INVENTORS FOR THE DIGITAL WORLD

SMARTc
SIMULATION MODELING ADAPTIVE RESPONSE FOR THERAPEUTICS IN CANCER

Mathematical Modelling of Chemotherapy Scheduling

Metronomics @ Mumbai
May 6th, 2016

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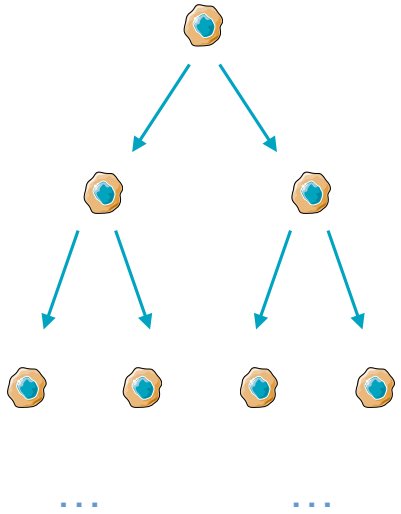
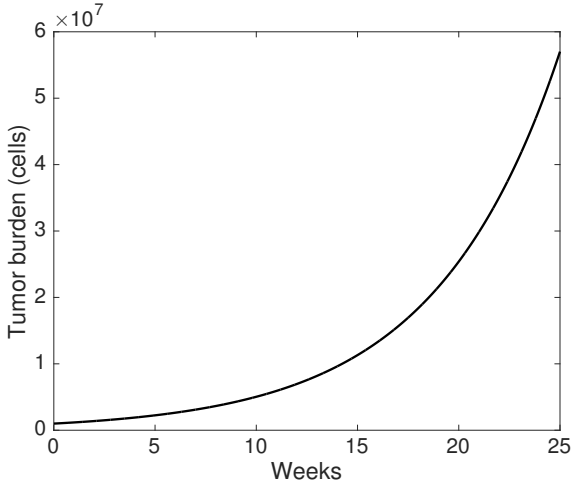
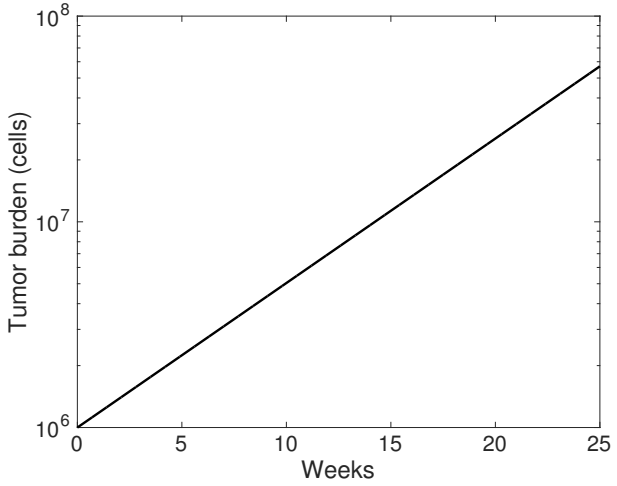
Where does the MTD paradigm come from ?

- **Skipper-Schabel-Wilcox** seminal papers in the 1960's
- Basic principle = **proliferation**
- **Exponential** growth of the tumor cell population *N(t)*







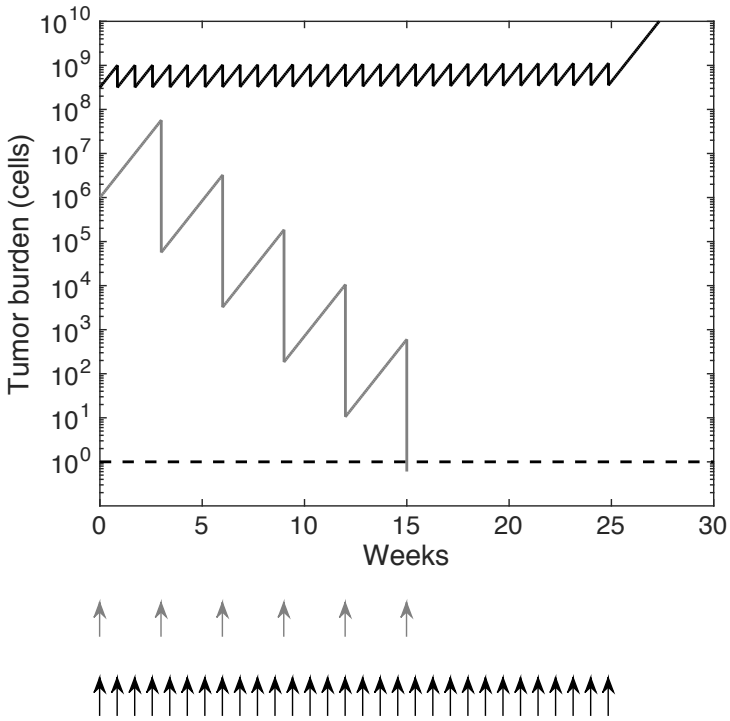
$$\frac{dN}{dt} = aN \qquad a \sim T^{-1} \quad T = \text{doubling time}$$

Where does the MTD paradigm come from ?

