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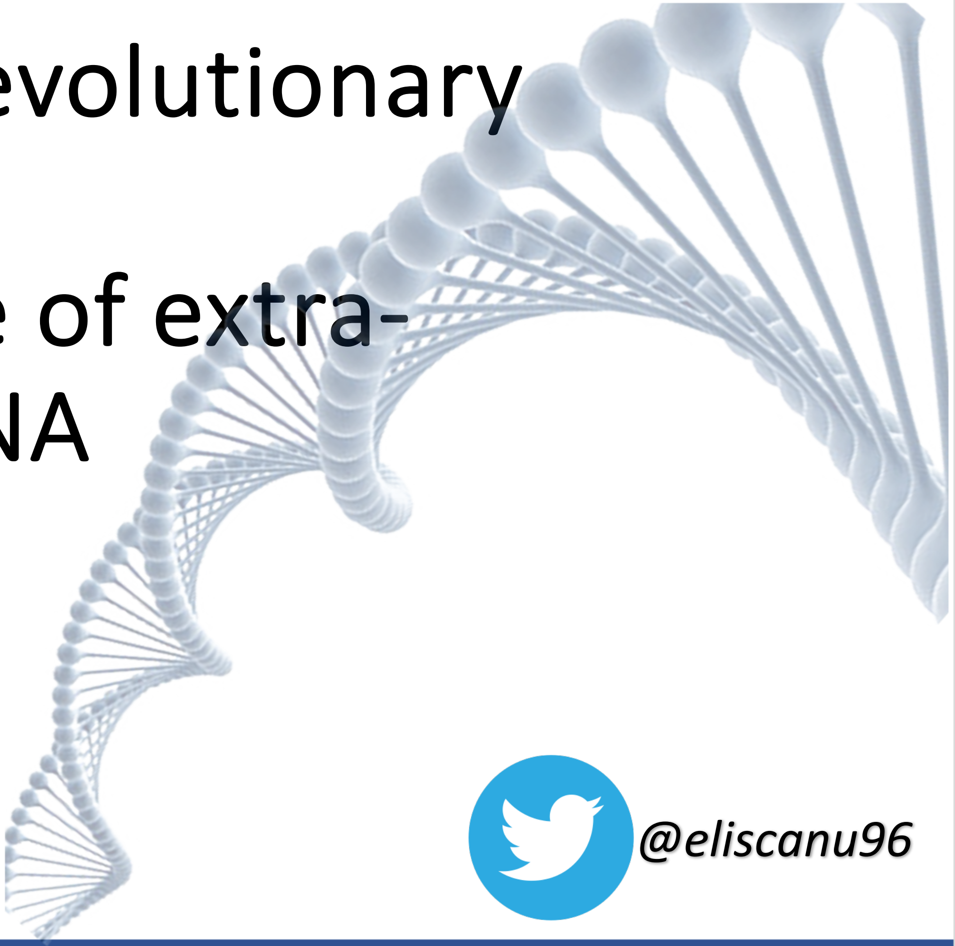

A mathematical model in evolutionary medicine: coordinated inheritance of extra-chromosomal DNA

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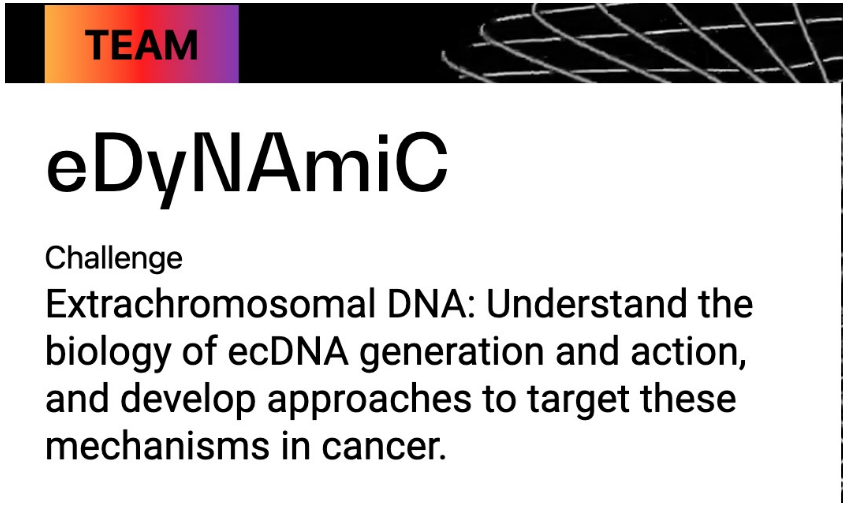
SMBE2023

