Effects of tissue size regulation on somatic evolutionary processes in hierarchical tissues

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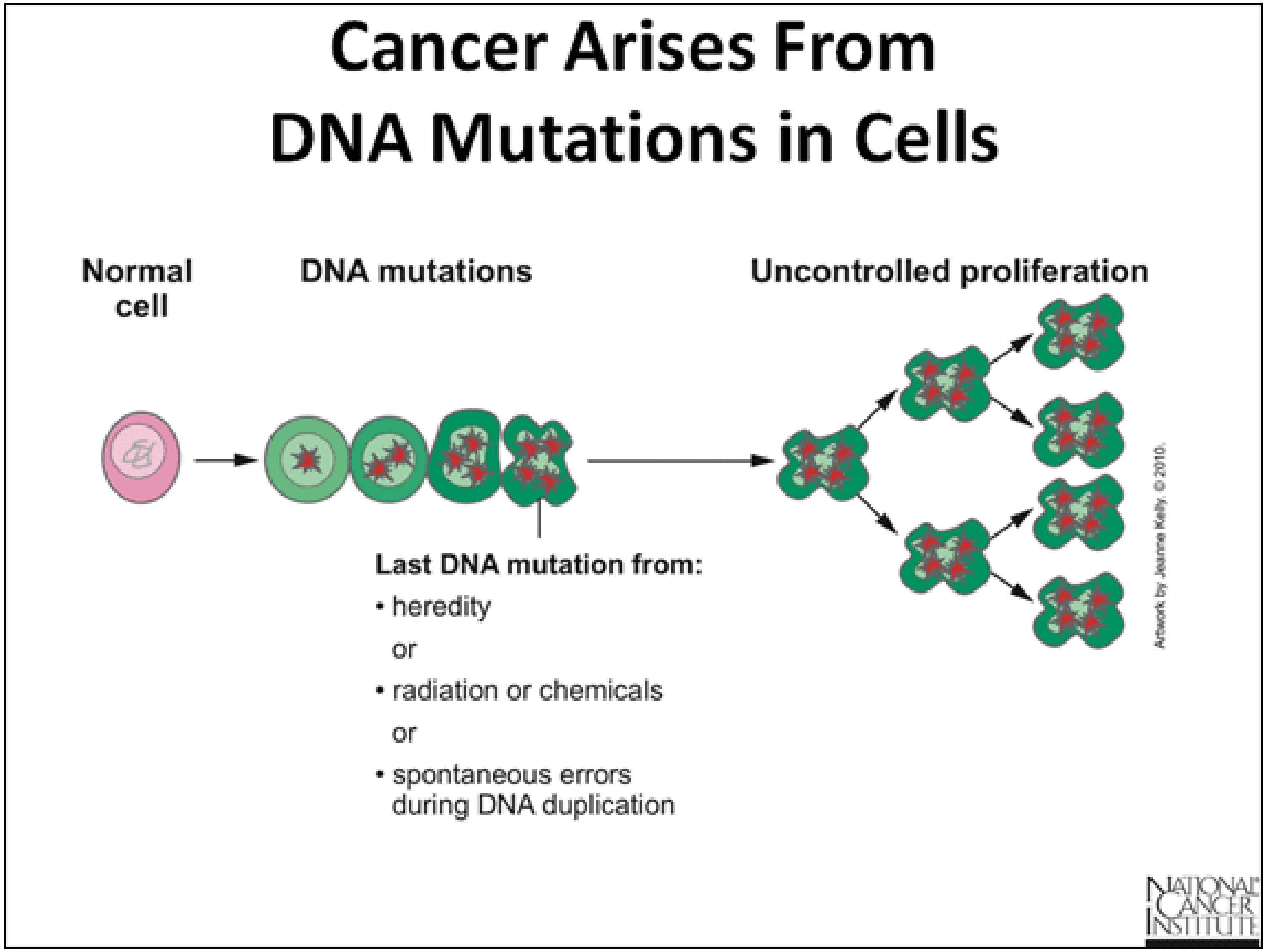
Motivation



