Istraživanje pojave tumorskih kariotipa

Samostalni seminar iz istraživanja u fizici

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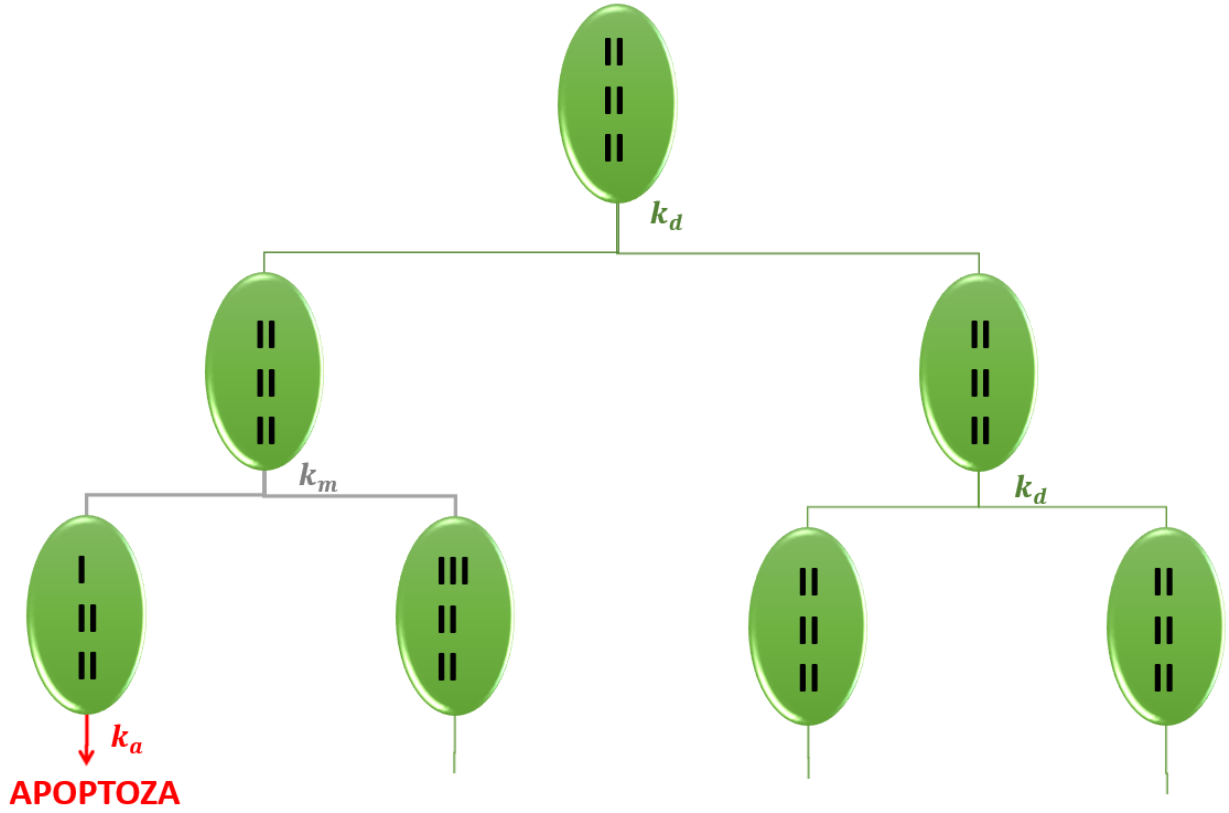
Uvod:

- nakon vremena T, stanica će doživjeti jedan od tri moguća ishoda:

$$p_d + p_m + p_a = 1$$

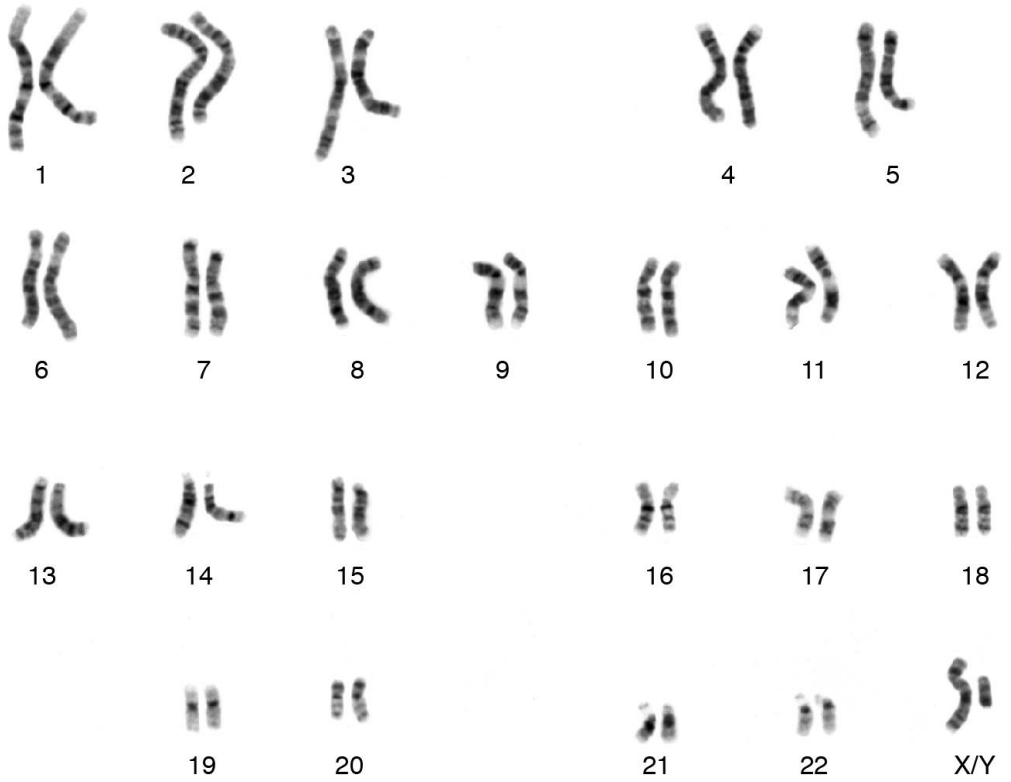
- brzine: $k_j = \frac{p_j}{T}$



Slika 1: Shematski prikaz diobe stanice

Kariotip stanice

- $\vec{K} = \begin{pmatrix} c_1 \\ c_2 \\ c_3 \\ \vdots \\ c_{22} \\ c_{23} \end{pmatrix}$
- c_i - broj kopija i-tog kromosoma
- ***euploidi***: haploidi (1n), diploidi (2n)…
- ***aneuploidi***



Slika 2: Kariotip čovjeka

Evolucija broja stanica određenog kariotipa, $N(\vec{K})$:

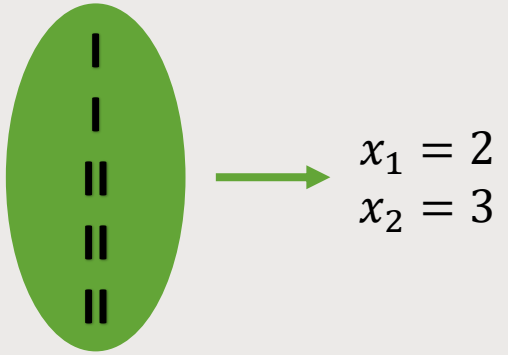
$$\frac{dN(\vec{K})}{dt} = \left(k_d(\vec{K}) - k_m(\vec{K}) - k_a(\vec{K})\right) N(\vec{K}) +$$

$$+ \sum_{i=1}^{23} k_m(\vec{K} + \vec{e_i}) N(\vec{K} + \vec{e_i}) +$$

$$+ \sum_{i=1}^{23} k_m(\vec{K} - \vec{e_i}) N(\vec{K} - \vec{e_i})$$

- promatramo stanice do dvije kopije → c_i = 1 ili 2
- misegregacija i-tog kromosoma ovisi samo o broju kopija tog kromosoma: $p_{m_i} = p_0 c_i$
- p_0 - misegregacija jedne kopije kromosoma

