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Science and Engineering

Maths

Barts Cancer Institute

TEAM

eDyNAmiC

Population dynamics of multiple extra-chromosomal DNA types

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ECMTB 2024

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Zixuan Yang

An abnormal genomic structure…

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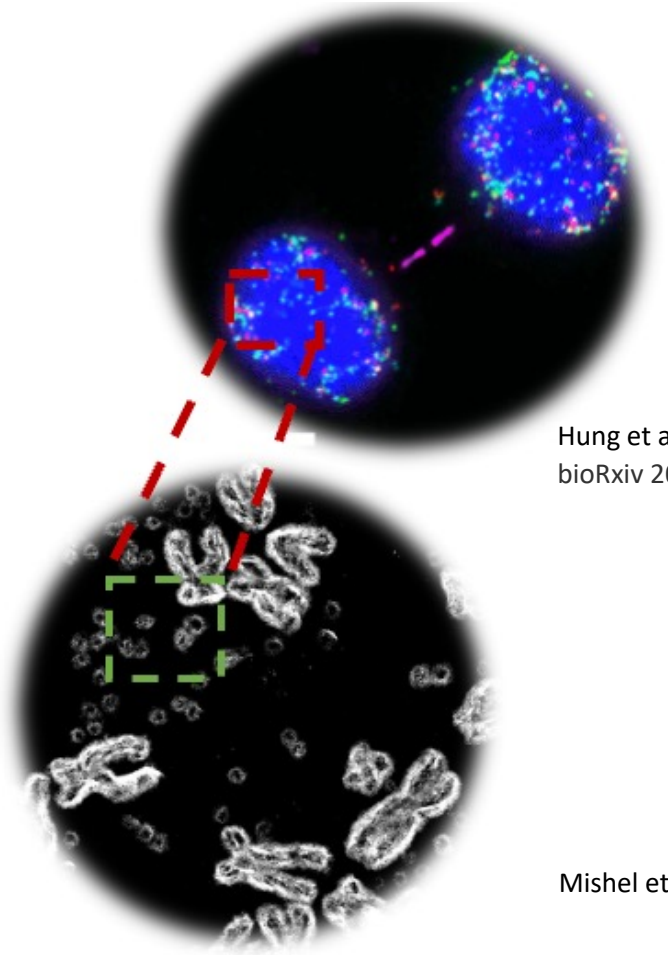

Hung et al.,
bioRxiv 2023.07.18.549597

Mishel et al., Nature, 2019

ecDNA: extra chromosomal DNA

↓

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

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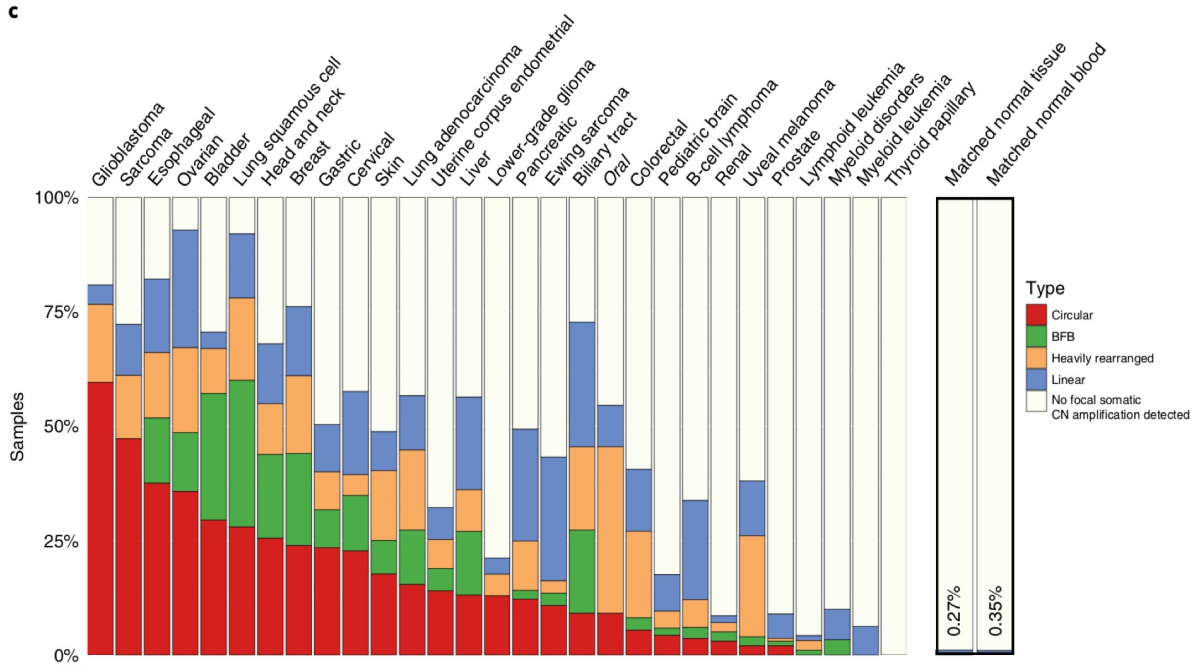
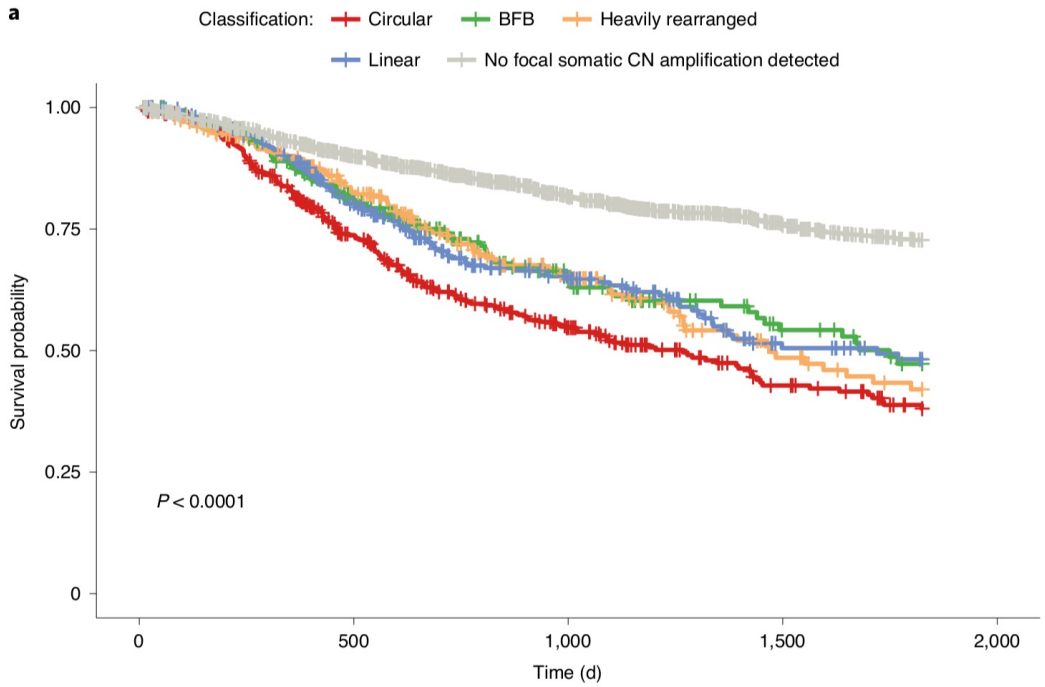
…that promotes tumorigenesis…





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).

