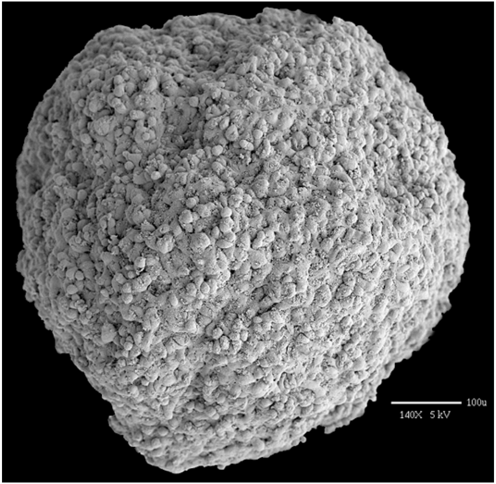
Matematičko modeliranje u biologiji

MODELI RASTA TUMORA

Tumorski sferoidi

- Biološki model tumora
- Nakupina stanica koje rastu u laboratorijskim uvjetima (*In vitro*)



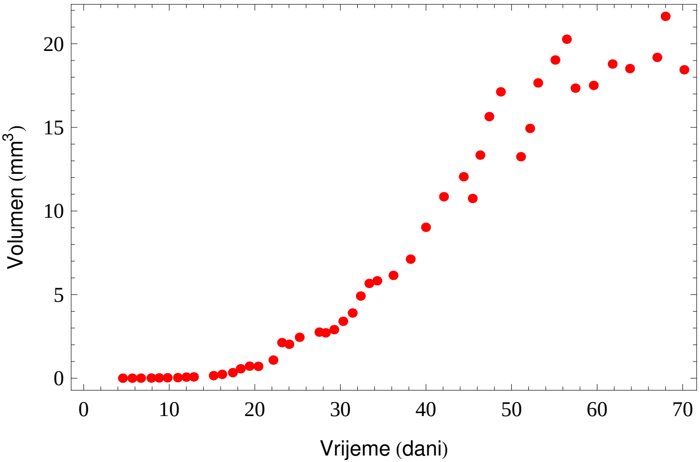
Podaci za rast tumora (tumorskih sferoida)

Vrijeme (dani)	Volumen (mm^3)
4.6	0.002
5.7	0.003
6.7	0.006
7.9	0.012
8.8	0.020
9.8	0.028
11.0	0.035
12.0	0.066
12.9	0.079
15.2	0.155
16.2	0.231
17.4	0.334
18.3	0.565
19.4	0.721
20.4	0.709
22.2	1.085

Vrijeme (dani)	Volumen (mm^3)
23.2	2.130
24.0	2.030
25.2	2.448
27.5	2.756
28.3	2.714
29.3	2.906
30.3	3.405
31.4	3.900
32.4	4.914
33.4	5.669
34.3	5.827
36.2	6.149
38.2	7.119
40.0	9.025
42.1	10.854
44.4	12.050

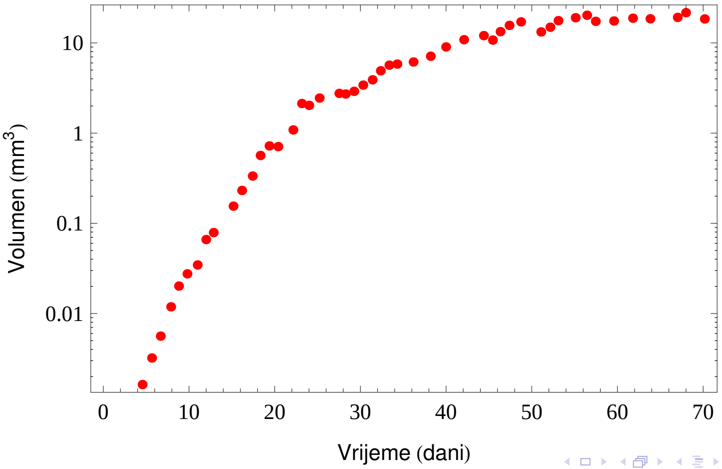
Vrijeme (dani)	Volumen (mm^3)
45.4	10.749
46.3	13.342
47.4	15.646
48.7	17.126
51.1	13.247
52.2	14.938
53.1	17.660
55.1	19.030
56.4	20.272
57.5	17.346
59.6	17.510
61.8	18.790
63.8	18.518
67.0	19.186
68.0	21.640
70.2	18.446