- ukupan broj različitih kariotipa: $2^{23} = 8\,388\,608$
- **makro-kariotip:** $\vec{M} = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$
- x_i - broj kromosoma sa *i* kopija
- $x_1 + x_2$ = broj kromosoma
- 24 različita makro-kariotipa



$x_1 = 2$
$x_2 = 3$

$$N(\vec{M}) = \frac{1}{x_1!\, x_2!} \sum_{all\ perm.} N(\vec{K})$$

Rate jednadžba za makro-kariotip:

$$\frac{dN(\vec{M})}{dt} =$$

$$\frac{1}{T(\vec{M})}(1 - 2\sum_{n=1}^{2} nx_n p_0(\vec{M}))N(\vec{M}) - 2\frac{p_a(\vec{M})}{T(\vec{M})}N(\vec{M}) +$$

$$+(x_1 + 1)\frac{p_0(\vec{M} + \vec{e_1} - \vec{e_2})}{T(\vec{M} + \vec{e_1} - \vec{e_2})}N(\vec{M} + \vec{e_1} - \vec{e_2}) +$$

$$+2(x_2 + 1)\frac{p_0(\vec{M} + \vec{e_2} - \vec{e_1})}{T(\vec{M} + \vec{e_2} - \vec{e_1})}N(\vec{M} + \vec{e_2} - \vec{e_1})$$

Rate jednadžba za makro-kariotip:

- koeficijent saturacije, α

$$\alpha \equiv (1 - \frac{\sum_{\vec{M}} N(\vec{M})}{N_{tot}})$$

- N_{tot}: ukupan broj stanica nakon kojeg dioba prestaje

$$\frac{dN(\vec{M})}{dt} =$$

$$\frac{\alpha}{T(\vec{M})}(1 - 2\sum_{n=1}^{2} n x_n p_0(\vec{M}))N(\vec{M}) - 2\frac{p_a(\vec{M})}{T(\vec{M})}N(\vec{M}) +$$

$$+(x_1 + 1)\frac{\alpha p_0(\vec{M} + \vec{e_1} - \vec{e_2})}{T(\vec{M} + \vec{e_1} - \vec{e_2})}N(\vec{M} + \vec{e_1} - \vec{e_2}) +$$

$$+2(x_2 + 1)\frac{\alpha p_0(\vec{M} + \vec{e_2} - \vec{e_1})}{T(\vec{M} + \vec{e_2} - \vec{e_1})}N(\vec{M} + \vec{e_2} - \vec{e_1})$$

→ **NELINEARAN SUSTAV OBIČNIH DIFERENCIJALNIH JEDNADŽBI**

stacionarno rješenje: $\frac{dN(\vec{M})}{dt} = 0$

$$\frac{1}{2p_a(\vec{M})}(1 - 2p_0(\vec{M})(x_1 + 2x_2))N(\vec{M}) +$$
$$+(x_1 + 1)\frac{p_0(\vec{M} + \vec{e_1} - \vec{e_2})T(\vec{M})}{2T(\vec{M} + \vec{e_1} - \vec{e_2})p_a(\vec{M})}N(\vec{M} + \vec{e_1} - \vec{e_2}) +$$
$$+(x_2 + 1)\frac{p_0(\vec{M} - \vec{e_1} + \vec{e_2})T(\vec{M})}{T(\vec{M} - \vec{e_1} + \vec{e_2})p_a(\vec{M})}N(\vec{M} - \vec{e_1} + \vec{e_2}) =$$
$$= \frac{1}{\alpha}N(\vec{M})$$

svojstvena jednadžba:

$$A\overrightarrow{N_0} = \lambda\overrightarrow{N_0}$$

24x24 trodijagonalna matrica

Svojstveni problem

- Svojstvene vrijednosti: $\lambda = \frac{1}{\alpha}$
- Svojstveni vektori: $\overrightarrow{N_0} = \begin{pmatrix} N(x_2{=}0) \\ N(x_2{=}1) \\ \vdots \\ N(x_2{=}22) \\ N(x_2{=}23) \end{pmatrix}$
- $\vec{N} = c\overrightarrow{N_0}$