Cancer Arises From
DNA Mutations in Cells
Normal cell
DNA mutations
Uncontrolled proliferation
Last DNA mutation from:
• heredity
or
• radiation or chemicals
or
• spontaneous errors during DNA duplication
Artwork by Jeanne Kelly. © 2010.
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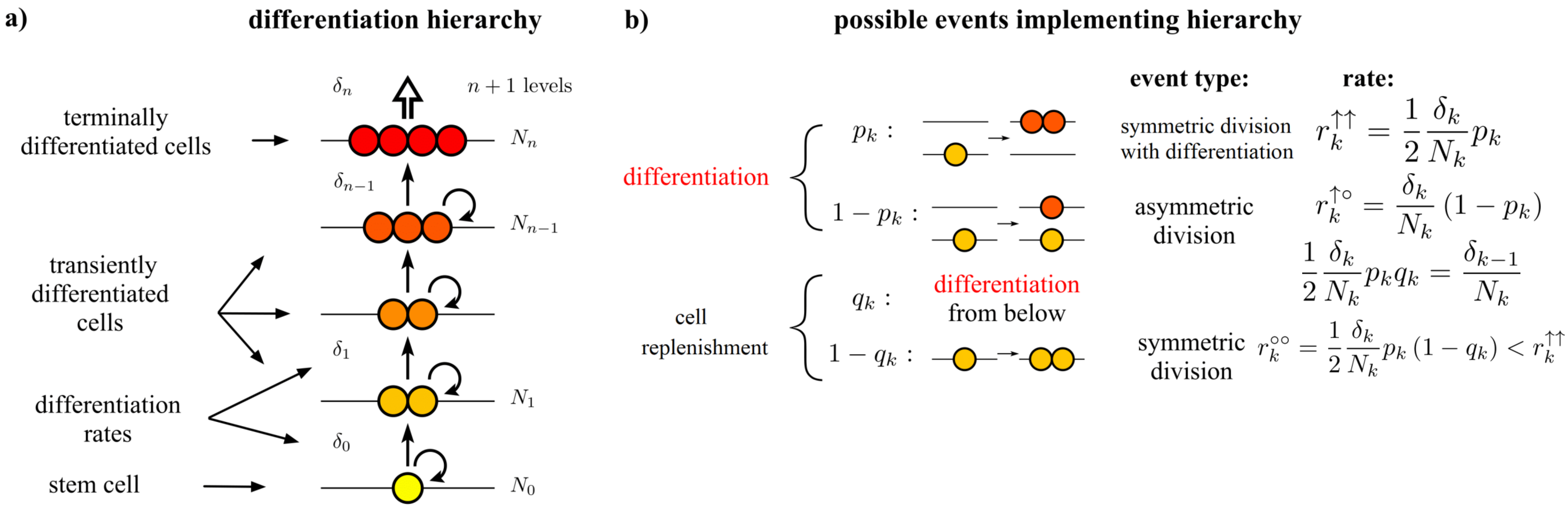
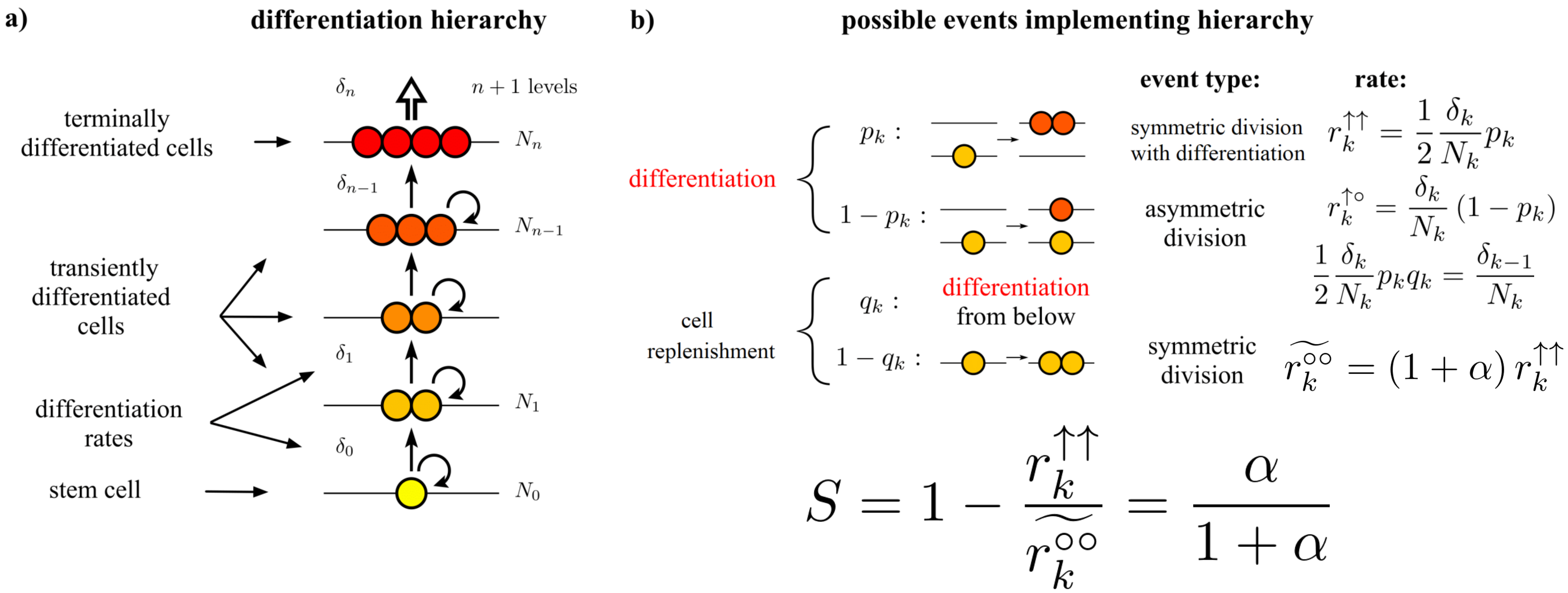
Hierarchical tissue model