Log-kill hypothesis

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

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



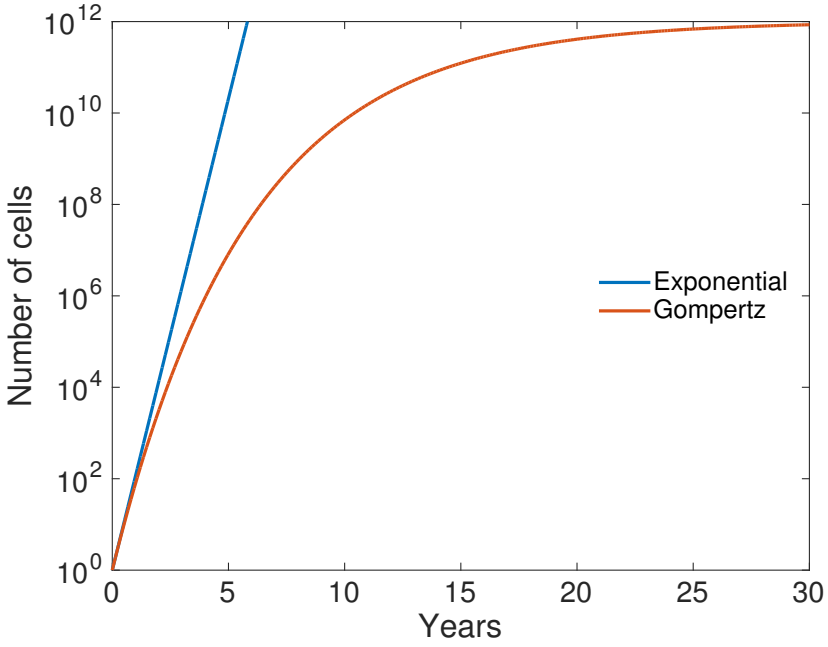
- Established on leukemic cell lines
- Focus: **curability**