Istraživanje prostora parametara

- Vjerojatnost za misegregaciju jedne kopije:
$$p_0(x_2) = a + bx_2(23 - x_2)$$
- Vjerojatnost za apoptozu:
$$p_a(x_2) = 10^{-2}\text{, za svaki } x_2$$
- Vrijeme života stanice:
$$T(x_2) = 1 \text{ dan, za svaki } x_2$$

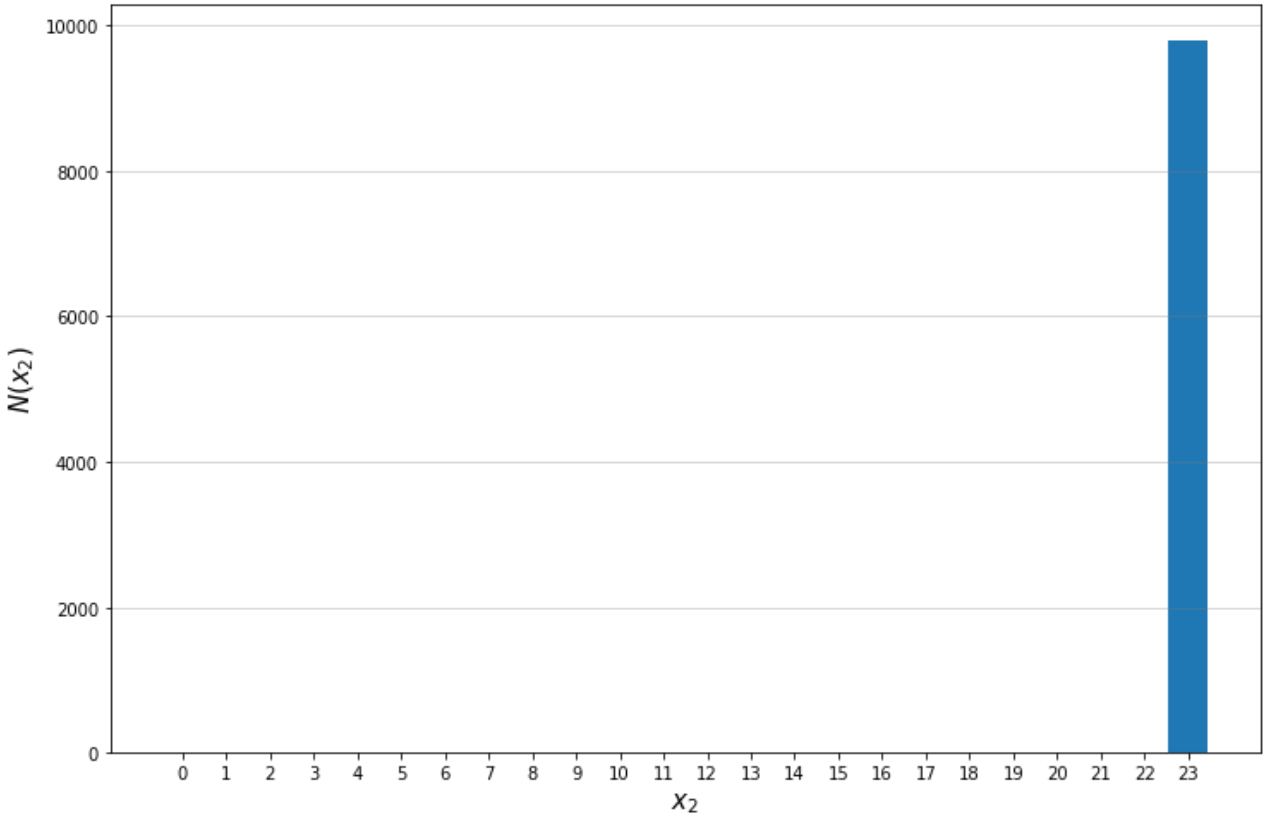
Rezultati i rasprava

1. Veća misegregacija haploidnih stanica:

$$a = \begin{cases} 10^{-4} & \text{za } x_2 = 0 \\ 10^{-5} & \text{za } x_2 = 23 \\ 10^{-3} & \text{inače} \end{cases}$$

