases}$$

stimulation of angiogenesis

inhibition of angiogenesis

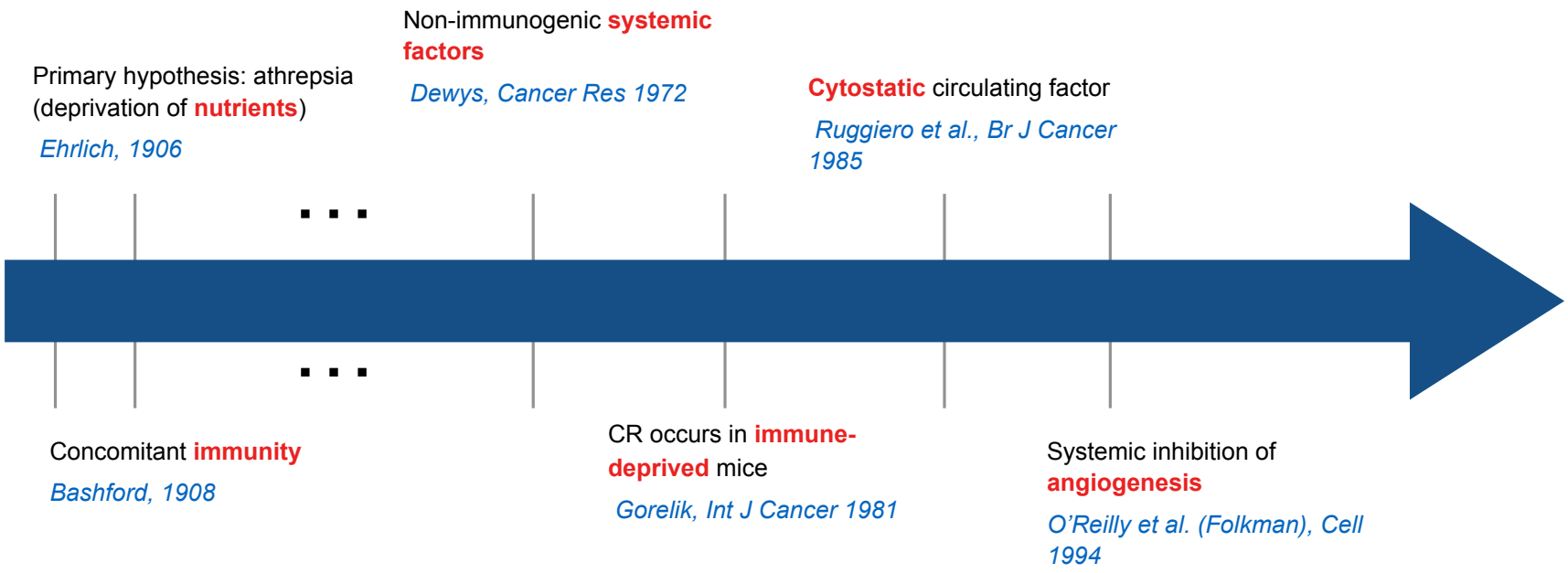


Hahnfeldt et al. (Folkman), Cancer Res, 1999

Concomitant tumor resistance

- **Inhibition** of secondary **growth** by a primary mass

- Critical clinical implications in terms of **post-surgery metastatic acceleration**



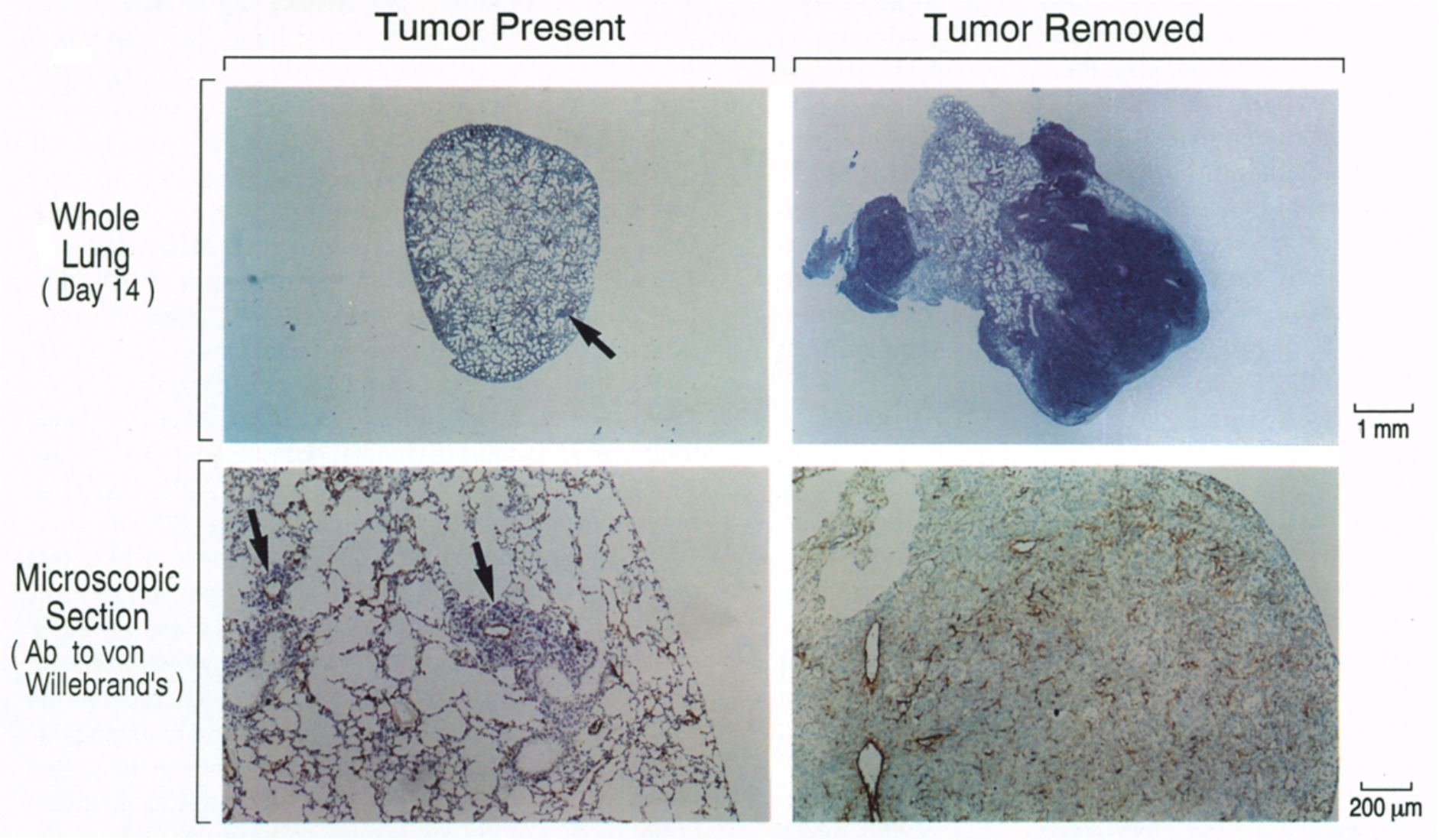


Figure 2. The Presence of a Primary Tumor Is Associated with an Inhibition of Neovascularization and Growth of Its Metastases

O'Reilly, Folkman et al., Angiostatin: A Novel Angiogenesis Inhibitor That Mediates te Suppression of Metastases by a Lewis Lung Carcinoma, *Cell 1994*

Questions and experiment

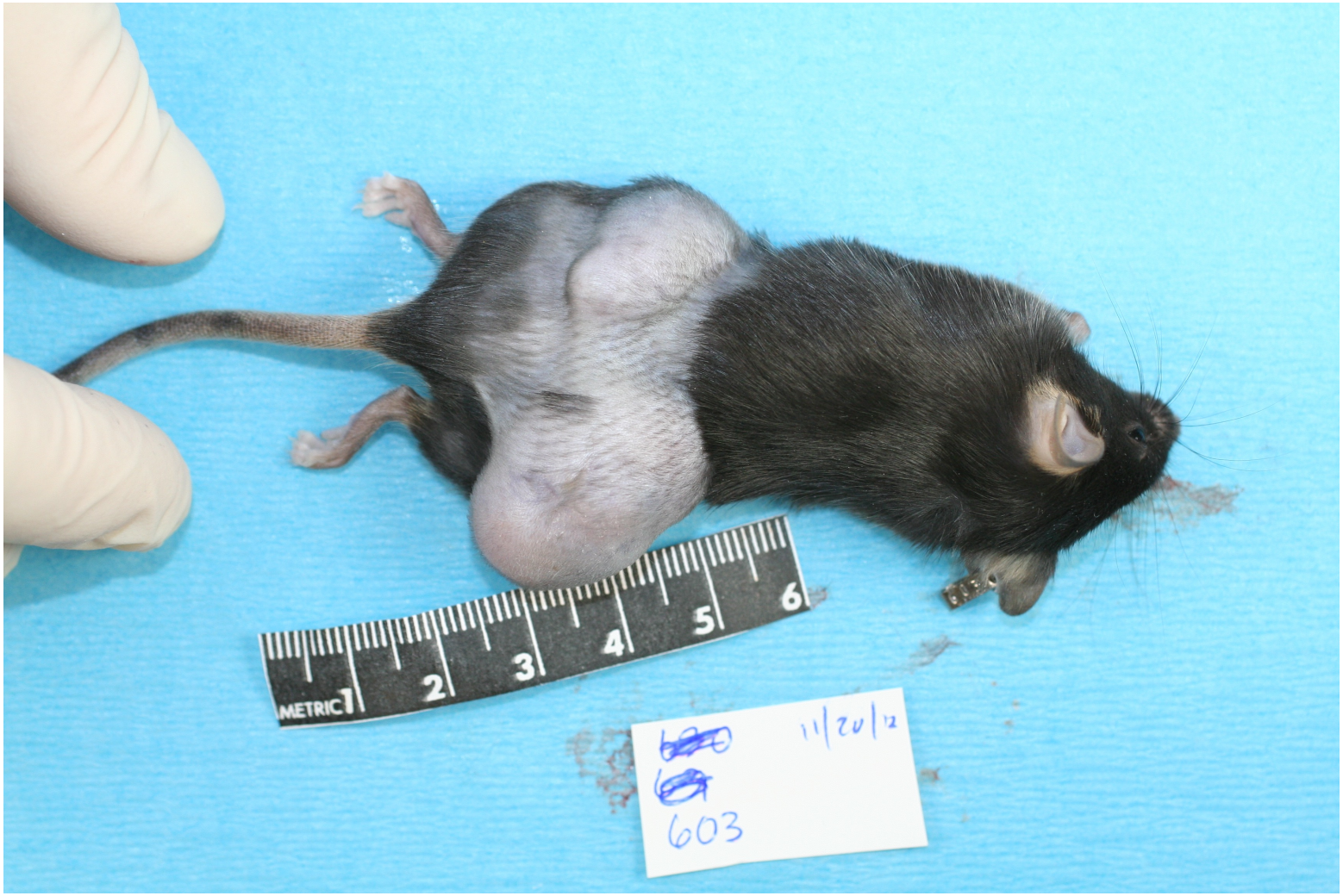
Questions

- **Quantitatively** distinguish between qualitatively valid **theories** of tumor-tumor interactions
- Establish and validate a **minimal model able to simulate tumor-tumor interactions**

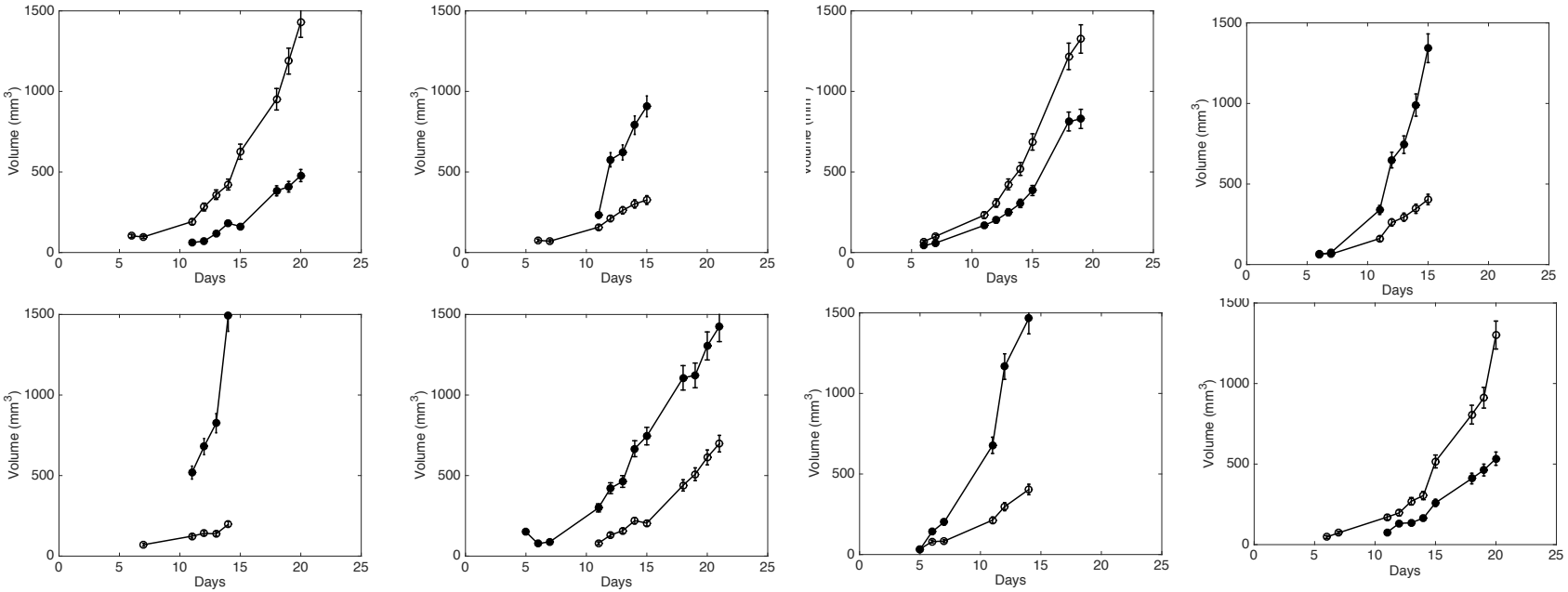
Experiment

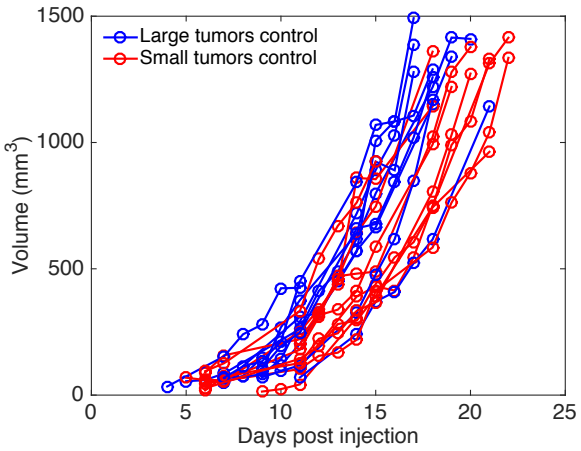
- Injection s.c. of **two tumors** of 10^6 LLC cells in C57/BL6 mice
- Two groups
  - Control: only one tumor
  - Group S: **simultaneous** injection of cells in two different sites

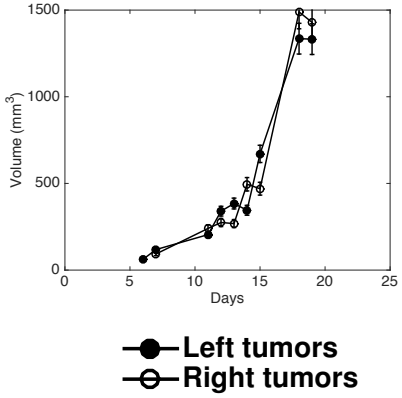
A mouse with two tumors

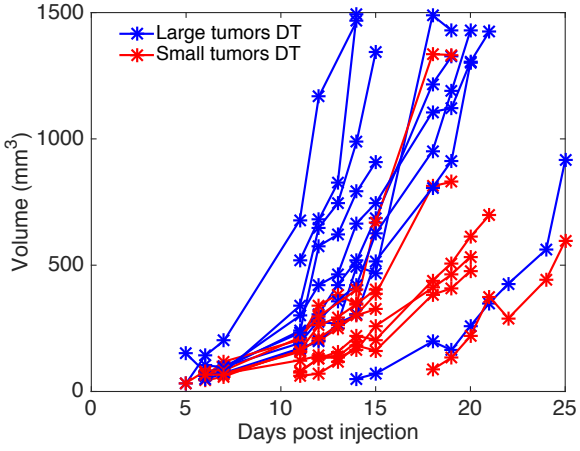


Something happens. One tumor has normal volume and the other is smaller







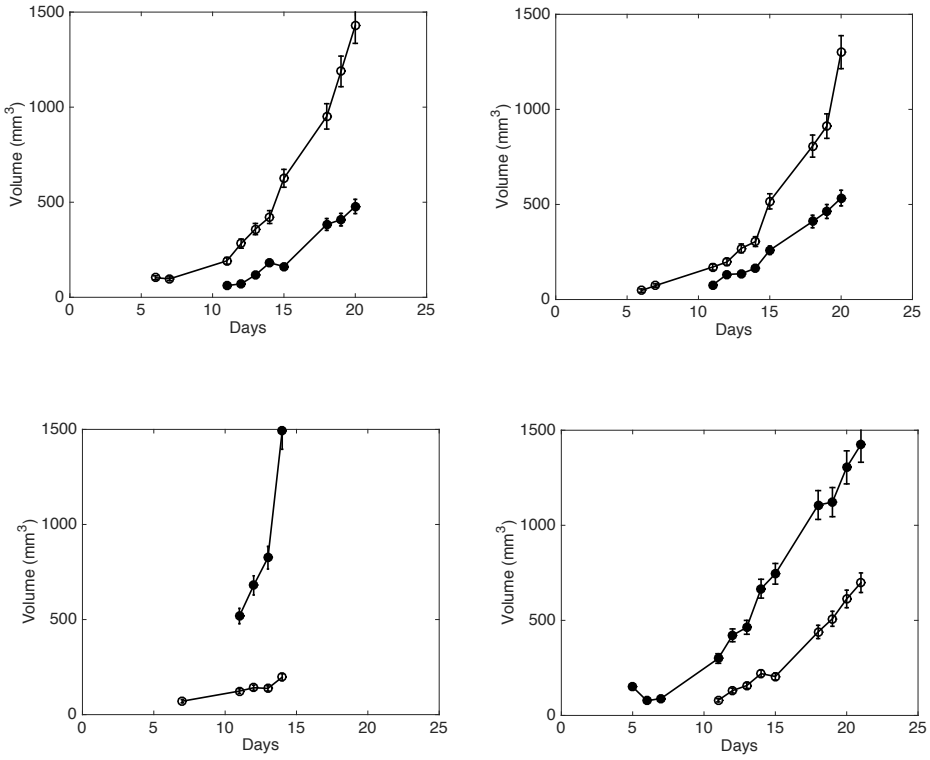


Control group (single tumors)

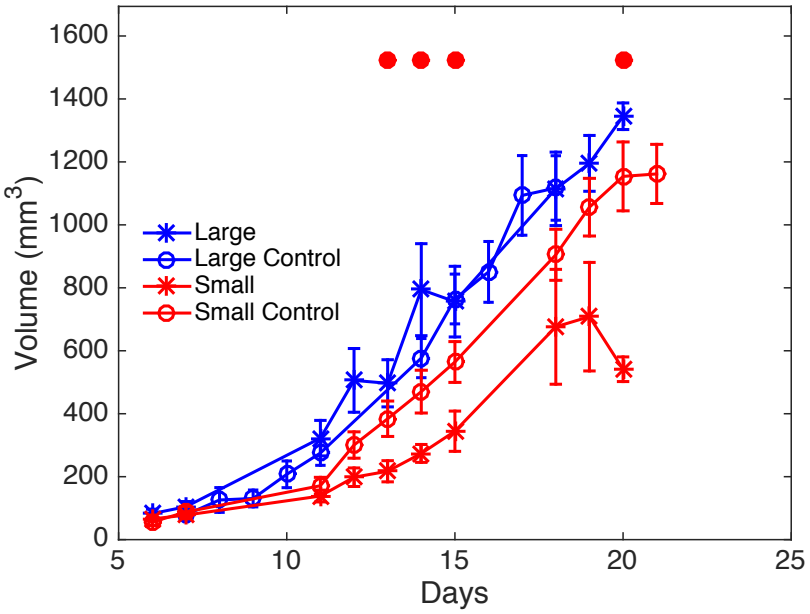
Double tumors

One tumor has normal growth and the other is suppressed

Individual growth kinetics



Small/Large in two-tumor bearing animals VS artificially paired small/large controls

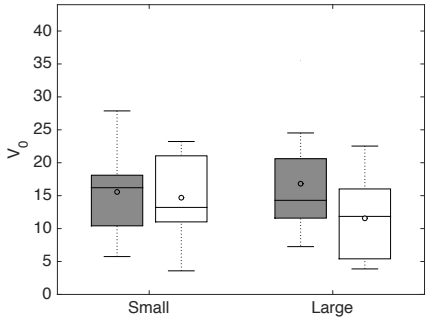


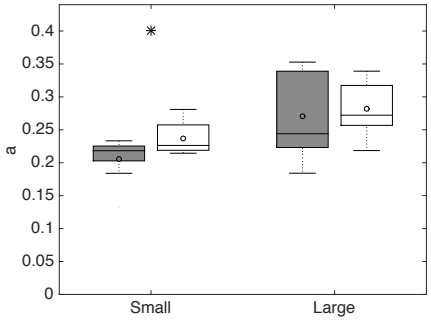
Benzekry et al., Cancer Res, 2017

Single-tumor growth models

Exponential V0

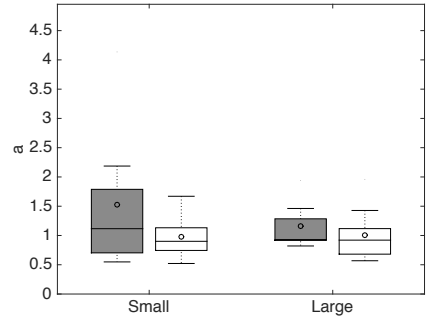
$$\begin{cases} \frac{dV}{dt} = aV \\ V(t=0) = V_0 \end{cases}$$

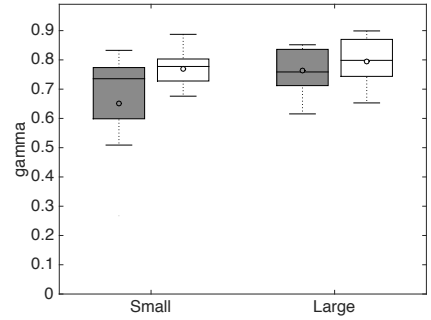




Power law

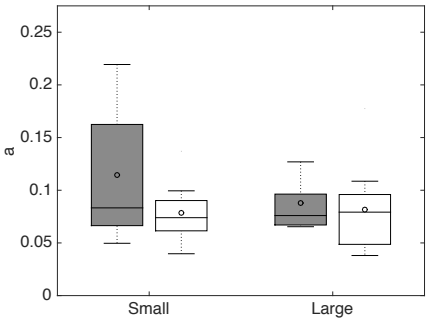
$$\begin{cases} \frac{dV}{dt} = aV^{\gamma} \\ V(t=0) = 1\ mm^3 = 10^6\ cells \end{cases}$$

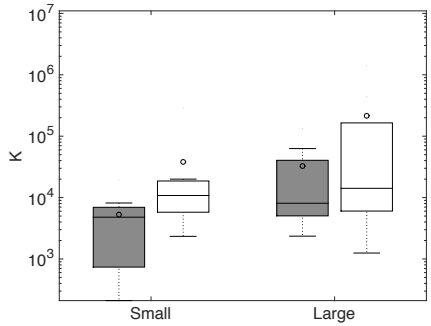


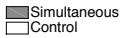


Gompertz

$$\begin{cases} \frac{dV}{dt} = aV \ln\left(\frac{K}{V}\right) \\ V(t=0) = 1\ mm^3 = 10^6\ cells \end{cases}$$







Two-tumors models

- Requirements:
  - **Symmetry:** same parameters for tumor 1 and tumor 2
  - Should resume to **single tumor growth** in the absence of the other tumor
- Main assumption for the difference between the two tumors: difference in **the initial take** ($V_{0,1}$ = 1, $V_{0,2}$ = 0.75)
- Difference in the growth kinetics should not result from difference in V_0
- Model selection (rejection) criteria: goodness-of-fit + parameter identifiability

Competition

$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K}{V_1+V_2}\right), & V_1(t=0) = V_{0,1} \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K}{V_1+V_2}\right), & V_2(t=0) = V_{0,2} \end{cases}$$

Angiogenesis inhibition

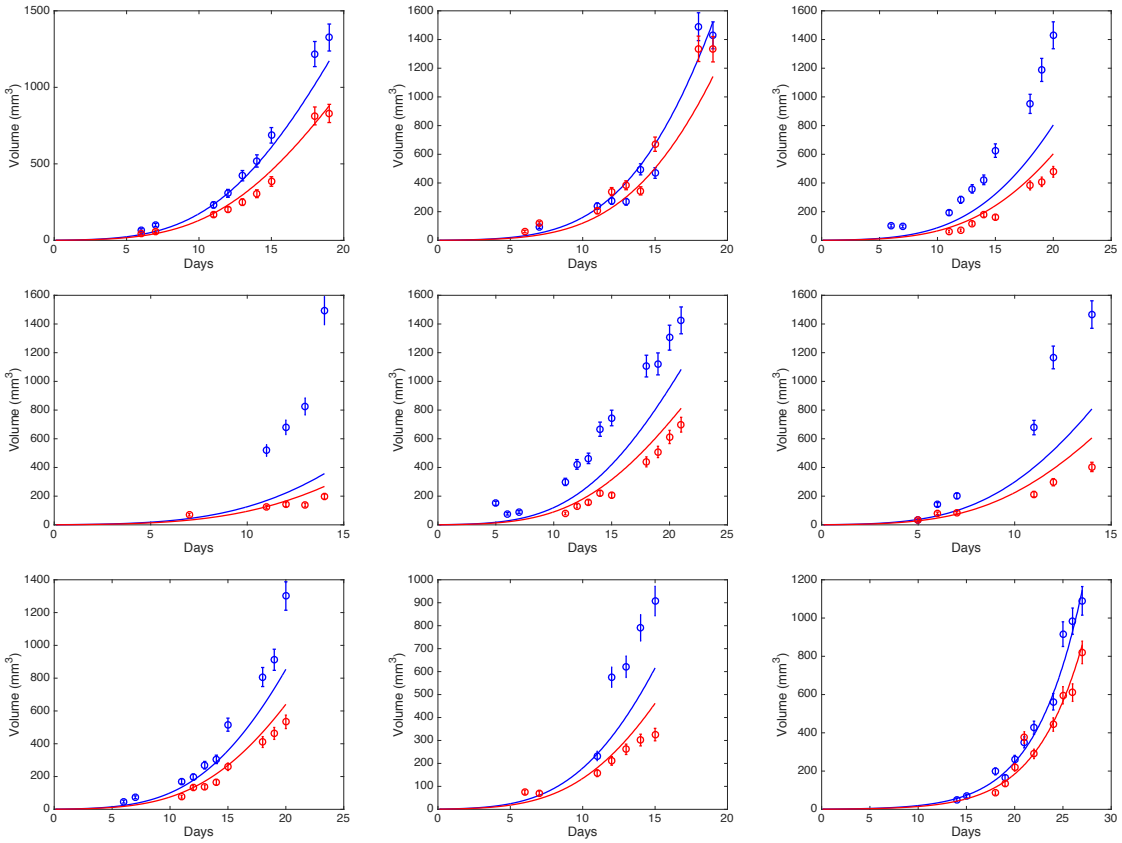
$$\begin{cases} \frac{dV_1}{dt} = aV_1 \ln\left(\frac{K_1}{V_1}\right), & V_1(t=0) = V_{0,1} \\ \frac{dK_1}{dt} = bV_1 - dV_1^{\frac{2}{3}}K_1 - eV_2 1_{K_1>K_0}, & K_1(t=0) = K_0 \\ \frac{dV_2}{dt} = aV_2 \ln\left(\frac{K_2}{V_2}\right), & V_2(t=0) = V_{0,2} \\ \frac{dK_2}{dt} = bV_2 - dV_2^{\frac{2}{3}}K_2 - eV_1 1_{K_2>K_0}, & K_2(t=0) = K_0 \end{cases}$$

