Cellular Automata: Muscles and Immunity

Abstract

Cellular automaton models have been used to study the behavior of cells, including their propagation, migration, and differentiation. In this study, we built a cellular automaton model based on the work of Garijo et al. (2012), which accounts for cell proliferation, dispersion and differentiation in muscle cell samples. The model was enhanced by incorporating natural cell death, viral infection, and Natural Killer cell immune response mechanisms. The modeled viral infection keeps cells alive to propagate spread of the virus, similar to HPV?. The resulting NK cell immune response targets and eliminates infected cells before they spread virus prevalently. Our results demonstrate that incorporating these mechanisms into the cellular automaton model can provide a more accurate representation of the growth of muscle cell samples. Our work contributes to the understanding of how we can use Python to simulate biological systems and develop accurate models that can then be tested with in-vitro experiments.

Introduction

Cellular automaton models have been used extensively to simulate the behavior of cells, including their propagation, migration, and differentiation. These models have been used to study a wide range of biological phenomena. In this study, we built a cellular automaton model based on the work of Garijo et al. (2012) and incorporated natural cell death, viral infection, and NK cell immune response mechanisms. Our supplemented model aims to provide a more accurate representation of muscle cell growth with the dynamics of cell death, viral infections and immune responses at the cellular level taken into account. It also aims to show the versatility and modularity of Python-based models and shed light on how simple representations of complex phenomena have potential to result with depth and significance that can be explored with further research.

Random cell death is the simplest supplement to the system proposed in Garijo et al. (2012). Cell death can be caused by many factors during tissue growth, such as by extracellular signals, proliferation limits, infections, or true randomness. For the simplicity of the simulation, cell death was kept random in that each selected live cell had the same random chance of dying.

Viral infections are a significant health concern worldwide, and many infectious diseases are caused by viruses. The immune system plays a crucial role in protecting the body against viral infections, but the interplay between viruses and the immune system is extremely complex and not well understood. Understanding the dynamics of viral infections and immune responses is

important for developing new treatments and therapies for viral diseases. Being able to visualize the dynamics of an infection in a small group of muscle cells, can yield a better understanding of how the immune system fights its battles at a local level. The parameter “infprob” in the update function can be altered to describe different viruses with different infectious probabilities. A growing culture was used in the modeled simulations, but inserting a universe with solely stem/ differentiated cells can depict how tissues will react to infection. The hypothetical virus introduced to the system is modeled after Human papillomavirus. Similar to HPV, the virus causes cells to proliferate more often and keeps infected cells alive so that the virus can be propagated

The existing cellular automaton model based on the work of Garijo et al. (2012) provides a framework for studying the behavior of muscle cells. The paper shows how this stochastic propagation model accurately represents the behavior of in-vivo cells. However, this model does not incorporate mechanisms for natural cell death, viral infection, or the NK cell immune response. Our modified model relies on the principles of propagation, migration and then differentiation and then, once the system seems to be homeostatic, successively adds stressors. By being able to modify the different parameters that govern the properties of each cell type, we could be able to observe what types of conditions result in a successful immune response, which results in complete muscle cell destruction,...

The main question that our study seeks to answer is how can we modify the existing cellular automaton model to incorporate natural cell death, viral infection, and NK cell immune response mechanisms, and how do these modifications affect the behavior of the model? By answering this question, we aim to provide a better understanding of the complex interplay between viral infections and the immune system and to contribute to the development of new treatments and therapies for viral diseases. We also hope to provide a baseline from which successive work can be performed, both experimentally and computationally. The model needs to be tested with cells in vivo, to check if it accurately portrays cellular behavior. Our model can also serve as the starting point for more additions, like the presence of chemical gradients, blood vessels or the addition of more innate immune cells, like antigen-presenting cells

Methods

As our simulation is a 2D cellular automata, all of the models used display stochastic process. As mentioned before, the purposes of our models are to provide general predictions to simplified interactions between different types of cells. A simple square lattice was incorporated to easily demonstrate that our models were capable of simulating these biological interaction.

The original simulation outlined in Garijo et al. (2012) looks at each cell and simulates its effects on surrounding cells (surrounding cells refers to the left, right, top, bottom cells of a central cell). However, our simulation is different in that it looks at each cell and simulates the effects of the surrounding cells to the current cell; this method of simulation is more efficient and was incorporated because more models and variables were simulated here than in Garijo et al. (2012). Specifically, our simulation models apoptosis, viral infection, and an immune response and includes two different types of differentiated cells, infected cells, and Natural Killer cells.