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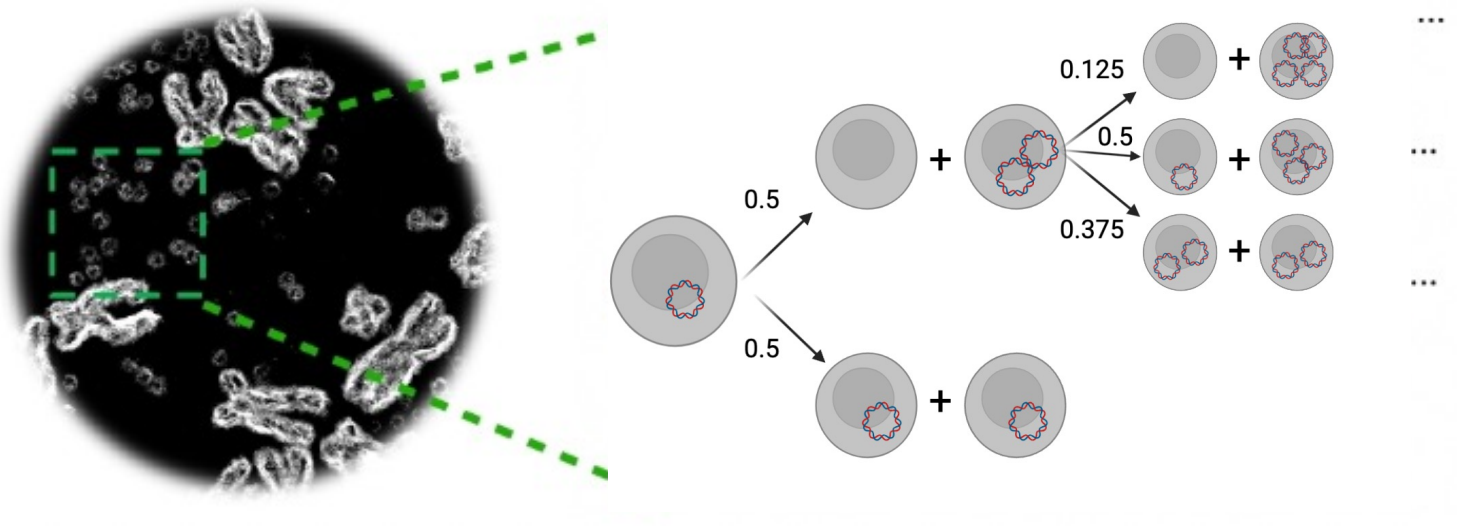
…and segregates unevenly into cells



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

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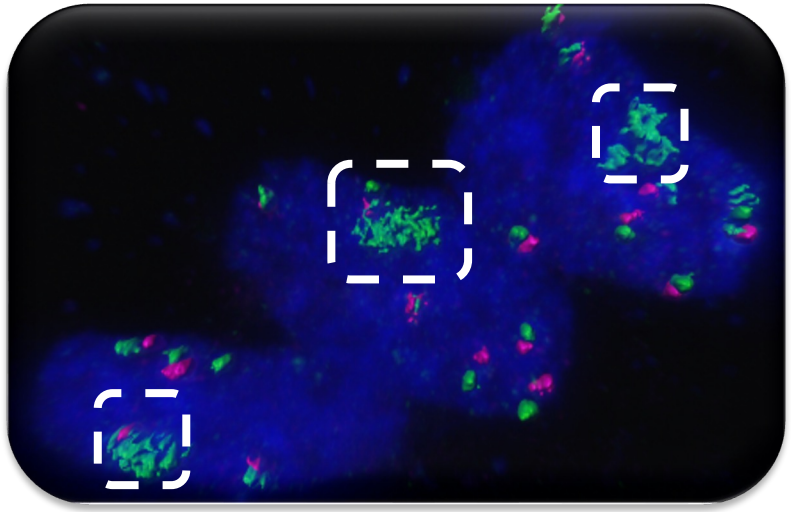
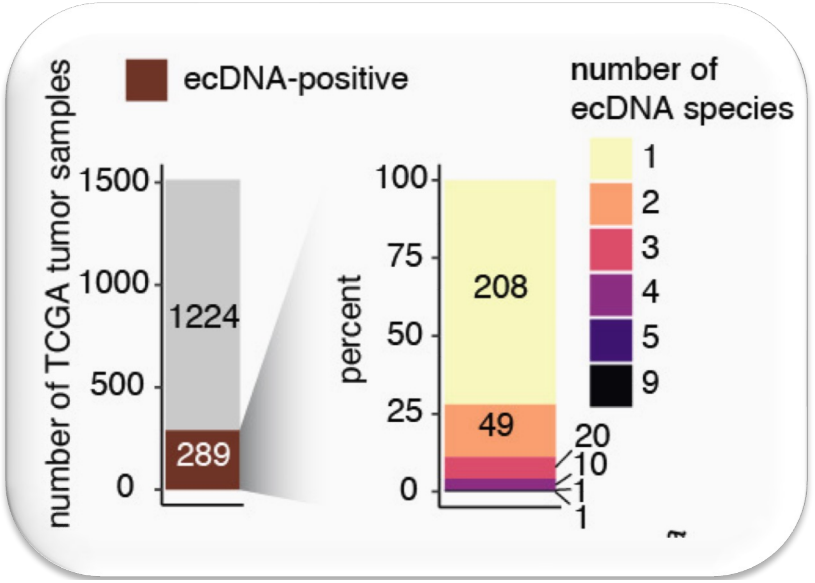
Multiple ecDNA species can co-exist in the same cancer cell and congregate in the nucleus

→ Enabling gene activation and mutual enhancing





Over 25% of TCGA tumor samples carry multiple ecDNAs, with a prevalence of two types

- Hung, K. L. et al. ecDNA hubs drive cooperative intermolecular oncogene expression. Nature 600, 731–736 (2021).
- Hung, K.L, Jones, M., et al., Coordinated inheritance of extra-chromosomal DNA in human cancer cells, bioRxiv 2023.07.18.549597

Coordinated inheritance of multiple ecDNA types

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Multiple ecDNA genotypes can co-exist, as ecDNA has a low repair efficiency

→ Common small indels and point mutations

Multiple ecDNA phenotypes (epigenetic states) can co-exist, as ecDNA shows higher chromatin accessibility than linear DNA

→ Sensitivity to histone modifications and methylation processes

→ Oncogene amplification or silencing

→ Different selection strengths

- Dong, Y., et al, Extrachromosomal DNA (ecDNA) in cancer: mechanisms, functions, and clinical implications., Frontiers in Oncology, 2023
- Nathanson. D.A., et al., Targeted therapy resistance mediated by dynamic regulation of extrachromosomal mutant EGFR DNA., Science, 2014
- Bergstrom, E.N., et al., Mapping clustered mutations in cancer reveals {APOBEC3} mutagenesis of ecDNA., Nature, 2022
- Wu, S., et al., Circular ecDNA promotes accessible chromatin and high oncogene expression, Nature, 2019

Coordinated inheritance of multiple ecDNA types

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Multiple ecDNA genotypes → Usual mutation rate is $10^{-9}, 10^{-8}$ per base pair
→ A rate of $10^{-3}, 10^{-2}$ can describe ecDNA mutation rate (length of ecDNA = 1 Mb)

Epigenetic alteration can happen with a slightly higher rate (10^{-1}) ← **Multiple ecDNA phenotypes**

- Dong, Y., et al, Extrachromosomal DNA (ecDNA) in cancer: mechanisms, functions, and clinical implications., Frontiers in Oncology, 2023
- Nathanson. D.A., et al., Targeted therapy resistance mediated by dynamic regulation of extrachromosomal mutant EGFR DNA., Science, 2014
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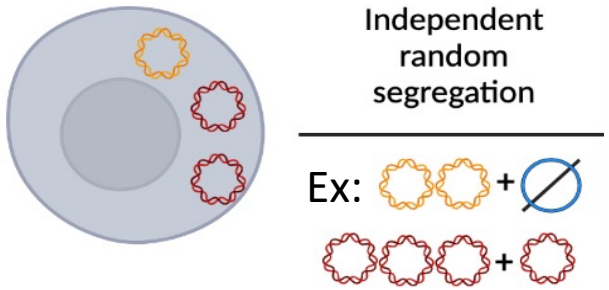
Our framework



- Two ecDNA types: **yellow** and **red**
- Independent random segregation following binomial distribution:

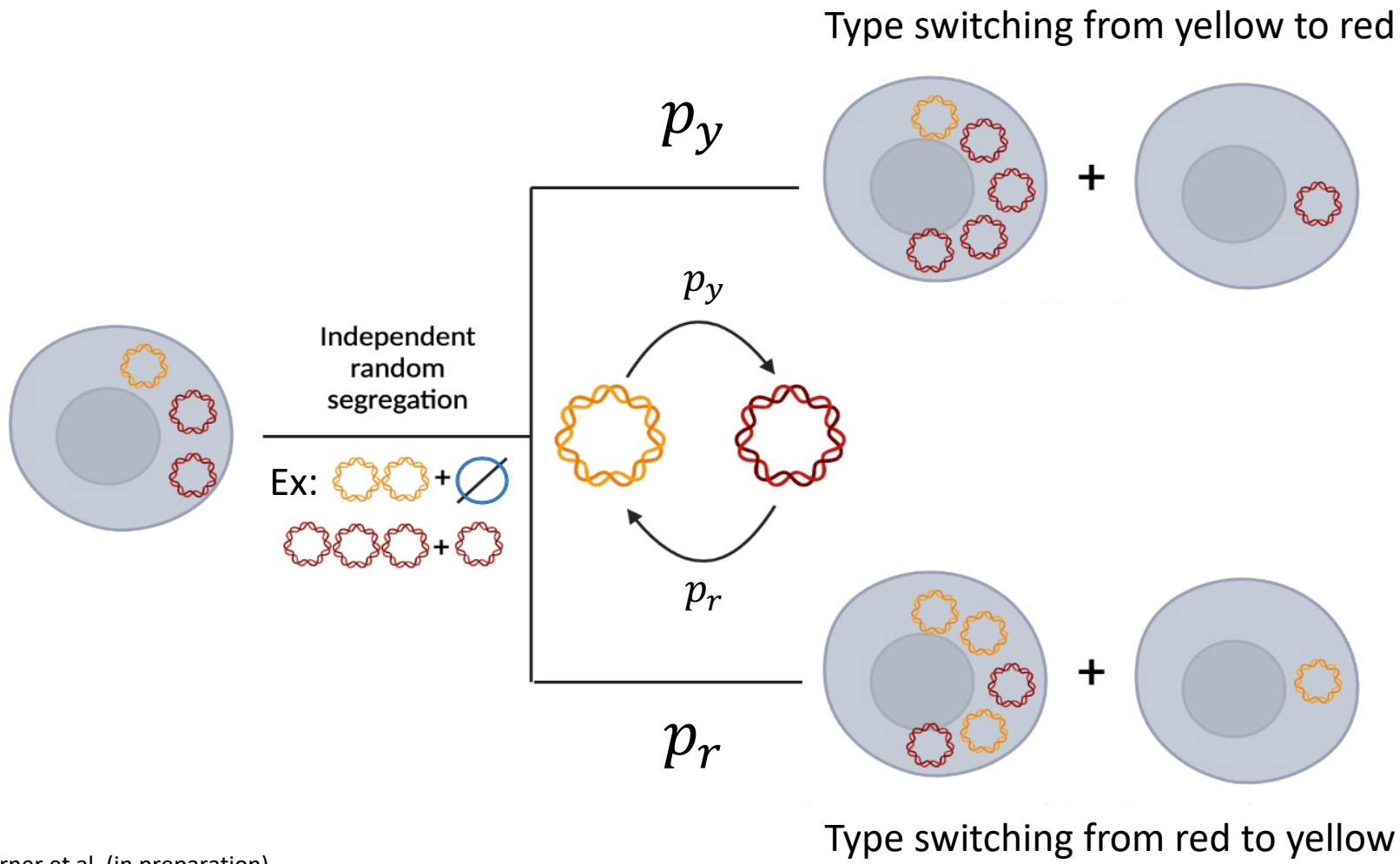
$$n_1 \sim Binomial\left(2N, \frac{1}{2}\right)$$

$$n_2 = 2N - n_1$$

- Division time depending on selection, modelled by coefficients s_y and s_r

Scanu, Huang, Werner et al. (in preparation)

Our framework



Scanu, Huang, Werner et al. (in preparation)

Our framework

Distinct ecDNA species

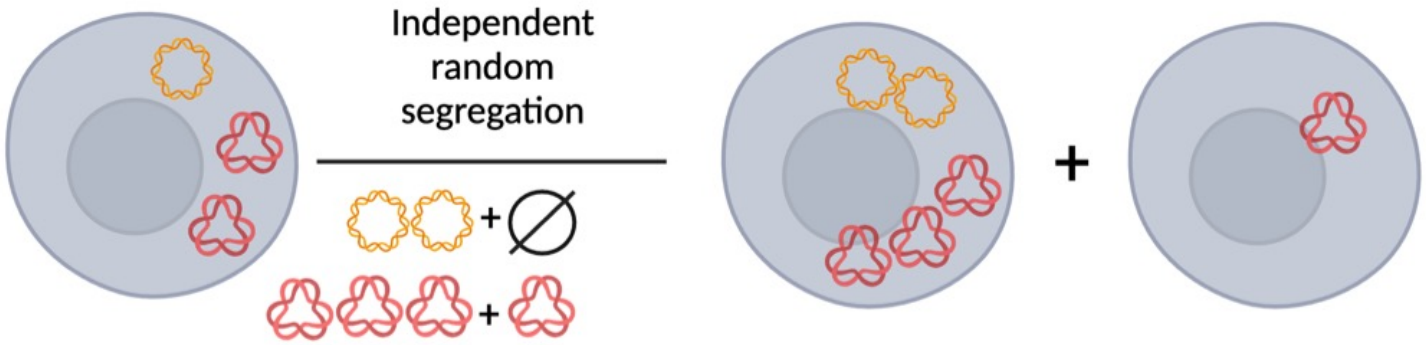
$$p_y = 0$$

$$p_r = 0$$

Scanu, Huang, Werner et al. (in preparation)

Our framework

Distinct ecDNA species



Scanu, Huang, Werner et al. (in preparation)

Our framework

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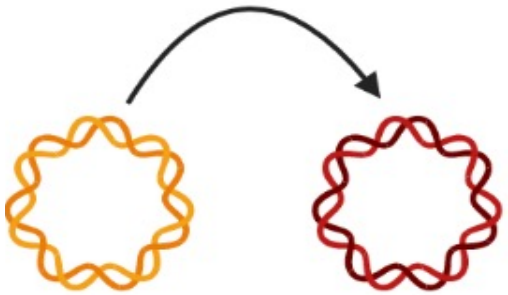
ecDNA mutant type

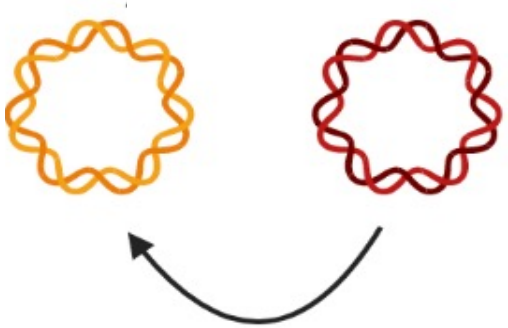
$p_y > 0$



$p_r = 0$

ecDNA mutant type

$p_y = 0$



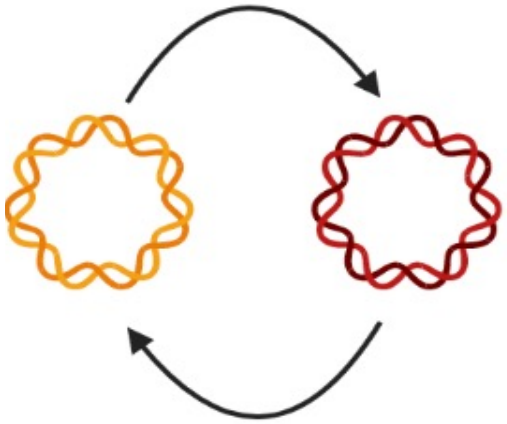
$p_r > 0$

Scanu, Huang, Werner et al. (in preparation)

