Université Paris-Saclay, Evry

Modelling and Simulation

Course Project: *"An agent-based model of avascular tumor growth: Immune response tendency to prevent cancer development"*[4] replication

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Note: this report is 5 pages if we don't count header page, references and the figures
Master 1 – GENIOMHE

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1 Introduction

Modeling tumor growth has become an essential tool in cancer research, providing a means to investigate the complex dynamics of tumor development and immune interactions without the time and cost constraints of in vivo experimentation. Among the various stages of tumor progression, the avascular phase—during which the tumor grows without its own blood supply—is particularly important, as it represents the initial stage of cancer development and offers a window for early therapeutic intervention.

Agent-based modeling (ABM) has proven to be a powerful method for simulating such biological systems, offering the ability to represent individual cell behaviors, stochastic events, and spatial dynamics. In particular, ABMs are well-suited to capturing emergent phenomena that arise from localized interactions between agents, such as immune cells and tumor cells.

In this project, we implemented the model presented in the paper *"An agent-based model of avascular tumor growth: Immune response tendency to prevent cancer development"*[4] which explores the interactions between tumor and immune cells during early tumor development. Unlike previous models, this one considers how the microenvironment influences tumor cell proliferation and how cancer cells may recruit or evade immune cells, using a spatially explicit, stochastic framework.

Our aim is to reproduce the original model using NetLogo and to analyze its behavior under various parameter settings, in order to better understand the dynamics of tumor-immune interactions in the avascular stage and validate the findings presented in the original study.

2 Modelling

2.1 Definition and Implementation

The model uses a 2D grid (lattice) of size $L \times L$, where each grid cell represents an agent. A Moore neighborhood is used for interactions. There are two main types of agents (defined as `breeds` in NetLogo), each representing living cells in a tissue. Every agent has a 'mode' attribute that defines its current state, which in turn governs its behavior.

The **NIC** has the following attributes: `mode`, `age`, `radius`, and `PT_type` (to distinguish mutated from non-mutated PT cells; ratio is user-defined). Each `mode` indicates a specific cell state:

- **Mode 1:** Proliferative Tumor Cell (PT) – actively dividing, may be mutated or non-mutated.
- **Mode 2:** Non-Proliferative Tumor Cell (NT) – dormant due to nutrient shortage.
- **Mode 3:** Necrotic Cell (Ne) – dead from nutrient depletion.
- **Mode 0:** Normal Cell or Empty Space – healthy cell or available space for division.

*An additional **mode 4** represents an unstable intermediate state during tumor–immune interactions.*

The **IC** agent has the following attributes: `mode` and `radius`.

- **Mode 1:** Cytotoxic T Cell (CTL) – an immune cell that specifically targets and kills tumor cells.
- **Mode 0:** Natural Killer Cell (NK) – an immune cell that kills tumor cells with less specificity.

Agents behavior and interaction:

1. Setting NIC cells

According to [4], the model is first instantiated by adding free cell agents on all patches. Then, a few proliferative tumor cells (PT) are set in the center. However, no ratio or grid size is mentioned in the original model. Therefore, we experimented with different sizes and set a radius in which we want to sprout PT cells in the middle as user-defined.

Algorithm 1 T agents behavior at time t (breed = NICs and (mode = 1 or mode = 2))

```
for each NIC agent do
  if agent is a PT cell then
    if has at least one neighboring NIC and probability r_p is satisfied then
      Proliferate
    else if age > threshold and radius ∉ allowed proliferative region then
      Enter quiescence
    else
      Increment age
    end if
  else if agent is a NT cell then
    if radius ∈ allowed necrotic region then
      Undergo necrosis
    else if radius ∈ allowed proliferative region then
      Revival of PT cell
    end if
  end if
end for
```

2. Behavior NIC cells

Implemented as `NICs_transitions` procedure in NetLogo, pseudocode: Algorithm 1. Some notes:

- $T = PT + NT + Ne$
- Proliferation probability r_p depends on the radius for mutant PT cells and both radius and neighboring NIC cells for non-mutant PT cells.
- **Proliferation**: A PT (NIC 1) mother cell produces two daughter cells:
  - One daughter remains at the same position with age reset to 0.
  - The second daughter occupies a random neighboring empty cell, becoming NIC 1 (PT) with age 0.
- **Quiescence**: The cell stops proliferating and transitions to NIC 2 (NT).
- **Necrosis**: The cell dies and transitions to NIC 3 (Ne).

3. Setting IC cells

For ICs, they initially start from one corner of the lattice and move, either in a biased or unbiased way, towards the center of the tumor, which is filled with necrotic debris that signals the immune cells to move towards it. This movement is called a random walk and is associated with a probability r_{walk}, which we will discuss in the behavior section. The number of IC cells sprouted depends on the total number of cells on the grid, with a ratio that we have decided to set as user-defined (k, the ratio of ICs to the total number of cells).