$$b = 10^{-3}$$

- $p_0(x_2) = a + bx_2(23 - x_2)$
- $N_{tot} = 10\,000$



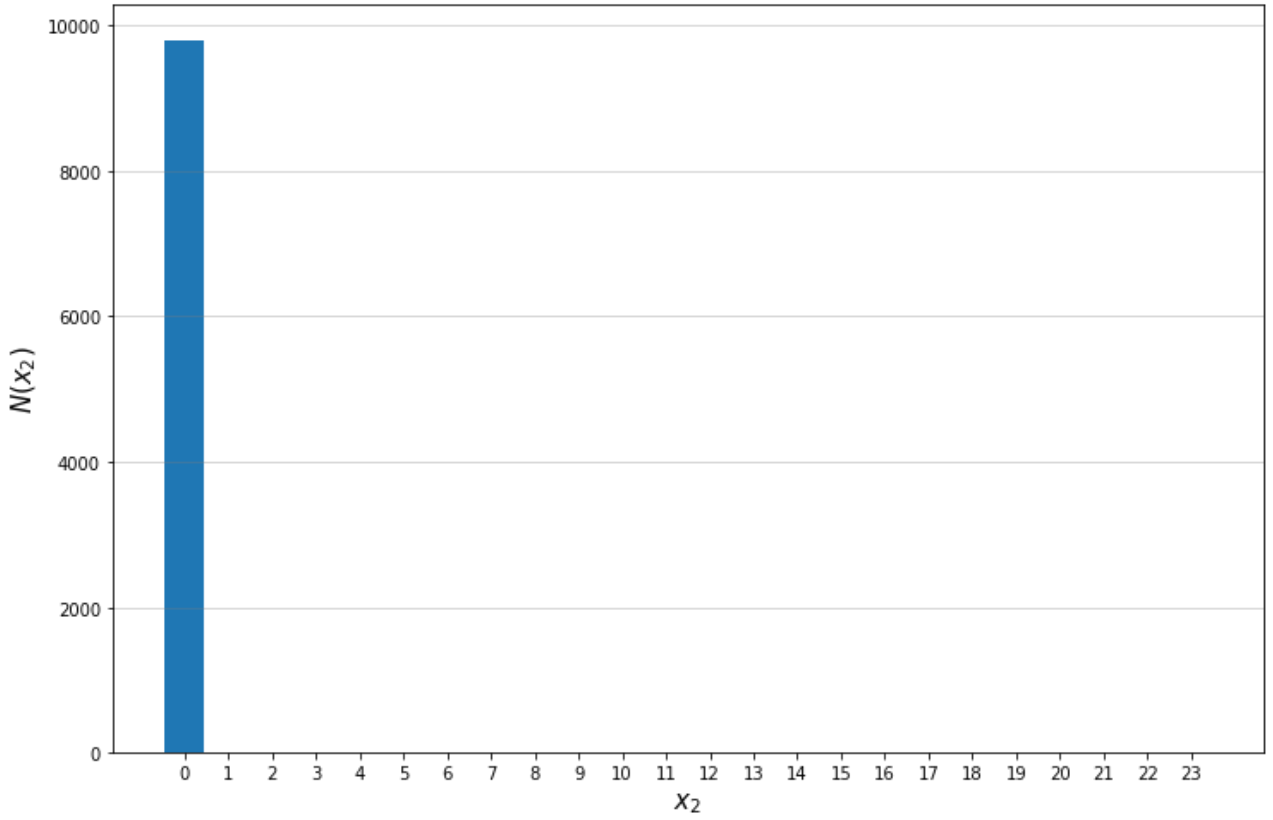
Slika 3: Graf ovisnosti broja stanica N o makro-kariotipu x_2