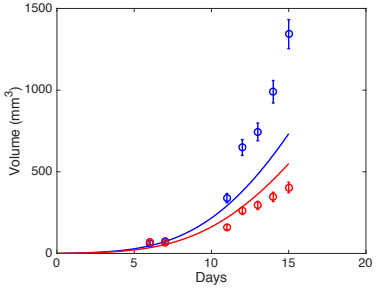
Proliferation inhibition

$$\begin{cases} \frac{dP_1}{dt} = \alpha P_1 - (\beta P_1 + \gamma(P_1+P_2))1_{P_1>0}, & P_1(t=0) = V_{0,1} \\ \frac{dQ_1}{dt} = \beta P_1 + \gamma(P_1+P_2), & Q_1(t=0) = 0 \\ \frac{dP_2}{dt} = \alpha P_2 - (\beta P_2 + \gamma(P_1+P_2))1_{P_2>0}, & P_2(t=0) = V_{0,2} \\ \frac{dQ_2}{dt} = \beta P_2 + \gamma(P_1+P_2), & Q_2(t=0) = 0 \end{cases}$$

Benzekry et al., Cancer Res, 2017

The competition model does not fit

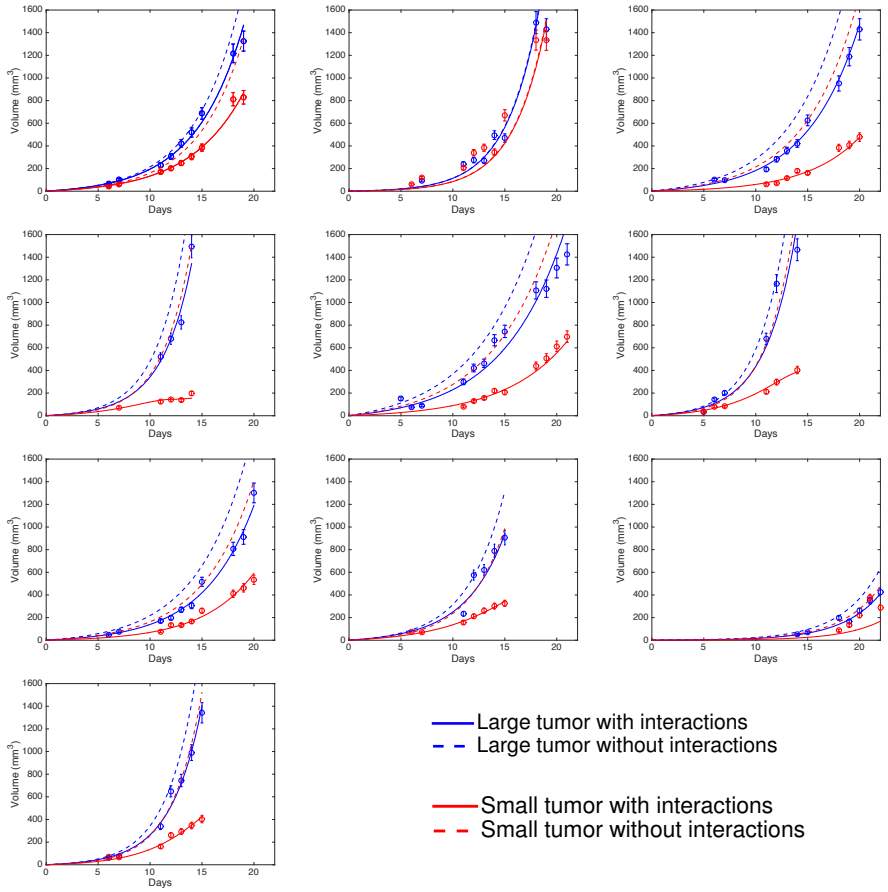


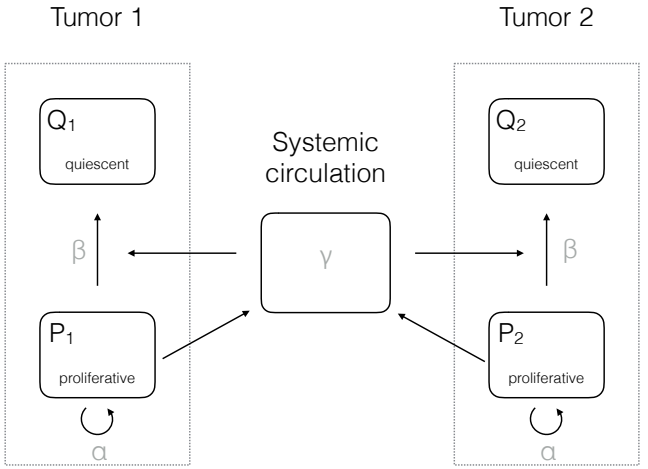


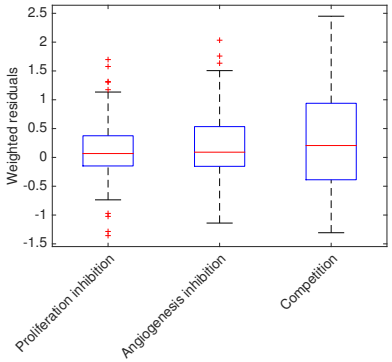
$$\begin{cases} \dfrac{dV_1}{dt} = aV_1 \ln\left(\dfrac{K}{V_1 + V_2}\right), & V_1(t=0) = V_{0,1} \\ \dfrac{dV_2}{dt} = aV_2 \ln\left(\dfrac{K}{V_1 + V_2}\right), & V_2(t=0) = V_{0,2} \end{cases}$$

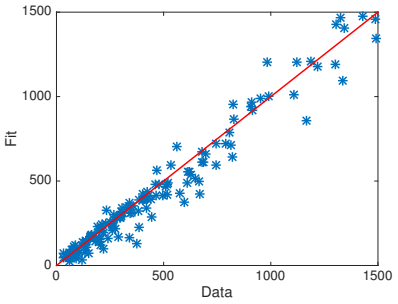
Benzekry et al., Cancer Res, 2017

The « inhibition of proliferation » model fitted best









Model	Par.	Unit	Median value (CV)	RSE (%)
Proliferation inhibition	α	day^{-1}	5.77 (67.4)	17.5
	β	day^{-1}	5.07 (49.3)	21.2
	γ	-	0.074 (2.69e+03)	2.47

Model	SSE	AIC	RMSE	R2	#
Proliferation inhibition	**0.204(0.0319 - 0.461)[1]**	**-14.2(-54 - -8.28)[1]**	**0.453(0.182 - 0.688)[1]**	**0.961(0.902 - 0.987)[1]**	3
Angiogenesis inhibition	0.336(0.154 - 0.772)[2]	-5.07(-27.5 - 5.67)[2]	0.588(0.4 - 0.891)[2]	0.957(0.645 - 0.986)[2]	3
Competition	0.666(0.141 - 2.2)[3]	0.71(-33.2 - 13.1)[3]	0.828(0.383 - 1.5)[3]	0.694(-0.0757 - 0.964)[3]	2

Benzekry et al., Cancer Res, 2017

Summary

- Exponential (proliferation) and logistic (competition) models **cannot explain tumor growth**
- **Gompertz** (phenomenological) and **power law** (biologically-grounded) models fit very well
- Hahnfeldt model for integration of **angiogenesis**
- There are **systemic interactions** between tumors in the same organism
- Competition alone cannot explain the phenomenon
- Systemic inhibition of angiogenesis or proliferation are **valid theories**

Outline

1. **Tumor growth**

    1.1. Introduction

    1.2. Tumor growth laws

    1.3. Angiogenesis and the Hahnfeldt model

    1.4. Tumor-tumor interactions

    1.5. Prediction

    1.6. Meningioma and heterogeneity

    1.7. Spatial models

Population approach: nonlinear mixed effects

- Usual fitting methods consider each **time series independently**

$$y_i^j = M(t_i^j, \theta^j) + \varepsilon_i^j$$

Individual $1 \le j \le N$

Time t_i

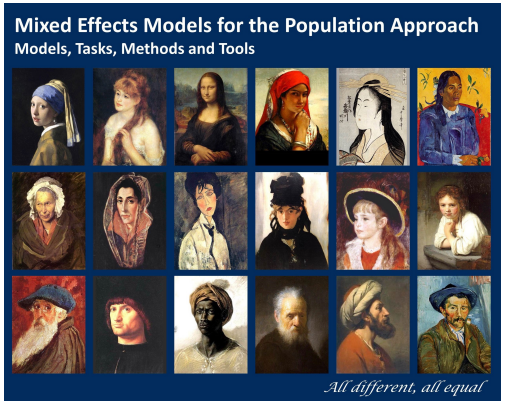
MLE →

$$\hat{\theta}^j = \underset{\theta}{\operatorname{argmin}} \sum \left(y_i^j - M(t_i^j, \theta)\right)^2$$

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

$$y_i^j = M(t_i^j, \theta^j) + \varepsilon_i^j$$

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



Lavielle,CRC press, 2014

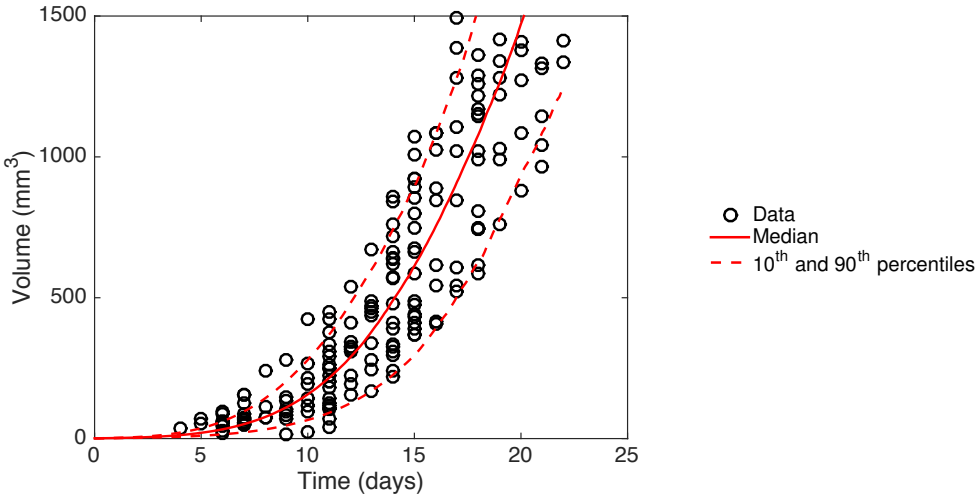
- **Reduces the number of parameters from *pxN to p+p²***

Population approach and its use for prediction

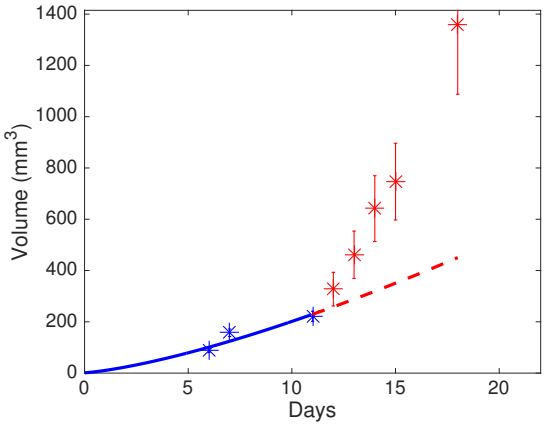
Nonlinear mixed-effects statistical modeling

$$y_j^i = M(t_j^i, \theta^i) + \varepsilon_j^i, \quad \varepsilon_j^i \sim \mathcal{N}(0, \sigma_j^i)$$

$$\theta^1, \cdots, \theta^N \sim \mathcal{LN}(\theta_{pop}, \theta_\omega), \quad \theta_{pop} \in \mathbb{R}^P, \theta_\omega \in \mathbb{R}^{P \times P}$$

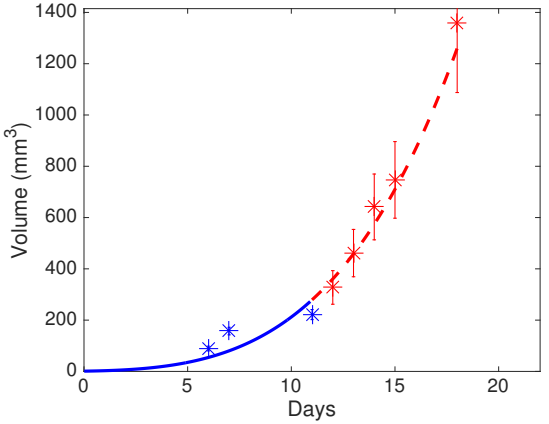


No a priori



With a priori (bayesian)

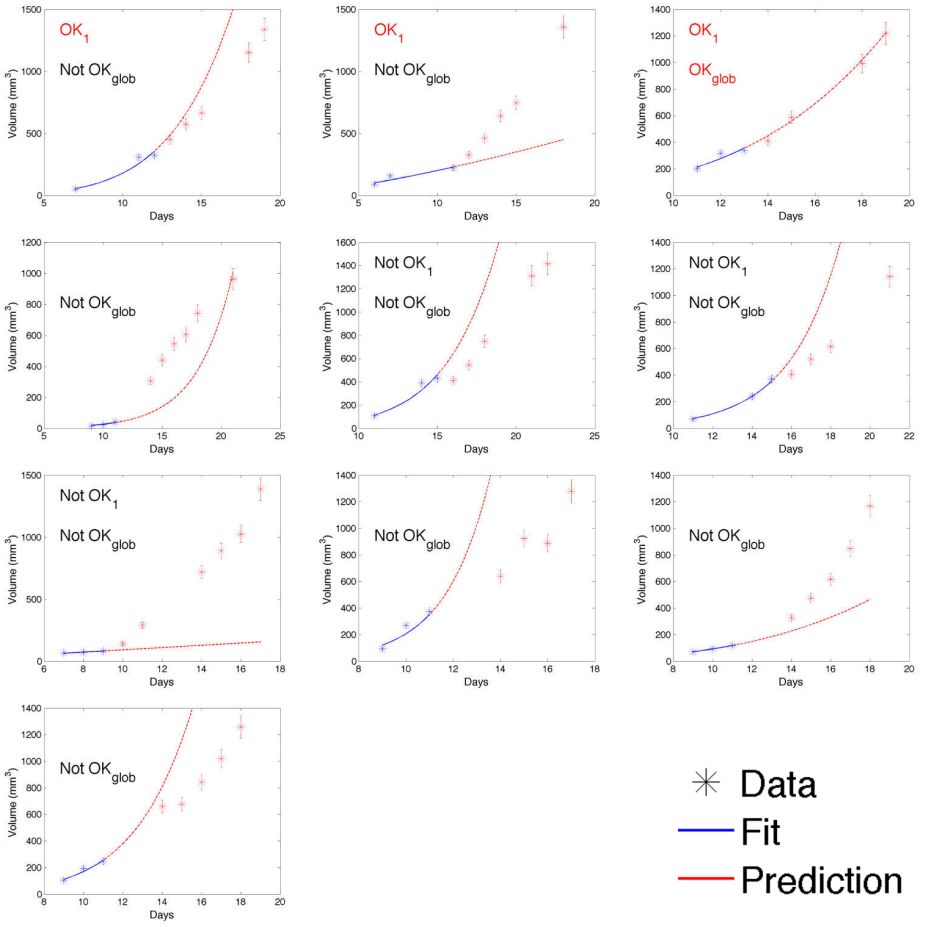
$$l(\theta^i) = \sum_{j=1}^{J^i} \frac{\left(y_j^i - M(t_j^i, \theta^i)\right)^2}{2\sigma^2} + \sum_{p=1}^{P} \frac{\left(\theta_p^i - \theta_{pop,p}\right)^2}{\theta_{\omega,p}^2} + C$$



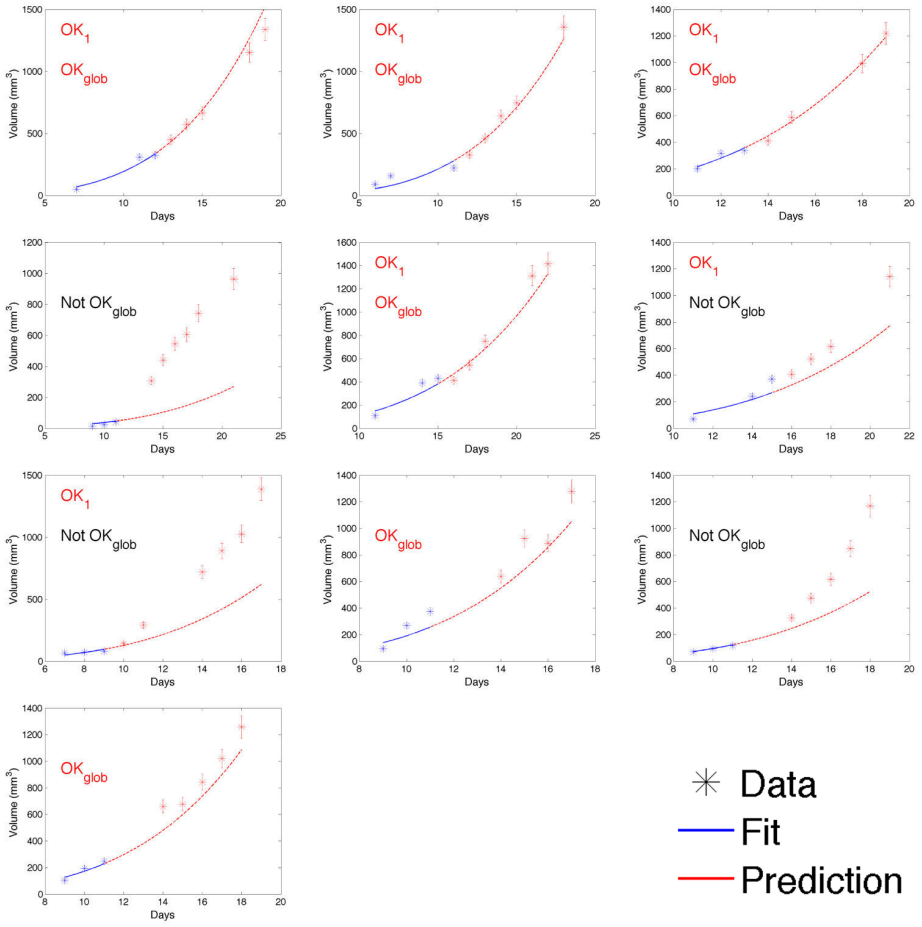
Benzekry et al., PloS Comp Biol, 2014

Power law model: all animals

No a priori

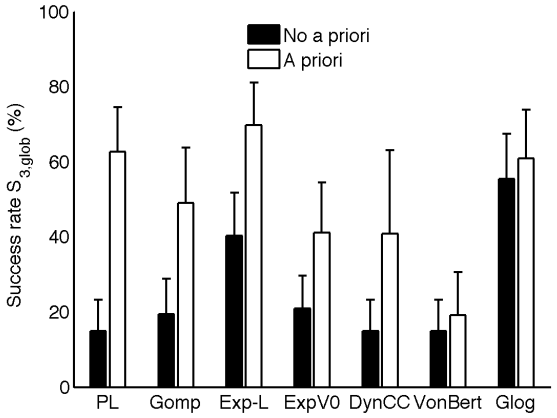


A priori

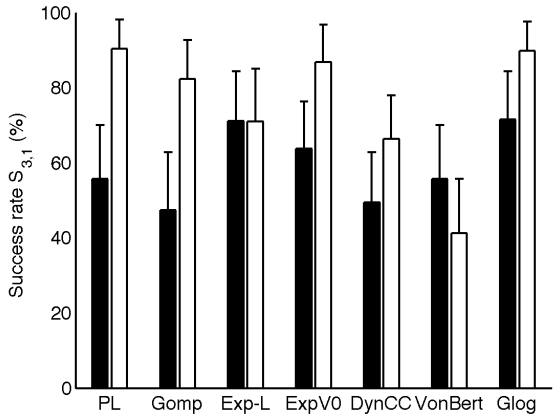


Prediction improvement for all models

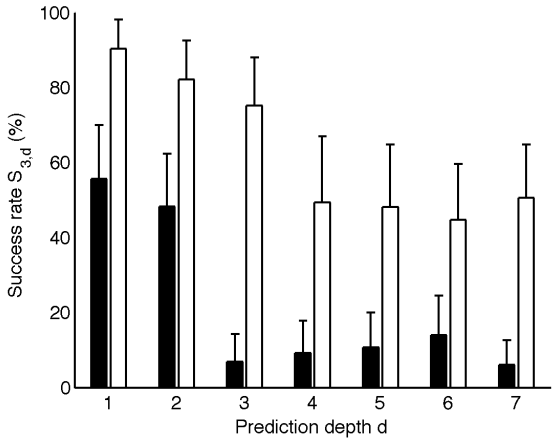
Full future curve



Next data point



All prediction depths Power law



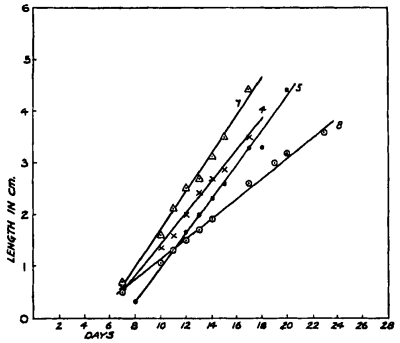
Randomly assign (100 replicates) half of the animals to the **« learning group »** and the other half to the **« predict » group**

Concise history of the development of spatial models

- First spatial considerations in a quantitative mathematical analysis of tumor growth in *Mayneord, Cancer Res, 1932*

  ⇒ derives the **linear growth** of rat sarcoma's

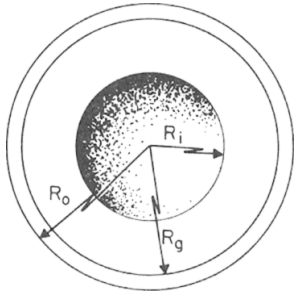
  radius the proliferative fraction is confined to a small rim



- Following J. Folkman's realization that avascular tumor growth is limited to a small size (mm) by the **diffusion** of nutrients, one of the first **partial differential equation** model of tumor growth was proposed by *Greenspan, Stud Appl Math, 1972*

  ⇒ tests hypotheses regarding the origin of a possible

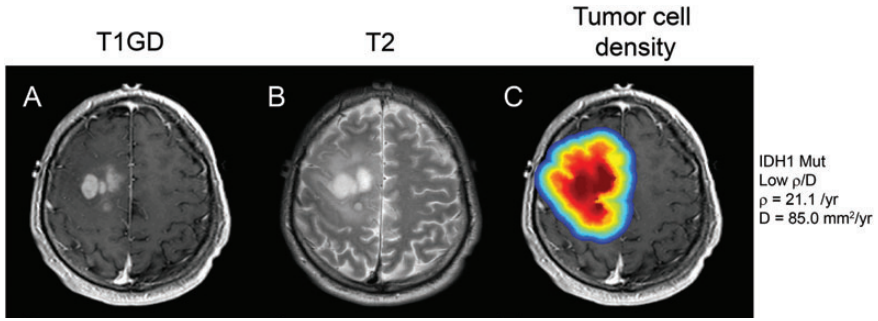
  inhibitory factor (necrotic core or proliferative cells)



Concise history of the development of spatial models, ctd

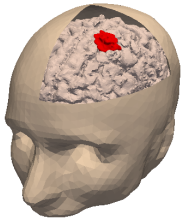
- Lots of **theoretical models** developed in the 1980s - 1990s *Adam, Byrne, Chaplain, Preziosi* : continuum mechanics based models viewing the tumor as a mixture

- Early 2000s: **reaction-diffusion** equations for the growth of gliomas (brain tumors) *Murray, Tracqui, Swanson*. Assumptions: proliferation + random motility ⇒ linear growth of the radius. Method to evaluate the invisible **infiltrative** part of the tumor

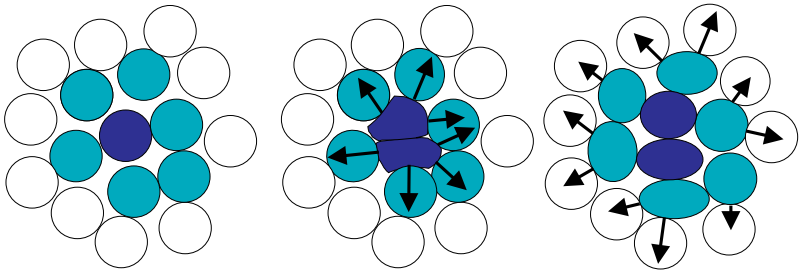


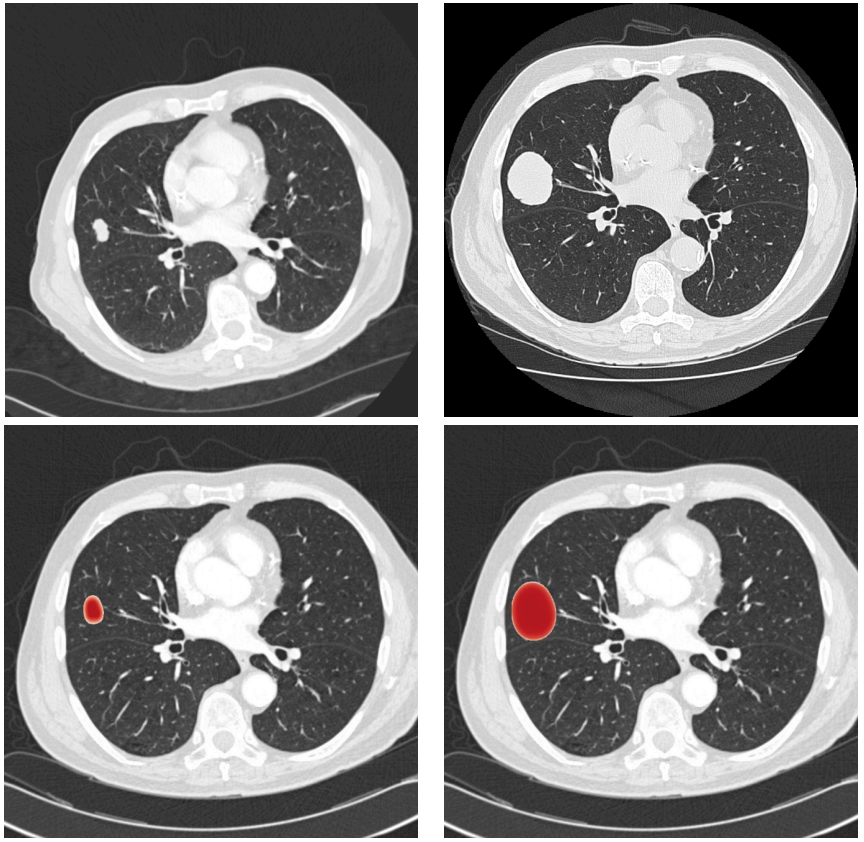
Baldock et al., Neuro-Oncology, 2014

- Early 2010s: use of clinical images to parameterize advection PDE models. *Saut, Colin*



Spatial models of tumor growth and clinical images





P = proliferative cells, S = healthy tissue

$$\partial_t P + \nabla \cdot (\mathbf{v} P) = (\gamma_p - \gamma_d) P,$$
$$\partial_t S + \nabla \cdot (\mathbf{v} S) = 0.$$

P+S = 1 $\Rightarrow$ $\nabla \cdot \mathbf{v} = (\gamma_p - \gamma_d) P.$

Closure hypothesis $\mathbf{v} = -k \nabla \Pi.$

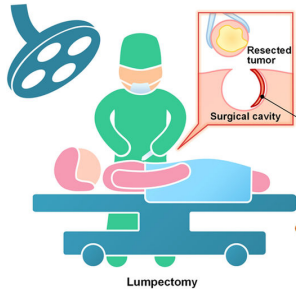
Jouganous, Palussière, Cornelis, Saut, Colin, J Comput Surg 2015

2 Therapies

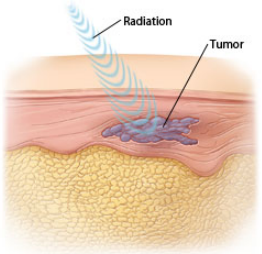
A brief overview of anti-cancer therapies

