



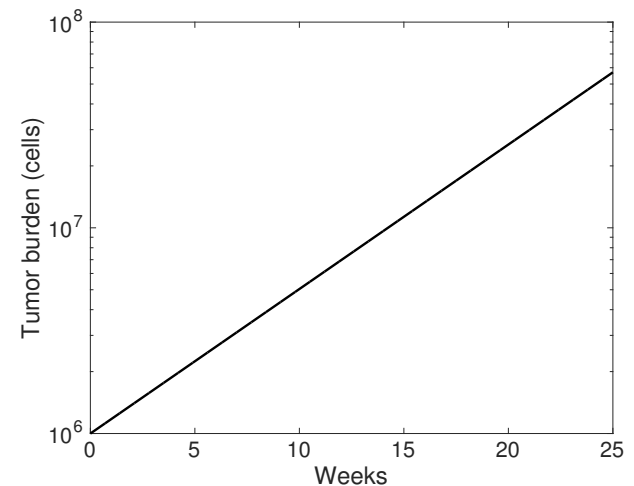
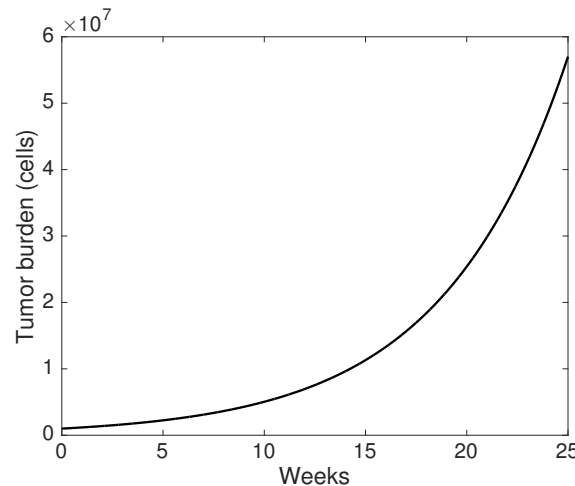
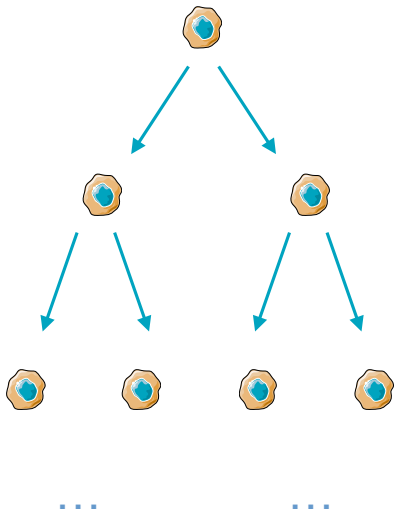
Mathematical Modelling of Chemotherapy Scheduling

*Metronomics @ Mumbai
May 6th, 2016*

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INRIA team MONC
Bordeaux

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 $N(t)$



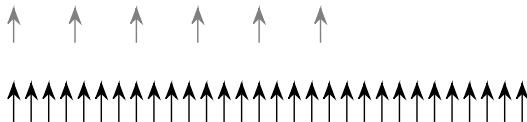
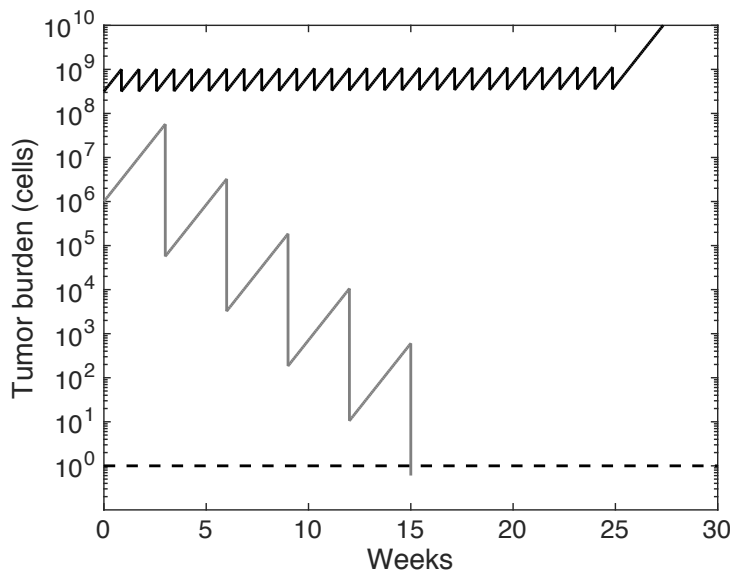
$$\frac{dN}{dt} = aN \quad a \sim T^{-1} \quad T = \text{doubling time}$$

Where does the MTD paradigm come from ?