source: Derenyi and Szollosi: Hierarchical tissue organization as a general mechanism to limit the accumulation of somatic mutations, Nature Communications, 2017

Hierarchical tissue model



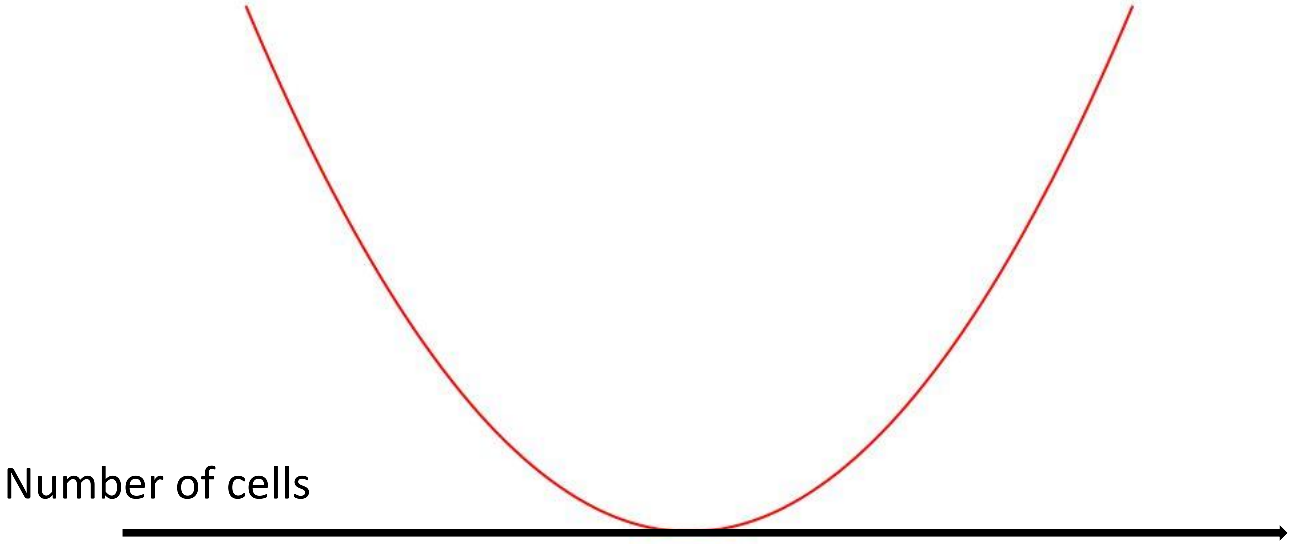
source: Derenyi and Szollosi: Hierarchical tissue organization as a general mechanism to limit the accumulation of somatic mutations, Nature Communications, 2017