Ancient Egypt ~ 2000 BC

- First treatment when disease is localized and resectable ⇒ **surgery**



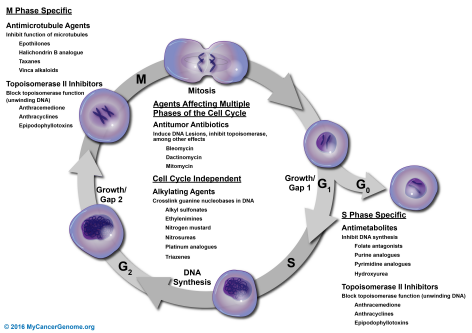
1900



- **Radiation** therapy

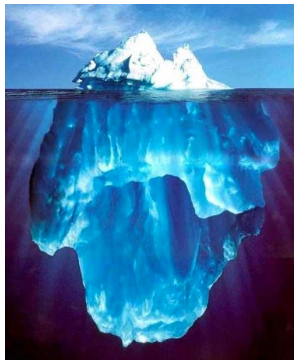
1950

- Cytotoxic **chemotherapy**



1970

- **Adjuvant** chemotherapy

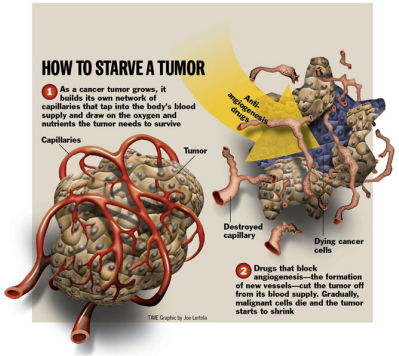


A brief overview of anti-cancer therapies

2001

- Biotargeted therapies

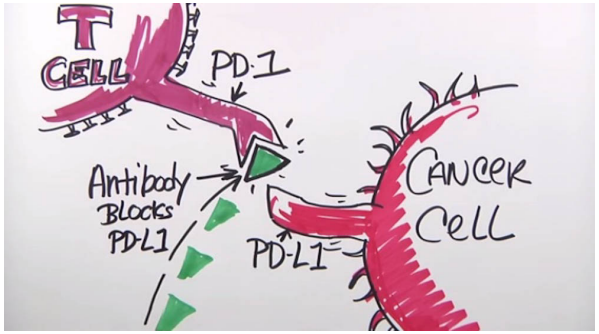
2004



- **Anti-angiogenic** therapy

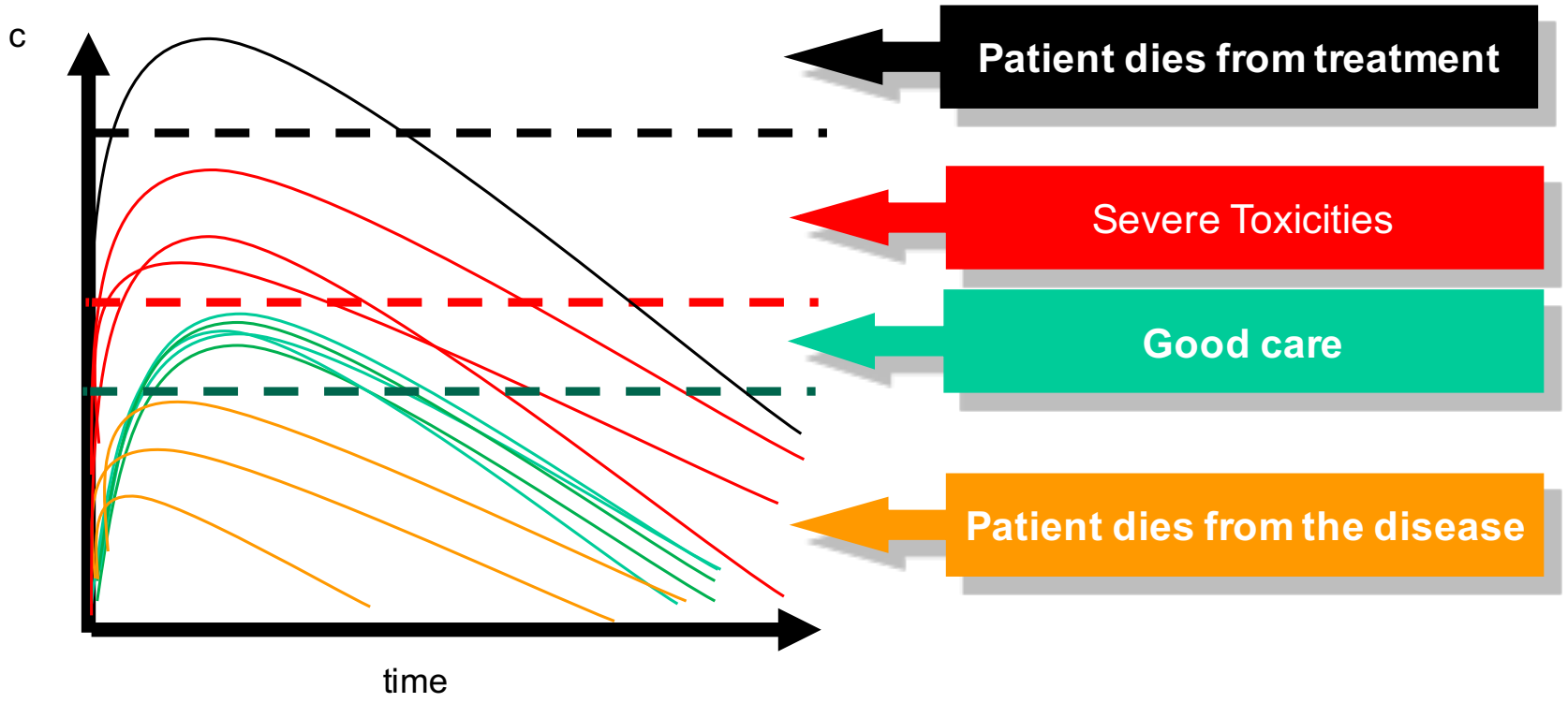
2010

- New generation **immunotherapy** (checkpoint inhibitors)

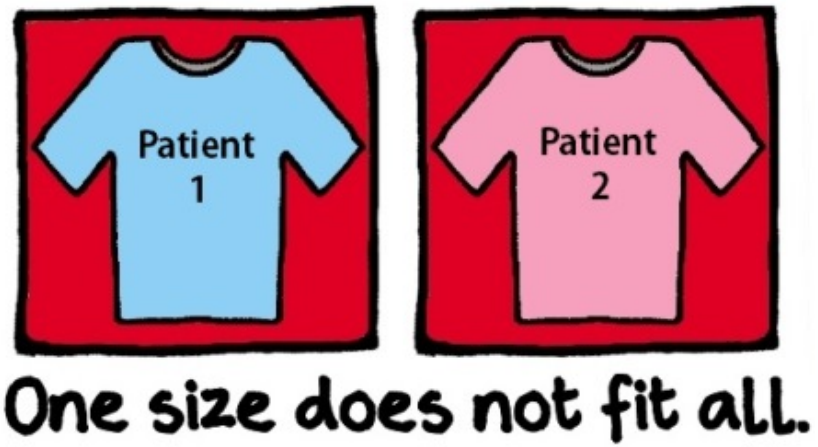


Where can mathematical models help?

Define the dose and scheduling of the drug administration



Personalize the treatment



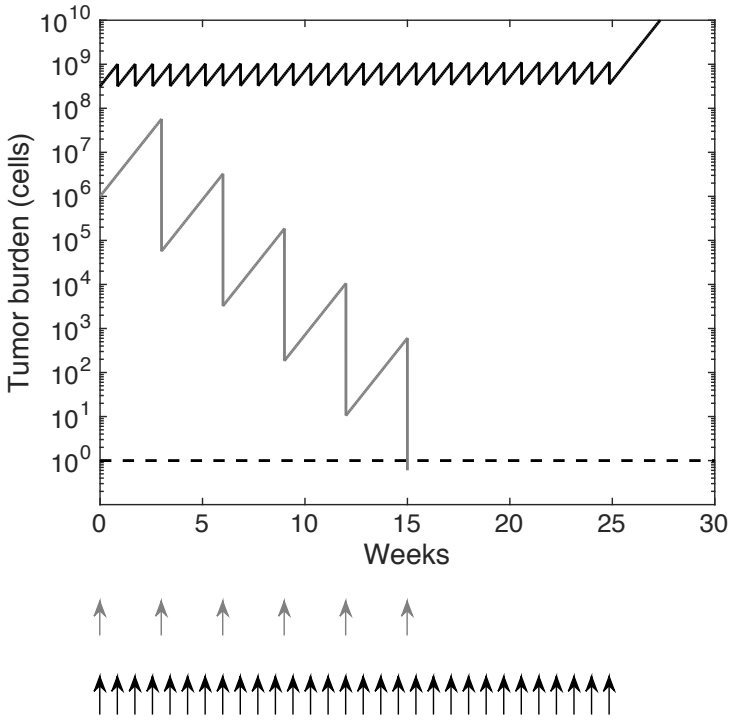
⇒ **adaptive** dosing strategies

Where does the Maximum Tolerated Dose (MTD) paradigm come from ?

Log-kill hypothesis

a given dose kills a **given fraction** of the tumor cell population

$$\frac{dN}{dt} = aN - eC(t)N$$



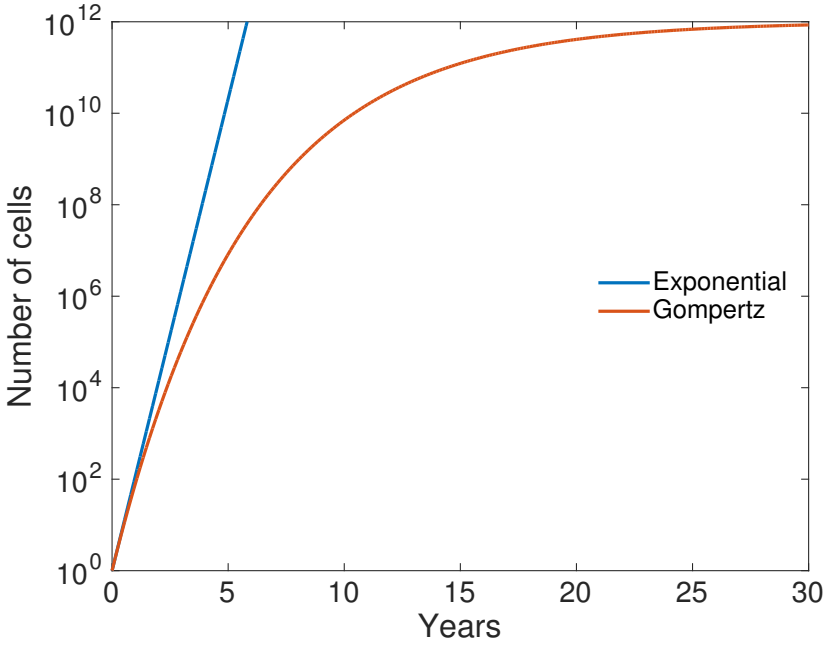
- Established on leukemic cell lines
- Focus: **curability**

"(...) it appears that **high-level, short-term** schedules offer considerably greater potential for obtaining "cures". This preference does not necessarily hold with regard to achieving **maximum increase in life** span of animals which die in spite of therapy"

Skipper, Schabel and Wilcox, Cancer Chemother Rep, 1964

The Norton-Simon hypothesis: tumor growth model

- Relative growth rate is not constant in time, it **decelerates**
- Challenges the exponential model ⇒ **Gompertz growth**

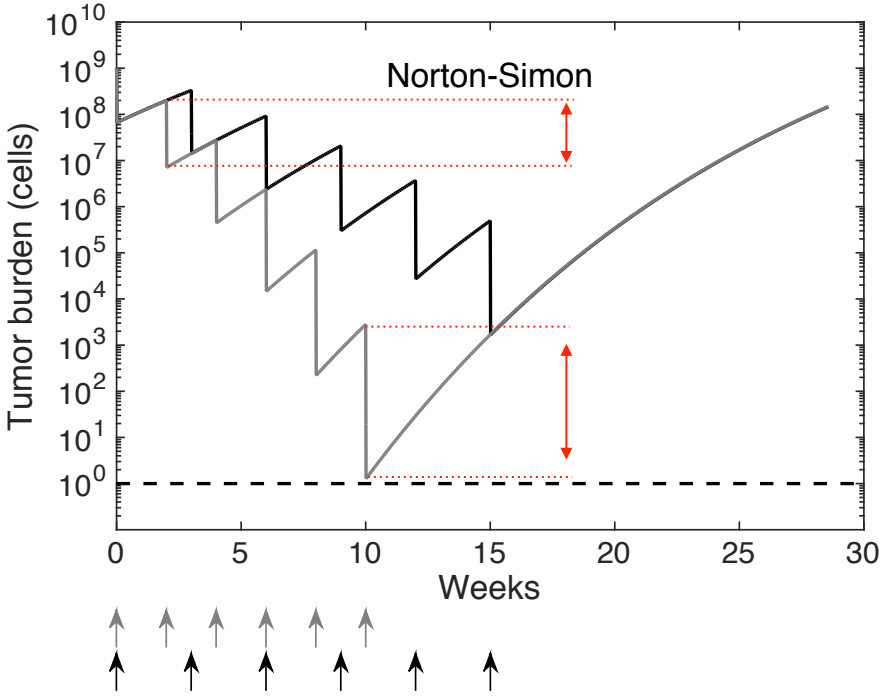


$$\frac{dN}{dt} = ae^{-bt}N$$

The Norton-Simon hypothesis

Second hypothesis: effect of the therapy is proportional to the **proliferative fraction only**

$$\frac{dN}{dt} = ae^{-bt}N - eC(t)e^{-bt}N$$



Norton, Simon, Cancer Treat Rep, 1976

- Suggested **densification of adjuvant chemotherapy** protocols in breast cancer
- Subsequently validated in phase III study

Citron et al., J Clin Oncol, 2003

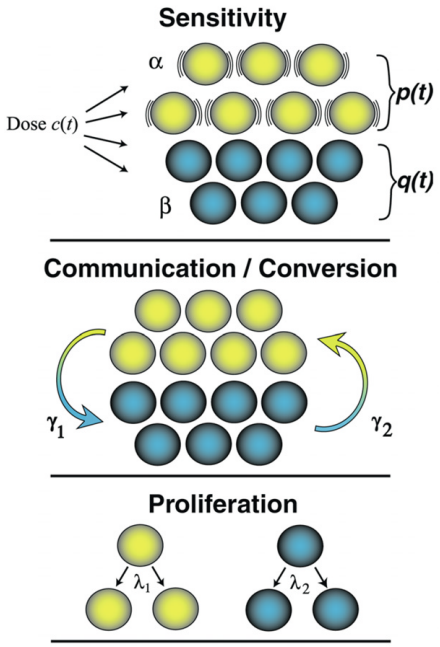
still focuses on **tumor eradication**

Tumor heterogeneity and re-sensitization

Minimizing Long-Term Tumor Burden: The Logic for Metronomic Chemotherapeutic Dosing and its Antiangiogenic Basis

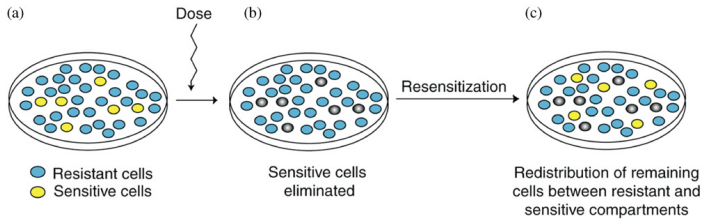
PHILIP HAHNFELDT*†‡, JUDAH FOLKMAN§‖¶ AND LYNN HLATKY†‡

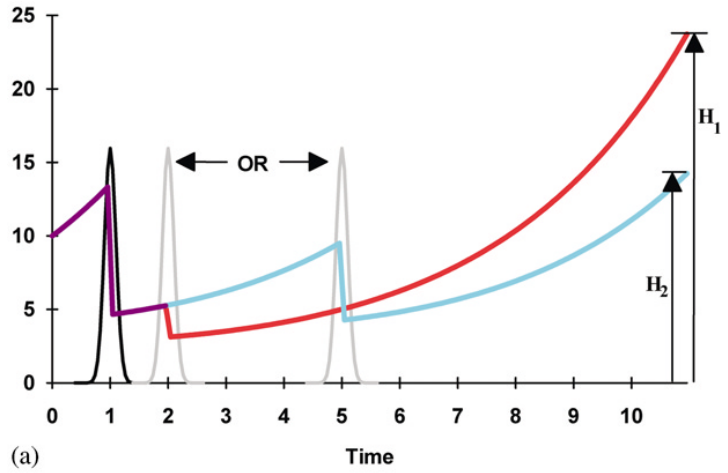
J Theor Biol, 2003

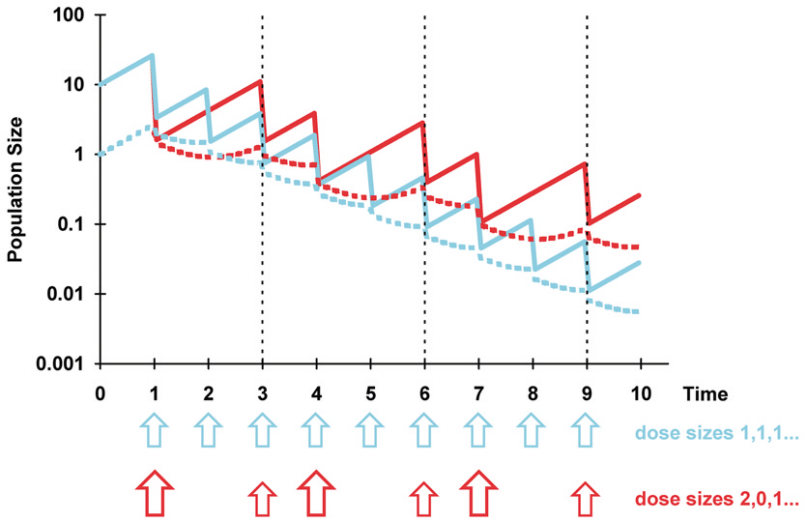


$$\frac{dp(t)}{dt} = \big(\lambda_1 - \gamma_1 - \alpha c(t)\big)p(t) + \gamma_2 q(t)$$

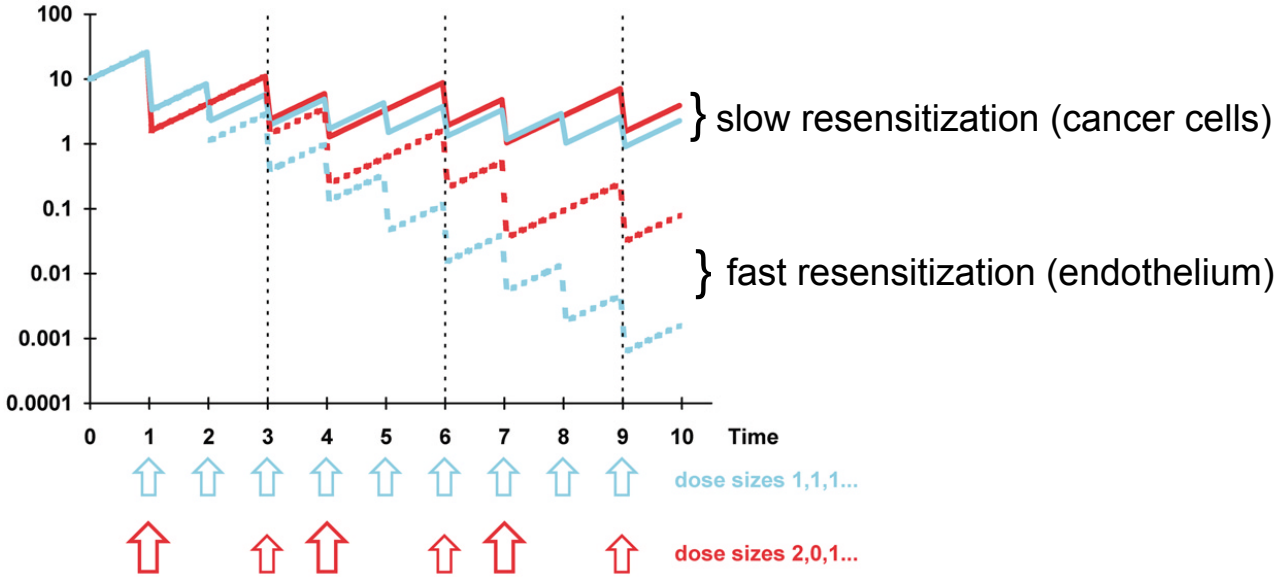
$$\frac{dq(t)}{dt} = \gamma_1 p(t) + \big(\lambda_2 - \gamma_2 - \beta c(t)\big)q(t)$$







Tumor heterogeneity and re-sensitization



- In the context of tumor heterogeneity, **long-term minimization** may often be the more practical objective
- **Metronomic scheduling** is the best way to achieve it
- Lends theoretical support to the **anti-angiogenic basis** of metronomic therapy as endothelial cells because of higher ability to desensitize

A dedicated model for metronomic chemotherapy

Hypotheses:

1. Chemo has an **anti-angiogenic** effect by killing proliferative endothelial cells.
2. Cancerous cells develop **resistances** to the CT whereas endothelial cells don't.
3. At low dose, the killing action of the drug is stronger on the endothelial compartment than on the tumor one

$$\begin{cases} \frac{dN}{dt} = aN\ln\left(\frac{K}{N}\right) - \alpha_1 e^{-R\int_0^t C(s)ds} C(t)N \\ \frac{dK}{dt} = bN - dN^{2/3}K - \alpha_2 C(t)K \end{cases}$$

AA effect — Resistance — CT effect

N = tumor cells

***K* = carrying capacity**

= vascular support

+ PK/PD model for exposure of the drug given the concentrations

Benzekry, Barbolosi, Andre et al., MMNP, 2012

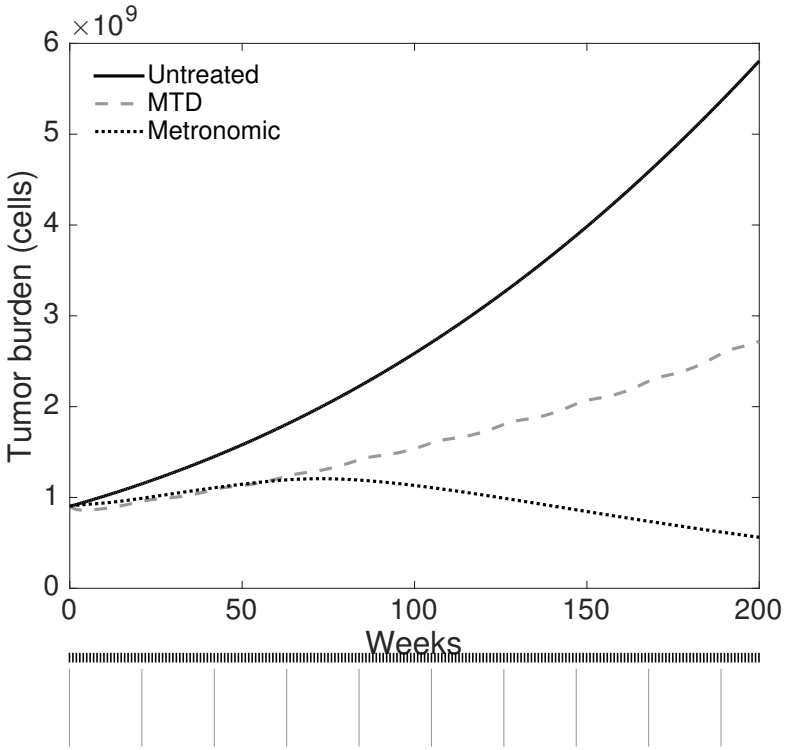
A dedicated model for metronomic chemotherapy

MTD schedule: 100 mg at day 0 of 21-days cycle

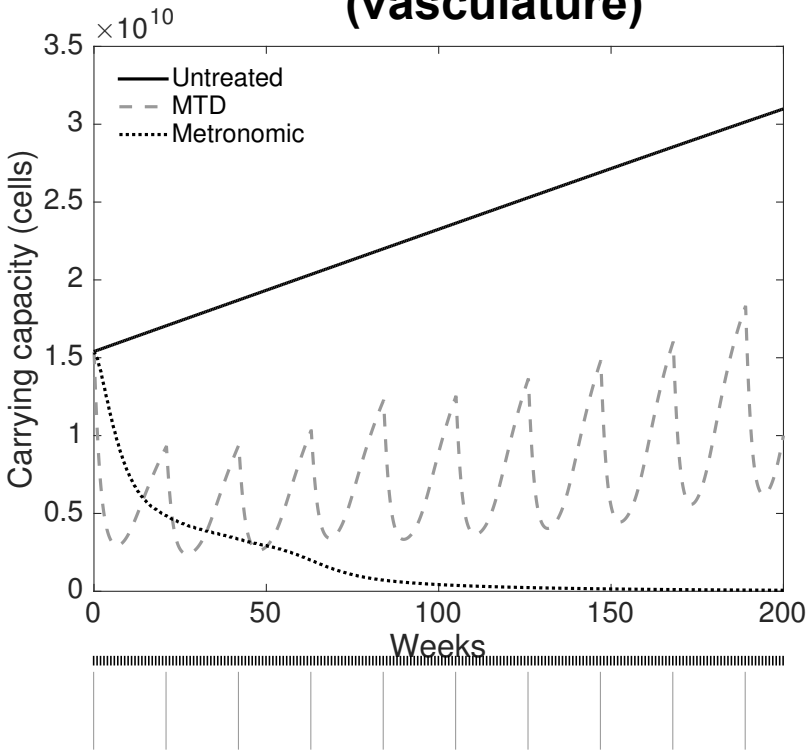
Metronomic schedule: 10 mg/day every day without resting period

Docetaxel PK/PD parameters

Tumor cells



Carrying capacity (vasculature)



Benzekry, Barbolosi, Andre et al., MMNP, 2012

Modeling of toxicity and scheduling of vinorelbine in NSCLC

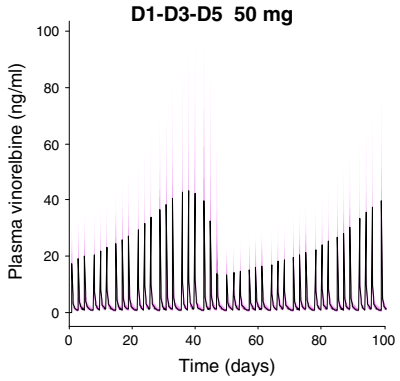
PK

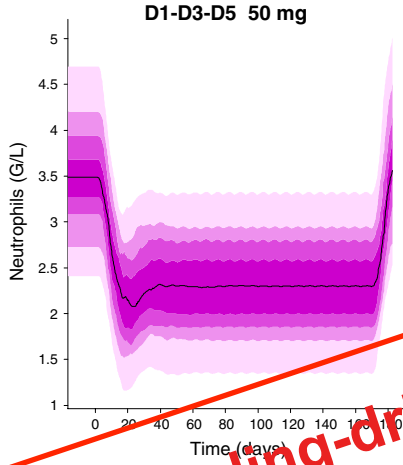
Toxicity

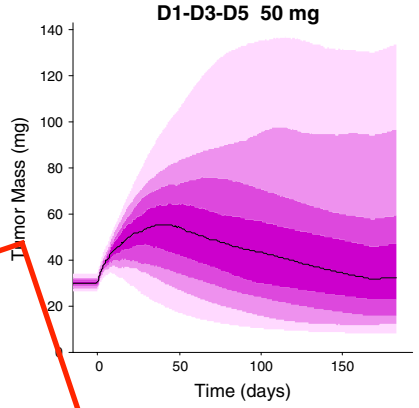
Efficacy

Standard scheduling

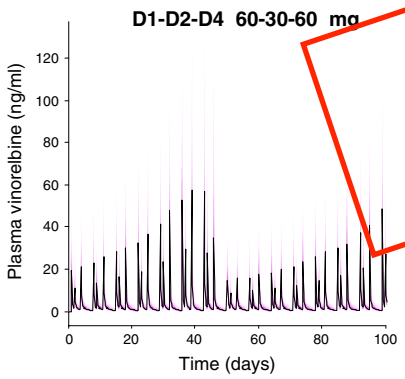
Briasoulis et al., Clin Cancer Res 2009

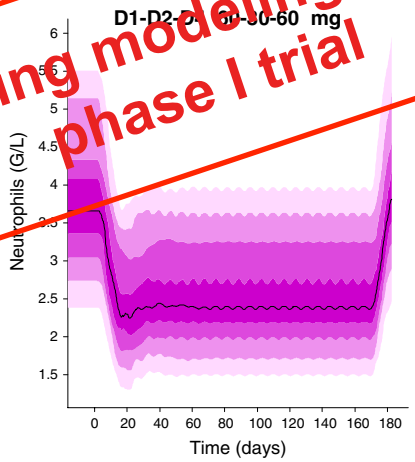


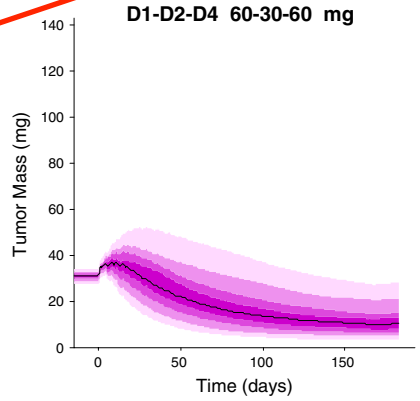




Model-based scheduling







Ongoing modeling-driven phase I trial

⇒ **ongoing phase I trial**

Barbolosi, André et al., Nat Rev Clin Oncol (2016)