2. Veća misegregacija diploidnih stanica:

$$a = \begin{cases} 10^{-5} & \text{za } x_2 = 0 \\ 10^{-4} & \text{za } x_2 = 23 \\ 10^{-3} & \text{inače} \end{cases}$$

$$b = 10^{-3}$$

- $p_0(x_2) = a + bx_2(23 - x_2)$
- $N_{tot} = 10\,000$



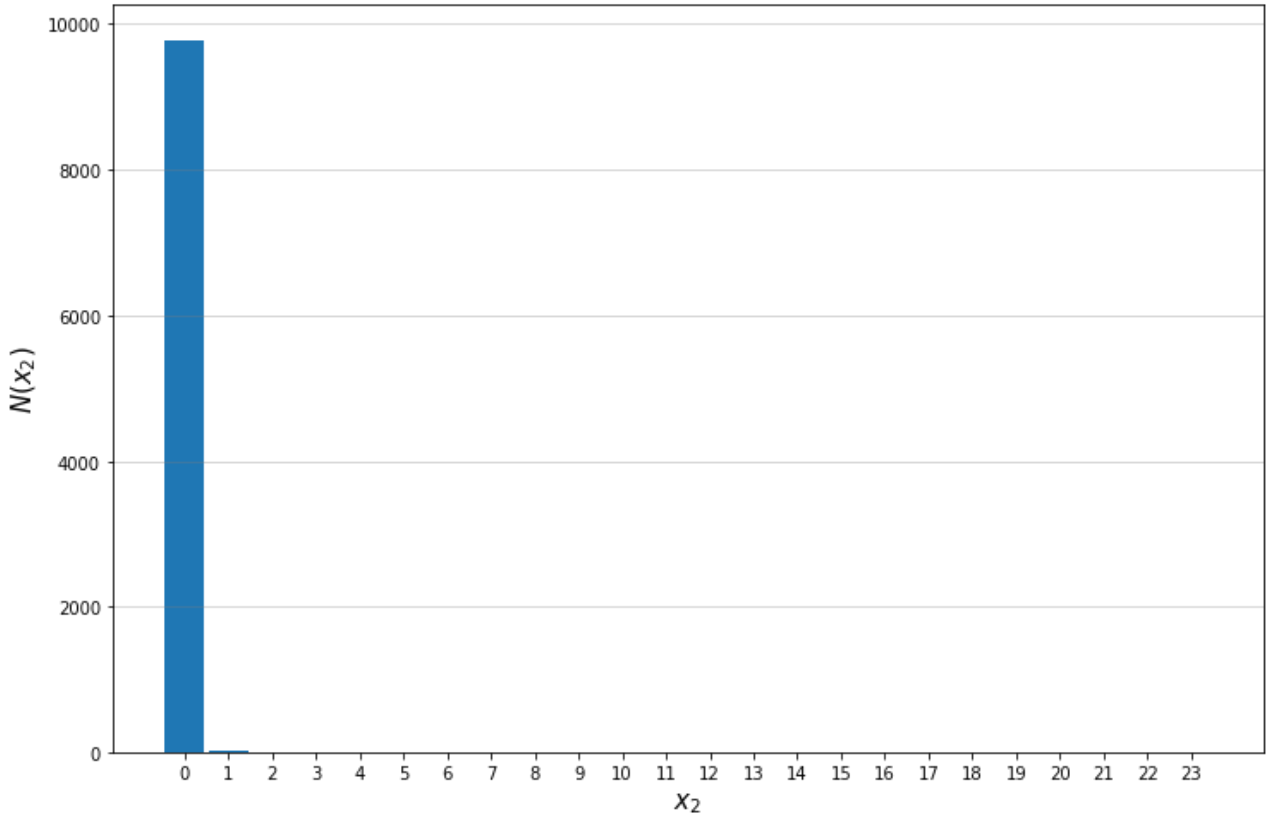
Slika 4: Graf ovisnosti broja stanica N o makro-kariotipu x_2