Our framework

Distinct ecDNA geno-/pheno-types

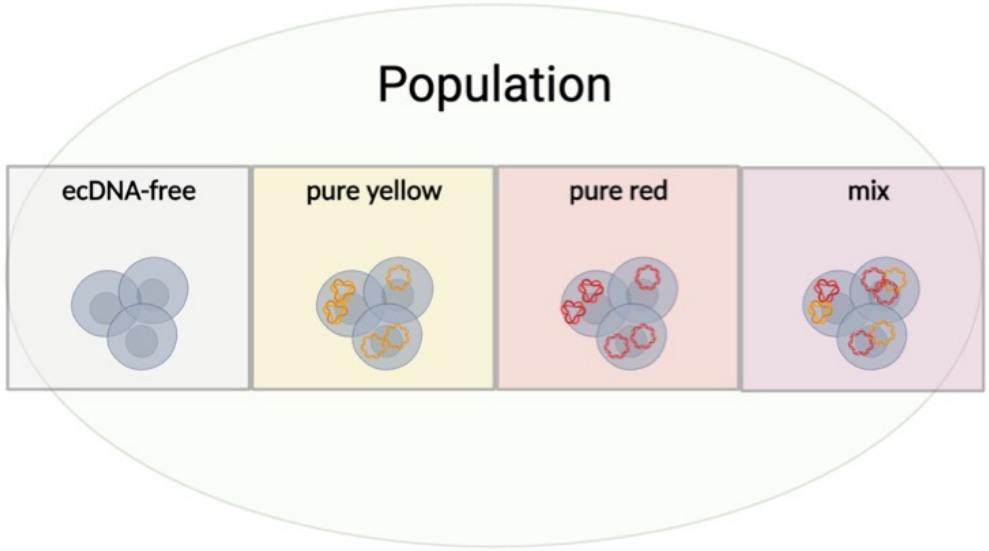
$p_y > 0$

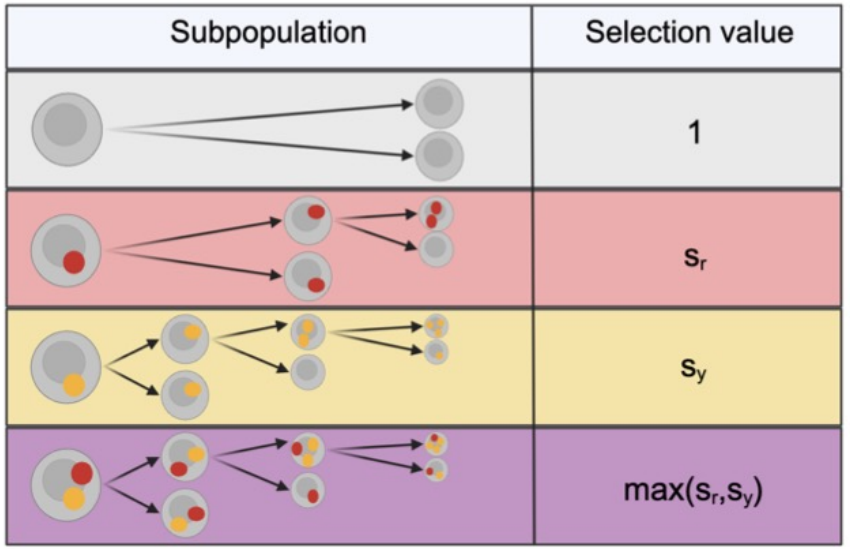


$p_r > 0$

Scanu, Huang, Werner et al. (in preparation)

Our framework





Scanu, Huang, Werner et al. (in preparation)

Mathematical description

$$\left.\frac{dC_{k,0}(t)}{dt}\right|_{k>0} = -s_y C_{k,0} + 2s_y \sum_{j=\left\lceil \frac{k}{2} \right\rceil}^{\infty} (1-p_y)^j C_{j,0} \binom{2j}{k} \frac{1}{2^{2j}}$$
$$+ 2s_y \sum_{\substack{j+h=\left\lceil \frac{k}{2} \right\rceil \\ j>0}}^{\infty} p_r^h (1-p_b)^j C_{j,h} \binom{2(j+h)}{k} \frac{1}{2^{2(j+h)}},$$

$$\left.\frac{dC_{0,k}(t)}{dt}\right|_{k>0} = -s_r C_{0,k} + 2s_r \sum_{h=\left\lceil \frac{k}{2} \right\rceil}^{\infty} (1-p_r)^h C_{0,h} \binom{2h}{k} \frac{1}{2^{2h}}$$
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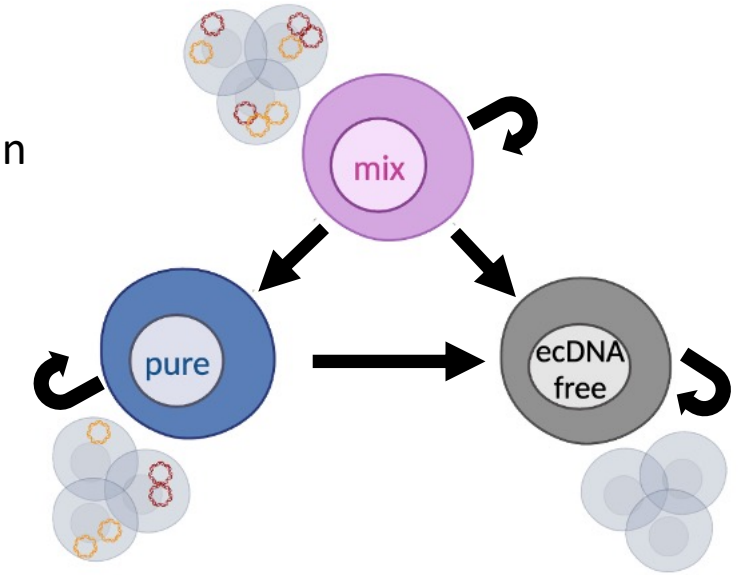
$$\left.\frac{dC_{i,k}(t)}{dt}\right|_{i,k>0} = -s_y C_{i,k}(t) + 2s_y \Bigg[\sum_{j=\left\lceil \frac{i}{2} \right\rceil, h=\left\lceil \frac{k}{2} \right\rceil}^{\infty} C_{j,h} \binom{2(j+h)}{(i+k)} \frac{1}{2^{2(j+h)}}$$
$$+ \sum_{j=\left\lceil \frac{i}{2} \right\rceil}^{\infty} p_y^j C_{j,0} \binom{2j}{i} \frac{1}{2^{2j}} - \sum_{j+h=\left\lceil \frac{k}{2} \right\rceil}^{\infty} (p_r^h (1-p_y)^j + p_y^j (1-p_r)^h) C_{j,h} \binom{2(j+h)}{k} \frac{1}{2^{2(j+h)}} \Bigg]$$
$$+ 2s_r \sum_{i=\left\lceil \frac{k}{2} \right\rceil}^{\infty} p_r^j C_{0,j} \binom{2j}{k} \frac{1}{2^{2j}},$$

$$\frac{dC_{0,0}}{dt} = -C_{0,0} + 2C_{0,0} + 2s_y \sum_{\substack{j+h=1 \\ j>0}}^{\infty} C_{j,h} \binom{2(j+h)}{0} \frac{1}{2^{2(j+h)}} + 2s_r \sum_{h=0}^{\infty} C_{0,h} \binom{2h}{0} \frac{1}{2^{2h}},$$

Differential equations describing stochastic dynamics of different subpopulations

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

Random segregation



Scanu, Huang, Werner et al. (in preparation)

Mathematical description

$$\left.\frac{dC_{k,0}(t)}{dt}\right|_{k>0} = -s_y C_{k,0} + 2s_y \sum_{j=\left\lceil \frac{k}{2} \right\rceil}^{\infty} (1-p_y)^j C_{j,0} \binom{2j}{k} \frac{1}{2^{2j}}$$
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$$+ \sum_{j=\left\lceil \frac{i}{2} \right\rceil}^{\infty} p_y^j C_{j,0} \binom{2j}{i} \frac{1}{2^{2j}} - \sum_{j+h=\left\lceil \frac{k}{2} \right\rceil}^{\infty} (p_r^h (1-p_y)^j + p_y^j (1-p_r)^h) C_{j,h} \binom{2(j+h)}{k} \frac{1}{2^{2(j+h)}} \Bigg]$$
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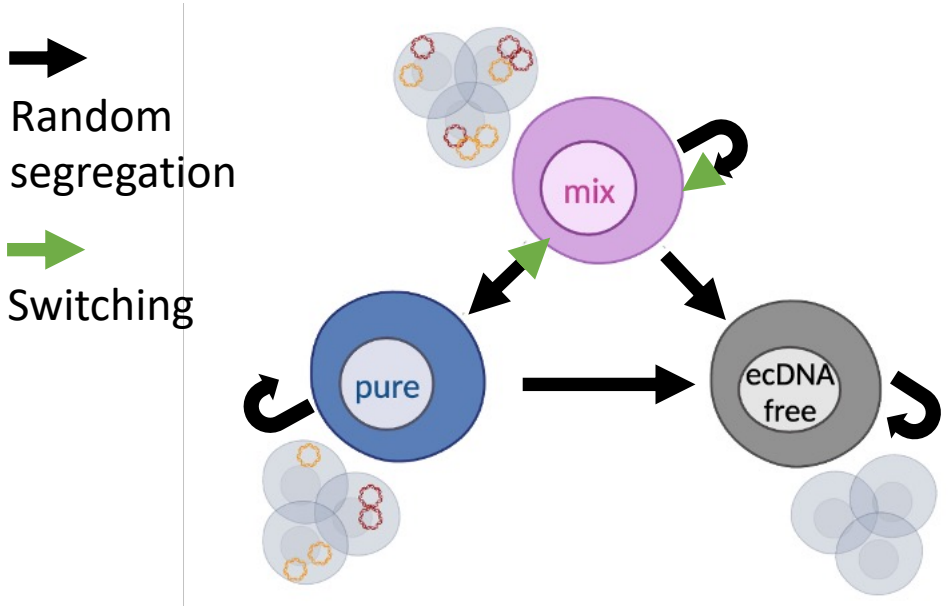
Differential equations describing stochastic dynamics of different subpopulations

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



Scanu, Huang, Werner et al. (in preparation)