Elharrar, Barbolosi, André et al. (2016)

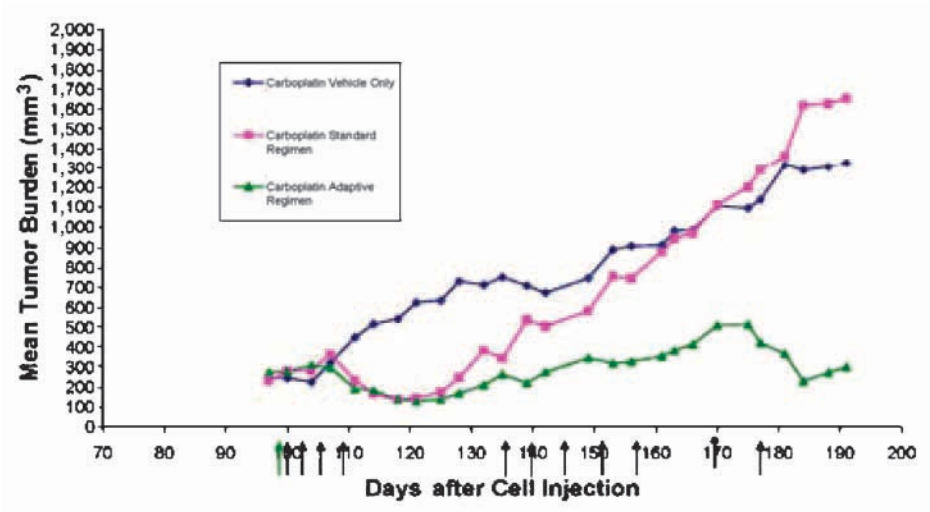
Adaptive therapy

- **Evolutionary** viewpoint of resistance to therapy. Darwinian selection
- **Complex** dynamics are hard to control. Why, then, use **fixed, rigid** protocols of drugs, dose and timing?
- Gatenby suggests to rather **adapt** the protocol as the tumor evolves in response to therapy

A change of strategy in the war on cancer

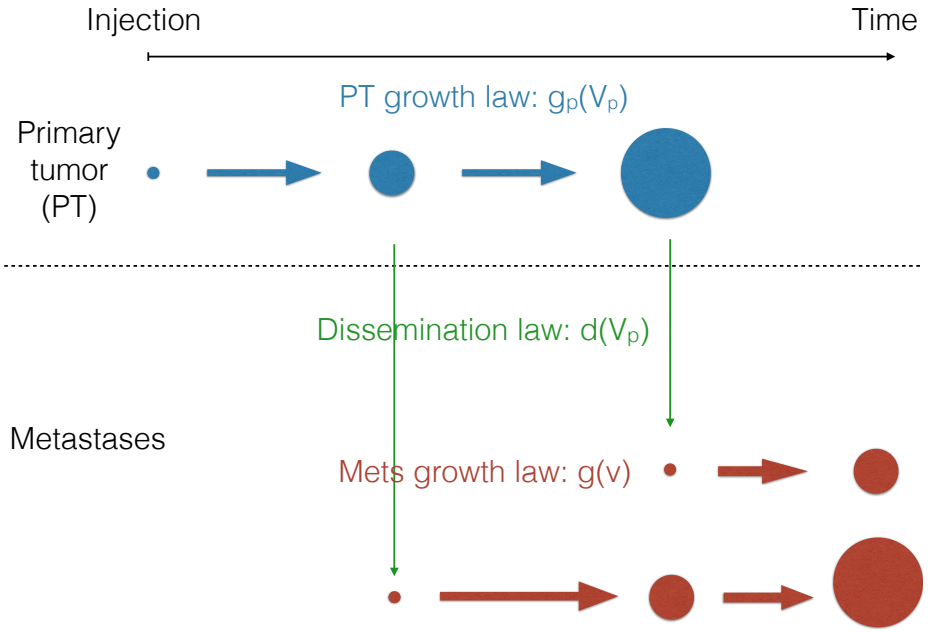
Patients and politicians anxiously await and increasingly demand a 'cure' for cancer. But trying to control the disease may prove a better plan than striving to cure it, says **Robert A. Gatenby**.

Gatenby, Nature, 2009

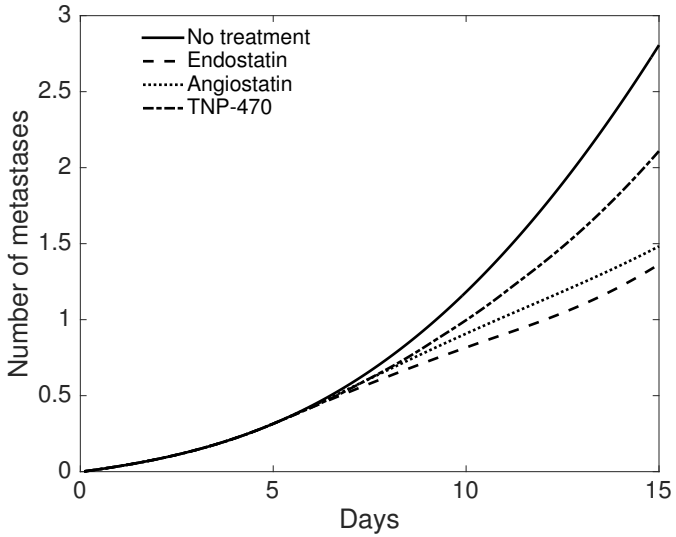


Gatenby et al., Cancer Res, 2009

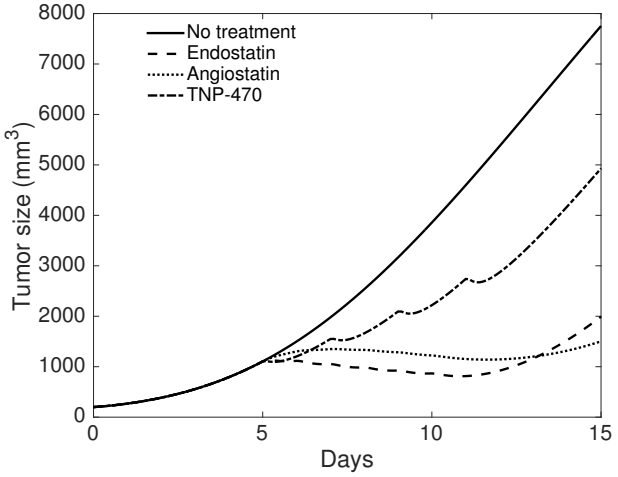
Primary tumor VS metastases



Primary tumor



Metastases



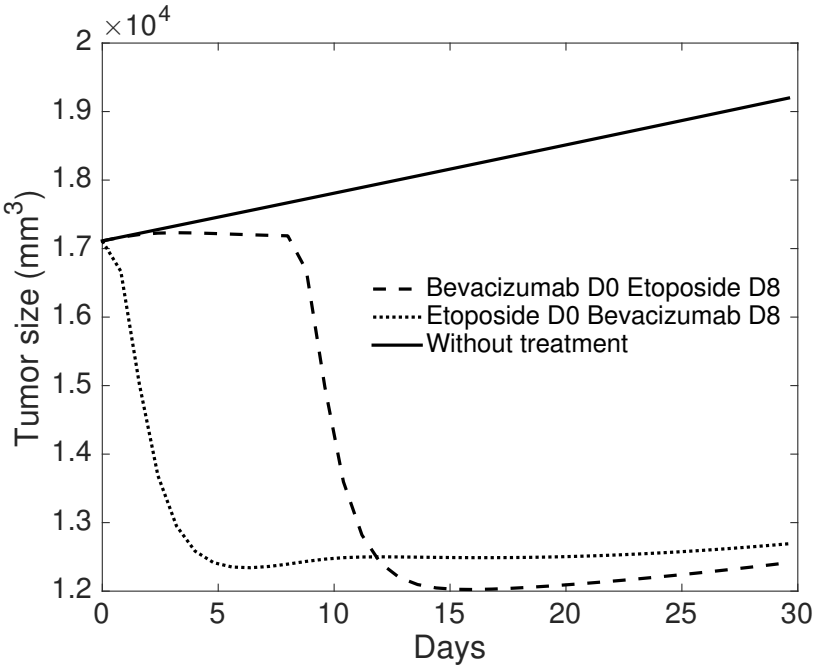
Benzekry, M2AN, 2012

Benzekry, Ebos et al., Cancer Res, 2015

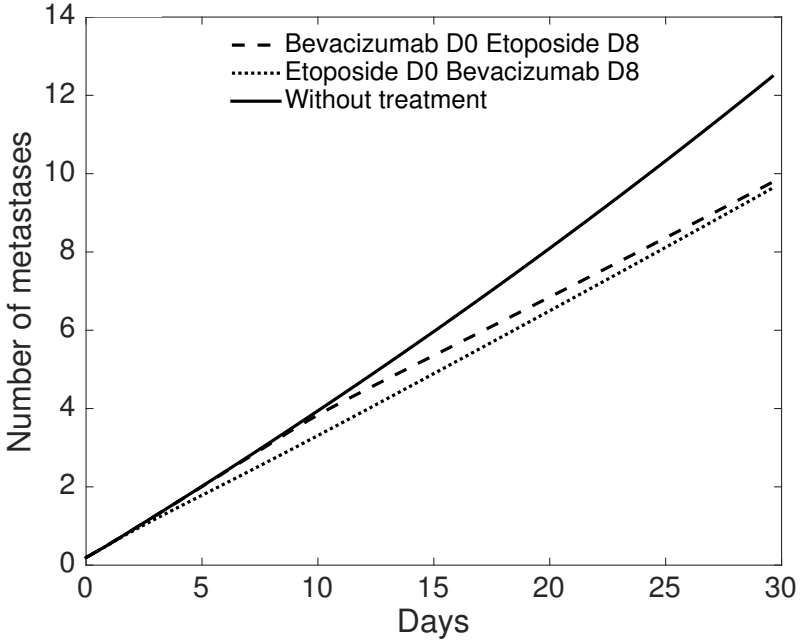
CT/AA combination. What sequence?

Bevacizumab D0 Etoposide D8 **versus** Etoposide D0 Bevacizumab D8

Primary tumor



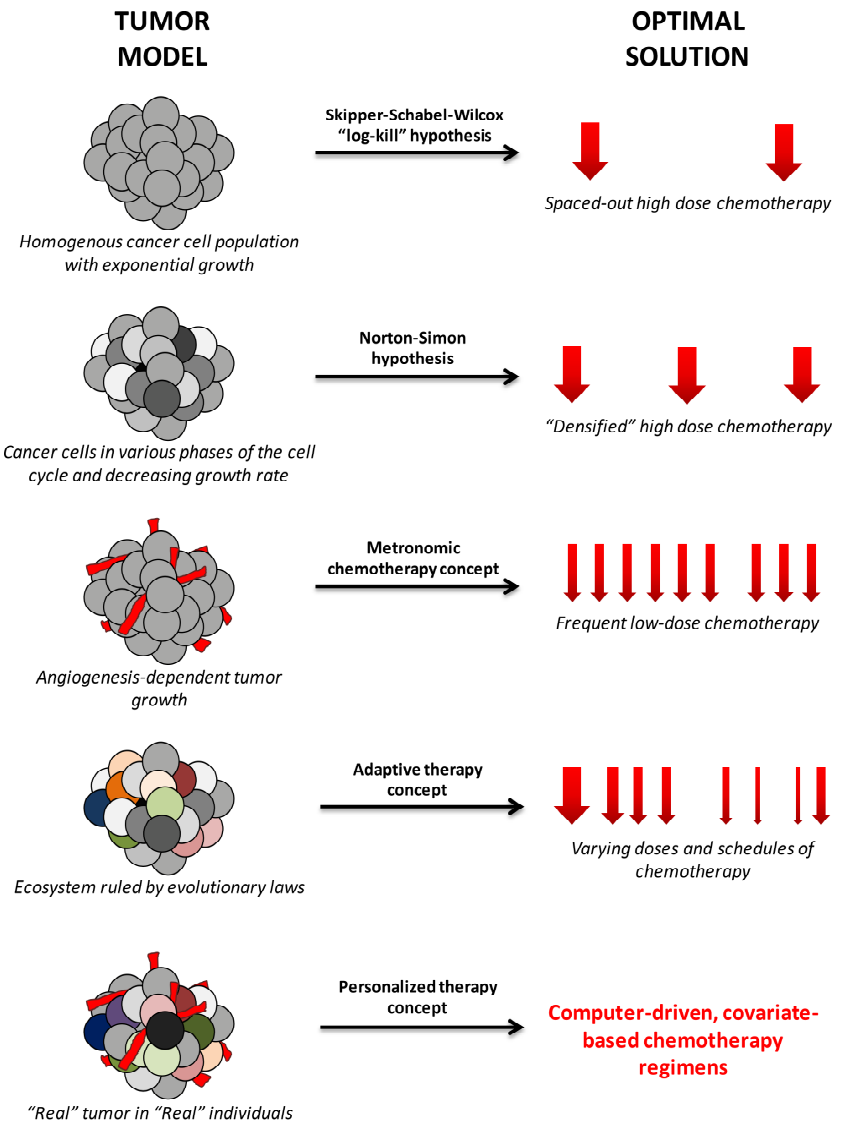
Metastases



⇒ The best sequence is **different for the PT and the mets**

Summary

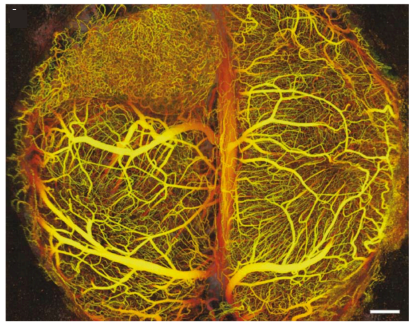
- Although mathematics are a discipline far from medicine, theoretical models have often driven the **paradigms underlying chemotherapy schedules**
- **Rational design** of chemotherapy protocols…
- …and **sequences** in combination therapies (CT/AA, radio-immuno therapy)



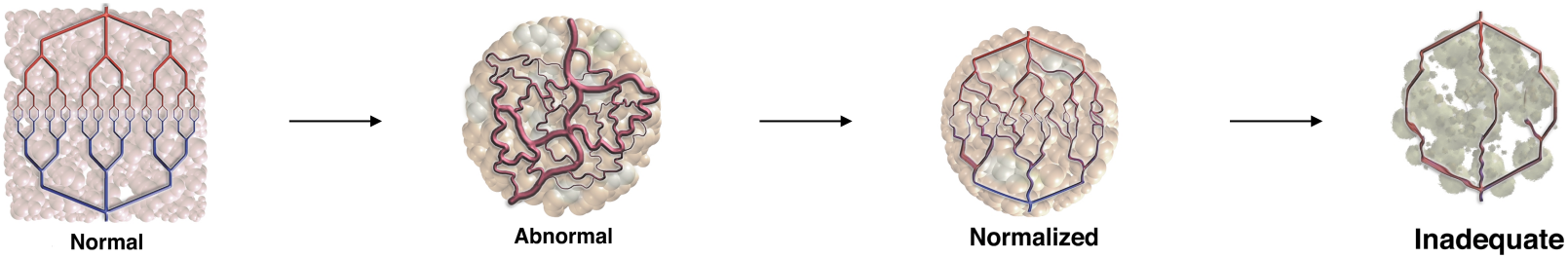
Benzekry, Pasquier, Andre et al., Semin Cancer Biol, 2015

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, Na



Jain, Nat Med, 2001

Therapeutic 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

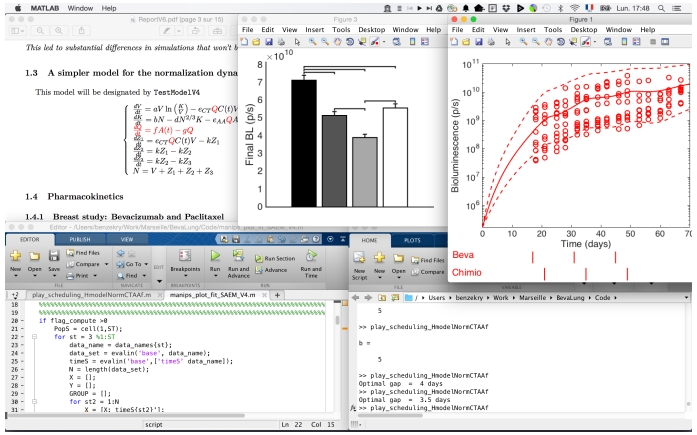
Lung cancer model

Experiment 1

Calibration

Experiment 2

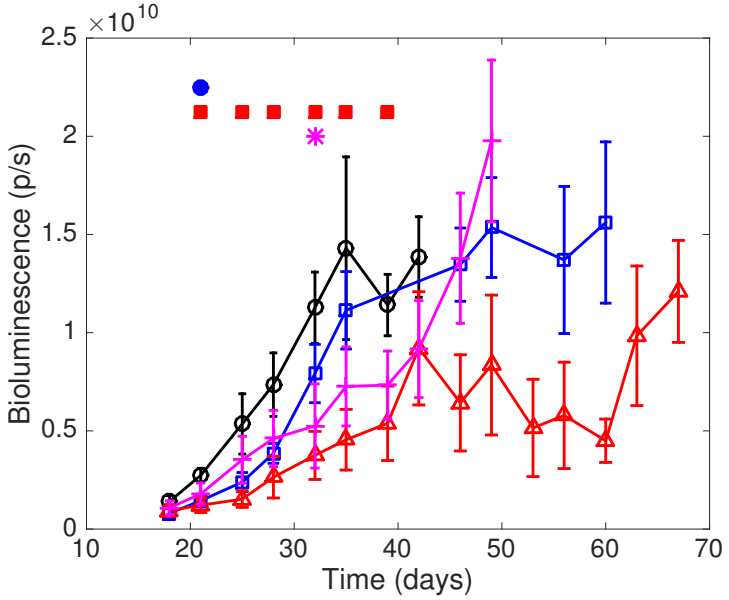
Prediction



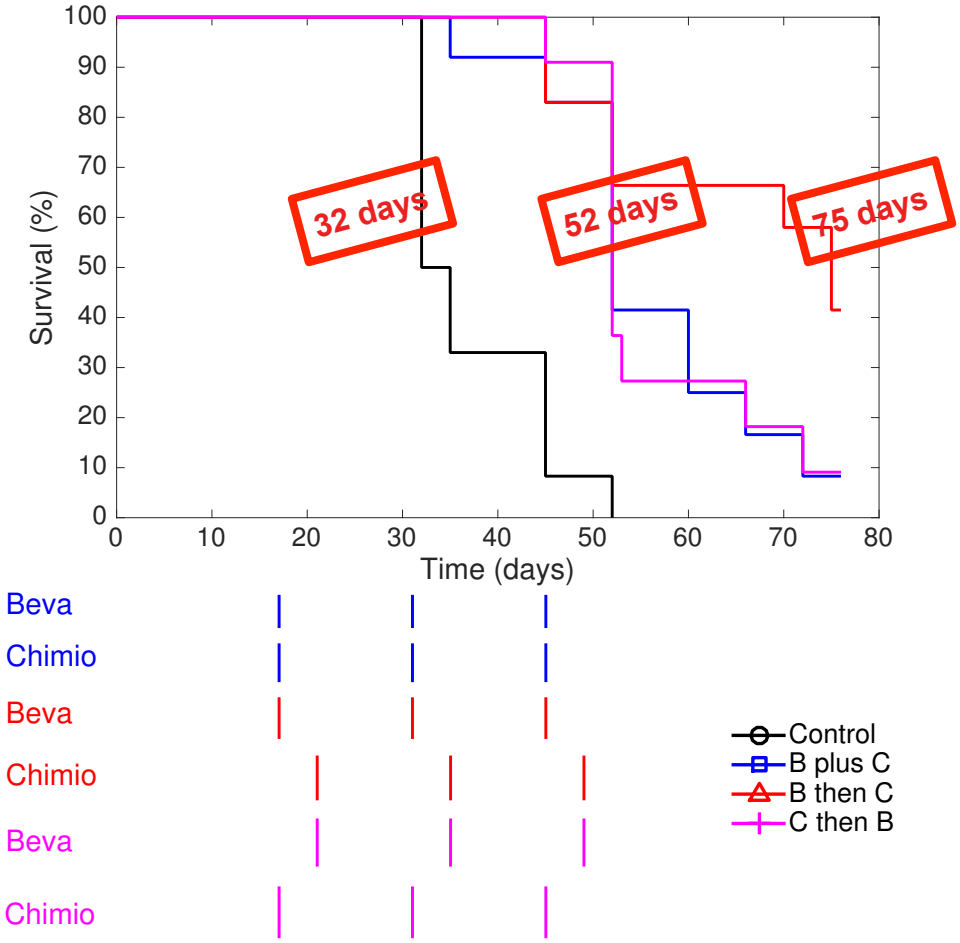
Modeling and Simulation

Imbs et al. (Benzekry), CPT: Pharmacometrics Syst Pharmacol, 2017

Sequential administration Beva then Chemo improves response and survival

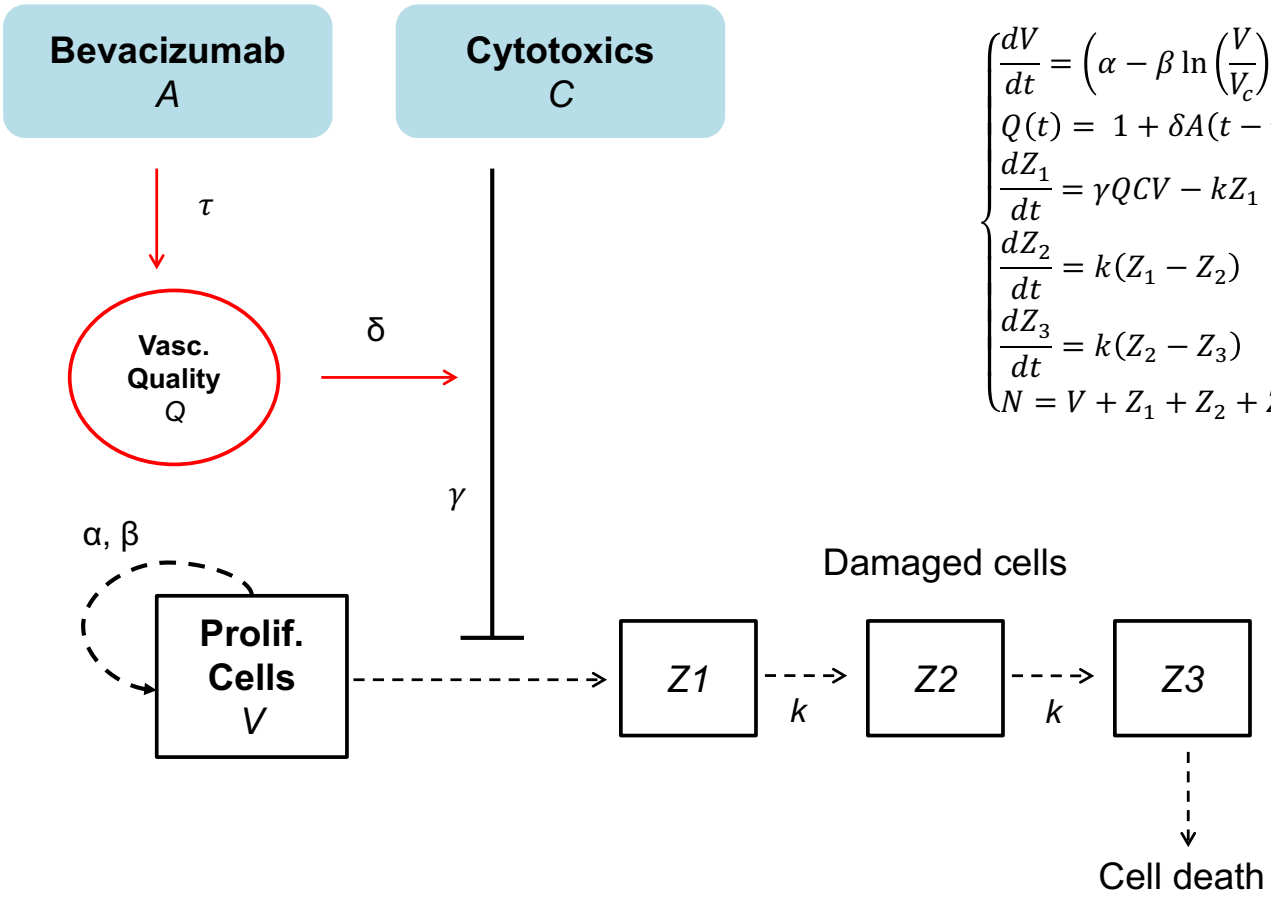


-71.2% tumor size at study conclusion (day 60)

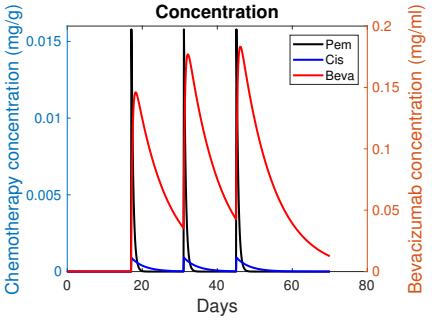


⇒ Sequential use increases **survival by 44%**

Semi-mechanistic mathematical model



$$\begin{cases} \dfrac{dV}{dt} = \left(\alpha - \beta \ln\left(\dfrac{V}{V_c}\right)\right) V - \gamma QCV & V(t=0) = V_0 \\ Q(t) = 1 + \delta A(t-\tau) & \\ \dfrac{dZ_1}{dt} = \gamma QCV - kZ_1 & Z_1(t=0) = 0 \\ \dfrac{dZ_2}{dt} = k(Z_1 - Z_2) & Z_2(t=0) = 0 \\ \dfrac{dZ_3}{dt} = k(Z_2 - Z_3) & Z_3(t=0) = 0 \\ N = V + Z_1 + Z_2 + Z_3 & \end{cases}$$

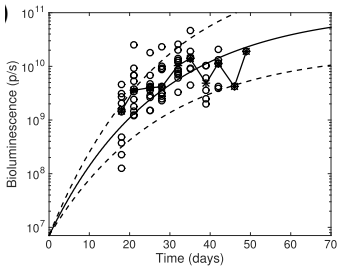


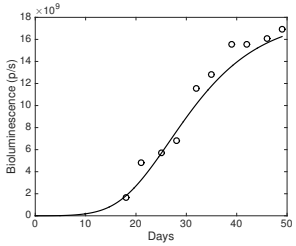
Simeoni et al., Rocchetti, Cancer Res, 2004
Benzekry et al., CRAS, 2012
Mollard et al., Benzekry, Oncotarget, 2017
Imbs et al., (Benzekry), CPT: Pharmacometrics Syst Pharmacol, 2018

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

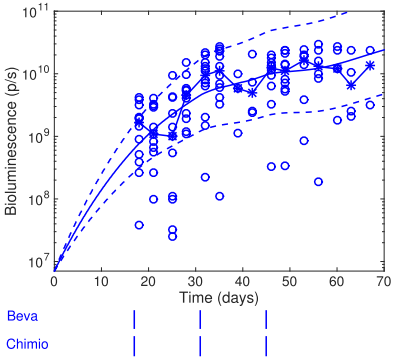
Model fits: individual + population level (NLME)