Tissue size regulation

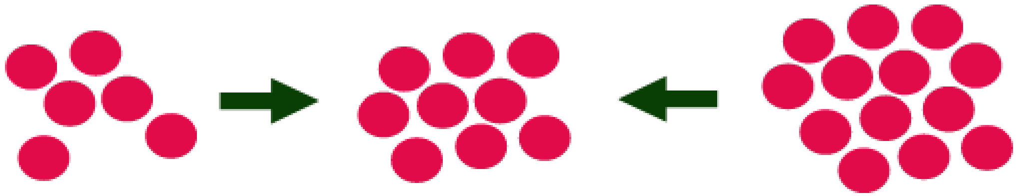
Confining potential: $\frac{1}{2}\beta\left(N_k(t) - N_k^0\right)^2$

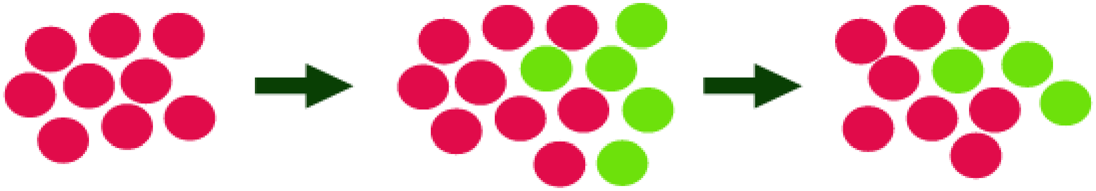
$+N_k$: $e^{\frac{-\beta}{2}\left(\frac{N_k(t)-N_k^0}{N_k^0}\right)}$

