Modeling Growth and Regrowth

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1 Rationale

Often, in mathematical biology and medicine we are concerned with *growth*.

- Growth of cancer cells.
- Growth of plant, tree, etc.
- Growth of people with age, height, weight, etc.

or *regrowth*

- Growth after cancer treatment.
- Tree growth/regrowth after fire, drought, or flood.

How mathematics can help modeling?

2 How it works

Three components of *good* modeling in medicine and biology.

- Modeling.
- Data analysis and statistics.
- Better modeling.
- Interpretation and conclusion in lay language.

3 Exponential growth of cancer cells

Cancer cells are cells with lost proliferation control (unstoppable cell division).

Consider cell population at time $t = 0, 2, 3, ...$, say on hour scale.

Let N_t denote the number of cells at time t. At division each cell (mother) produces two cells (daughters).

Each cell divides in two with probability p.

Main equation

$$N_{t+1} = 2 \sum_{i=1}^{N_t} X_i, \quad t = 0, 1, 2....$$

where X_i is a random binary variable (division) such that

$$X_i = \begin{cases} 1 \text{ with probability } p \\ 0 \text{ with probability } 1 - p \end{cases}.$$

Assumptions:

1. Cell division events are independent.

2. Cells have the same probability of division (homogeneity).

3. Probability is constant over time and does not depend on the number of cells (isotropic probability).

Take expectation:

$$E(N_{t+1}) = 2E(N_t)p.$$

Denote the average/expected cell number

$$Y_t = E(N_t).$$

Then the expected number of cells grows according geometric progression

$$Y_t = Y_0(2p)^t.$$

Denote

$$\alpha = \ln(2p).$$

Exponential growth

$$Y_t = e^{\alpha t}.$$

Exponential function is linear on the log scale.

If growth data look like a straight line the growth is exponential.

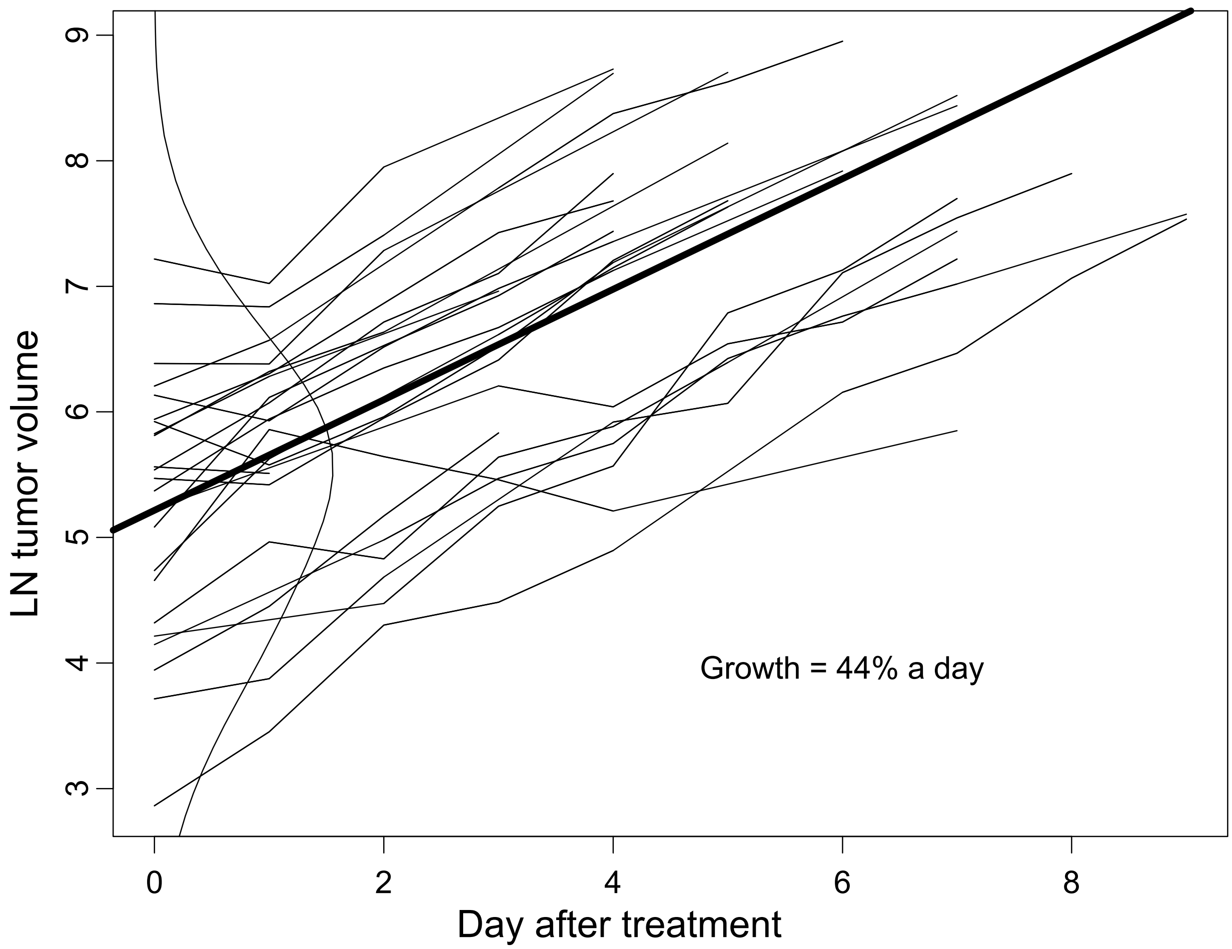

Figure 1: Cell population *in vivo*: tumor growth in control group (each line represents one mouse).

