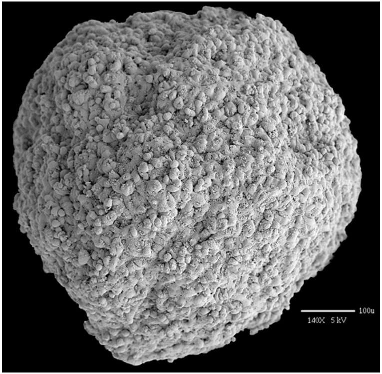
PRINCIPLES OF MATHEMATICAL MODELLING

2. TUMOUR GROWTH MODELS

2.1. Data and logistic model

Tumour spheroids

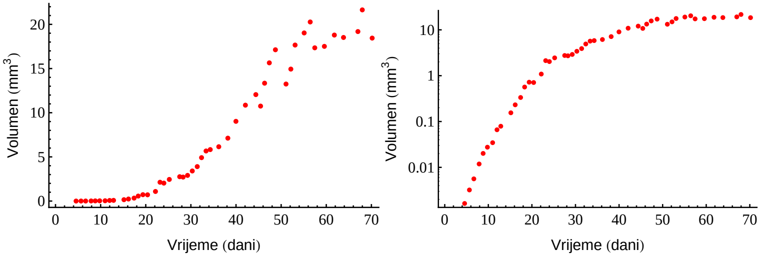
- Biological model for tumours
- Agregation of cells growing in laboratory conditions (*In vitro*)



Tumour growth data (tumour spheroids)

Time (days)	Volume (mm^3)	Time (days)	Volume (mm^3)	Time (days)	Volume (mm^3)
4.6	0.002	3.2	2.130	45.4	10.749
5.7	0.003	24.0	2.030	46.3	13.342
6.7	0.006	25.2	2.448	47.4	15.646
7.9	0.012	27.5	2.756	48.7	17.126
8.8	0.020	28.3	2.714	51.1	13.247
9.8	0.028	29.3	2.906	52.2	14.938
11.0	0.035	30.3	3.405	53.1	17.660
12.0	0.066	31.4	3.900	55.1	19.030
12.9	0.079	32.4	4.914	56.4	20.272
15.2	0.155	33.4	5.669	57.5	17.346
16.2	0.231	34.3	5.827	59.6	17.510
17.4	0.334	36.2	6.149	61.8	18.790
18.3	0.565	38.2	7.119	63.8	18.518
19.4	0.721	40.0	9.025	67.0	19.186
20.4	0.709	42.1	10.854	68.0	21.640
22.2	1.085	44.4	12.050	70.2	18.446

Tumour growth data (tumour spheroids)



Logistic model

$$y'(t) = \alpha \left(1 - \frac{y(t)}{C}\right) y(t), \quad y(0) = y_0$$

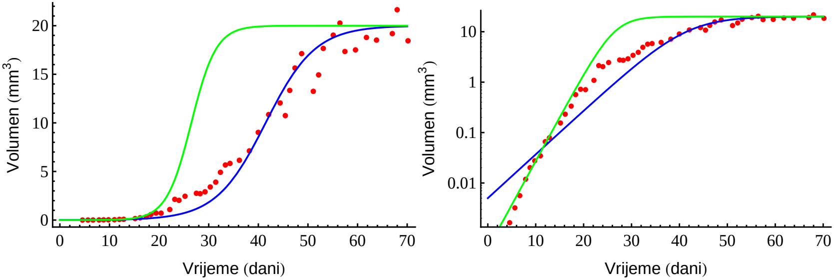
$$y' = \alpha \left(1 - \frac{y}{C}\right) y, \quad y(0) = y_0$$

$$y(t) = \frac{C\, e^{\alpha t}\, y_0}{C - y_0 + y_0\, e^{\alpha t}}$$

Logistic model

$$\alpha = 0.2,\ C = 20,\ y_0 = 0.005$$

$$\alpha = 0.4,\ C = 20,\ y_0 = 0.0005$$



Logistic model - Least squares method

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FindFit[data, y[x, a, c, y0],
  {{a, 0.2}, {c, 20}, {y0, 0.1}}, x]
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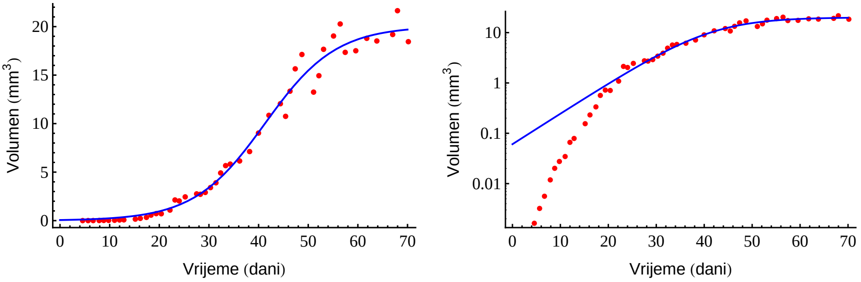
$$\alpha = 0.140315,\ C = 20.044,\ y_0 = 0.0607316$$