4. Behavior of IC cells

Random walk probability is defined by a ratio of ratios, that is $\frac{nT}{ncell^2}$ over $nPTnT$, and multiplied by k, as a damping constant. This is important to defined whether the walk will be biased towards the center or not. The logic behind it is that at the very beginning the ratio of PT cells over total tumor is very high, which will aid in the mouvement towards the center. On the other hand, with time, the number of T cells will get higher and PT will be lower (due to increase in necrosis, explained in simulation section), which will contribute in making it unbiased.

5. Recruitement of IC cells

IC have the ability to recruit other IC cells by signalling them whenever they are able to kill more tumor cells. This will be done by recruiting new IC randomly from corners again, at the same rate as current ICs are killing the PT cells. This allows the constant fight against the growing tumor, making this simulation a competition between tumor and immune cells. Their movement will be directed to the tumor because of k (nIC/total) that is included in the random walk probability.

Algorithm 2 IC agents behavior at time t

```
for each IC agent do
  if has at least one PT neighbor then
    if agent is a CTL cell then
      for each PT neighbor do
        if probability r_I is satisfied then
          Kill PT cell
          Add to list of killed PTs
        end if
      end for
      if any PT cells were killed then
        Move to one of the killed PT locations
      else
        Stay in place
      end if
    else if agent is a NK cell then
      Select a random PT neighbor
      if probability r_I is satisfied then
        Kill PT cell
        Keep track of killed PT
        Move to killed PT location
      else
        Stay in place
      end if
    else if probability of protumor behavior is satisfied then
      IC cell dies
    end if
  else
    random walk
  end if
end for
```

2.2 Outcome

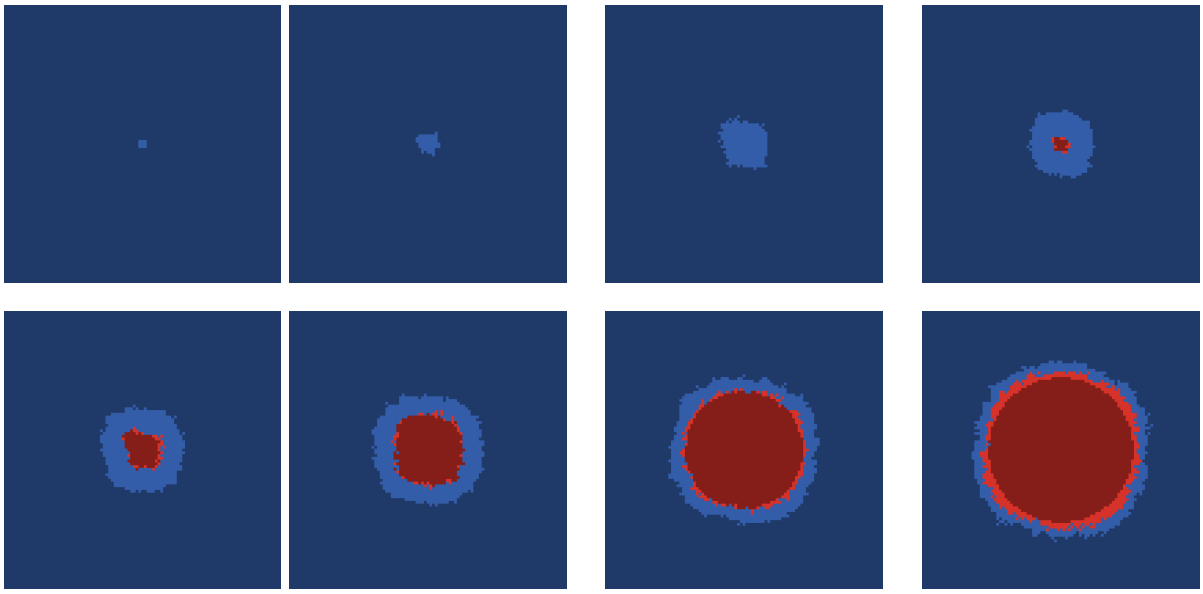
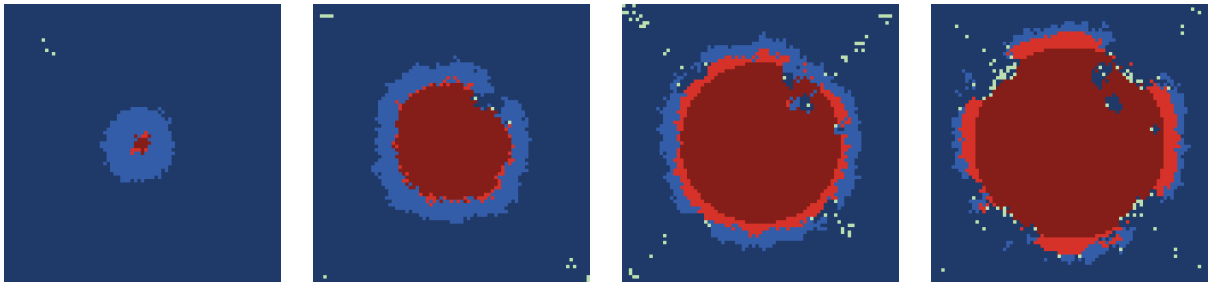


