# A mathematical model in evolutionary medicine: ecDNA dynamics

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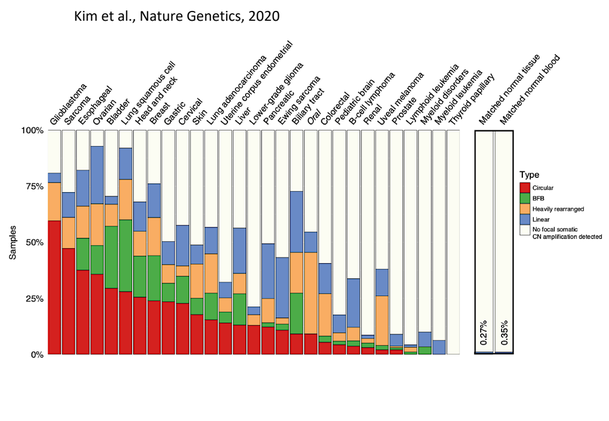
## BIOLOGICAL CONTEXT

**e**xtra-**c**hromosomal **DNA**: any DNA found off the chromosomes.
It is a genetic mutation caused by episodes of chromosomal instability.

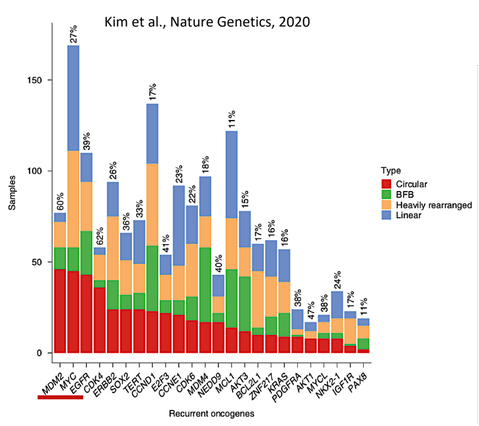
**Why are we studying it?**

- promotion of **tumorigenesis** and **oncogene amplification**;
- **random segregation** into daughter cells during replication ➔ **stochasticity** of its proliferation path.

Kim et al., Nature Genetics, 2020




Kim et al., Nature Genetics, 2020



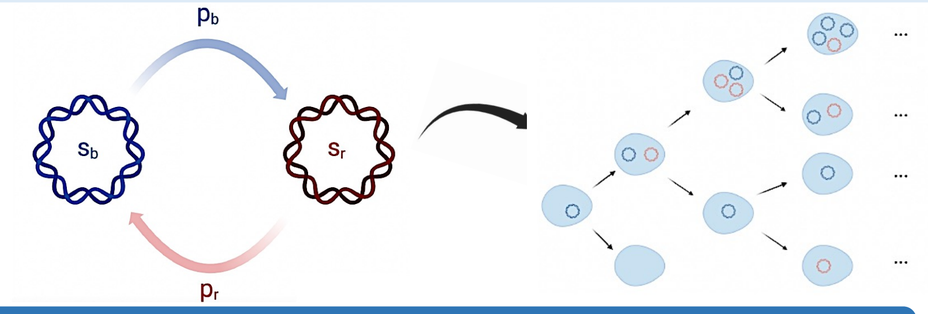

ecDNA properties lead to our hypothesis:
**cells with ecDNA elements which amplify oncogenes have fitness advantage, thus is ecDNA proliferation a driver event to cancer?**

## INTRODUCTION TO THE MODEL

We describe a multiple species ecDNA somatic evolutionary process by considering two types of ecDNA, which differs for biological and genetic properties:
red ecDNA & blue ecDNA

- Instability of mutations modeled by probabilities $p_r \in [0,1]$ & $p_b \in [0,1]$.
- Fitness advantage of each type modeled by reproduction rates $s_r \geq 1$ & $s_b \geq 1$.

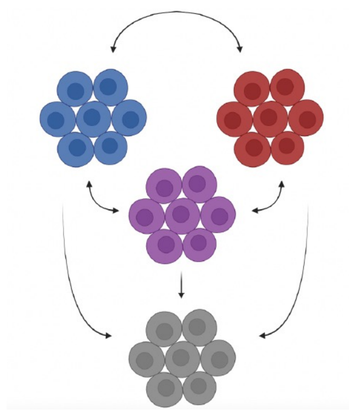
**Key point of the model**: different values for parameters lead to different biological scenarios ➔ connection between theoretical and real population proliferation.