Log-kill hypothesis

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

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

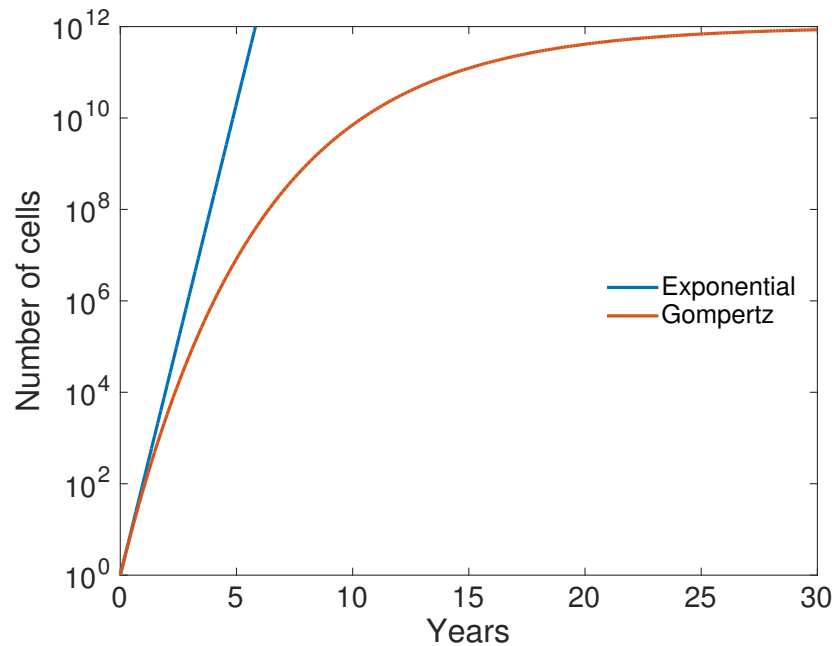


- Established on leukemic cell lines
- Focus: **curability**

“(…) 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”

