# Spatial models of cellular competition in *Notch1* clonal takeover

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## Background

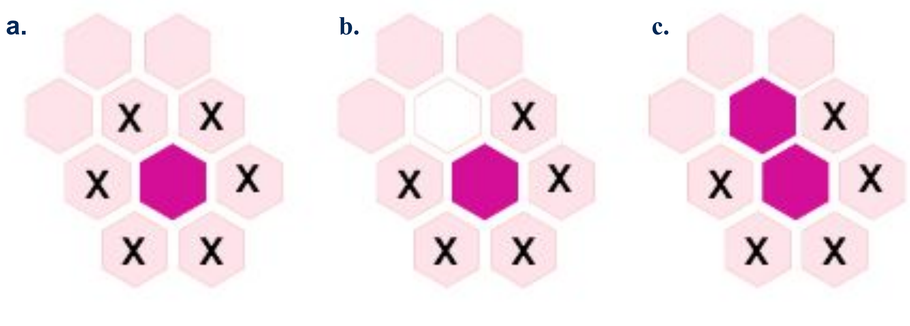


**Figure 1.** 2-dimensional Moran style model of clone dynamics. In each generation, cells get an opportunity to reproduce. If fitnesses of neighboring cells are similar then chances for them to reproduce are equal. Cells with higher fitness are more likely to generate daughters and win competition for space replacing less fitted.

- **Healthy human tissues acquire mutations with age.** Over the lifetime, mutated cells can persist and spread in the tissue depending on gained fitness (1). As aging progresses, fit clones spread replacing wild type cells and substantially collide with similar or more fitted mutants. These mutant confrontations may lead to clone stopping or regressing (2).
- NOTCH1 is gene encoding protein Notch 1 involved cell fate decision, homeostasis and cancer. **Mutant clones of gene NOTCH1 occur in majority of healthy human oesophagus, but are rare in in esophageal cancer (3).** While promoting clonal expansion, they seem to prevent carcinogenesis (4).
- Previous research has shown how NOTCH1 mutations overtake the tissue, however the impact of less fit mutations to NOTCH1 and other genes was less clear. This study seeks to explore the impact of less fit mutations to NOTCH1 and other genes by using computational models.

## Spatial Moran-style processes

### Spatial models of cellular competition

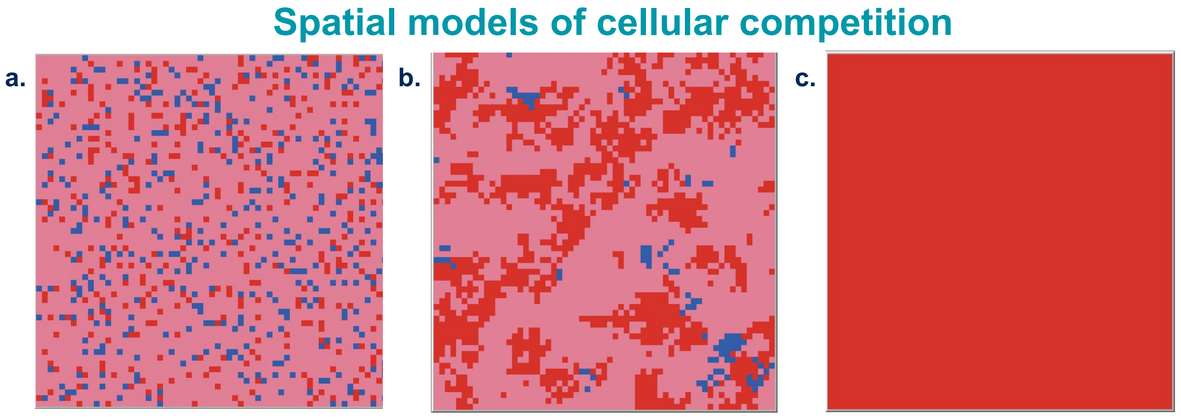


**Figure 2**. Representative images of competitive mutants overtake in finite population created using NetLogo. a. initial simulation showing 10% of primary mutation cells (red) vs secondary mutation cells (blue) vs wild type cells (pink). b. More fitted mutants start to reproduce overtaking tissue c. Tissue colonised entirely by more fitted mutants.

**tissue size:**
61 x 61
**cell number:**
3721

cells with fitness primary mutation

cells with fitness secondary mutation

wild type cell

| | |
|---|---|
| Total number of studied groups | 6 |
| Total number of parameters in each group | 7 |
| Number of trials within each competition group (1 vs 2) | 10 |

Table 1. Number of groups and trials conducted in each simulation combination.

- Simulation set up is defined by number of clones with a fitness advantage (10% of primary and secondary mutant type in the grid).
- Clones rapidly expand until they collide slowing down takeover.

### Statistical analysis

Data is presented as mean values with standard deviation error bars illustrating how data differs from different stages of takeover.