@eliscanu96

Thanks to our multidisciplinary and worldwide team

INSTITUTIONS	LOCATIONS	FUNDED BY	SPECIALISMS
13	UK, US, Germany	Cancer Research UK, National Cancer Institute	cancer biology, genetics, chemistry, evolutionary biology, computer science, maths and clinical research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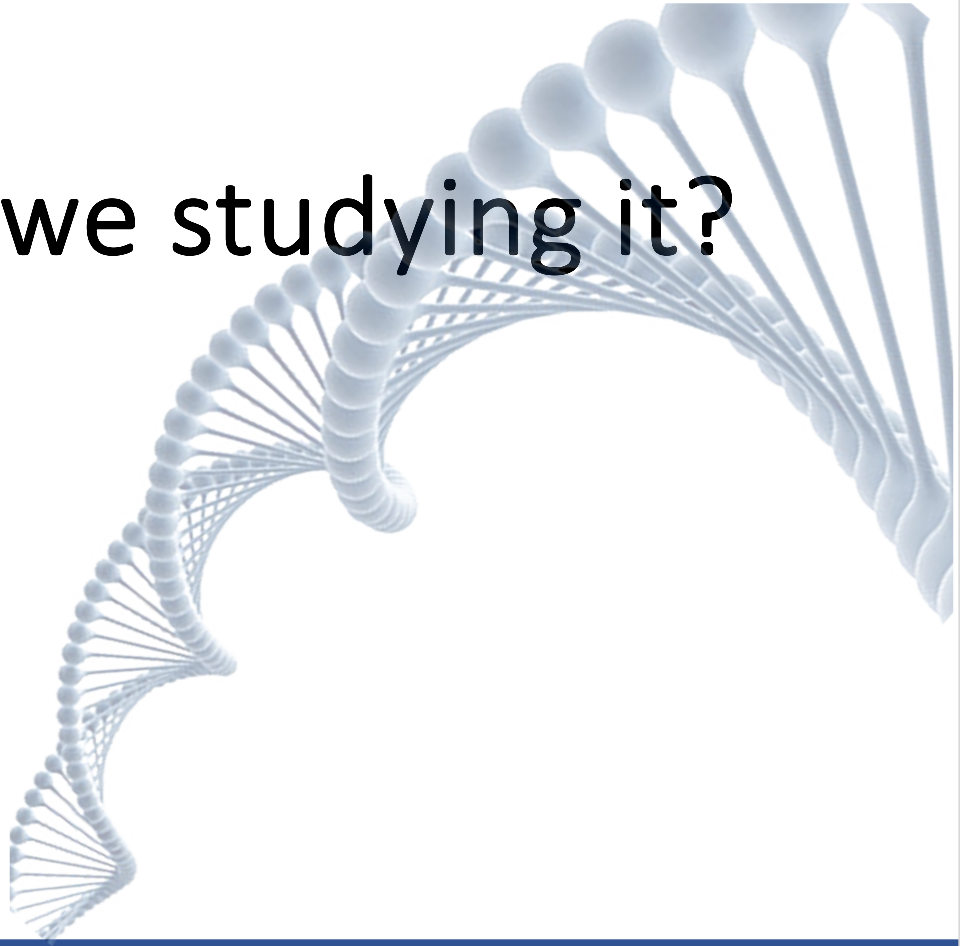
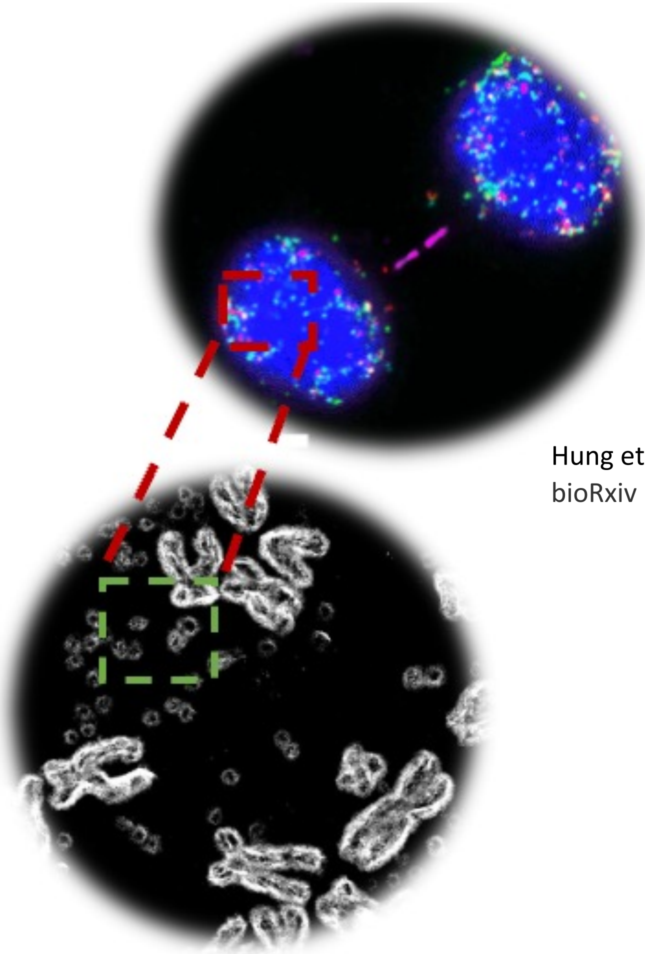
Challenge

Extrachromosomal DNA: Understand the biology of ecDNA generation and action, and develop approaches to target these mechanisms in cancer.

What is ecDNA and why are we studying it?