The Norton-Simon hypothesis: tumor growth model

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

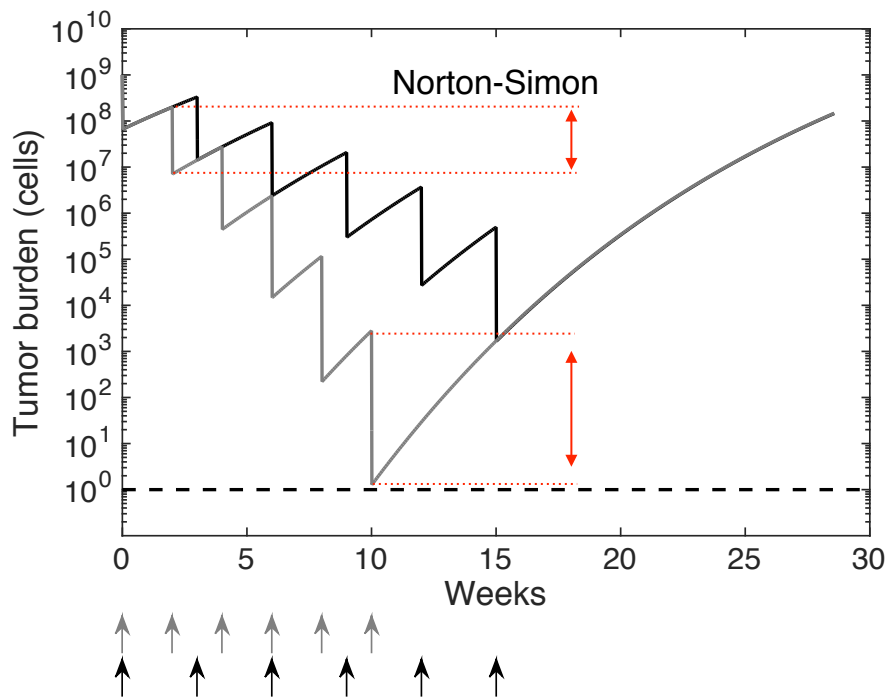


$$\frac{dN}{dt} = a e^{-bt} N$$

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

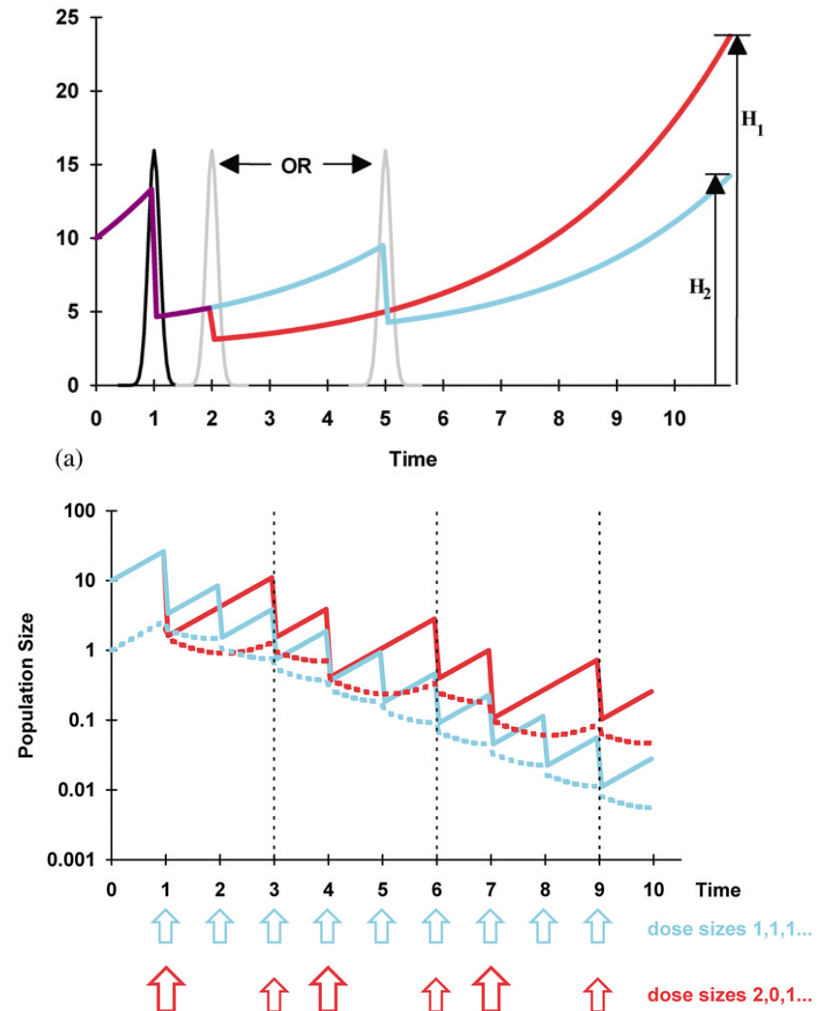
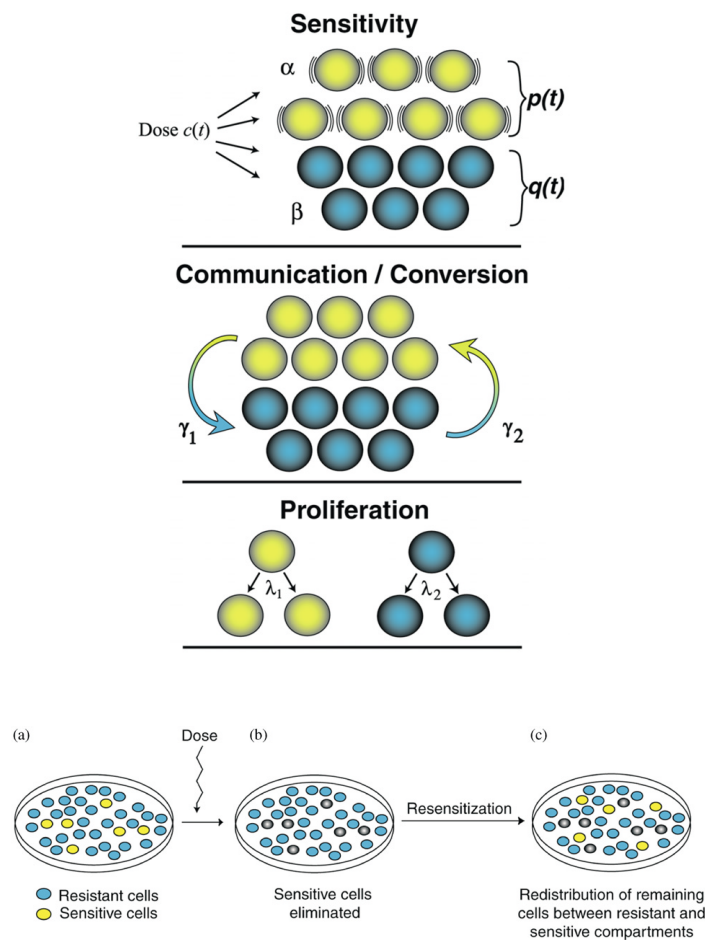
still focuses on **tumor eradication**

Tumor heterogeneity and re-sensitization

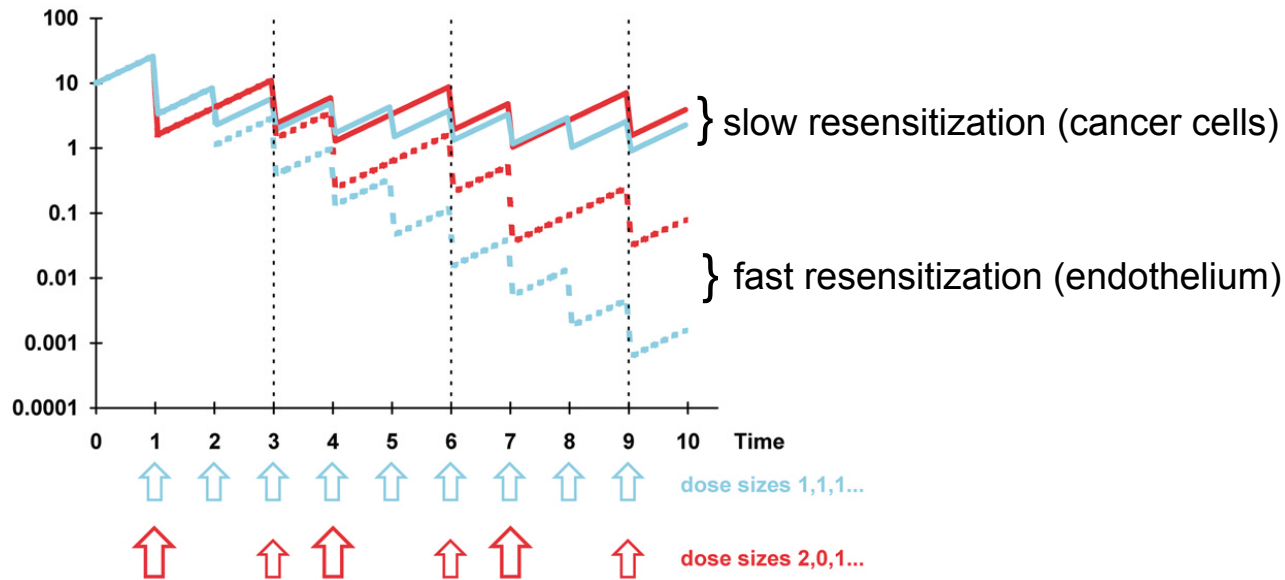
Minimizing Long-Term Tumor Burden: The Logic for Metronomic Chemotherapeutic Dosing and its Antiangiogenic Basis