"(...) 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**



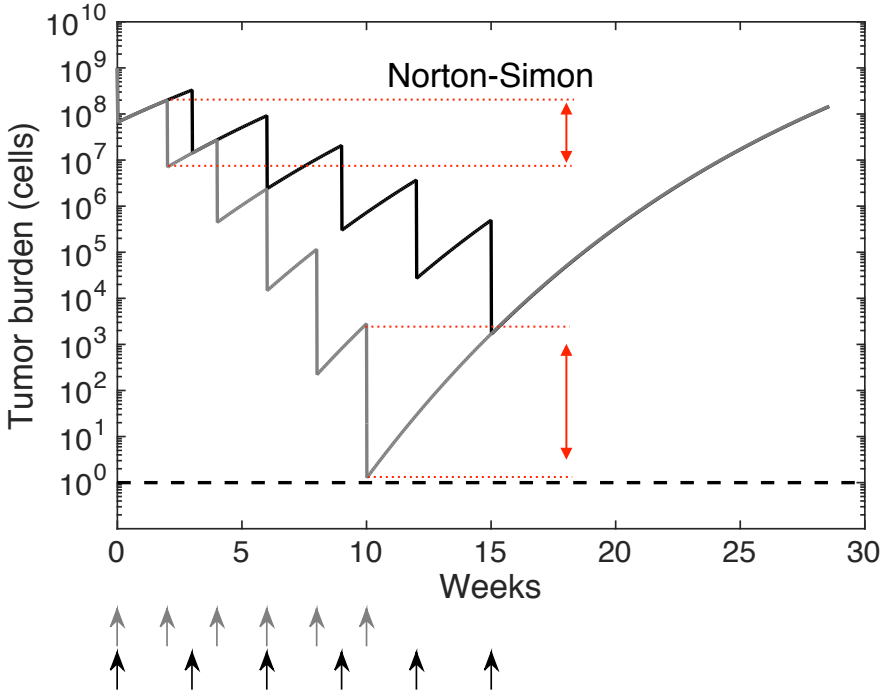
$$\frac{dN}{dt} = ae^{-bt}N$$

The Norton-Simon hypothesis

Second hypothesis: effect of the therapy is proportional to the

proliferative fraction only

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



- 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**

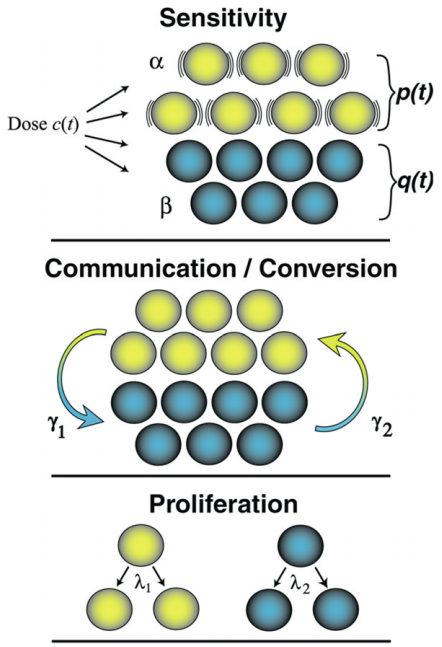
Norton, Simon, Cancer Treat Rep, 1976

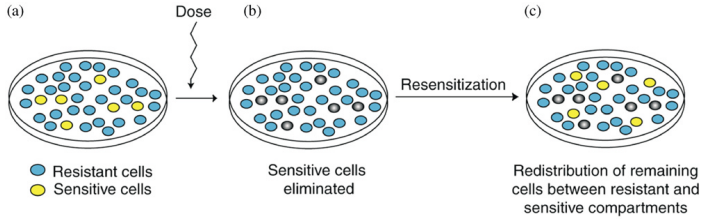
Tumor heterogeneity and re-sensitization

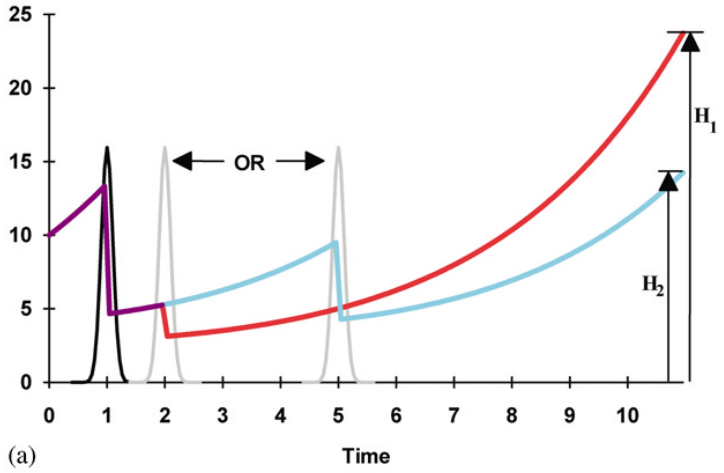
Minimizing Long-Term Tumor Burden: The Logic for Metronomic Chemotherapeutic Dosing and its Antiangiogenic Basis