$-N_k$: $e^{\frac{+\beta}{2}\left(\frac{N_k(t)-N_k^0}{N_k^0}\right)}$



N_k^0





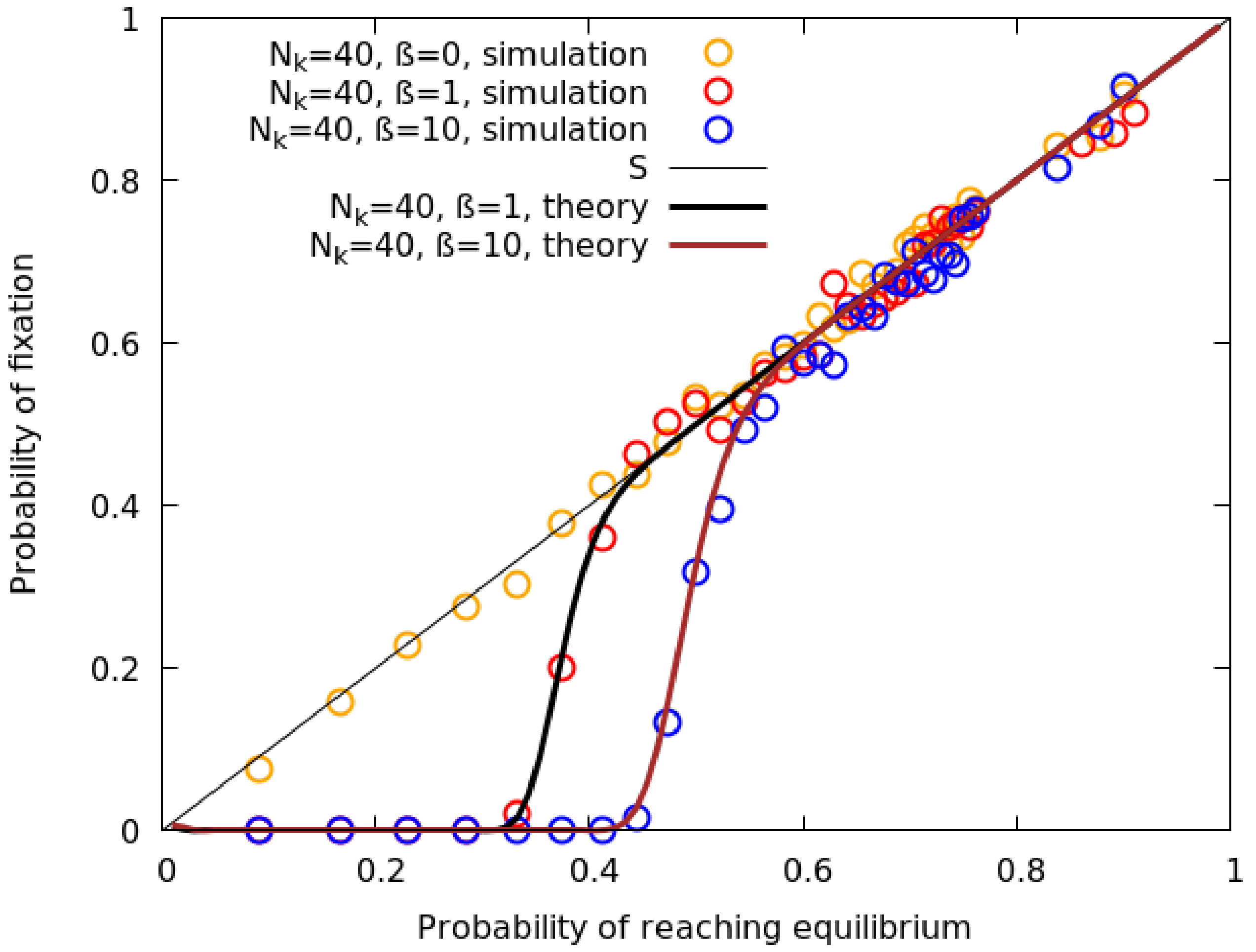
N_k^0 $N_k(eq)$

$$N_k(eq) = N_k^{wt}(eq) + N_k^{mt}(eq)$$

$$N_k^{wt}(eq) = N_k^0(1 - S)$$

$$N_k^{mt}(eq) = N_k^0\left(S + \frac{ln\left(\frac{1}{1-S}\right)}{\beta}\right)$$