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

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

N = tumor cells

K = carrying capacity

= **vascular support**

AA effect

Resistance

CT effect

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

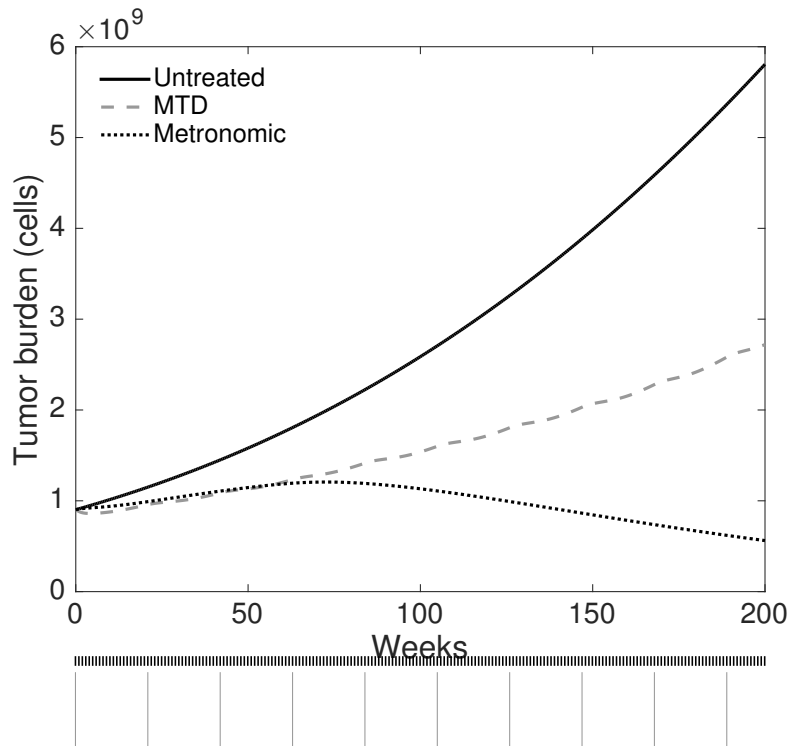
A dedicated model for metronomic chemotherapy

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

Docetaxel PK/PD parameters

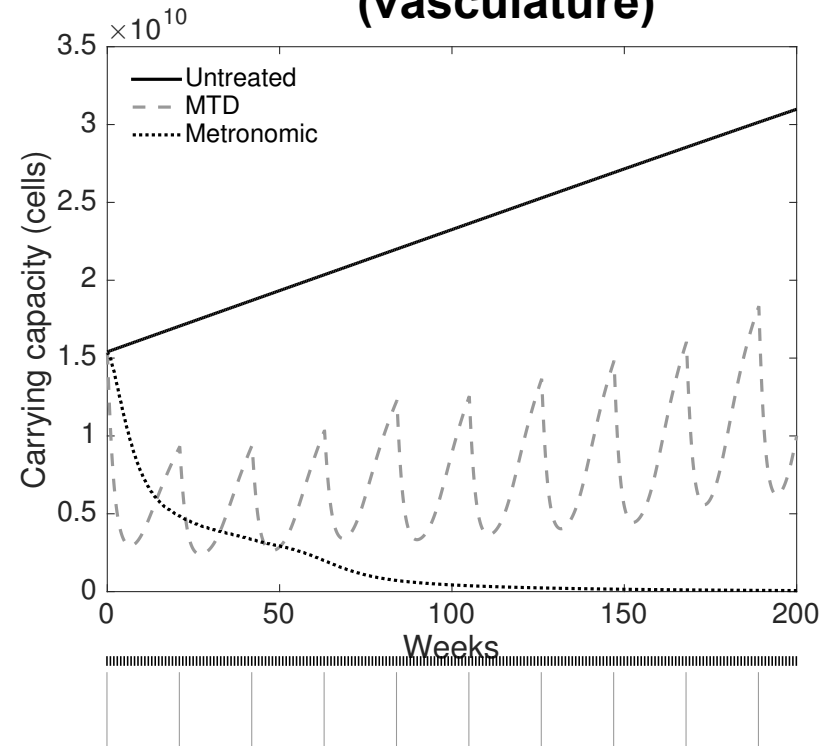
Metronomic schedule: 10 mg/day every day without resting period