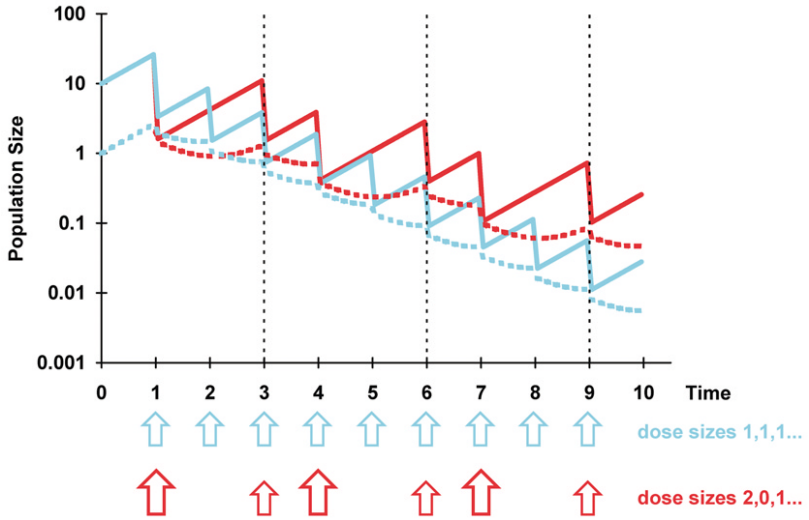
J Theor Biol, 2003

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

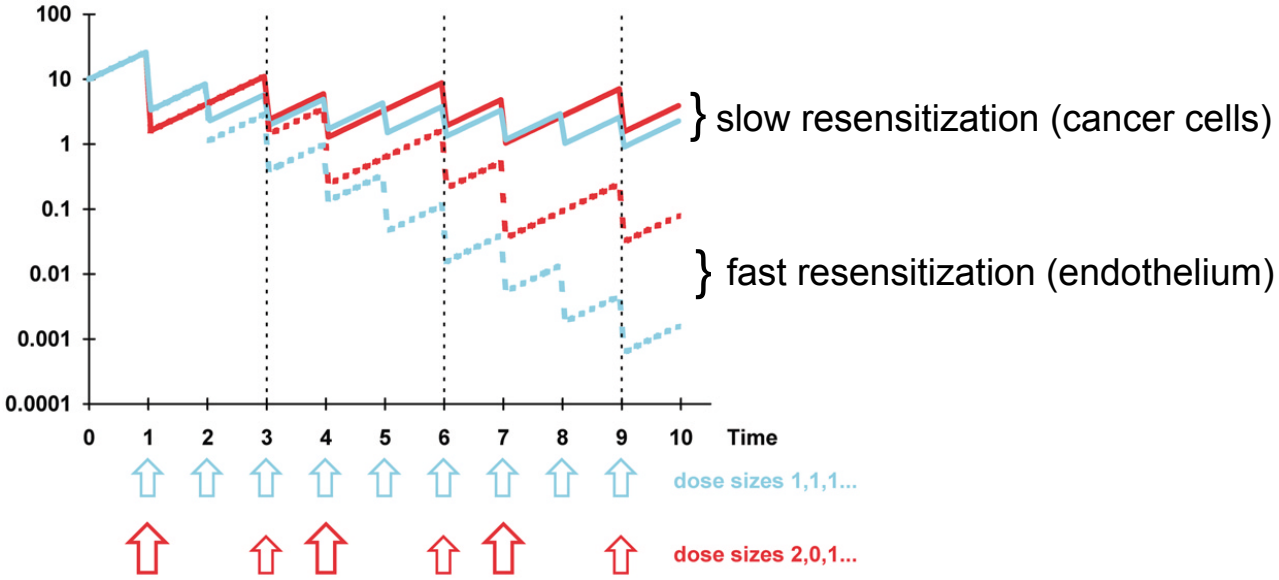








Tumor heterogeneity and re-sensitization



- 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

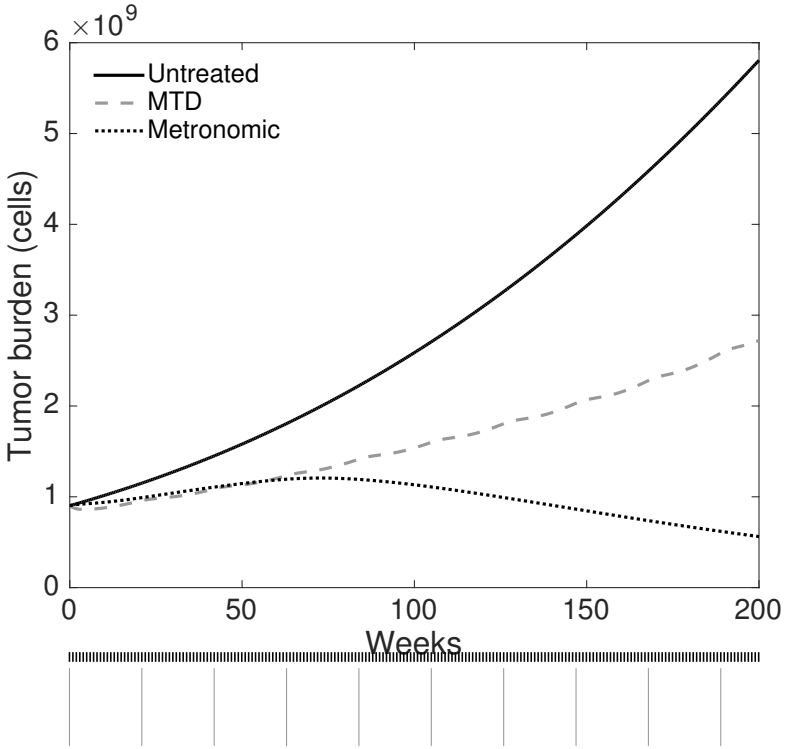
A dedicated model for metronomic chemotherapy