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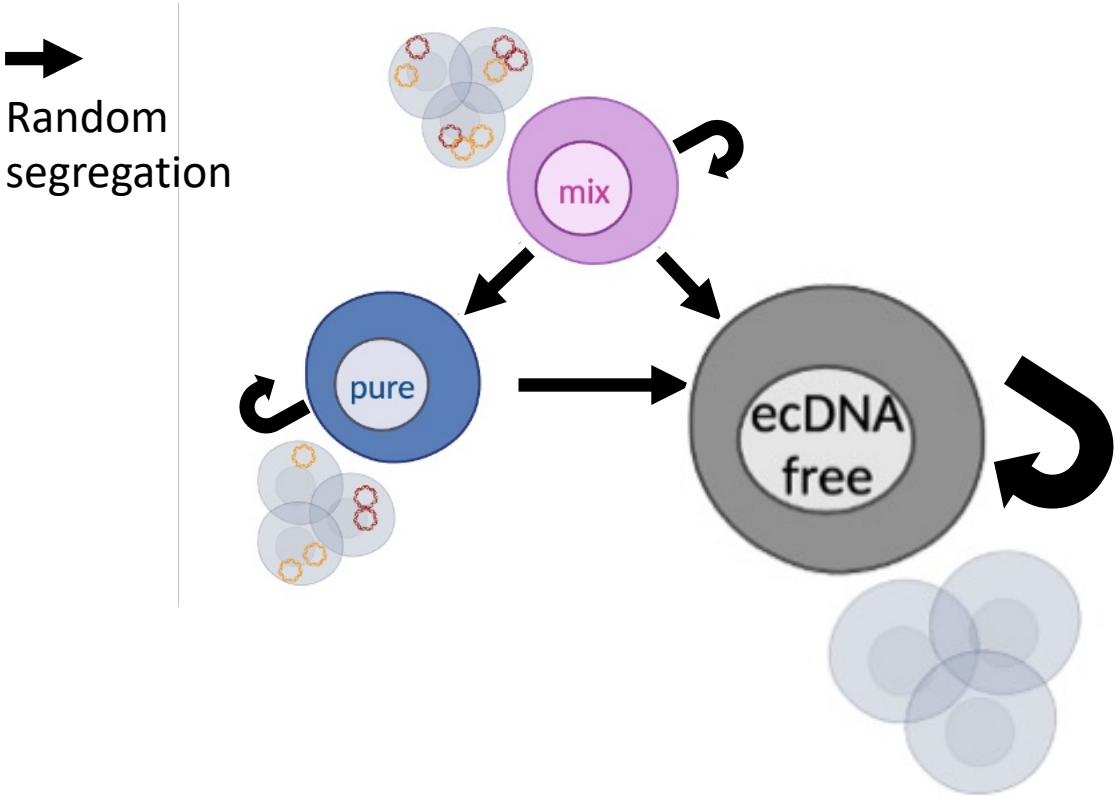
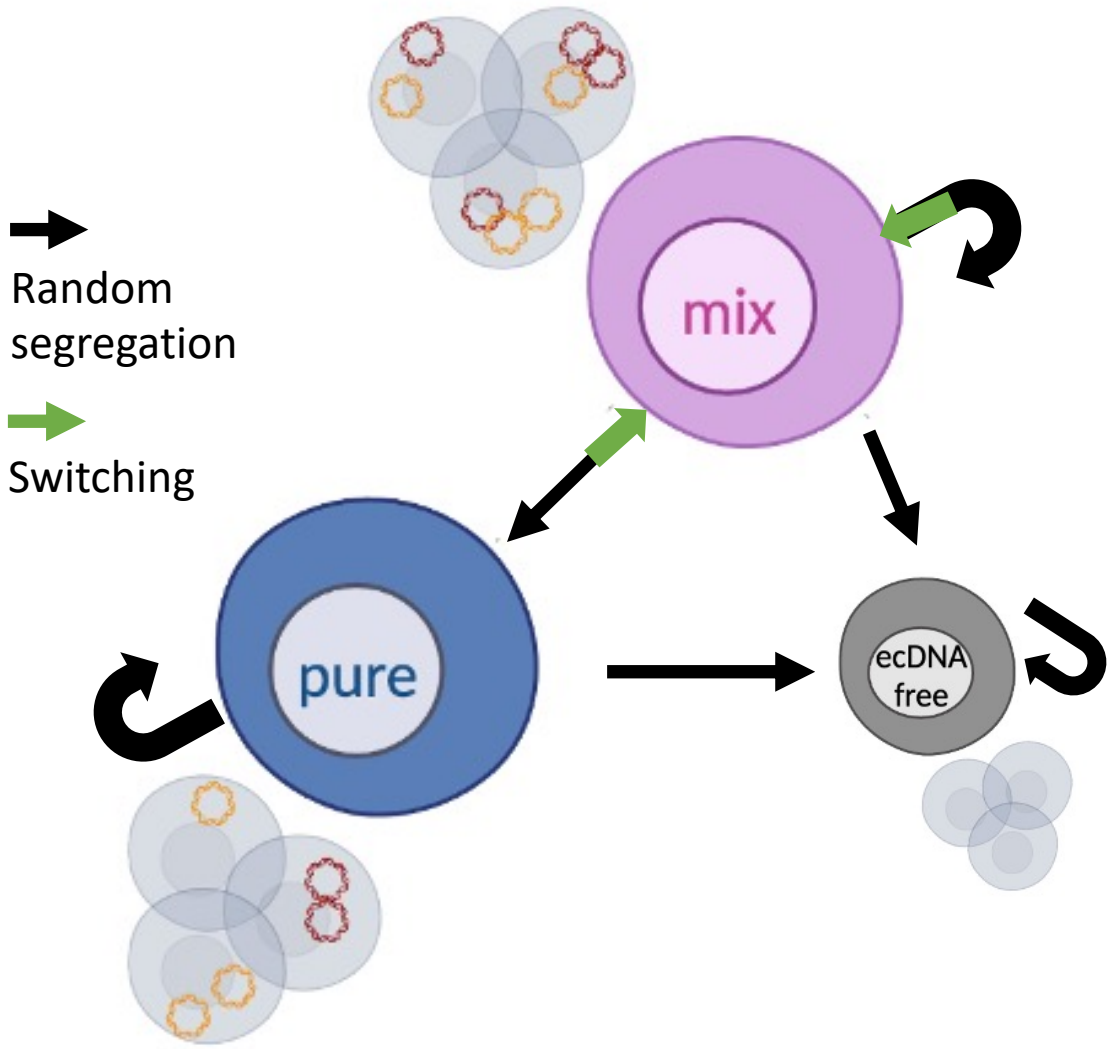
Mathematical description



- If carrying ecDNA has no reproduction advantage, ecDNA free is the equilibrium as absorbing state. Indeed, in our model ecDNA does not arise by chance

Scanu, Huang, Werner et al. (in preparation)

Mathematical description



- If carrying ecDNA has no reproduction advantage, ecDNA free is the equilibrium as absorbing state
- Considering positive selection, there is the possibility to maintain a stable subpopulation of mix cells!

Scanu, Huang, Werner et al. (in preparation)

Studying moment dynamics - species

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Setting $p_y = p_r = 0$, we focus on **ecDNA species**.

We study the **weigthed first moment dynamics** for each subpopulation (i.e. mean copy number weighted on the total population size):

$$\mathbf{M}_j^{(l)}(t) = \sum_{i,k} (i+k)^l \rho_{i,k},$$

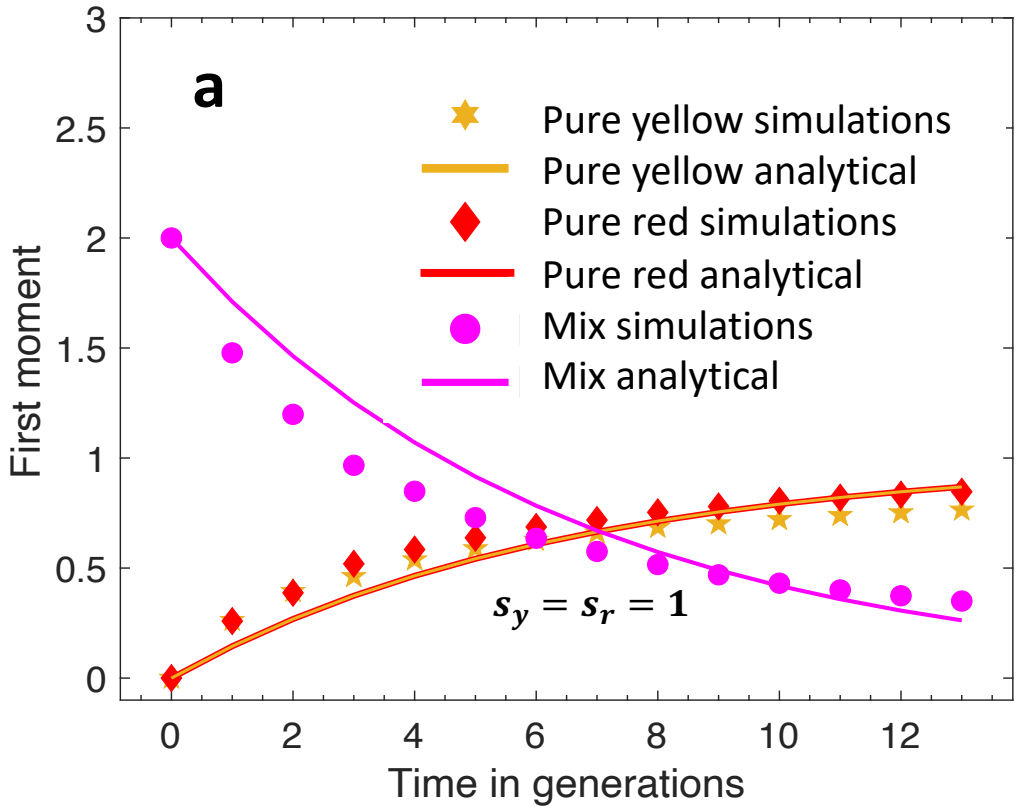
and we produce analytical solutions

Scanu, Huang, Werner et al. (in preparation)