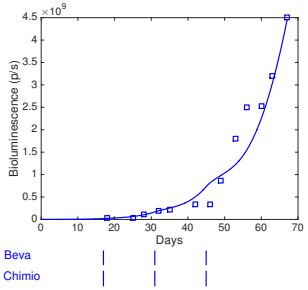
Control



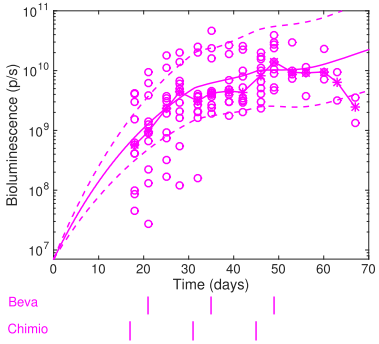


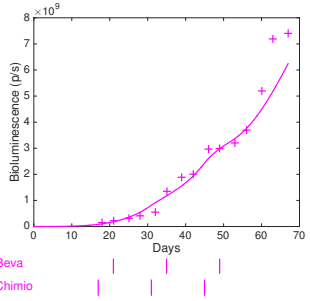
Simultaneous



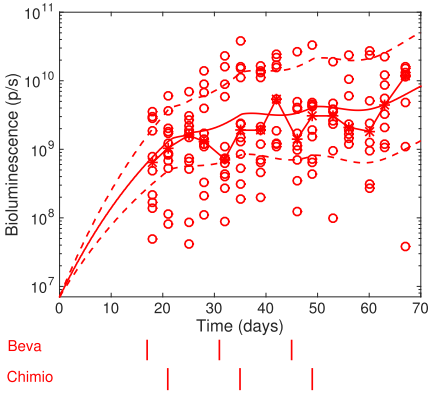


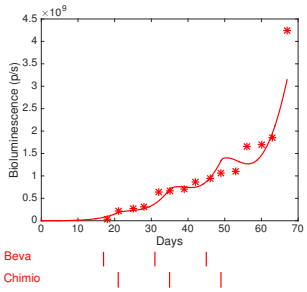
Sequential C/B



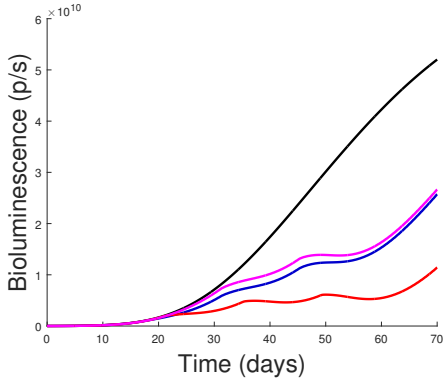


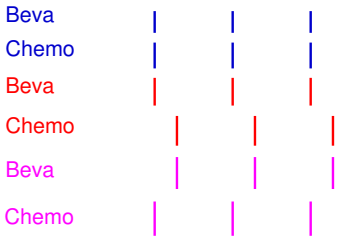
Sequential B/C





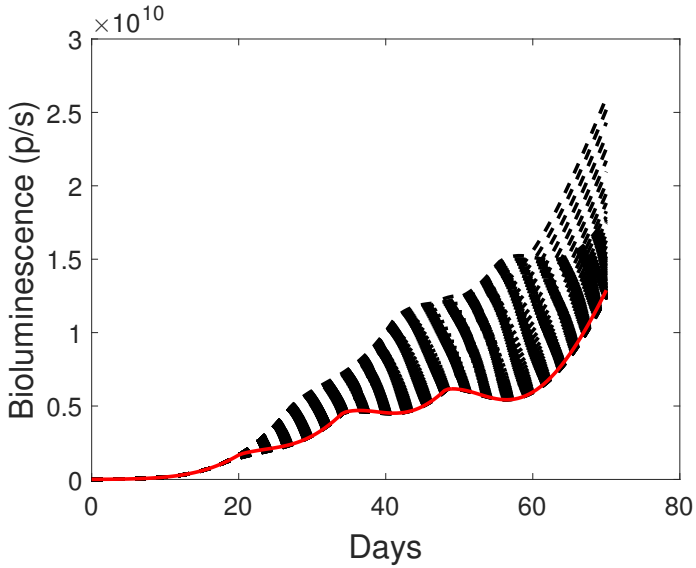
Median growth curves

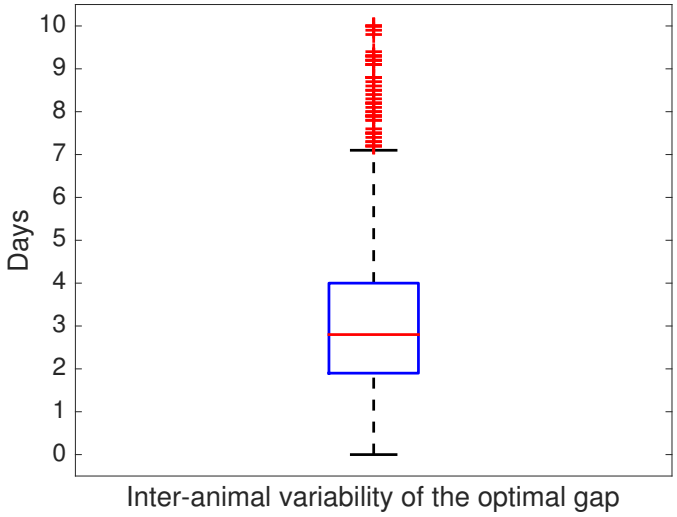


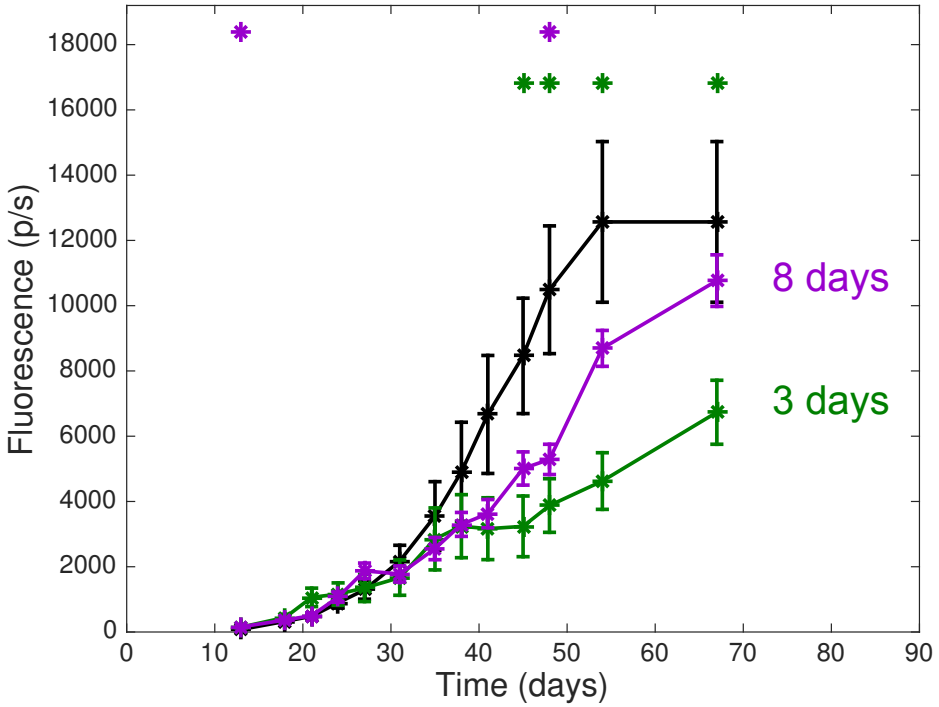


Imbs et al., Benzekry, CPT: Pharmacometrics and Systems Pharmacology, 2018

Prediction of the optimal delay







⇒ to be **tested experimentally**

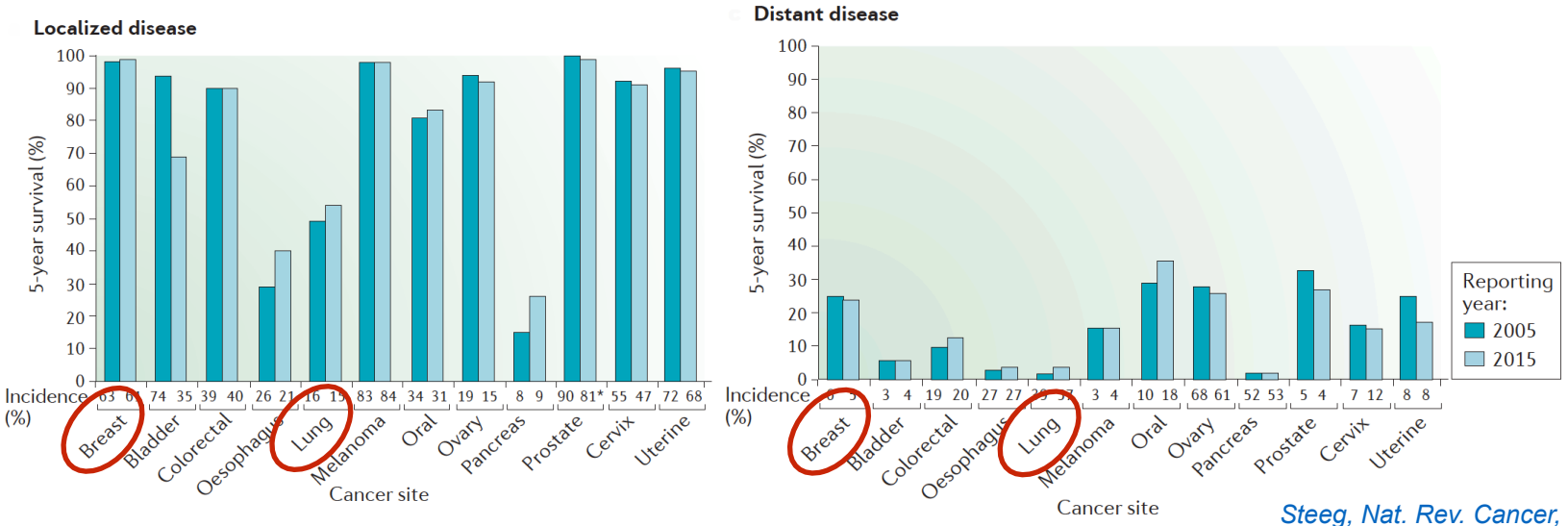
⇒ **personalized** scheduling

Imbs et al., Benzekry, 2018, CPT: Pharmacometrics and Systems Pharmacology

3 Metastasis

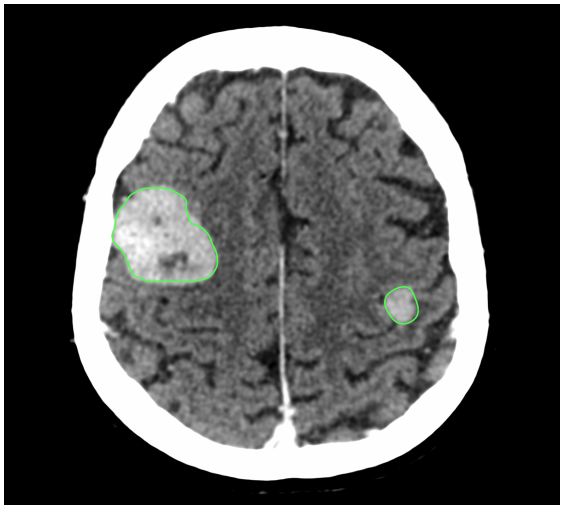
Clinical problems related to metastasis

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



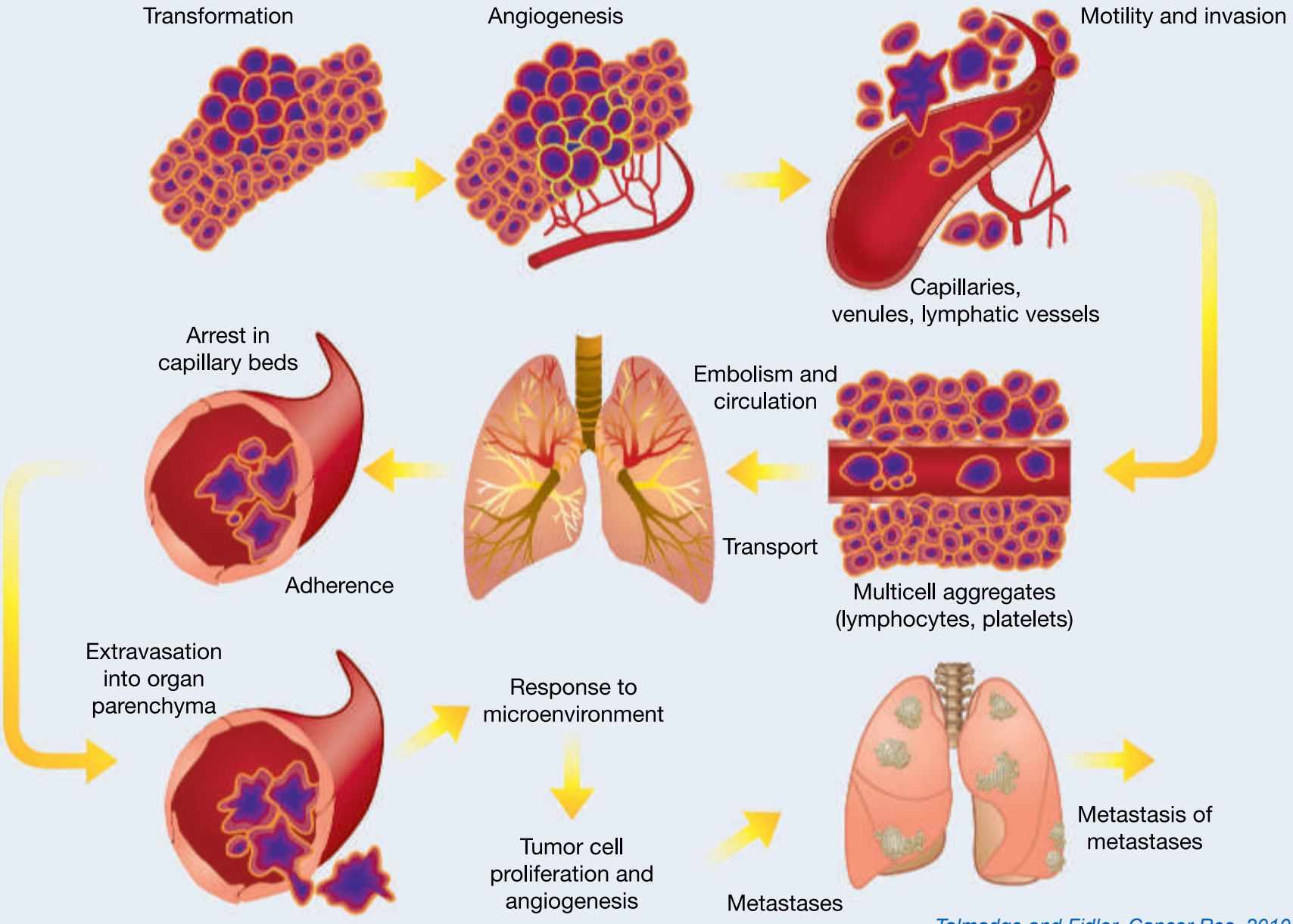
Steeg, Nat. Rev. Cancer, 2016

- **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 unnecessary, heavy **toxicities**
- **Lung**
  - 57% of cases are metastatic
  - For a patient with one or little brain metastases, decide whether to use **whole brain radiation therapy** or just (stereotactic) surgery
  - Avoid cognitive impairment of the patient



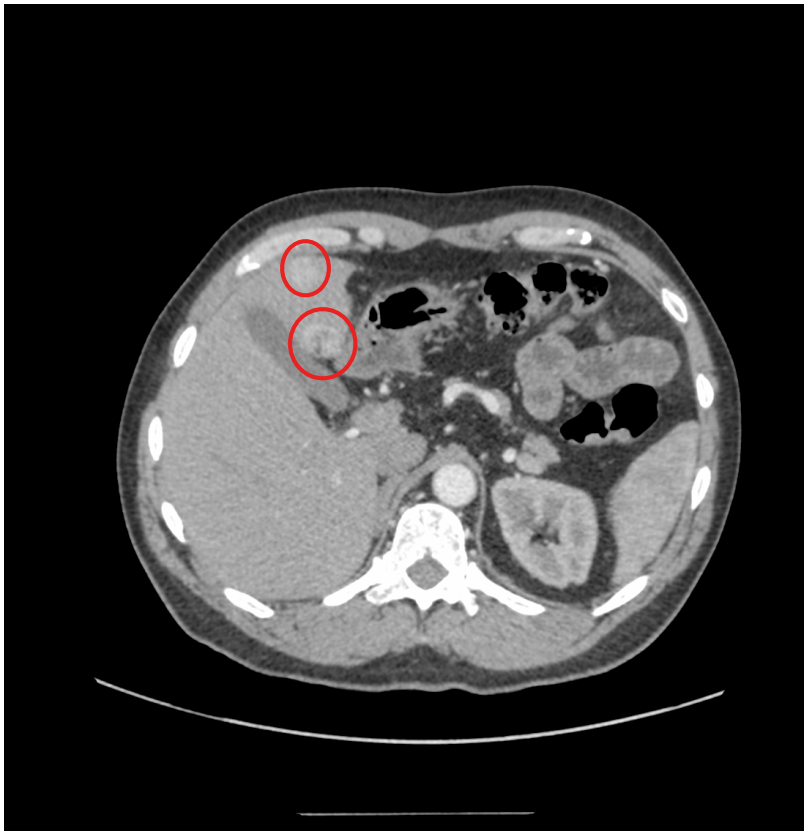
Institut Bergonié, Bordeaux

The Sequential Process of Metastasis

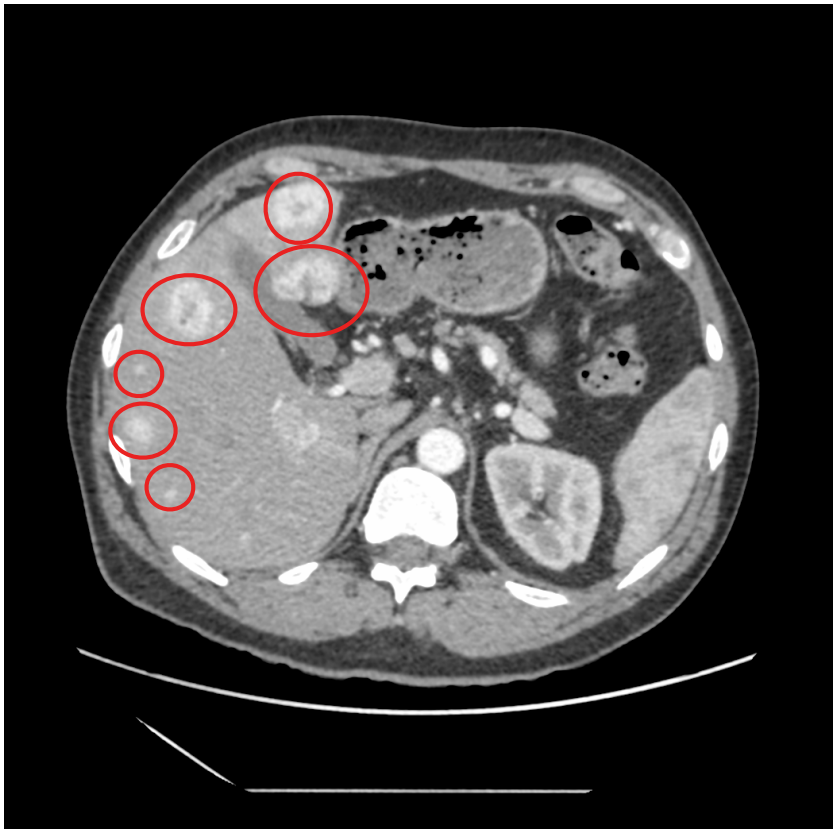


Talmadge and Fidler, Cancer Res, 2010

Clinical presentation



20/01/2015



06/11/2015

Enhanced CT scan of the liver of a kidney cancer patient with multiple metastatic tumors

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

F. Cornelis, CHU Bordeaux

Outline

3. Metastasis

3.1 Modeling spontaneous metastasis following surgery : an in vivo-in silico approach

3.2 Challenging the classical view of metastasis initiation and growth

3.3 Clinical applications

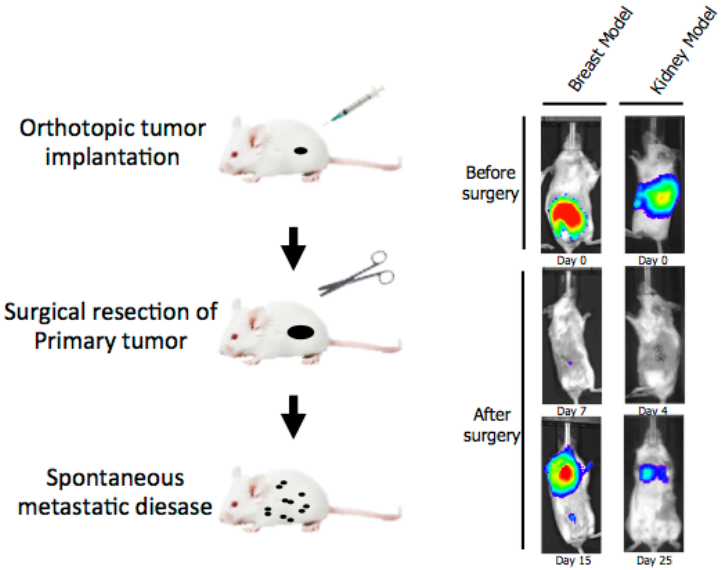
Questions and data

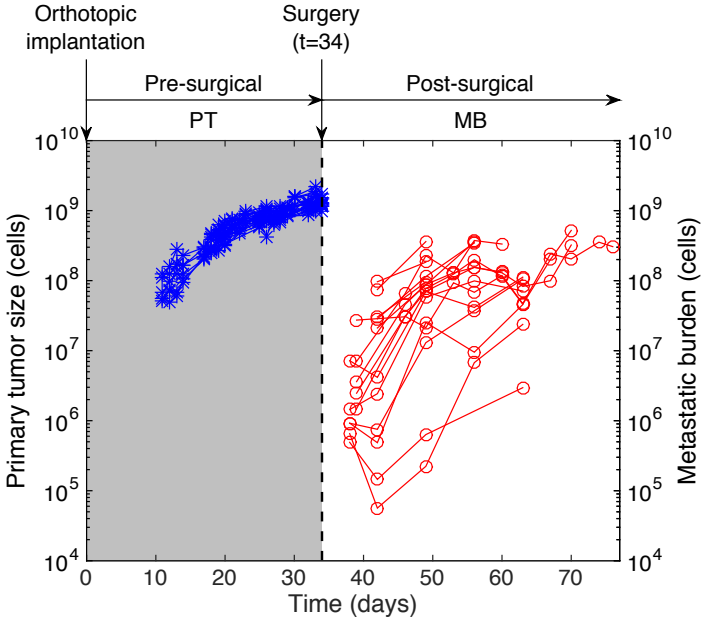
Questions

- Minimal model of metastatic development. **Dissemination** law? Differences between mets and primary tumor **growth**?
- Quantify the **inter-subject variability** of metastatic development
- What is the impact of the primary tumor size at surgery on metastatic development and survival?

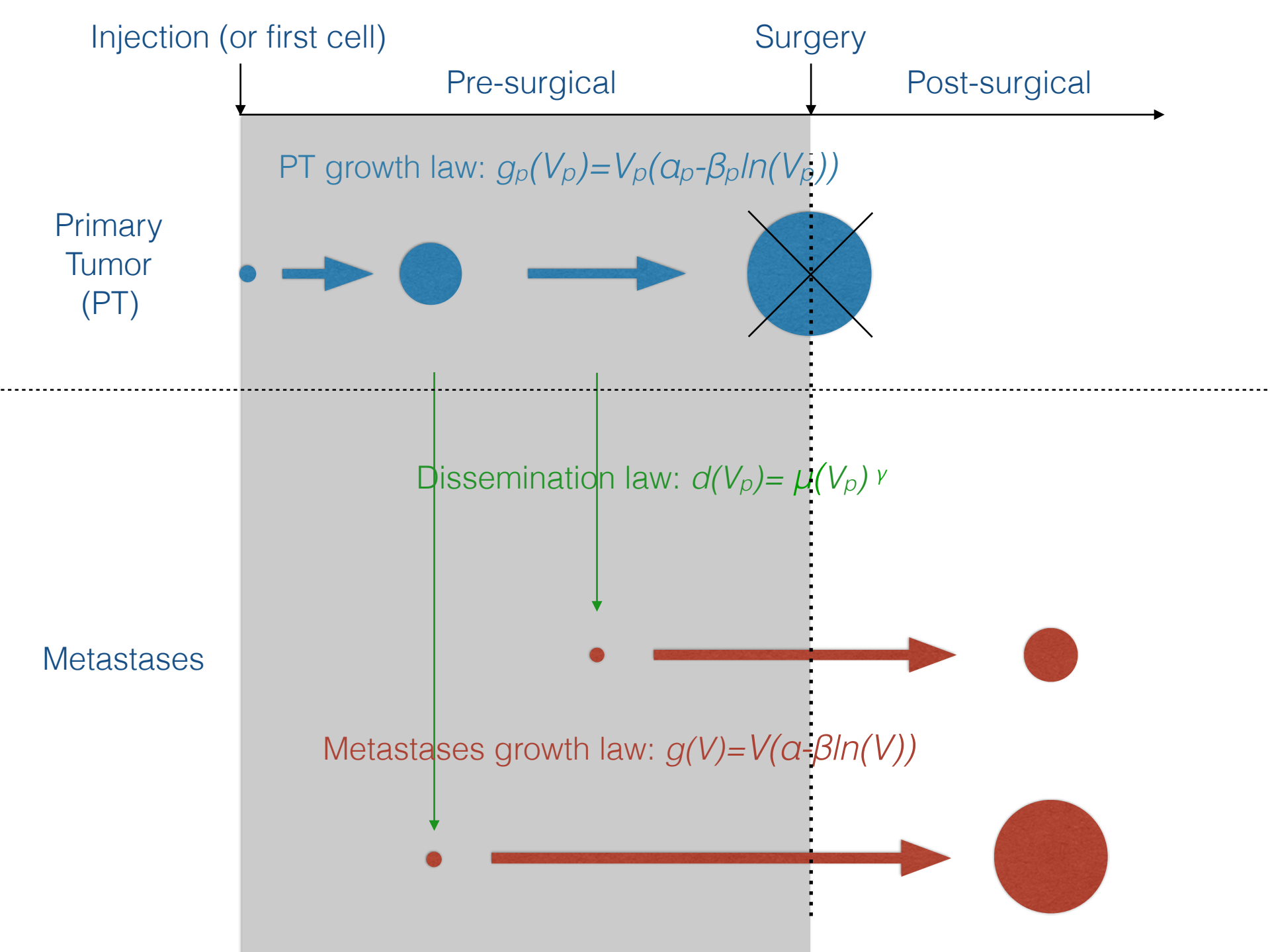
Data

- Clinically relevant ortho-surgical **animal models** of metastasis
- **Longitudinal** measurements of primary tumor size and total **metastatic burden**





Dr Ebos' lab, Roswell Park Cancer Institute


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}]

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

- **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)*

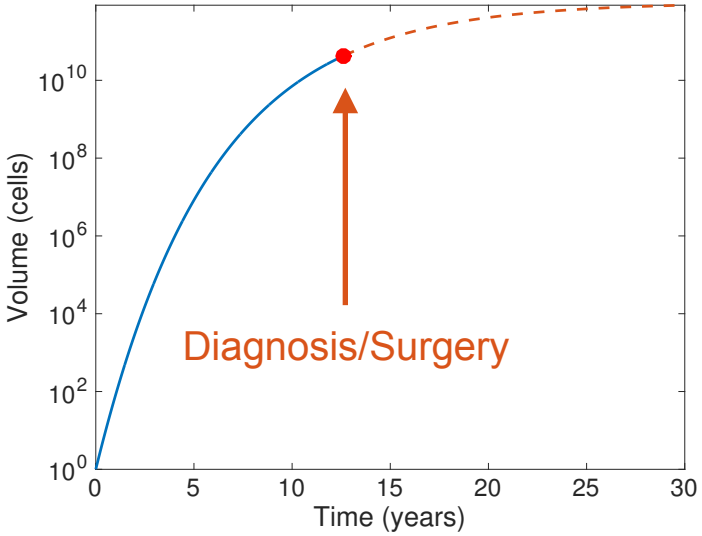
$$\partial_t \rho(t,v) + \partial_v(g(v)\rho(t,v)) = 0$$