Podaci za rast tumora (tumorskih sferoida)

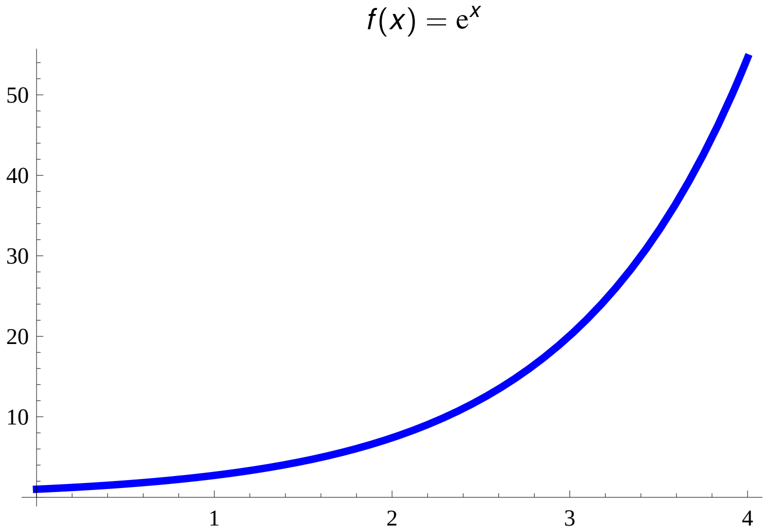


Podaci za rast tumora (tumorskih sferoida)

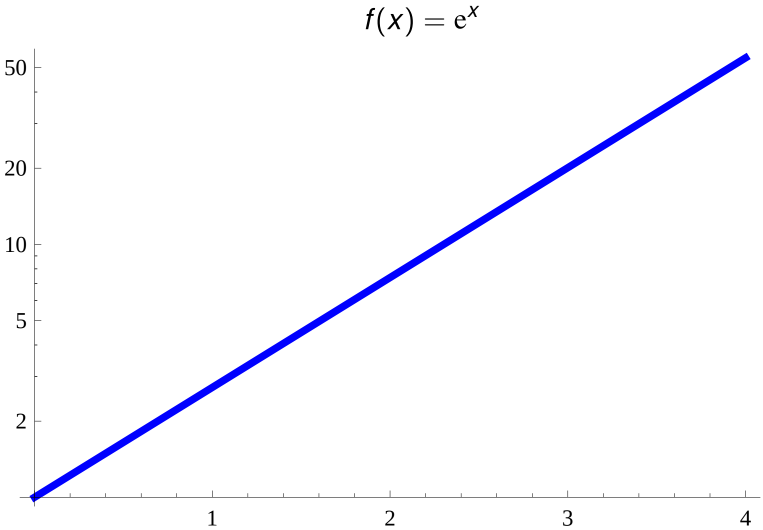
Prikaz u logaritamskoj skali:



Logaritamska skala



Logaritamska skala



Podaci i logistički model

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

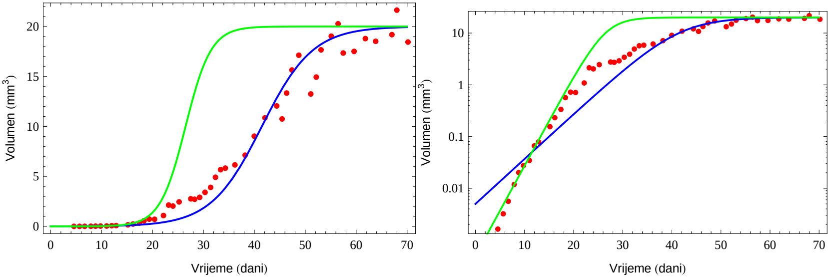
$$y' = \alpha \left(1 - \frac{y}{C}\right) y, \quad y(0) = y_0$$