Exponential growth via calculus/differential equation

$$\frac{1}{Y}\frac{dY}{dt} = \alpha$$

with the solution

$$Y(t) = y_0 e^{\alpha t}.$$

Definition. If $Y = Y(t)$ is a function of time,

$$\frac{1}{Y}\frac{dY}{dt}$$

is called the *rate* of growth.

Interpretation: If t is measured in days, $100 \times \alpha$ the % growth per day.

Exponential growth is the growth with constant rate.

Definition. Doubling time is the time required to double the initial tumor volume.

$$y_0 e^{\alpha t} = 2y_0$$

so that

$$T_D = \frac{\ln 2}{\alpha}.$$

4 Limited growth

Limited growth: rate of growth decreases with growth.

Linear decrease

$$\frac{1}{Y}\frac{dY}{dt} = a - bY.$$

The solution is the logistic growth curve

$$Y(t) = \frac{A}{1 + Be^{-at}}$$

with asymptote

$$\max Y(t) = A.$$

Log decrease

$$\frac{1}{Y}\frac{dY}{dt} = a - b \ln Y$$

The solution is the Gompertz curve

$$Y(t) = Ae^{-e^{B-bt}}.$$

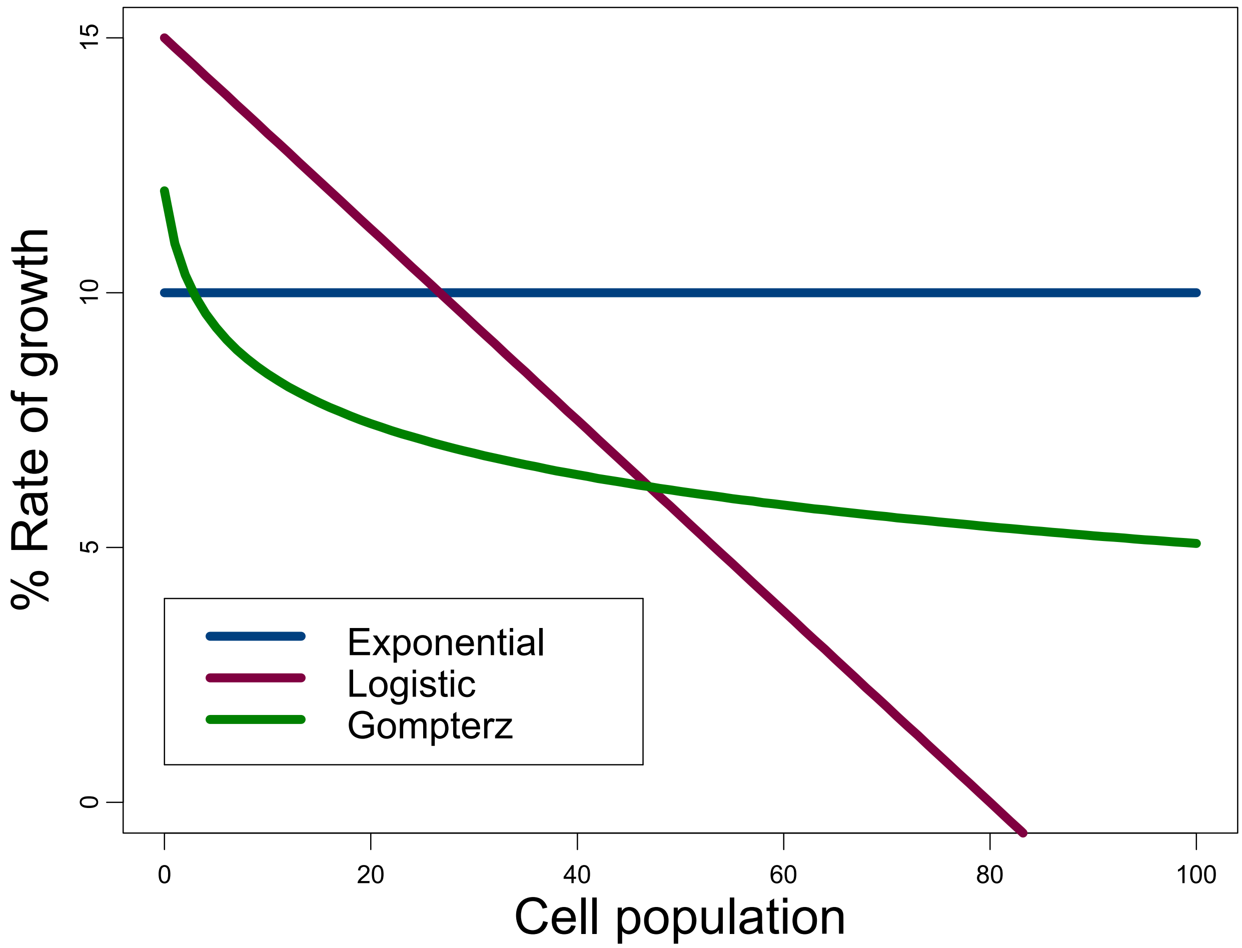

Figure 2: Three types of growth.