The simulation starts with an initial population of 961 lattice sites. Each lattice site can only be occupied by one cell. The initial population of Garijo's simulation consists of empty spaces (ES) and undifferentiated cells (UC) while the initial population of our simulation consists of ES, UC, infected cells (IC), and Natural Killer (NK) cells. While this was not a feature in the Garijo simulation, our simulation includes the ability to change the probabilities of each type of cell occuring; probabilities of ES and UC occurring were set to be higher than the probabilities of NK cells and IC.

Cell Proliferation

Like the Garijo simulation, our approach to modeling cell proliferation was based on random-walk theory (Pérez and Prendergast, 2007). In the Garijo simulation, only UC were able to proliferate, but in our simulation IC also followed this proliferation model. Relevant variables for this model includes the probability of proliferation. The general process for proliferation is shown below:

Current site is ES → UC or IC present among surrounding cells → proliferation probability is hit → Current site turns into a UC or IC

Cell Migration

Like cell proliferation, this model was also based on the random-walk theory (Pérez and Prendergast, 2007). In the Garijo simulation, only UC were able to migrate, but in our simulation NK cells also followed this migration model. Relevant variables for our simulation include the number of jumps, jump size, and probability of migration (The Garijo simulation did not include a probability of migration, but our simulation did for the sake of a more accurate simulation). The general process for migration is shown below:

Current site is ES → UC or NK cells present among surrounding cells → migration probability is hit → Current site turns into the same cell as the corresponding surrounding cell; the surrounding cell turns into ES

In instances where multiple migrations were possible into an ES:
All surrounding cells that are able to migrate turn into ES → one out of the surrounding cells (chosen randomly) is migrated into the current site → the cells that are 'left out/deleted' are counted as cell deaths due to collision

In instances where cell proliferation and cell migration were possible into an ES:
Cell migration takes precedent because it is faster and cell proliferation does not occur

Cell Differentiation

In a biological context, cell differentiation tendsed to take longer than proliferation and migration. In order to model this, our simulation started differentiation in the cellular automata around two days after the simulation is run. UC were able to differentiate into either cell A (AC) or cell B (BC). The relevant variables for our simulation included the probability of differentiation into AC, the probability of differentiation into BC, and the starting time of differentiation. The general process for differentiation is shown below:

Current site is UC → AC or BC present among surrounding cells → differentiation probability is hit → current site turns into AC or BC

Apoptosis

For our own simulation, we included the natural death of cells. Under our model, UC, AC, and BC are able to undergo apoptosis. Relevant variables include the probability of apoptosis occurring. The general process for apoptosis is shown below:

Current site is UC/AC/BC → apoptosis probability is hit → current site changes into ES

Viral Infection

Our simulation also includes a model for a viral infection similar to HPV. Therefore, the IC in our simulation do not exhibit cell death (De Tomaso). Relevant variables include the probability of infection The general process for viral infection is shown below:

Current site is UC/AC/BC → IC is present among surrounding cells → infection prob is hit → current site turns into IC

Immune Response

Our final model simulates an immune response from NK cells against IC. NK cell proliferation is generally increased due to an increase of cytotoxic activity against IC (De Tomaso); our simulation models this by replacing IC killed by NK cells with NK cells. This general process is outlined below:

Current site is IC → NK cell is present among surrounding cells → current site turns into an NK cell

Our immune response model also simulates NK cell apoptosis, in which the probability of NK cell apoptosis becomes a relevant variable. This general process is outlined below:

Current site is NK cell → No IC present among the surrounding cells → Current site turns into ES

Results

We first tried to replicate the Garijo simulation using our own. The graphs below demonstrate a simulation of cell proliferation of different types of mice (wild-type or transgenic) and their different muscle cells (fast or slow proliferation). Cell percentage refers to the percentage of all living cells (UC, AC, BC) in the cellular automata.