Tumor cells



Carrying capacity

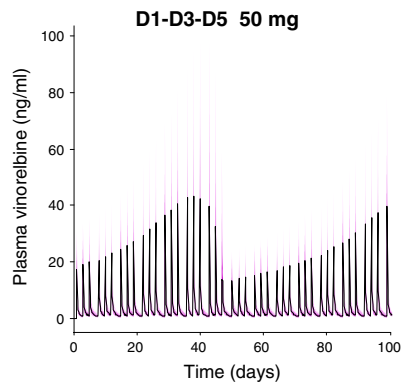
(vasculature)



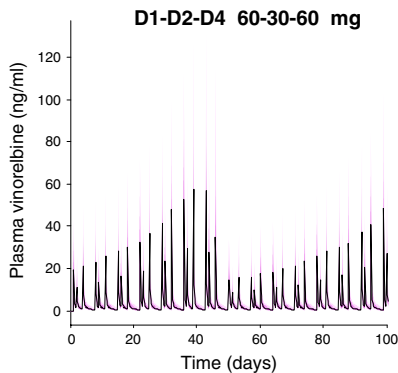
Modeling of toxicity and scheduling of vinorelbine in NSCLC

Sched 1

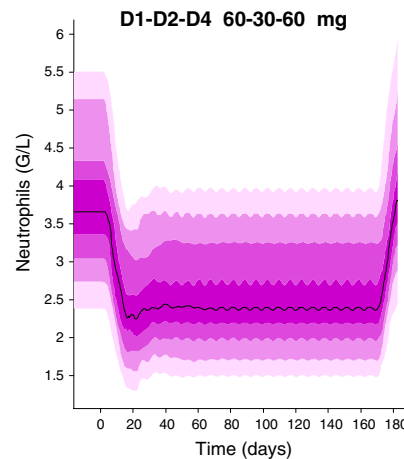
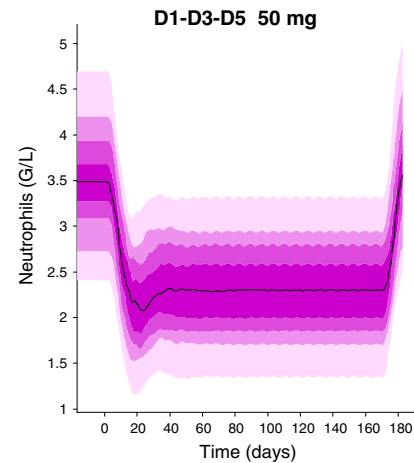
*Briasoulis et al.,
Clin Cancer Res 2009*



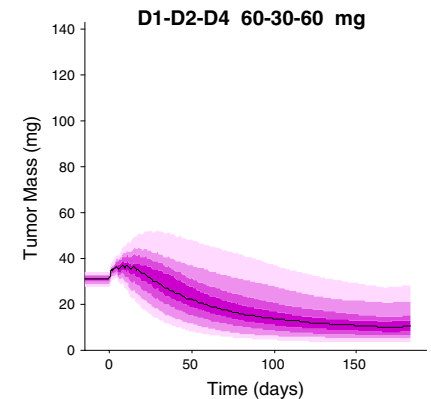
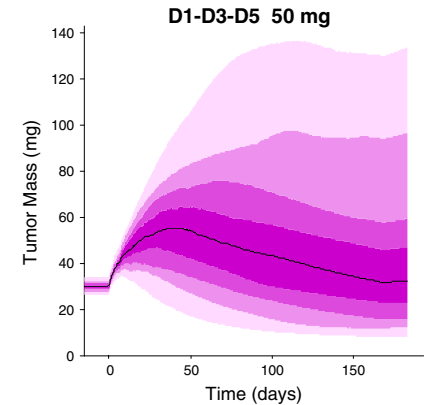
Sched 2



Toxicity



Efficacy



⇒ ongoing phase I trial

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

Elharrar, Barbolosi, André et al. (2016)