Figure 1: Tumor growth model at different time steps: 0, 5, 15, 20, 30, 50, 75; age threshold set at 10, radius of initial PT is 2 and Nmm=0.02



(a) time=15 (b) time=40 (c) time=60 (d) time=90

Figure 2: Tumor-immune interaction model evolution through time; age threshold set at 10, radius of initial PT is 2, Nmm=0.02 and k initial is 0.001

2.3 Discrepencies

In the paper, it is made clear that mutants are more likely to proliferate than non-mutants (which is also showing in the probability formula). However, in the flowchart, the authors made the mistake of looking if this probability ¡ random number, instead of the opposite, hence results are flipped. If we look at non-muts/mut counts in Figure 6, it shows non-mutants as the dominant type, even though they were starting at Nmm=0.2 (nonmutant/mutant is 1/4 initially) and mutants are more likely to proliferate by definition. This has a huge effect on the model, as growth will be largely affected by the proliferation probability, mutants will no longer prefer to proliferate as much, yielding some wrong results. For that we flipped the condition in our model, which fixed this issue and made the plot more logical, portraying that mutants are indeed dominant in this case.

In the beginning of the paper, it was mentioned that NK cells are supposed to die immediately after a collision with cancer cells and CTL cells are supposed to die after the maximum n-times, where n is a random number. However, this was not included in the methodology and transition rules. ICs died with probability r_t if they didn't kill PT cells, and if there were no PT neighbors, they continued walking if there were normal cell neighbors; otherwise, they stayed in their position.

3 Simulation Analysis

3.1 Replication and Validation

Tumor growth model

The main simulation was set for the same initial parameters as the ones mentioned in the paper (fixed ones and Nmm=0.2). Age threshold and initial radius were not, we experimented on several values and got the following pattern in general:

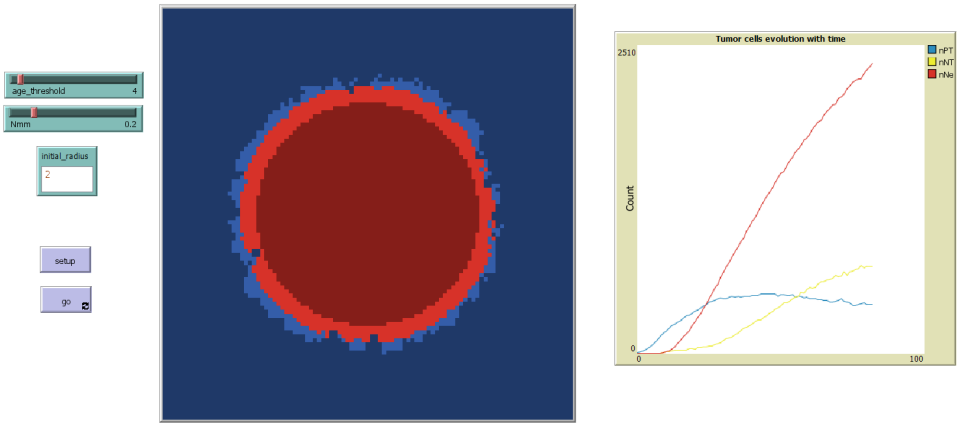


Figure 3: nPT, nNT and nNe through time

As expected, and matching with the paper's results, the number of necrotic cells increase exponentially, validating the fact that this is an avascular tumor growth model. In other words, due to the lack of nutrients, the necrotic mass is set to get bigger. This can also be seen in the following plot, showing GF (growth fraction) and NF (necrotic fraction), where GF is becoming null with time with the absence of nutrients. Likewise, we see the changes in the average radius of the external edge of the tumor (Rt) and the radius of the necrotic core (Rn). Hence, validating by having similar plot that the avascular model has indeed growth limitations.