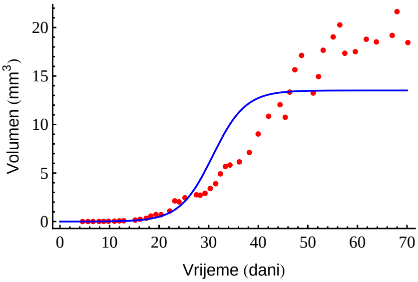
- Initial growth phase is described badly
- Solution: use logarithmic transformation to data -

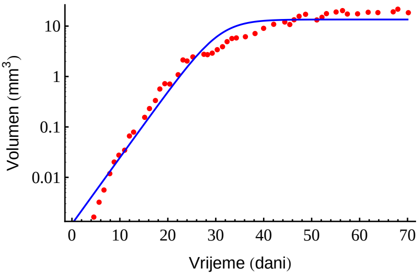
  Model: $\ln y(x; \alpha, C, y_0)$
  Data: $(t_i, \ln y_i), \quad i = 1, \ldots, n$

- Large span of values: from $2 \cdot 10^{-3}$ to 18.446 - increase of $\approx 10^4$ times
- Measurement errors are proportional to the volume size

Logistic model - Least squares method - logarithmic transformation of data

$$\alpha = 0.303882,\ C = 13.4899,\ y_0 = 0.00117449$$



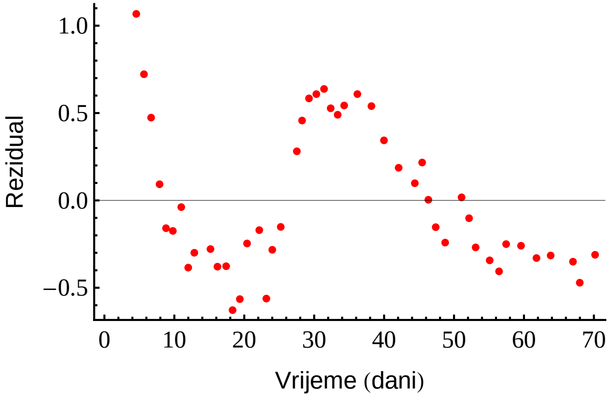


Mean squared discrepancy (error) $= 0.168612$

Reziduali

Residuals (r_i):

$$r_i = y(t_i; \alpha*, C^*, y_0^*) - y_i.$$



Can we do better?

2.2. Gompertz model

$$y' = -\alpha\, y \ln \frac{y}{C}, \quad y(0) = y_0$$

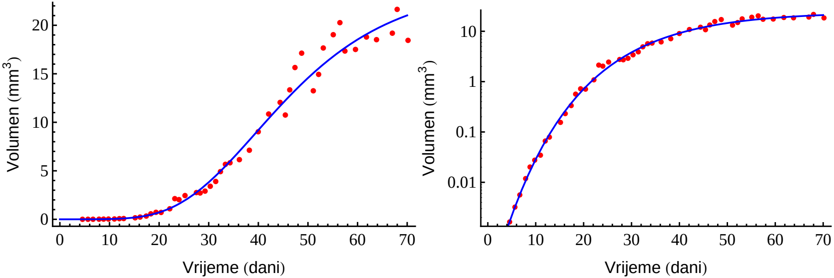
$$y' = a\, y - b\, y \ln y, \quad y(0) = y_0$$

$$y(t) = C e^{\ln \frac{y_0}{C} e^{-\frac{\alpha}{\ln C} t}}$$

- Benjamin Gompertz (London,England, 1779–London, England, 1865)
- mathematician i actuary
- demographic model model
- Gompertz, Benjamin (1825). "On the Nature of the Function Expressive of the Law of Human Mortality, and on a New Mode of Determining the Value of Life Contingencies". Philosophical Transactions of the Royal Society of London 115: 513–585

Gompertz model. Least squares method.