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

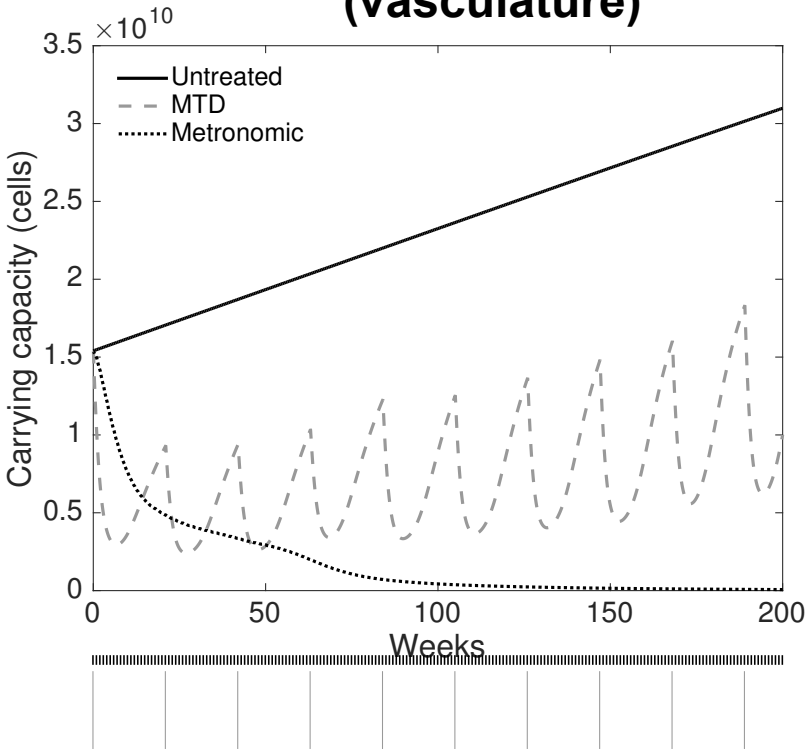
Metronomic schedule: 10 mg/day every day without resting period