Fig 1a: WT-FAST	Fig 1b: WT-SLOW

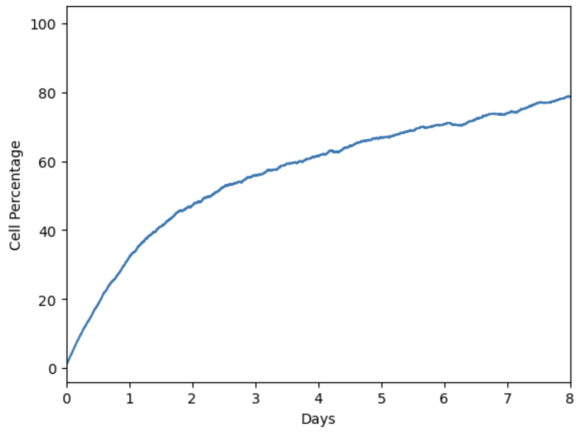
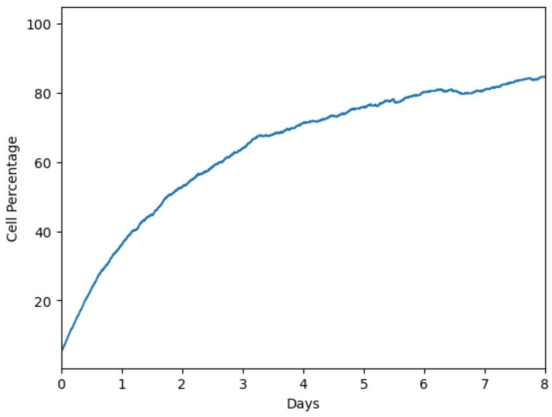
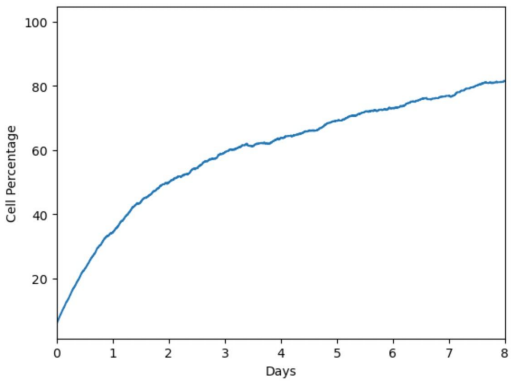
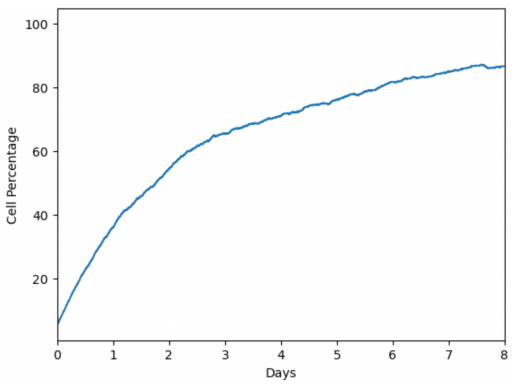

	

Fig 1c: TR-FAST	Fig 1d: TR-SLOW





