Primjena koncepta makrokariotipa u modeliranju evolucije stanica kvasca

Ina Mihalj

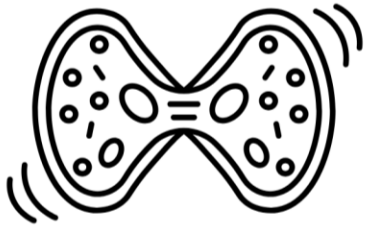
Mentor: Nenad Pavin

- biološka motivacija
- problem

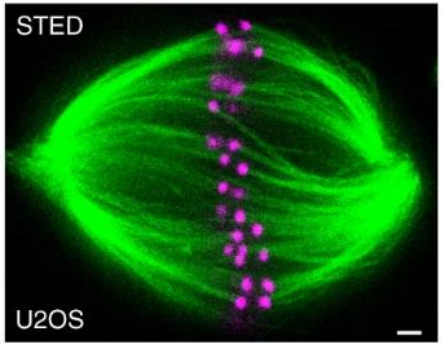
- koncept makrokariotipa
- Monte Carlo simulacija
- teorija srednjeg polja

- rezultati
- zaključak

Dioba stanica

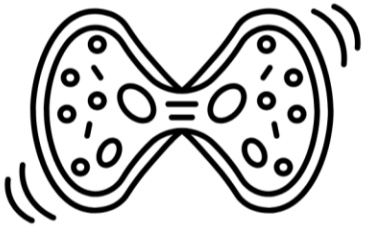


† SiR-tubulin, CENP-A-GFP



† Novak, M., Polak, B., Simunić, J. *et al.* The mitotic spindle is chiral due to torques within microtubule bundles. *Nat Commun* **9**, 3571 (2018).

Dioba stanica



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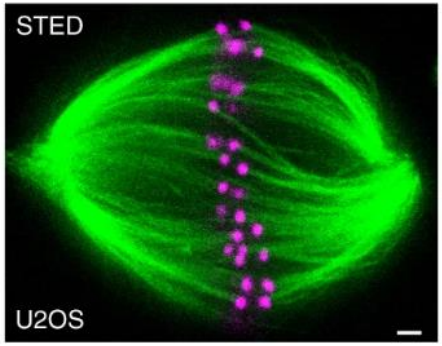
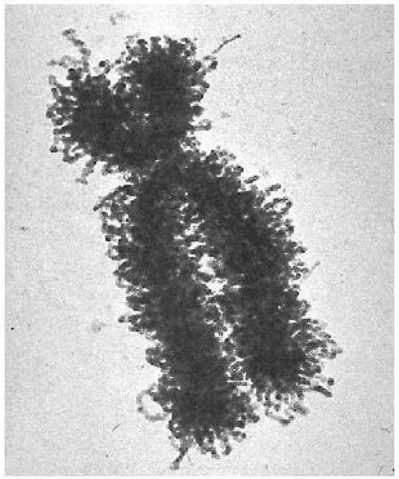


‡



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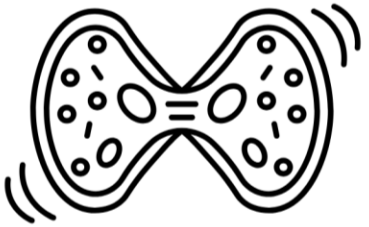
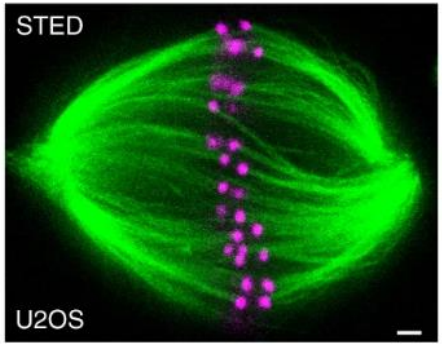
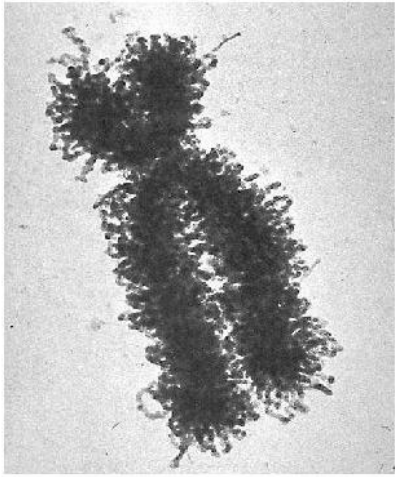
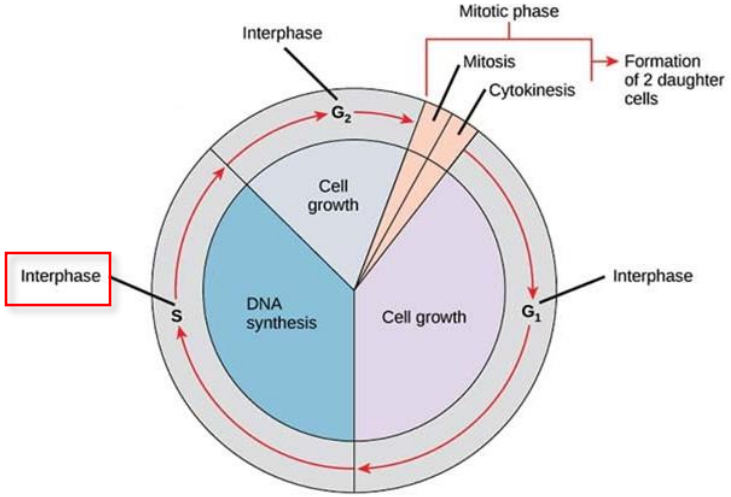


† 

‡ 



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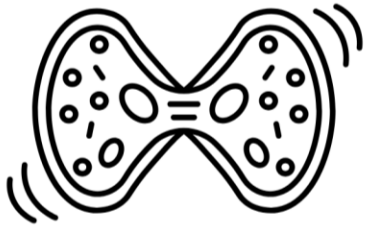
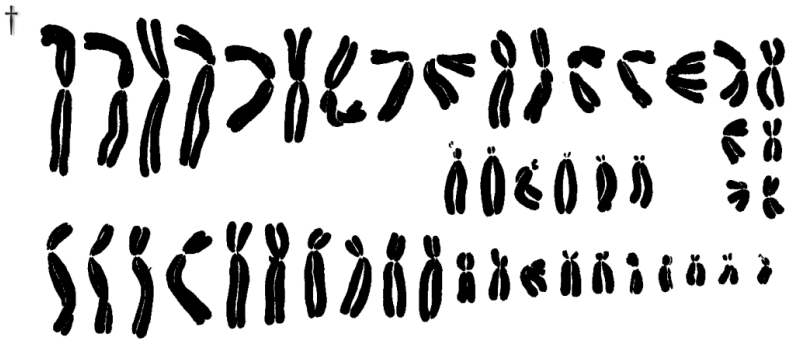
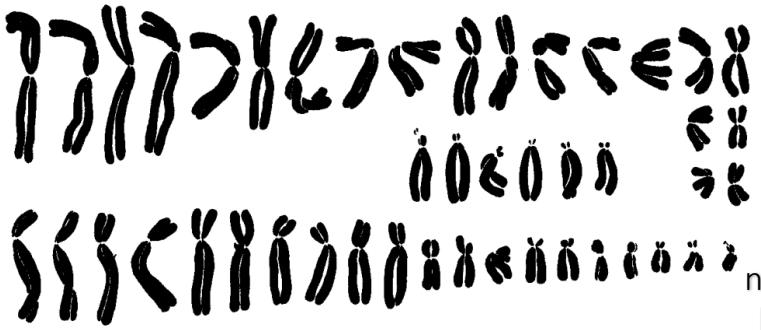




† Tjio, J.H., Levan, A. (1956). The Chromosome Number of Man. In: Persaud, T.V.N. (eds) Problems of Birth Defects. Springer, Dordrecht.

Dioba stanica

†



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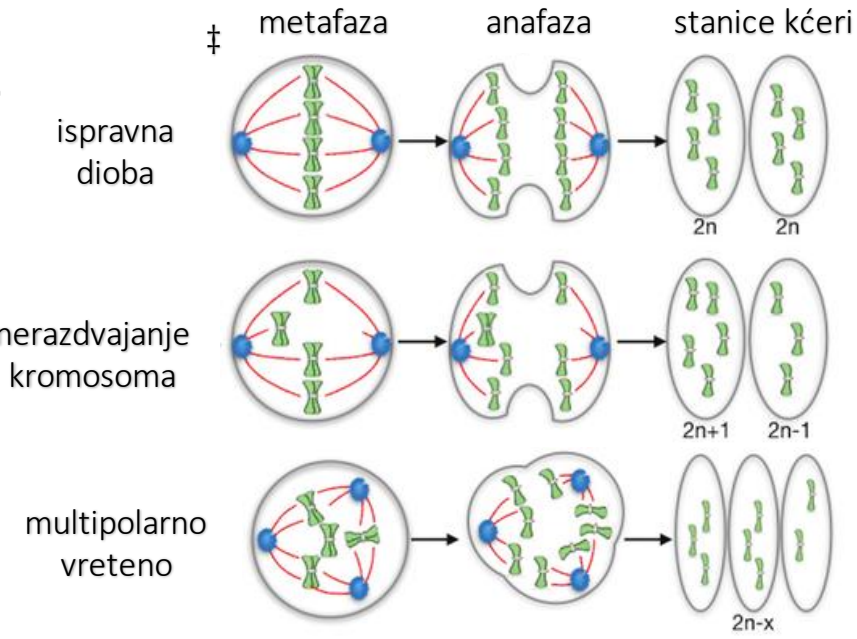