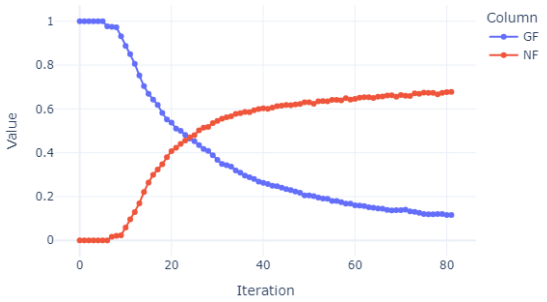


Figure 4: GF and NF plot

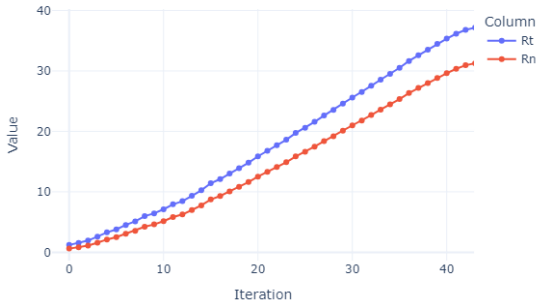


Figure 5: Rt and Rn plots

In the next plot, starting as well with Nmm ratio=0.2 (i.e. 20% are non mutant, 80% are mutant), in an attempt to replicate their figure. We notice that first the population becomes strictly mutants, that's because we started with a larger proportion of mutants and by being ultimately way more advantageous to proliferate (it does not depend on micorenviroenment, and the formula re-enforces and describe its higher multiplication tendency). he population of mutant PT cells grows following a Gompertz growth pattern and eventually represents a small fraction of the total PT cell population. Their proliferation is influenced by the tumor microenvironment, where reduced availability of nearby empty spaces around a parent cell leads to decreased cell division. Worth noting that this curve starts to go down a bit aggressively since again we're dealing with an avscular model, as previously explained, we would expect the total number of PTs to go down.

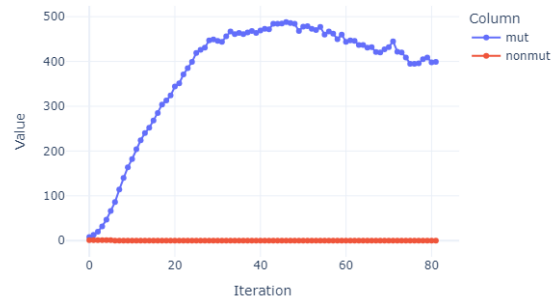


Figure 6: Mutant and Non-mutant evolution with Nmm=0.2, portraying Gompertz growth

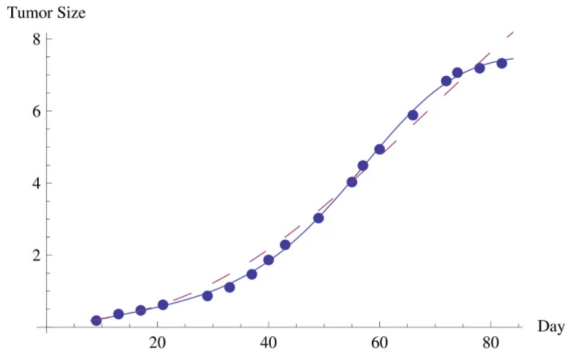
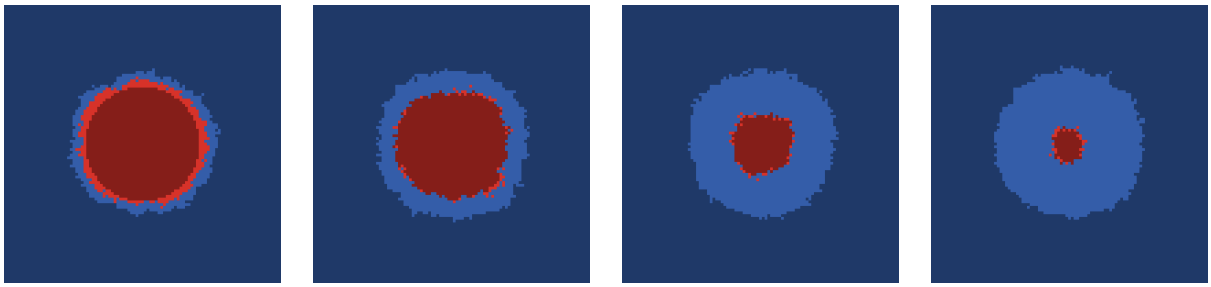


Figure 7: Growth of tumor biomass following Gompertz growth curve; Figure 1 from [1]

3.2 Exploration

Tumor growth model

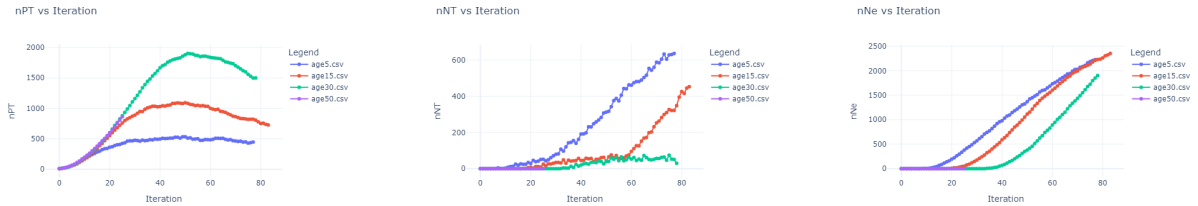
We first tried to set different age thresholds to test for growth, since it's a parameter with no mention on what its value could be and with no further references. In here age is set by the number of iteration. We notice that its a crucial parameter to set the speed of growth. We can also notice the affected thickness of the proliferative part.



