Evolutionary Dynamics of Mutator Phenotypes in Cancer: Implications for Chemotherapy

1 Summary of the baseline paper

Genetic instability is a factor closely related to the appearance and development of cancer. The selection of this instability in cells is not clear yet, but with the use of mathematical models the paper aims to determine the conditions that determine it. Out of a wide variety of factors, it finds that the one with most impact is the rate of DNA damage.

The parameters used in the models are shown in the following table:

Symbol	Interpretation
S	Stable Cell pop.
M	Mutator Cell pop.
r	Replication rate
u	DNA hit rate / prob. of genetic alteration
ϵ	Prob. of genetic alteration repair
$1-\epsilon$	Prob. of genetic alteration turning into mutation
β	Prob. of cell cycle arrest during repair
α	Prob. of mutant being viable
$1-\alpha$	Prob. of mutant being nonviable
ϕS and ϕM	Competition terms
n	Maximum number of consecutive mutations
a	Prob. of cell apoptosis

The first model for the competition dynamics between stable and unstable (mutator) populations of cells, which differ in the probability with which they repair genetic damage. Damaged cells can either be repaired or become mutated, and mutated cells are either neutral (continue to replicate) or non-viable (cannot replicate). These are the differential equations that describe the development of the cell populations over time for stable and unstable cells respectively:

$$\dot{S} = r_s S(1-u-\beta u\epsilon_s) + \alpha u r_s S(1-\epsilon_s) - \phi S \tag{1}$$

$$\dot{M} = r_m M(1-u-\beta u\epsilon_m) + \alpha u r_m M(1-\epsilon_m) - \phi M \tag{2}$$

We also present the equation $f_{s,m}$ describing cell fitness, which is used to predict the outcome of the competition in the model:

$$\begin{aligned} f_{s,m} &= r_{s,m}[1-u(1-\alpha+\epsilon_{s,m}(\alpha-\beta))] = \\ &= r_{s,m} - u r_{s,m}[C_{del} + \epsilon_{s,m}(C_{arr} - C_{del})] \end{aligned} \tag{3}$$

This initial model is then extended with the assumption that cells can accumulate mutations (mutation cascade), which increase their replication rate. We now consider the populations of stable and unstable cells S_i and M_i with $i = 1, \ldots, n$, where i is the number of accumulated mutations. They replicate at a rate r_i that satisfies $r_{i+1} > r_i$, bounded by the value r_n, and the model starts with two populations S_0 and M_0. Moreover, a mechanism is introduced to limit the increasing replication rate: the apoptotic response a, which is a mechanism of self-destruction by the cells. An impaired apoptosis will mean that a is low enough so that $r_0 < r_n(1-a)$. We consider an intrinsic replication rate $R_i = r_i(1-a)$, with $R_0 = r_0$ because there are no mutations.

Now, the equations defining the behaviour of the system are, for an initial, intermediate, and limit populations of stable cells, respectively:

$$\dot{S}_0 = \overbrace{R_0 S_0(1-u_S)}^{\text{Cells w/o genetic alterations}} - \phi S \tag{4}$$

$$\dot{S}_i = \underbrace{\alpha u R_{i-1} S_{i-1}(1-\epsilon_S)}_{\text{Mutated cells from prev. gen}} + R_i S_i(1-u_S) - \phi S_i, \qquad 1 \leq i \leq n-1 \tag{5}$$

$$\dot{S}_n = \alpha u R_{n-1} S_{n-1}(1-\epsilon_S) + R_n S_n[1 - u_S + \underbrace{\alpha u(1-\epsilon_S)}_{\text{Mutated cells now do not reproduce at a higher rate}}] - \phi S_n \tag{6}$$

Another three analogous equations describe the populations of mutator cells M_i.
Defining $C_{arr} = 1-\alpha$ and $C_{del} = 1-\beta$ as the cost of entering cell cycle arrest and creating non-viable mutants respectively, the results of the baseline paper can be summarized in the following table:

Table 1 *Summary of the basic competition dynamics and results from the model that includes evolution and mutation cascades*

	A. Summary of basic competition dynamics[a]	
	Mutator slower than stable cells	Mutator faster than stable cells
Low DNA hit rate	Stable cells win	Mutators win
High DNA hit rate	Mutators win if $C_{arr} > C_{del}$[b]	Stable cells win $C_{arr} < C_{del}$
	B. Results from model[c]	
	Apoptosis intact	Apoptosis impaired
Low DNA hit rate	Stable cells win	Mutators win
High DNA hit rate	Mutators win if $C_{arr} > C_{del}$	Stable cells win $C_{arr} < C_{del}$