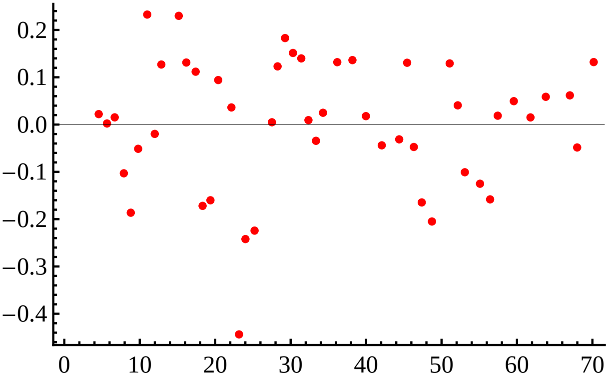
$$\alpha = 0.206226, \ C = 24.1316, \ y_0 = 0.0000619827$$



Mean squared discrepancy (error) $= 0.0198408$

Logistic model: MSE$= 0.168612$

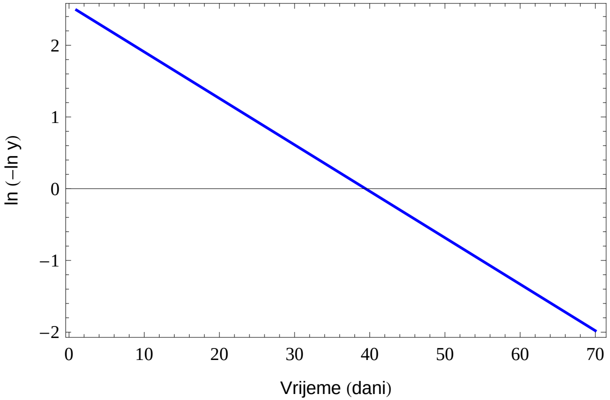
Residuals



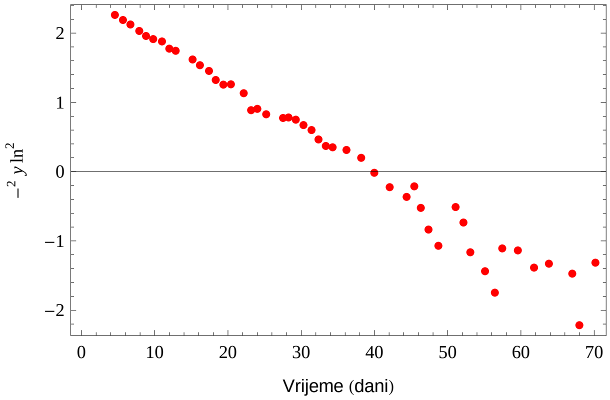
$$
\begin{aligned}
y(t) &= C e^{\ln \frac{y_0}{C} e^{-\frac{\alpha}{\ln C} t}} \\
\ln y(t) &= \ln C + \ln \frac{y_0}{C} e^{-\frac{\alpha}{\ln C} t} \\
\ln \frac{y(t)}{C} &= \ln \frac{y_0}{C} e^{-\frac{\alpha}{\ln C} t} \\
\ln\left(-\ln \frac{y(t)}{C}\right) &= \ln\left(-\ln \frac{y_0}{C}\right) - \frac{\alpha}{\ln C} t
\end{aligned}
$$

Linear function

Transformed Gompertz curve



Transformed data



2.3. von Bertalanffy model

- Karl Ludwig von Bertalanffy (Atzgersdorf, Austria, 1901– Buffalo, New York, SAD, 1972)
- biologist (general system theory)
- biological models

von Bertalanffy model

$$y' = ay^{2/3} - by, \quad y(0) = y_0$$

-Growth is determined by surface ($y^{2/3}$)

Remark.

Earlier, von Bertalanfy have studied model for fish length (L):

$$L'(t) = \alpha(L_\infty - L(t)), \quad L(0) = L_0.$$

Model function:

$$L(t) = L_\infty - (L_\infty - L_0)e^{-\alpha t}$$

Equation for volume

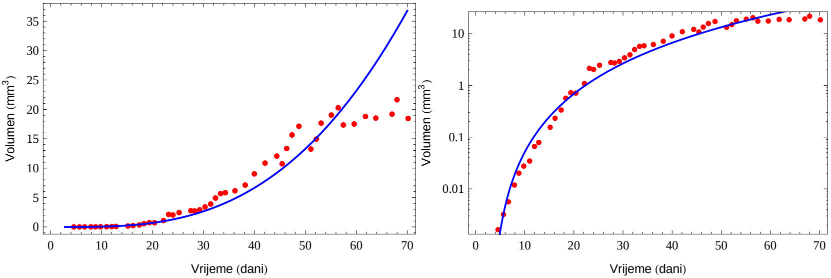
$$L' = \alpha(L_\infty - L), \quad L(0) = L_0.$$