(a) threshold=5 (b) threshold=15 (c) threshold=30 (d) threshold=50

Figure 8: Trying different values of age thresholds and capturing them at iteration 50, where Rmax is already reached and its no longer advancing forward

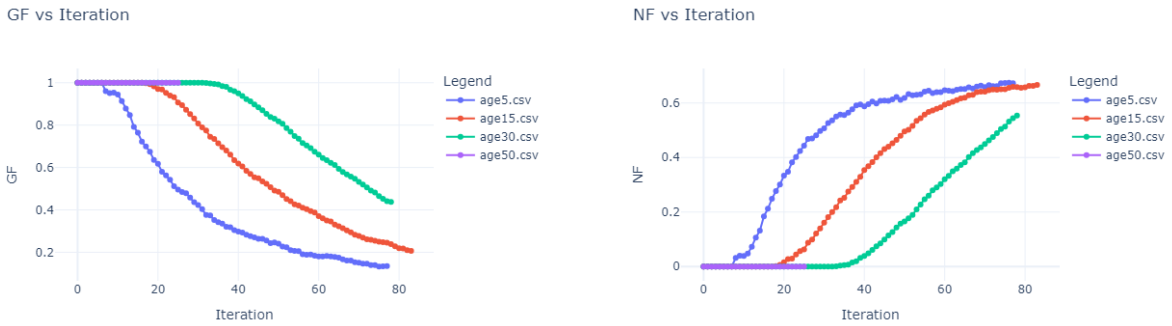
For these different runs, we have saved and plotted the updated parameters to compare:



(a) nPT (b) nNT (c) nNe

Figure 9: Evolution of number of tumor cells using different thresholds

We can notice at first that age 50 and 30 are confounded, to explain this, it might mean that at one point it converges in a way the threshold no longer affects the growth of the tumor. Another observation is that necrotic rate in age 5 is far more greater than 15 then 30. Which is also logical, since at very low age thresholds, the cell would die directly when it no longer belongs to the area that is defined by thickness of proliferative cells (δ_p) . As we raise the age, we make the propagation to reach this thickness slower, allowing more time for growth. And as age 15 is in between, it conveys an equilibrated depiction



(a) GF (b) NF

Figure 10: Growth and Necrotic fractions evolution with different thresholds

of the growth, whereas age 5 for instance provide a smoother curve due to the strict restriction enforced by the growing radius in comparison with the thickness.

Then, we want inspect the differences between mutant and non mutant proliferation, so we simulated the growth model for different value of Nmm (nonmutant/mutant ratio), and we set the age threshold to a low value to make more pressure on proliferation. We also took snapshots at early states of the modet, t=20 because we want to study the early propagation of tumor and got the following results:

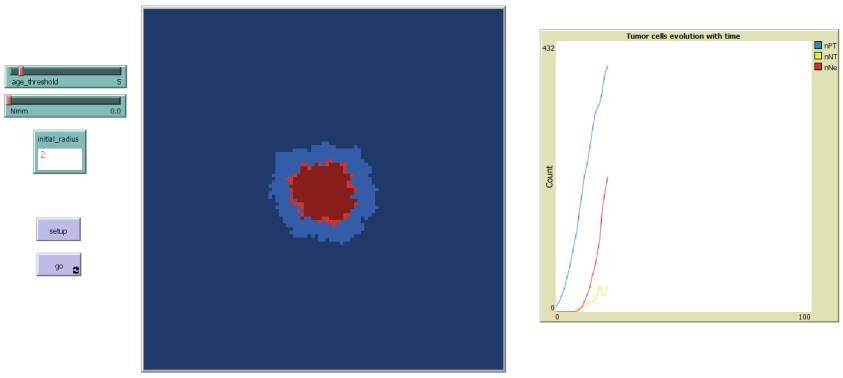


Figure 11: All mutant PT simulation

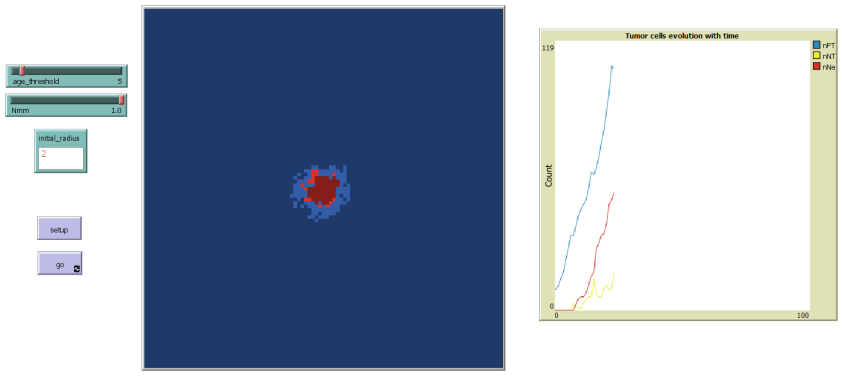


Figure 12: All non-mutant PT simulation

Logically, from the definition of the model and biologically speaking, mutants should be able to multiply better. In the first simulation in figure 11 we set Nmm=0 which means all are mutants, we can see at time 20 that the tumor starts to divide pretty quickly. On the other hand, same conditions, when we