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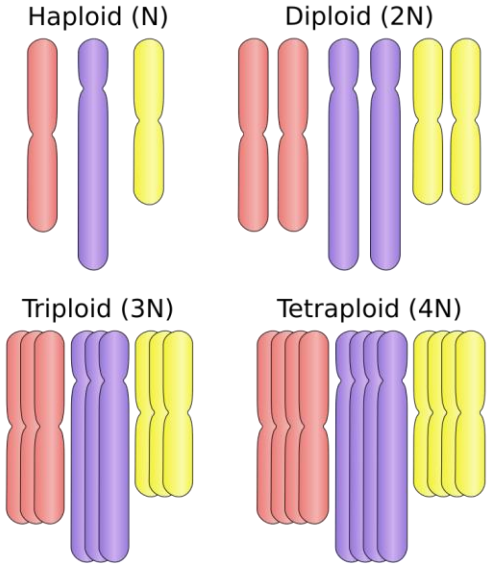

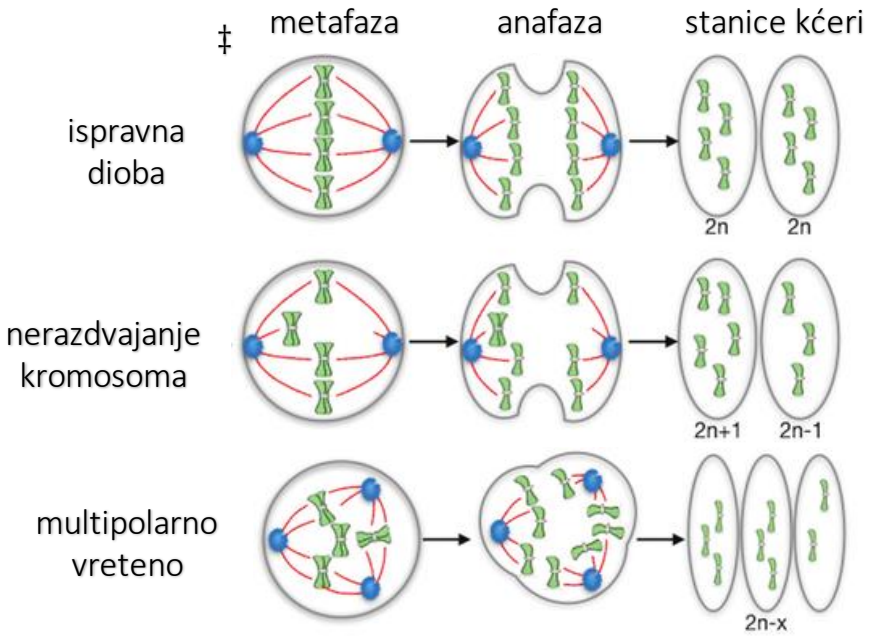

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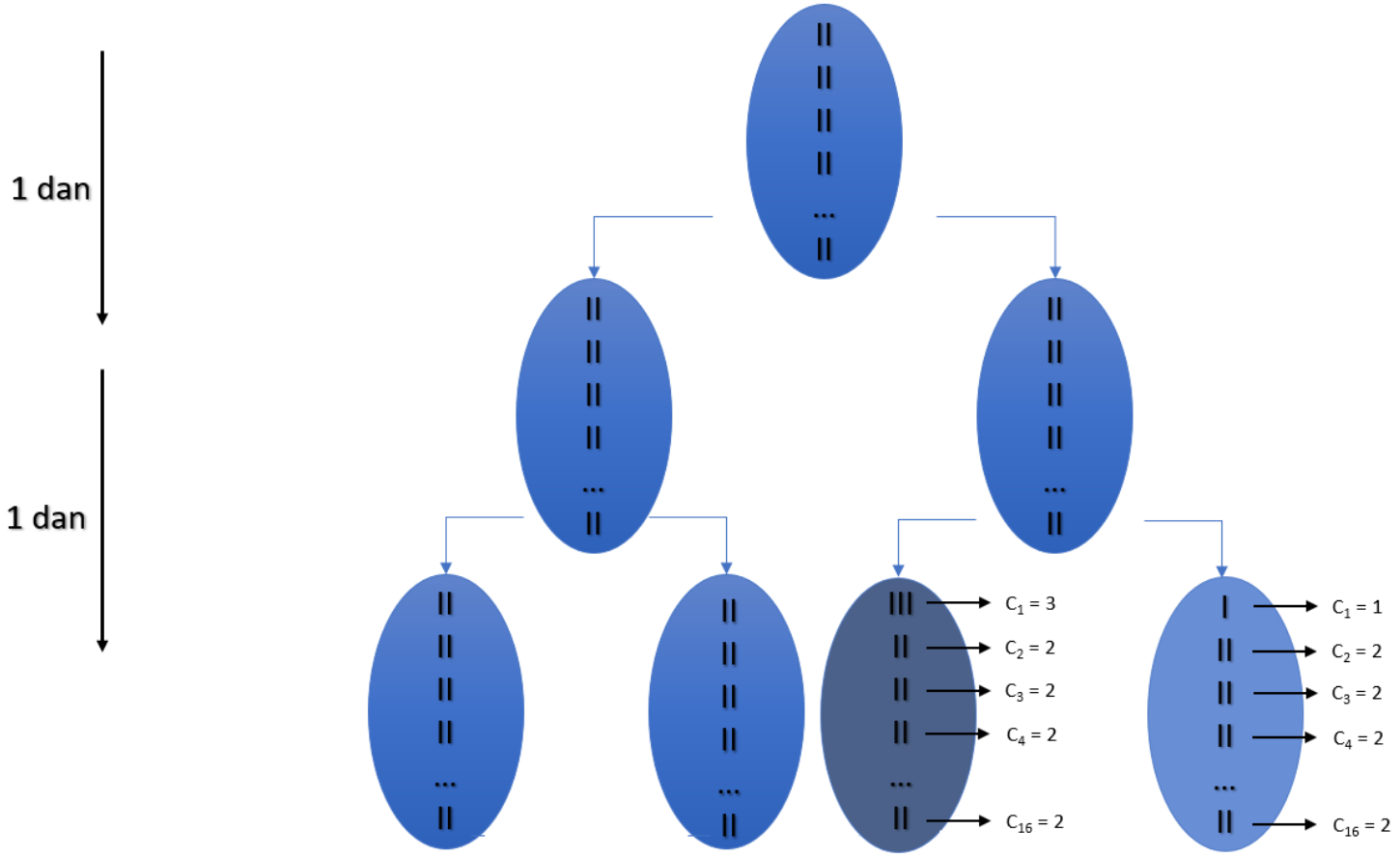
Teorijski model za evoluciju kariotipa

NUMERIČKE KROMOSOMSKE ABERACIJE

Teorijski model za evoluciju kariotipa



Teorijski model za evoluciju kariotipa

prilagodba organizama na okolinu

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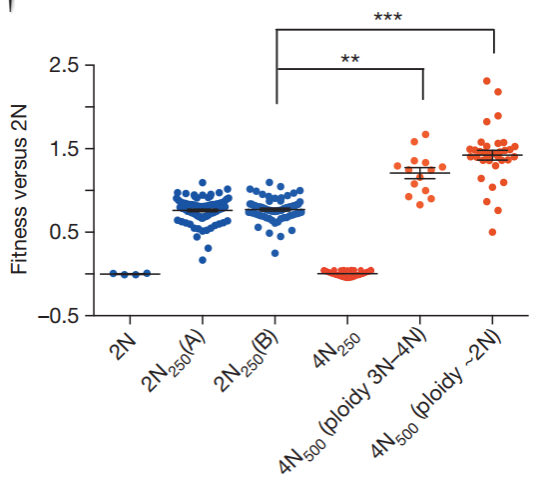

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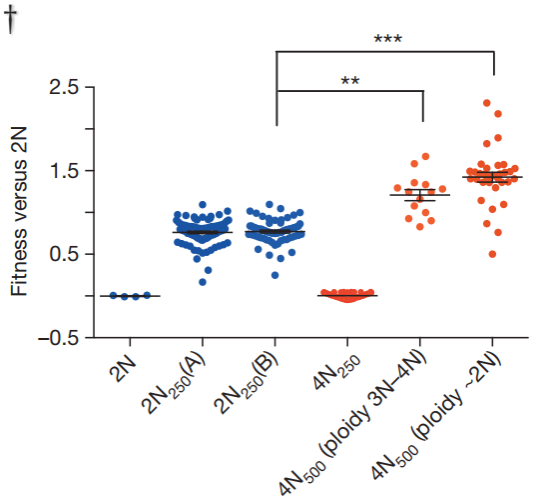

tumorska i predtumorska tkiva

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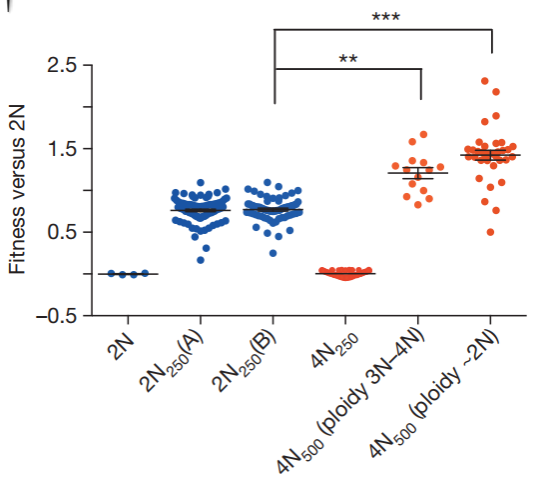