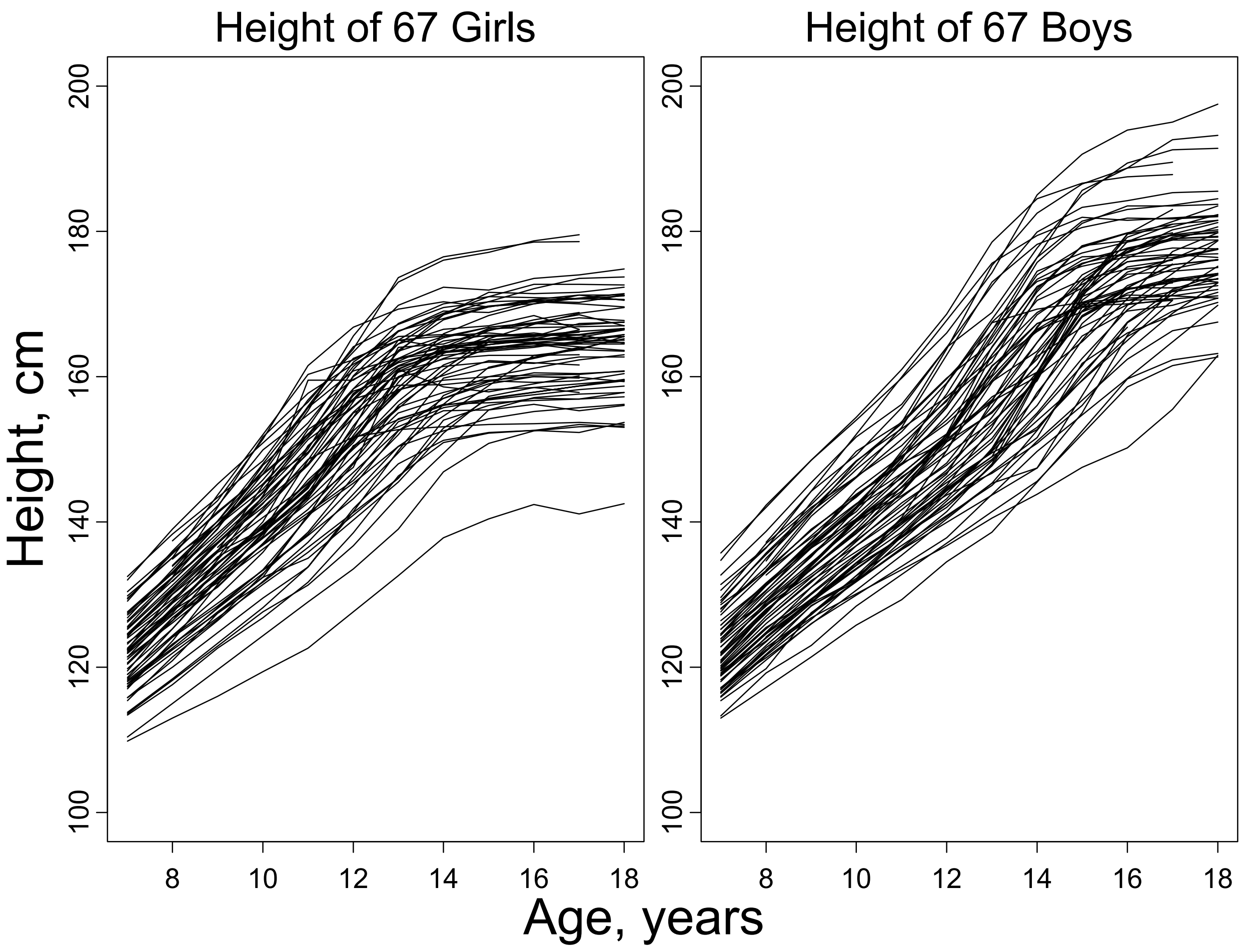

Figure 3: Growth of boys and girls.