set Nmm=1 (all non-muts), we see way less PT cells in teh outer layer, in fact, some NT cells are very close to the surface, which would create problems while simulating an immune interaction (tumor is not well developing). This should not be a problem, since in reality, there is no tumor with 0 mutant cells, but on the contrary. Hence these finding validate the first assumption that mutants are more capable of proliferating (as was in the intention of building the model).

Tumor-immune model

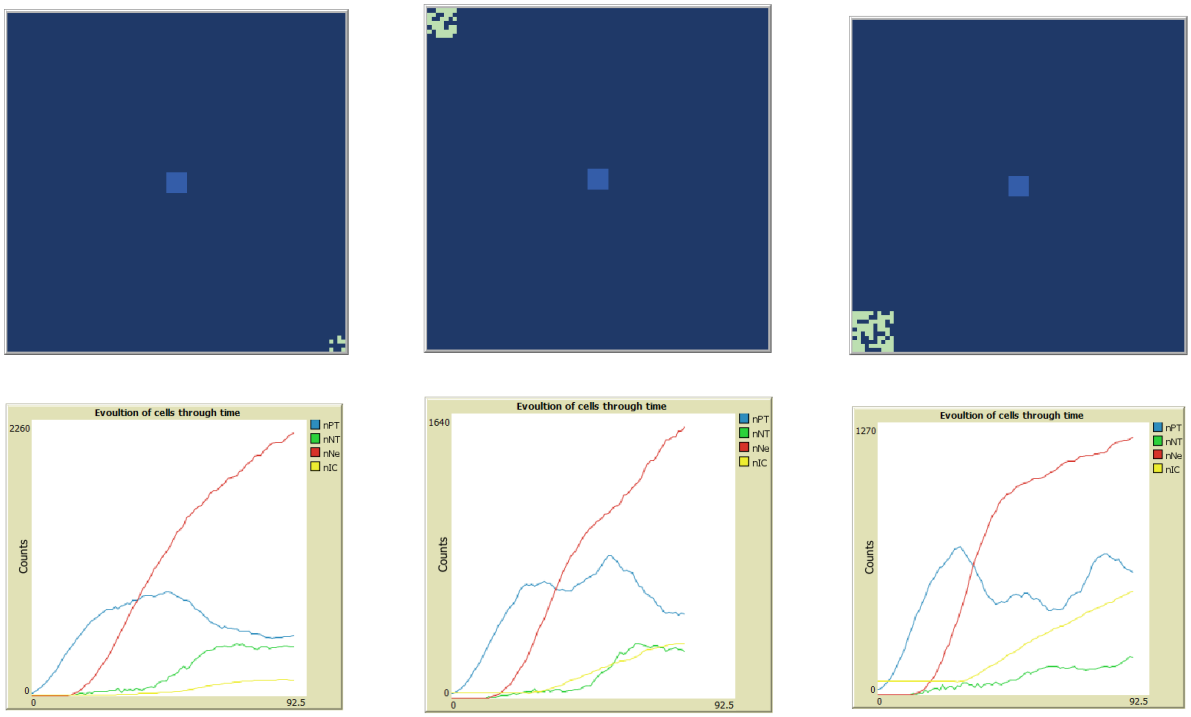


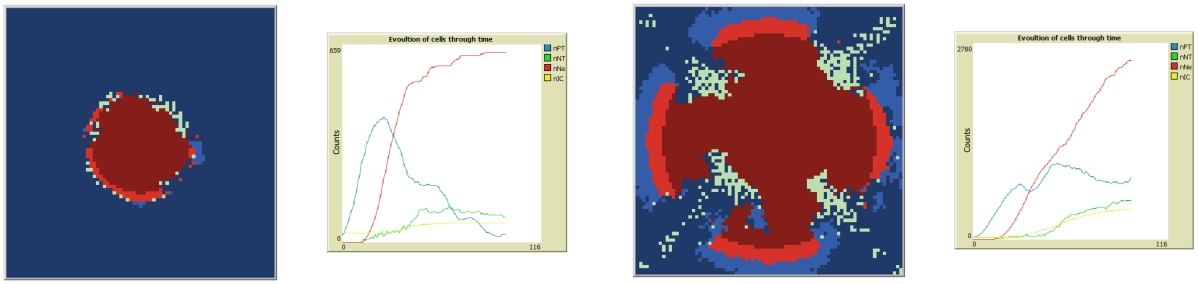
Figure 13: Trying simulation with different values of k: 0.001, 0.05 and 0.01 respectively in each column. Row 1 show the initialized grid and row 2 show statistics on the number of cells at time=80