3. Jednaka misegregacija haploidnih i diploidnih stanica:

$$a = \begin{cases} 10^{-4} & \text{za } x_2 = 0 \\ 10^{-4} & \text{za } x_2 = 23 \\ 10^{-3} & \text{inače} \end{cases}$$

$$b = 10^{-3}$$

- $p_0(x_2) = a + bx_2(23 - x_2)$
- $N_{tot} = 10\,000$



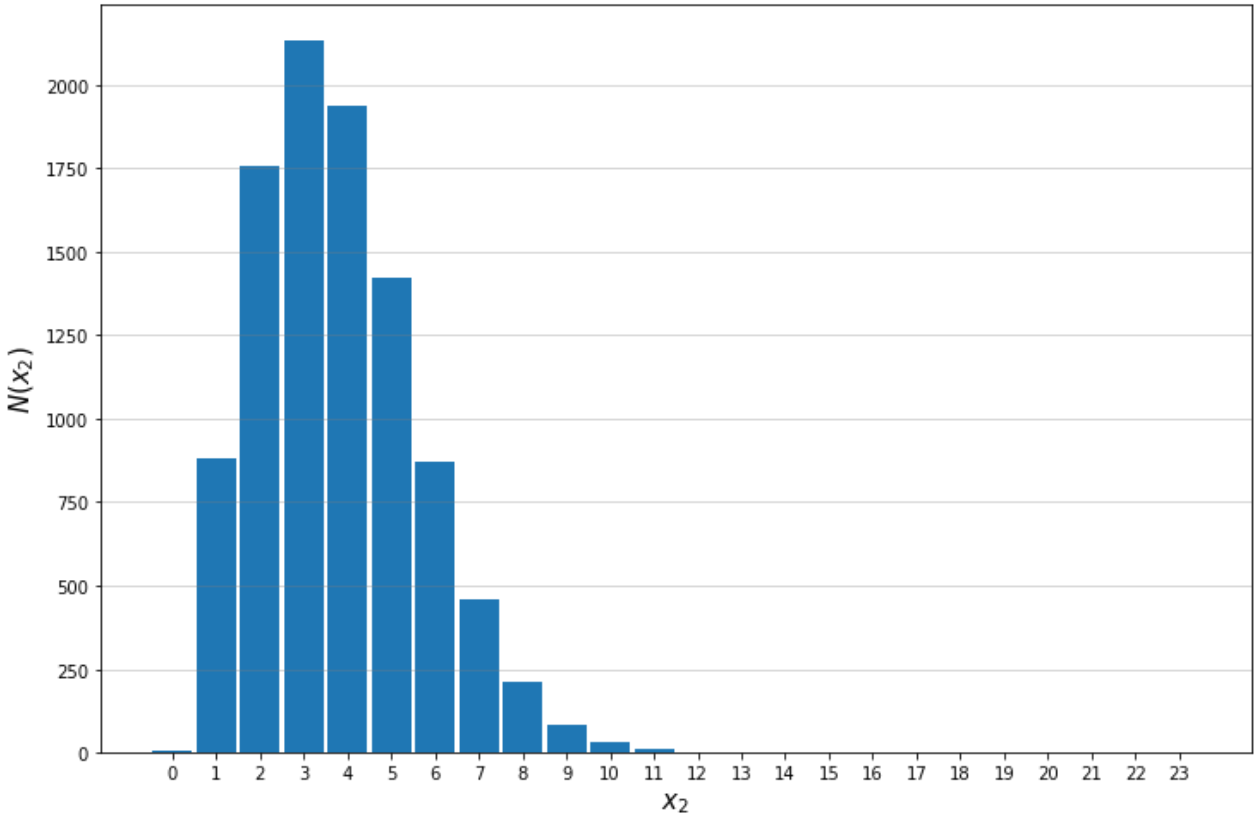
Slika 5: Graf ovisnosti broja stanica N o makro-kariotipu x_2