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

Podaci i logistički model

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

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



Logistički model - Metoda najmanjih kvadrata

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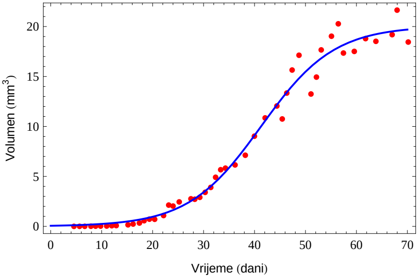
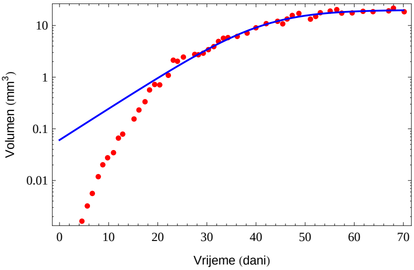
$$\alpha = 0.140315,\ C = 20.044,\ y_0 = 0.0607316$$

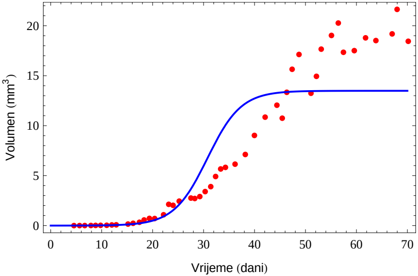


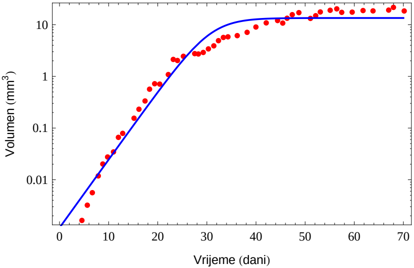


- Loše opisan početni dio rasta
- Rješenje: koristiti logaritmirane podatke -

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

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

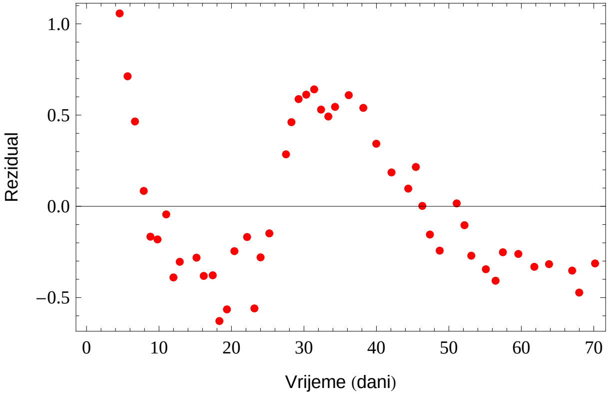




Reziduali

Rezidual (r_i):

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



Srednje kvadratno odstupanje $= 0.168612$

Može li bolje?

Gompertzov model

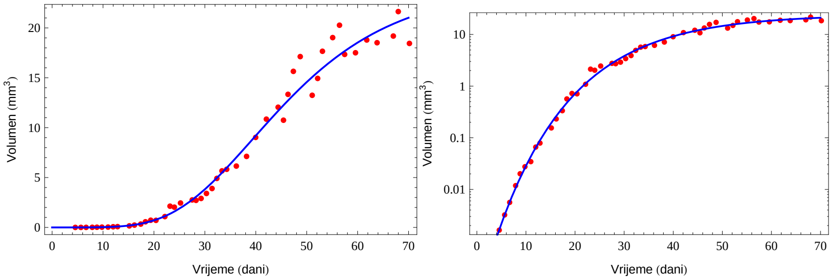
$$y' = \alpha\left(1 - \frac{\ln y}{\ln C}\right)y, \quad y(0) = y_0$$