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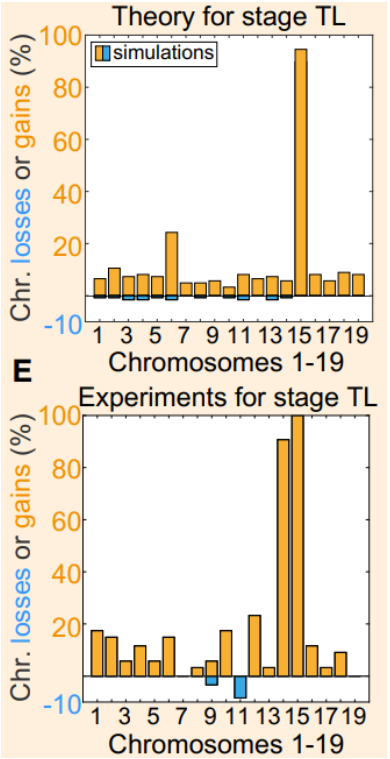

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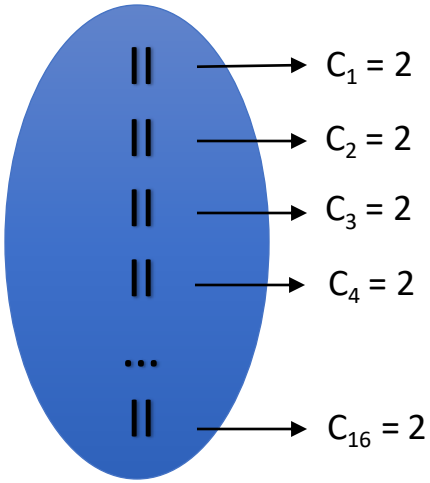
‡ Ban I, Tomašić L, Trakala M, Tolić IM, Pavin N. Proliferative advantage of specific aneuploid cells drives evolution of tumor karyotypes. Biophys J. 2023 Feb 21;122(4):632-645.

Teorijski model za evoluciju kariotipa

$$\vec{K} \equiv (c_1, c_2, ..., c_n)$$

velik broj mogućih kombinacija kariotipa u stanici



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velik broj mogućih kombinacija kariotipa u stanici

$$L = 6$$
$$n = 16$$
$$\overline{2.8 \times 10^{12}}$$

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velik broj mogućih kombinacija kariotipa u stanici

velik broj stanica u populaciji

$$L = 6$$
$$n = 16$$
$$\overline{2.8 \times 10^{12}}$$

2^g

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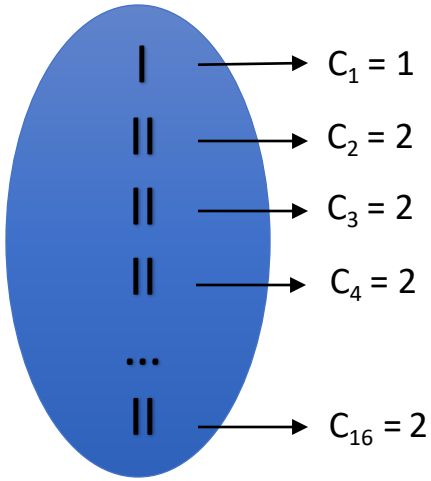
Koncept makrokariotipa

$$\vec{K} \equiv (c_1, c_2, \ldots, c_n)$$
$$\vec{K} = (1, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2)$$



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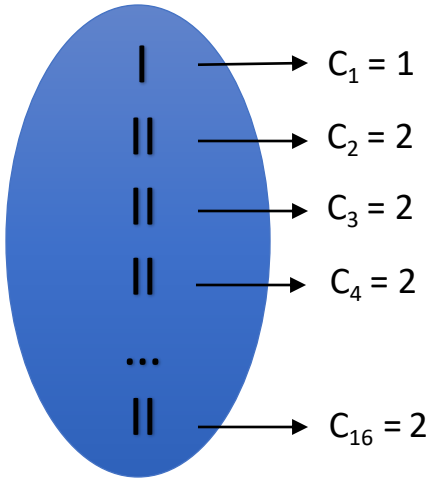

$$\vec{M}(\vec{K}) \equiv (x_1, x_2, ..., x_L)$$
$$\vec{M}(\vec{K}) = (1, 15)$$

$$x_1 + x_2 + ... + x_L = n$$

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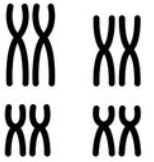
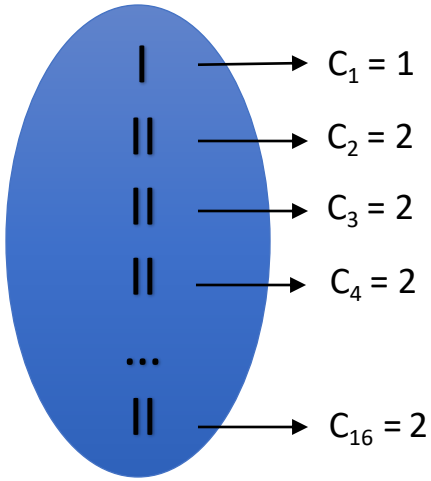
Koncept makrokariotipa



$$\vec{K} \equiv (c_1, c_2, ..., c_n)$$
$$\vec{K} = (1, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2)$$

$$L = 6$$
$$n = 16$$
$$4.6 \times 10^6$$



$$\vec{M}(\vec{K}) \equiv (x_1, x_2, ..., x_L)$$
$$\vec{M}(\vec{K}) = (1, 15)$$

$$x_1 + x_2 + ... + x_L = n$$

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Stohastički pristup evoluciji populacije stanica

Parametar	Oznaka	Definicija
Missegregacija kromosoma s 1 kopijom	p_{m_1}	$1 \times x_1 \times p_0$
Missegregacija kromosoma s 2 kopije	p_{m_2}	$2 \times x_2 \times p_0$
Ispravna stanična dioba	p_d	$1 - p_m - p_v$
Životni vijek stanice	t_0	$1 + 0.005 \times (x_1)^{1.5}$

