QMUL EVOLUTIONARY THEORY TEAM
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Coordinated inheritance of extra-chromosomal DNA species in human cancer cells

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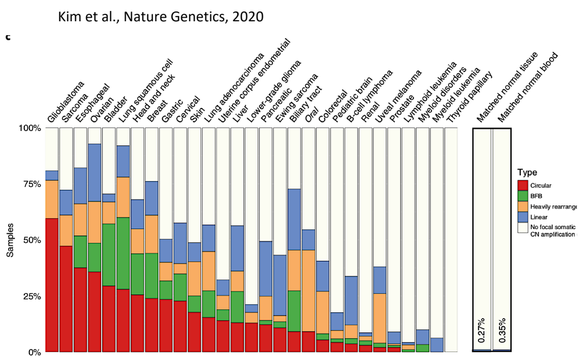
BIOLOGICAL CONTEXT

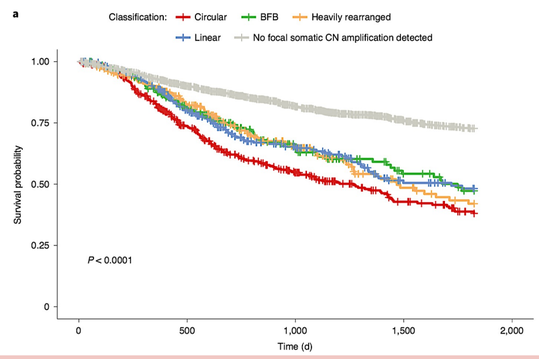
extra-**c**hromosomal **DNA**: a collective term that includes abnormal portions of genomic structures released outside the chromosomes

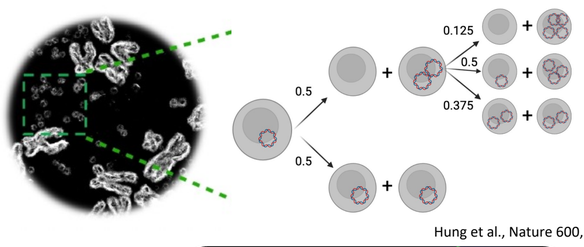
Why are we studying it?

- promotion of **tumorigenesis** and **poor prognosis**
- **random segregation** into daughter cells → copy number heterogeneity, meaning fast changes in the DNA content and **rapid adaptation to drug treatment**

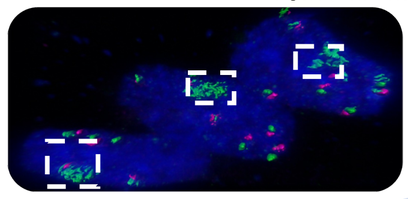
Kim et al., Nature Genetics, 2020







Hung et al., Nature 600, 2021



Why are we studying multiple ecDNA types?

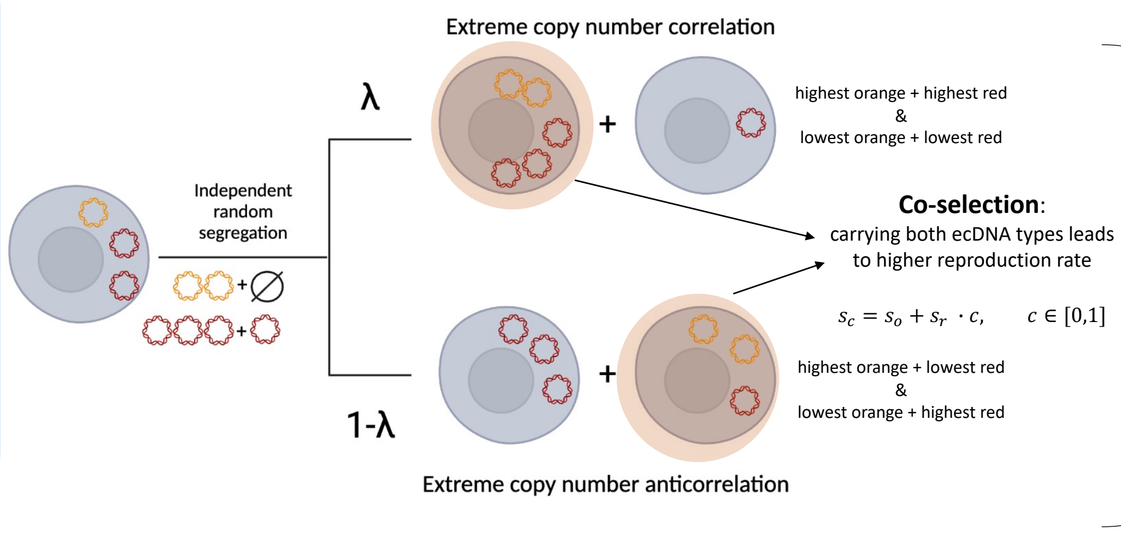
Multiple ecDNAs can co-exist in the same cancer cells and congregate in micron-sized hubs, , enabling gene activation and mutual enhancing