Quadratic-logistic model

$$Y(t) = \frac{A}{1 + e^{a+bt-ct^2}}.$$

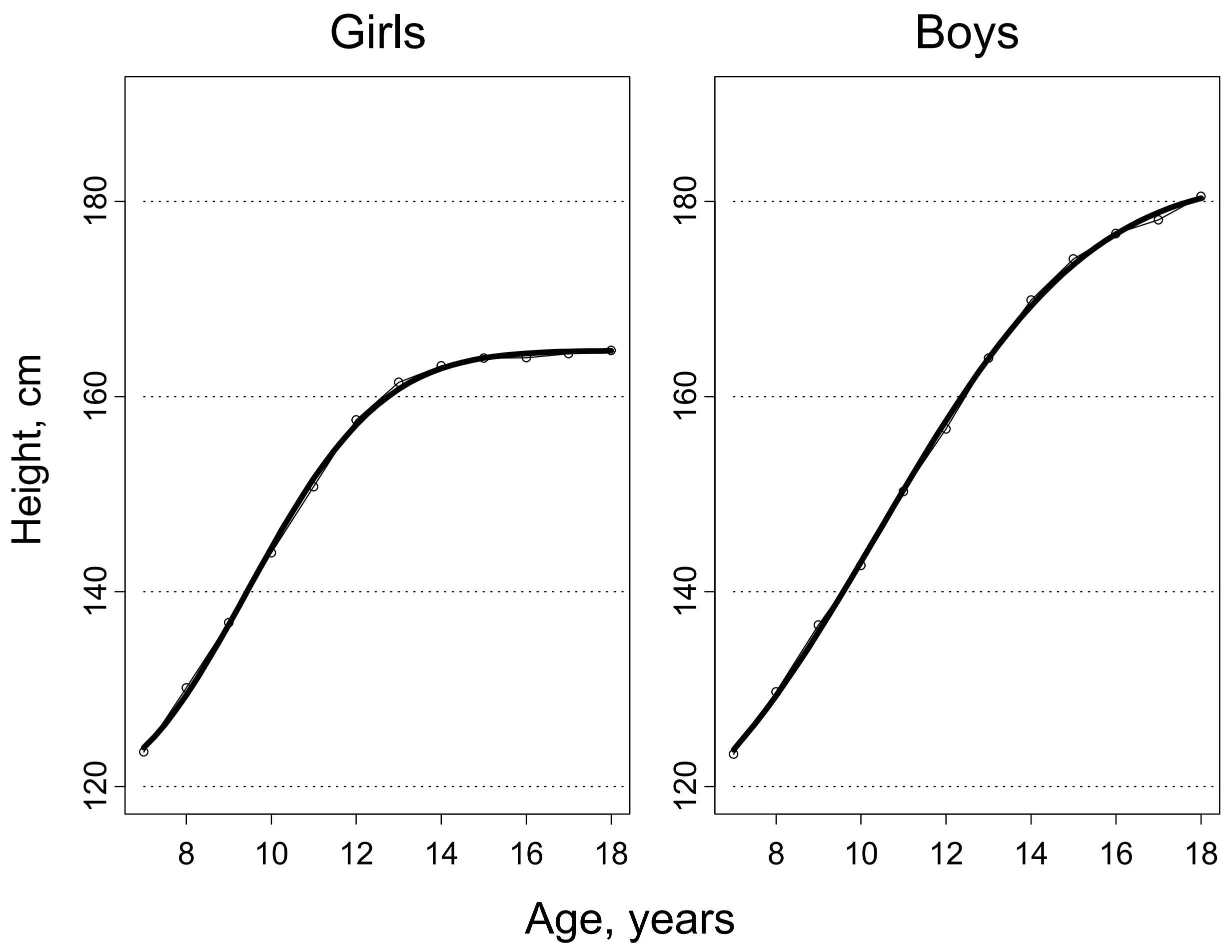

Figure 4: Fit of quadratic-logistic model to the mean height data.

5 Gompertz curve

Many studies confirmed that the growth of cancer cells follows Gompertz curve (1825)

$$Y(t) = Ae^{-e^{B-bt}}$$

on the log scale

$$y(t) = a - e^{B-bt}.$$

Three critical points/phases on the Gompertz curve:

1. Time of maximum/aggressive growth (TG), $Y'' = 0$.

2. Slow growth ends (TD), tumor vasculature completed. Time when second derivative is maximum, $Y''' = 0$.

3. Fast growth ends (TS), limited nutrients supply. Time when second derivative is minimum, $Y''' = 0$.

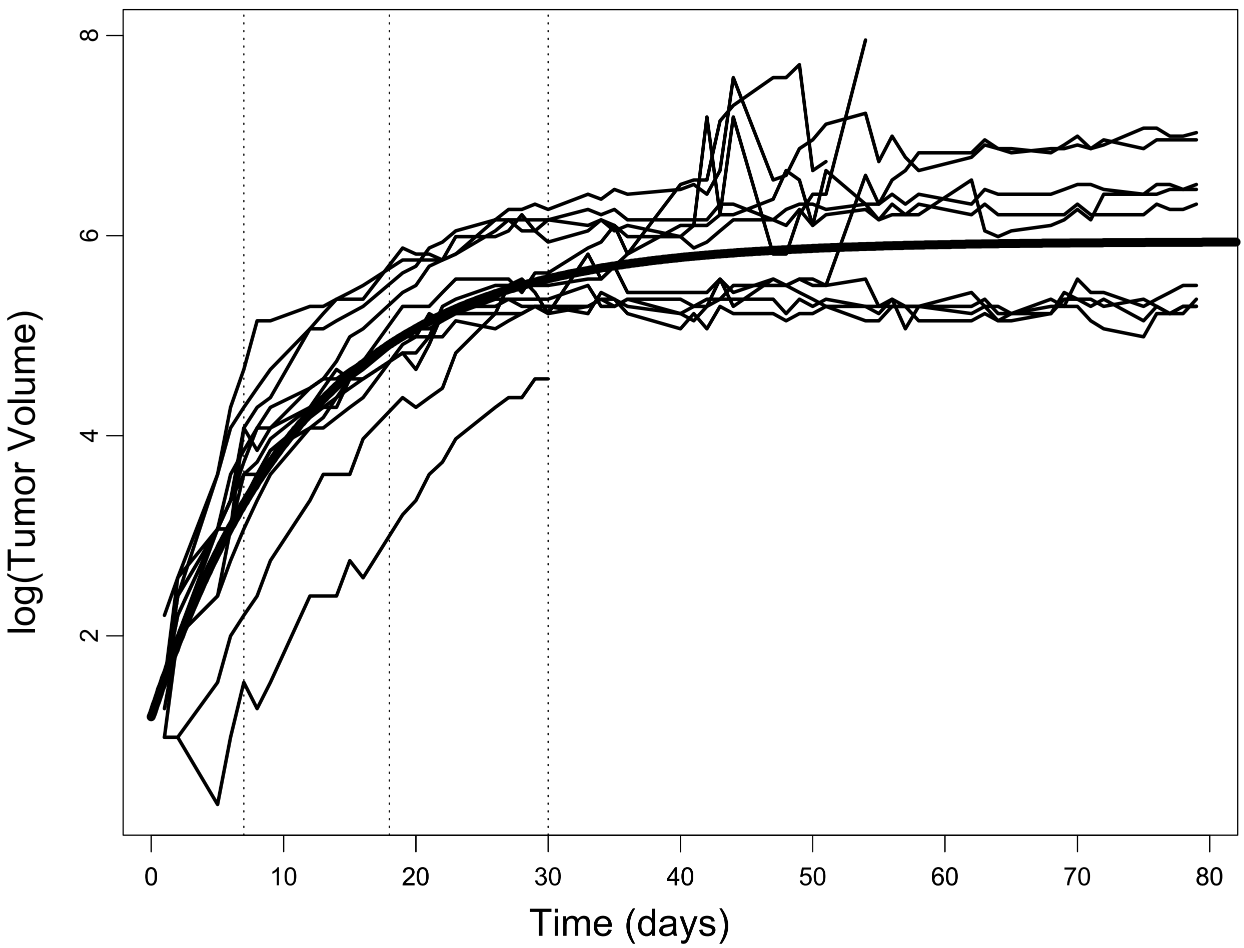

Figure 5: Growth trajectories of 12 polyclonal unperturbed multicellular tumor spheroids. Apparently, each spheroid has its own growth pattern. Clearly, the tumor volume limit is a tumor-specific parameter.