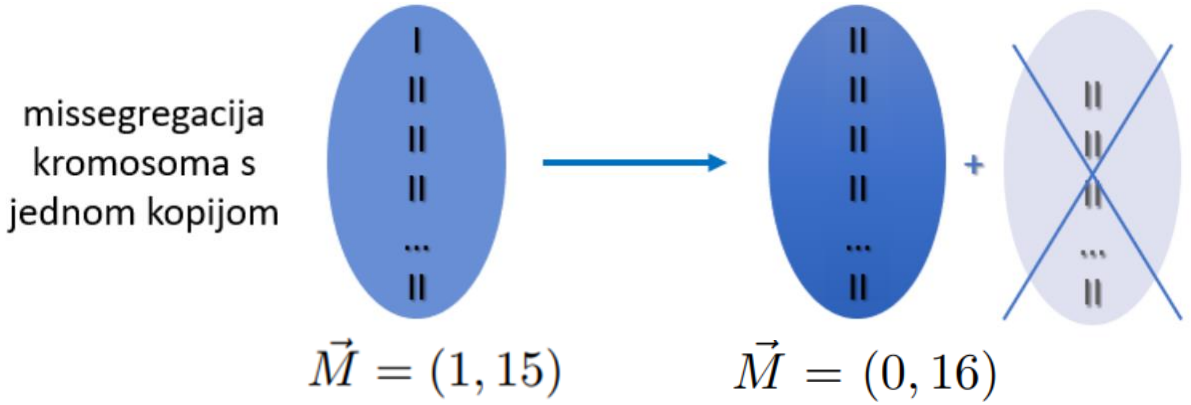
$$p_0 = 0.0025$$

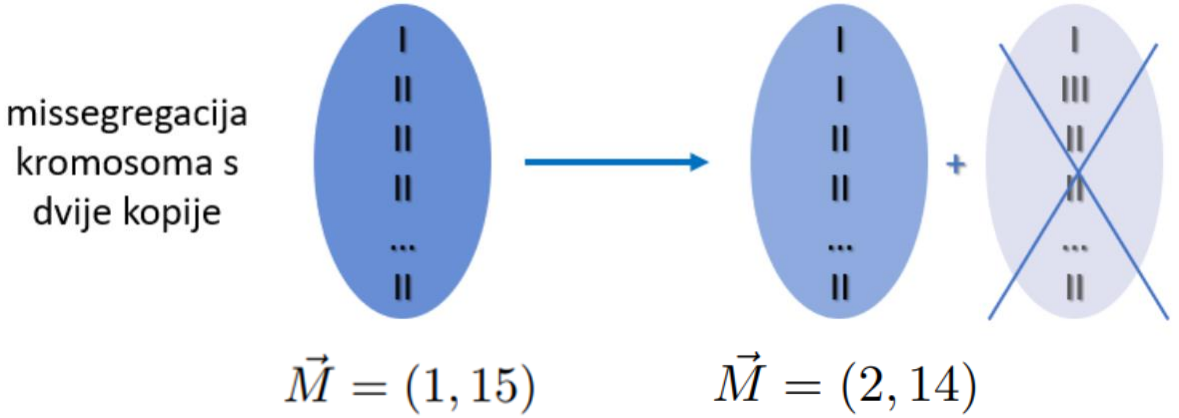
+

vrijeme početka života stanice

Stohastički pristup evoluciji populacije stanica

$L = 2$





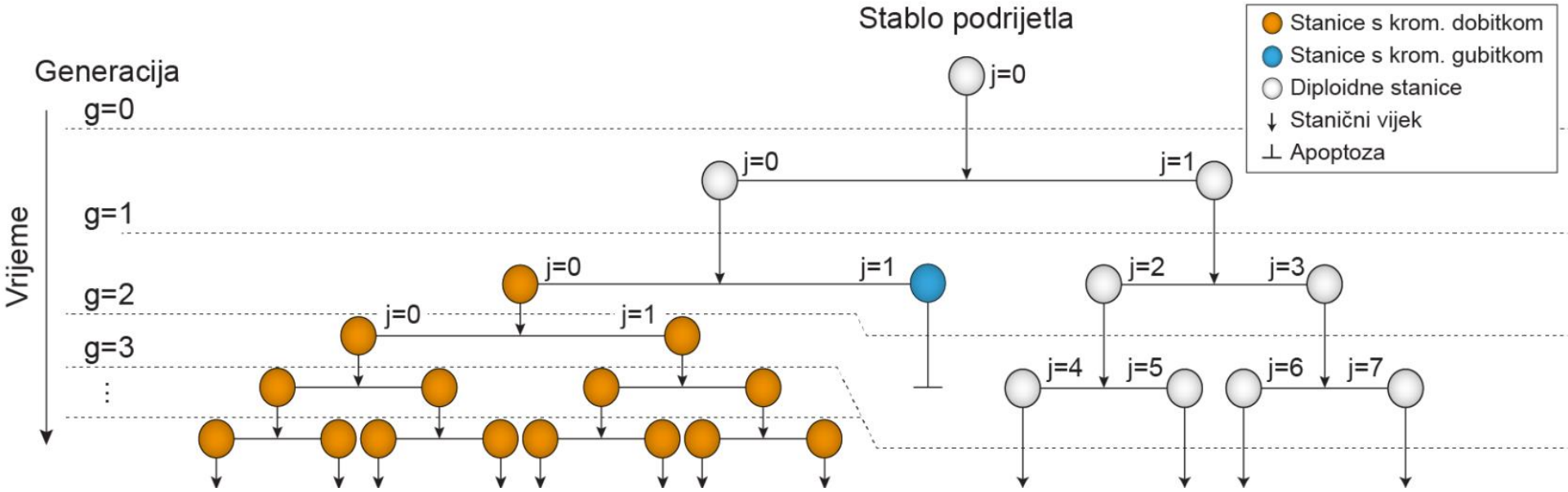
Stohastički pristup evoluciji populacije stanica

NEDOSTATAK

ovisnost o ishodu

nemogućnost praćenja velikog broja stanica

Pristup srednjeg polja



Pristup srednjeg polja

$$\frac{dP_{g,j}(\vec{K})}{dt} = k_d(\vec{K})P_{g-1,\lfloor \frac{j}{2} \rfloor}(\vec{K}) \quad +$$

Pristup srednjeg polja

$$\frac{dP_{g,j}(\vec{K})}{dt} = k_d(\vec{K})P_{g-1,\lfloor \frac{j}{2} \rfloor}(\vec{K}) \quad +$$

$$+ \frac{1}{2}\sum_{i=1}^{n} k_{m_i}(\vec{K}+\vec{e_i})P_{g-1,\lfloor \frac{j}{2} \rfloor}(\vec{K}+\vec{e_i}) \quad +$$

Pristup srednjeg polja

$$\frac{dP_{g,j}(\vec{K})}{dt} = k_d(\vec{K})P_{g-1,\lfloor\frac{j}{2}\rfloor}(\vec{K}) +$$

$$+ \frac{1}{2}\sum_{i=1}^{n} k_{m_i}(\vec{K}+\vec{e_i})P_{g-1,\lfloor\frac{j}{2}\rfloor}(\vec{K}+\vec{e_i}) +$$

$$+ \frac{1}{2}\sum_{i=1}^{n} k_{m_i}(\vec{K}-\vec{e_i})P_{g-1,\lfloor\frac{j}{2}\rfloor}(\vec{K}-\vec{e_i}) +$$

Pristup srednjeg polja

$$\frac{dP_{g,j}(\vec{K})}{dt} = k_d(\vec{K})P_{g-1,\lfloor\frac{j}{2}\rfloor}(\vec{K}) +$$

$$+ \frac{1}{2}\sum_{i=1}^{n} k_{m_i}(\vec{K}+\vec{e_i})P_{g-1,\lfloor\frac{j}{2}\rfloor}(\vec{K}+\vec{e_i}) +$$

$$+ \frac{1}{2}\sum_{i=1}^{n} k_{m_i}(\vec{K}-\vec{e_i})P_{g-1,\lfloor\frac{j}{2}\rfloor}(\vec{K}-\vec{e_i}) +$$

$$- \left[k_d(\vec{K}) + k_m(\vec{K}) + k_a(\vec{K})\right] P_{g,j}(\vec{K})$$

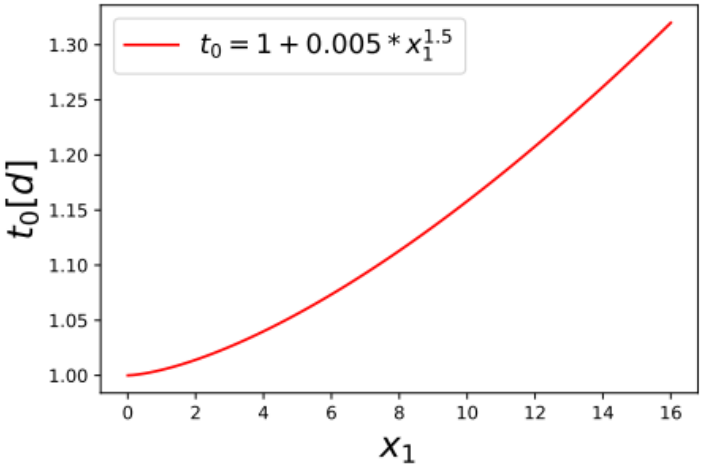
Pristup srednjeg polja

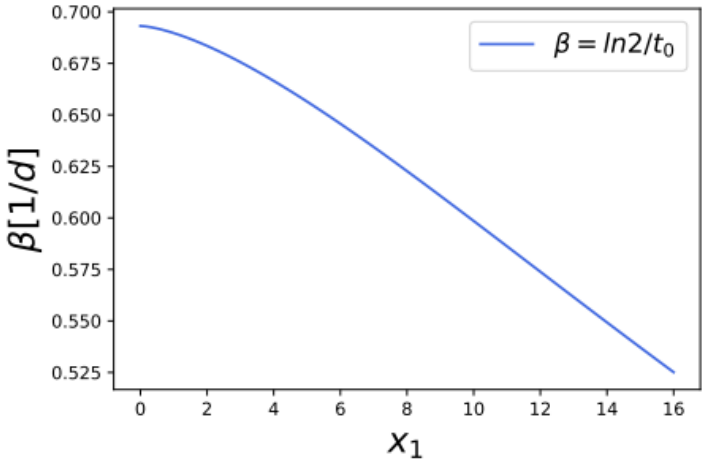
$$\frac{d\widetilde{N}(\vec{M})}{dt} = \left[\tilde{k}_d(\vec{M}) - \tilde{k}_m(\vec{M}) - \tilde{k}_a(\vec{M})\right]\widetilde{N}(\vec{M}) \quad +$$

$$+ \sum_{l=2}^{L} \tilde{k}_{m_l}(\vec{M} - \vec{\epsilon}_{l-1} + \vec{\epsilon}_l)\widetilde{N}(\vec{M} - \vec{\epsilon}_{l-1} + \vec{\epsilon}_l) \quad +$$

$$+ \sum_{l=1}^{L-1} \tilde{k}_{m_l}(\vec{M} + \vec{\epsilon}_l - \vec{\epsilon}_{l+1})\widetilde{N}(\vec{M} + \vec{\epsilon}_l - \vec{\epsilon}_{l+1})$$