## GOALS OF OUR RESEARCH

1. Understanding how the presence of blue and red ecDNA changes the mutation's dynamics over time under different selection scenarios;
2. Understanding how the switching between ecDNA types could impact the intercellular heterogeneity and copies distribution among the population.

## METHODS



We propose two versions of our model:
- **Deterministic**: modeled by a four ODEs system describing proportions of cells for each subpopulation over time;
- **Demographic**: modeled by four stochastic equations describing number of cells for each subpopulation over time.

We model the ecDNA inheritance through Binomial distribution with success probability ½.

→ Codependence between subpopulations due to instability parameters.

Solutions of deterministic (i.e. **densities** $\rho_{i,k}(t)$) and demographic system (i.e. **number of cells** $C_{i,k}(t)$) are linked by

$$C_{i,k}(t) = \rho_{i,k}(t) \cdot M(t)$$

where $M(t)$ is the population growth factor and $M(t) \sim e^{\varphi(s_r, s_b, p_r, p_b, t)}$.

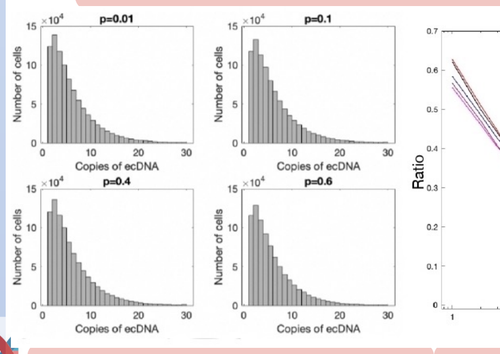
Eveness and population diversity are measured through Shannon diversity index $H$ and Shannon equitability index $E_H$

$$H = -\sum_{i=1}^{\infty} c_i \ln c_i, \qquad E_H = \frac{H}{\log k}, \qquad E_H \in [0,1]$$

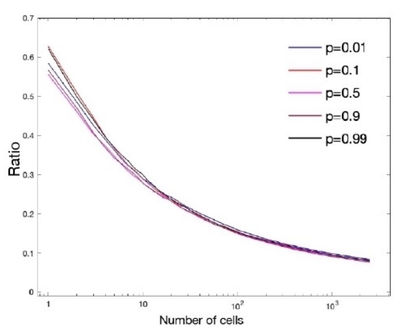
where $c_i$ is the abundance of category $i$ and $k$ is the number of categories.
→ The more unequal the abundances of types, the smaller the corresponding entropy.

## RESULTS

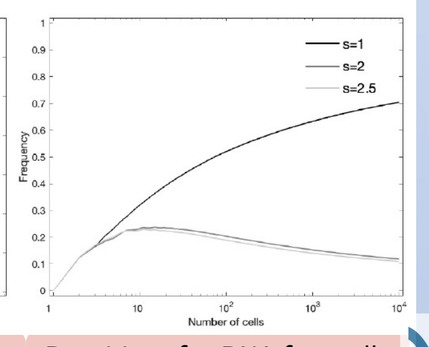
We discover that the model presents **some invariant quantities on $p = p_r = p_b$**, fixing $s_b$ and $s_r$. These are