THE MODEL

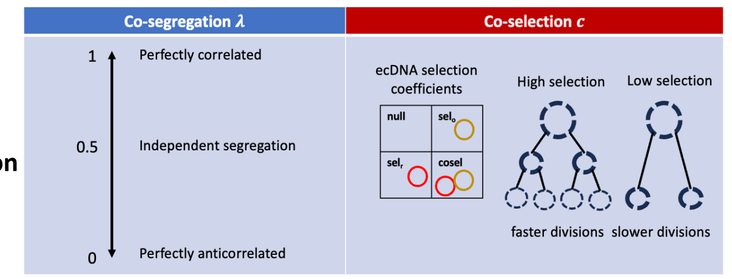
- Two ecDNA species: **orange** and **red**
- Independent random segregation following binomial distribution:

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

- Division time depending on selection, modelled by coefficients s_o, s_r



ecDNA evolution parameters

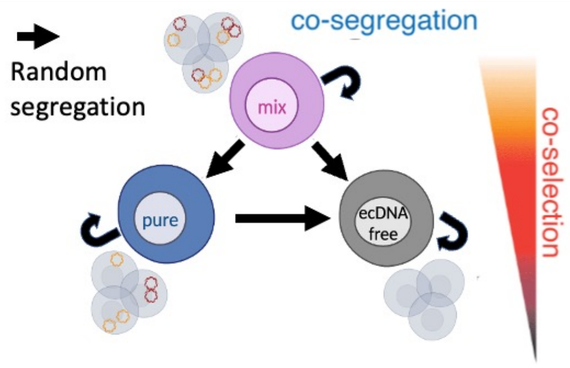


Hung et al., bioRxiv 2023.07.18.549597

MATHEMATICAL DESCRIPTION

System of differential equations describing the stochastic dynamics of different subpopulations over time:

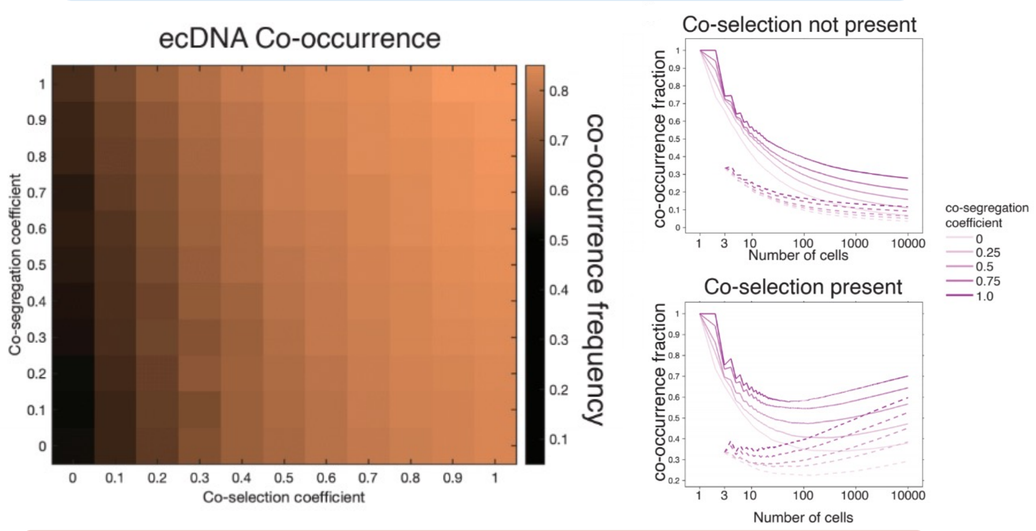
$C_{i,k}(t)$ = number of cells with i orange and k red ecDNA copies at time t



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

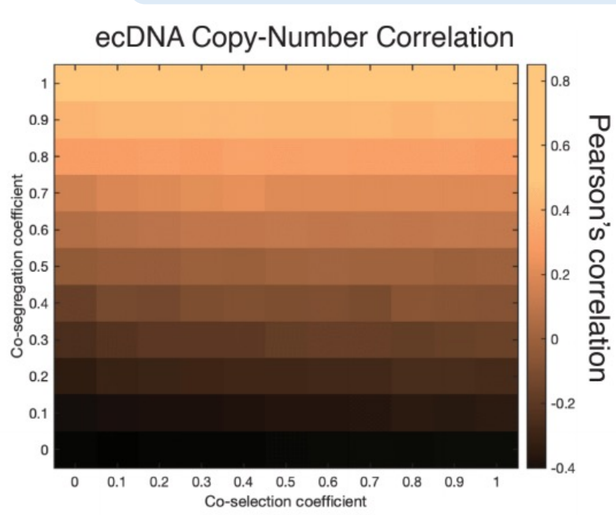
RESULTS

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



Co-segregation crucial for co-occurrence maintenance

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



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

Co-segregation crucial for co-occurrence maintenance

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