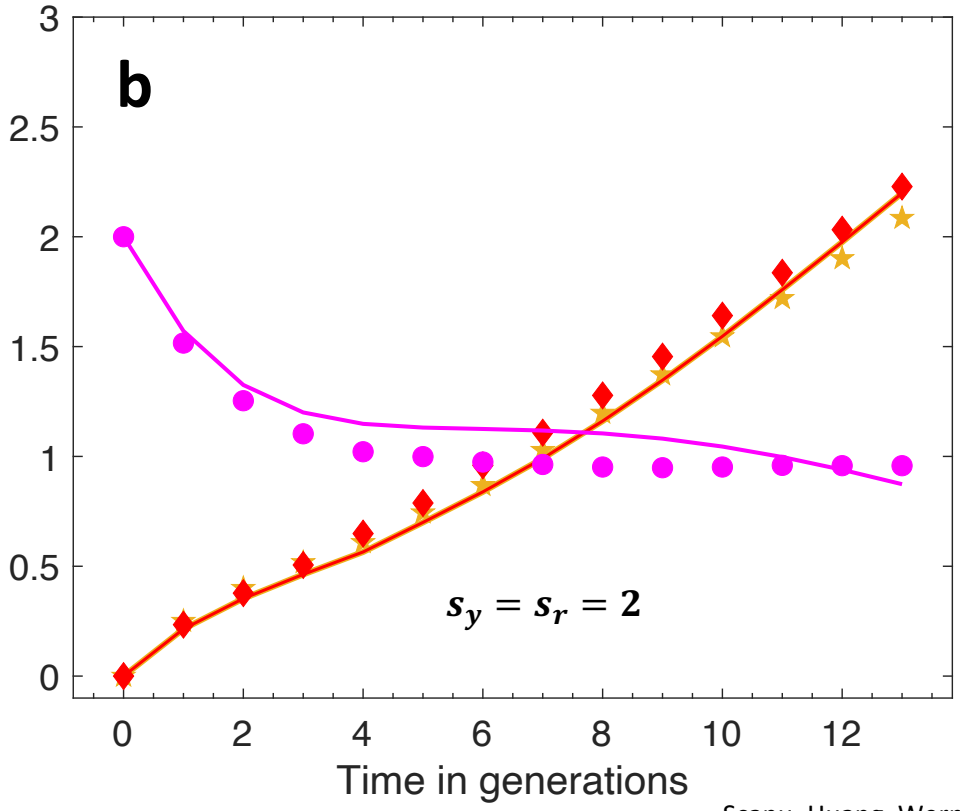
Studying moment dynamics - species

Starting by a single cell with 1 yellow and 1 red ecDNA copies

Neutral selection



Identical positive selection



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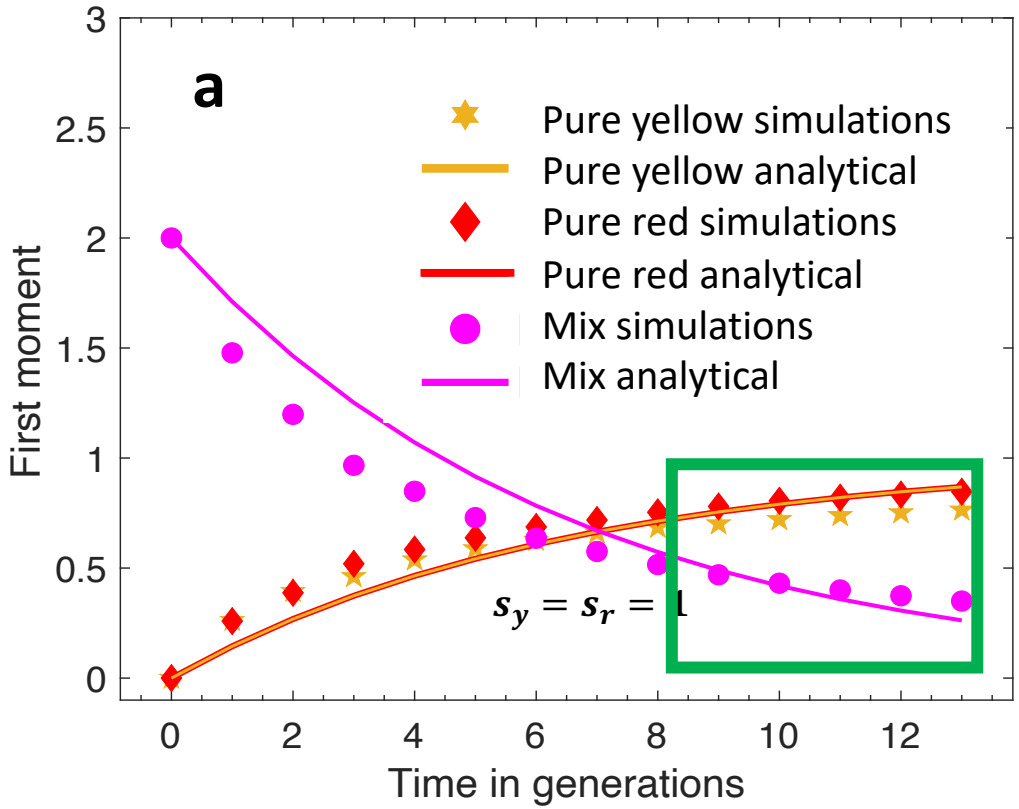

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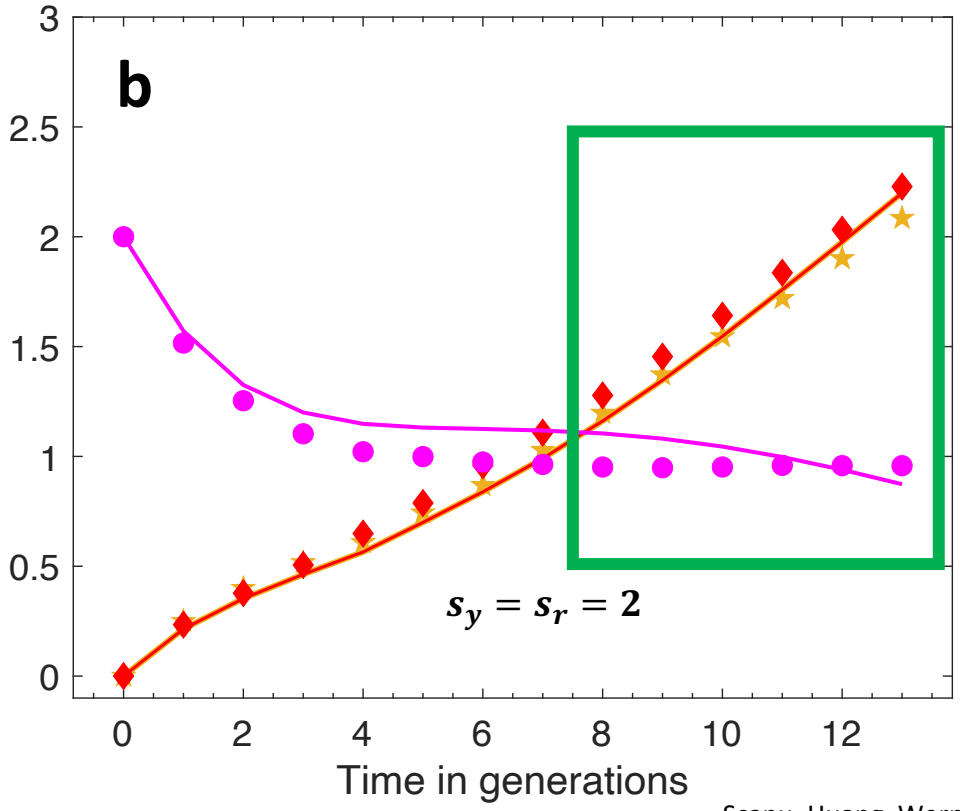