If we take a middle value of k (here 0.005), we can see that the number of PT cells has a sudden drop then picks up what it has lost before starting to frop again. We notice that this drop is not met in parallel with an increase in NT, but rather, in first signs of increase in IC. This means that it's casue by an initial attack coming from this medium group immune cells. In fact, this group is not large enough to keep fighting tumor cells, as it doesn't pick up speed until new recruited cells collide with them and NT transitions start to occur cause of age (picked age threshold 10 to account for this case).

In the case where k is small (0.001), the number of initial attacks are relatively small. This is why we don't see a drop in PT when they start attacking, another proof that the killed PTs are not direct result from the attack is the slow increase in IC, met in parallel with a larger increase in NT, meaning that this PT that's missing is entering non-proliferative phase instead of actually being killed, we can conclude this range of k to be non effective to attack that mass of tumour.

Finally, when k is large (0.01), it creates a lot of empty spaces in short time that proliferation sells thus have more space to proliferate, initiating some kinf of a feedback loop: sudden drop in PT and increase in N $\implies$ sudden increase in PT thanks to new available nutrients sources $\implies$ more attack from the large group of ICs leading to deacrease in PT.

We were also interested to test and see the effects of max allowed radius (Rmax) of the mass, since Rmax is set to 37.5 in the paper basing on previous work by Kansal et al. (2000) [3] where they defined this value to be optimal for brain tumor growth in the cellular automata model. For this experimentation, we will try 2 values around 37.5, that are 50 (because that's the maximal radius in our 101 x 101 grid) and 20 (because it's almost as away from 37.5 as 50). We're gonna take k=0.005 as a middle value with age trheshold =10, as discusses in the figure right before.



(a) Rmax=20 (b) Rmax=50

Figure 14: time step of the model between 80-90

For the firt case (Rmax=20), the immune cells almost destroyed the proliferative layer, essentially killing the active part of the tumor, which is a behavior we did not see previously when we increased the number of ICs. This tells us something about the importance of restricting a tumor's growth capabilities, maybe with the sufficient deprivation of nutrients of some tumorous body, effect of ICs can be larger.

Secondly, as Rmax gets bigger, there exists larger margin for PT to be conserved in. The more the attack creates gaps, the more it can fill this empty space through cell division, as we can see the shifts in the number of PT. This resembles the positive feedback loop that we have previously discussed, and agrees with the findings inferred from when Rmax=20.

4 Our contribution

First we would like to mention that 2 things mentioned in the paper did not have initial values which are: age threshold and k initial (initial nICs over total cells) . This is why we have started each of the tumor growth and tumor-immune models analysis by exploring different values of them respectively (see Simulation Analysis - Exploration).

On the other hand, we have added a useful and valid contribution to the paper's model, that was not mentioned in any way but is crucial to fix some behaviors, and that's concerning tumor cell mutations. We have added in another nlogo file, possibility for the user to input mutation probability. In a real case scenario, tumor cells constantly mutate, as it's one of the hallmarks of cancer [2]. Therefore this is one point the model is missing while trying to simulate a real tissue. In fact, one of the things that we have refuted in the model and validated through analysis, that a model with only non mutant cells (Nmm=1) is not able to proliferate in the required speed, as 1. they depend on micro-environment, and 2. mutants are more fit for that. For this reason, the model does not capture a good growth as we have seen in the figure, analysis section. Since this is a stochastic model, it's worth trying adding this probability in an attempt to make it more realistic.

4.1 Mutation probability is tumor-immune model

We have created the file `tumor-growth-contribution.nlogo` with the added contribution, as you'll find a box to enter the probability. We tested a model with all non-mutants and set probability to 0.05 which is the scientific logical mutation probability to use.