An abnormal genomic structure…


Hung et al.,
bioRxiv 2023.07.18.549597

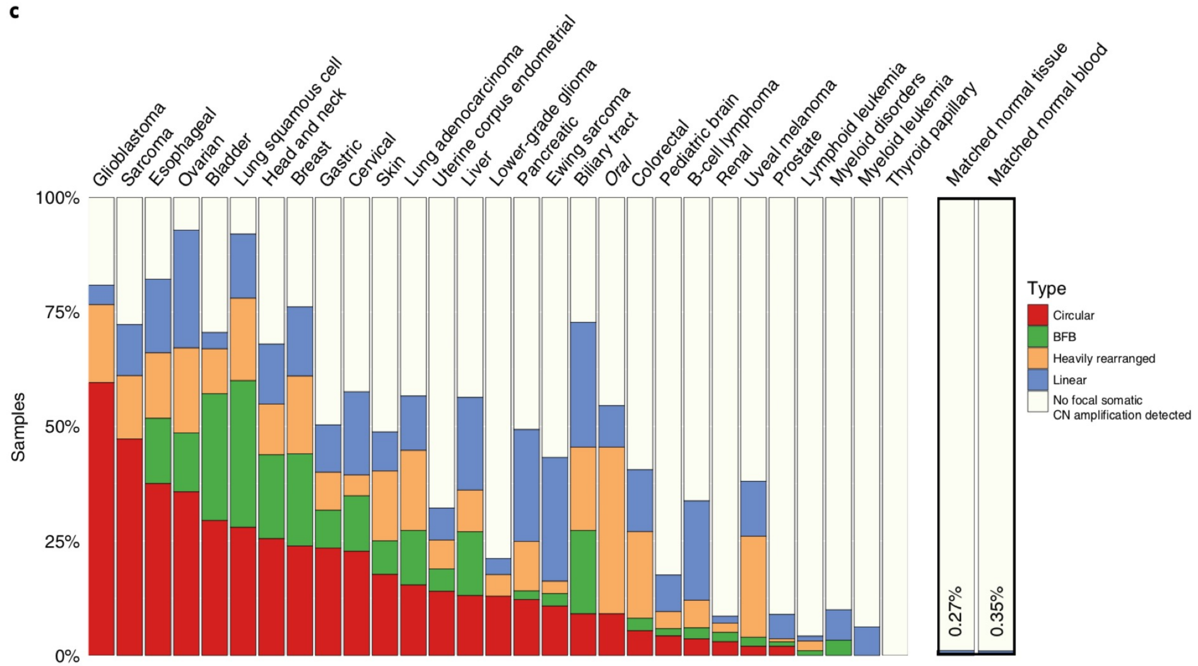
Mishel et al., Nature, 2019

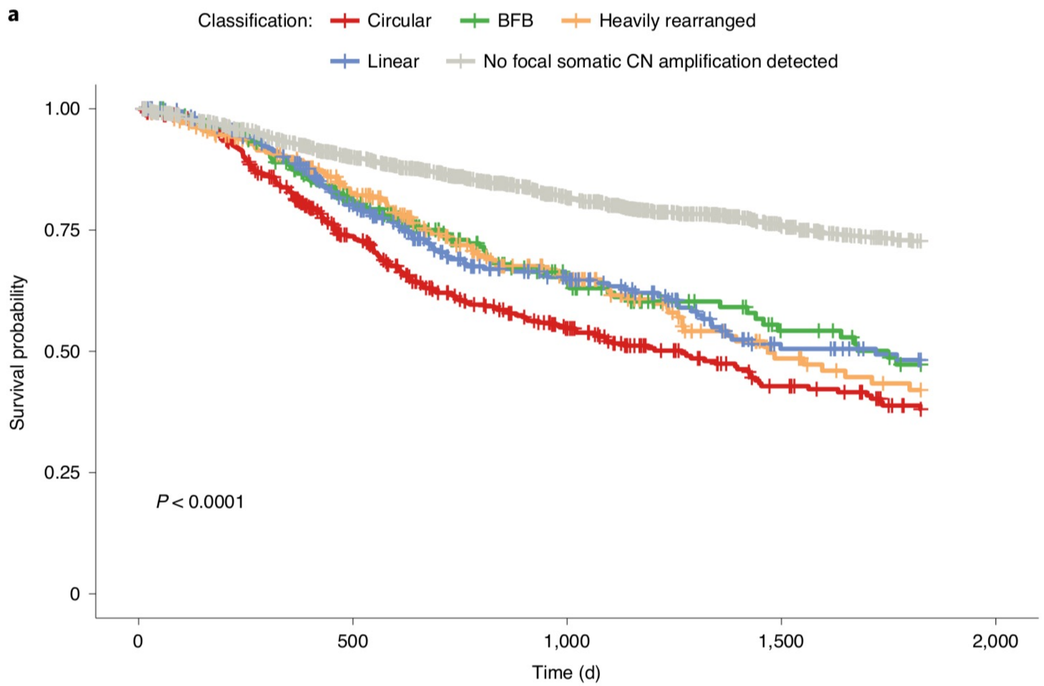
ecDNA: extra chromosomal DNA

↓

collective term that includes abnormal portions of genomic structures released outside the chromosomes

…that promotes tumorigenesis…

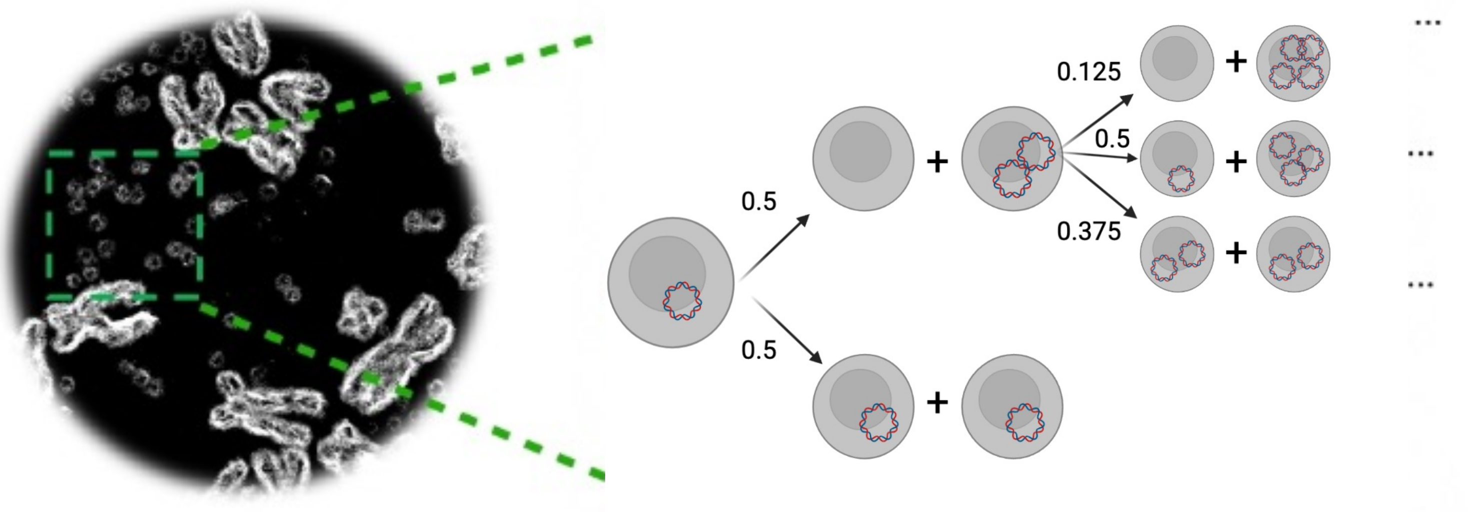




ecDNA is present in many types of tumours and leads to significantly shorter survival for patients

- Yi E, et al., Extrachromosomal DNA amplifications in cancer (2022).
- Kim H, et al., Extrachromosomal DNA is associated with oncogene amplification and poor outcome across multiple cancers (2020).