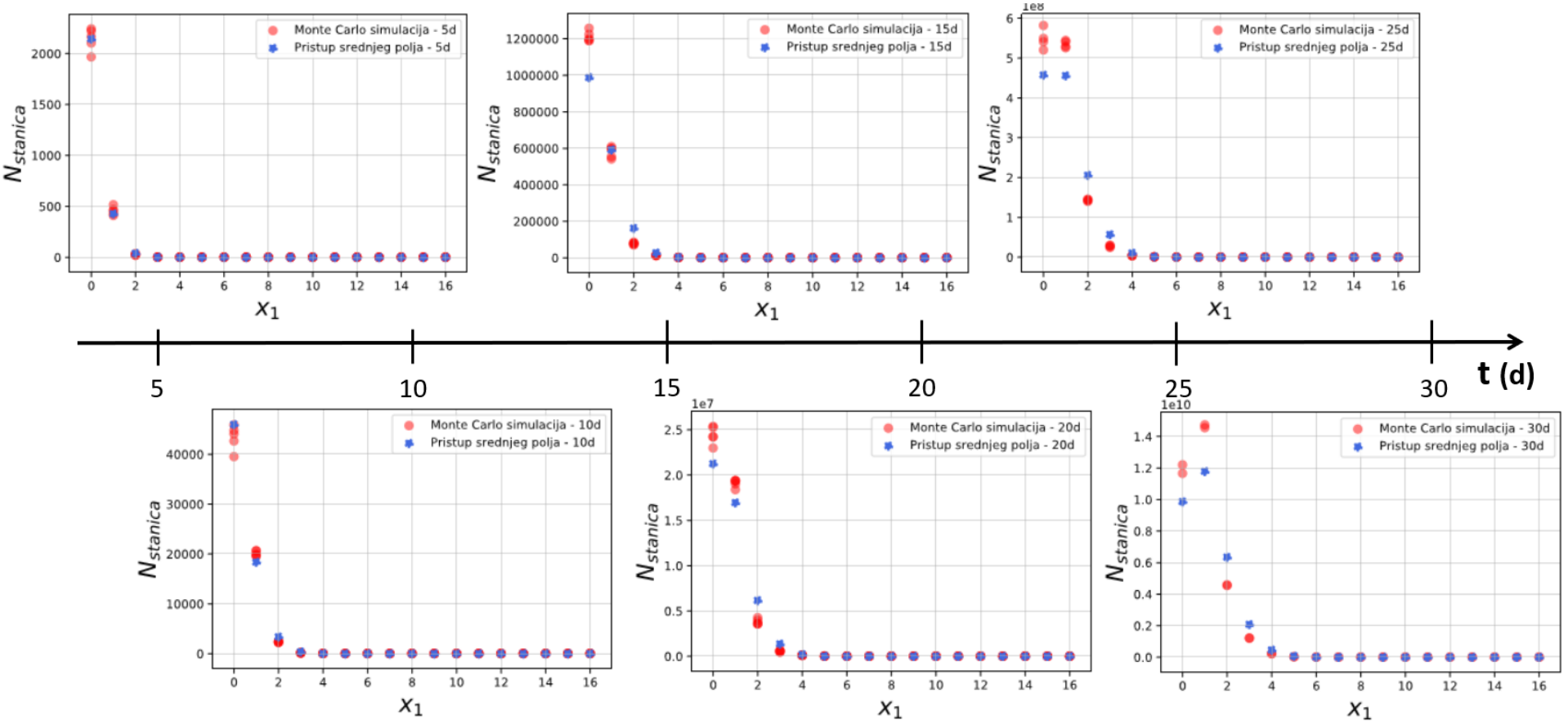
Rezultati


$t_0 = 1 + 0.005 * x_1^{1.5}$
$t_0[d]$
1.30
1.25
1.20
1.15
1.10
1.05
1.00
0
2
4
6
8
10
12
14
16
x_1


$\beta = ln2/t_0$
$\beta[1/d]$
0.700
0.675
0.650
0.625
0.600
0.575
0.550
0.525
0
2
4
6
8
10
12
14
16
x_1