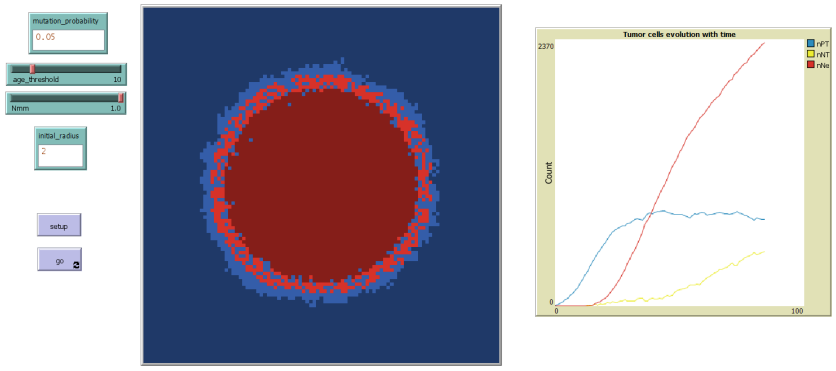
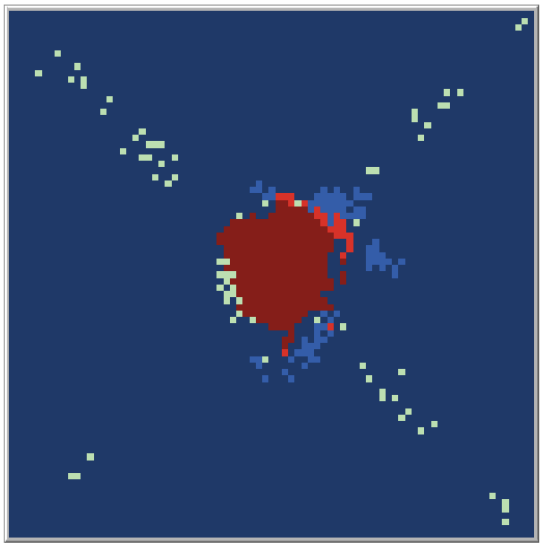


Figure 15: All non-mutant PT simulation with p mutation=0.05

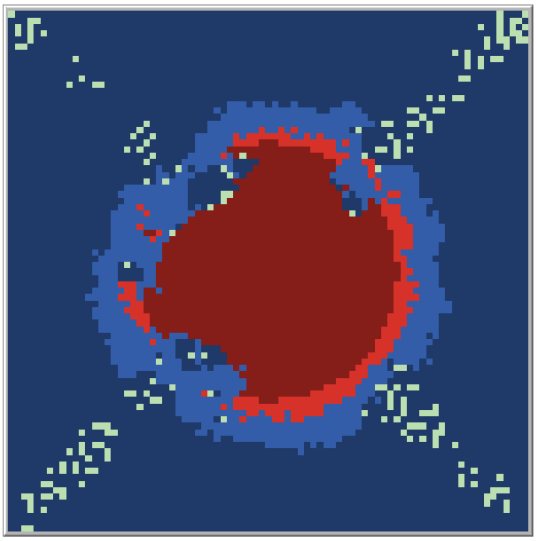
Comparing with figures 11 and 12 that show the typical proliferation in both mutants and non-mutants, we see that this probability has fixed the non mutant proliferative behavior.

4.2 Mutation probability is growth model

We have created the file `tumor-immune-contribution.nlogo` with the added contribution, as you'll find a box to enter the probability. We tested a model with all non-mutants and set probability to 0.05 which is the scientific logical mutation probability to use.



(a) All non-mutant PT simulation, immune interaction



(b) All non-mutant PT simulation with p mutation=0.05, immune interaction

Figure 16: time step of the model between 80-90

Due to the non-mutant under developped proliferative growth we can see that the immune easily vanquish the system, which can be an artifact due to the missed mutation probability assumption. In this figures, we can see that setting p mutation to 0.05, which has previously improved the growth model, also makes quite a competetion between tumor and immune, with the same parameters set, making it worth studying.

5 Conclusion

In this work, we replicated tumor growth and tumor-immune interaction models as described in the literature, validating their core assumptions and behaviors. Building on these foundational models, we introduced a small but meaningful contribution that enhances the biological realism of immune-tumor dynamics.

While the original models rely on short-range, contact-dependent interactions—where immune cells affect tumor cells only upon physical contact— we propose in the future incorporating non-local links to represent long-distance signaling, enabling cells to interact beyond immediate proximity, such as through cytokine-mediated communication. This extension better reflects biological processes like immune recruitment and chemotaxis. Additionally, extending the model to explore therapeutic interventions, including immunotherapy, offers a valuable direction for predicting treatment responses. Altogether, these enhancements would contribute to a more comprehensive and predictive framework for studying tumor progression and immune modulation.

Closing Note

You can find the code for this project on this GitHub repository: `https://github.com/raysas/modelling-project/`. Model was implemented in NetLogo, 2 main models: growth (tumor-tumor) and interaction (tumor-immune) models. Data of parameters were saved in csv files and plotted in python using plotly. You will find the code files along with the zip folder, consisting of 4 nlogo files and 1 jupyter notebook for visualization of data.

References

[1] Wayne M Eby, Mohammad A Tabatabai, and Zoran Bursac. Hyperbolastic modeling of tumor growth with a combined treatment of iodoacetate and dimethylsulphoxide. *BMC cancer*, 10:1–8, 2010.

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[4] Fateme Pourhasanzade, SH Sabzpoushan, Ali Mohammad Alizadeh, and Ebrahim Esmati. An agent-based model of avascular tumor growth: Immune response tendency to prevent cancer development. *Simulation*, 93(8):641–657, 2017.