…and segregates unevenly into daughter cells

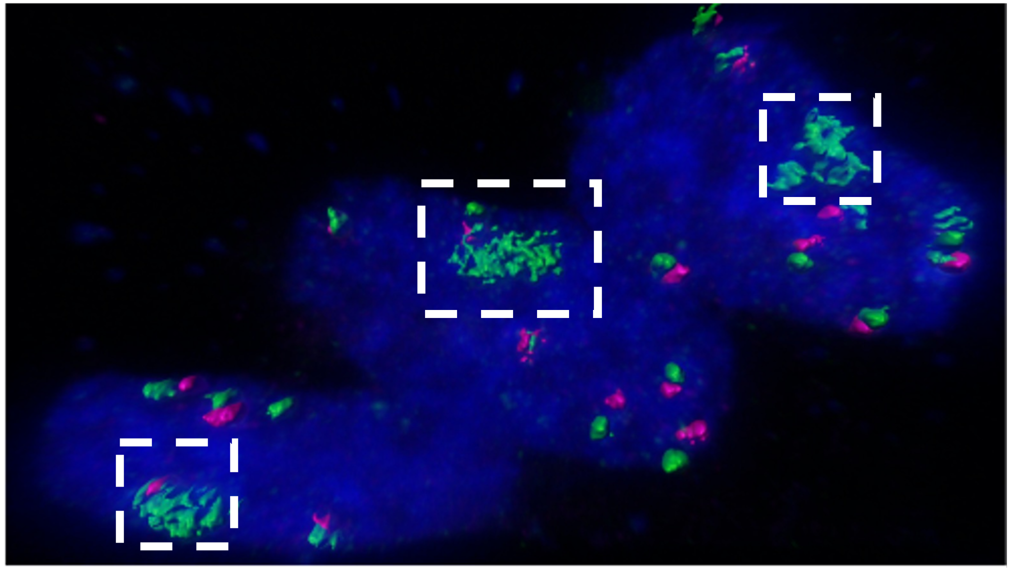


Copy number heterogeneity

→ Faster changes to the DNA contents of cells and adaptation to metabolic stress and drug treatment

- Lange JT, et al., Principles of ecDNA random inheritance drive rapid genome change and therapy resistance in human cancers (2021).
- Lange JT et al., The evolutionary dynamics of extrachromosomal DNA in human cancer cells (2022).

Coordinated inheritance of multiple ecDNA types

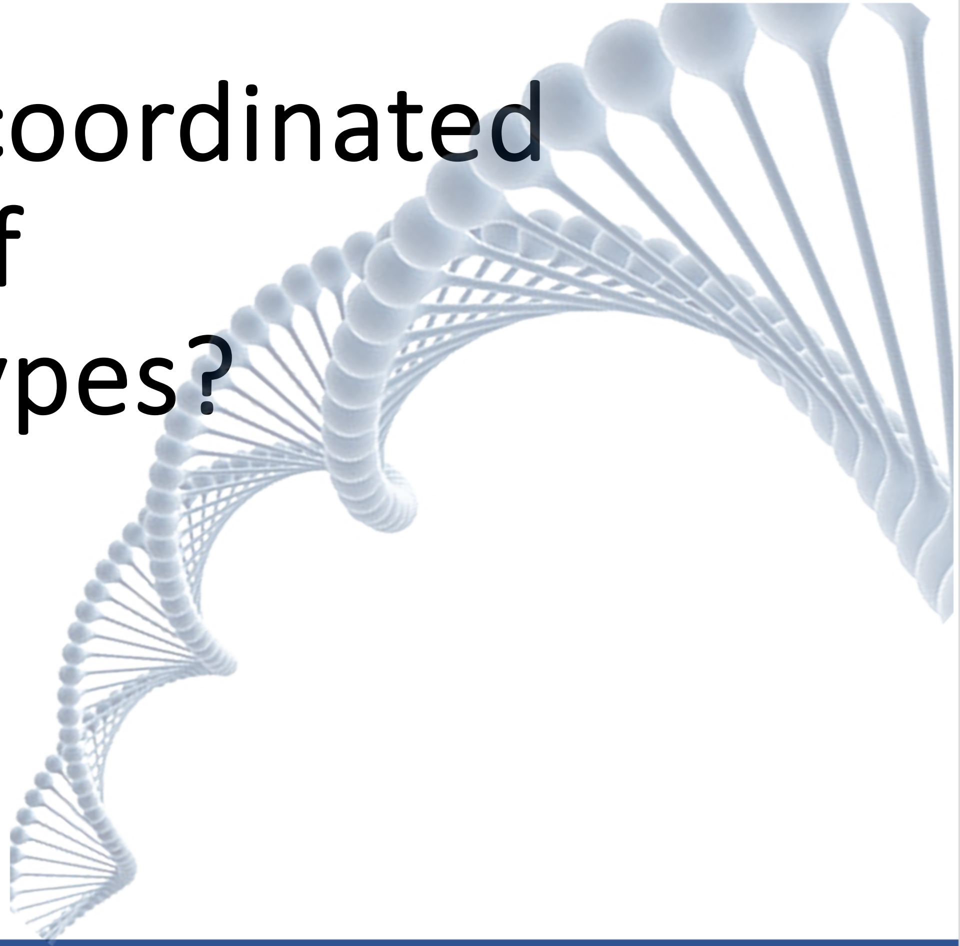


- Multiple ecDNAs can co-exist in the same cancer cells and congregate in micron-sized hubs in the nucleus

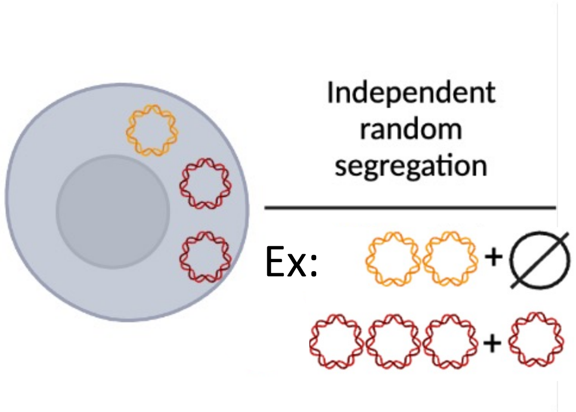
→ Enabling gene activation and mutual enhancing

Hung, K. L. et al. ecDNA hubs drive cooperative intermolecular oncogene expression. Nature 600, 731–736 (2021).

How can we model the coordinated inheritance of multiple ecDNA types?