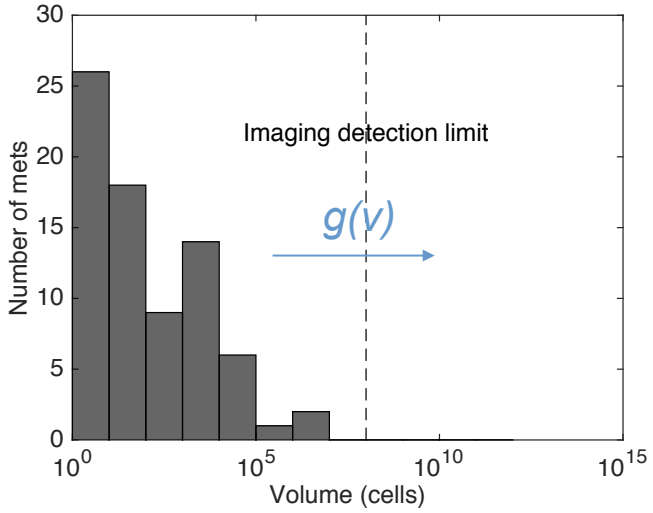
- They are spread by the PT with **dissemination rate** *d(V$_p$(t))* [day^{-1}]

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

⟶ fast computation of the metastatic burden

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

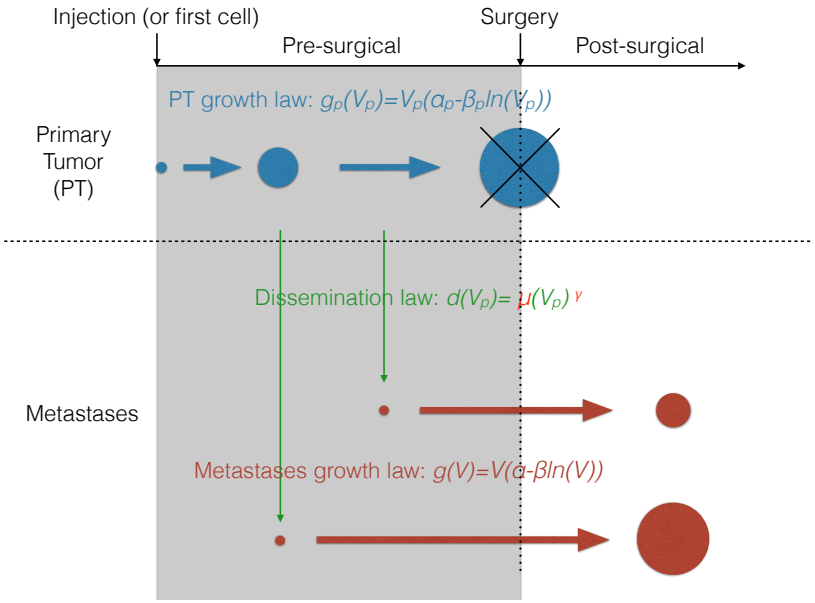




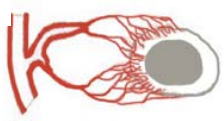
Iwata, Kawasaki, Shigesada, J Theor Biol, 2000

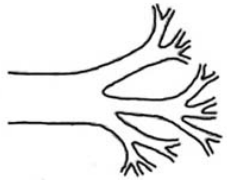
Model coefficients

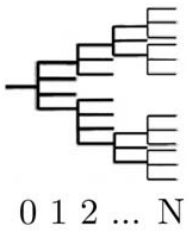
- 4 **growth** parameters
  - 2 PT growth parameters α_p and β_p
  - 2 mets growth parameters α and β



- 2 **metastatic dissemination** parameters
  - γ = fractal dimension of the metastatic susceptible cells (MSC)
  - μ = per day probability for an MSC to establish a successful met





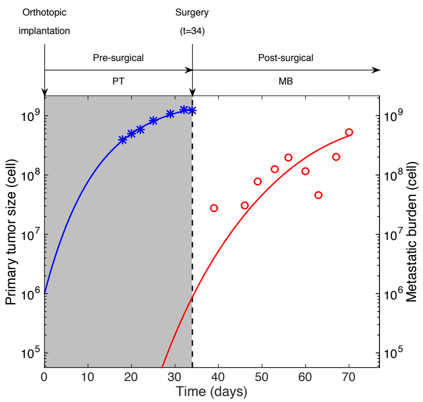


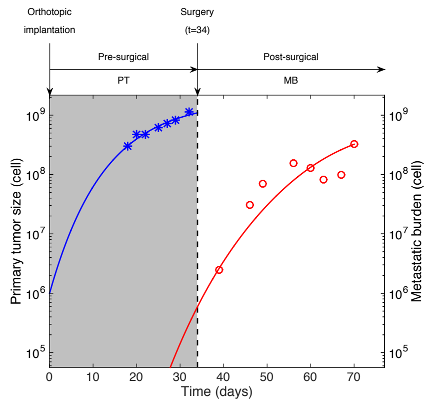
Stochastic/discrete version of the model:

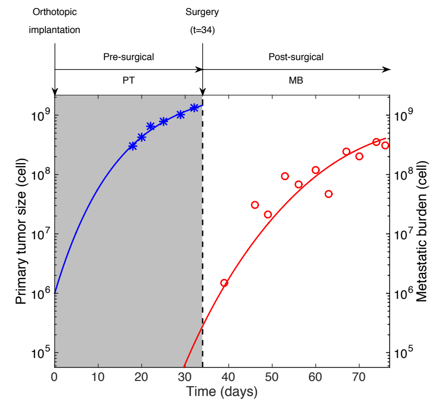
- Exponential distribution of the mets birth times with inhomogeneous intensity $d(V_p(t))$
- Number of metastases = Poisson process $\mathcal{N}(t)$

$$N(t) = \int_0^t d(V_p(s))ds = \mathbb{E}\left[\mathcal{N}(t)\right]$$

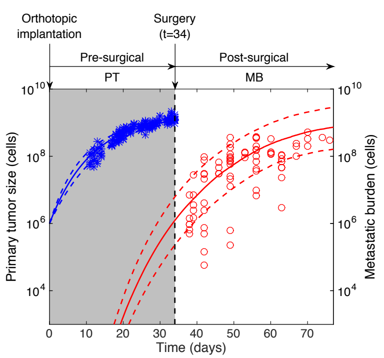
The model fits at the individual and population levels



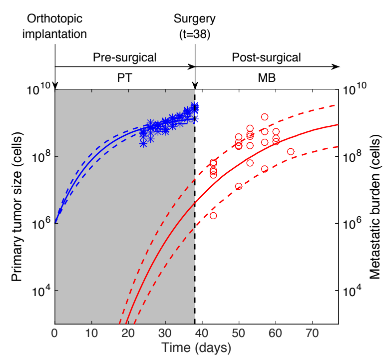




Fit



Prediction



Nonlinear mixed-effects

⇒ model with **same growth** for PT and mets is the most parsimonious

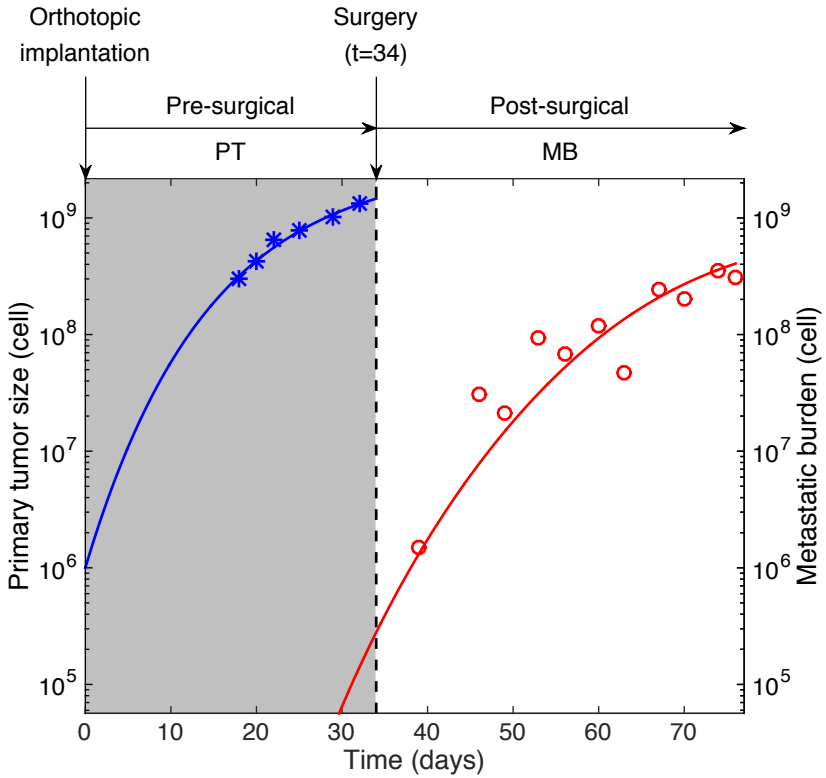
⇒ good **identifiability** (all rse < 30%)

⇒ parameter μ is a critical coefficient of inter-animal **variability** of metastatic potential (CV = 176%)

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

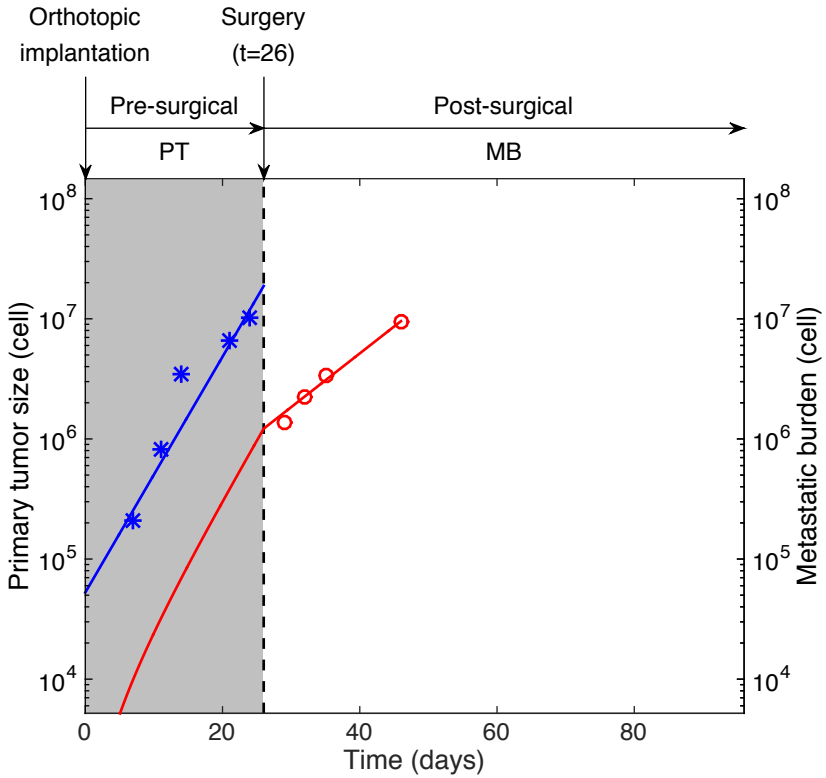
Benzekry et al. (Ebos), Cancer Res, 2016

Breast model
(human cells, immune-deprived)



- **Slow** dissemination
- **Same** PT/met growth rate
- Metastatic dynamics driven by **growth**

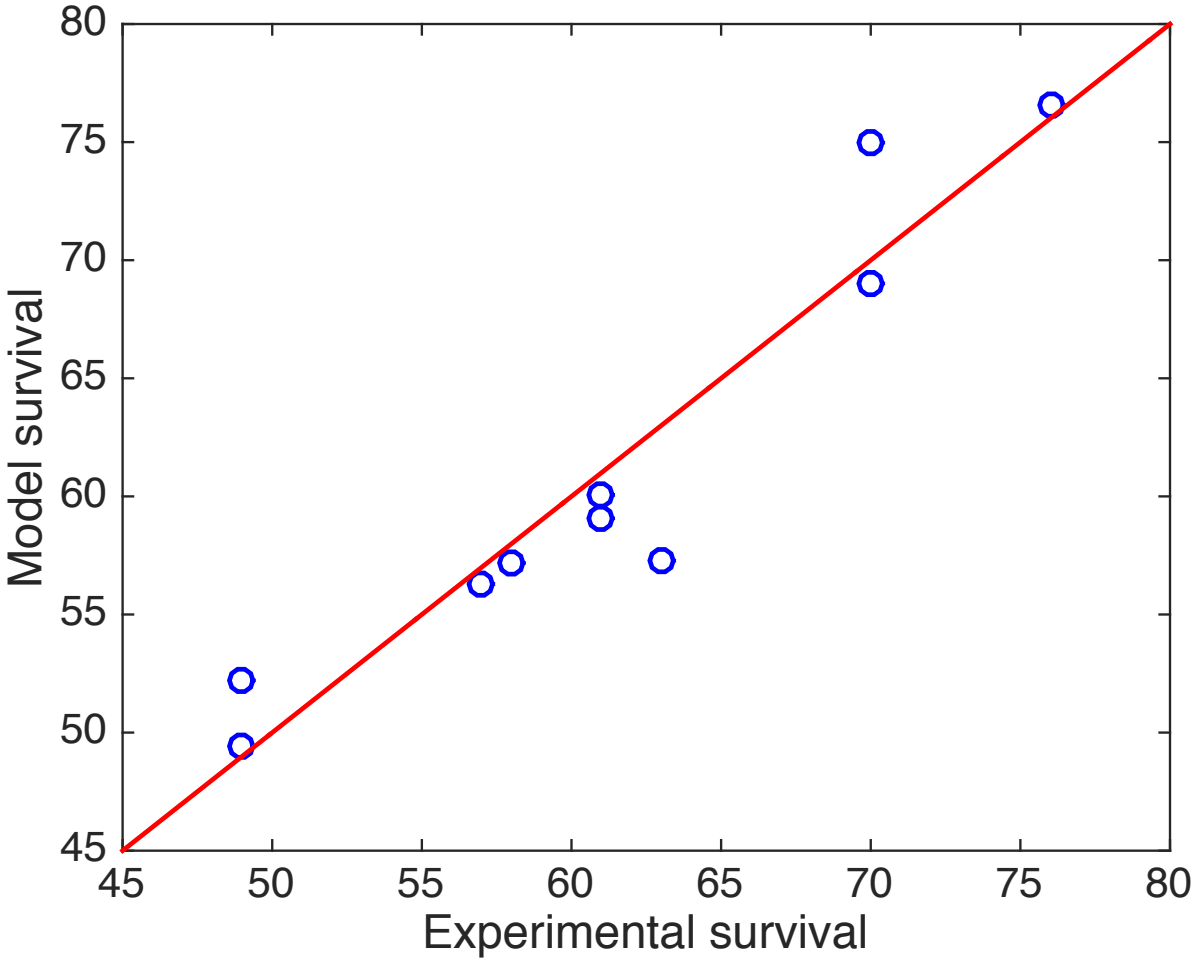
Kidney model
(murine cells, immune-competent)



- **Fast** dissemination
- **Different** PT/met growth rate
- Metastatic dynamics driven by **dissemination**

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

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.

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

Modeling the effects of therapeutic agents in the peri-operative setting

Kidney cancer

- **neo-adjuvant** Sunitinib
- **adjuvant** immune-checkpoint inhibitor (nivolumab)
- identify **biomarkers/covariates** predictive of response

Published online: October 31, 2014

Research Article

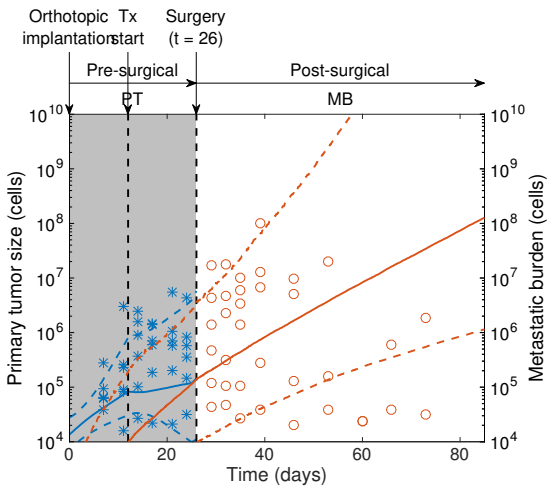
TRANSPARENT PROCESS OPEN ACCESS

EMBO Molecular Medicine

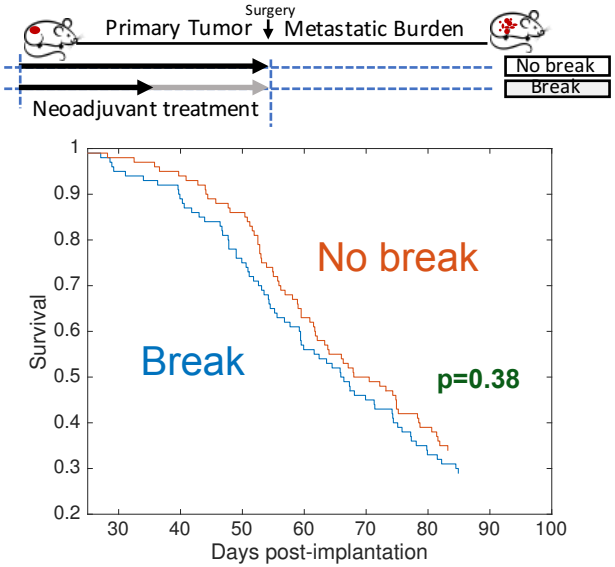
Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy

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]

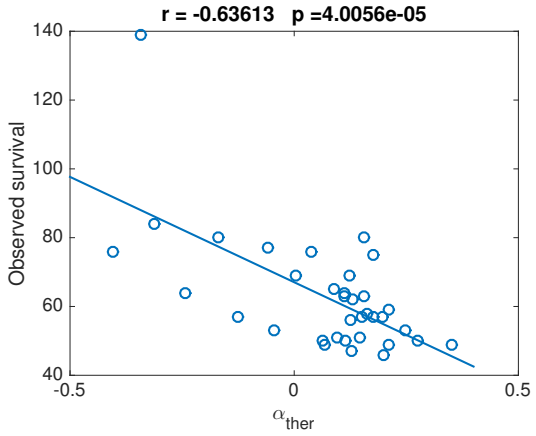
Differential effect PT/mets



Break VS no break



Numerical biomarker



(RECIST)

Mastri, Nicolo et al. (Benzekry, Ebos), in preparation, 2018

Outline

3. Metastasis

3.1 Modeling spontaneous metastasis following surgery : an in vivo-in silico approach

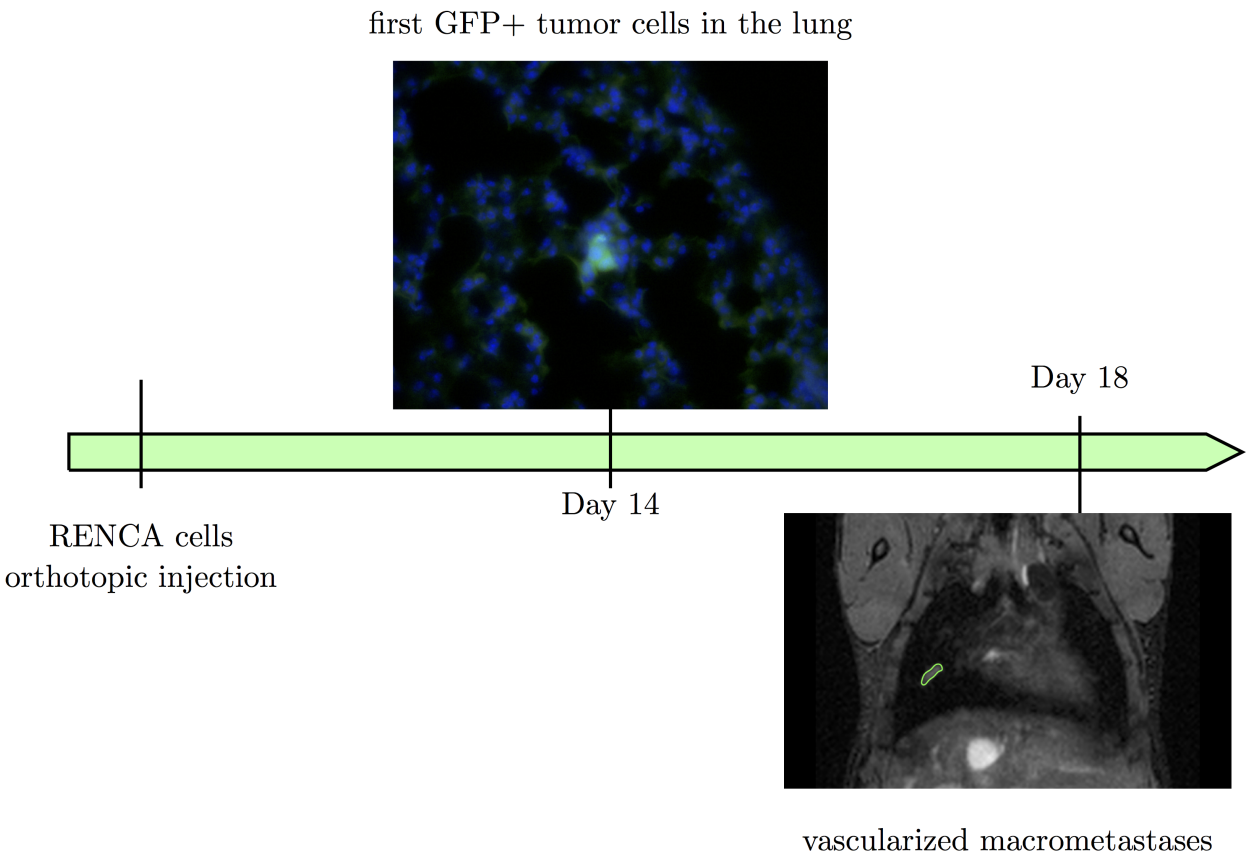
3.2 Challenging the classical view of metastasis initiation and growth

3.3 Clinical applications

Kidney animal model of metastatic development

Biological question

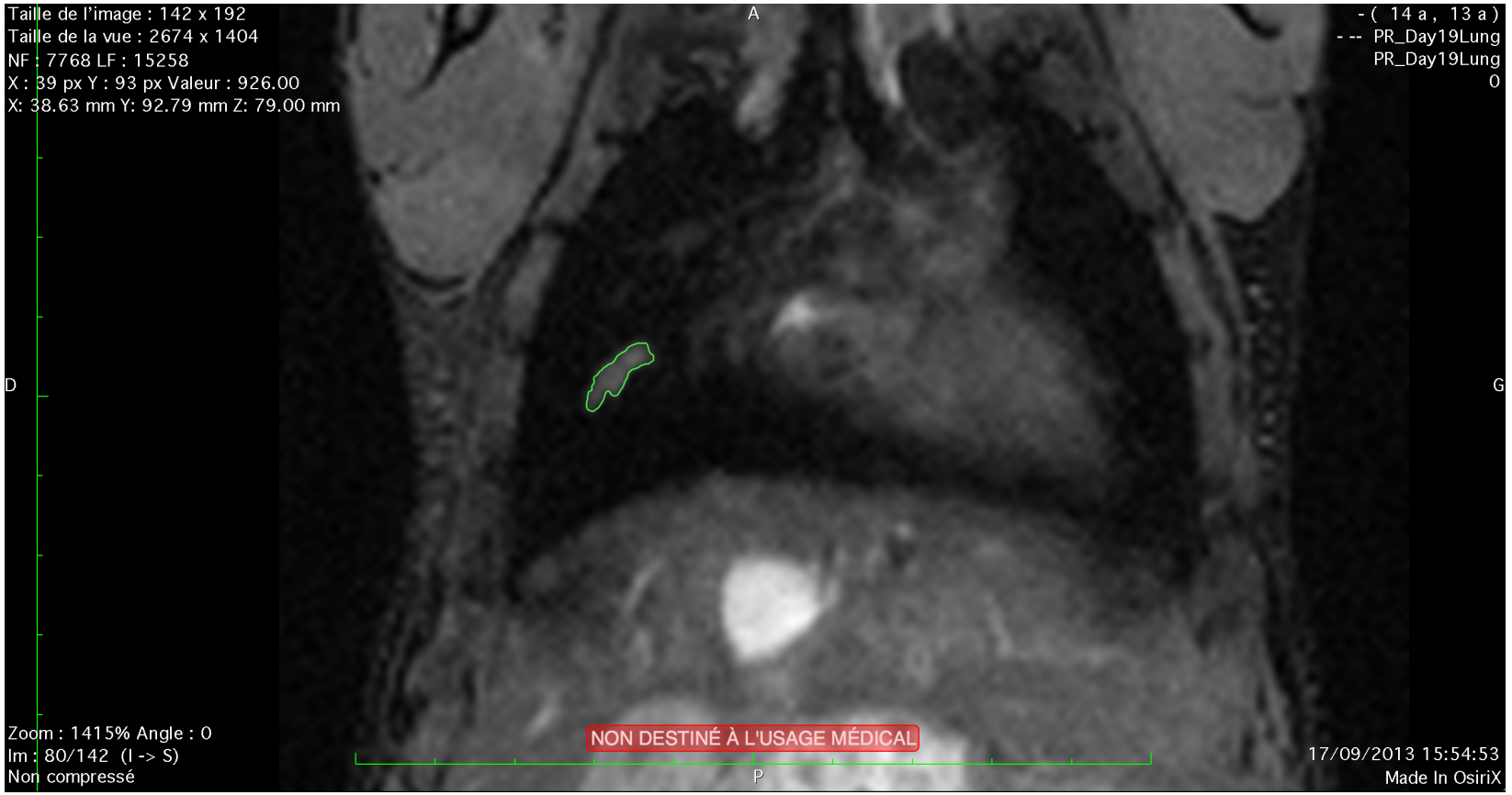
Is the « standard » view of metastatic initiation and growth – that secondary lesions once established grow without interactions with each other or with the primary tumor – quantitatively valid for description of the dynamics of the **number and size** of metastases?