$$y' = ay - by\ln y, \quad y(0) = y_0$$

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

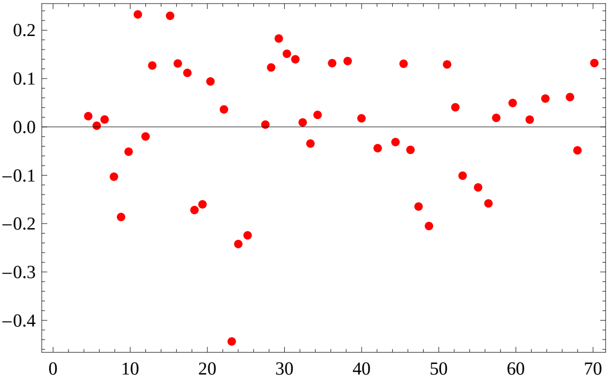
Metoda najmanjih kvadrata

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



Srednje kvadratno odstupanje $= 0.0198408$

Reziduali



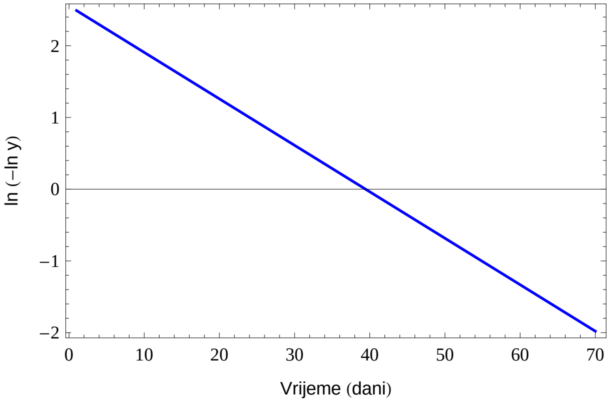
Srednje kvadratno odstupanje = 0.0198408

- Benjamin Gompertz (1779–1865)
- matematičar i aktuar
- demografski 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

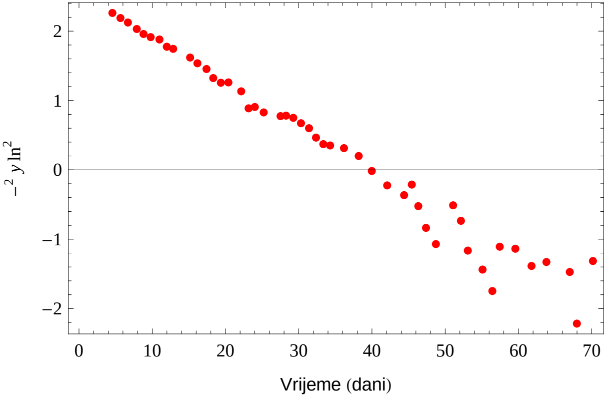
$$
\begin{aligned}
y(t) &= Ce^{\ln \frac{y_0}{C} e^{-\frac{\alpha}{\ln C} t}} \\
\ln y(t) &= \ln C + \ln \frac{y_0}{C} e^{-\frac{\alpha}{\ln C} t} \\
\ln \frac{y(t)}{C} &= \ln \frac{y_0}{C} e^{-\frac{\alpha}{\ln C} t} \\
\ln \left(-\ln \frac{y(t)}{C} \right) &= \ln \left(-\ln \frac{y_0}{C} \right) -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

Linearna funkcija

Transformirana Gompertzova krivulja



Transformirani podaci



von Bertalanffy-jev model

- Karl Ludwig von Bertalanffy (1901–1972)
- biolog (opća teorija sustava)
- biološki model
- originalni model je opisivao duljinu riba (L)

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

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

Jednadžba rasta za volumen

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

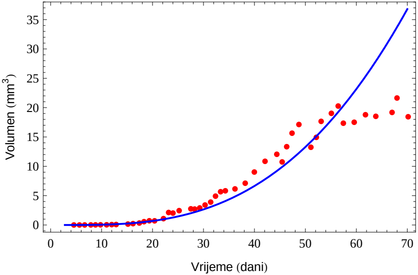
Volumen - y: $\quad L = ky^{1/3}$

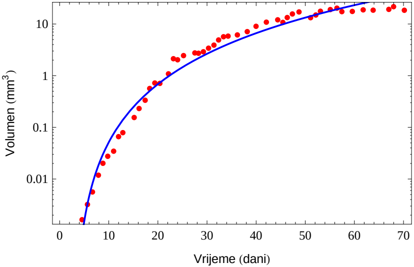
$$\begin{aligned} L' &= \frac{k}{3} y^{-2/3} y' \\ \frac{k}{3} y^{-2/3} y' &= \alpha(L_\infty - ky^{1/3}) \\ y' &= 3\alpha \left(\frac{L_\infty}{k} y^{2/3} - y \right) \end{aligned}$$

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

Rast je vezan uz površinu ($y^{2/3}$)