Modeling ecDNA hubs and cumulative selection advantage



- Two ecDNA species: **orange** and **red**

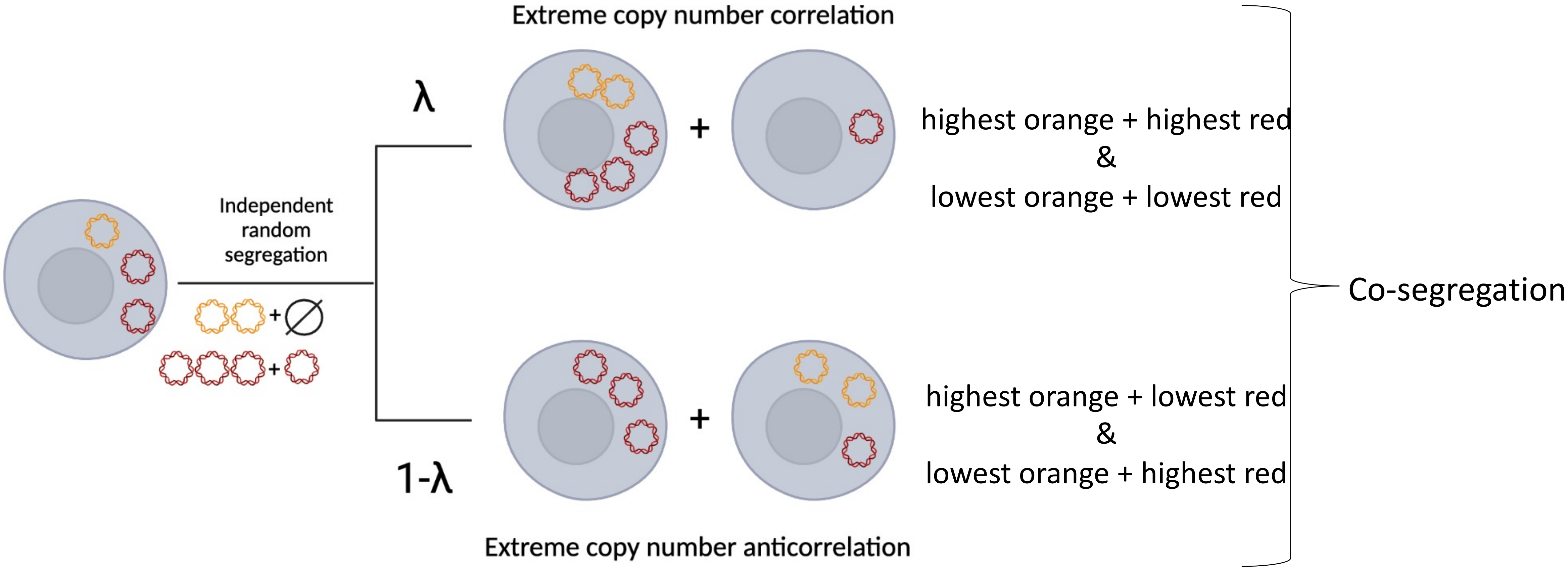
- Independent random segregation following binomial distribution:

$$n_1 \sim Binomial\left(2N, \frac{1}{2}\right)$$
$$n_2 = 2N - n_1$$

- Division time depending on selection, modelled by coefficient $s_o,\ s_r$

Hung et al., bioRxiv 2023.07.18.549597

Modeling ecDNA hubs and cumulative selection advantage



Independent random segregation

Extreme copy number correlation

λ

highest orange + highest red
&
lowest orange + lowest red

$1-\lambda$

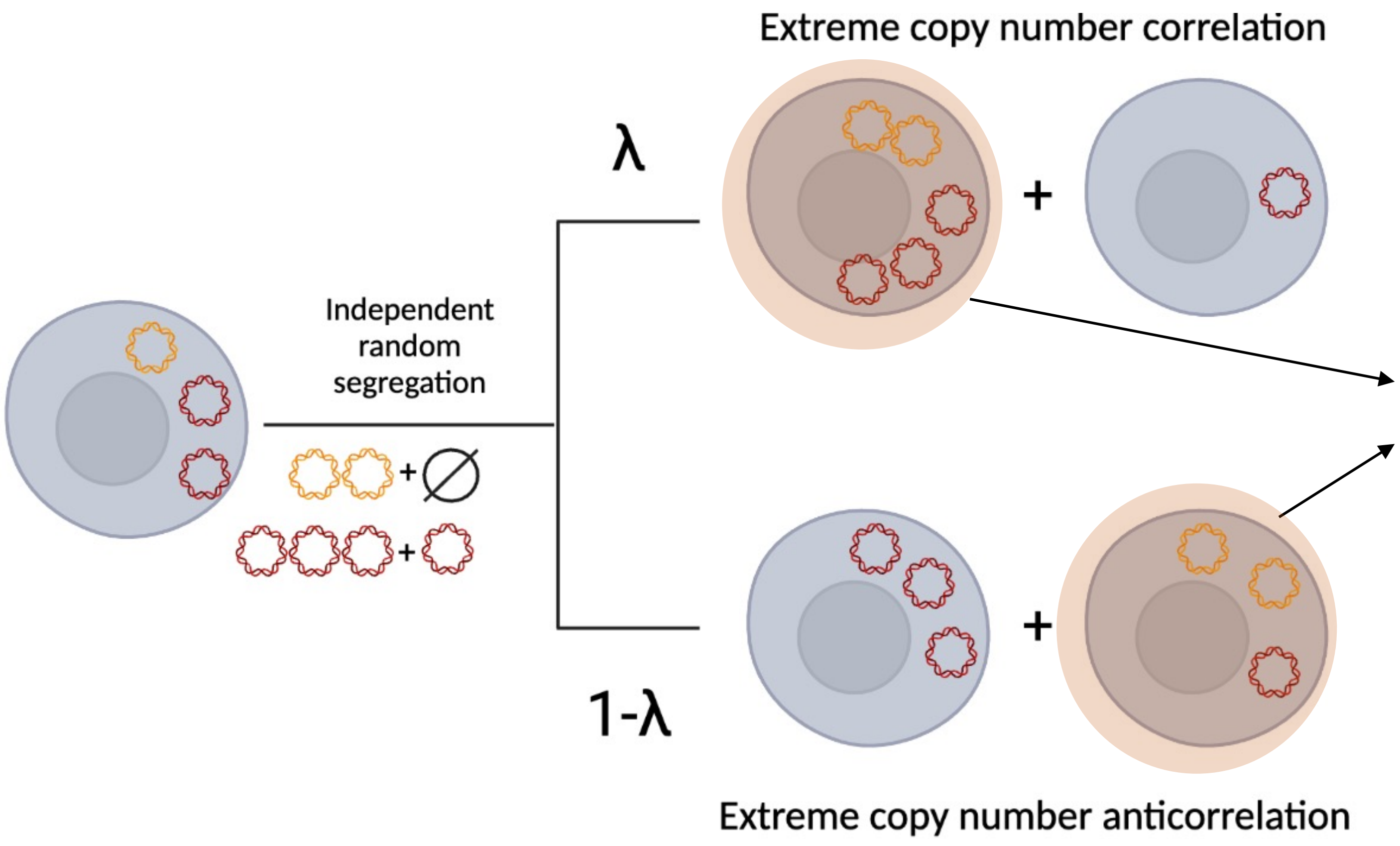
Extreme copy number anticorrelation

highest orange + lowest red
&
lowest orange + highest red

Co-segregation

Hung et al., bioRxiv 2023.07.18.549597

Modeling ecDNA hubs and cumulative selection advantage



Extreme copy number correlation

λ

Independent random segregation

1-λ

Extreme copy number anticorrelation

Co-selection:
carrying both ecDNA types leads to higher reproduction rate

$$s_c = s_o + s_r \cdot c, \qquad c \in [0,1]$$

Hung et al., bioRxiv 2023.07.18.549597

Modeling ecDNA hubs and cumulative selection advantage

------------------------------ ecDNA evolution parameters ------------------------------