[a] If the mutators have a lower intrinsic replication rate than the stable cells, a high DNA hit rate can select in favor of mutators. If the intrinsic replication rate of the mutators is higher than that of the stable cells, then a highDNA hit rate can select for stable cells.
[b] C_{arr}, cost of cell cycle arrest. C_{del}, cost of generating deleterious mutations.
[c] If apoptosis is intact, unstable cells have a lower intrinsic growth rate than stable cells. Hence, a high DNA hit rate can select for instability. If apoptosis is impaired, unstable cells have a higher overall intrinsic growth rate than stable cells. Thus, a high DNA hit rate can select in favor of stable cells. C_{arr} stands for cost of cell cycle arrest, and C_{del} stands for cost of generating deleterious mutations.

2 Cellular Automata & our approches

Cellular automata (CA) are discrete dynamical systems with simple construction but complex self-organizing behaviour. They usually consist of a square grid of cells, which can be in several different states, and a set of rules which are used to iteratively update the cells in the grid. The rules to update a cell usually depend on its current state and on a set of other cells in the grid assigned to it, called its neighborhood. An initial state of the grid is selected by assigning a state to each cell, and then a new grid is generated repeatedly applying the rules to some or all the cells in the current one.

We have implemented two cellular automaton schemes to simulate the competition dynamics of stable and unstable cells. One of them tries to replicate the schema presented in the baseline paper [1], and the other considers hetero-catalytic replication and mutation, among other changes.

2.1 Cellular automaton A

The simulations of the first scheme are based off diagram 1, which describes the first model of the baseline paper. The aim will be to compare the results of the simulations and the paper.

The cells in this CA can be found in one of seven states. There are three primary states: empty, stable cell and unstable cell, and stable and unstable cells can be either healthy, repairing or mutated. The damaged state in diagram 1 is not needed and the empty state is used for dead cells.

The grid, a square of side length L, is initialised mostly full, half of them healthy stable cells and the other half healthy unstable cells. At every generation, firstly healthy and mutated cells replicate according to their replication rates, creating a copy of themselves in a random cell in their Moore domain. Then, $L * L$ random cells are updated according to the probabilities in diagram 1.

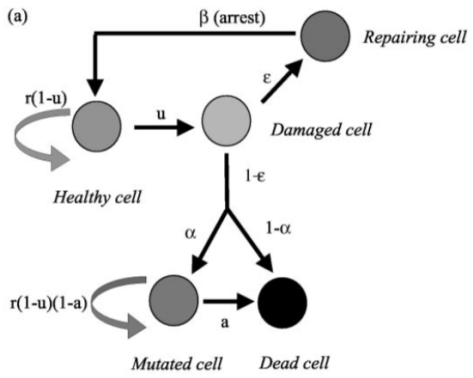


Figure 1: diagram 1

2.2 Cellular automaton B

In the case of the second cellular automata scheme, only a specified proportion of the grid is initialised, with stable and mutator cells randomly placed according to some probabilities. The two cell populations are competing for the space and the one with higher fitness will win. The implementation process is nearly the same as in the first case, but we have considered some aspects from other points of view. In diagram 2 can be observed the terms and probabilities that we are taking into account when implementing the scheme.

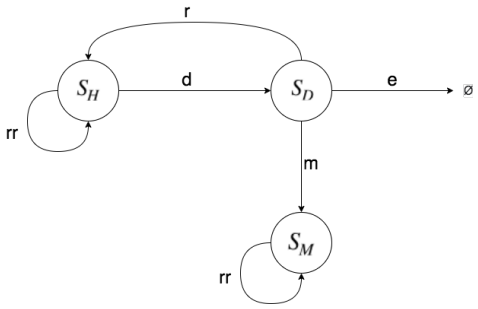


Figure 2: diagram 2

Once the grid initialisation is complete, we randomly pick L^2 grid spots (where L is the height or width of the grid). Consider a non-empty picked spot as the "center cell". The center cell can be of either type, be it stable or mutator. For each of the center cells, the simulator is going to perform each of the following steps, in order:

1. Auto-replication: healthy and mutated cells auto-replicate in a hetero-catalytic way. Consider the Moore domain of the center cell (the 8 adjacent cells that surround it). Two random spots are picked from its Moore domain. If one of them is of the same type as the center cell and the other is empty, we will obtain a copy of the center cell in the empty grid spot with a probability rr.