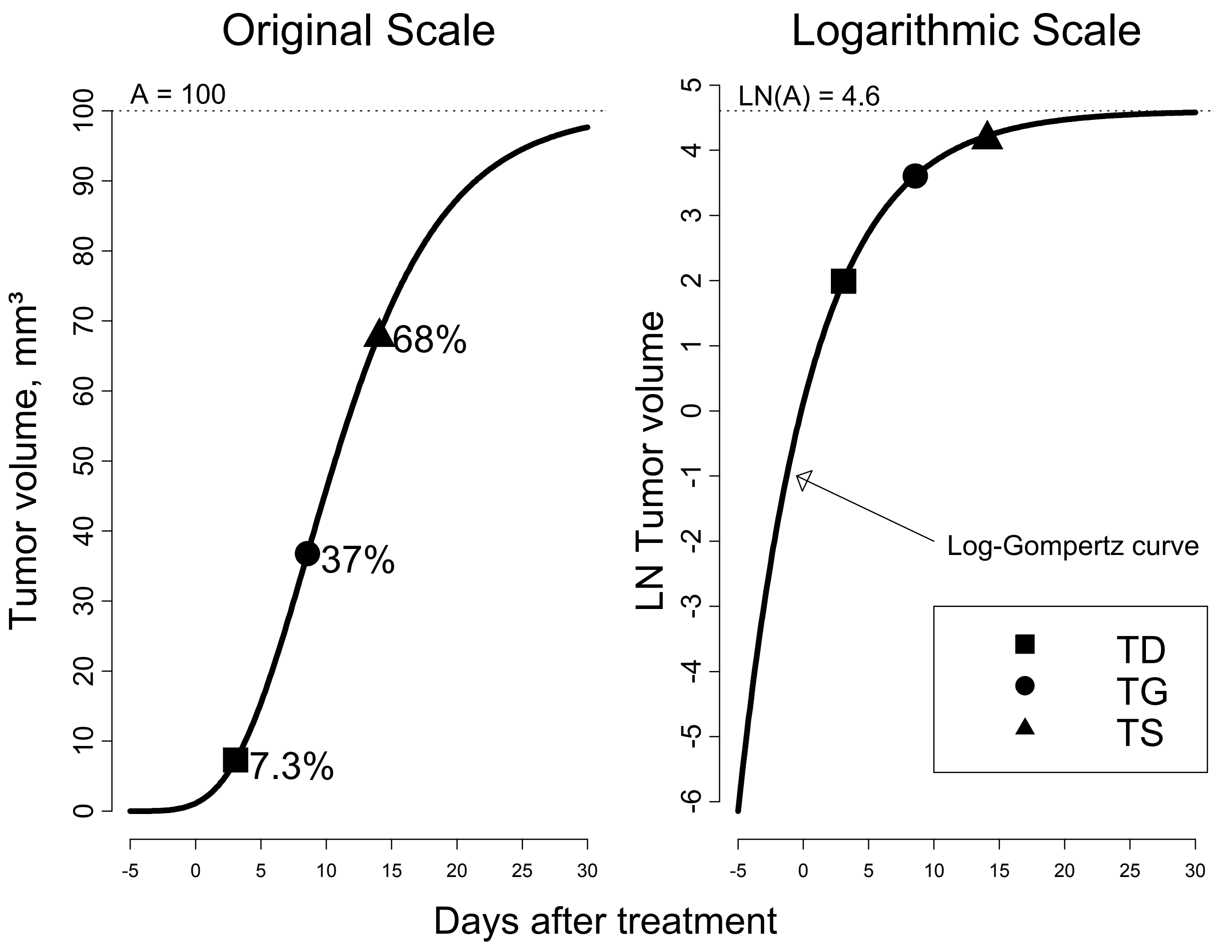

Figure 6: Gompertz curve and three critical points of growth.

6 Regrowth curves

How tumor grows after treatment?

Two-compartment model (birth-death model):

1. Proliferating cells, $P = P(t)$.

2. Quiescent cells, $Q = Q(t)$.

System of ODEs:

$$\begin{aligned}\frac{dP}{dt} &= \nu P, \\ \frac{dQ}{dt} &= \tau P - \phi Q.\end{aligned}$$

where $t \geq 0$.

The solution is the Double Exponential (DE) regrowth curve,

$$N(t) = N_0(\theta e^{\nu t} + (1-\theta)e^{-\phi t})$$

Two compartments after treatments (say, radiation).