## Results

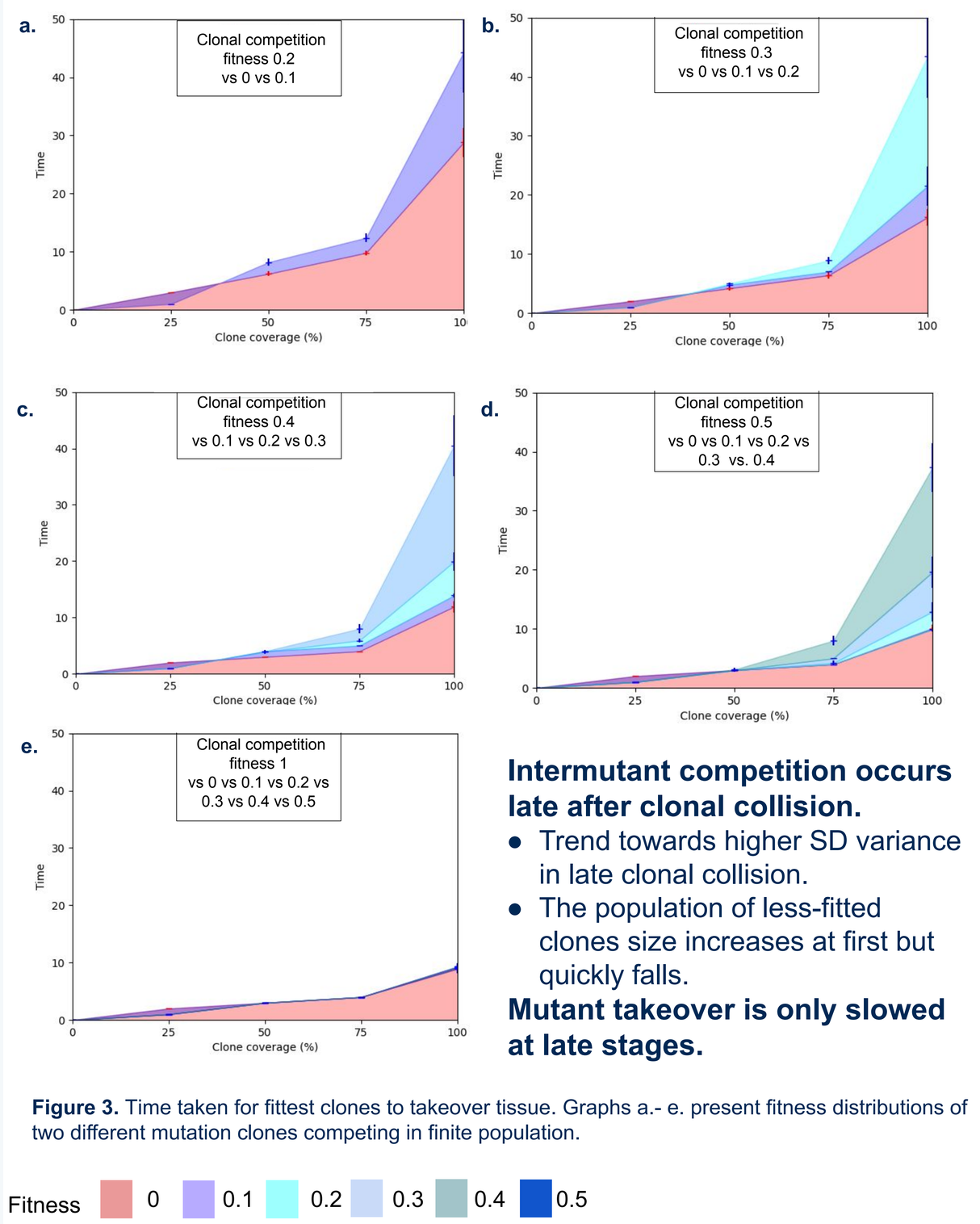


**Figure 3.** Time taken for fittest clones to takeover tissue. Graphs a.- e. present fitness distributions of two different mutation clones competing in finite population.

**Intermutant competition occurs late after clonal collision.**

- Trend towards higher SD variance in late clonal collision.
- The population of less-fitted clones size increases at first but quickly falls.

**Mutant takeover is only slowed at late stages.**

## Discussion

**Primary and secondary mutations can be identified with mutation of two genes: NOTCH1 and p53.**

- These genes were found to be under strong positive selection in aging human epithelium and seem to play major role in carcinogenesis (5). They compete for space with other mutants and wild type cells in the tissue. The winner gets better opportunity to persist longer in the environment, acquire additional mutations and get a chance to establish larger clones.

**Late intermutant competition could slow down p53 dispersion.**

- During initial phases of spatial competition mutants compete mostly with wild type cells and therefore, mutants' takeover is relatively quick. At late stages due clonal collision, mutants start to compete. In oesophagus and skin of both humans and mice NOTCH1 is considered to be more fit. Therefore, introducing highly competitive clones could lead to tumour stop or regression.

## Key references

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