Adaptive therapy

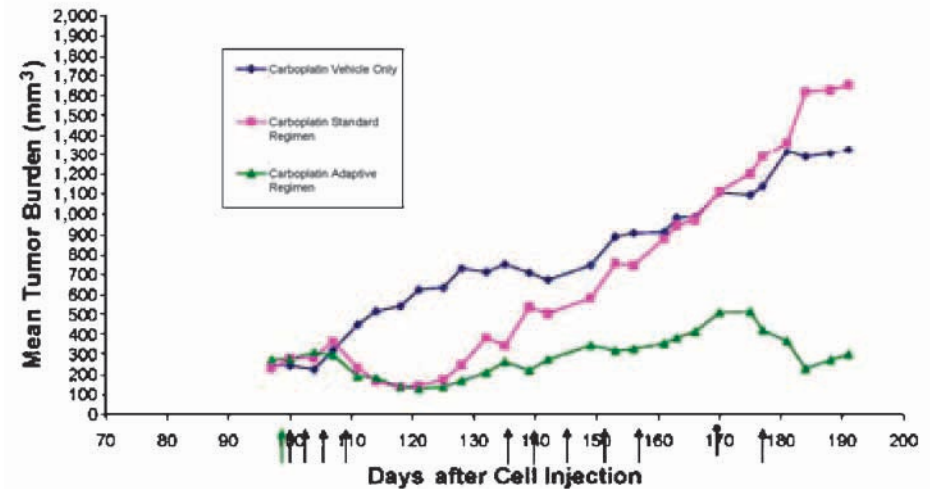
- **Evolutionary** viewpoint of resistance to therapy. Darwinian selection
- **Complex** dynamics are hard to control. Why, then, use **fixed, rigid** protocols of drugs, dose and timing?
- Gatenby suggests to rather **adapt** the protocol as the tumor evolves in response to therapy



A change of strategy in the war on cancer

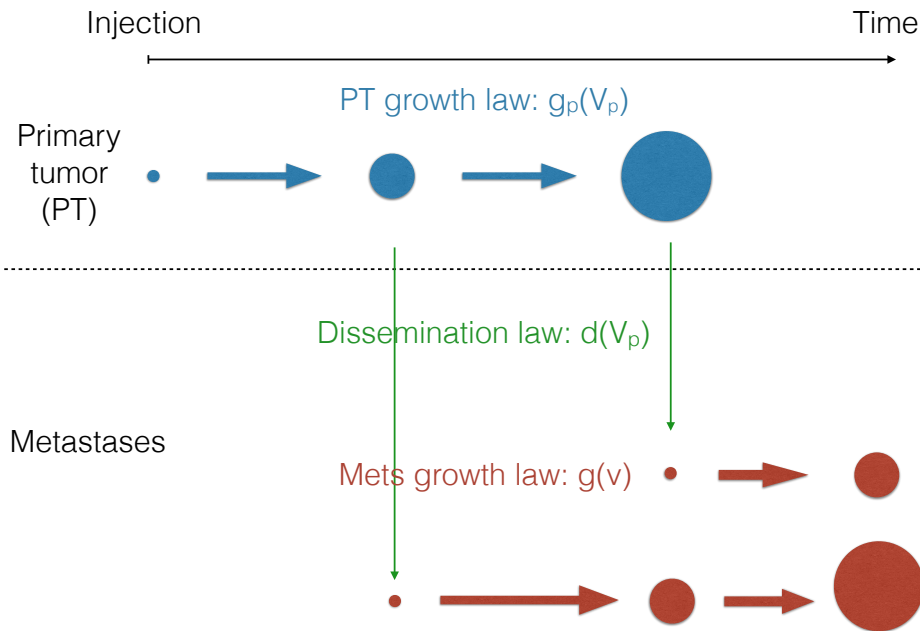
Patients and politicians anxiously await and increasingly demand a 'cure' for cancer. But trying to control the disease may prove a better plan than striving to cure it, says **Robert A. Gatenby**.