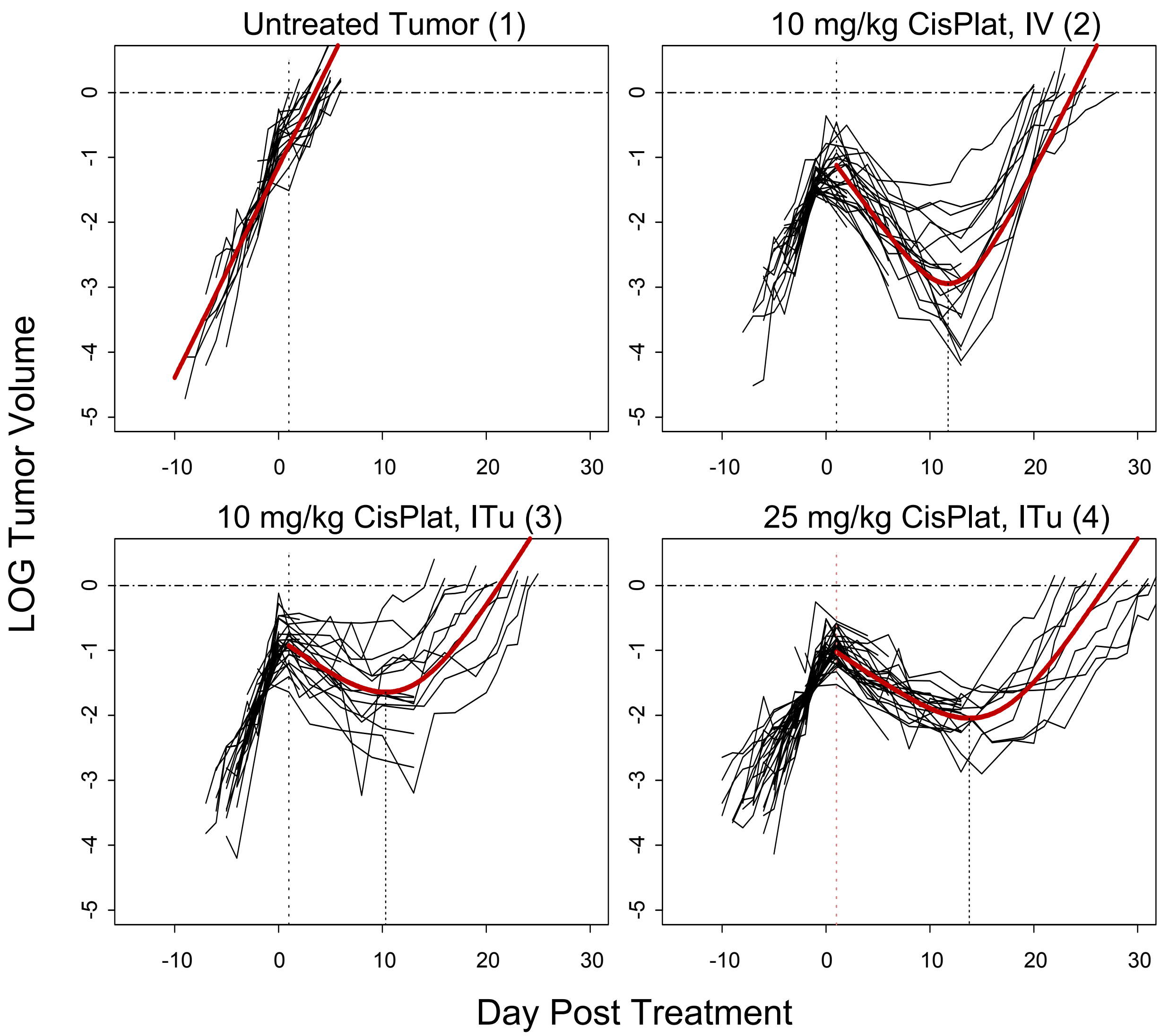

Figure 7: Four groups of treated mice with a chemotherapy drug (cisplatin).

Unaffected cancer cells

$$N_1(t) = N_0 \theta e^{\nu t}.$$

Dying (washing out) cells

$$N_2(t) = N_0(1 - \theta) e^{-\phi t}.$$

DE parameters interpretation:

- N_0 is th tumor volume (number of cancer cells).
- ν is the rate of untreated tumor.
- ϕ is the rate at which cells die after treatment.
- θ is the proportion of affected cells.