Scanu, Huang, Werner et al. (in preparation)

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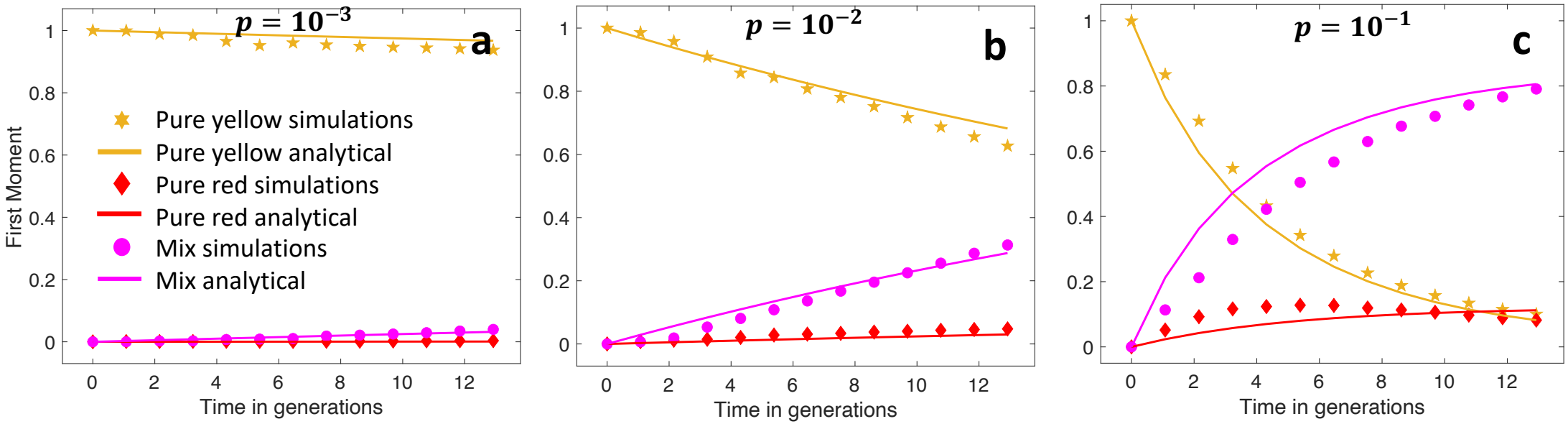
Studying moment dynamics – geno/phenotypes

Setting $p = p_y = p_r > 0$, we focus on **ecDNA geno-/pheno-types**

Neutral selection, starting by a single cell with 1 yellow ecDNA copy



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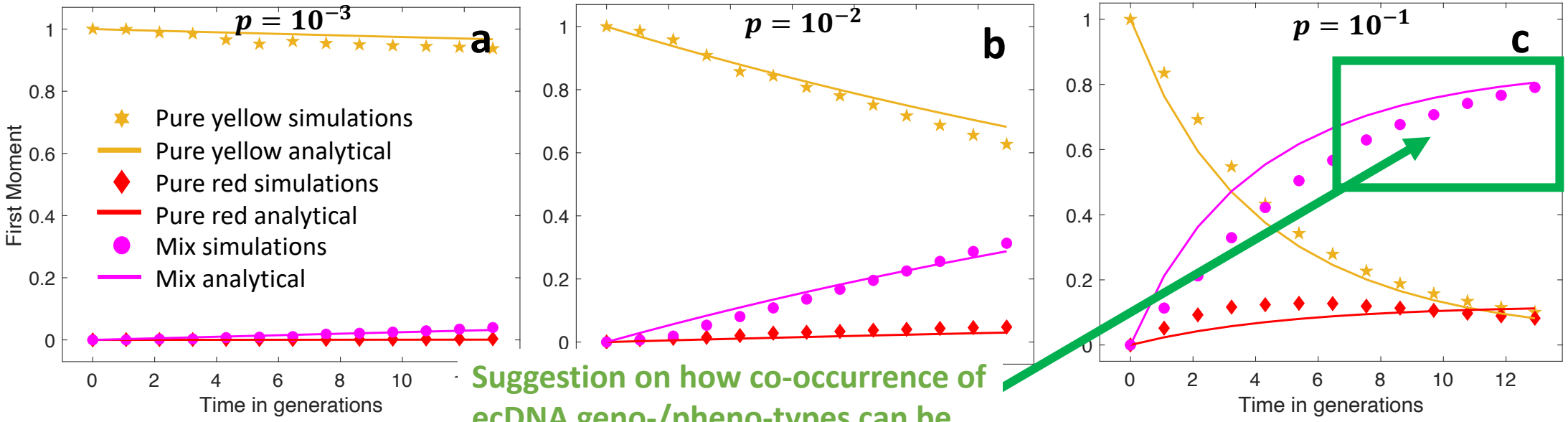
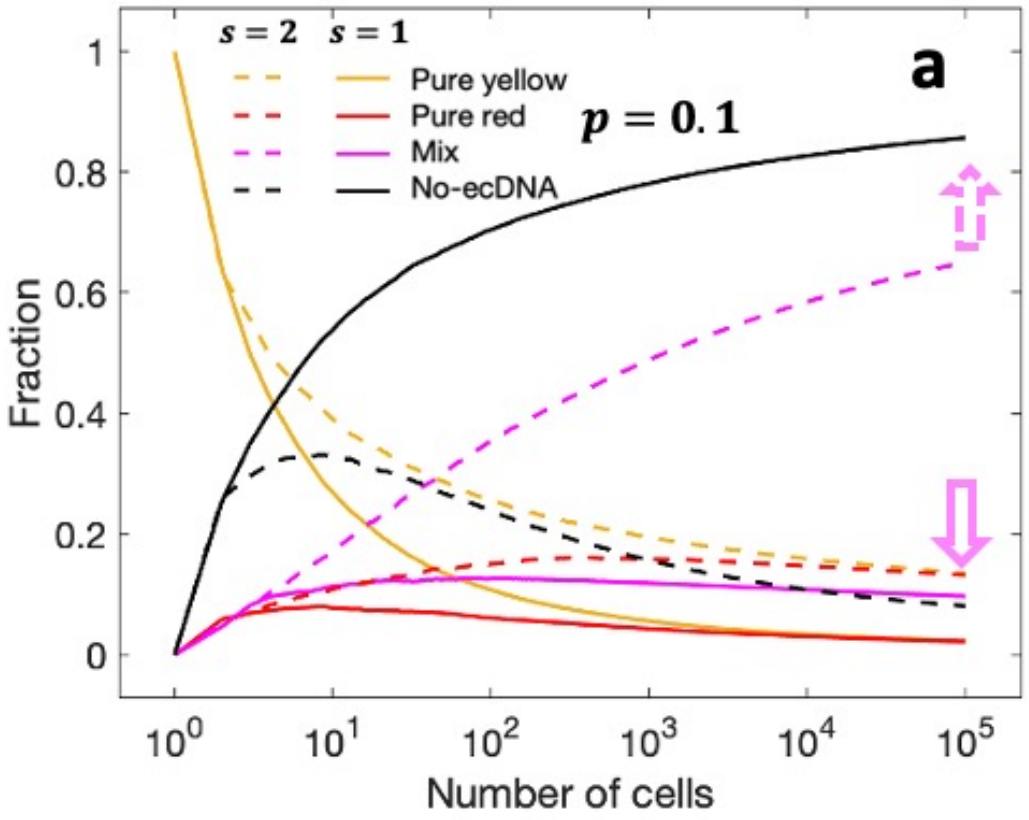


Suggestion on how co-occurrence of ecDNA geno-/pheno-types can be maintained?