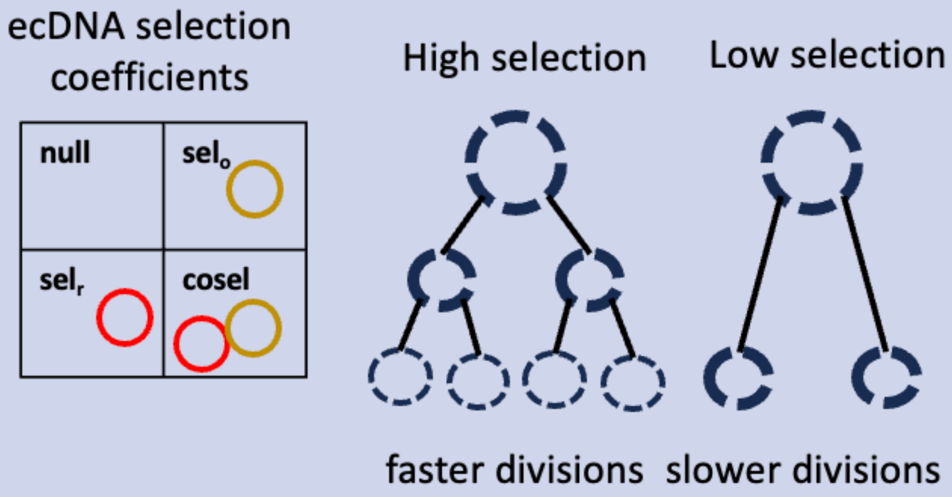
Co-segregation λ

1 Perfectly correlated

0.5 Independent segregation

0 Perfectly anticorrelated

Co-selection c

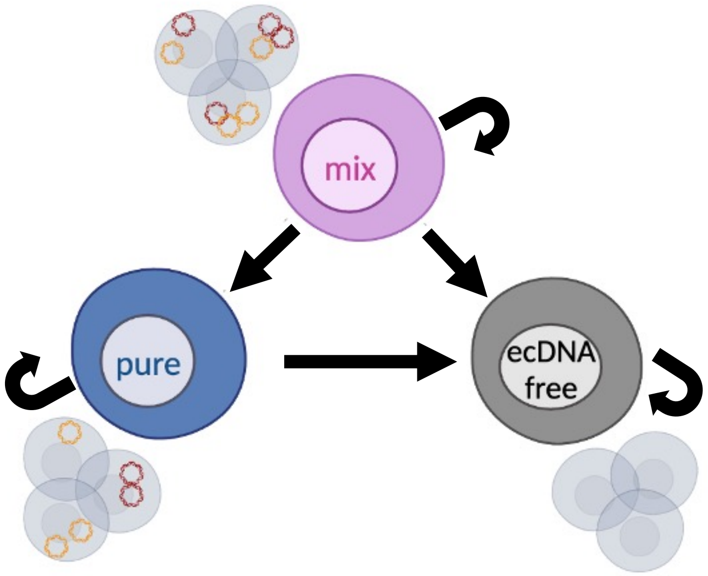


Hung et al., bioRxiv 2023.07.18.549597

Mathematical description

Differential equations describing stochastic dynamics of different subpopulations, summarised as:

→ Random segregation



Mathematical description

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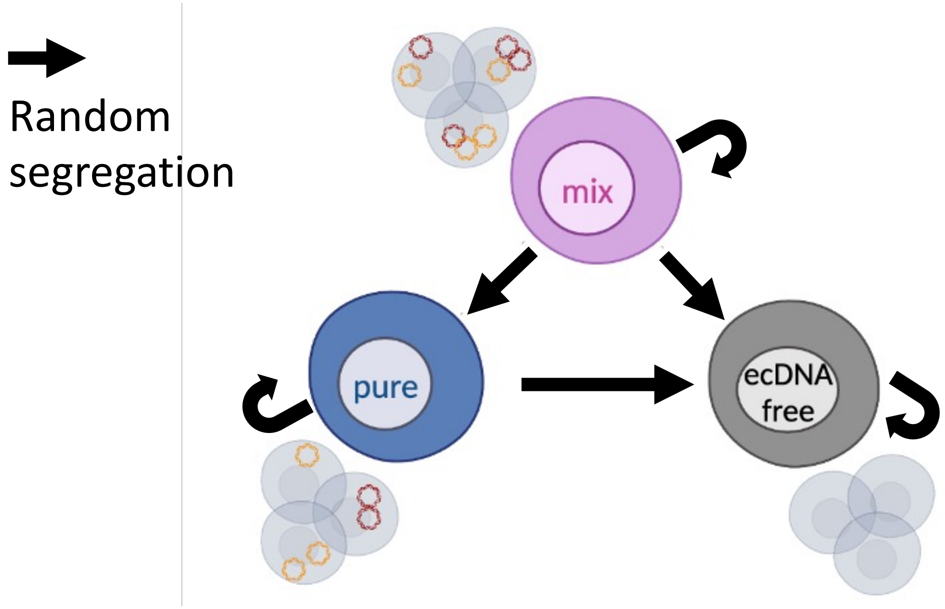
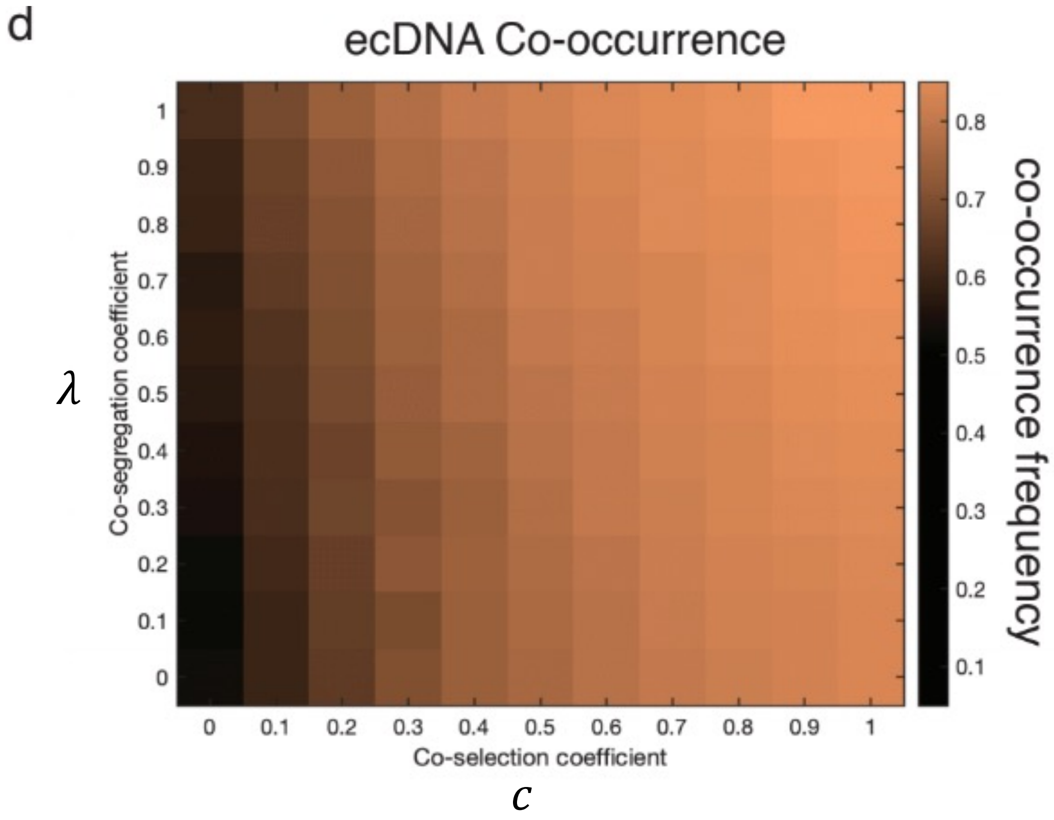