Distribution of cells regardless their compartment



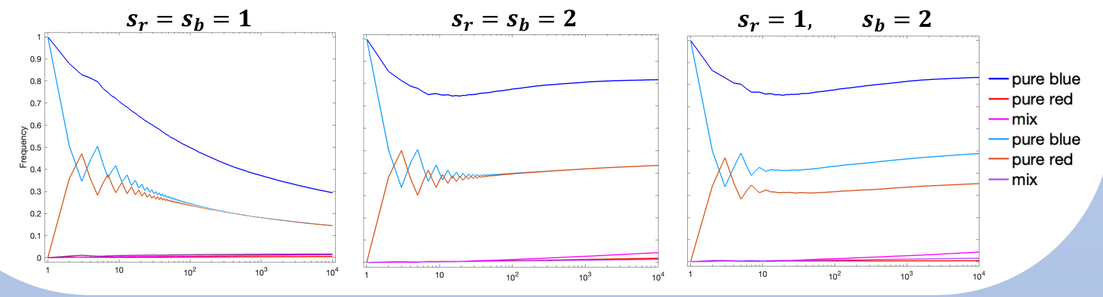

Ratio of cells carrying one ecDNA copy




Densities of ecDNA-free cells when $s_r = s_b$

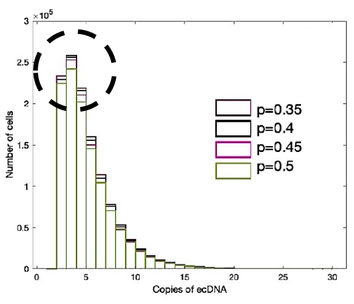
We investigate **how the dynamics changes with $p$**, especially for low and high $p$-values scenarios, **and with $s_r$ and $s_b$**, especially when a neutral or a positive selection scenario is considered.

$\boldsymbol{p = 0.01\ vs\ p = 0.99}$

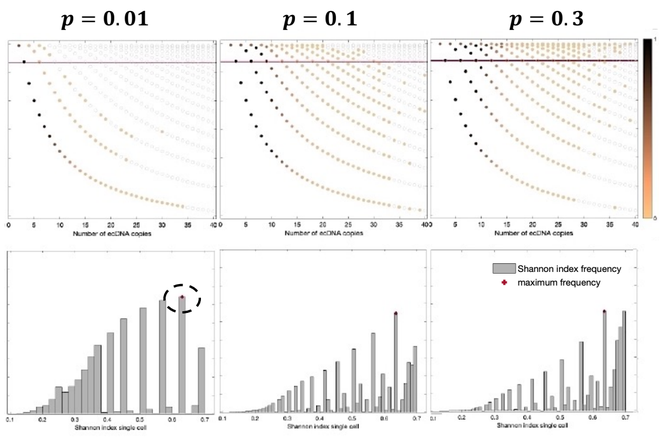


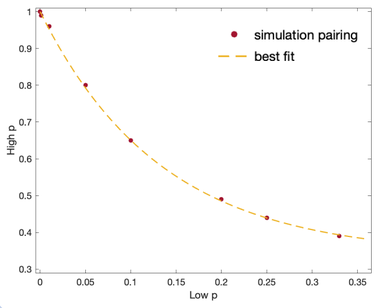

## RESULTS

Distribution of copies and Shannon index at single cell level's investigations in neutral scenario suggest that **mix population is dominated by cells with 3 ecDNA copies**.




The maximum frequency of Shannon index is always reached at $H \sim 0.635$, and the most frequent copy number related to this value is always 3.




We identify similar behaviour of the dynamics for low and high $p$ values, but there is not a symmetric relation, thus **there is a value range for $p$ for which the mix population has the biggest increase**, and this range is not around 0.5.
We set this range as the interval $(0.33, 0.35)$ and approximate the mapping function as

$$f(p) \cong \frac{c + e^{-dp}}{1 + c}, \qquad c = 0.51, d = \frac{3}{4}$$

## CONCLUSIONS AND FUTURE WORK

- **Our work is biologically motivated**, as it takes into account some peculiar properties of this mutation, such as its instability, random segregation, species diversity and fast spread, and, due to the results we already have, **it represents a big contribution to theoretical study of cancer**;
- **We can focus on specific parameters values to model biological scenarios**.
  - Oncogene expression does not affect ecDNA proliferation → neutral fitness scenario (i.e. $s = s_r = s_b \geq 1$);
  - Oncogene expression promotes the increasing of mutation's reproduction rate → heterogeneous fitness scenario (i.e. $s_b > 1, s_r = 1$).

Upcoming goals:
- **Interpretating the biological reasons behind our results in order to validate them**;
- **Performing a detailed investigation for positive selection scenarios**;
- **Including into the model more complex ecDNA proliferation's aspects**, for example epistasis, co-selection and/or competiton between ecDNA types, epigenetic factors, etc…

## References

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