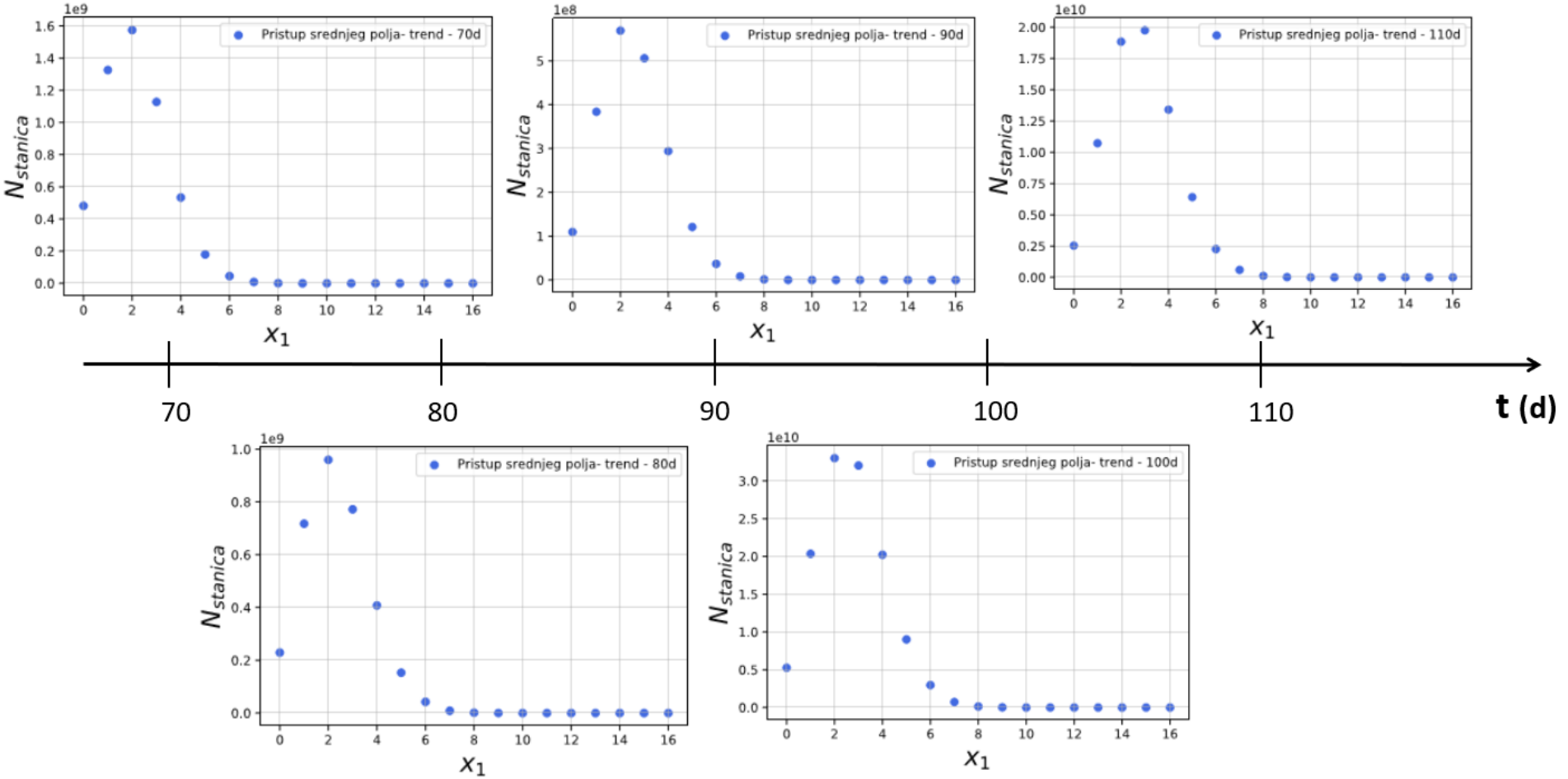
Rezultati

početno diploidna populacija



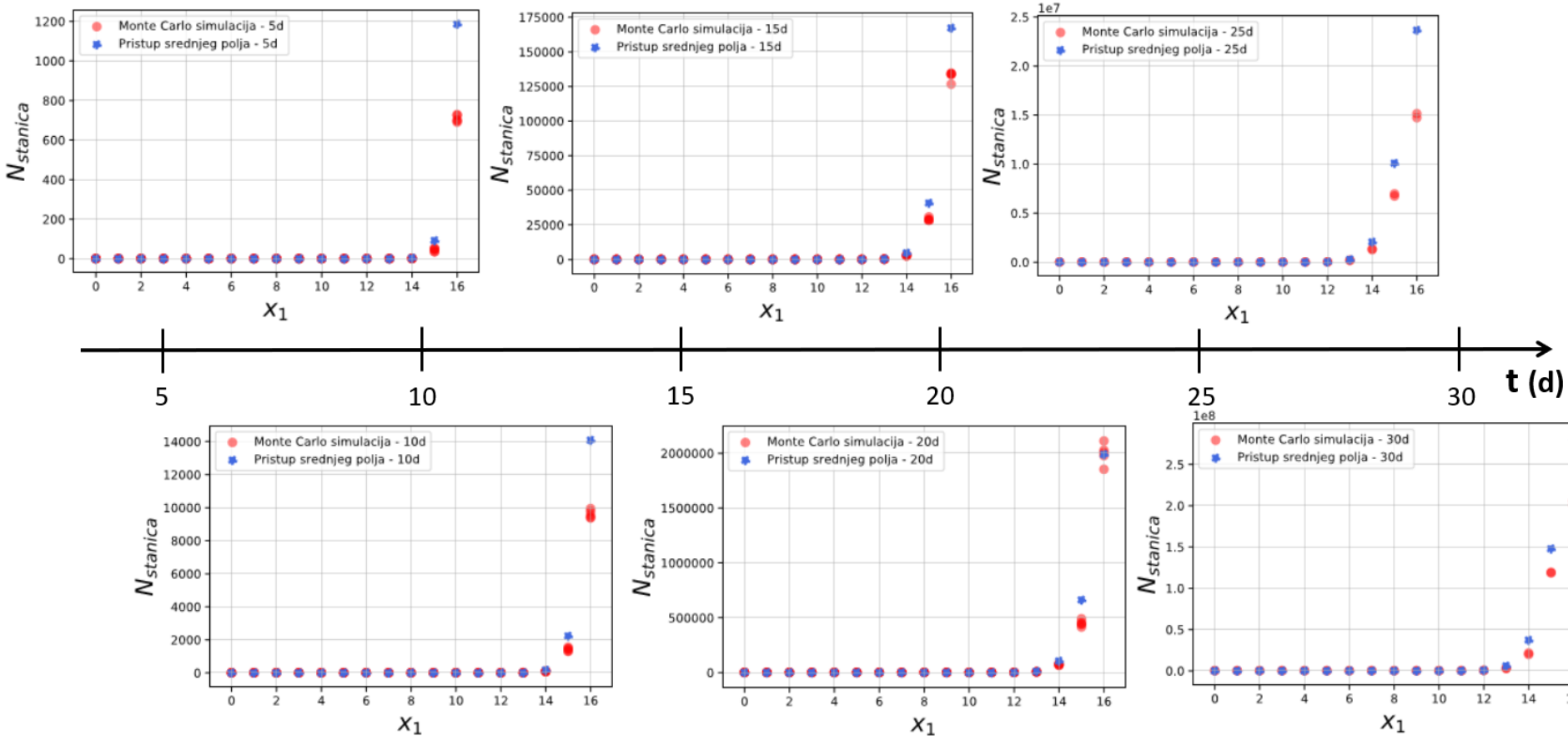
Rezultati

početno diploidna populacija



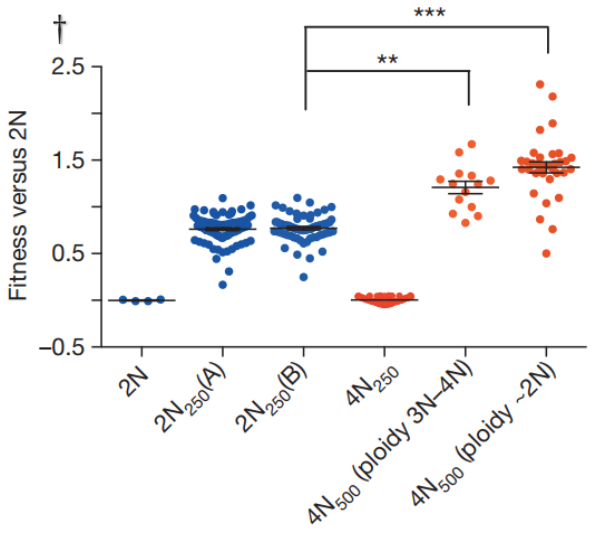
Rezultati

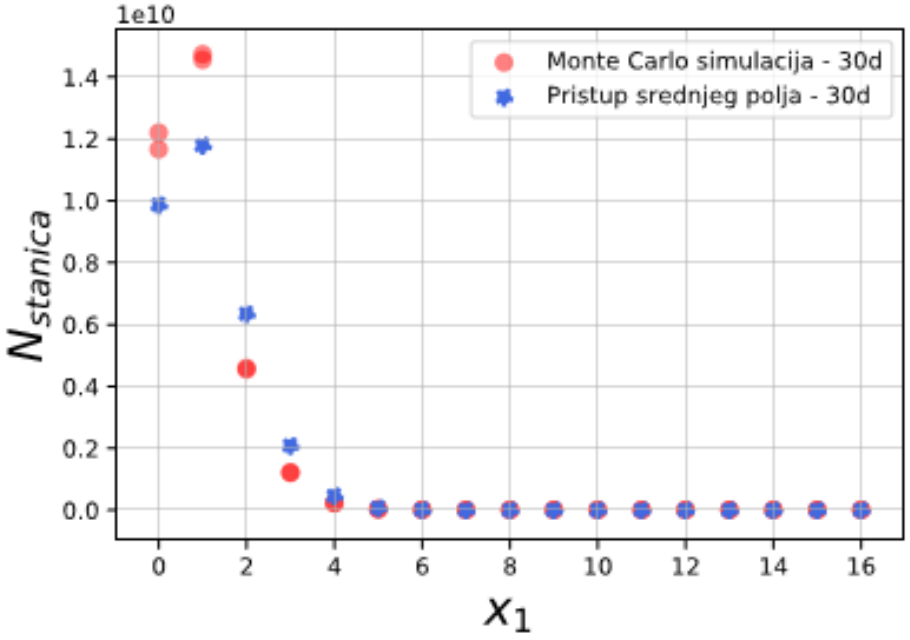
početno haploidna populacija



Zaključak

prilagodba organizama na okolinu





L=2 (II) → L=6 (IIIIII)

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HVALA!

Tehnikalije

	0.00-0.01 d	0.01-0.02 d	0.02-0.03 d	…	0.99-1.00 d	1.00-1.01 d	1.01-1.02 d	…	1.99-2.00 d	2.00-2.01 d	2.01-2.02 d	…	2.99-3.00 d	3.00-3.01 d	3.01-3.02 d
X_1=0	1	0	0		0	0	0		0	0	0		0	0	0
X_1=1	0	0	0		0	0	0		0	0	0		0	0	0
X_1=2	0	0	0		0	0	0		0	0	0		0	0	0
X_1=3	0	0	0		0	0	0		0	0	0		0	0	0
X_1=4	0	0	0		0	0	0		0	0	0		0	0	0
X_1=5	0	0	0		0	0	0		0	0	0		0	0	0
…					…				…				…		
X_1=15	0	0	0		0	0	0		0	0	0		0	0	0
X_1=16	0	0	0		0	0	0		0	0	0		0	0	0

Tehnikalije

NEDOSTATAK

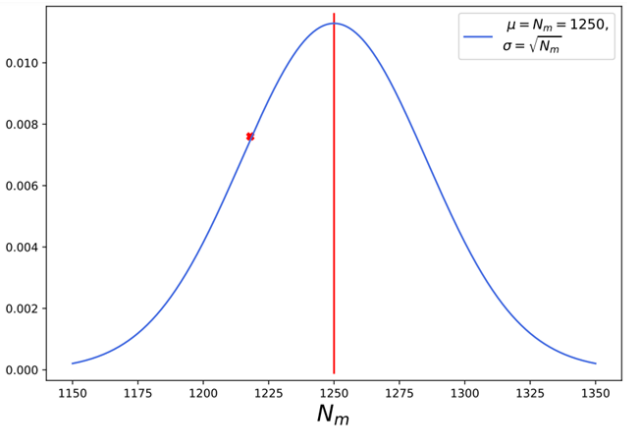
ovisnost o ishodu

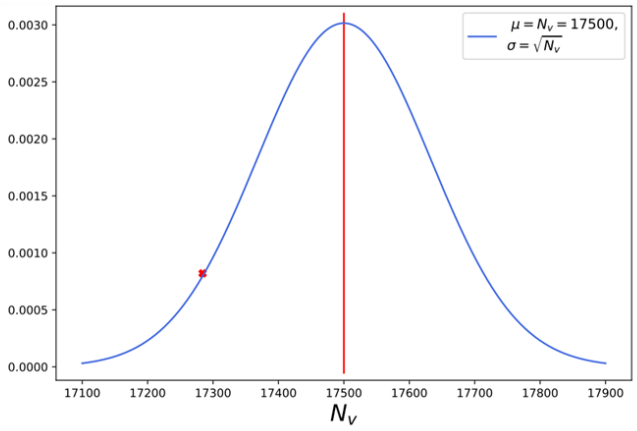
~

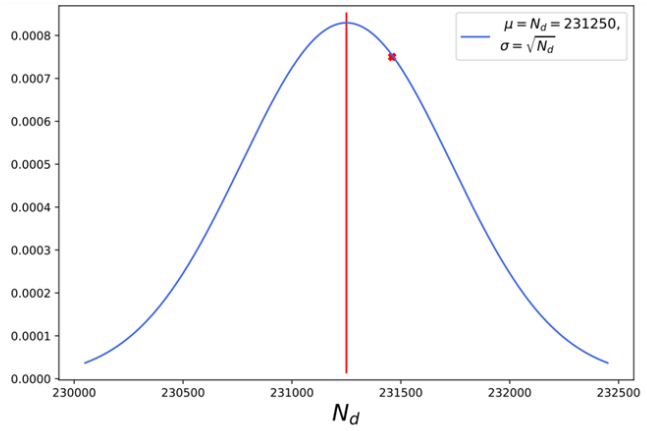
nemogućnost praćenja velikog broja stanica

Tehnikalije

$$N_0 = 250000$$
$$\vec{M} = (2, 14)$$







$$N_m = N_0 \times p_{m_1} = 1250 \quad N_v = N_0 \times p_{m_2} = 17500 \quad N_d = N_0 \times p_d = 231250$$