Gatenby, Nature, 2009

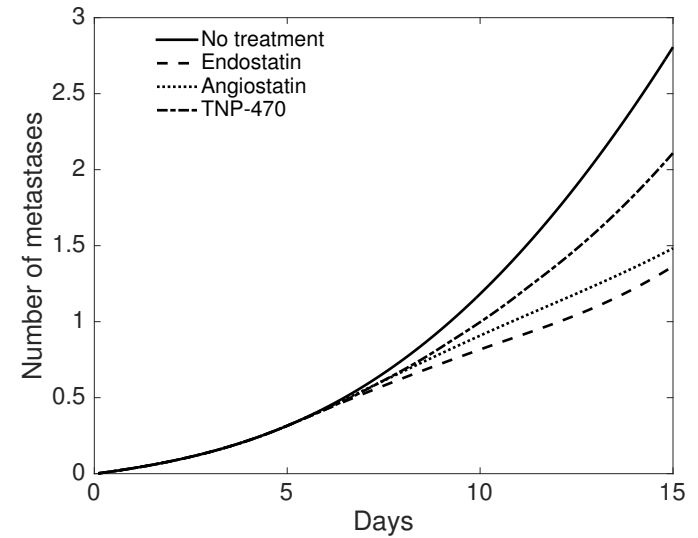


Gatenby et al., Cancer Res, 2009

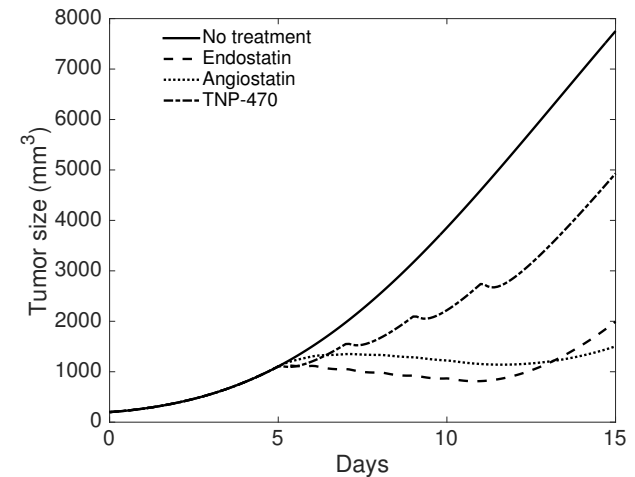
Primary tumor VS metastases



Primary tumor



Metastases



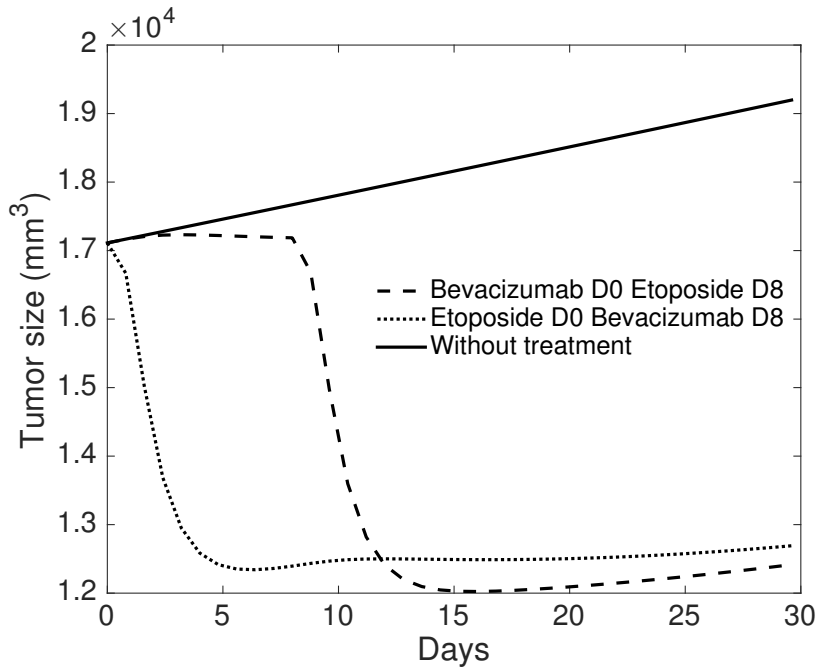
Benzekry, M2AN, 2012

Benzekry, Ebos et al., Cancer Res, 2015

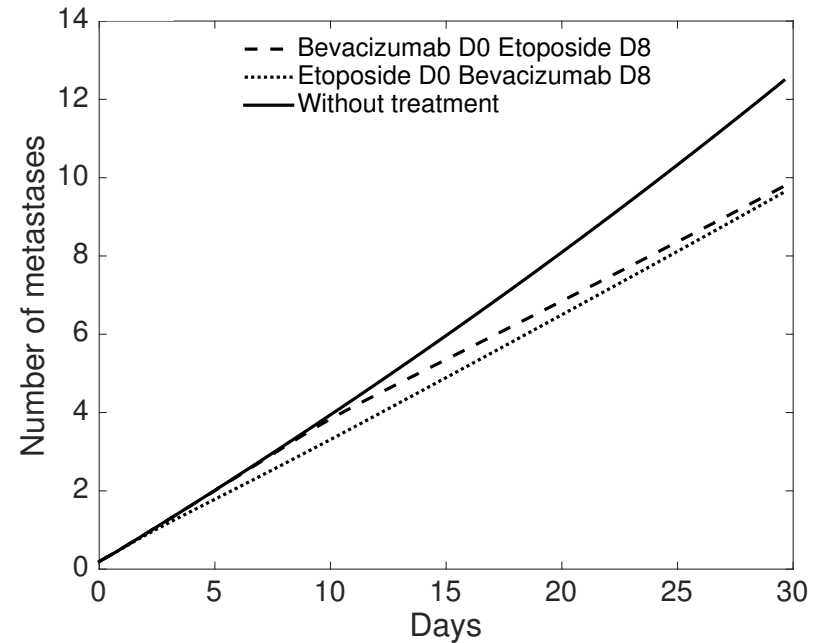
CT/AA combination. What sequence?