4.1. Pojava aneuploidnih stanica:

$$a = \begin{cases} 10^{-2} & \text{za } x_2 = 0 \\ 10^{-3} & \text{za } x_2 = 23 \\ 10^{-3} & \text{inače} \end{cases}$$

$$b = 10^{-5}$$

- $p_0(x_2) = a + bx_2(23 - x_2)$
- $N_{tot} = 10\,000$



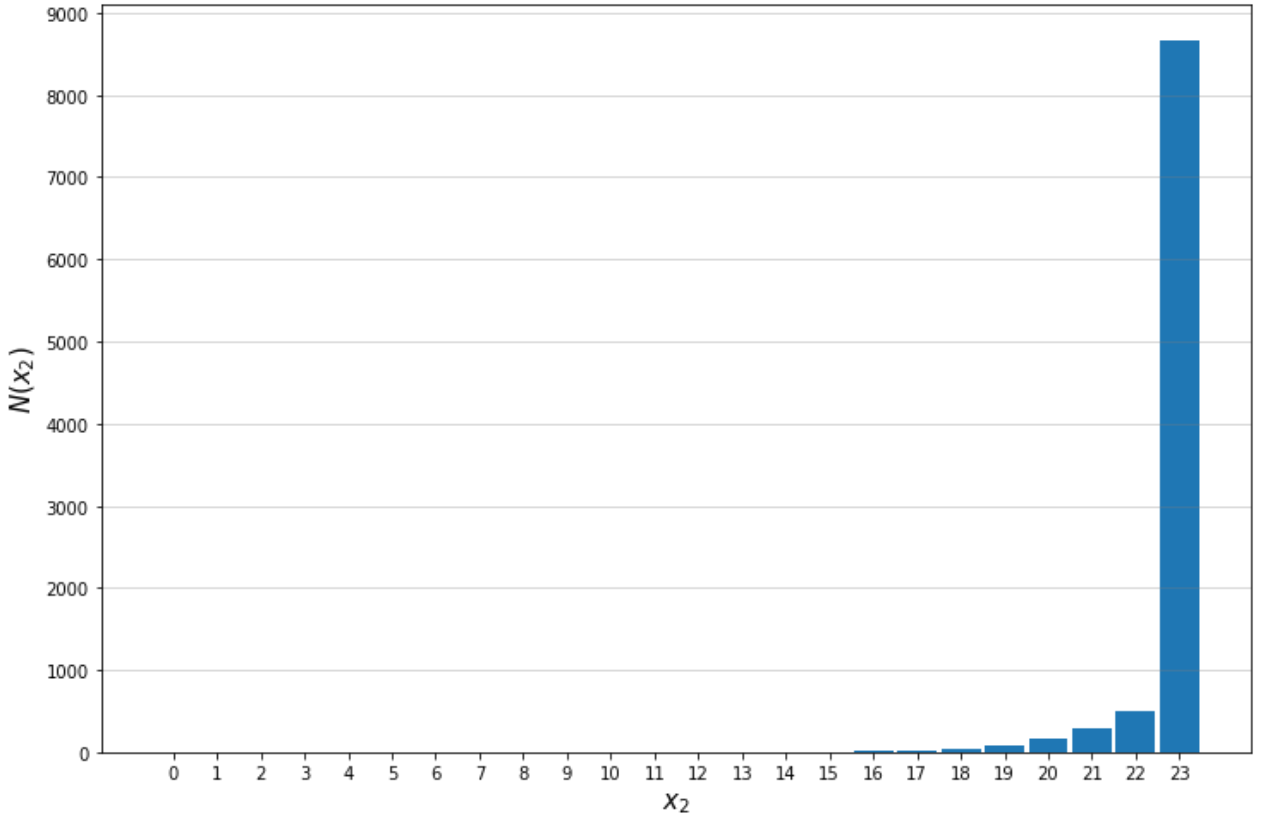
Slika 6: Graf ovisnosti broja stanica N o makro-kariotipu x_2

4.2 Pojava aneuploidnih stanica:

$$a = \begin{cases} 10^{-2} & \text{za } x_2 = 0 \\ 10^{-4} & \text{za } x_2 = 23 \\ 10^{-3} & \text{inače} \end{cases}$$

$$b = 0$$

- $p_0(x_2) = a + bx_2(23 - x_2)$
- $N_{tot} = 10\,000$



Slika 7: Graf ovisnosti broja stanica N o makro-kariotipu x_2

Zaključak

- Kariotip
- Marko – kariotip
- Rate jednadžba za marko – kariotip → stacionarno rješenje → svojstveni problem
- Istraživanje prostora parametara → pojava aneuploidnih stanica