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

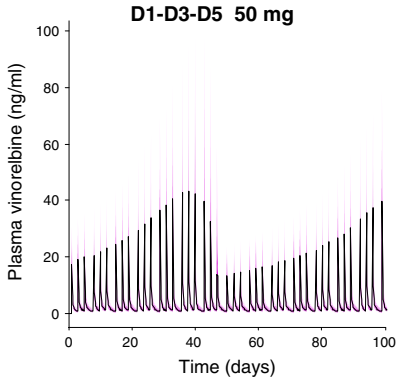
Toxicity

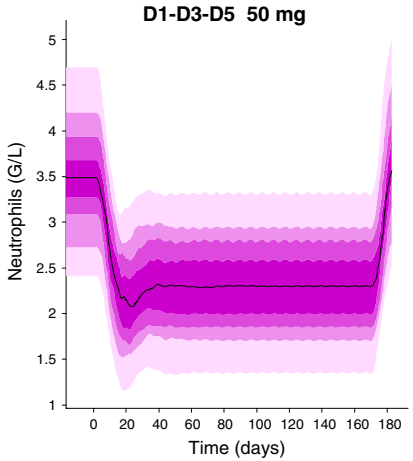
Efficacy

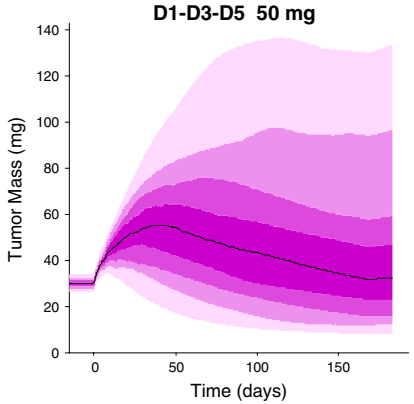
Sched 1

Briasoulis et al.,

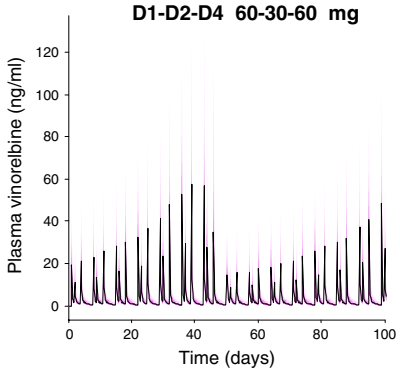
Clin Cancer Res 2009

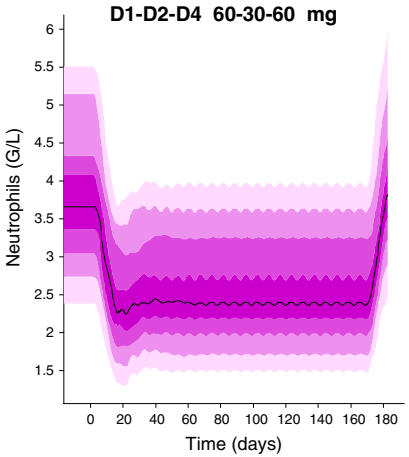


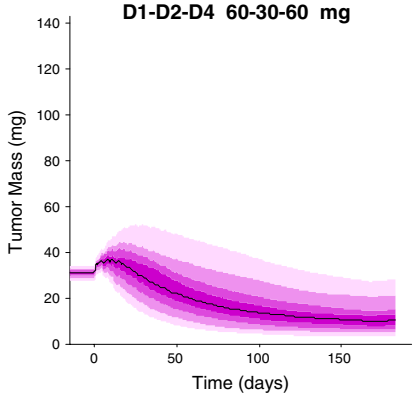




Sched 2







⇒ **ongoing phase I trial**

Barbolosi, André et al., Cancer Chemother Pharmacol (2014)

Elharrar, Barbolosi, André et al. (2016)

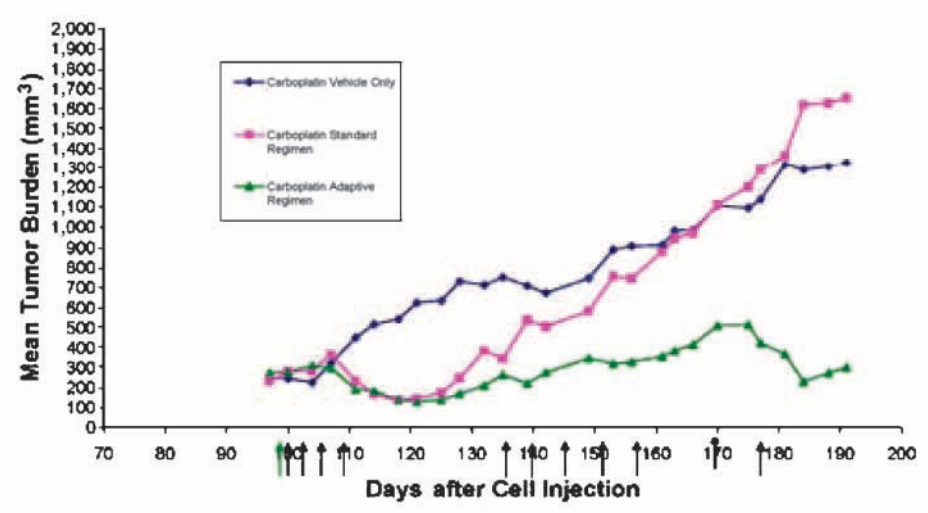
Adaptive therapy

- **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

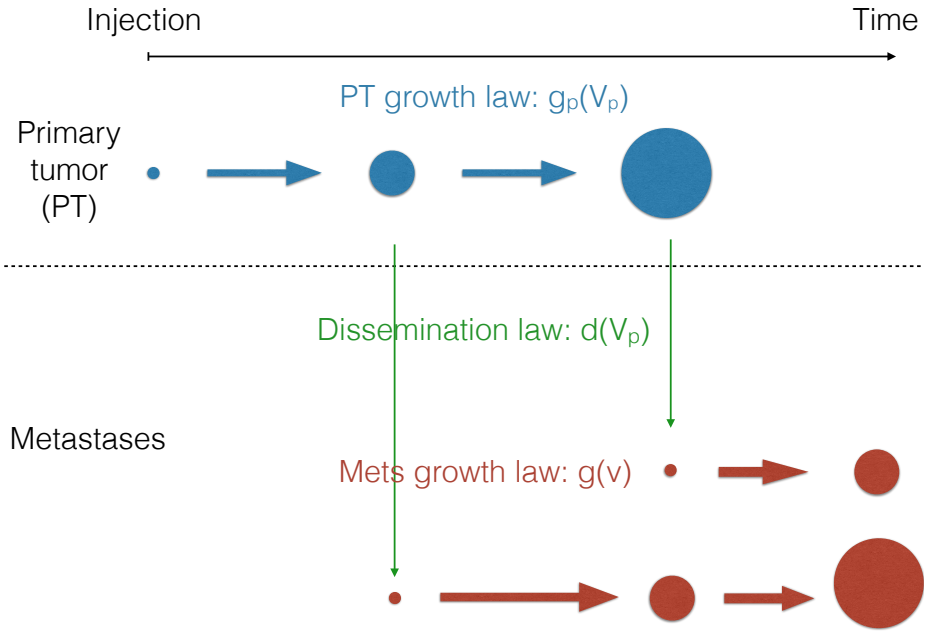
Patients and politicians anxiously await and increasingly demand a 'cure' for cancer. But trying to control the disease may prove a better plan than striving to cure it, says **Robert A. Gatenby**.