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

Primary tumor



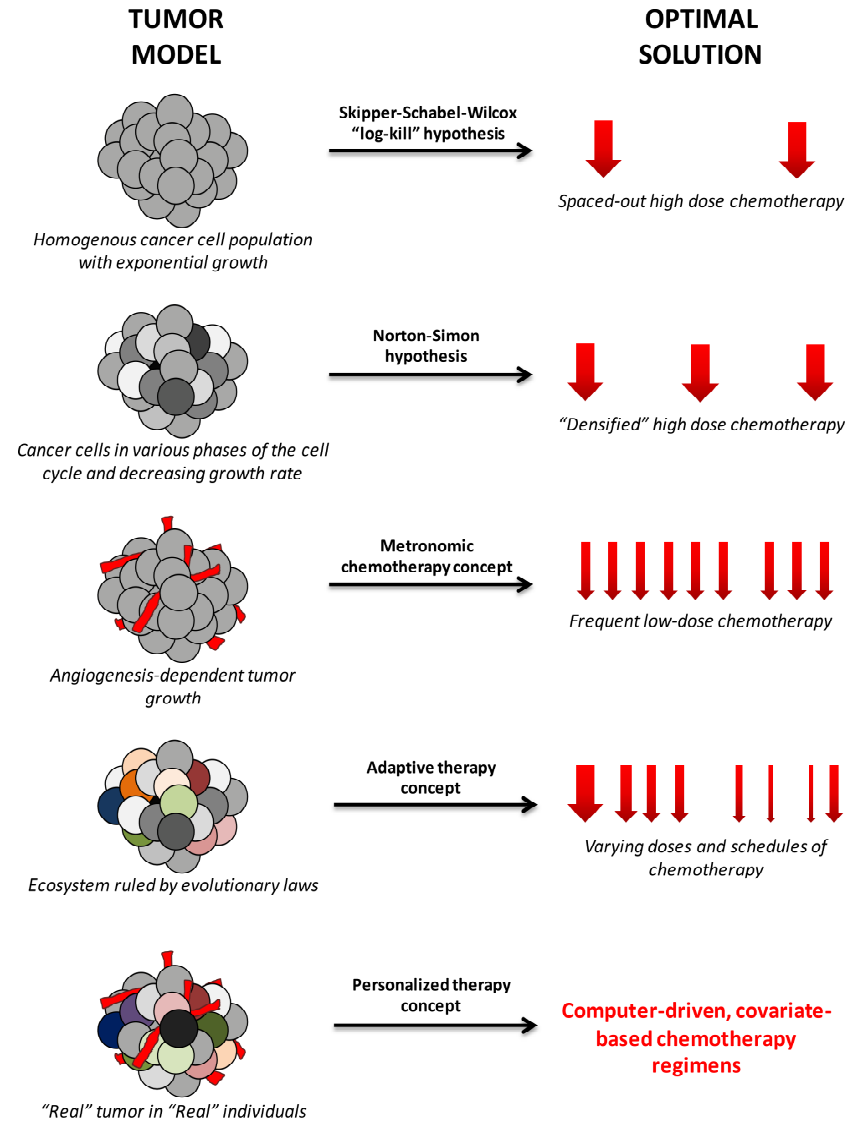
Metastases



⇒ 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)



Thank you for your attention!

The screenshot displays a MATLAB environment with several windows and a code editor. The top-left window shows a PDF document with the following text:

This led to substantial differences in simulations that won't b

1.3 A simpler model for the normalization dyna

This model will be designated by `TestModelV4`

$$\begin{cases} \frac{dV}{dt} = aV \ln\left(\frac{K}{V}\right) - e_{CT}QC(t)V \\ \frac{dK}{dt} = bN - dN^{2/3}K - e_{AA}QA \\ \frac{dQ}{dt} = fA(t) - gQ \\ \frac{dZ_1}{dt} = e_{CT}QC(t)V - kZ_1 \\ \frac{dZ_2}{dt} = kZ_1 - kZ_2 \\ \frac{dZ_3}{dt} = kZ_2 - kZ_3 \\ N = V + Z_1 + Z_2 + Z_3 \end{cases}$$

1.4 Pharmacokinetics

1.4.1 Breast study: Bevacizumab and Paclitaxel

The top-right window, titled 'Figure 3', shows a bar chart of 'Final BL (p/s) × 10¹⁰' for four different conditions. The bars are approximately 7.2, 5.2, 3.8, and 5.5 units high. The bottom-right window, titled 'Figure 1', is a semi-log plot of 'Bioluminescence (p/s)' vs 'Time (days)'. It shows two data series: 'Beva' (red circles) and 'Chimio' (black circles). Both series show an initial increase in bioluminescence, peaking around day 30, and then stabilizing. The 'Beva' series reaches a higher plateau than 'Chimio'. The bottom window shows MATLAB code for a scheduling model:

```
+2 play_scheduling_HmodelNormCTAAF.m | manips_plot_fit_SAEM_V4.m |
18 ~~~~~
19 ~~~~~
20 if flag_compute >0
21 PopS = cell(1,ST);
22 for st = 3 %1:ST
23     data_name = data_names(st);
24     data_set = evalin('base', data_name);
25     timeS = evalin('base', ['timeS' data_name]);
26     N = length(data_set);
27     X = [];
28     Y = [];
29     GROUP = [];
30     for st2 = 1:N
31         X = [X; timeS{st2}'1];
```

```
>> play_scheduling_HmodelNormCTAAF
b =
    5

>> play_scheduling_HmodelNormCTAAF
Optimal gap = 4 days
>> play_scheduling_HmodelNormCTAAF
Optimal gap = 3.5 days
f>> play_scheduling_HmodelNormCTAAF
```