Tehnikalije

$$\frac{dP_{g,j}(\vec{K})}{dt} = k_d(\vec{K})$$

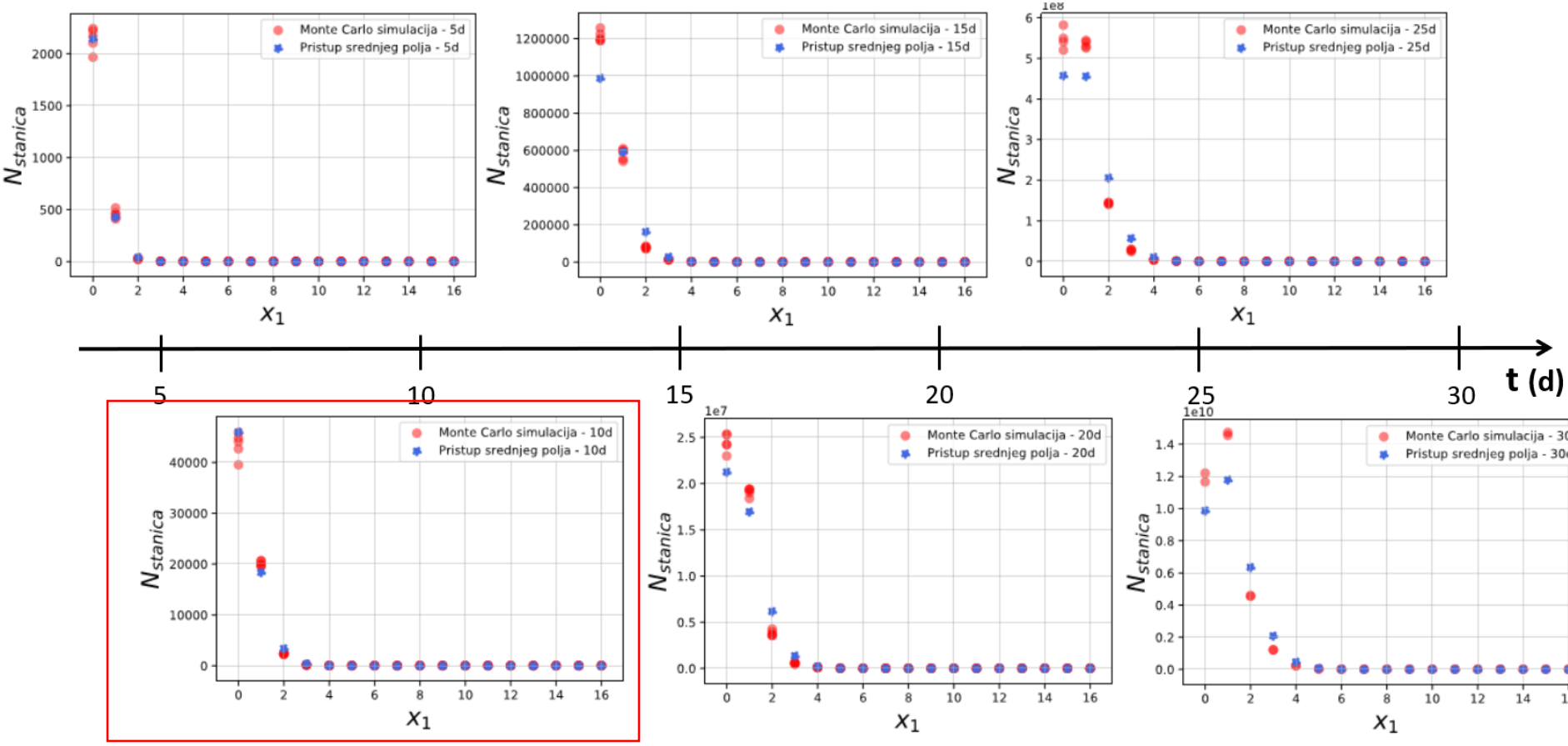
$$+ \frac{1}{2}$$

$$N(\vec{K}) \equiv \sum_{g=0}^{\infty} \sum_{j=0}^{2^g-1} P_{g,j}(\vec{K})$$

$$\widetilde{N}(\vec{M}) = \frac{1}{x_1!x_2!...x_L!} \times \sum_{perm.} N(\vec{K})$$