E. Baratchart's PhD

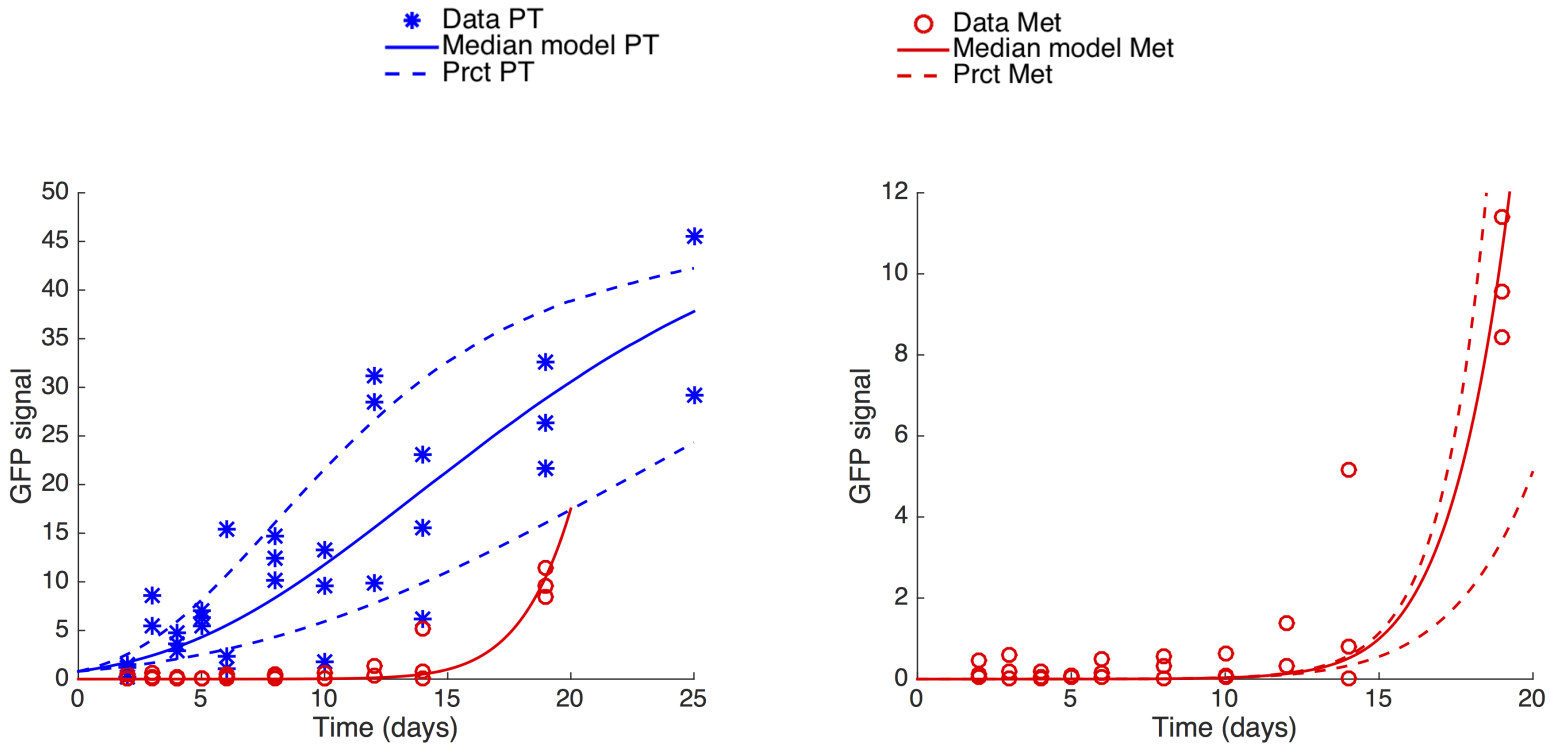
Collaboration with the LAMC (Inserm) and the RMSB (CNRS), Bordeaux, Fr

Quantitative analysis: metastatic growth rate



- From one cell to macrometastatic volumes (0.5 − 2.5 mm^3) in 4 days
- Gives a doubling time between 6 and 8 hours (in vitro doubling time of the RENCA cell line: 25h)⇒ **too fast!**

Metastatic burden fit

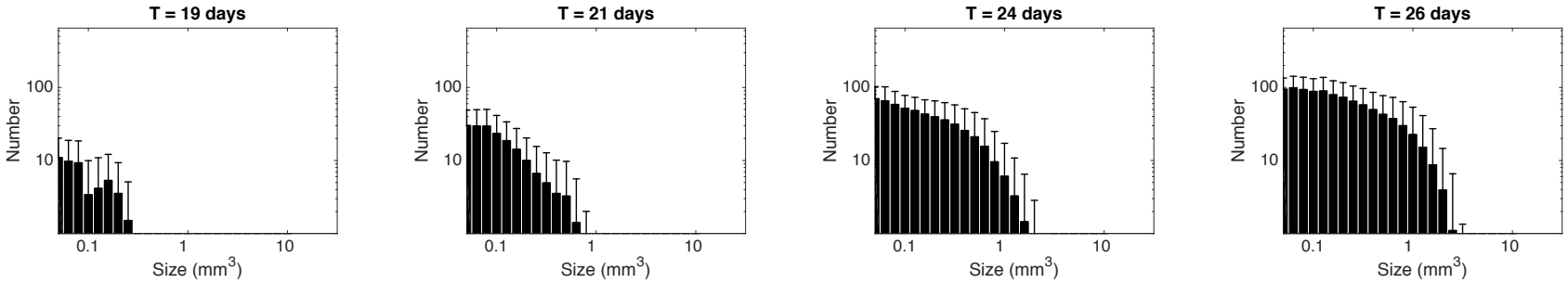


Par.	Unit	Median value	CV (%)	95% CI
α	day^{-1}	0.427	26	(0.329 - 0.558)
β	day^{-1}	0.0735	27.9	(0.0372 - 0.145)
μ	$cell^{-1} \cdot day^{-1}$	1.49×10^{-5}	553	$(0.277 - 8.00) \times 10^{-5}$

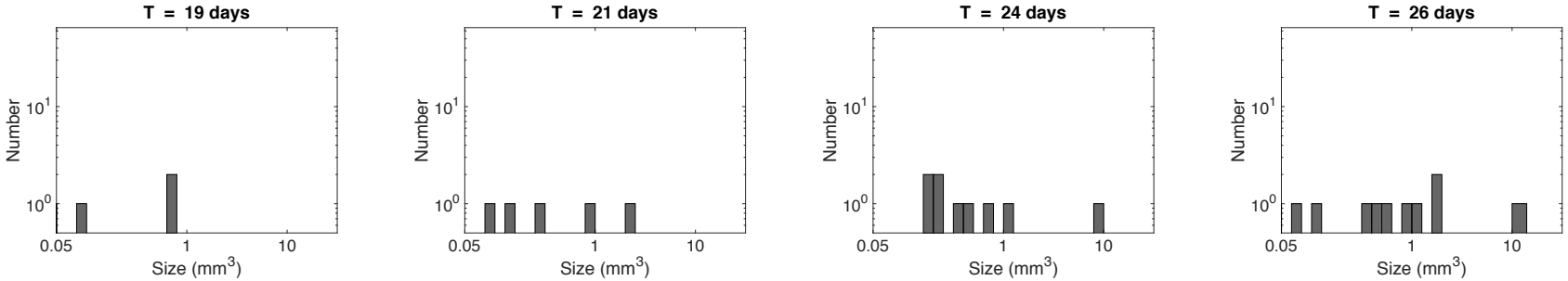
Baratchart et al. (Benzekry), PloS Comp Biol, 2015

Size distribution: theory VS data

Model



Data



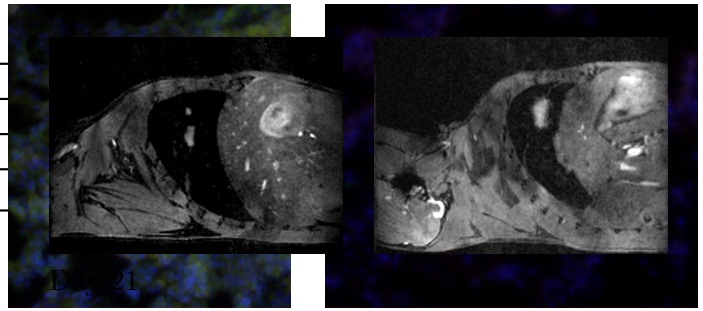
More but smaller metastases in the theory than in the data!

L. Cooley, W. Souleyreau, A. Bikfalvi LAMC, Bordeaux

Possible hypotheses:

- non trivial mechanical interactions between metastatic tumors (**tumors merging**)
- interactions between the metastatic tumors and the circulating tumor cells (**cells attraction**)

T	19		21	
	Data	Model	Data	Model
Number	4	3	5	12
Macro-burden (mm^3)	1.58	0.452	3.55	1.94



Baratchart et al. (Benzekry), PloS Comp Biol, 2015

A mathematical model of spatial tumor growth

Variables

- P the proliferative tissue density
- S the healthy tissue density
- v the velocity of the passive motion due to proliferation
- Π the exerted pressure by the proliferative tissue

Modeling hypotheses

- Passive movement due to proliferation
- Major assumption: **increase of pressure** slows down proliferation

  Styglianopoulos, PNAS, 2012; Montel et al, New J Phys, 2012

Model

$$\frac{\partial P(t,x)}{\partial t} + \nabla .(v(t,x)P(t,x)) = \gamma(\Pi)P(t,x)$$

$$\frac{\partial S(t,x)}{\partial t} + \nabla .(v(t,x)S(t,x)) = 0$$

Saturation hypothesis:

$$P + S = 1 \Rightarrow \nabla.v = \gamma P$$

Darcy Law :

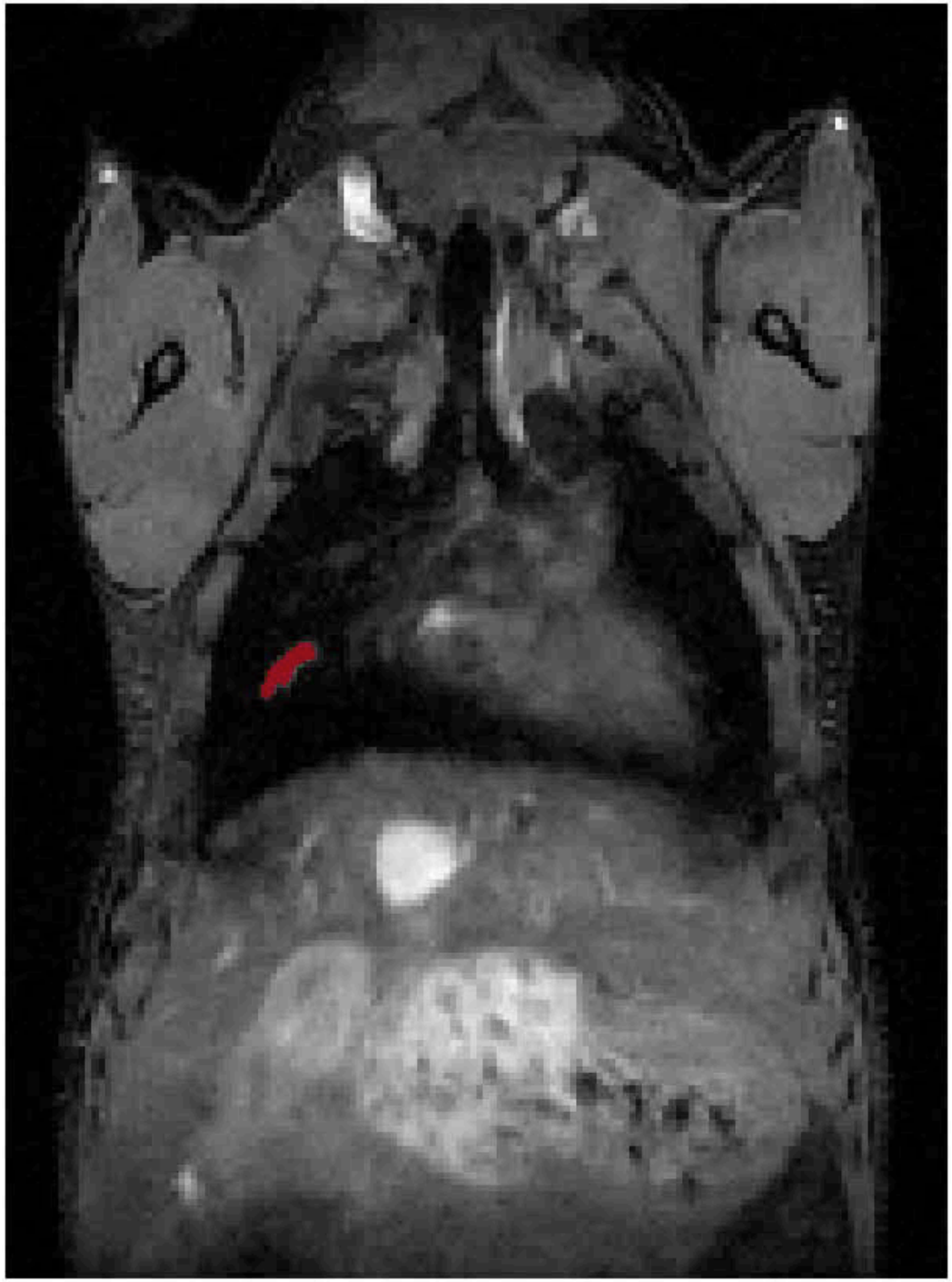
$$v = -k\nabla\Pi$$

Pressure mediated growth law :

$$\gamma(\Pi) = \gamma_0 \exp\left(-\frac{\Pi}{\Pi_0}\right)$$

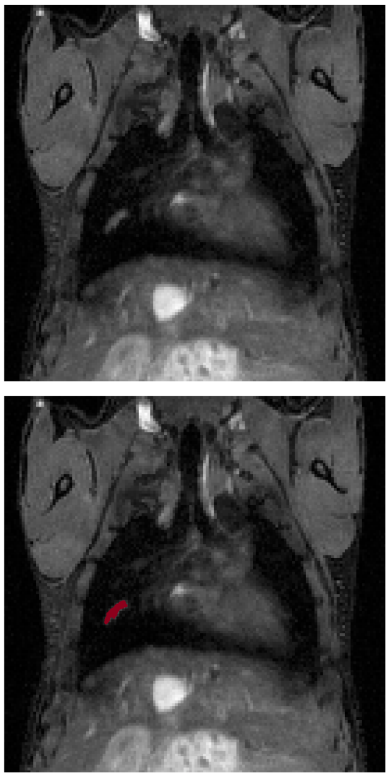
Parameters

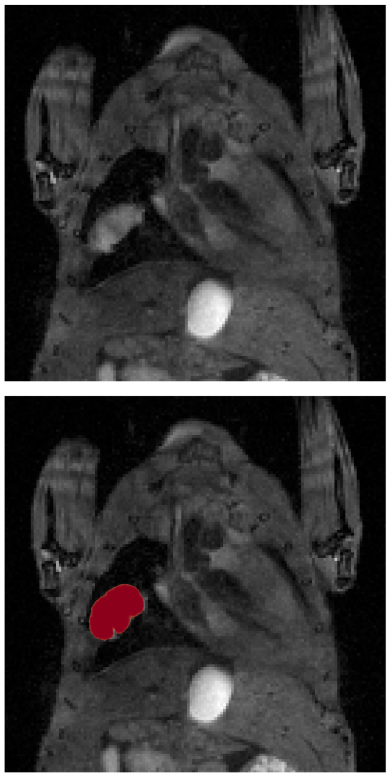
- γ_0 the maximal proliferation rate
- Π_0 A characteristic pressure of decreasing



Day 19

Day 26





Baratchart et al. (Benzekry), PloS Comp Biol, 2015

Outline

3. Metastasis

3.1 Modeling spontaneous metastasis following surgery : an in vivo-in silico approach

3.2 Challenging the classical view of metastasis initiation and growth

3.3 Clinical applications

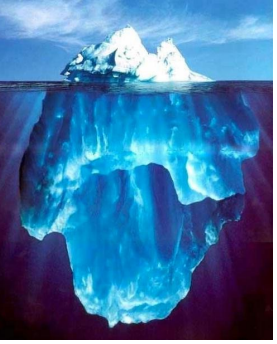
Metastatic relapse probability in a breast cancer clinical dataset

Diameter of PT (cm)	Prop. of relapse (Data)	Prop. of relapse (Model)
$1 \leq D \leq 2.5$	27.1	27.3
$2.5 < D \leq 3.5$	42.0	43.1
$3.5 < D \leq 4.5$	56.7	56.6
$4.5 < D \leq 5.5$	66.5	65.6
$5.5 < D \leq 6.5$	72.8	74.0
$6.5 < D \leq 7.5$	83.8	80.1
$7.5 < D \leq 8.5$	81.3	84.5

- 20 year follow-up of 2648 patients *Koscielny et al., Br J Cancer, 1984*
- **Assumptions**
  - (lognormal) distribution of μ for **inter-individual variability**
  - Doubling time from median values of the literature (7 months) *Coumans et al., BMC Cancer 2013*
  - Maximal reachable size = 10^{12} cells ≃ 1 kg *Klein, Nat Rev Cancer, 2009*
- Probability of developing a met = probability of having one at diagnosis

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

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

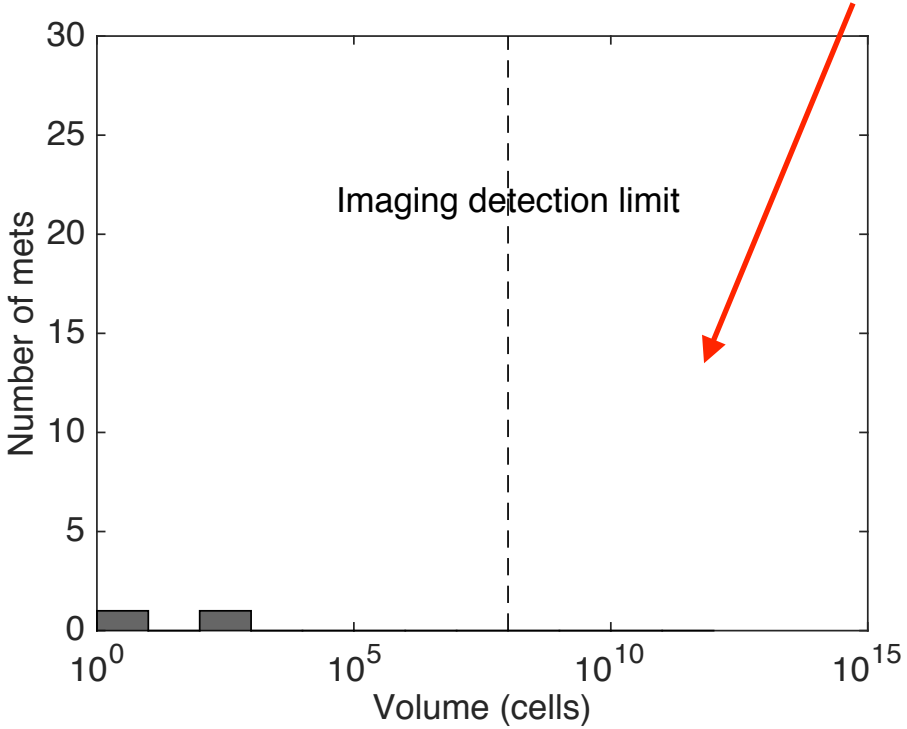


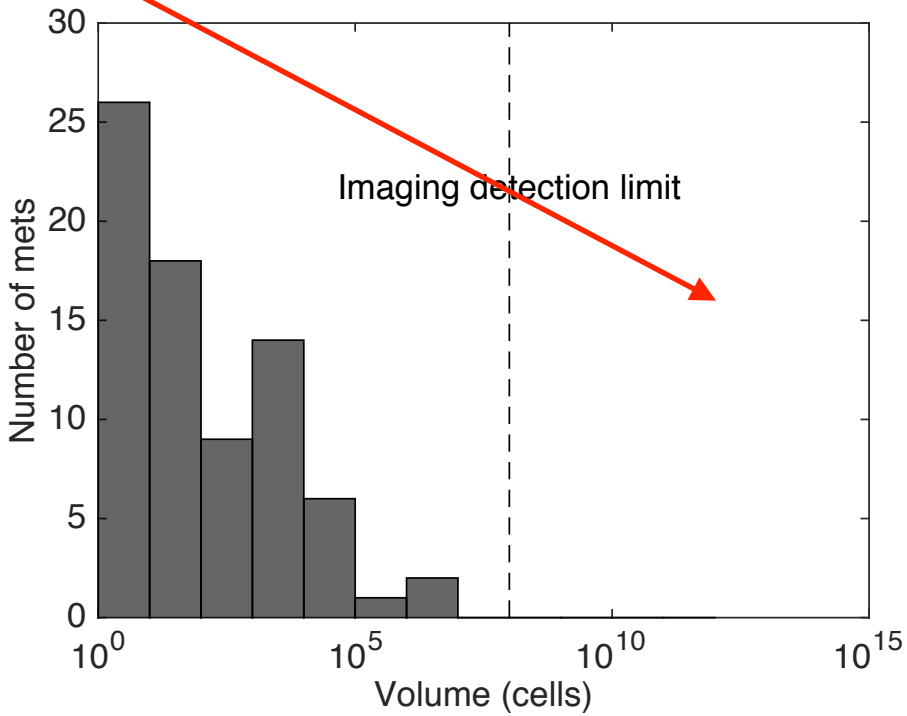
Diagnosis personalization

Virtual patient with median μ

Nothing visible

Virtual patient with large μ (90th prct)





Breast cancer patient with primary tumor of 4.32 cm

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

Chemotherapy personalization

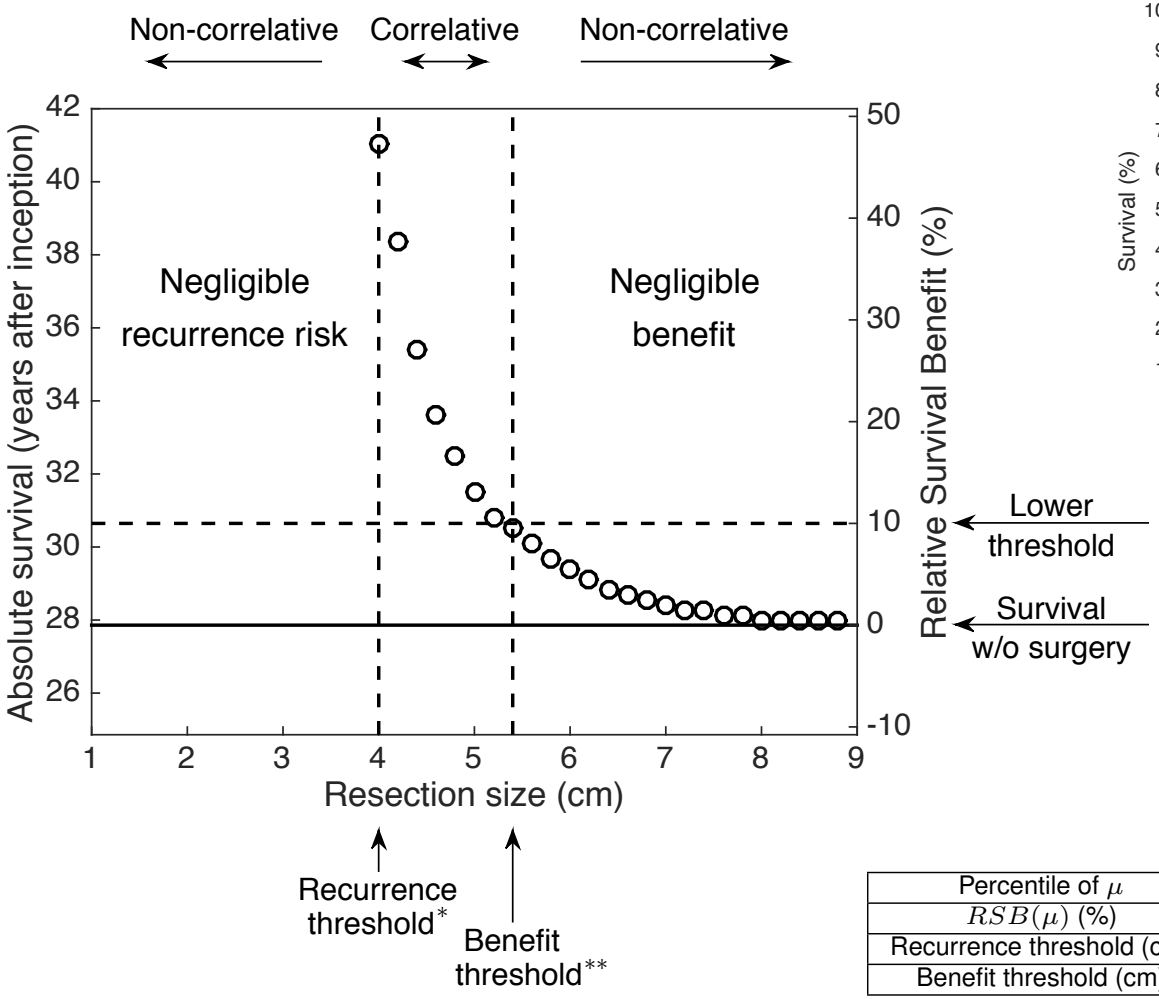
Toward taking into account inter-individual variability

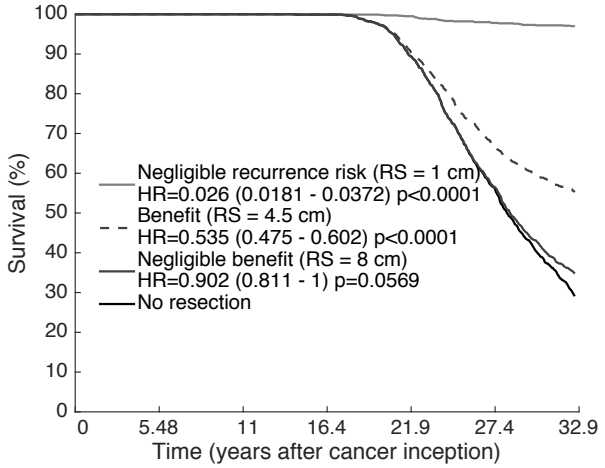
- 10 virtual patients with breast cancer detected at stage **T1N0M0**. Size of the tumor at detection: 1 gram.
- Chemotherapy : 6 cycles of 21 days (75mg of DTX and 100mg d'EPI) *Viens & al., Am. J. Clin. Onc. 2001*
- Number of visible metastases (> 10^8 cel.) 5 years after the end of the treatment

Adapt the number of cycles to each patient

μ	Protocole de Viens			Optimized protocol		
	6 cycles 126 days	9 cycles 189 days	12 cycles 252 days	9 cycles 126 days	13 cycles 182 days	18 cycles 252 days
1.3×10^{-7}	**1**	0	$\star$	0	$\star$	$\star$
2.7×10^{-7}	**2**	1	0	2	0	$\star$
4.0×10^{-7}	**3**	2	1	3	1	0
6.1×10^{-7}	**5**	4	3	4	3	1

Impact of PT size at surgery on survival



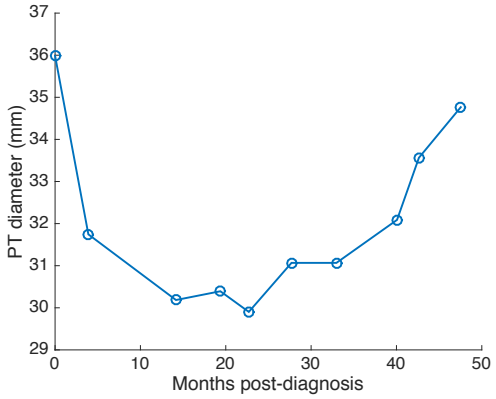


Percentile of μ	10	25	37.5	50	62.5	75	90
$RSB(\mu)$ (%)	∞	∞	∞	47	14	6.4	1.9
Recurrence threshold (cm)	-	6.6	5.2	4	3	2.4	1.4
Benefit threshold (cm)	-	7.8	6.4	5.4	4.6	3.6	2.6

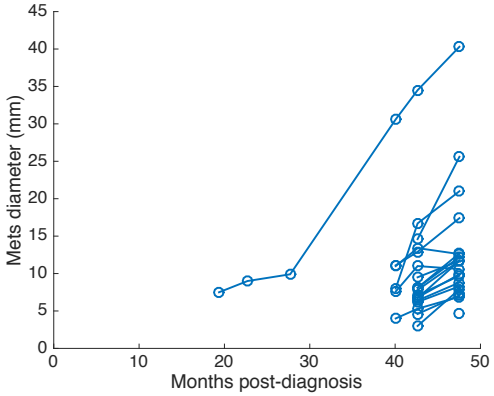
Benzekry et al. (Ebos), Cancer Res, 2016

Data of a NSCLC patient with brain mets

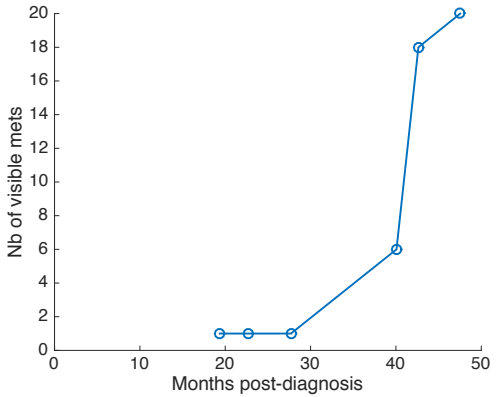
Primary tumor size



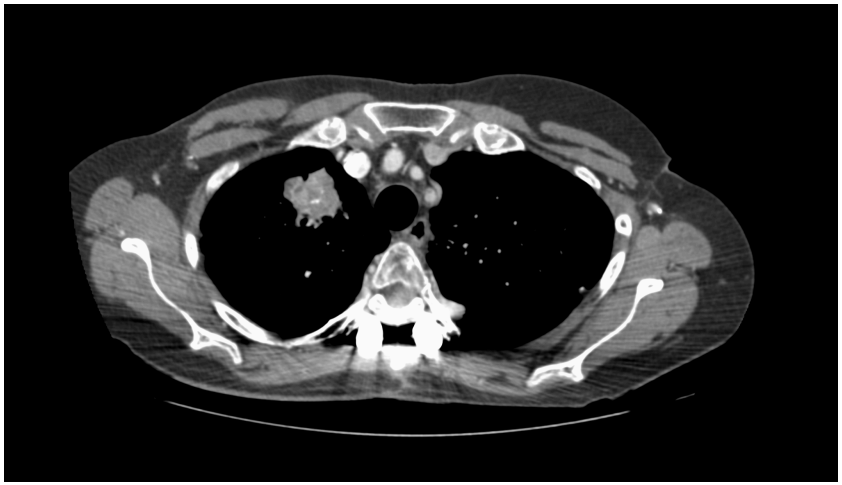
Metastases size



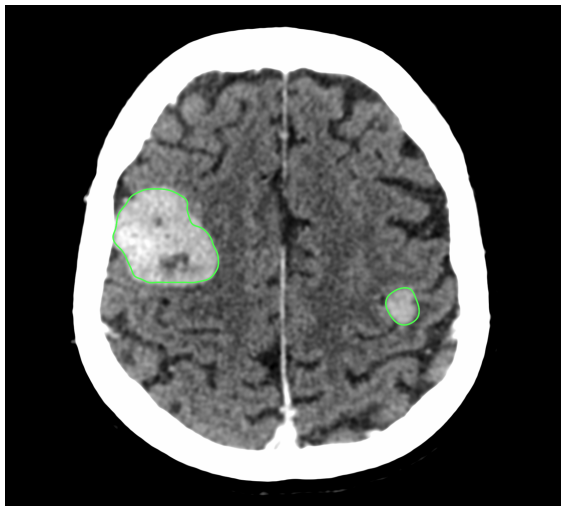
Number of visible mets



Lung CT



Brain CT scan

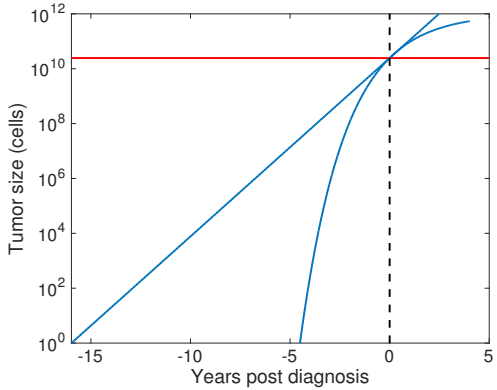


Institut Bergonié, Bordeaux, FR

Parameters estimation

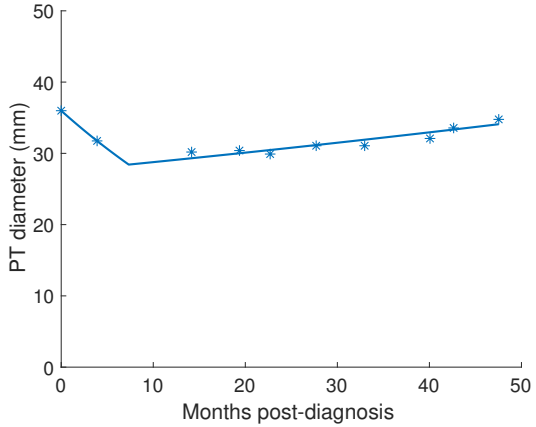
Primary tumor growth pre-diagnosis: α_p, β_p