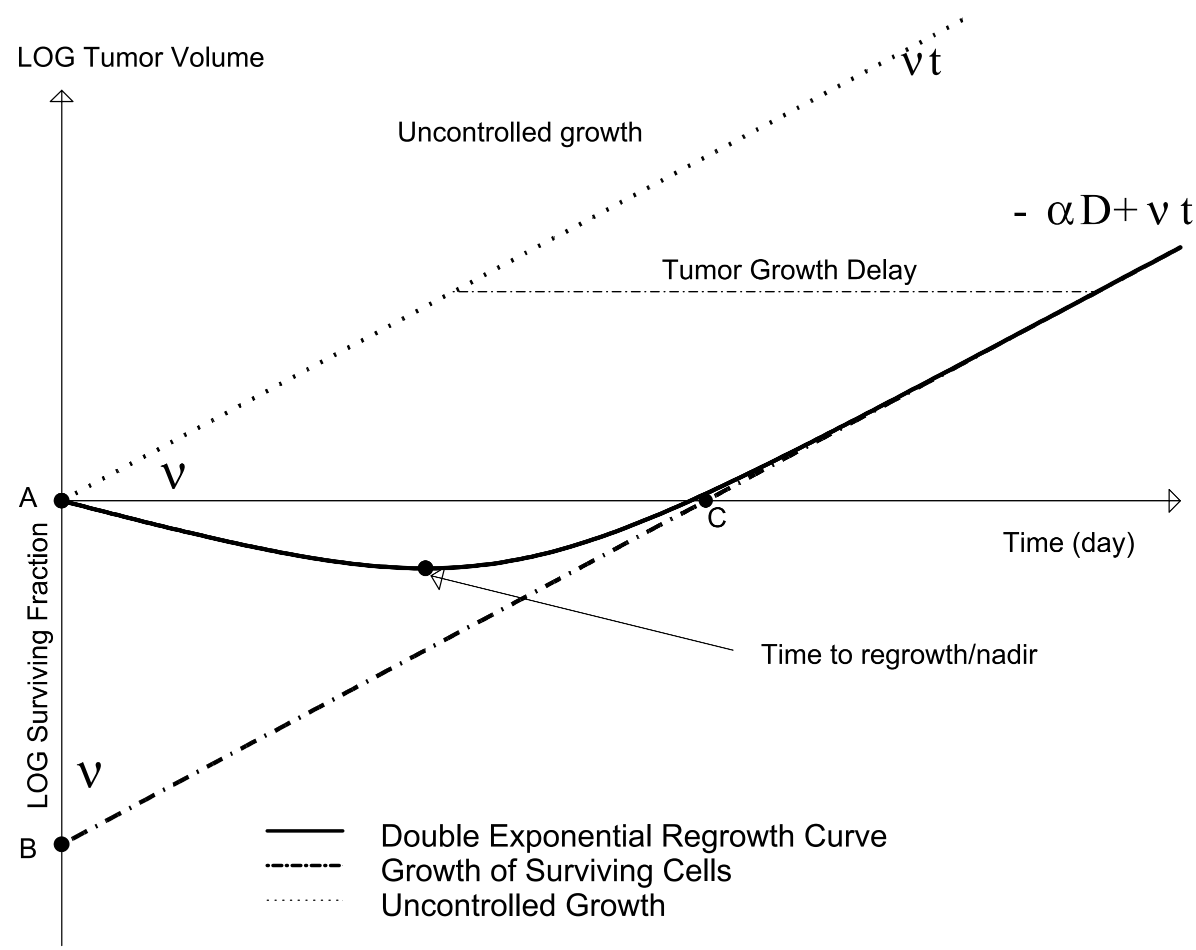

Figure 8: Double–Exponential (DE) regrowth curve on a logarithmic scale. Uncontrolled cell growth has rate ν, and on a log scale it is a straight (dotted) line because the growth is exponential. After treatment (e.g., radiation) the proportion of surviving cells is θ so that the length of the segment $AB =$ - LOG Surviving Fraction $=$ -log $\theta = \alpha D$. It is assumed that after treatment the surviving cells proliferate with the same rate ν, dashed bold line with slope ν.

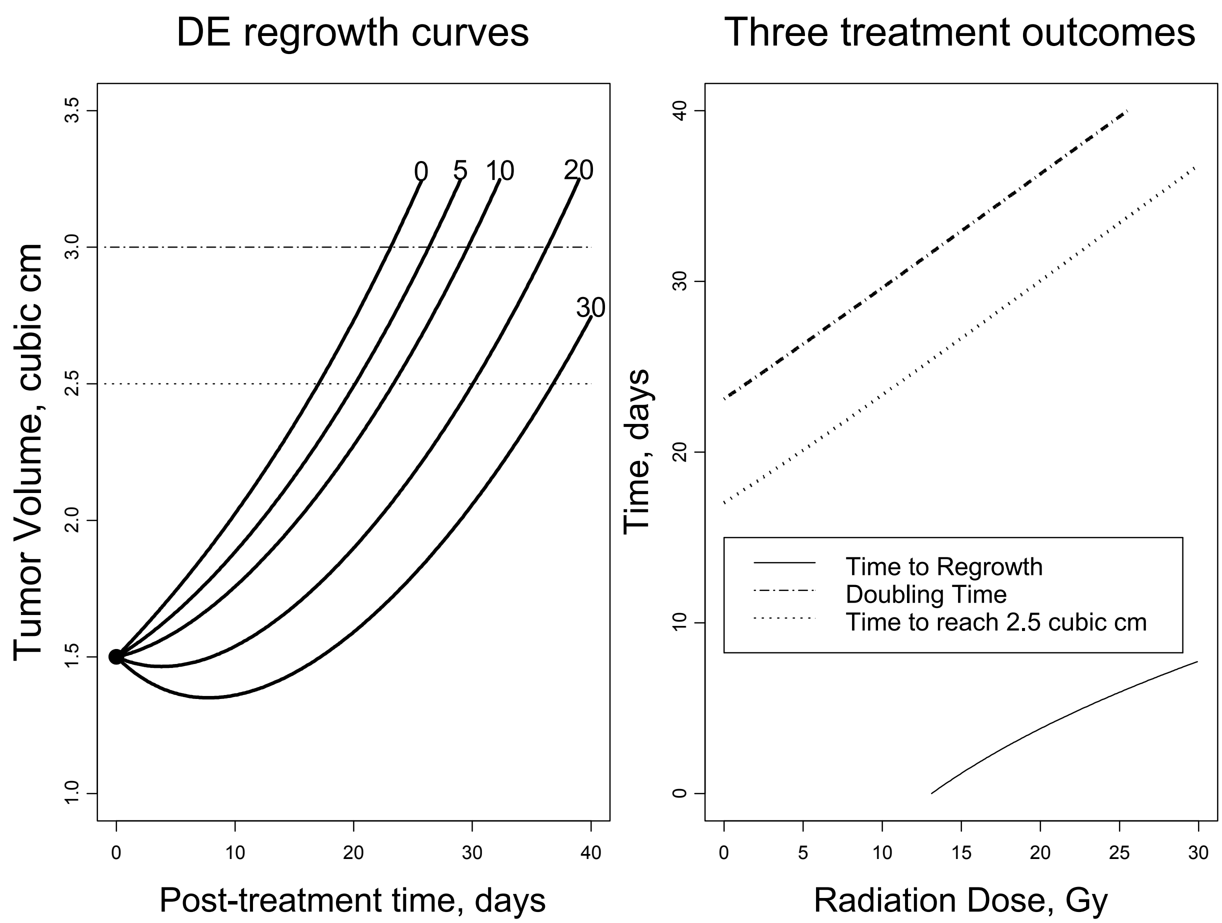

Figure 9: Double exponential regrowth curves with three radiotherapy treatment outcomes as functions of a single radiation dose. Left: tumor volume as a function of time with initial volume 1.5 cm^3. Right: Time to regrowth, Doubling time and Time to reach 2.5 cm^3 as functions of radiation dose. As we see, the tumor shrinks when the dose exceeds 13Gy. Doubling time and Time to reach 2.5 cm^3 as functions of D are close to straight lines.