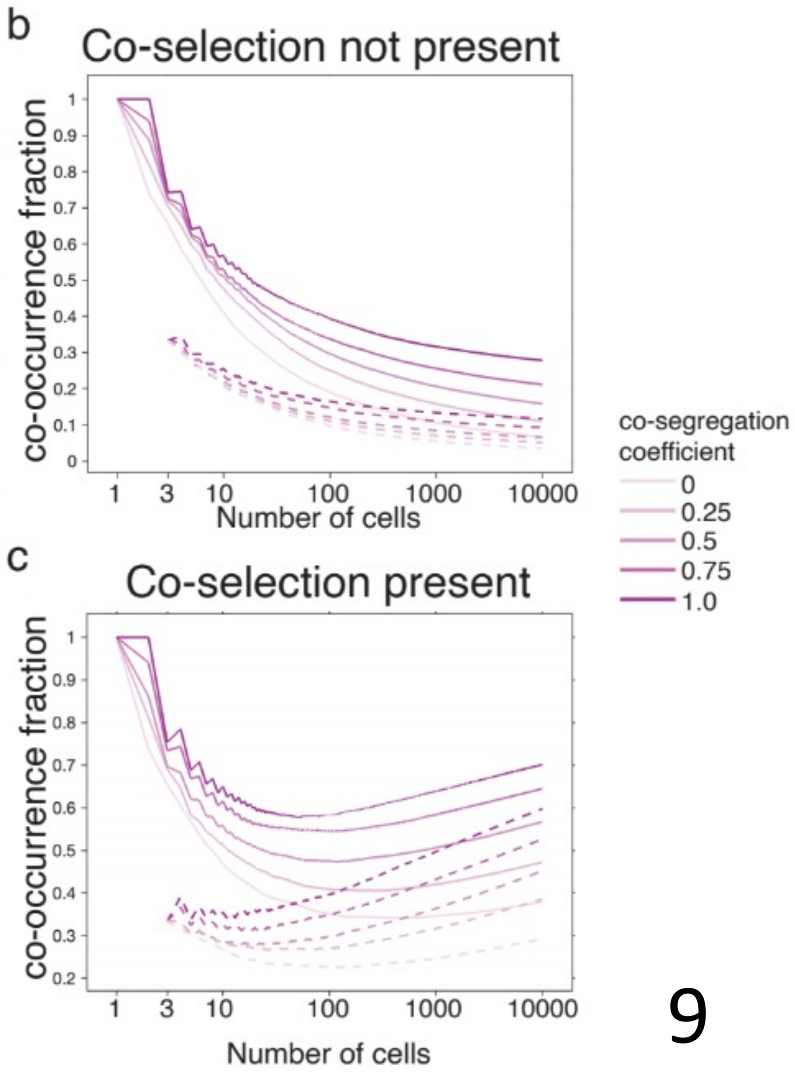
→ Random segregation

Is there the possibility to maintain a stable subpopulation of mix cells (coordinated inheritance) over time by modulating co-segregation and co-selection?