2. Damage: healthy cells can be damaged. Each center cell is going to be damaged with a probability d.

3. Mutation: Only a damaged cell can be mutated. We repeat the auto-replication procedure, and if one of picked grid spots from the Moore domain is mutated and the other empty, a mutated cell will fill the empty cell with a probability m. If this mutation does not occur, the damaged cell will change state to mutated with a small percentage of the mutation probability. This is to jump-start mutation when there are no mutation cells in the grid.

4. Degradation / Repair: This step is applied to damaged cells. The center cell will die with a probability of death e and be repaired (turned healthy) with a probability r.

5. Diffusion: the center cell will change spots with a random cell in its Moore domain with probability i.

Note that this procedure is applied to both stable and mutator (unstable) cells.

3 Conclusion

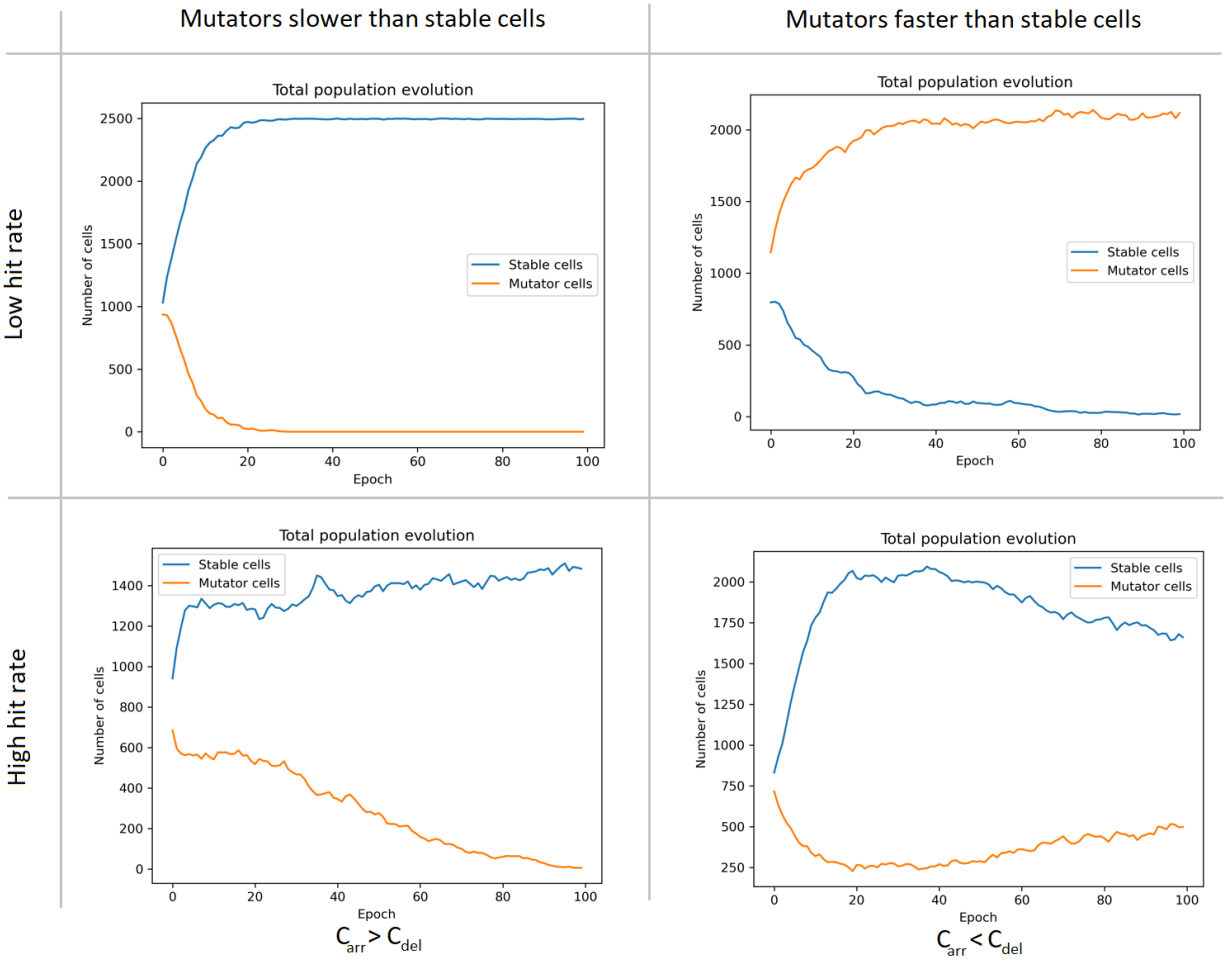
Once we have created our cellular automata models, we are going to comment some results and graphics that we have obtained during the process.