Gatenby, Nature, 2009

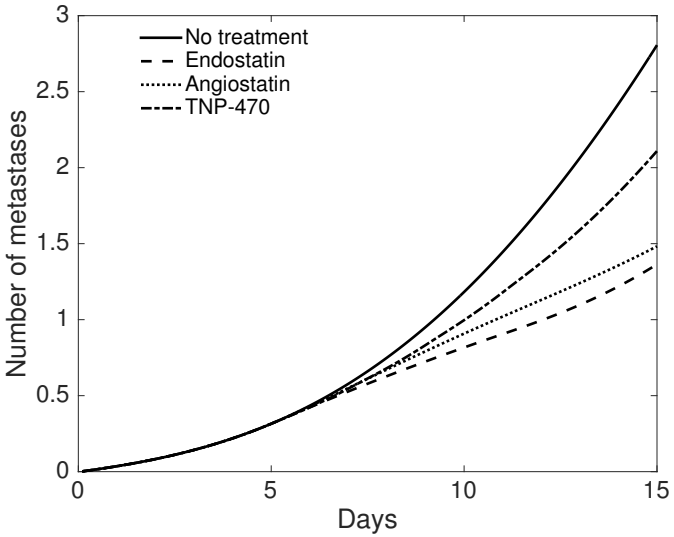


Gatenby et al., Cancer Res, 2009

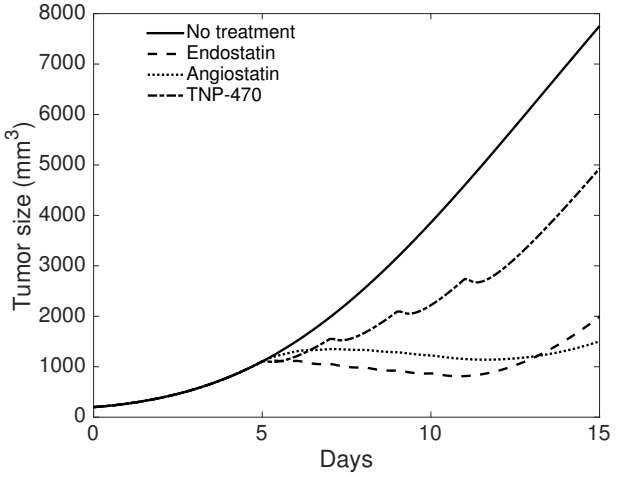
Primary tumor VS metastases



Primary tumor



Metastases



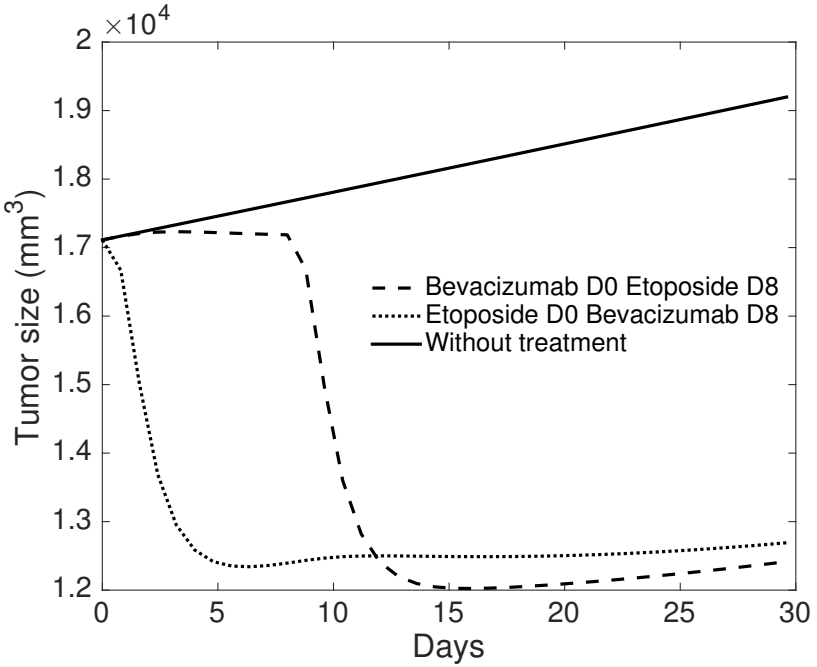
Benzekry, M2AN, 2012

Benzekry, Ebos et al., Cancer Res, 2015

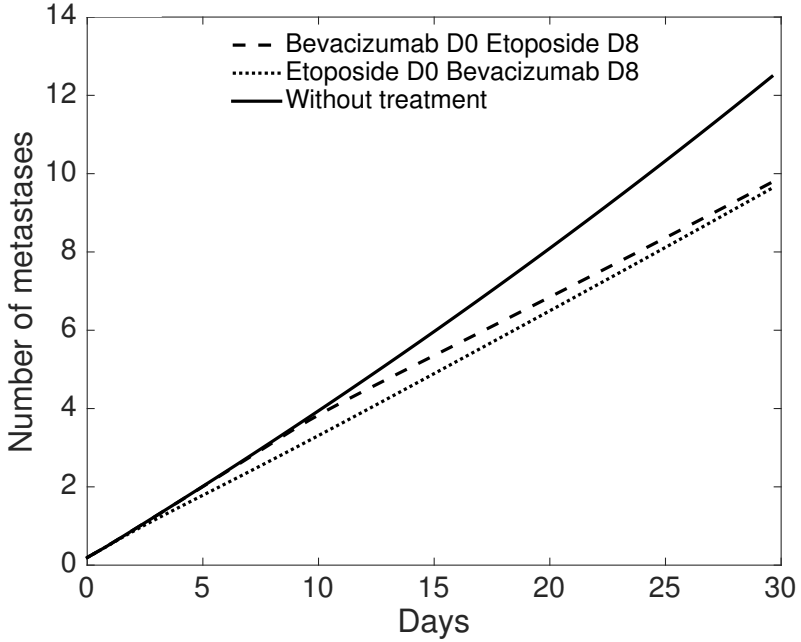