Main results

Studying the **co-occurrence** as function of co-selection and co-segregation





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Main results

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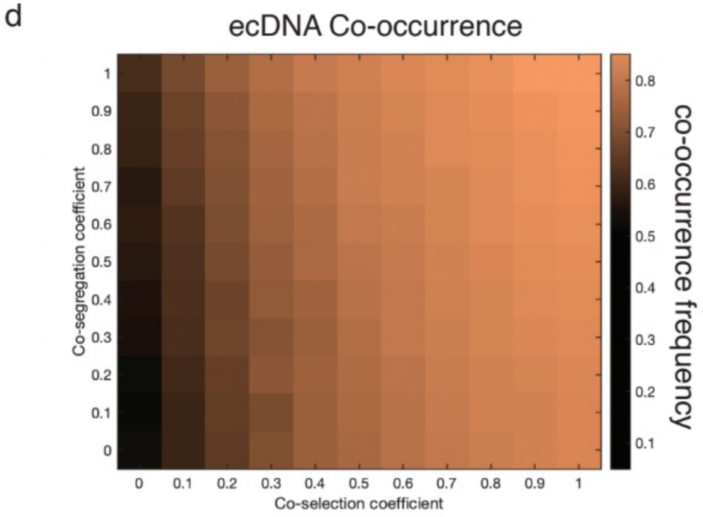
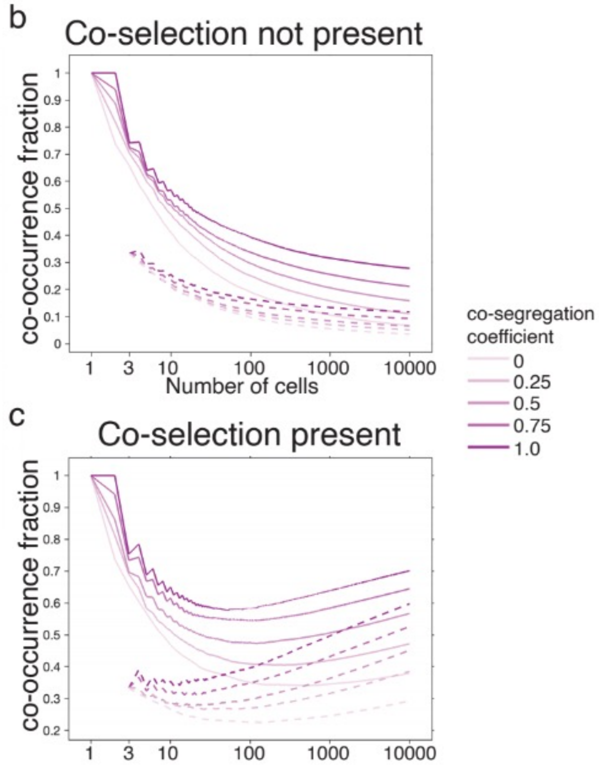


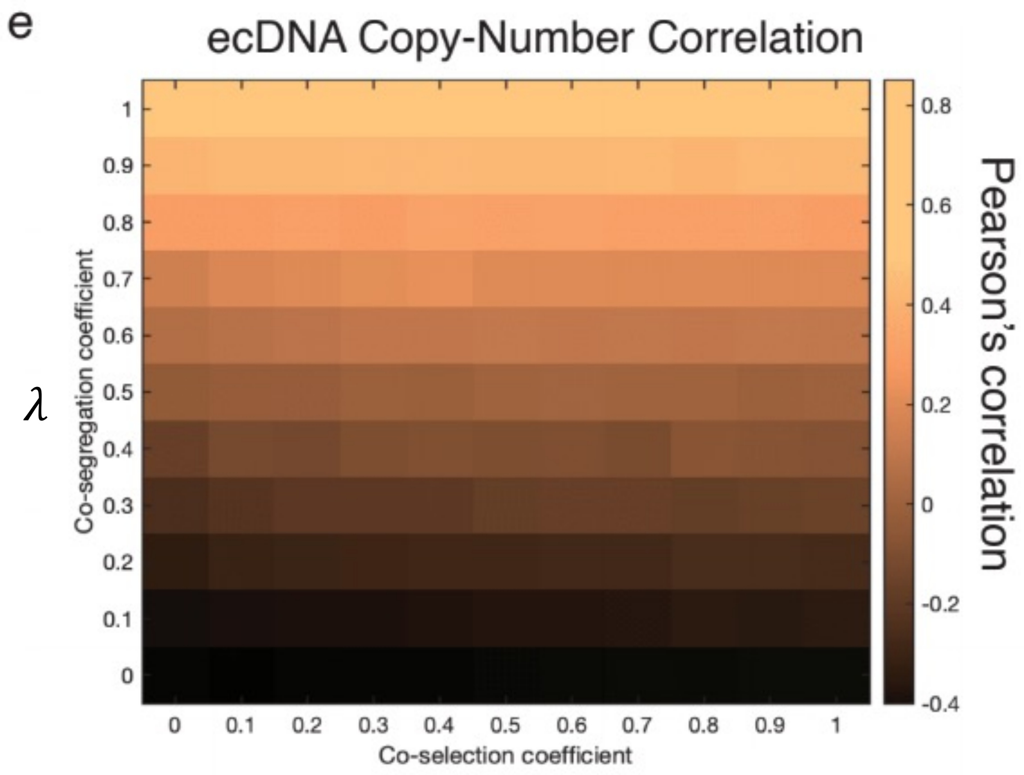


Co-selection is crucial for the maintenance of co-occurrence

Hung et al., bioRxiv 2023.07.18.549597

Main results

Studying the **copy number correlation** as function of co-selection and co-segregation



λ

c

$$\rho = \frac{\sum_{i=1}^{N}(n_o(i)-\mu_o)(n_r(i)-\mu_r)}{(N-1)\sigma_o\sigma_r} \in [-1,1]$$

Hung et al., bioRxiv 2023.07.18.549597

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Main results

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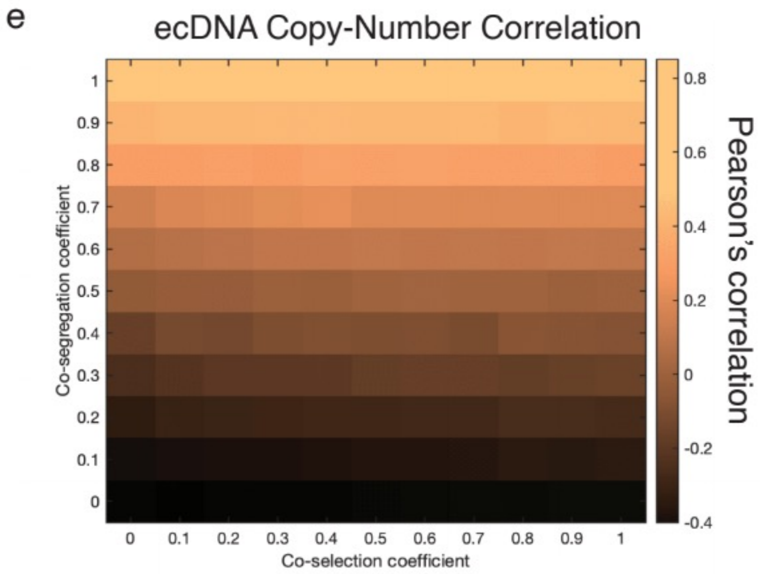

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Co-segregation is crucial for the copy number correlation

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Scan it to check out our paper!

Thanks for your attention!

Evolutionary Theory Research Group

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