3.1 Case A simulation

We will consider the four cases in *Table* 1.*A*. The low and high DNA hit rates will be 0.2 and 0.95.
If mutators are slower than stable cells, $r_m = 1.0$ and $r_s = 1.25$ and in the other case the values are swapped, $r_m = 1.25$ and $r_s = 1.0$.
For $C_{arr} > C_{del}$, $\alpha = 0.05$ and $\beta = 0.5$, and for $C_{arr} < C_{del}$, $\alpha = 0.5$ and $\beta = 0.05$. The other parameters, which are not changed, are the following:

Variable	Value
totalPopDensity	1.0
stablePopDensity	0.45
epochs	100
worldSize	50
stableRepairProb	0.99
mutatorRepairProb	0.1
deathProb	0.5
randomSeed	0

Table 2



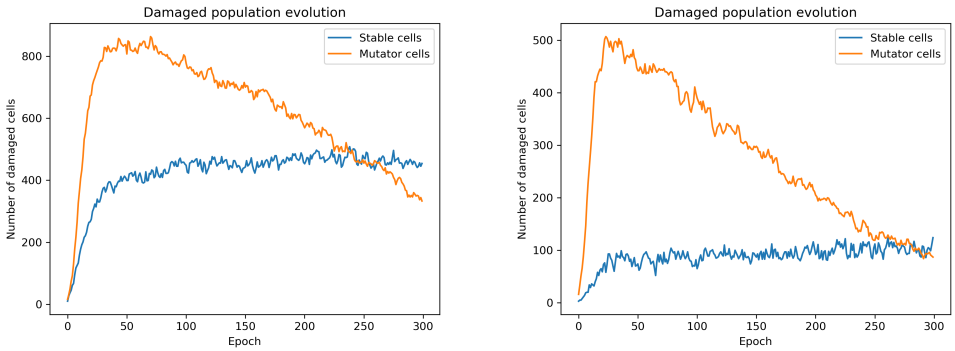
The results shown in Table 2 coincide with what was expected, except for the bottom left cell. However, the competition in that case is not won as straight forward as in the other cases. In order to see how stable are these outcomes, this work could be extended by varying the parameters or repeating these experiments using different seeds.

3.2 Case B simulation

At the beginning of this experiment, just the ten percentage of the whole domain is filled, half of which are stable cells and the other half mutator cells. We are compering two different experiments where changing a factor can reverse the evolution of the cells. The value of the parameters considered are the following ones:

Variable	Value Experiment 1	Value Experiment 2
simulationType	caseB	caseB
totalPopDensity	0.1	0.1
stablePopDensity	0.5	0.5
epochs	300	300
worldSize	50	50
mutatorRR	3.0	3.0
stableRR	1.0	1.0
diffusionRate	0.01	0.01
damageProb	0.2	0.2
deathProb	0.02	0.02
mutationProb	0.3	0.3
stableRepairProb	0.2	0.8
mutatorRepairProb	0.1	0.1
createAnimation	True	True
randomSeed	1	1

The different value from one experiment to the other is the term "stableRepairProb". In the first case is 0.2 and in the second one is 0.8. We are going to explain some graphics and the differences observed between one experiment and the other.
In these first graphics, we can appreciate the damaged population evolution. As the probability of stable cells to be repaired is lower in the first experiment, there will be more stable damaged cells in the first case rather than in the second one. Despite that fact, in both experiments the mutator damaged cells have nearly the same evolution.