CT/AA combination. What sequence?

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

Primary tumor



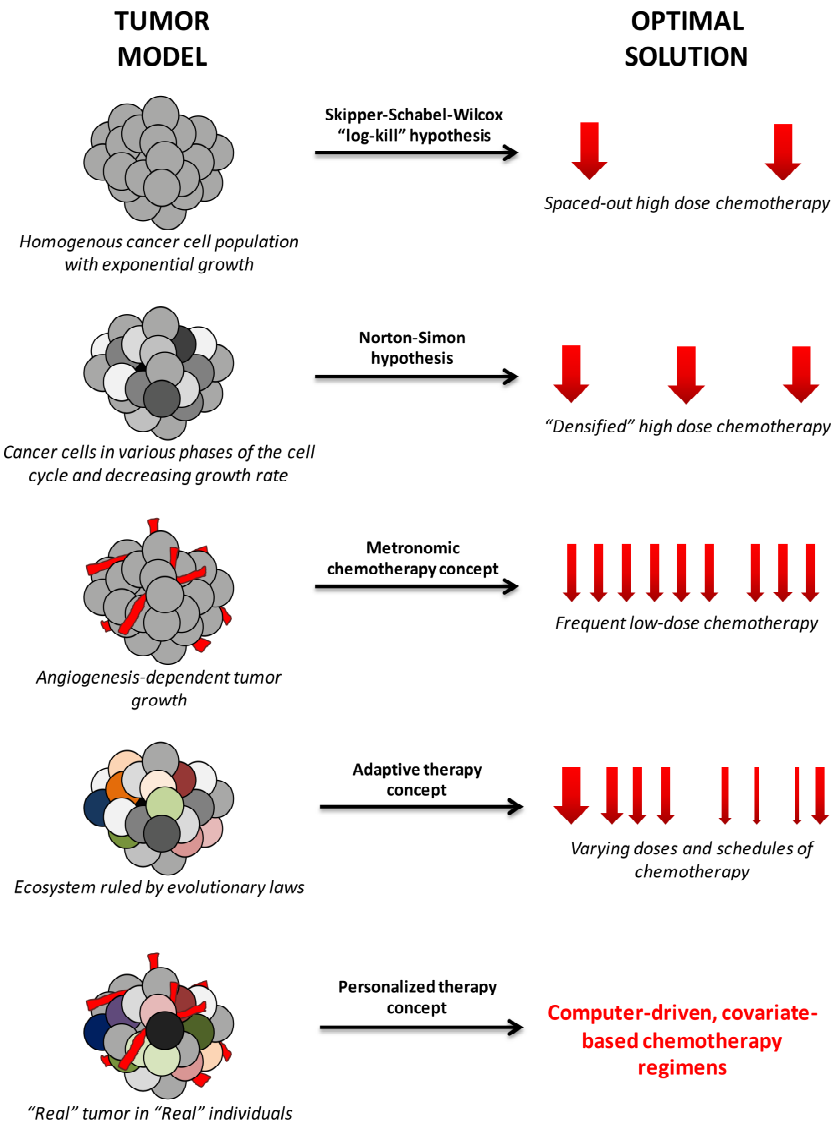
Metastases



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

Conclusions

- 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

Thank you for your attention!