Corresponding pictures of the cellular automata at 8 days given below:

Fig 1a: WT-FAST	Fig 1b: WT-SLOW

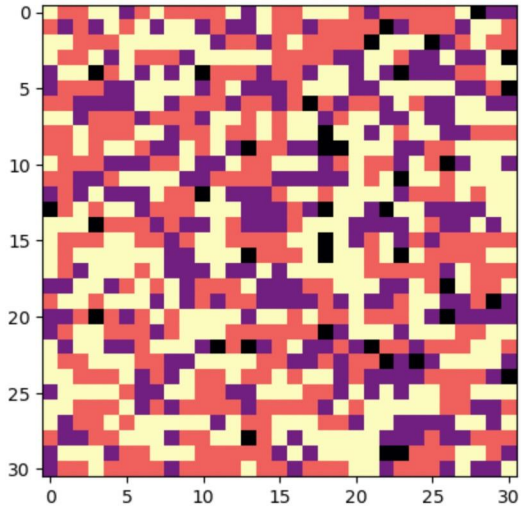
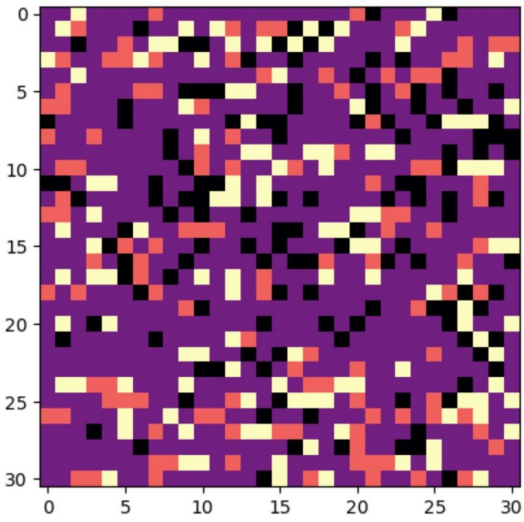
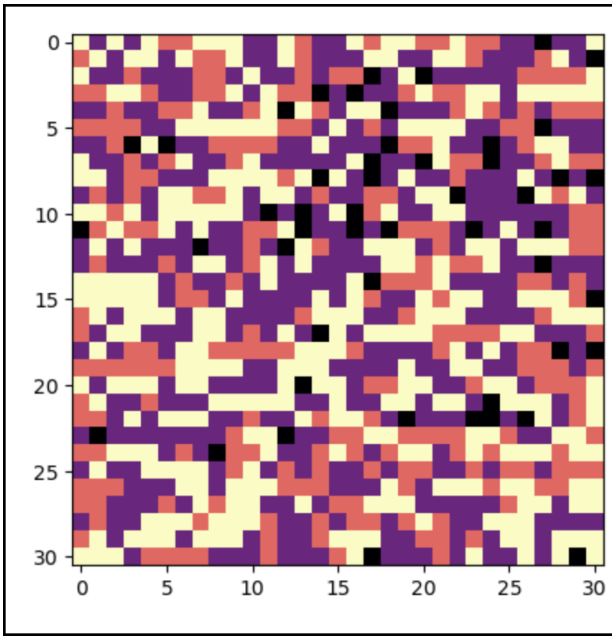
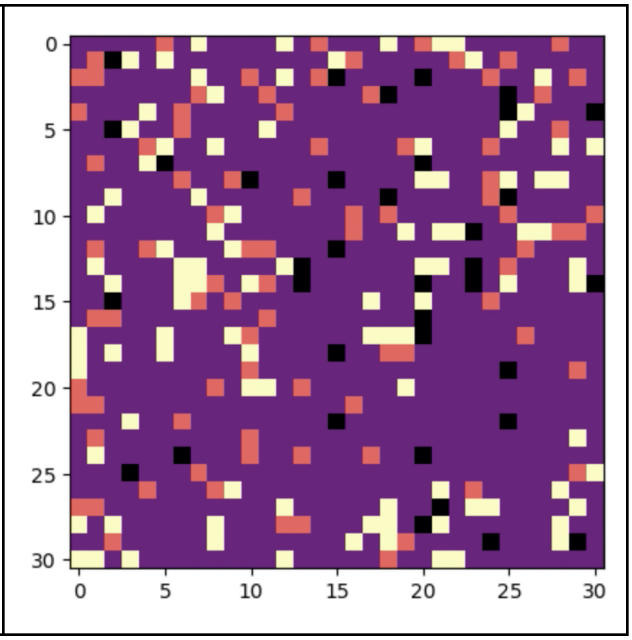