Volume - y: $\quad L = ky^{1/3}$

$$\begin{aligned} L' &= \frac{k}{3} y^{-2/3} y' \\ \frac{k}{3} y^{-2/3} y' &= \alpha(L_\infty - ky^{1/3}) \\ y' &= 3\alpha \left(\frac{L_\infty}{k} y^{2/3} - y \right) \end{aligned}$$

$$y' = ay^{2/3} - by, \quad y(0) = y_0$$

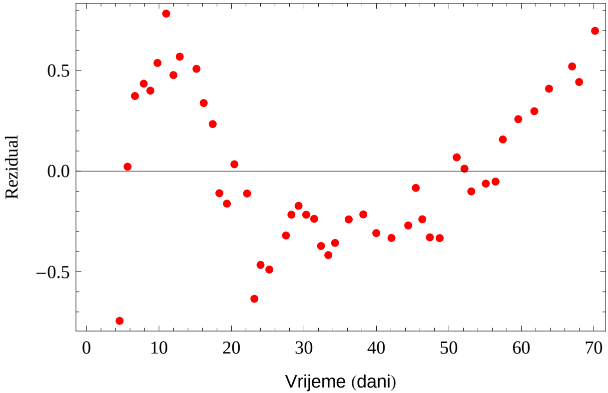
Least squares method



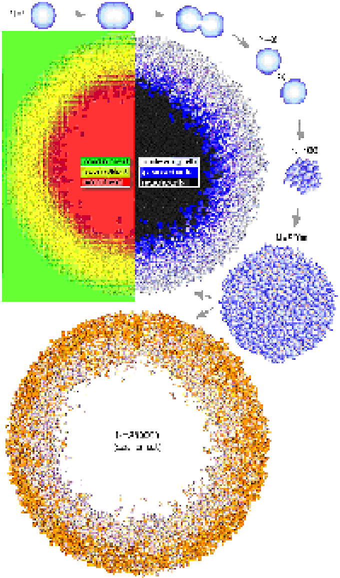
Mean squared discrepancy (error) = 0.136447

Logistic model: MSE= 0.168612
Gompertz model: MSE= 0.0198408

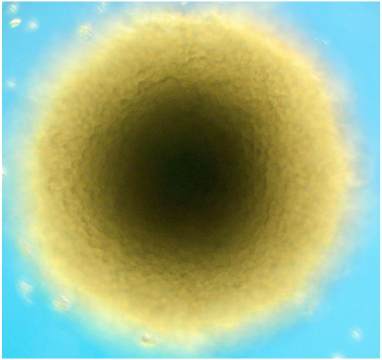
Reziduals

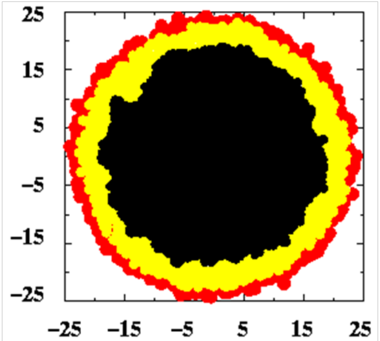


2.4. Simple spheroid model

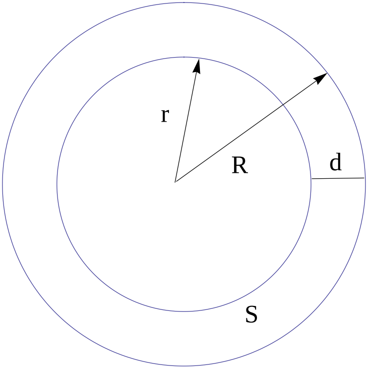


Uper picture:
Left - distribution (density) of nutritions
Right - proliferation (growth activity)




25
15
5
−5
−15
−25
−25
−15
−5
5
15
25

Simple spheroid model



- d - thickness of viable rim
- S - proliferating cells (volume)
- d is constant (experimental result)

$$
\begin{aligned}
r &= R - d \\
S &= \frac{4}{3}\pi\left[R^3 - r^3\right] = \\
&= \frac{4}{3}\pi\left[R^3 - (R-d)^3\right] = \\
&= \frac{4}{3}\pi\left[3R^2 d - 3Rd^2 + d^3\right]
\end{aligned}
$$

- von Bertalanffy: $V' = aV^{2/3} - bV$
- Modification: $S \rightarrow V^{2/3}$
- Model: $V' = aS - bV$
- $V' = a\frac{4}{3}\pi\left[3R^2d - 3Rd^2 + d^3\right] - bV$
  $V(0) = V_0, \quad R = \left(\frac{3}{4\pi}V\right)^{1/3}$
- Ŵhat if $R < d$? (all cells proliferate) $\Rightarrow$ exponential growth
- Modification: $V' = a\,V \quad$ for $R \leq d$.