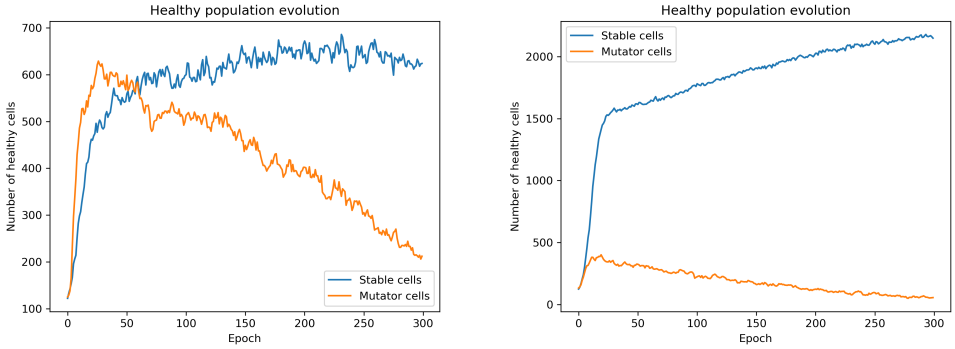


(a) Experiment 1

(b) Experiment 2

Figure 3: Damaged cells evolution

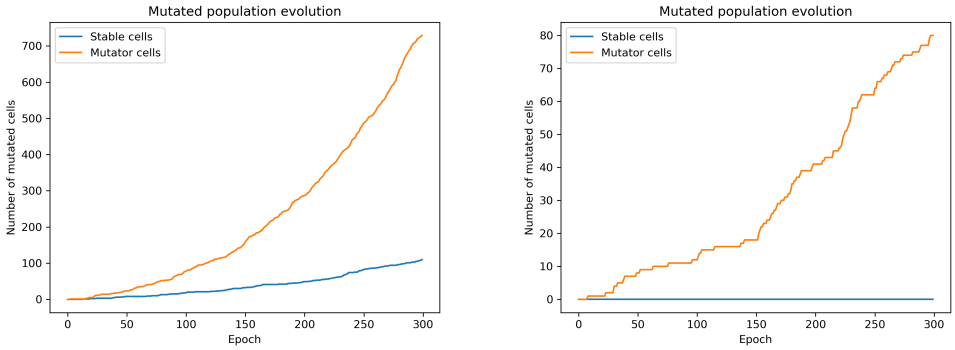
Besides, the healthy population evolution is quiet different from the first experiment to the second one. The amount of stable healthy cells is higher in the second experiment due to the fact that the probability of stable repairing rate is increased. The impact on mutator cells is minimum because increasing the "stableRepair-Prob" involves increasing the amount of stable healthy cells, so there will be a bit less of mutator healthy cells.



(a) Experiment 1 (b) Experiment 2

Figure 4: Healthy cells evolution

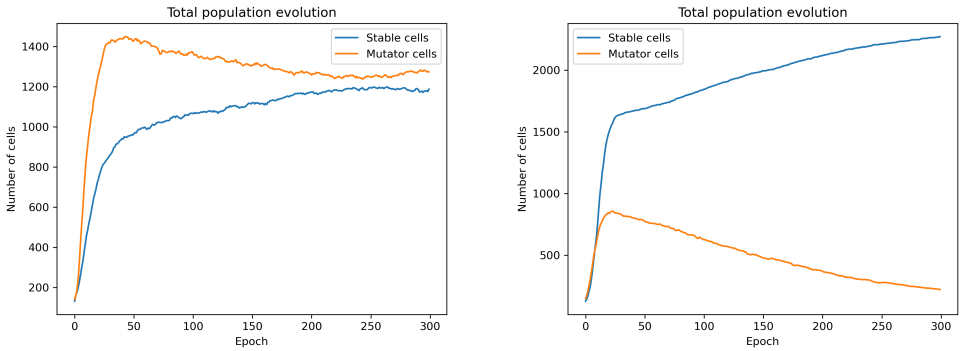
In the next two figures, we can observe the mutated population evolution. The mutator or unstable cells are more or less the same in both experiments, the ones that have more impact on the appearance of cancer. But in the case of stable cells, as "stableRepairProb" is increased there will be less probability to be mutated.



(a) Experiment 1 (b) Experiment 2

Figure 5: Mutated cells evolution

In the total population evolution of cells, we can appreciate that in the first graphic the mutator cells are going to win the competition, as in the second one occurs the opposite. This fact can be possible because in the second figure the probability of stable cells to be repaired is higher, so they are strong enough to win the competition.