	

Fig 1c: TR-FAST	Fig 1d: TR-SLOW

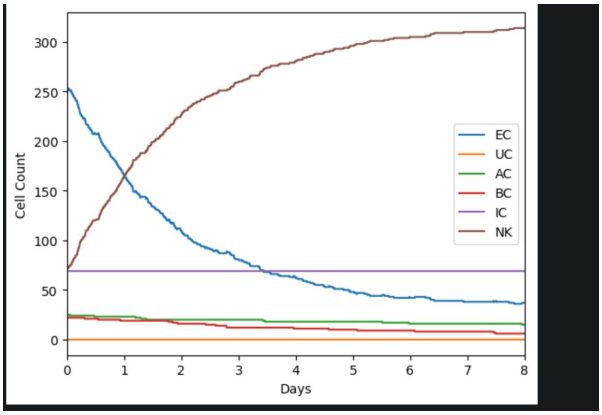




For our own simulation, we graphed the cell count of the different parameters (ES is mistakenly labled as EC) :

Fig 1a: WT-FAST

Fig 1b: WT-SLOW



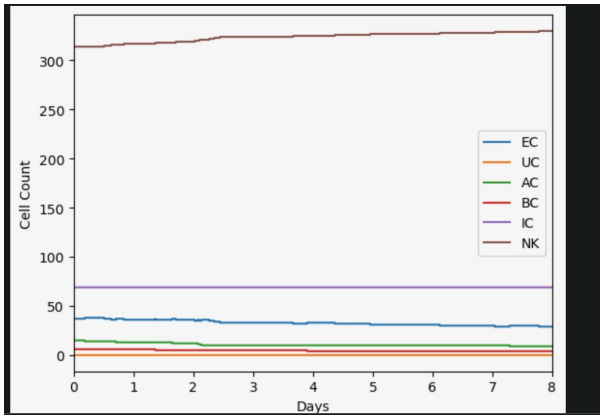
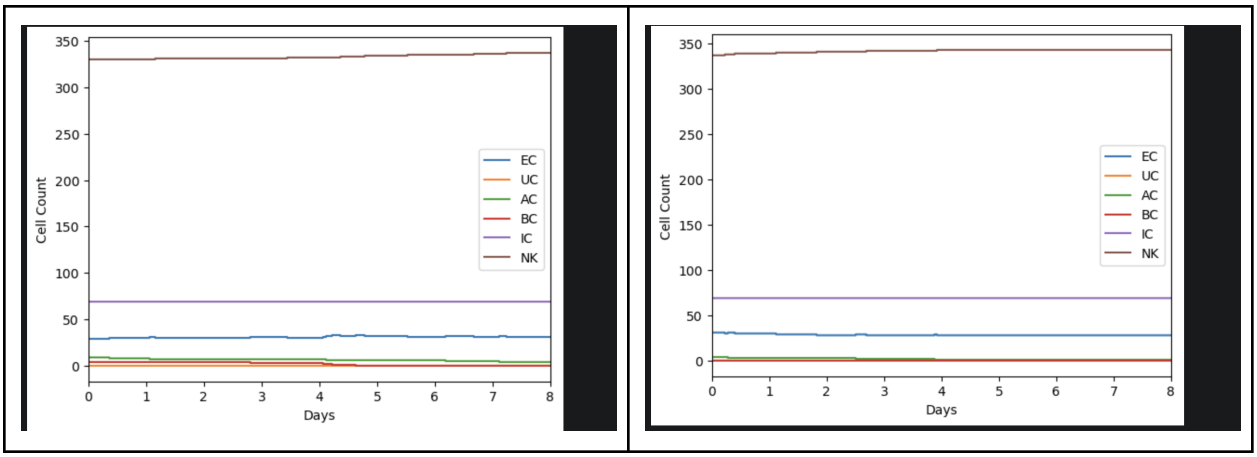


Fig 1c: TR-FAST

Fig 1d: TR-SLOW



Discussion

Our replication of the original model yields satisfactory results. It shows the expected cell proliferation, which occurs rapidly. The difference between fast and slow cells becomes evident in the 2D visual simulation, with fast cells experiencing increased amounts of differentiation in the 8 days that the simulation was run. For our own simulations, we ran into difficulties modeling the interaction between immune cells and infected cells, disrupting the simulation. When graphed up to infected cells, the system showed a compelling dynamism, with cell numbers significantly changing through time as different mechanics were introduced. Observing how the viral infection progresses in each of the different muscle cell types and how the immune response is able to deal with it gives us an insight into how important the specific characteristics of each fiber type are. The relationships between all the different cell types can be visualized, and conclusions drawn from them. These could inform how we think about vaccination and treatment delivery. It might be more advantageous to inject intramuscularly into one fiber cell type or the other, as they show a more dynamic immune response. It could also show that if you have certain mutations in cell type, you could be more or less susceptible to certain viral infections, which opens up the idea of how predictive models can impact our diagnostics methods and tools to maximize disease prevention and facilitate more direct treatment for people who already know what mutations they carry. This model is extremely open to additions. The addition of other kinds of innate immune cells, like macrophages, could bring about a variety of mechanics, such as the release of cytokines, creating a chemical gradient around the universe with a variety of characteristics related to inflammation. Adaptive immune cells could also be introduced, working together with the innate cells. This would comprise CD4 T_H cells, CD8 T_C cells and antibodies from B-cells. The cell types could be added sequentially, mimicking the progression of a full immune response. The model could incorporate the damage caused by an immune response, which when coupled with the cell proliferation rates could give an idea of how well muscular cellular systems are able to recover from such events. In a different direction, it could be interesting to incorporate a blood vessel into the model that carries nutrients

and such and explore how cells closer to the blood vessel might proliferate and differentiate at different rates than those further away, and how the nutrient gradient affects the cells around it. The blood vessel could be played with, with clogs or carrying immune cells or toxins. The scientific community should pursue the modularity of these types of models to tailor them to whatever specific situation they wish to represent, or what particular set of initial conditions they wish to operate in. This model carries several limitations. Whilst the proliferation, migration and differentiation dynamics have been experimentally verified, there is a need for in vivo-testing of the immune systems dynamics so that the values for certain parameters can be adjusted. It also relies on a multitude of assumptions. The immune system is extremely complicated and a huge amount of signaling interactions are not well understood, so to truly fine-tune the model there needs to be a dynamic and thoroughly mapped out cytokine and chemokine system.

Works Cited

Pérez, M. A., & Prendergast, P. J. (2007). Random-walk models of cell dispersal included in mechanobiological simulations of tissue differentiation. *Journal of biomechanics*, *40*(10), 2244–2253. https://doi.org/10.1016/j.jbiomech.2006.10.020

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Garijo, N., Manzano, R., Osta, R., & Perez, M. A. (2012). Stochastic cellular automata model of cell migration, proliferation and differentiation: Validation with in vitro cultures of muscle satellite cells. *Journal of Theoretical Biology*, *314*, 1–9. https://doi.org/10.1016/j.jtbi.2012.08.004