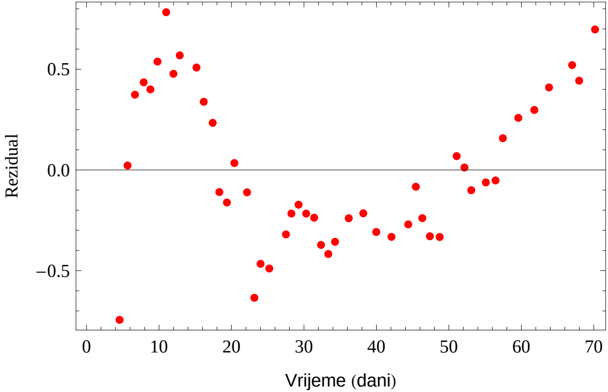
Metoda najmanjih kvadrata



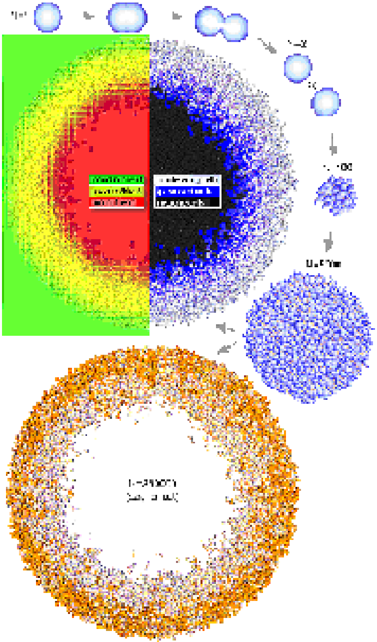


Srednje kvadratno odstupanje $= 0.136447$

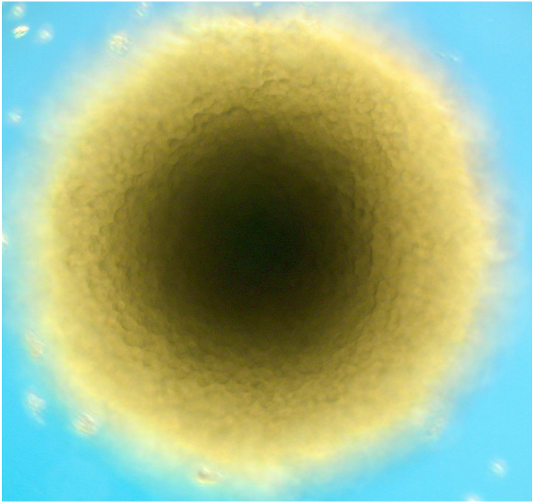
Reziduali



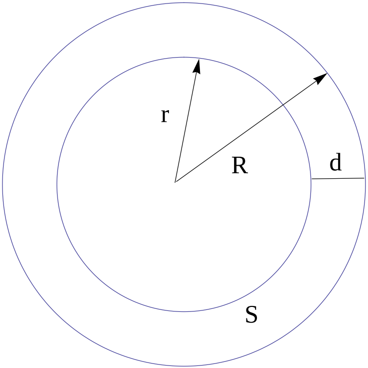
Srednje kvadratno odstupanje $= 0.136447$



Gornja slika:
Lijevo - distribucija (gustoća) hranjivih sastojaka
Desno - proliferacija (aktivnost rasta)



Jednostavni model rasta tumora



- d - debljina sloja stanica koje se dijele
- S - stanice koje se dijele (volumen)
- d je konstantan (eksperimentalni rezultat)

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

Model

- von Bertalanffy: $V' = aV^{2/3} - bV$
- Modifikacija: $S \to V^{2/3}$
- Model: $V' = aS - bV$
- $V' = a\frac{4}{3}\pi\left[3R^2d - 3Rd^2 + d^3\right] - bV$

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

Domaća zadaća

Iz podataka rasta tumorskih sferoida odredite vrijeme udvostručenja.

Vrijeme (dani)	Volumen (mm^3)
4.6	0.0016308
5.7	0.0032148
6.7	0.0056140
7.9	0.0118598
8.8	0.0201500
9.8	0.0275380
11.0	0.0345460
12.0	0.0660800
12.9	0.0789320
15.2	0.1550000