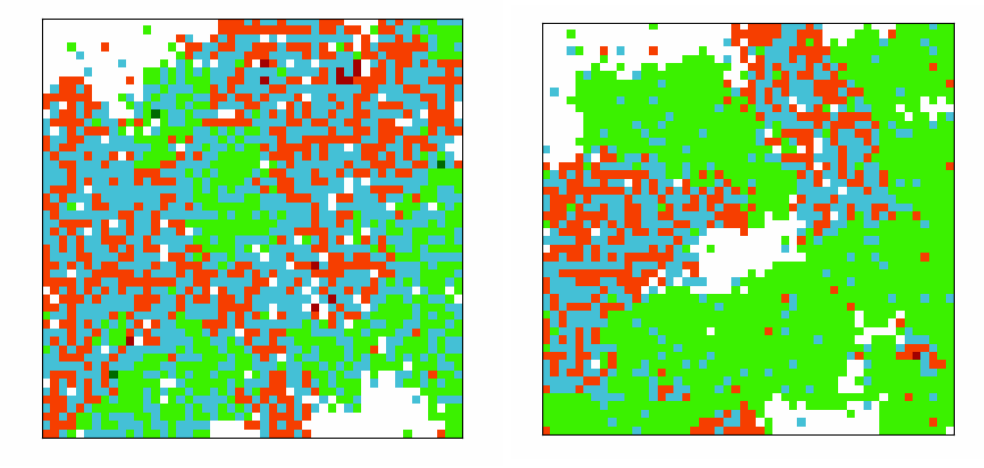


(a) Experiment 1 (b) Experiment 2

Figure 6: Cells total evolution

Once we have analyzed those graphics, we can also obtain some curious information from the gifts. It is much more visual and we can see clearly the competition of both population of cells. The colours significance is the next one: stable healthy cells (light green), stable mutated cells (dark green), damaged cells (blue), mutator

healthy cells (light red), mutator mutated cells (dark red) and dead cells (white).
At the beginning of the process, we can observe that we have stable and unstable cells competing for the space. As the "stableRepairProb" is higher in the second experiment, there are more stable cells.

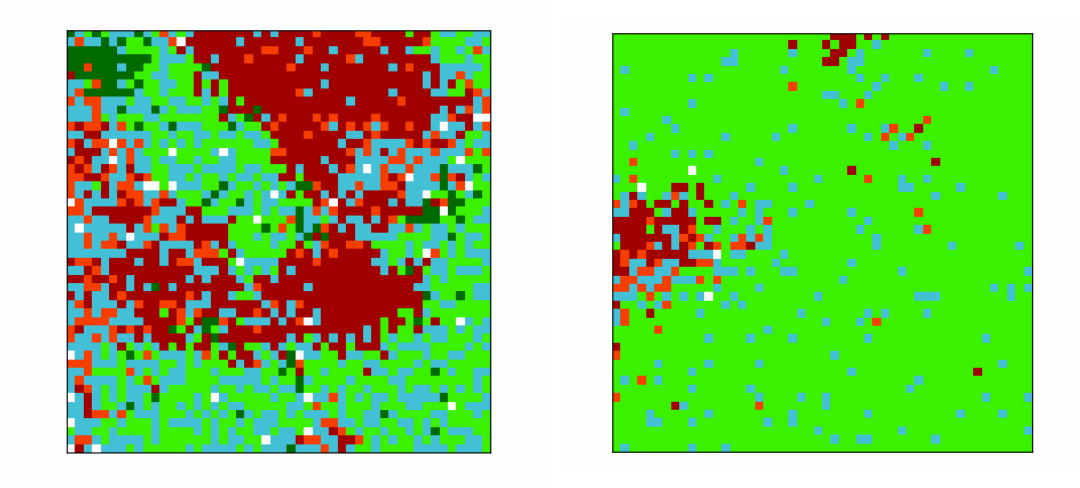


(a) Experiment 1

(b) Experiment 2

Figure 7: Type of cells at the beginning

At the end of both experiments, we can appreciate what cells win the competition. In the first one, there is a huge amount of unstable mutated cells so the probability to suffer from cancer is higher. However, in the second experiment, the stable cells are winning the competition, so the cancer may not appear.



(a) Experiment 1

(b) Experiment 2

Figure 8: Type of cells at the end

Looking forward towards future work. We didn't have enough time to extend in this topic as much as we wanted and we have been left with the desire to continue researching about this subject: what would happen to the graphics when chemotherapy is introduced? Would they be reversed? What if other parameters are added or the current ones modified?

4 Implementation details

The software used in this report can be found on github.com/chus-chus/cellular-automata along with a short installation and usage tutorial.

References

[1] Natalia Komarova and Dominik Wodarz. Evolutionary dynamics of mutator phenotypes in cancer: Implications for chemotherapy. *Cancer research*, 63:6635–42, 11 2003.