Simple spheroid model

$$V' = \begin{cases} a\,V, & \text{for } R \le d \\ a\frac{4}{3}\pi\left[3R^2 d - 3Rd^2 + d^3\right] - bV, & \text{for } R > d \end{cases}$$

$$V(0) = V_0, \quad R = \left(\frac{3}{4\pi}V\right)^{1/3}$$

Mean squared discrepancy (error) $= 0.022419$

von Bertalanffy $= 0.136447$

Logistic model: MSE$= 0.168612$
Gompertz model: MSE$= 0.0198408$

Model nondimensionalization.

Exsponential model:

$$y' = \alpha\, y, \quad y(0) = y_0$$

How different measurement units (hours, days, ...) for time impact equation?
For example,

$$y'(t) = 0.5y(t), \quad y(0) = 0$$

t - time in hours
Solution

$$y(t) = \mathrm{e}^{0.5t}$$

After 1 day, population size is

$$y(24) = \mathrm{e}^{0.5 \cdot 24} = \mathrm{e}^{12}$$

How equation looks if a time is measured in days?

$$\tau = t/24, \quad t = 24\,\tau$$

τ - time in days

$$Y(\tau) = y(t) = y\,(24\,\tau)$$

$$\begin{aligned} Y'(\tau) &= \frac{d}{d\tau} y\,(24\,\tau) = \\ &= 24 y'\,(24\,\tau) = \\ &= 24 \cdot 0.5\, y\,(24\,\tau) = \\ &= 12\, Y(\tau) \end{aligned}$$

Equation

$$Y' = 12\, Y$$

α is changed!

Consider exponential model

$$y' = \alpha\, y$$

Use a substitution of the form

$$\tau = a\, t$$

$$z(\tau) = y(t) = y\left(\frac{\tau}{a}\right)$$

$$\begin{aligned} z'(\tau) &= \frac{d}{d\tau} y\left(\frac{\tau}{a}\right) = \\ &= \frac{1}{a} y'\left(\frac{\tau}{a}\right) = \\ &= \frac{1}{a}\alpha\, y\left(\frac{\tau}{a}\right) = \\ &= \frac{\alpha}{a} z\left(\tau\right) \end{aligned}$$

Equation

$$z' = \frac{\alpha}{a} z$$

$$z' = \frac{\alpha}{a} z$$

If we choose $a := \alpha$:

$$z' = z$$

Initial condition:

$$z(0) = y(0) = y_0$$

Example

Nondimensionalization of logistic model.

Solution. Model:

$$y' = \alpha y \left(1 - \frac{y}{C}\right), \quad y(0) = y_0$$

1. C - carrying capacity (= horizontal asymptote).
Substitution

$$z := \frac{y}{C}$$

$$\begin{aligned} z' &= \frac{1}{C} y' = \\ &= \frac{1}{C} \alpha y \left(1 - \frac{y}{C}\right) = \\ &= \alpha z (1 - z) \end{aligned}$$

2. Apply substitution of the form

$$\tau = a\,t$$

$$u(\tau) = z(t) = z\left(\frac{\tau}{a}\right)$$

$$\begin{aligned} u'(\tau) &= \frac{d}{d\tau} z\left(\frac{\tau}{a}\right) = \\ &= \frac{1}{a} z'\left(\frac{\tau}{a}\right) = \\ &= \frac{1}{a}\,\alpha\,z\left(\frac{\tau}{a}\right)\left(1 - z\left(\frac{\tau}{a}\right)\right) = \\ &= \frac{\alpha}{a}\,u\,(\tau)\left(1 - u\left(\frac{\tau}{a}\right)\right) \end{aligned}$$

Equation

$$u' = \frac{\alpha}{a}\,u(1-u)$$

$$u' = \frac{\alpha}{a} u(1-u)$$

If we choose $a := \alpha$:

$$u' = u(1-u)$$

Initial condition:

$$u(0) = z(0) = \frac{y(0)}{C} = \frac{y_0}{C} =: u_0$$

Using this type of transformations (scaling) we may reduce number of parameters in the model (equation) for two.

Problem

Check the stability of equilibriums for Gompertz and von Bertalanffy model.
Nondimensionalize both models.