Results

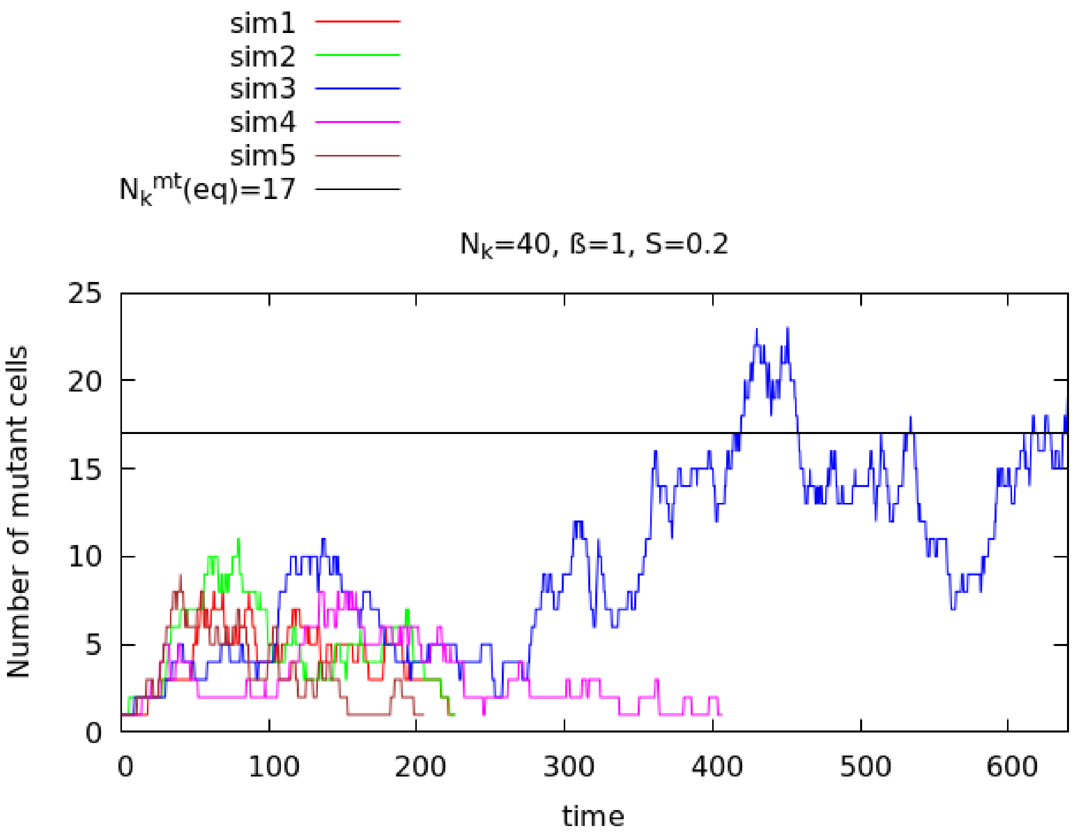


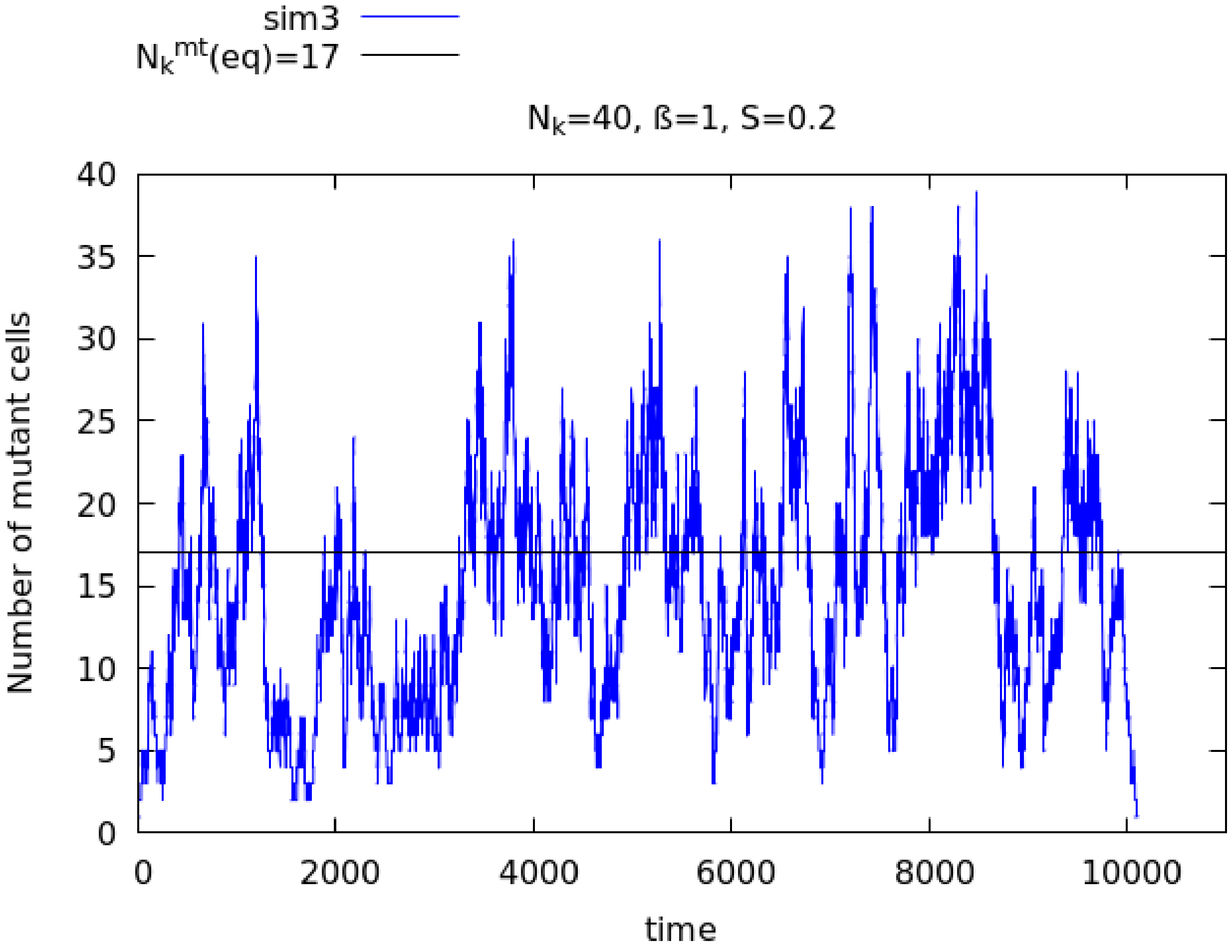
$$S = 1 - \frac{r_k^{\uparrow\uparrow}}{\widetilde{r_k^{\circ\circ}}} = \frac{\alpha}{1+\alpha}$$