Scanu, Huang, Werner et al. (in preparation)

Maintenance of multiple ecDNAs upon proliferation



Under positive switching, positive selection ensures maintenance of mix cells…

Scanu, Huang, Werner et al. (in preparation)

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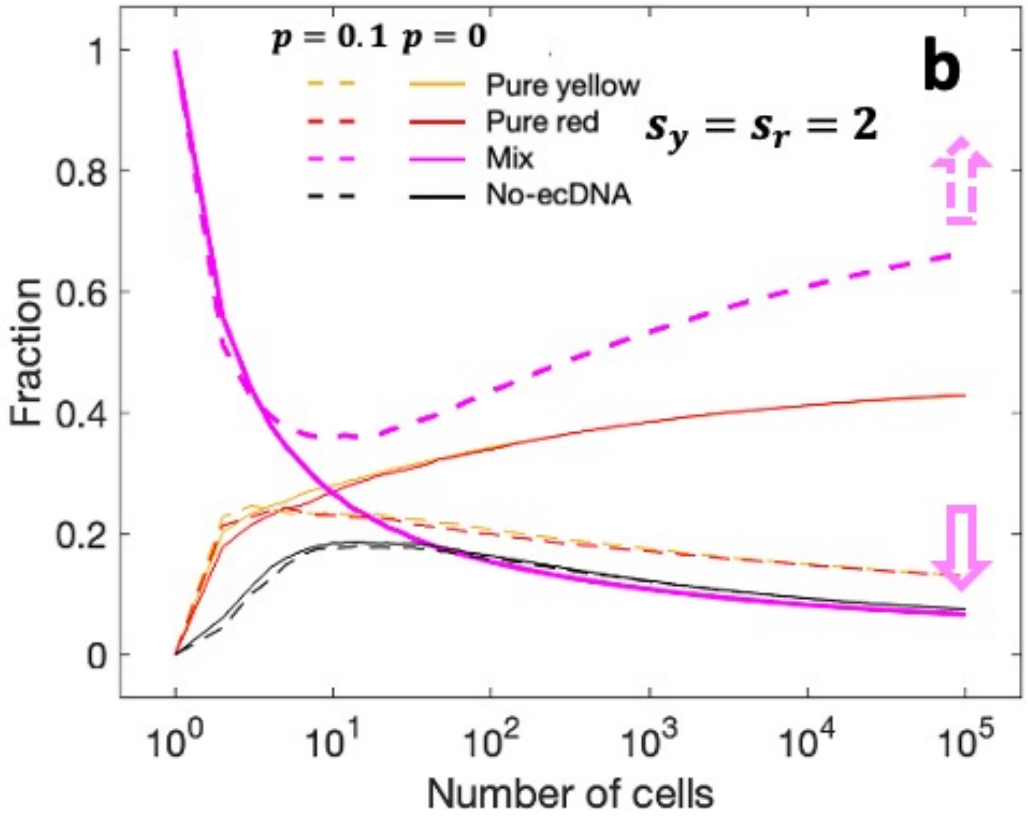
Maintenance of multiple ecDNAs upon proliferation

…However, **both positive selection and positive switching are required for this maintenance**, otherwise under positive selection and absence of switching mix cells will still go extincted



Scanu, Huang, Werner et al. (in preparation)

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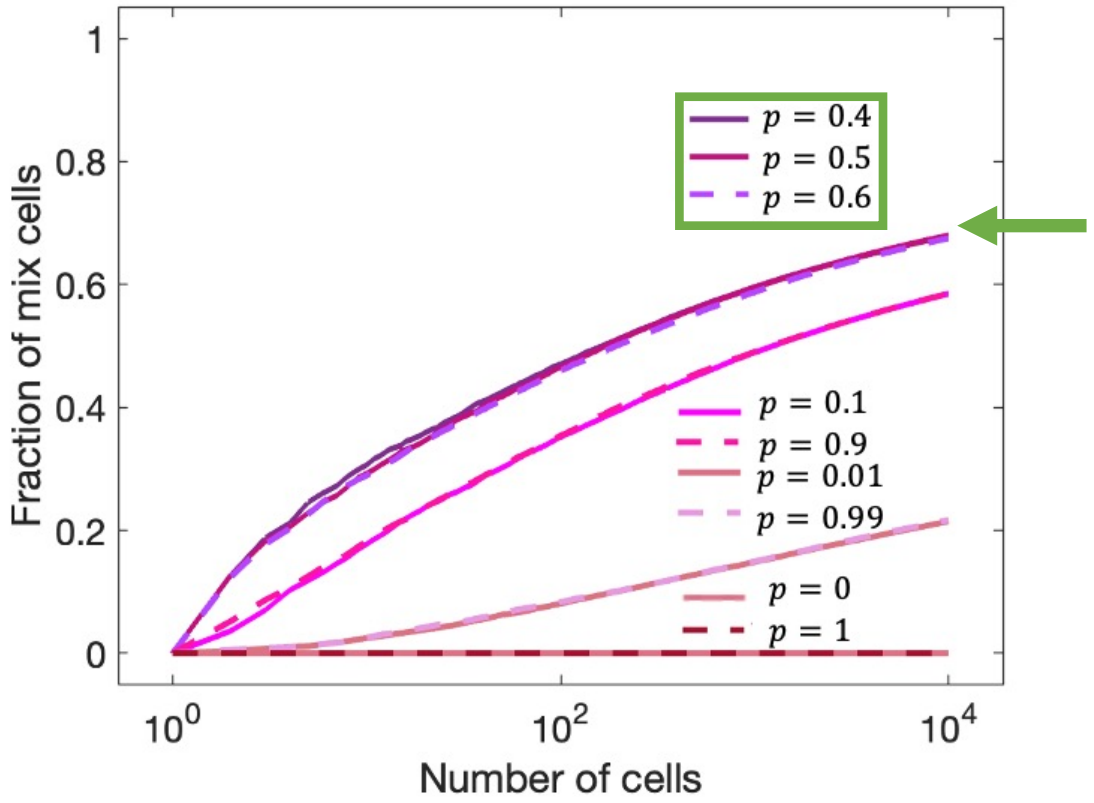
Maintenance of multiple ecDNAs upon proliferation

Furthermore, high switching does not lead to high frequency of mix cells, but instead intermediate p does



Scanu, Huang, Werner et al. (in preparation)

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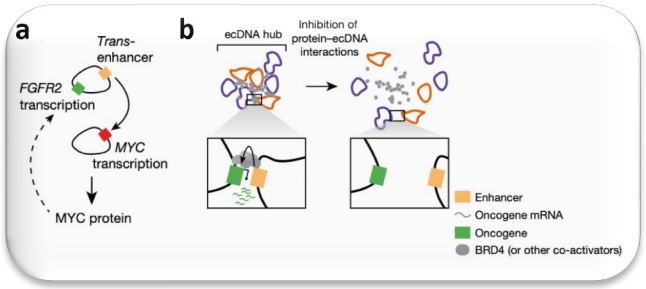
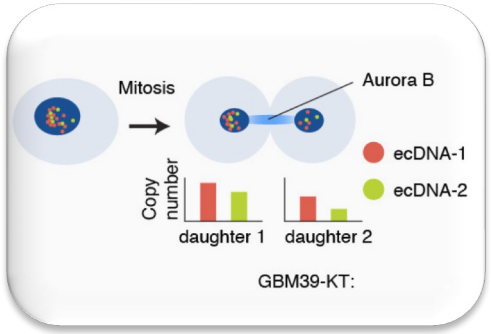
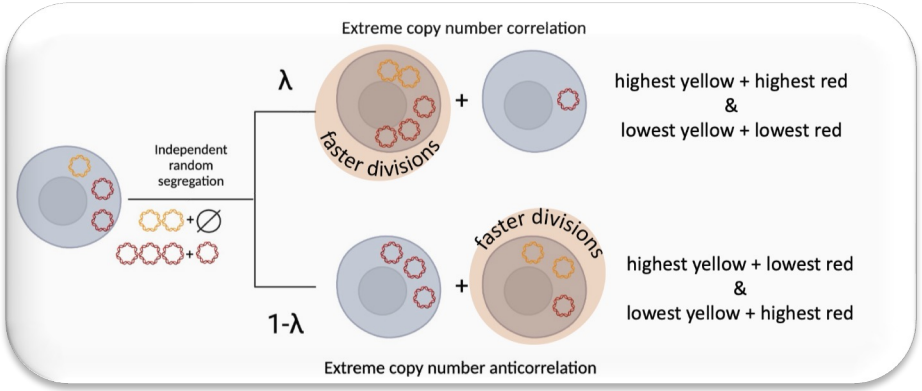
On-going work

- Alternative model for multiple ecDNA species which includes further properties found in data







- Investigation of spatial signature of multiple ecDNA with agent-based modelling (**Magnus Haughey, Contributed Talk on Monday at 3pm in "Cell Biology" session)**

Outlook

- We build a solid mathematical framework for modelling the proliferation of multiple ecDNA types, considering their genotypical and phenotypical attributes

- We investigated the sensitivity of the system to the evolutionary parameters: selection and switching

- We investigated the conditions which ensure the maintenance of multiple ecDNAs upon division

Outlook

- We build a solid mathematical framework for modelling the proliferation of multiple ecDNA types, considering their genotypical and phenotypical attributes
- We investigated the sensitivity of the system to the evolutionary parameters: selection and switching
- We investigated the conditions which ensure the maintenance of multiple ecDNAs upon division

Thanks for your attention!

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