- Doubling time from histological type *Detterbeck and Gibson, J Thorac Oncol, 2008*
- Maximal size = 10^{12} cells



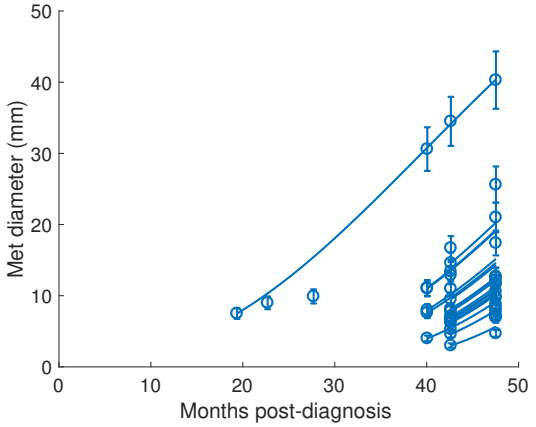
Post-diagnosis: treatment + resistance

Sum of two exponentials



Metastatic growth

First approximation : same as PT: $\alpha, \beta = \alpha_p, \beta_p$

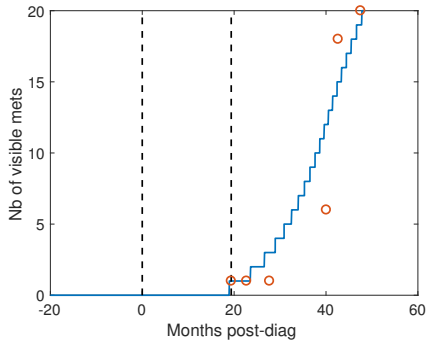


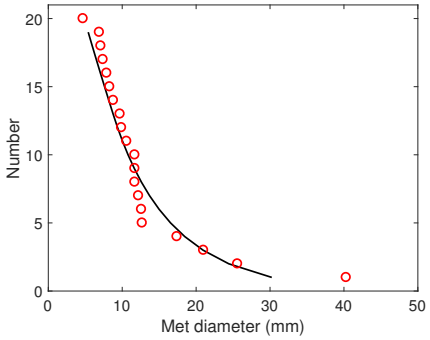
Dissemination: μ γ

Least-square fit to the cumulative distribution (or number of visible mets)

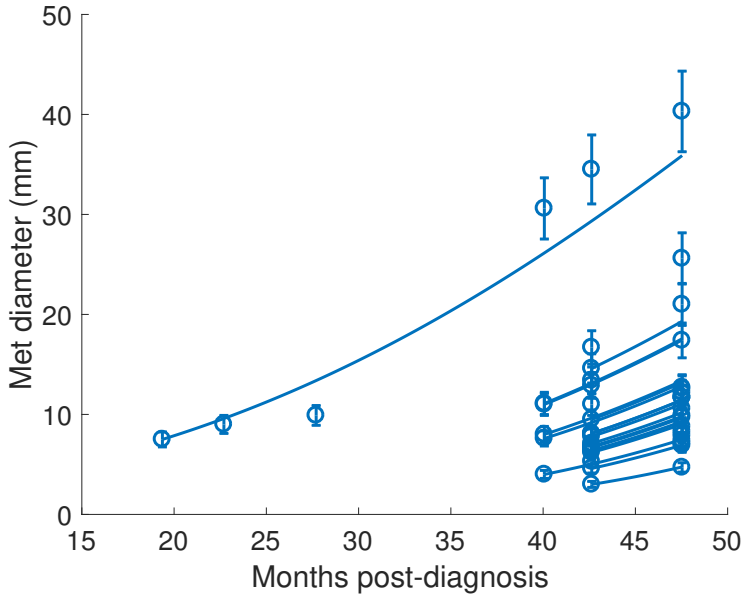
$$N_{vis}(t) = \int_{V_{vis}}^{+\infty} \rho(t,v)dv = \int_0^{t-\tau(V_{vis})} d\left(V_p\left(s\right)\right) ds$$

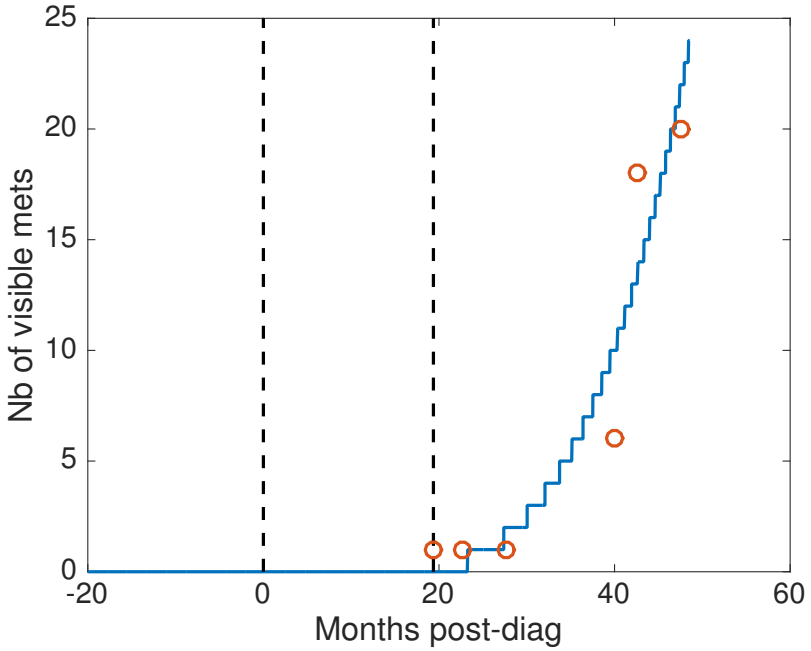
$$f(t,v) = \int_v^{+\infty} \rho(t,u)du = N\left(t-\tau\left(v\right)\right)$$





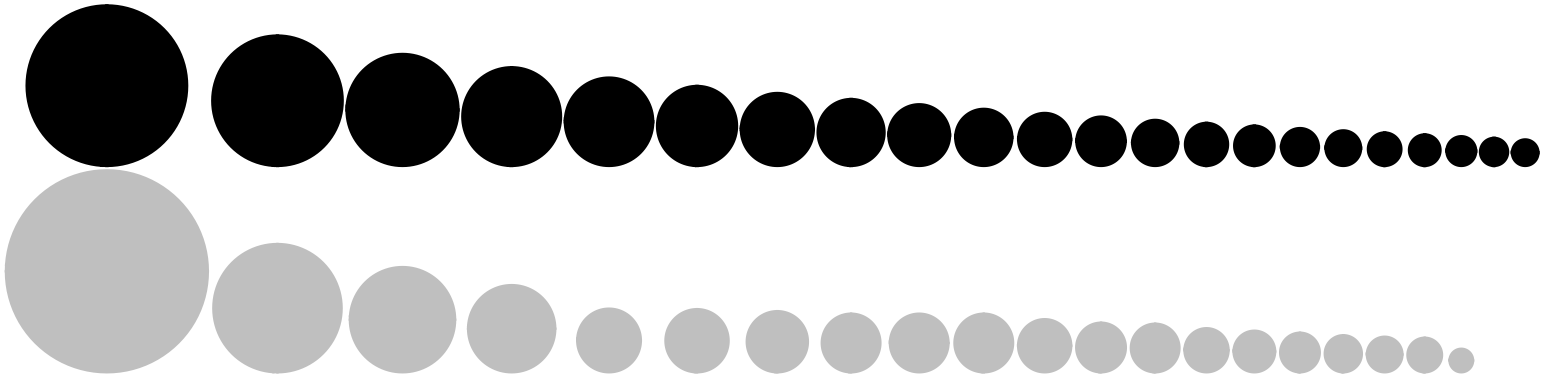
The model could describe the data

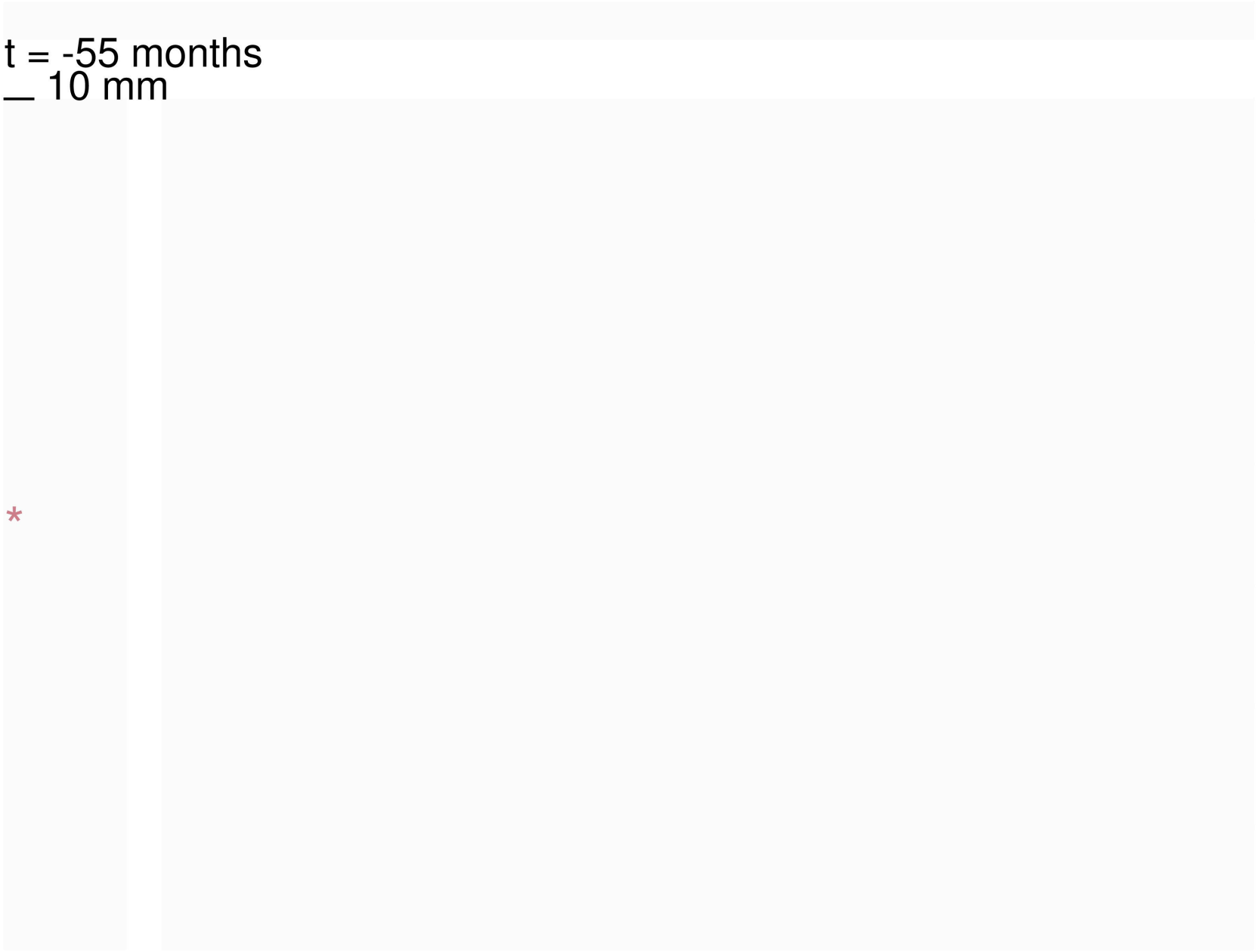


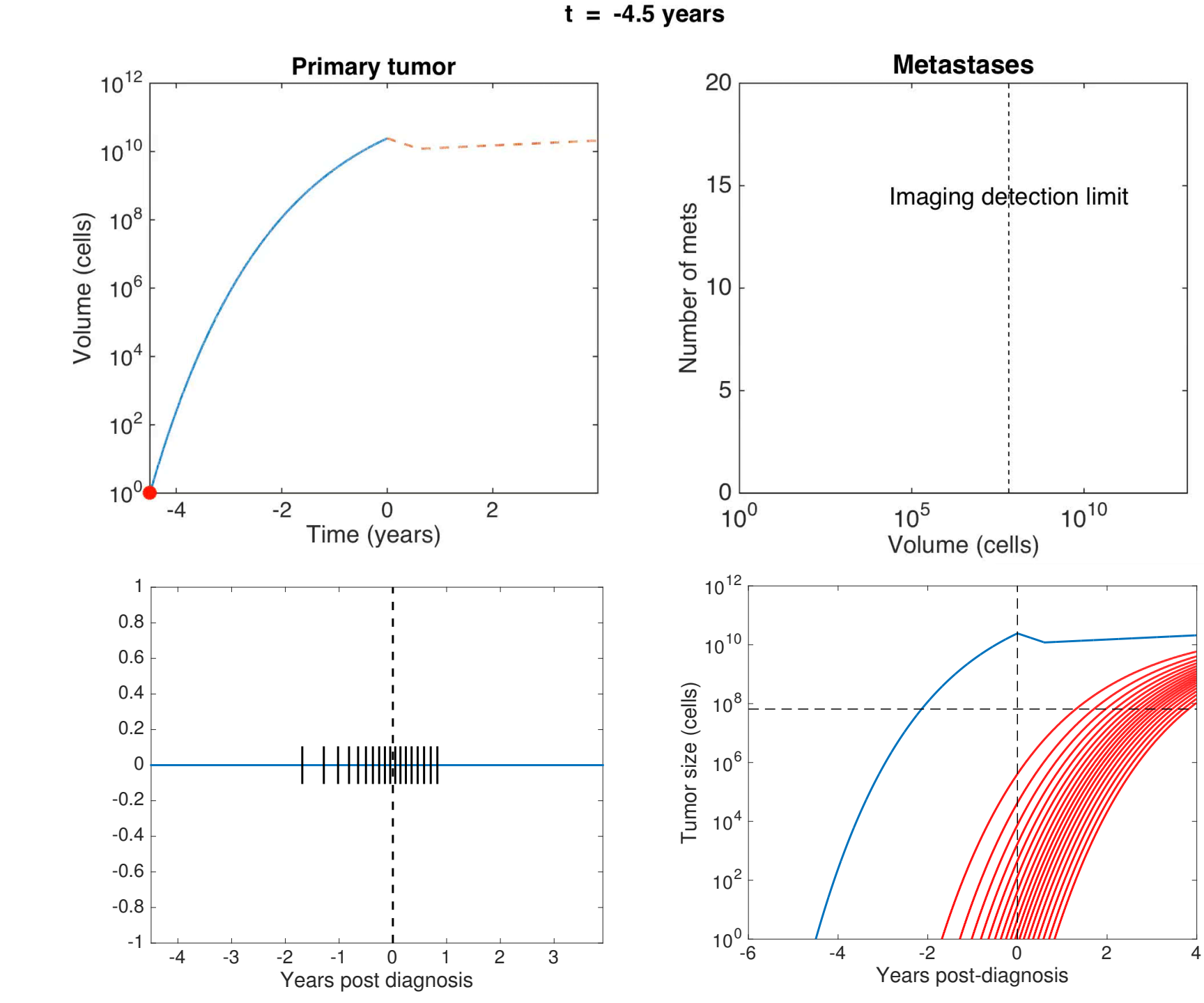


Model

Data




t = -55 months
10 mm
*
Primary tumor (lung)
Metastases (brain)


t = -4.5 years
Primary tumor
Volume (cells)
Time (years)
Metastases
Number of mets
Imaging detection limit
Volume (cells)
Years post diagnosis
Tumor size (cells)
Years post-diagnosis

Current effort: towards personalized predictions from mechanistic modeling

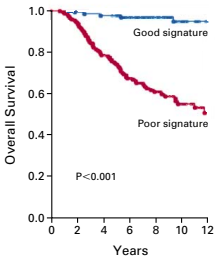
Model

Prediction

Biomarkers

PT size, lymph node status, histological grade, molecular receptors (ER, PR, HER2), ***Ki67***, ***TRIO expression (cadherins)***,…

Black box



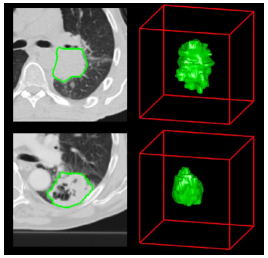
Prognosis

Current effort: towards personalized predictions from mechanistic modeling

Biomarkers

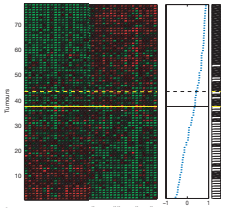
PT size, lymph node status, histological grade, molecular receptors (ER, PR, HER2), ***Ki67***, ***TRIO expression (cadherins)***,…

Imaging data



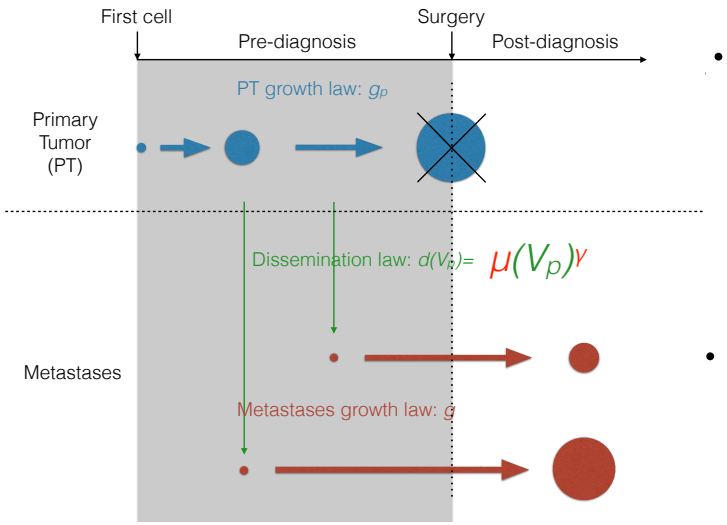
Aerts et al., Nat Commun, 2014

Molecular data

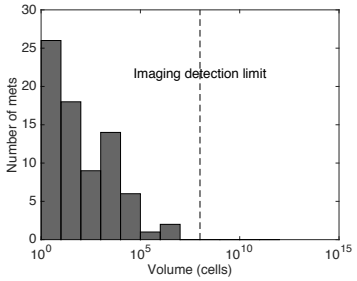


van't Veer et al., Nature, 2002

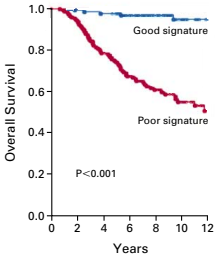
Model



Prediction

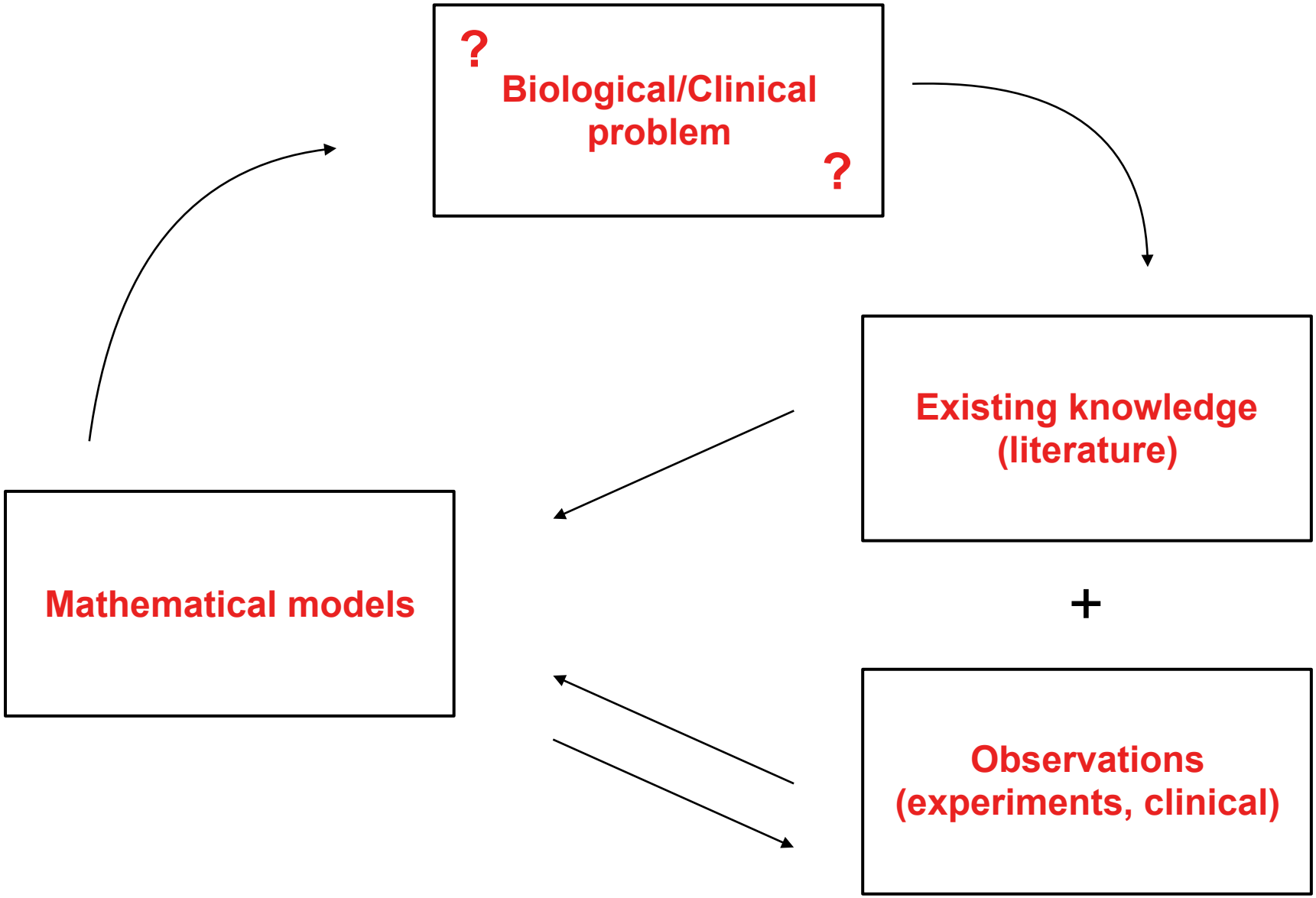


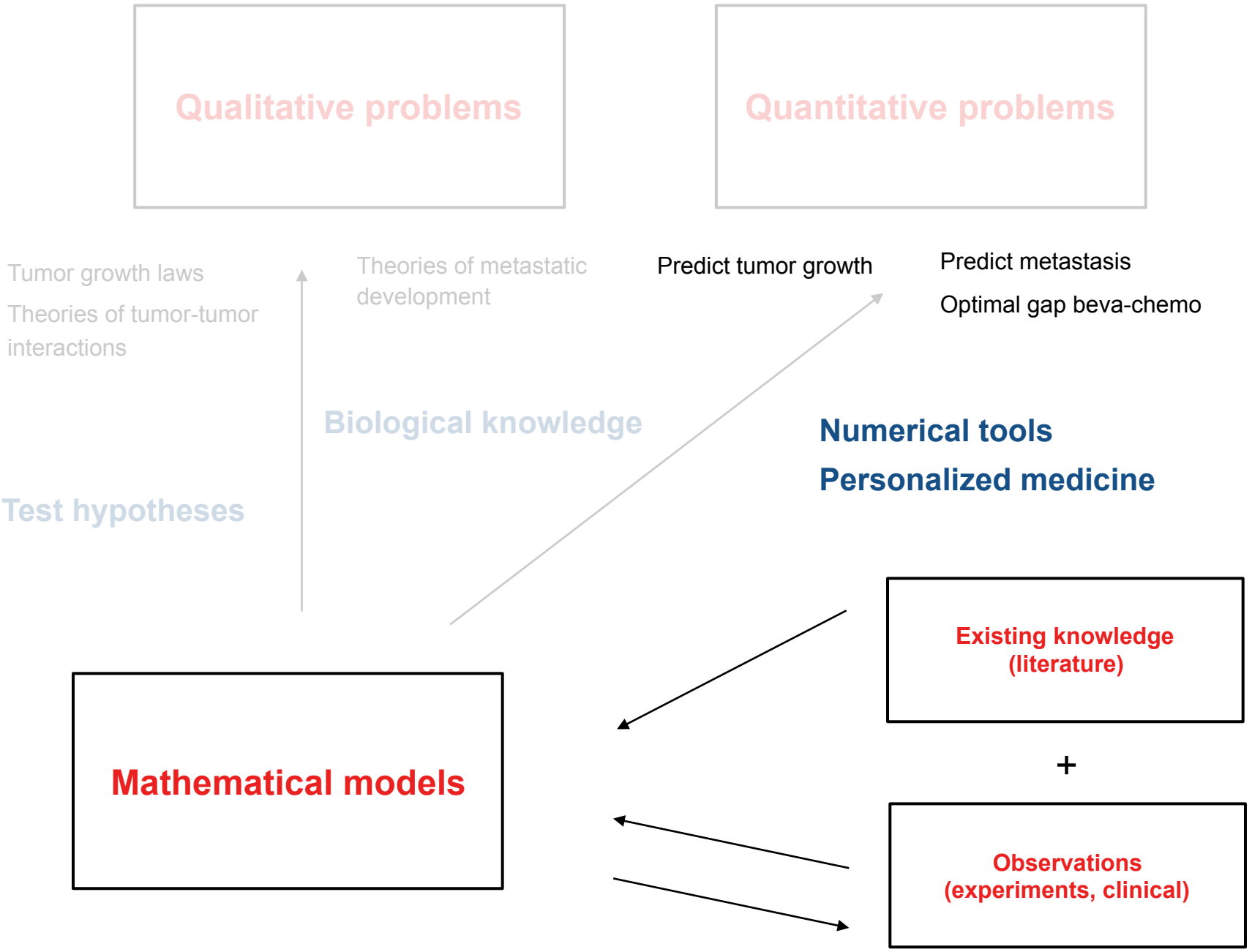
Diagnosis



Prognosis

Simulation and individualization of therapy


?
Biological/Clinical problem
?
Existing knowledge (literature)
+
Observations (experiments, clinical)
Mathematical models


Qualitative problems
Quantitative problems
Tumor growth laws
Theories of tumor-tumor interactions
Theories of metastatic development
Predict tumor growth
Predict metastasis
Optimal gap beva-chemo
Biological knowledge
Numerical tools
Personalized medicine
Test hypotheses
Mathematical models
Existing knowledge (literature)
+
Observations (experiments, clinical)

Thank you all for your attention !!

Want to do a PhD/postdoc? Join us!

⇒ sebastien.benzekry@inria.fr