$$\widetilde{r_k^{\circ\circ}} = (1+\alpha)\, r_k^{\uparrow\uparrow}$$

- Regulation leads to threshold in proliferation rate of mutant cells

Results





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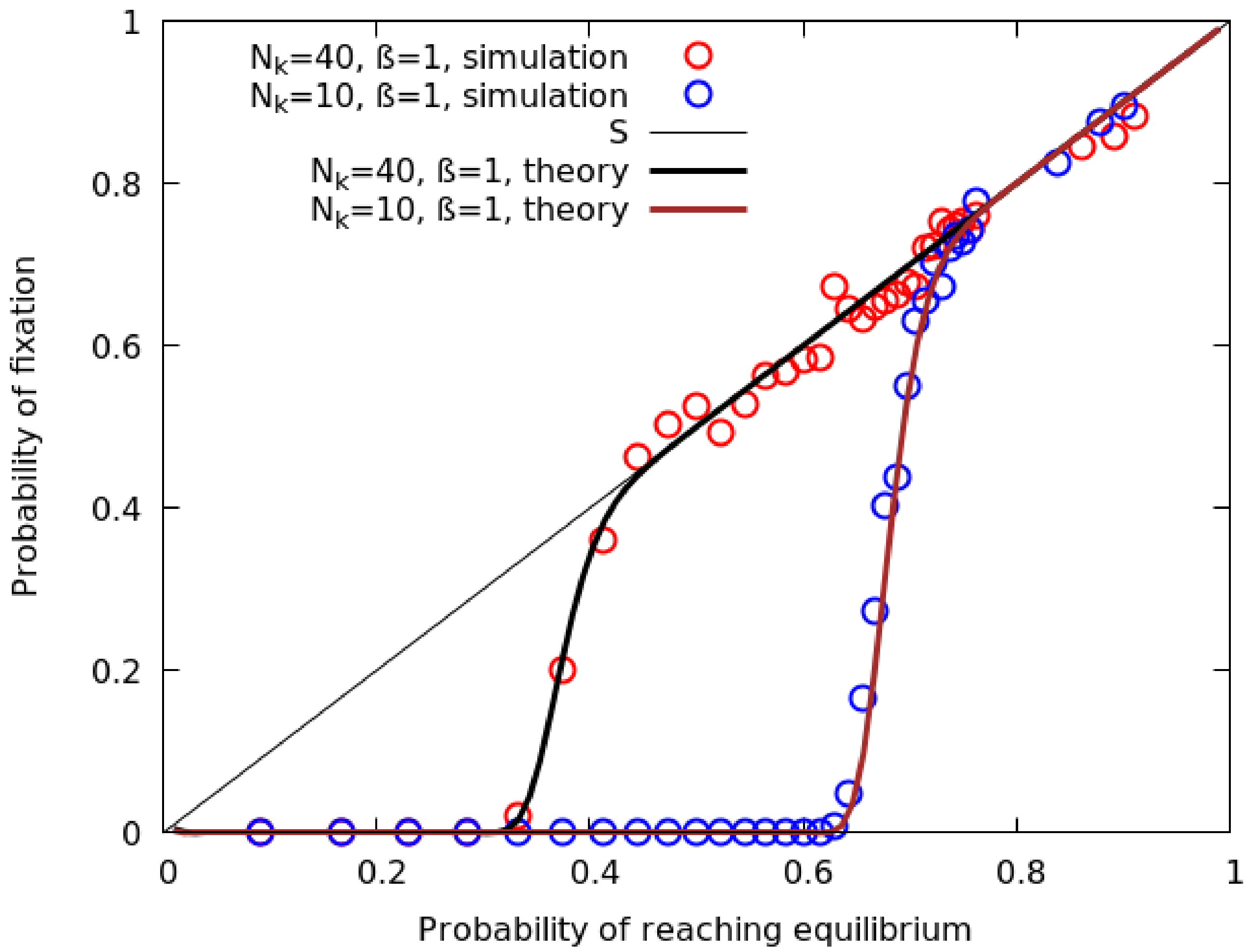

$$S = 1 - \frac{r_k^{\uparrow\uparrow}}{\widetilde{r_k^{\circ\circ}}} = \frac{\alpha}{1+\alpha}$$

- Smaller compartment size shifts this threshold to higher S values

$$\widetilde{r_k^{\circ\circ}} = (1+\alpha)\, r_k^{\uparrow\uparrow}$$

Summary

- Regulation leads to a threshold in proliferation rate
- The transition point depends on the strength of regulation, compartment size
- There is a stationary number of mutant and wild type cells which depends on the strength of regulation, compartment size and proliferative advantage
- Biological example: Colonic crypts are hierarchically organized, they have a relative small number of cells in a compartment
- In order to minimize the risk of cancer it is preferable to have smaller compartment size and a hierarchical organization

Thank you for the attention!

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