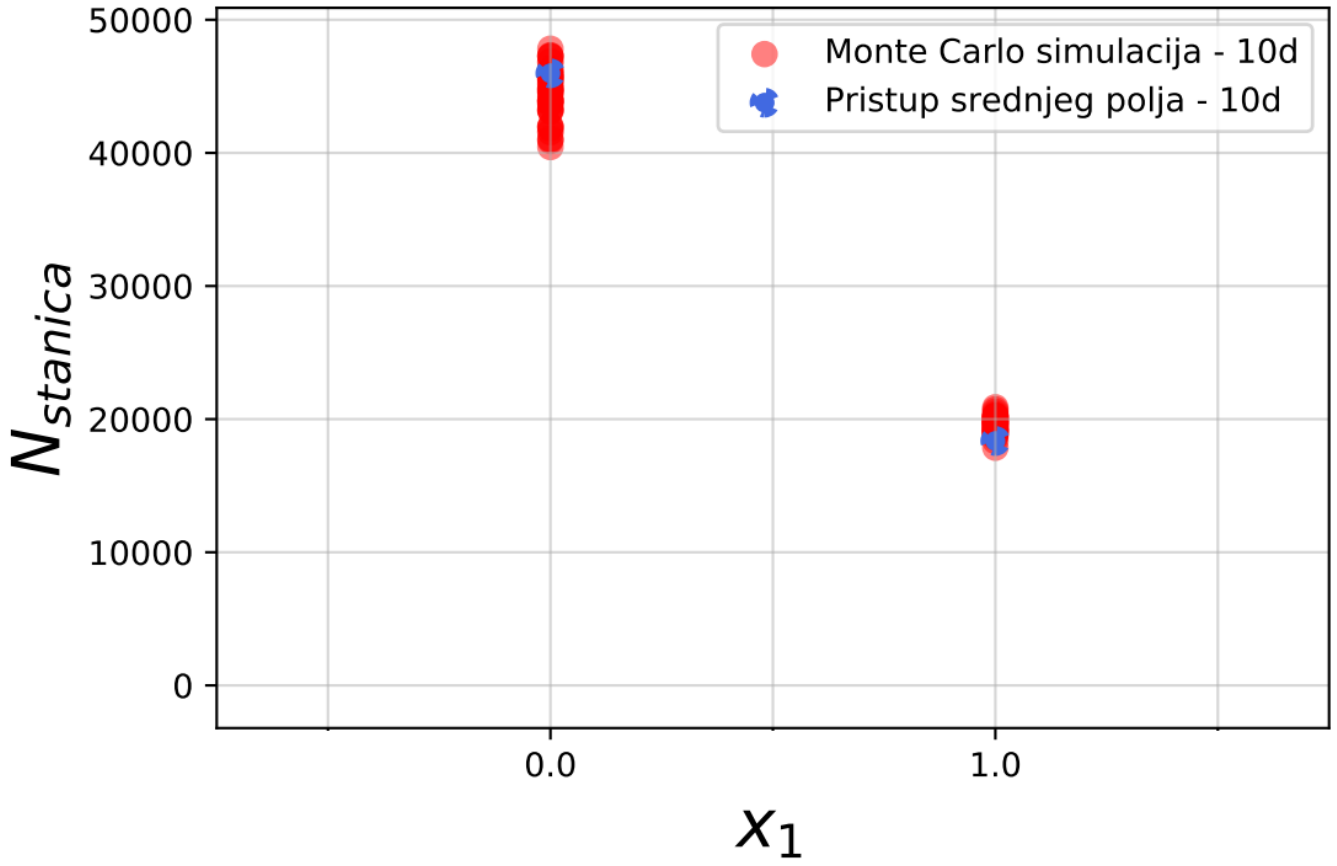
Tehnikalije

početno diploidna populacija



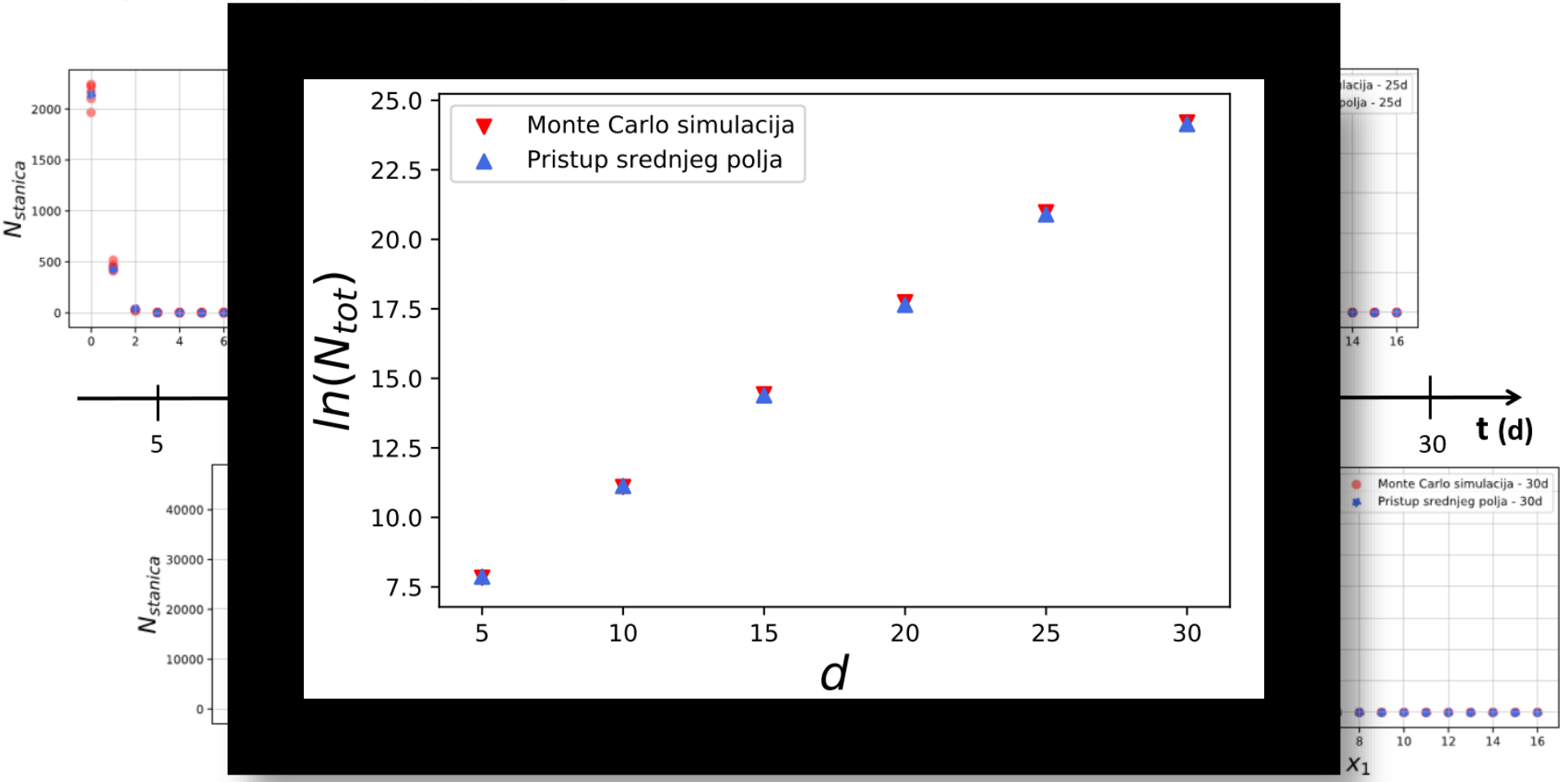
Tehnikalije

početno diploidna populacija, 50 ishoda



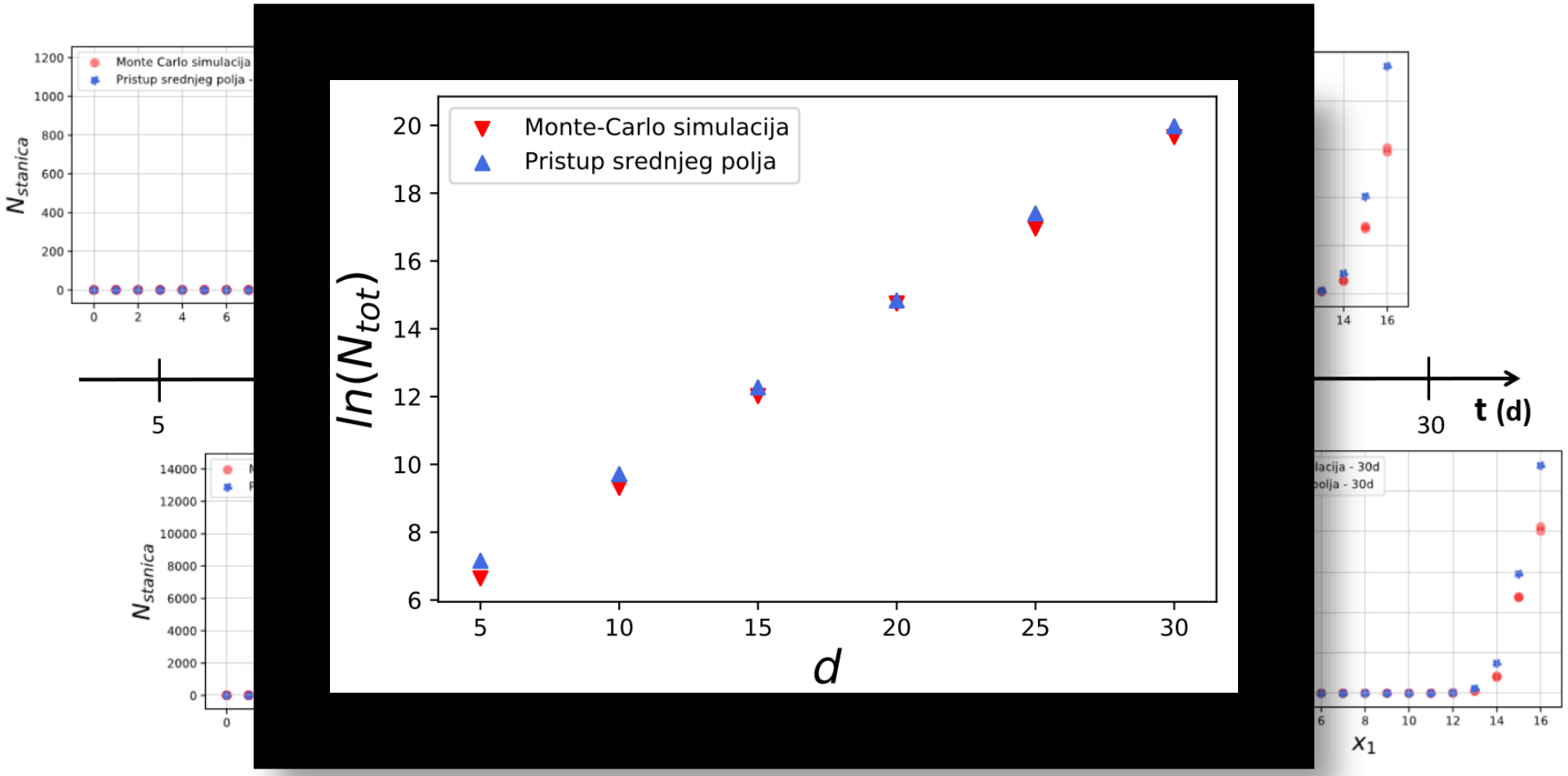
Tehnikalije

početno diploidna populacija



Tehnikalije

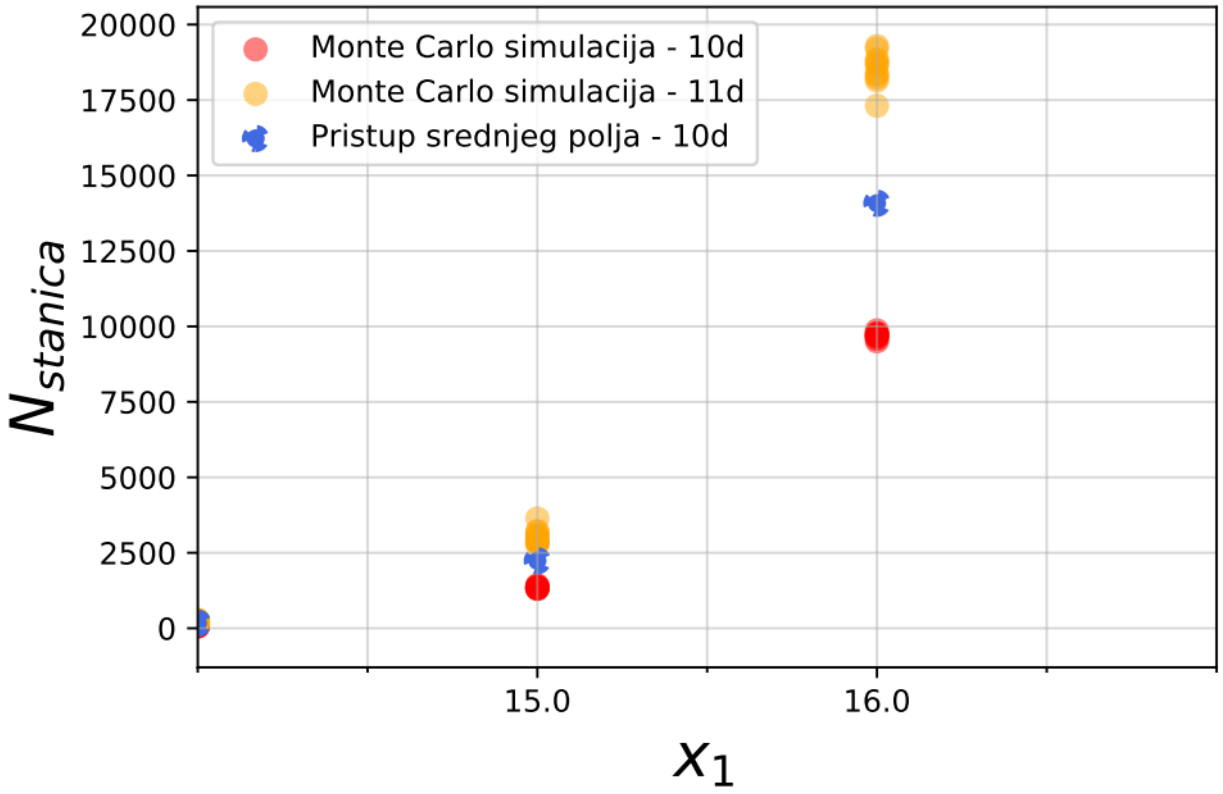
početno haploidna populacija



Tehnikalije

početno haploidna populacija

Broj stanica $N_{stanica}$ s obzirom na broj kromosoma s jednom kopijom x_1



Tehnikalije

10(10d)&10(11d) avg