6.1 Treatment outcomes

- Time to regrowth (nadir)

$$T_R = \frac{1}{\nu + \phi} \ln \left(\frac{1 - \theta}{\theta} \frac{\phi}{\nu} \right).$$

- Time to reach a specific tumor volume, N_*

$$N_0(\theta e^{\nu t} + (1 - \theta) e^{-\phi t}) = N_*$$

- Doubling time

$$N_0(\theta e^{\nu t} + (1 - \theta) e^{-\phi t}) = 2N_0$$

or

$$\theta e^{\nu t} + (1 - \theta) e^{-\phi t} = 2.$$

7 More on growth and regrowth curves

Journals:

Journal of Theoretical Biology

Mathematical Biosciences

Books:

Banks, R.B. (1994). *Growth and Diffusion Phenomena.* Berlin: Springer-Verlag.

Knolle, H. (1988). *Cell Kinetic Modelling and Chemotherapy of Cancer.* New York: Springer-Verlag.

Seber, G.A.F. and Wild, C.J. (1989). *Nonlinear Regression.* New York: Wiley.

Demidenko, E. (2004). *Mixed Models: Theory and Applications*. Hoboken, NJ: Wiley.

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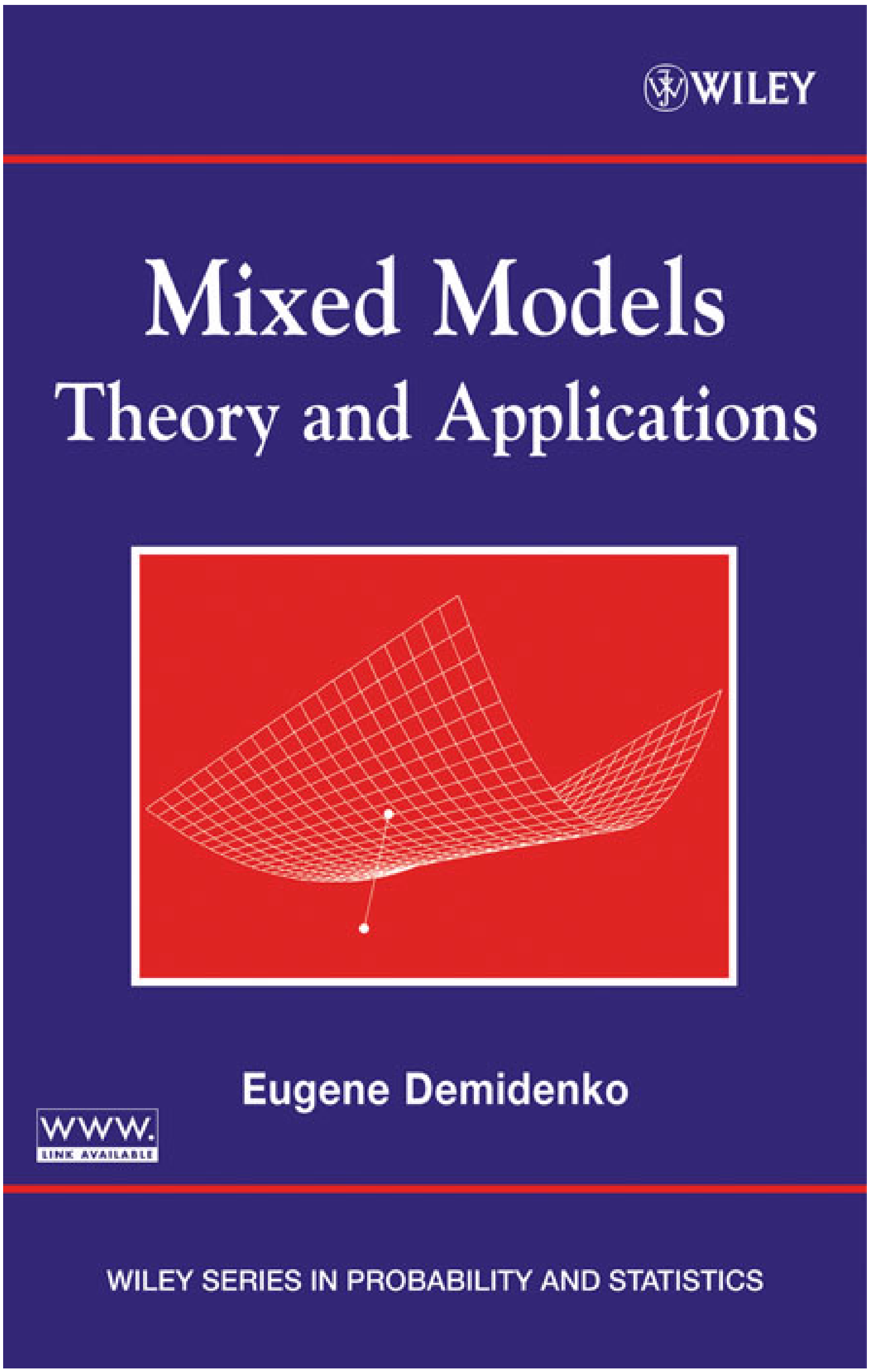

8 Summary

- Calculus is the major tool of mathematical biology.

- Theory is beautiful, data are ugly.

- Mathematical biology: calculus + statistics.

- Biostatistics: data analysis + biomathematics.

- The future of biomathematics is bright.